REVIEW ARTICLE

Facing small ravagers and big threats in the Americas

Eloísa Le Riverend[1]

■ INTRODUCTION

When some months ago, in the summer of 2015, a review of dengue, chikungunya and Zika viruses, all mosquito-borne viruses or arboviruses (arthropod-borne viruses), the diseases they cause and their epidemiology seemed necessary, the most important by far was dengue virus, both by incidence and mortality, in the case of hemorrhagic fever. Dengue has been present for more than 50 years in the Americas. Chikungunya virus was a newcomer; the virus was detected for the first time in the Caribbean in Saint Martin in December 2013. It spread fast because almost all of the population was susceptible. And Zika virus had recently been found in the Chile´s Easter Island (Feb 2014); spread fast since May 2015 in Brazil and at present has expanded explosively. Due to the enormous incidence of the zika disease and its possible complications (microcephaly in newborns, when women are infected during pregnancy and Guillain Barré syndrome), it is now the center of attention of world health institutions. The World Health Organization (WHO) on February 1, 2016, declared the recently reported clusters of microcephaly in Brazil and other neurological disorders a Public Health Emergency of International Concern (PHEIC) and established different task forces to study and fight the virus and their vectors. The main vectors of these diseases (mosquitoes of the *Aedes* spp.) circulate in parts of USA, Mexico, the Caribbean, Central and South American countries, where many of the underlying causes of their spread are present: warm, humid climate; huge socio-economic differences; rapid and ever increasing migration of people, to and from places where these diseases have been identified, increase in communications and tourism; changes in land use patterns (migration from rural to urban areas, new plantations, urbanization); variations in temperature and precipitation due to climate change, etc. There are some other arboviruses in the area, particularly in South America (Mayaro, Una and other), which could potentially cause new pandemics. Moreover, the already existing viruses can mutate to more aggressive forms. For diseases caused by these viruses, traditionally considered a problem for developing countries in tropical areas, there is as yet no specific treatment or vaccine. The intention of this review is to comment and raise awareness of certain aspects common to all of these diseases and how we can use them to prevent vector proliferation, as of today the most important prevention method for these diseases. An extensive and complete review of all aspects was not the purpose, since that would certainly require a full treatise. Many specific topics are covered by the reviews and papers found in the references.

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■ MOSQUITO-BORNE DISEASES

Mosquitoes are the best known disease vectors (Table 1); although, there are other disease vectors as, certain species of ticks, flies, sandflies, fleas, bugs, freshwater snails, etc.(1)

Table 1: Main mosquito vectors and diseases they trasmit

Mosquito vectors	Diseases
Aedes aegypty	Dengue yellow fever, chikungunya, Zica virus (potentially also Mayaro and Una viruses).
Aedes albopictus	Chikungunya, dengue, West Nile virus, Zika virus.
Haemagogus	Yellow fever, Mayaro and Una viruses.

Modified from: A Global Brief on Vector-borne diseases WHO Press, Geneva Switzerland. 2014

Aedes species, especially *Ae. aegypti* (Linnaeus) the most studied (Figure 1), are the main species of mosquitoes in urban areas. *Ae. aegypti*, identified by the white stripes on its legs, is originally native to Africa, and has become widely distributed and adapted to tropical and subtropical regions across the world. It feeds mainly on primates during the daytime (generally early in the morning and before evening) and breeds mostly in man-made containers in urban settings. Apart from being an irritating nuisance, these mosquitoes are very important from an epidemiological point of view, because they transmit various arboviruses, and are now present in more than 20 European countries;(2,3) in some cases, *Ae. albopictus* also transmits these illnesses, especially in more temperate areas.

Aedes albopictus (Asian tiger) mosquitoes are more commonly found in rural and periurban settings, feeding readily on a variety of mammalian and avian species, although *Ae. albopictus* shows similar larval development in artificial containers. It is particularly resilient and also a daytime feeder.(4) This mosquito species can survive in cooler temperate regions of Europe and North America, as far north as the Great Lakes,(2) largely due to international trade and travel, and therefore

Figure 1 Aedes egypti, the main ravager, feeding

has a wide geographical distribution.

Nearly 700 million people suffer mosquito-borne diseases each year resulting in more than one million deaths.(5)

■ FACTORS AFFECTING MOSQUITO-BORNE INFECTIOUS DISEASE

Many factors can affect transmission of vector-borne infectious diseases. Different risk factors have been classified as micro- and macrodeterminants. Microdeterminants are those related to host, disease agent, and vector (suitable conditions for vector proliferation, adult female density, etc.). Macrodeterminants can be environmental in nature (latitude, longitude, altitude, temperature, relative humidity, etc.) or socioeconomic (population density, unplanned urbanization, migration, etc.).(6)

Climate factors

Climate change and variability shorten the reproductive cycle of vectors of medical importance, such as mosquitoes transmitting dengue, malaria, equine encephalitis, West Nile encephalitis, and other diseases. Mosquitoes grow more easily in humid weather and intense heat, and sometimes expand their areas of influence when improperly stored water or poor environmental hygiene practices originate breeding sites.(7)

For centuries, links have been demonstrated between climate and diseases with various modes of transmission (vector, water, food, soil, and airborne)(8,9) with the strongest associations between climate and mosquito borne diseases. In this regard the most studied diseases are malaria and dengue. (10,11,12)

Climate factors such as temperature and atmospheric humidity have been related to the biology (vector dynamics, agent development, and mosquito/ human or animal interactions) and breeding foci density of *Aedes aegypti*.(13,14,15)

Temperature

Temperature that interacts with many other factors is a crucial element in dengue virus (DENV) transmission. Temperature influences vector development rates, mortality, behavior (16,17) and viral replication within the mosquito.(18) Higher temperatures are associated with faster rates of viral replication within the vector and shorter extrinsic incubation period (EIP; the time required for DENV to become transmissible to another host after initial infection of a mosquito).The time between feeding and virus detection in the salivary glands of *Ae. aegypti* mosquitoes decreases from 9 days at 26°-28°C to 5 days at 30°C.

Temperature considerably influences mosquito population dynamics: egg and immature mosquito development, ovarian development, and survival at all stages of the mosquito life cycle.(19) Tun-Lin and coworkers (2000) reported that *Ae. aegypti* egg, larvae, and pupae development is faster at higher incubation temperatures and ceases at temperatures lower than 8.3°C with the ideal range for survival through all phases of development (88-93%) occurring between 20°-30°C.(17)

Adult mosquito survival is required, since only mosquitoes that live beyond the EIP can act as potential vectors. Mark–release–recapture studies have estimated that adult daily survival rates are between 86 % and 91 %.(20,21) Christophers (1960) provided evidence of increased mortality with exposure to prolonged extreme heat (higher than 40°C) and cold (less than 0°C) in a laboratory setting.(22)

The reproductive cycle of the female mosquito is also determined by the temperature. At less than 20°C, fertilization decreases.(22) De Garin and coworkers (2000) established that increased minimum temperatures resulted in accelerated oviposition cycles and egg laying. Female *Ae. aegypti* require a blood meal for ovarian development, and feeding is also influenced by temperature. Feeding activity is reduced or stops at temperatures below 15°C and can also be reduced at temperatures over 36°C.(23)
Temperature effect is observable in the following map of areas

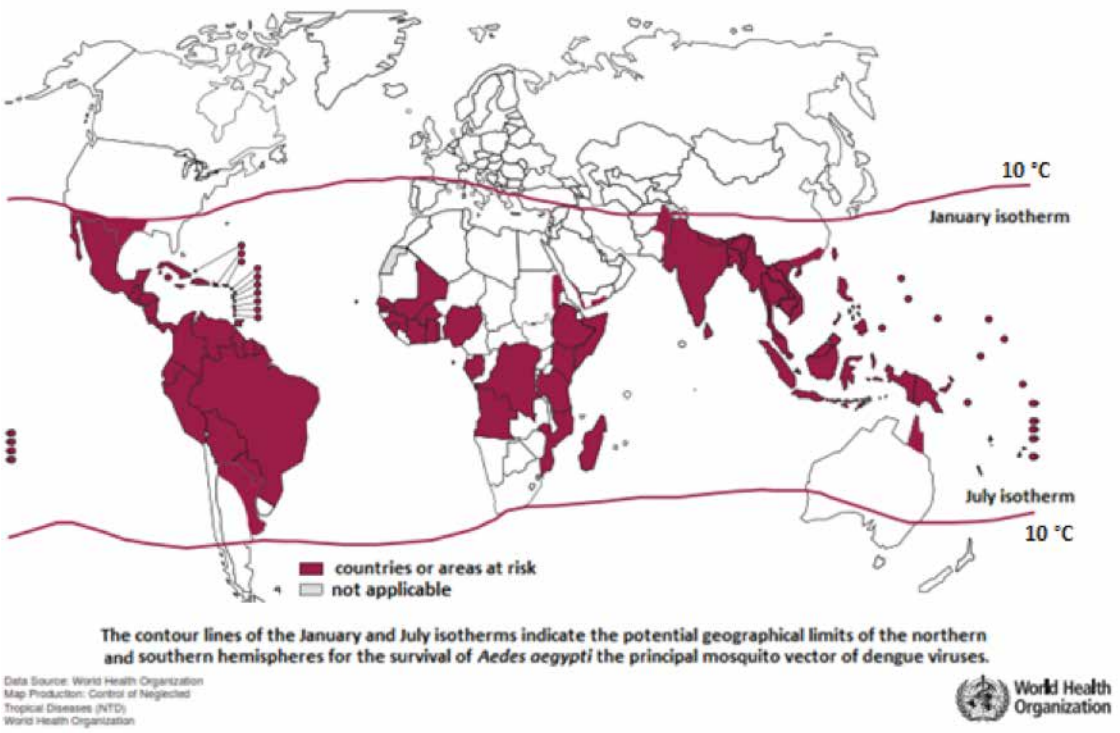

Figure 2 Countries or areas at risk of dengue transmission worldwide, 2012
Source: A Global Brief on Vector-borne Diseases WHO Press, Geneva, Switzerland. 2014

of dengue transmission risk (Figure 2), which shows the limits for the survival of the *Aedes aegypti* vector.(24)

Furthermore, mosquitoes seem to select breeding containers based on temperature and sun exposure.(25) These authors also found the presence of trees to be associated with Ae. aegypti pupal productivity; suggesting that although dense vegetation may promote growth by contributing organic material to the habitat, it can also affect water temperature and evaporation.

Precipitation

Variability in precipitation affects habitat availability for *Ae. aegypti* and *Ae. albopictus* larvae and pupae. Temperature further interacts with rainfall as the chief regulator of evaporation, thereby also affecting the availability of water habitats for immature mosquitoes, although the eggs are resistant to desiccation over extended time periods.(22)

Higher rates of precipitation combined with higher temperatures also result in increased humidity. Higher humidity is associated with increased *Ae. aegypti* feeding, survival, and egg development.(4,22) El Niño-Southern Oscillation (ENSO) is thus an important factor, since it is associated with warm temperatures and increased precipitations that may promote development of previously laid eggs.(8,26)

Indirectly, rainfall, temperature, and humidity all influence land cover and land use, which increases or reduces vector population growth. The incidence of dengue fever has been associated with vegetation indices, tree cover, housing quality, and surrounding land cover.(18,27) An examination of the spatial distribution of adult *Ae. aegypti*, regarding land use and land cover, indicated that it prefers areas with structures and medium height trees to areas with bare earth.(28)

SOCIOECONOMIC, DEMOGRAPHIC AND CULTURAL FACTORS

These are well known factors affecting the incidence of any disease in general. Dr. Margaret Chan's (Director General of the WHO) words summarize it well: "As vectors thrive under conditions where housing is poor, water is unsafe, and environments are contaminated with filth, these diseases exact their heaviest toll on the poor —the people left behind by development." These diseases also exacerbate poverty, since illness and disability prevent people from working and supporting themselves and their family, causing further hardship. There is no health care for the poor. Malnourished people and those with weakened immunity are especially vulnerable.(4)

Among socioeconomic factors, rapidly increasing trade, migration and travel in general, exert great influence on the transmission of mosquito borne viruses. Growing traffic volumes within the global transport network have been proposed as important in determining biological invasion success. Successful biological invaders can be difficult to predict given the lack of evidence of a universal trait related to invasion. The identification of the principal routes of movement of *Ae. albopictus* among thousands of possible alternatives is evidence that, within the global transport network, the seaports and airports at greatest risk of future spread of disease vectors can be identified through a combination of climate and traffic data.(29)

■ MAIN VIRAL DISEASES CIRCULATING IN THE AMERICAS AT PRESENT

DENGUE VIRUS

Before 1970, only nine countries had experienced severe dengue epidemics; the disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, India, South East Asia and the Western Pacific (Figure 2).(4) Dengue has been the most rapidly spreading mosquito-borne disease in the world, the incidence has increased about 30-fold and it has spread geographically to new areas, and also from urban to rural settings. Recent estimates consider that dengue fever (DF) cases may be as high as 400 million per year, of which around 96 million cause severe disease (Figure 3).(30)

During the past few decades, Mexico, the Caribbean, Central

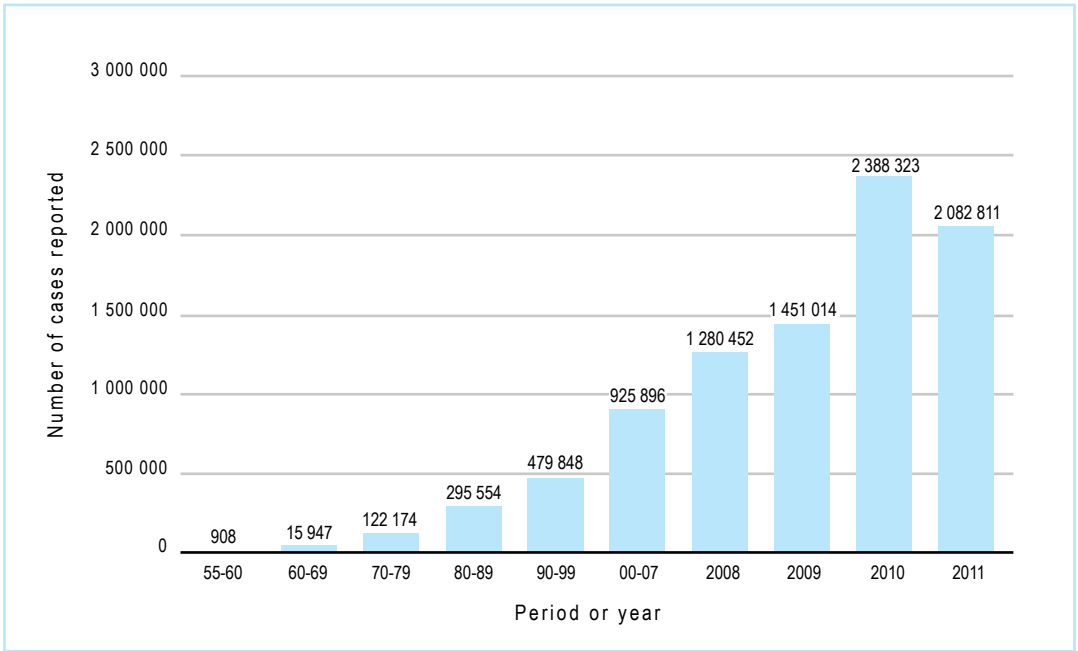

Figure 3 Average number of cases of dengue and severe dengue reported to WHO annually during 1955–2007 compared with the number of cases reported during 2008–2011
Source: A Global Brief on Vector-borne Diseases WHO Press, Geneva, Switzerland. 2014

and South America have gradually evolved from a low dengue-endemic to a hyperendemic region with transmission in most countries and those parts of USA where the *Ae. aegypti* mosquito (the main vector) exists.(31)

Dengue fever is the most important human disease caused by flaviviruses (single-stranded RNA virus). [This assertion may just be starting to change due to the fast growing Zika virus epidemic in the Americas and its potential neurological complications -the author]. There are four closely-related, antigenically-distinct serotypes (DEN-1 to -4), all of which circulate in our region.(24) In its spread throughout warm regions of the world, dengue virus (DENV) has had to adapt to new environments. Distinct genotypes or lineages (viruses highly related in nucleotide sequence) have been identified within each serotype, exposing the extensive genetic variability of the dengue serotypes.(24) Diversification in viral strains has resulted in the development of strains that appear associated with greater potential for sparking epidemics. Outbreaks have occurred when new dengue strains emerged and displaced the native strains to which the local population had already developed immunity. Until now, the mechanisms governing how and why some viral strains are more suited for causing widespread disease have been poorly understood.(32) Recovery from infection by one serotype provides lifelong immunity against that particular serotype. However, subsequent infections by other serotypes increase the risk of developing severe disease. Among them, the "Asian" serotypes DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections.(33) Infants born to mothers with immunity to dengue virus are at high risk for dengue hemorrhagic fever and hospitalization during primary infection in the first year of life.(34,35)

Dengue diagnosis is generally done clinically: symptoms, physical examination, low white cell count, tourniquet test (application of pressure cuff for 5 minutes followed by pethechial hemorrhage count, there should be more than 10 per sq. inch, 6.25 cm2). Laboratory methods include virus isolation, detection of viral nucleic acid, antigens or antibodies or a combination of them. After onset of illness the virus can be detected in serum, plasma, blood cells and other tissues for 4-5 days. During the early stages it is best to use virus isolation and detection of viral nucleic acid or antigens. After the acute phase specific, antibodies can be detected: IgM, during primary infection, (detectable in 50% of patients by day 3, 80% by day 5 and 99% by day 10); an increase in IgG titers for a secondary infection (Figure 4).(24)

Dengue infection is a systemic and dynamic disease. After 4 to 10 days incubation, disease onset is abrupt with high fever and three main phases: febrile, critical and recovery. The first phase lasts 2 to 7 days and there may be facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache. Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. Mild hemorrhagic manifestations like petechial and mucosal membrane bleeding may be seen.

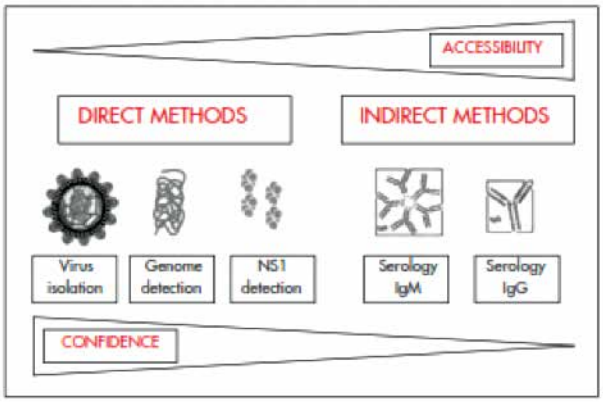

Figure 4 Comparison of dengue diagnostic tests according to accessibility and confidence
Source: WHO. Dengue guidelines for diagnosis, treatment, prevention and control, 2009

Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase but are not common. The liver is often enlarged and tender after a few days of fever. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue.(24)

Individual risk factors determine the severity of disease and they include secondary infection, age, ethnicity and possibly chronic diseases (bronchial asthma, sickle cell anemia and diabetes mellitus). During the clinical phase, when temperature drops to 37.5° - 38° C or less, usually on days 3 to 7 of illness, an increase in capillary permeability in parallel with increasing hematocrit levels may occur. This marks the beginning of the critical phase. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. The period of clinically significant plasma leakage usually lasts 24 -48 hours. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume. The degree of plasma leakage varies. Young children in particular may be less able than adults to compensate for capillary leakage and are consequently at greater risk of dengue shock.(24) Patients infected with the dengue virus can transmit the infection for 4 -5 days; maximum, 12.(4)

If the patient survives the critical phase, a gradual reabsorption of extravascular fluid takes place in the following 48 to 72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of "isles of white in a sea of red". Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage. The hematocrit stabilizes or may be lower due to the dilution effect of reabsorbed fluid. White blood cell count usually starts to rise, but the recovery of platelet count typically takes place later.(4)

In 1981, an unprecedented major outbreak of DHF/DSS in Cuba caused by a DENV-2 strain was acknowledged as the

first laboratory-confirmed hemorrhagic dengue epidemic in the Americas. Retrospective epidemiologic studies suggested that the epidemic had begun at the end of 1980 with outbreaks in three municipalities located far apart in eastern, central and western Cuba. Cases were reported during the same epidemiologic week in individuals with no history of travel abroad. This epidemic was controlled in approximately four months and characterized by rapid dispersal of the virus throughout the country, with extraordinarily high transmission rates. Today the origin has been irrefutably demonstrated to be a laboratory strain (NGC, Den-2 prototype), not a circulating one, simultaneously introduced in three different municipalities of the country with great geographical distance between them. A total of 344 203 cases were registered, including 10 312 of DHF/DSS, resulting in 158 deaths (101 of them were children).(36) Secondary infection was the most notable risk factor found for development of severe forms of the disease (DHF/DSS).(37) Cuba had undergone an epidemic of DENV-1 in 1977; and in the 1981 epidemic, mainly the patients seropositive to DENV-1, now infected by DENV-2, suffered DHF/DSS.(38)

Thus, dengue infection can lead to a wide range of clinical manifestations, from mild fever to potentially fatal dengue shock syndrome. Dengue itself is rarely fatal, but severe dengue, dengue hemorrhagic fever and/or dengue shock syndrome (DHF/DHS), is a potentially fatal complication, with symptoms including severe plasma leakage with or without hemorrhage, severe organ dysfunction, low temperature, severe abdominal pain, rapid breathing, and other.(36) DENV has also been found to cause neurological alterations, which can be encephalitis, neuromuscular complications (for example Guillain-Barré syndrome (GBS) or transient muscle dysfunctions, dengue encephalopathy, neuro-ophthalmic involvement, which may overlap.(39,40)

There are many dengue vaccines being tested, but only the Sanofi Pasteur vaccine has made it through Phase III trials. Yet it is not efficacious against DENV-2, although it induces neutralizing antibodies. Its highest efficacy is against serotypes 3 and 4. Since there is no established correlate of protection for an effective dengue vaccine, new methods must be found for evaluating and characterizing immunogenicity to predict efficacy better.(41) The ideal dengue vaccine should be safe, effective after one or two injections, cover all serotypes, not contribute to antibody dependent enhancement (a major concern, since it could increase the risk of severe dengue), be easily transported and stored, and be both affordable and cost-effective.

Chikungunya virus

The disease caused by this virus was first described in 1955 by Robinson and Lumsden after a 1952 outbreak in the Makonde Plateau in Tanzania (Tanganyika, at the time).(42,43) Chikungunya virus (CHIKV), an arbovirus as DENV, is mainly transmitted by *Ae.s aegypti* and *Ae. albopictus* mosquitoes. In contrast to dengue, for which only primates are hosts, CHIKV has also been found in birds, cattle, and rodents.(44) It is an alphavirus, also an RNA virus, but unrelated to dengue, though it causes similar disease in humans. Local transmission in the Western Hemisphere was first detected in Saint Martin, in the Antilles, in December 2013. It has since spread to 31 countries of Latin America, including part of the United States and its territories: Florida, Puerto Rico and Virgin Islands (Figure 3).(45) By August 8, 2014, 575 535 suspected and confirmed CHIKV cases had been reported in the Americas. The rapid spread of the virus is probably caused by lack of population immunity, broad distribution of the vectors capable of transmitting the virus and the movement of people throughout the area. Imported cases of CHIKV have been reported in Europe and the United States. (46) As for DENV, different genotypes of

Figure 5 Emergence of chikungunya virus in the Americas
Source: Garcia de Figueiredo ML and Moraes Figueiredo LT Emerging alphaviruses in the Americas: Chikungunya and Mayaro. 2014

chikungunya virus circulate in the Americas (Figure 5).
The incubation period of the chikungunya virus ranges from 1 to 12 days, most typically, from 3 to 7 days. The disease may be asymptomatic, but generally 72% to 97% of those infected will develop symptoms. Characteristic symptoms include sudden onset with high fever, myalgia, migratory polyarthritis, severe arthralgias, joint pain (mainly small joints), and rash (that may begin on day 2 to 3). Other symptoms include headache, fatigue, digestive complaints, and conjunctivitis, slight photophobia, and partial loss of taste.. Shock or death is rare in CHIKV infections. A strong immune response limits CHIKV disease and confers protection from re-infection. The mortality rate is a little less than 1 in 1000, with the elderly or people with underlying chronic medical problems most likely to have severe complications.(47, 48, 49, 50)

Similar to dengue, CHIKV induces chronic disease, likely by

deregulated inflammation during the acute phase. This causes inflammation to continue for many months.(43) Viral antigen and viral RNA were found in macrophages in the synovial joint of a person experiencing a relapse of musculoskeletal disease 18 months after initial infection.(44) Several animal models have also suggested chikungunya virus may establish persistent infections. In a nonhuman primate model, chikungunya virus was found to persist in the spleen for at least six weeks.(49,51)

Other modes of transmission have been documented for CHIKV, including through blood, in utero, and intrapartum transmission, but they are rare.(52,53)

Mayaro virus

Mayaro virus (MAYV) is another arthropod-borne alphavirus, related to chikungunya. As yet it is mainly restricted to the Amazon region of Brazil* and countries surrounding it: Brazil, Venezuela, Peru, and Colombia.(54) MAYV has been isolated or its presence has been implicated by antibody surveys in countries throughout tropical South America and into Central America and the Caribbean. Imported cases have been diagnosed in Europe (in Netherlands and France. Contrary to the two previous viruses, its origin does not seem to be in Africa; it was first described in forest workers in Trinidad in 1954(55). Two genotypes of Mayaro virus (D and L) have been isolated.(54)

Mayaro virus, like most other alphaviruses, is transmitted to humans by the bite of infected mosquitoes, in this case mainly *Haemagogus janthinomys*, but also *Ae. serratus*, *Culex* spp. and *Psorophora ferox*, mosquitos that live in tree tops in forest settings. Although MAYV is a zoonotic illness, its mosquito vectors, and wild vertebrate hosts have undoubtedly coexisted for a long time in tropical forests. Recent demographic and land use changes in tropical South America appear to be altering the frequency of this endemic disease in people. As the human population in the region increases and as more people enter forested areas for work and recreation, the number of persons at risk of MAYV infection increases. Unlike dengue, Mayaro virus has also been isolated in monkeys (probably the main reservoirs), birds and horses.(56) Typically, MAYV affects individuals who work or reside in contact with the natural environment. However, cases have also been reported in large cities.(57) Introduced by travellers or migratory birds it could affect other tropical Central and South American countries. CHIKV and MAYV are able to mutate and/or adapt to new zoonotic cycles and thus acquire a higher potential for emergency. These arboviruses may emerge as a result of environmental degradation and socio-economic disturbances. (58) Therefore, after the outbreak in Manaus, Brazil (first one reported in a metropolitan setting), it is possible to consider that in the future MAYV, after adaptation to an urban cycle, could causes major epidemics.(59)

MAYV disease is an acute febrile illness of 3 to 5 days duration, characterized by headache, retro-orbital pain, arthralgia, myalgia, vomiting, diarrhea, and rash.(56) It is difficult to differentiate from dengue and chikungunya; thus the importance of laboratory confirmation: virus isolation, RT-PCR (during viremia, to identify the virus)(57,58) and serology (usually ELISA to detect IgM in paired serum samples)(. The convalescence of this disease may require several weeks; persons with acute Mayaro fever often have many nonspecific symptoms, but, similar to chikungunya disease, may continue to have chronic joint pain for at least 1 year after acute illness. This study indicates the need to consider MAYV infection in patients with seronegative arthritis (i.e. negative rheumatoid factor and antinuclear antibodies) in regions where MAYV is endemic. The physiopathology of Mayaro fever has not been studied.(59,60,61)

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Una virus

Closely related to the Mayaro virus, Una virus (UNAV) is widely distributed in tropical and subtropical regions of Central and South America, such as Brazil, Colombia, French Guiana, Panama, Surinam, Trinidad and Venezuela.(63) It was first isolated from *Psorophora ferox* mosquitoes in Brazil;(64) but has since been isolated from other mosquitoes and vertebrate hosts such as humans, birds and horses.(65) It has also been found in black howler monkeys of Paraguay and Argentina.(66)

Zika virus

A formerly disregarded mosquito-borne flavivirus, related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses, Zika virus (ZIKV) was first isolated in 1947 from a primate in the Zika Forest of Uganda during routine surveys for yellow fever.(67) It is a single stranded RNA and has two major lineages: African and Asian.(68) Following the spread of its vectors (mainly *Ae.aegypti* and *Ae.albopictus* in more temperate zones), as previously described, ZIKV spread in 2007 from Africa to Asia(69)**, and appeared in the Americas in Chile's Easter Island in February 2014 in an outbreak that lasted until June 2014 (as cited in Hidalgo J, Morazán G, Arriaga P. Zika virus infection, Belize J Med, 2016, this issue). Since then it has spread throughout our region from Mexico, Central America, and the Caribbean to South America (Figures

* Where up to 1991, 183 different types of arboviruses had been isolated (Vasconcelos PFC, Travassos da Rosa APA; Degallier N, da Rosa Travassos JFS, Pinheiro FP. Clinical and ecoepidemiological situation of human arboviruses in Brazilian Amazonia. J Braz Assoc Advancement Science 1992; 44: 117–124.

** Researchers have traced ZIKV spread to sports events by phylogenetic DNA analysis of the virus. Thus Brazilian researchers have suggested that the virus arrived from the French Polynesia during the 2014 FIFA World cup (Musso D. Zika Virus Transmission from French Polynesia to Brazil. Emerging Infectious Diseases. Centers for Disease Control and Prevention 2015; 21 (10): 1887. doi:10.3201/eid2110.151125. Accessed on: January 14, 2016.) or when canoeing teams from the Zika-afflicted Cook Islands, French Polynesia, New Caledonia, and Easter Island attended the Va'a World Sprint Championships in Rio de Janeiro in August 2014

6 and 7). Especially difficult epidemiological situations are confronted in the northeastern states of Brazil, since May 2015 (70) and from October 2015 in Colombia, (71) as they have the highest infection rates in the area. In Brazil it is aggravated by the increase in cases of microcephaly and other neurological disorders, including Guillain Barré syndrome (GBS).(72)

Currently (February 2016), in the Americas there is local virus transmission in 31 countries: Aruba; Barbados; Bolivia; Bonaire; Brazil; Colombia; Costa Rica; Curaçao; Ecuador; El Salvador; Guadeloupe; Guatemala; Guiana; French Guiana; Haiti; Honduras; United States Virgin Islands; Jamaica; Martinique; Mexico; Nicaragua; Panama; Paraguay; Puerto Rico; Dominican Republic; Saint Vincent and the Grenadines; Saint Martin; Sint Maarten; Suriname; Trinidad and Tobago; Venezuela.(73)

Since the vast majority of the population in the Americas lacks immunity to this virus and there is no vaccine or specific treatment for it, it is estimated that at least four million people may be infected before the present pandemic is controlled. The most efficient way to prevent infection is through vector control and individual protection against mosquito bites by insect repellents, wearing long sleeves and long pants and screens and nets.

The preferred form of transmission is through mosquitoes of the *Aedes spp.*, but unlike other arboviruses, ZIKV can also be transmitted sexually,(74,75) which is further suggested by detection of the virus in patient sperm samples.(76) Blood borne transmission, the virus has been found in blood donors,(77) led the FDA on February 16, 2016, to regulate blood screening and cell and tissue donation for zika infection. (78,79) Transplacental (80) and perinatal routes of transmission have also been documented.(81)

Clinical symptoms appear 3 to 12 days after infection; are self-limiting and resolve within 5 to 7 days. Symptoms mainly include: mild fever, rash (maculopapular), joint pain, head ache, myalgia, general malaise and conjunctivitis. One in four infected persons develops symptoms (25%).(82)

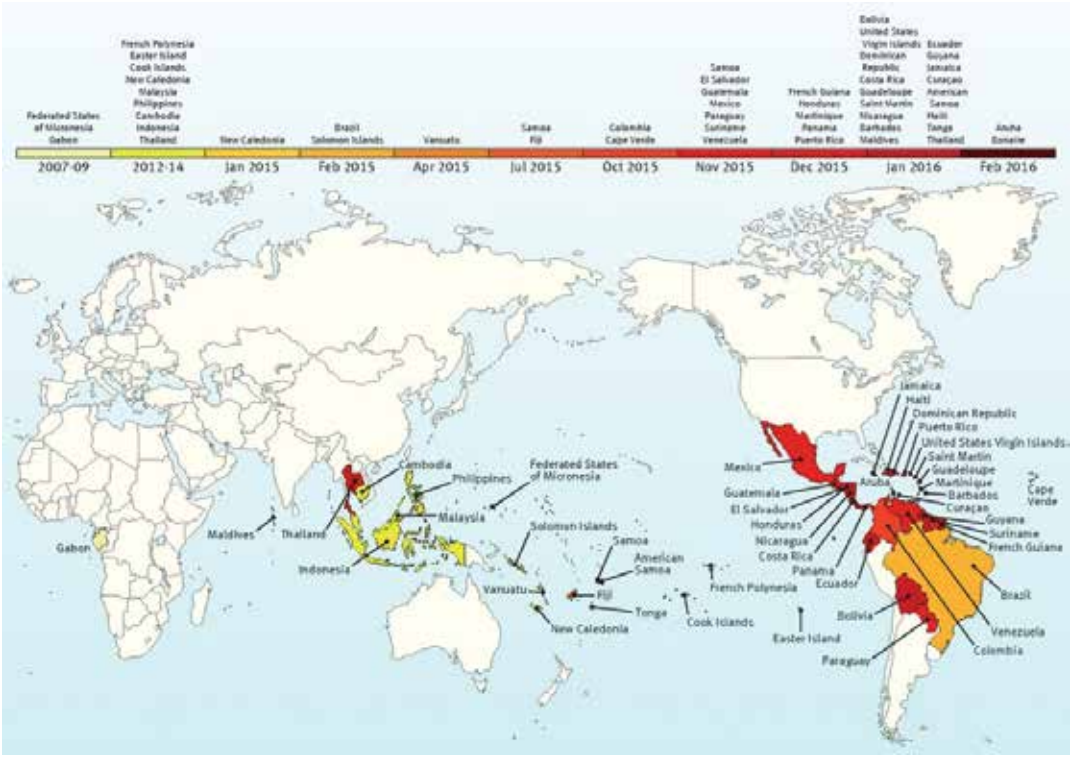

Figure 6 Time line of Zika virus spread and countries with Zika virus transmission
Source: Basarab M, et al. Zika virus BMJ 2016; 352 http://dx.doi.org/10.1136/bmj.i1049

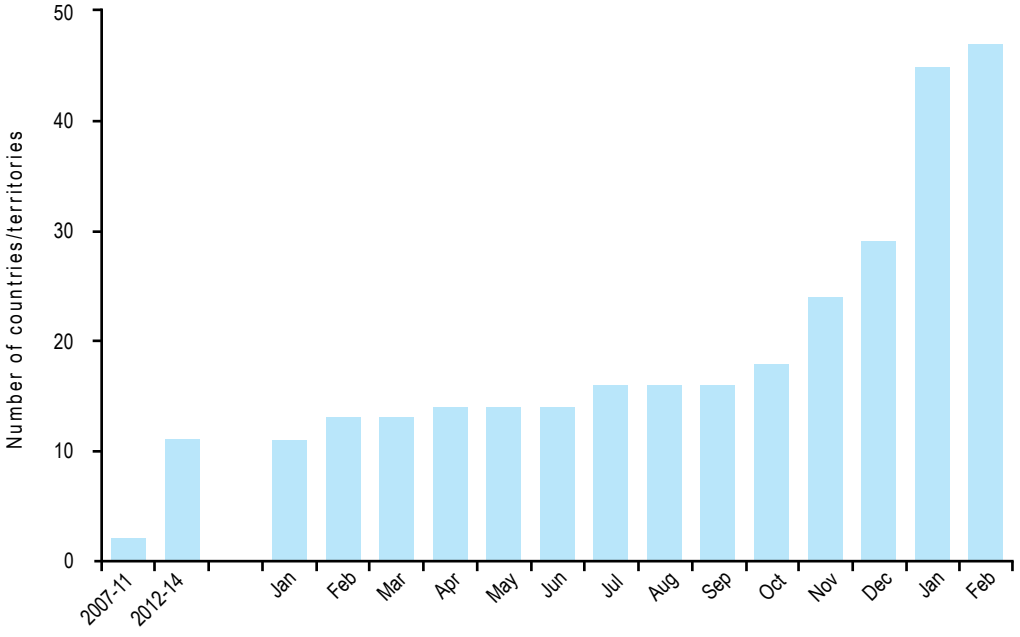

Figure 7 Cumulative number of countries/territories reporting Zika transmission, from 2007 to 2014, and monthly from January 2015 to February 2016 Source: WHO. Zika Virus; Microcephaly; and Guillain-Barré Syndrome; Situation report; 26 February 2016

Severe neurological complications, diagnosed as GBS, were described in some patients in the French Polynesian outbreak (83) and more recently in the Brazilian, Salvadoran, Colombian and Venezuelan outbreaks.(72) In Brazil a 20-fold increase in microcephaly cases (an increase from 5.7/100 000 live births in 2014 to 99.7/100 000 in 2014) has also been observed. From November 2015 to February 2016, 5280 cases were reported, in contrast to a 163 yearly average of cases from 2001 to 2014. (Figure 8).(72) Some of the ZIKV infected children with microcephaly have also shown ophthalmological alterations. (84) Although association between microcephaly and ZIKV infection has been found, research on whether it is a causal relationship is ongoing. But the fact that there is transmission of Zika virus in utero,(85) has prompted CDC guidelines for pregnant women and those planning to become pregnant.

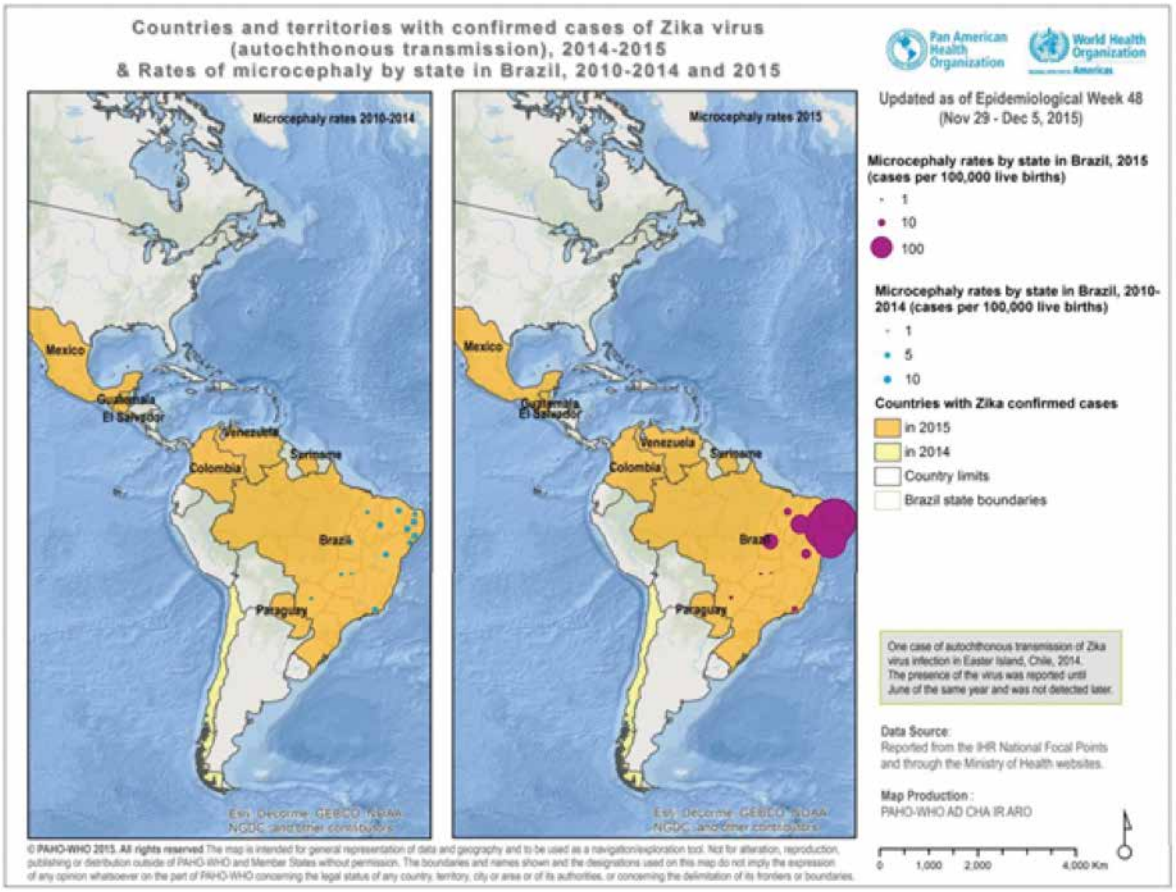

Figure 8 Comparative rate of microcephaly cases in Brazil from 2010 to 2014 and for 2015. (Observe that the increase in microcephaly cases geographically overlaps with the areas with higher rate of ZIKV transmission (northeastern states). Source: PAHO/WHO. Epidemiological Update: Neurological syndrome, congenital anomalies and Zika virus infection. 17 January, Washington, D.C.: PAHO/WHO; 2016

In the Pacific concurrent outbreaks of dengue, chikungunya and Zika viruses have occurred in recent years.(86) And that is exactly what the region of the Americas is facing right now.

Not surprisingly, due to the spatial and temporal overlap of transmission areas, simultaneous infection by dengue and Zika was reported by the Research Center of the Oswaldo Cruz Foundation.(70)

■ CONCLUSIONS AND RECOMMENDATIONS

Further research is central to understanding the potential of these and other arboviruses that invade new geographic areas, and become important public and veterinary health problems. More knowledge is required on the viruses, their vectors and hosts, but also on climate variability and human behaviors that may impact emergence of these diseases to cope with them and improve patient care.

Inexpensive and specific diagnostic tools must be found for each virus that can be used for quick diagnosis in the field. Blood, cells and tissues must be screened before their use.

Medical personnel in primary health care must be trained to recognize symptoms and diagnose the different circulating arboviruses (dengue, chikungunya, Zika and other, depending on the region). Training must be updated as new knowledge becomes available.

Other measures, requiring longer time to implement, consist in improving the national socioeconomic and cultural levels to eliminate conditions in which mosquitoes thrive. This requires will of the government and organizations, but also awareness of the population that must participate.

There is no specific treatment for these diseases, it is symptomatic.

Vaccine research is ongoing for all arboviruses, but efficacious vaccines do not seem to be close yet. Even the available DENV vaccine, the most investigated and for a longer period, has many shortcomings. It is 60% effective and prevents from 80 to 90% of severe cases. (88) The other problem with vaccination is that outbreaks are sporadic and unpredictable rendering preemptive vaccination of large populations very expensive. And rapid deployment of stored vaccines may be too slow to counter sudden explosive epidemics.(89)

For now the best way to fight these diseases that represent a great socioeconomic burden is vector control with quick measures to reduce their numbers and their possibility of feeding, thus reducing transmission of the viruses, using insect repellents, clothing that covers the body (including arms and legs), window screens and bed mosquito nets. On a community and national level it is decisive to carry out campaigns to decrease vector density in all foci by using insecticides and the careful surveillance and treatment of potential breeding places. This effort must be maintained for years if these diseases are to be stopped. Zika will probably not be the last disease to emerge; there is a great number of viruses waiting their turn to "spillover" from their regions. Therefore, it is essential to be efficient in controlling mosquito populations in the long term. This is a difficult task because of the coste, logistics, public resistance and problems posed by inner-city crowding and poor sanitation (88). Furthermore, it is important to consider that mosquitoes become resistant to insecticides, so it is necessary to alternate them.

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