Netherlands Journal of Critical Care
Submitted August 2021; Accepted January 2022

SPECIAL REVIEW

Potential pandemic pathogens series: Zika virus

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Keywords - **pandemic pathogens, Zika virus, pandemics, infectious disease, mosquito-borne disease**

In the last two years we have experienced the effects of the COVID-19 pandemic in our lives and hospitals. Pandemics are part of the history of humanity and we can be certain that in the future new pandemics will appear. In fact, due to the growth in the human population, increased travel and global warming, it is to be expected that new pandemic pathogens will arise more frequently than before. Additionally, decreased barriers between animals and humans which will give rise to spillover events which will result in the introduction of new zoonotic pathogens in humans. In each of the parts of this series we will, in a short format, highlight a potential pandemic pathogen and describe its characteristics, history and potential for global pandemics. This part of the series is devoted to the Zika virus (ZIKV). We describe the history of ZIKV, the clinical picture and finally, we conclude with a discussion about the pandemic risk of ZIKV infection.

History of Zika virus

In the Zika forest in Uganda, in 1947, scientists were conducting routine surveillance for yellow fever and isolated the Zika virus (ZIKV) in samples taken from captivated, sentinel rhesus monkeys. One year later the virus was recovered from the mosquito *Aedes africanus*, caught on a tree platform in the Zika forest. ZIKV is primarily spread by mosquitoes from the *Aedes* genus, which is also known as a vector for viruses causing dengue fever, yellow fever, West Nile fever and chikungunya, although spread by other species has also been reported,[1] which is also known as a vector for viruses causing dengue fever, yellow fever, West Nile fever and chikungunya.

In 1952, the first human cases were detected in Uganda and in the United Republic of Tanzania. Subsequently, in 1954, human infection with ZIKV was documented in Nigeria where infection was unintentionally self-inflicted by a researcher during his lab work, but thereafter further reports of Zika infection in humans remained scarce for years. Serological studies, however, showed that ZIKV had already been circulating in several parts of Africa from the 1970s,[2,3] indicating that ZIKV had been present in the human population for a long time.

From the early 1970s, the known geographical distribution of ZIKV expanded to Asia, including India, Indonesia, Malaysia and Pakistan, where the virus was detected in mosquitoes and human serosurveys indicated circulation of the virus.[4] As in Africa, sporadic human cases occurred but no large outbreaks were detected and the disease in humans continued to be regarded as rare, with only mild symptoms. The first documented large outbreak occurred in 2007, on Yap Island in Micronesia,[5] followed by one in French Polynesia between 2013 and 2014 and especially the largest one to date in Brazil from 2015 until 2017. In the Brazil outbreak, over 270,000 cases were reported in 2016 alone,[6] but this is a significant underestimation as unreported and subclinical cases are not included. Moreover, 2693 confirmed cases of microcephaly were reported in newborns in three epidemic regions.[7] Eventually over 80 countries reported cases of ZIKV infection, including isolated cases diagnosed after travel to endemic areas.[8-10] Although the main route of virus transmission is via the *Aedes* mosquitoes, person-to-person circulation of ZIKV has also been described. Whether transmission by blood transfusion and sexual transmission is of epidemiological importance remains, however, unclear.[11]

Clinical picture

Comparable with some of the other flaviviruses, it is thought that 80% of infections remain asymptomatic.[12] If present, clinical symptoms are usually mild including rash, fever,

conjunctivitis, and arthralgia.[13,14] Case reports about more critical complications, including Guillain-Barré syndrome and severe thrombocytopenia, are limited. Still, a large study from 2016 showed a prevalence of severe thrombocytopenia (<20×10^9/l or <50×10^9/l and treatment necessary) of 0.1%[15] and prevalence of ZIKV-associated Guillain-Barré syndrome was estimated to be around 1.23%.[16] Therefore, case numbers can be substantial in large outbreaks. As hospitalisation is rare, and symptoms mimic mild dengue fever and chikungunya (*table 1*), infection with ZIKV is thought to be underreported.[5] Epidemiological studies reporting high prevalence of neutralising antibodies among people in mosquito endemic areas support this hypothesis.[3,5] In 2015 the first reports emerged linking ZIKV to increased incidence of microcephaly (*figure 1*) among newborns following the outbreak in Brazil.[17,18] Besides an increase in cases of microcephaly in areas with a high incidence of ZIKV infection, other causes of adverse congenital outcomes including growth restriction and miscarriage[19] were noticed, but studies were generally too small to confirm a significant association. A systematic review (including three cohort studies) updated in 2018 found that the risk of congenital abnormalities was 3.5 times higher after Zika infection.[20] Other clues supporting the role of ZIKV in congenital abnormalities are studies confirming the presence of ZIKV RNA particles in several body fluids, including semen,[21] amniotic fluid,[22] breast milk[23] and in the brain, placenta or serum of newborns with microcephaly and aborted pregnancies.[24-26] As of now, it is clearly established that whereas ZIKV infection leads to mild human disease in the majority of infections, it may significantly influence foetal development on a larger scale.

Table 1. Clinical symptoms of Zika, Chikungunya and Dengue virus

Comparison of clinical characteristics			
	Zika	**Chikungunya**	**Dengue**
Incubation period (days)	3-12	2-12	3-14
Symptomatic (%)	20-25	75	25%
Fever	++ (mild)	+++	++++
Arthralgia	+++ (mild)	+++ (sometimes long standing)	++
Peripheral oedema	++	-	-
Skin rash	+++	++	++
Headache (retro orbital)	++	+	++
Conjunctivitis	+++	+	+
Lymphadenopathy	+	++	++
Hepatomegaly	-	+++	-
Thrombopenia	-	+	++
Leucopenia	+	++	++

Reference: RIVM, LCI guideline on ZIKA virus, 2021

Diagnosis, prevention and treatment

Until recently, serological testing of ZIKV was confounded by cross-reactivity with other flaviviruses including dengue virus.[27,28] From 2016 a novel anti-ZIKV ELISA based on recombinant ZIKV non-structural protein 1 was implemented with high sensitivity and specificity.[29] RT-PCR for ZIKV generally has high sensitivity and specificity as well,[30,31] but is only usable in the initial phase of the disease, when actual

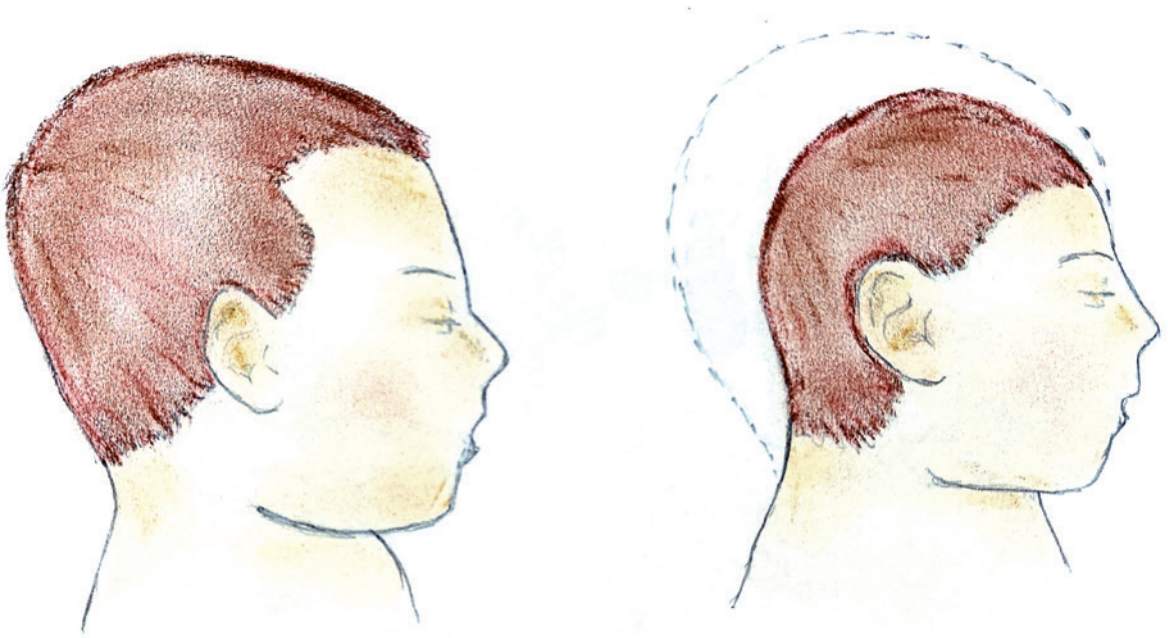

Figure 1. Baby with typical head shape (left) and baby with microcephaly (right)

viraemia is present, although this may be a substantial period. It is currently recommended that RT-PCR testing is done within the first six days of the onset of illness.[27]

Diagnosis made on clinical grounds can be difficult as physical symptoms as well as endemic areas with dengue and chikungunya virus overlap and is therefore unreliable. In case of mild infection, which is in the majority of cases, there is generally no need for PCR/serological testing and as a consequence high infection rates are usually found by active surveillance.

Principally vector source control measures are taken by governments to control the ZIKV epidemic, as no treatment or vaccines are available to date. Measures include removing mosquito breeding grounds and the use of insect sprays. Education of the public[32] and travel advice for pregnant woman as well as women and men wanting to have a child (as ZIKV can harbour in semen) to restrict travel to endemic areas and to prevent vertical transmission, are cornerstones of prevention strategies of various governments and health organisations.

Pandemic potential of Zika virus

Irrespective of the biological class of a pathogen, several attributes are likely to be essential components of the pandemic threat potential of pathogens. These traits include efficient human-to-human transmissibility, an appreciable case fatality rate, the absence of an effective or widely available medical countermeasure, an immunologically naïve population, virulence factors enabling immune system evasion and respiratory mode of spread. Additionally, the ability to transmit during incubation periods and/or the occurrence of mild illnesses would further augment spread. Zika is mainly transmitted to humans through mosquitoes and human-to-human transmission is rare. Case fatality rate is low and there is no respiratory spread. Taken together, the severity of pandemic potential could be classified as low. However, the uniquely dangerous trait of ZIKV that it can circulate unnoticed for years among populations and infection of populations without previous acquired immunity against ZIKV provides a substantial risk for large outbreaks.[33] Subsequently, it causes large-scale negative reproductive effects, represented by foetal complications, which only become manifest months after introduction of the virus.[33]

Invasion of a new (immune naive) population was probably an important factor in the explosive emergence of ZIKV in Brazil, as the decline in Zika cases was particularly attributed to the rise in immunity with a peak seroprevalence of 63% in 2016.[33] As associated congenital complications were not reported previously in endemic areas, the number of associated cases in Brazil was unexpected. It is likely that ZIKV infection at a young age protects pregnant women against foetal complications later on and that foetal complications mainly occur in primo infections[34] such as in Brazil. Besides immune naivety, ZIKV infection was associated with higher population density, the incidence of dengue, *Aedes* larvae infestation index and average rainfall.[35] Other issues that potentially influenced this outbreak, including evolution of the virus and potential domestic and wild animal reservoirs, remain largely unresolved to date.

Mosquitoes from the *Aedes* genus were originally found in tropical and subtropical areas but they are gradually spreading, including to the south of Europe and the United States following climate change.[36] In particular, the distribution area of the mosquito species *Aedes albopictus* has been increasing over the years and several models predict that 83% of urban areas in Europe will become suitable over time.[37] *Aedes albopictus* has been shown to be a competent vector of ZIKV[38] and other viruses including dengue and chikungunya. Besides Europe, numerous other immunologically naive populations have been identified as high-risk countries, including those with limited medical resources and (pre) pregnancy surveillance.[39]

In 2016, the first autochthonous ZIKV disease cases acquired via vector-borne transmission in Europe were reported in France. In this cluster, three persons became infected in a short period of time and no travel history to any of the Zika endemic areas was present. These cases reinforce the hypothesis that autochthonous vector-borne transmission of ZIKV in non-endemic areas is possible and could be aided by *Aedes albopictus* or other mosquito species that have yet to be determined.

Introduction of the virus by travellers from endemic areas has been described[10,40] and could potentially be the source of circulating ZIKV in new mosquito populations in non-endemic areas, as mosquito-to-mosquito infection has not been reported. The role of human-to-human infection has to be investigated, but several studies showed long-standing viral loads in body fluids including semen, in some cases leading to late human-to human transmission.[21] Compared with other flaviviruses, sexual transmission and persistence in the genitourinary tract seem to be unique.

During outbreaks, humans act a reservoir, but it is proposed that especially monkeys are a natural reservoir in endemic areas, as the virus was isolated from several species and experimental inoculation caused viraemia and seroconversion.[41] However, antibodies have also been detected in domestic sheep, goats, horses, cows, ducks, rodents, bats, orangutans and carabaos[1] and in a surveillance study from Brazil in 2018 ZIKV was detected in numerous other vertebrates.[42] The role of possible reservoirs in currently non-endemic areas has not been established and detection of ZIKV in animals does not necessarily imply that animal-to-mosquito-to human infection takes place, as this also depends on other characteristics of the host, the vector and

the virus itself. Still, if for instance domestic animals emerge to be suitable as a reservoir, it could potentially enhance further spread and maintain circulation of ZIKV in the absence of current known reservoirs, including monkeys.

Conclusion

ZIKV is a vector-borne virus that generally causes no or mild clinical symptoms. However, the uniquely dangerous aspect of ZIKV infection is that maternal infection is associated with serious congenital disorders. From 2007, increasing numbers of cases of ZIKV are being described and in 2015 a large outbreak was reported in Brazil followed by a substantial number of newborns with microcephaly several months later. The spread of mosquitoes from the *Aedes* genus to areas such as the US and Europe will significantly increase the potential of upcoming Zika infections in these regions in the near future.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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