

# Zika, chikungunya and dengue: the causes and threats of new and re-emerging arboviral diseases

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## ABSTRACT

The recent emergence and re-emergence of viral infections transmitted by vectors—Zika, chikungunya, dengue, Japanese encephalitis, West Nile, yellow fever and others—is a cause for international concern. Using as examples Zika, chikungunya and dengue, we summarise current knowledge on characteristics of the viruses and their transmission, clinical features, laboratory diagnosis, burden, history, possible causes of the spread and the expectation for future epidemics. Arboviruses are transmitted by mosquitoes, are of difficult diagnosis, can have surprising clinical complications and cause severe burden. The current situation is complex, because there is no vaccine for Zika and chikungunya and no specific treatment for the three arboviruses. Vector control is the only comprehensive solution available now and this remains a challenge because up to now this has not been very effective. Until we develop new technologies of control mosquito populations, the globalised and urbanised world we live in will remain vulnerable to the threat of successive arbovirus epidemics.

## INTRODUCTION

The emergence and re-emergence of viral diseases transmitted by vectors, given the capacity of vectors to transmit a number of viral infectious agents, raises global concerns about the causes of the emergence, threats to health, burden and the feasibility of prevention and control. There are many vector-borne viral diseases: West Nile fever, dengue, tick-borne, yellow fever, chikungunya, Rift Valley fever, Zika and Japanese encephalitis, among others. Zika virus (ZIKV), chikungunya virus (CHIKV) and dengue virus (DENV) have similar epidemiology, transmission cycles in urban environments and clinical symptoms at onset (although complications vary markedly). They attracted interest in recent years due to their increasing incidence, expanding geographical range, possible effects caused by cocirculation and the unpredictable health threats and burden. An indication of this concern was WHO declaring the increase in microcephaly and Guillain-Barré syndrome (GBS), now known to be caused by

## Key questions

### What is already known about this topic?

- ▶ The emergence and re-emergence of mosquito-borne disease has attracted interest in recent years due to their increasing incidence and geographical expansion.

### What are the new findings?

- ▶ The cocirculation of three arboviruses transmitted by the same mosquito is a reality in many places; however, the burden to the population's health is still not known.

### Recommendations for policy

- ▶ The situation is worrying; there is an urgent need for development of vaccines, better diagnostic tests and vector control tools.

ZIKV infection, a Public Health Emergency of International Concern.

In this review, we address (using as examples Zika, chikungunya and dengue): (1) the diseases—virus, transmission, clinical symptoms and diagnosis; (2) the history; (3) the possible causes of the recent outbreaks; and (4) the burden and the threats.

## The viruses

More than 50% of the viruses in the genus *Flavivirus*, family Flaviviridae, cause disease in humans, including dengue, yellow fever, West Nile and Zika viruses.<sup>1</sup> *Flavivirus* virions are small in size of 40–50 nm, spherical with lipid envelopes, which contain a single-stranded, non-segmented RNA. The genome of flaviviruses is approximately 11 000 bases long and they share common group epitopes on the envelope protein that can cross-react in serological tests.<sup>2</sup>

Our knowledge of ZIKV is limited. The molecular information reveals that it originated in East Africa and subsequently spread to West Africa, Asia and the Americas in three main clusters, two African clusters (the Nigerian cluster and the MR766 cluster) and the



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Asian strain, which is the one found in the Americas, Pacific Islands and Cape Verde epidemics.<sup>3</sup> It is not yet known whether the genetic variations have implication for transmissibility or clinical manifestations, nor if a previous flavivirus infection increases severity, although mutations in flavivirus genome are known to impact virulence and immunogenicity.<sup>4</sup>

Chikungunya is a member of the genus *Alphavirus* and family *Togaviridae*; it has a capsid, a phospholipid envelope and a single-stranded RNA genome. The *Alphavirus* group contains 28 known viruses including o'nyong-nyong, Ross River and Mayaro.<sup>5</sup> There are four CHIKV genotypes: the East-Central-South Africa, West Africa, Asian and Indian Ocean lineage.<sup>6</sup>

There are four genetically distinct serotypes of DENV (DENV-1, DENV-2, DENV-3 and DENV-4), and multiple lineages of each serotype, which are often geographically based.<sup>7</sup> DENV infections with one serotype provide long immunity against that particular serotype; cross immunity to the others is temporary and may lead to increased severity.<sup>1</sup>

## TRANSMISSION

The most common mode of transmission of Zika, chikungunya and dengue is by their common vector, *Aedes*. The mosquito is infected during a viraemic blood meal and after the extrinsic incubation period, the virus is present in the mosquito salivary gland and can be transmitted to humans by a mosquito bite. Several factors can influence the dynamics of transmission, such as environmental and climate factors, the interaction between host and pathogen, and the development of immunity in the population.<sup>8</sup>

*Aedes aegypti* and *A. albopictus* are the main vectors of Zika, chikungunya and dengue, but a larger range of *Aedes* species are likely vectors in Africa and Asia.<sup>9–11</sup> *A. aegypti* is one of the most capable vectors: it feeds primarily on humans, frequently bites several times in a single meal, has an almost imperceptible bite and lives very close to humans<sup>11</sup>; however, it is geographically restricted because it does not winter well in cold climates. *A. albopictus* has a wider geographical distribution (it can be found in subtropical and temperate climates), it is resilient and aggressive, can survive in rural as well as urban environments, is relatively long lived (4–9 weeks) and is more able to survive through cold winters.<sup>12</sup> Both *A. aegypti* and *A. albopictus* bite primarily during the day, limiting the usefulness of insecticide-impregnated bednets. Overall, the ability of a vector species to transmit a pathogen depends on the location and time. It is notably difficult to avoid mosquito bites and to control mosquito populations, especially in tropical climates.<sup>13</sup>

Non-vector transmission of arbovirus has been reported by vertical transmission,<sup>14–16</sup> sexual transmission,<sup>17 18</sup> by transfusion<sup>18 19</sup> and in nosocomial settings.<sup>20</sup> It is not known what role these routes of transmission play during the current Zika epidemics: vector transmission is likely

to be required for fast epidemic spread—epidemics of sexually transmitted diseases tend to be characterised by slower progress and require long infectious periods. Vertical transmission of ZIKV from pregnant women to the fetus is responsible for the epidemic of microcephaly.<sup>21</sup> Reservoirs were part of the initial cycle in Africa, but no animal reservoir has been identified, so far, outside Africa.

## Clinical symptoms

Asymptomatic and mild clinical forms of Zika, chikungunya and dengue may account for a large proportion of all infections. When present, initial symptoms can be similar, and clinically non-specific, including fever, headache, myalgia, arthralgia, maculopapular rash, retro-orbital pain and lymphadenopathies.<sup>22</sup> In the early phase, it can be difficult to distinguish between these three diseases, so clinical diagnosis is challenging. Algorithms comparing clinical manifestation of Zika, chikungunya and dengue have been proposed<sup>22</sup>; however, their sensitivity and specificity have not been estimated.

Little is known so far of the natural history of Zika infection, and the initial perception as a mild disease has been challenged by the continued discovery of severe neurological complications, including but not restricted to congenital Zika infection and GBS. Preliminary estimates of the incubation period were done based on recipients of blood transfusions in French Polynesia who tested positive to Zika by RT-PCR and who reported clinical symptoms of the disease from 3 to 10 days after the transfusion.<sup>18</sup> A more recent study, with 197 symptomatic travellers with recent Zika, indicated an estimated incubation period of 3–14 days.<sup>23</sup> Common symptoms of uncomplicated Zika are short term and include low-grade fever descending rash, myalgia, conjunctivitis, headache, oedema and vomiting.<sup>9</sup>

The incubation period of chikungunya ranges from 1 to 12 days. Clinical onset is usually abrupt with high fever, headache, myalgia and moderate or severe arthralgia that affects especially extremities.<sup>5</sup> The joint pain associated with chikungunya can be very severe; duration can vary from few days to years, resulting in an acute, subacute or chronic disease. Estimating the disability burden caused by chikungunya complications is a research priority.

The incubation period of dengue ranges from 3 to 14 days. Most cases are self-limiting: typically, patients develop high fever, sudden-onset skin rash, myalgia and headache, and in some cases mild haemorrhagic manifestations. There are no differences, in the early phases, between cases that will and will not progress to severe dengue, characterised by rapid onset of capillary leakage with or without haemorrhage accompanied by thrombocytopenia and liver injury and, in some cases, death.<sup>1</sup>

## Diagnosis

The challenge in differential clinical diagnosis between these three diseases highlights the importance of laboratory diagnostic tests. RT-PCR in serum is the main test

for detection of viral nucleic acid of Zika, chikungunya and dengue during the initial viraemic phase. The detection of Zika RNA in serum is limited to the first 5 days of the disease.<sup>24</sup> Urine may be the specimen of choice to enlarge the window of detection of DENV and ZIKV after viraemia has faded: PCR positivity is possible for a longer window and higher viral loads facilitate virus typing.<sup>25 26</sup> In dengue, ELISA can detect NS1 antigen in the acute phase, but this test was not yet available for Zika at time of writing.<sup>27</sup> Because viraemia is short lived, a negative RT-PCR does not rule out Zika infection and serologic tests should be performed.

Typically, IgM antibodies last for 2–12 weeks. In patients with clinical symptoms, the serum should be collected 4 days after disease onset and tested for Zika, chikungunya and dengue.<sup>24</sup> The applicability of IgM might depend on the clinical situation; the duration of anti-Zika IgM has not yet been established and there are initial indications that anti-Zika IgM might be useful in diagnosing congenital Zika syndrome.<sup>28</sup> The sensitivity and specificity of IgM and IgG tests are poorly established and there is strong cross-reactivity between ZIKV, DENV and other flaviviruses. There are research groups working to develop new diagnostic approach to consistently differentiate Zika infection from other flavivirus; although we have had advances, there is still no ideal diagnostic test capable to be used in a large scale.<sup>29</sup>

Plaque reduction neutralisation tests (PRNT) can measure virus-specific neutralising antibodies and may be able to determine the cause of the primary infection with high specificity and clarify cross-reacting results; however, PRNT is expensive and very labour intensive.<sup>24</sup>

### History of the three diseases

Dengue has a long history of human interaction. During the 19th century, it was recognised as a sporadic disease causing occasional epidemics. Records describe a dengue-like illness in China as early as the third century and are consistent with a dengue epidemic in 1779–1788, coinciding with the increase in global naval commerce.<sup>7</sup> A second series of dengue-like pandemic lasted from 1823 to 1916 moving from Africa to India, to Oceania and to the Americas. A new pattern to DENV began with the World War II, which brought ecological, demographic and epidemiological changes which allowed the vector to reach high densities and facilitated dispersal of DENV serotypes among diverse geographical regions. In 1950, only nine countries reported cases of dengue; the average annual number of cases reported to WHO varied from 908 in 1950–1959 to 514139 in 1990–1999.<sup>30</sup>

The discovery of Zika and other arboviruses resulted from programmes of research on yellow fever sponsored by Rockefeller Foundation from 1914 to 1970.<sup>27</sup> ZIKV was isolated for the first time in 1947 from the blood of a sentinel rhesus monkey (*Macaca mulatta*) in the Zika Forest, Uganda.<sup>31</sup> The first evidence of human infection was the presence of neutralising antibodies in human sera collected from East Africa in 1952.<sup>32</sup> Since then, sporadic

cases and serological evidence of Zika were found in Africa and Asia; the first large outbreak occurred in Yap in 2007.<sup>9</sup>

CHIKV was first isolated from the blood of a febrile individual during an outbreak in Tanzania in 1952.<sup>33</sup> According to Halstead, this virus has escaped from a complex African zoonotic cycle into an urban cycle at 40–50 year intervals since 1823 causing large epidemics worldwide.<sup>34</sup> Human infections have been documented in Thailand, where the virus was first introduced in the Asia region; in 1958, over 50 000 cases were recorded<sup>35 36</sup>; Calcutta had an intense circulation of chikungunya in 1963 and Chennai in 1965. During this period, the disease directly affected thousands of people, especially children and the elderly. After 1973, there were CHIKV circulation reports until the mid-2000s, when the disease re-emerged.<sup>36</sup>

### WHAT ARE THE CAUSES OF THE RECENT SPREAD?

Ecological and human factors appear to play a role in determining the increased incidence of vector-borne diseases; increasing availability of tests and better awareness of clinicians contribute to more frequent recognition.<sup>37</sup> Climate change, urbanisation (in particular with degraded urban environments), human behaviours, mass gathering events, migration of humans and animals, development of air transport and extensive agriculture have all been suggested to have contributed to the rapid worldwide spread of vector-borne diseases.<sup>38</sup>

The 2014 Climate Change Report lists points to mechanisms by which climate change can facilitate the spread of vector-borne infections: by directly affecting the biology of the vectors, their abundance and geographical distribution, including territorial expansion to new areas, and changes in the extrinsic incubation period of the pathogens. Environmental changes such as flood protection, increased urban green spaces, designed to mitigate the effects of climate change, can increase the risk of vector-borne diseases.<sup>12</sup> The impact of man on the environment, modifying the ecosystems with modern infrastructures, irrigation and massive solid waste production, also facilitates the development of vectors. Finally, urbanisation in poor settings with lack of consistent water supply and garbage collection can facilitate mosquito breeding.

The main trigger of the recent pathogen introduction is suggested to be the increasing trade and travel, as the invasive mosquito can be imported through global trade in used tyres, ornamental plants and moving with vehicles.<sup>38</sup> The recent development in air travel enables pathogens to reach other continents within the few days in which a host is infectious, and even during the latent period for some diseases. Travellers could be infected in one country and introduce the virus in the other; imported cases might result in local transmission and spread the virus in areas that have the appropriate mosquito vectors establishing local transmission. A key consequence of having a well-established vector population and a suitable

environment is that a recently introduced pathogen can cause an explosive epidemic due to the high number susceptible in the population.

Finally, the increased number and density of the human population, global land use change and the introduction of human commensal vectors may act as selective pressure on pathogens to evolve to take advantage of the new environments.<sup>38</sup>

### THE BURDEN AND THE THREATS ASSOCIATED WITH THESE THREE ARBOVIRUSES

DENV is the most common vector-borne disease worldwide, with a 30-fold increased incidence in the past 50 years,<sup>39</sup> endemic in more than 100 countries mostly in South America and Southeast Asia and still spreading to new areas, including Europe, where outbreaks were reported in more than 10 countries since 2010.<sup>30</sup> The annual average number of dengue cases has increased dramatically in recent years: an estimated 390 million of people infected, 96 million with clinical symptoms every year.<sup>40</sup> Although the incidence rates differ according to location and season, a prospective cohort showed an incidence of virologically confirmed DENV of 4.6 episodes per 100 person-years in Asia and 2.9 episodes per 100 person-years in Latin America, approximately 10% of all episodes of febrile disease.<sup>41</sup>

The risk of severe cases and death from DENV has increased, with the associated economic burden. In a prospective cohort of school-age children in a rural area in Thailand, febrile DENV had longer duration and higher costs than non-DENV febrile illness<sup>42</sup>; even mild clinical dengue adds a significant hospitalisation burden in some countries (and more than 70% of hospitalised cases of dengue do not meet the definition of severe dengue).<sup>41</sup> The number of DENV-related deaths is large worldwide. In 2013, it was estimated that DENV is responsible for 576 900 years of life lost and 1.14 million disability-adjusted life years (DALY), which considers fatal and non-fatal outcomes.<sup>43</sup>

Although ZIKV has a high rate of transmission, with an estimated 73% of the population infected in the outbreak in Micronesia<sup>9</sup> and 66% in French Polynesia,<sup>44</sup> until 2015, ZIKV was considered a mild disease, without complications, hospitalisations or mortality. Now we know Zika can cause congenital ZIKV infection, GBS and other severe neurological complications. In late 2015, in French Polynesia, 42 patients were diagnosed with GBS during the ZIKV outbreak.<sup>45</sup> Based on the 66% attack rate of ZIKV infection, the risk of GBS in the population was estimated to be 1 for each 4000 ZIKV infections.<sup>46</sup> A case-control study in French Polynesia showed a 34-fold increase in risk of GBS in those with markers of ZIKV infection.<sup>46</sup> If we apply the same attack rate and the risk of GBS to the Brazilian population, we can expect 32.390 cases of Zika-related GBS in Brazil. Other neurological complications such as acute myelitis<sup>47</sup> and meningoencephalitis<sup>48</sup> have been associated with Zika.

An increase in neonates with microcephaly was noticed initially in Brazil, and retrospectively in the French Polynesia. The number of notified suspected cases in Brazil reached more than 10.000 and almost 3000 confirmed congenital syndrome associated with Zika.<sup>49</sup> At the time of writing, microcephaly has been reported in the Americas, Pacific Islands and African countries and territories, where the ZIKV epidemic started later than in Brazil. Scientific evidence for the causal relationship between congenital transmission of ZIKV and microcephaly was produced fast and the link recognised.<sup>50</sup> A preliminary report of follow-up of pregnant women with Zika conducted in Brazil showed a risk of 22% of microcephaly after symptomatic ZIKV infection in the first trimester, and started the long process of describing the whole spectrum of the congenital Zika syndrome, of which microcephaly appears to be only at the tip of the iceberg.<sup>21 51</sup> There are numerous cohorts of pregnant women going on and we will be able to describe the spectrum of the syndrome and answer others' important questions such as the risks of adverse outcomes among fetuses whose mothers were infected and factors associated with adverse fetal outcomes. So far, Zika is the only flavivirus to cause congenital infection in humans, and the response to this epidemic required addressing the state of sexual and reproductive rights.<sup>52</sup>

Chikungunya infection outbreaks can affect a large proportion of the population. Chikungunya can severely reduce quality of life due to postchikungunya rheumatism that can destroy joints, impair daily life and require treatment with antirheumatic drugs; chikungunya can also worsen pre-existing chronic inflammatory rheumatism. Among confirmed cases of chikungunya in France, 15 months after the acute disease, 57% of the patients were still experiencing rheumatic manifestations.<sup>53</sup> The chronic pain and rheumatism among patients after chikungunya infection might have impact on mental health of patients.<sup>54</sup> It was estimated that according to the number of reported cases of chikungunya during 2014 in the Americas, 38 million patients will develop chronic inflammatory rheumatism.<sup>55</sup>

In La Reunion Island, a range of new clinical forms (respiratory and cardiovascular failure, meningoencephalitis and other central nervous system problems, severe acute hepatitis, severe cutaneous effects and kidney failure) was identified; 57 patients were diagnosed with central nervous system disease, including 24 with encephalitis.<sup>56</sup> In Latin America, the burden of chikungunya was estimated in 25.45 DALYs per 100 000 of population.<sup>57</sup> The fatality rate of chikungunya was considered low, but there are indications that this was in part due to underascertainment. Although not causing congenital malformations, vertical transmission of chikungunya (predominantly during delivery) has been described as causing neurological complication in the neonate with cognitive development delays.<sup>58</sup>

## CONCLUSION

The emergence of ZIKV and CHIK and the re-emergence of DENV in Brazil established a situation that was probably unprecedented: the circulation at high incidence of three arboviruses transmitted by the same mosquito, *A. aegypti*, in the same, mostly urban, space: DENV, CHIKV and ZIKV. The three arboviruses are causing epidemics in several cities in Brazil and the Americas, causing morbidity and high levels of unpredicted complications, increasing demand on health services, and other support services. This is not trivial because the situation is new, and because it exposed the limitation of the current available measures for control, which do not appear to be effective in preventing, or reducing sufficiently the circulation of these arboviruses, two of which (ZIKV and CHIKV) are new to the Americas, and therefore are meeting a totally susceptible population. As they disseminate through the Americas (and further) in cities infected by *A. aegypti* and/or *A. albopictus*, epidemics will follow.

There are many other arboviruses waiting in the wings, and the experience with DENV, CHIKV and ZIKV makes it clear that introductions of new pathogens are likely to happen, causing new explosive epidemics and increasing the burden caused by the cocirculation. Preparing for new and current epidemics requires measures that are specific to each virus, and measures that are common, mainly directed at controlling mosquito populations.

The current situation is complex, because there is no vaccine (except for dengue, recently licensed in Mexico, Philippines and Brazil), and no specific treatment for the three arboviruses. Vector control is the only comprehensive solution and this remains a challenge because no measure achieved effective mosquito control yet, in the decades of dengue programme control worldwide. Until we develop better technologies to control mosquito populations, the globalised and urbanised world we live in will remain vulnerable to the threat of successive arbovirus epidemics.

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## Correction: Zika, chikungunya and dengue: the causes and threats of new and re-emerging arboviral diseases

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