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ZIKA VIRUS INFECTION: AN UPDATE

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Abstract

Since the ZIKV outbreak in Brazil in 2015, the scientific community has joined efforts to gather more information on the epidemiology, clinical features and pathogenicity of the virus. Here, we summarize the most important advances made recently and discuss promising, innovative aproaches to understand and control ZIKV infection.

Keywords : Zika; Arbovirus; Vector control; Epidemiology; Innate immunity; Treatment

1. Introduction

Zika virus (ZIKV) is an emerging mosquito-borne Flavivirus, belonging to the *Flaviviridae* family. ZIKV contains a positive single-stranded RNA encoding a polyprotein precursor that is processed by cellular and viral proteases to yield its three structural proteins: the capsid (C), the precursor of membrane (prM) and the envelop (E) proteins, as well as seven non-structural protein: NS1 to NS5. ZIKV was discovered following scientific research on the enzootic cycle of the Yellow fever virus and other unknown arboviruses in the Zika forest of Uganda. The first case of human ZIKV infection has been reported in Uganda in 1952 [1] and the virus was later isolated from humans in South East Asia [2]. Viral pathology was associated with a few sporadic cases in tropical Africa and the south of Asia until 2007 when the number of human cases of ZIKV infection unexpectedly increased, initially in Micronesia, then in Pacific Ocean Island to finally reach the South American continent in 2015. Although the reasons for the sudden emergence of the virus are not clear, several hypotheses can be put forward. Many factors may determine the emergence of arboviruses, such as the actual climate change, which affects the distribution of vectors, viral mutation frequency leading to an increasing virulence, as well as changes in anthropological behaviour resulting in increased host-pathogen interactions. ZIKV entry in Brazil from Pacific countries [3,4] has been linked to two major social events, the World cup soccer game and the World Sprint Championships [5] that were held in this country in 2014. At present, three different major lineages of ZIKV, belonging to African, Asian and Brazilian strains, have been characterized according to phylogenetic investigations. While Asian and Brazilian strains show low nucleotidics differences, mutations have been highlighted between Asian strain and African strain. Moreover, *in vitro* and *in vivo* studies revealed differential infection outcome, particularly between the African and Asian/Brazilian strains, suggesting that the African strain seems to be more virulent and to cause more cellular damage than the Asian/Brazilian strain [6–8].

Nonetheless, further investigations are needed to understand why both the Asian and Brazilian strains are particularly associated with neurological disorders.

2. Epidemiology

2.1 Geographic distribution

Despite its broad geographical distribution, human infections with ZIKV have remained sporadic and limited to small-scale epidemics for decades, until 2007 when a large epidemic was reported on Yap Island with nearly 75% of the population being infected with the virus [9]. Moreover, an outbreak of a syndrome due to ZIKV fever has been reported in French Polynesia, associated with ZIKV-infection-related neurological and an unexpected increase in the incidence of Guillain Barré syndrome by 20 fold [10]. Subsequently, several cases of ZIKV infection in New Caledonia, Easter Island and the Cook Islands have been described indicating a rapid spreading of the virus in the Pacific [3]. The ZIKV epidemic in 2015 has been the start of an international public health emergency when the virus reaches the American continent, with 33 countries reporting autochthonous transmission of ZIKV infection and an increase in the incidence of cases of microcephaly and/or Guillain-Barré syndrome. Moreover, ZIKV infection has also been associated with imported cases, notably in Europe [11], indicating a rapid world-wide spread of the virus. On February 2016, the WHO started to issue monthly reports on the situation of the ZIKV epidemy. On March 2017, the WHO published the last report following the ZIKV outbreaks establishing a total of 61 areas with ongoing virus transmission: 13 countries with evidence of person to person virus transmission: 31 countries reporting neurological disorders associated with ZIKV infection (microcephally, congenital malformations …) and 23 countries reporting an increased incidence of Guillain-Barré in ZIKV-infected patients (situation report, 10 March 2017, WHO). During this period an estimate of 400 000 to 1.5 million cases of ZIKV infection have been reported in these countries. Since 2017, the number of cases declined, although the virus

is still circulating in many countries, even in those that were not involved in the last outbreak. For example, three laboratory-confirmed cases of ZIKV infection have been reported in India (Bapunagar area) showing that the virus is still circulating in this country (Disease Outbreak News, 26 May 2017, WHO). For several years, new informatic tools have been developped to improve the modelisation of infectious disease outcome. As a consequence, many studies have been performed to develop predictive models of ZIKV spread by taking into account determining parameters of the infection (vector abundance, local temperature, mode of transmission, surveillance information and human behavior) to obtain meaningful projections of the number of ZIKV infections in countries around the world [12,13]. These models will allow public health authorities to better anticipate the propagation of ZIKV infection or to project the end of the epidemy.

2.2 Transmission and vector control

The main mode of ZIKV transmission occurs via the female mosquitoe bite during blood feeding, although the human to human transmission route, among which perinatal transmission [14], sexual transmission [15,16] and breast milk feeding [17–19] has been described as well. Many different species of *Aedes* mosquito can account for the transmission of ZIKV, including *Ae.aegypti and albopictus* [20,21]. Nevertheless, the competence of this two *Aedes* genus seems to be variable according to geographic sites and the viral strain it has been infected with [22,23]. The *Aedes* genus is dispersed in predominantly tropical areas on three continents (Asia, Africa, America), but shows increased spreading, particularly in North America, Europe and China [24], which highlights the importance to develop efficient tools to control the spread of the vectors. Strategies to contain and reduce the development of mosquitoe populations have already been established to limit arbovirus propagation (**Figure 1**). To this aim, the WHO promotes a combination of methods, such as individual and household protection (clothing, air–conditionning, repellents, net …), procedures to limit

backwater and the safe use of insecticides. However, these methods are not sufficient to halt vector-borne disease spread and there is a real need for innovative, efficacious, approaches. Recently, the Worldwide Insecticide resistance Network (WIN) [25] symposium (https://www.winsingapore2018.com/) has provided an overview of the alternative methods currently under development for the control of arbovirus vectors [26–28]. Amongs these new tools feature novel larvicides (entomopathogenic Ascomycetes fungi, pyroproxyfen, autodissemination), classical and biotechnology-based sterile insect techniques, spatial repellents, insect traps, attractive targeted sugar baits, insecticide-treated materials and gene drives (ex : CRISPR-Cas like system C2c2). Moreover, an emerging method showing impressive results to prevent arbovirus propagation is the use of the bacterial *Wolbachia* genus to either eliminate *Ae.aegypti* mosquitoe (mosquitoe population suppression) [29,30] or restrict the arbovirus infection (i.e. mosquitoe population replacement) [31]. In fact, it has been shown that the endosymbiotic bacterium Wolbachia, naturally present in up to 40% of all arthropods [32] is able to block the transmission of many human pathogens in mosquitoes, such as CHIKV, DENV and Plasmodium [33,34], by cytoplasmic incompatibility [35]. More recently, several experimental studies showed that the wMel Wolbachia strain si able to also restrict ZIKV infection in *Ae. aegypti* [36–38]. Nevertheless these methods show efficacy limits and ethical issues and need to also integrate a sustainable, effective, community-based, locally adapted vector control management to reduce the burden of *Aedes*-transmitted disease [27].

ZIKV outbreaks have mainly been investigated in countries where the infection was associated with severe symptoms. Nevertheless, it remains important to provide more information about the prevalence of the infection in other countries where the virus is circulating, or has circulated probably with more asymptomatic effects, to better understand the evolutive propagation of the virus. In particular it is of importance to define and

characterize the different factors that are associated with its emergence and pathogenicity and in this respect, it appears crucial to obtain more information about the circulation and infection outcome of ZIKV in Africa and India where the virus has started its course.

3. Pathogenicity of ZIKV in humans

3.1 Symptoms of Zika virus infection

The sudden emergence of ZIKV has rapidly become a major public health due to the severe symptoms developped by newborn babies. In fact, the latest outbreak has raised major concerns about the pathogenicity of ZIKV since severe neurological complications in fetuses, neonates and adults were found to be associated with the infection [39–41]. Previous outbreaks of ZIKV were characterized by a classic clinical pattern, fever, rash, arthralgia and conjunctivitis in infected individuals [42]. However, in ZIKV-infected pregnant women in Brazil, a remarkable 42% of fetuses exhibited some type of ultrasound abnormality [43]. The clinical phenotype of congenital ZIKV infection was variable and included cerebral calcifications, microcephaly, intrauterine growth restriction and fetal demise. Computed tomography and magnetic resonance imaging of the brains of congenitally infected neonates in Brazil further demonstrated hypoplasia of the cerebellum and brainstem, ventriculomegaly, delayed myelination, enlarged cisterna magna, abnormalities of the corpus callosum, calcifications, and cortical malformations [44]. It is of note that retrospective assessment of the ZIKV epidemic in French Polynesia also found an increased risk of microcephaly associated with ZIKV infection, with 95 cases occurring per 10,000 women infected in the first trimester [45]. In comparison to the encephalitic flaviviruses (e.g., West Nile virus and Tick-born encephalitis virus), ZIKV generally is less neuroinvasive in adults, rarely causing meningitis and encephalitis [46]. ZIKV infection has also been associated with the development of Guillain-Barré Syndrome (GBS) in a lower percentage of patients

[10,39,47,48]. GBS is an auto-immune disease associated with aberrant inflammation that targets peripheral nerves and leading to muscle weakness and paralysis [49]. It is hypothesized that the production of neutralizing antibodies against ZIKV target peripheral nerve glycolipids, thereby inducing injuries of myelin or axonal membranes that leads to inflammatory demyelinating polyneuropathy [49–51]. Further research is needed to better characterized the immune response mechanism involved in the GBS development associated with ZIKV infection.

3.2 Zika virus permissiveness and replication

The epidemy of Zika in Brazil has been followed by an exceptional effort from the scientific community to identify the key biological factors associated with the pathogenicity of the virus and to help the health system to contain the epidemic. ZIKV infection studies using patients samples, *in vivo* and *in vitro* models [52,53] allowed to characterized differents tissue and cell lines permissive to infection. ZIKV has been detected in placenta, brain, eye, testis, uterus, vagina and body fluids (blood, tears, saliva, semen, cervical mucus and urine) in human [54], but also in liver, spleen, lung, kidney, heart and muscle in various animal models [55–59]. Moreover, *in vitro* studies characterized a broad range of cell lines showing differential susceptibility to ZIKV infection, providing new tools to study its pathogenesis [60,61]. Interestingly, cell lines derived from the placenta or genital tract are susceptible to infection with ZIKV, but not with other while other flaviviruses, such as DENV [61] which could explain the association of ZIKV with congenital disorders. In addition, ZIKV was found to replicate in human testicular tissue and male germ cells and furthermore persisted in semen [62,63] resulting in a high risk of sexual transmission. More precisely, a recent study investigating ZIKV dissemination in the male reproductive tract proposed a model in which ZIKV infects the testis through the hematogenous route, whereas infection of the epididymis

can occur through both hematogenous/lymphogenous and excurrent testicular routes [64]. Nevertheless, ZIKV preferentially infects brain cells, in particular human neural progenitor cells (hNPC) [65–68], which may explain its ability to impair development of the fetal brain and cause microcephaly and other neurodevelopmental injuries. ZIKV-induced microcephaly can have several different causes [69] since the virus can affect the neuronal progenitors which results in either cell death or neurogenesis dysregulation [66,67,70]. ZIKV can also infect glial cells and disturb their role in neuronal development. In addition, it is yet unknown if these mechanisms could vary according to viral strain, being from African or Asian origin. Like all viruses, ZIKV depends heavily on the cellular machinery of the host to accomplish its life cycle. The permissiveness of ZIKV is dependent on the presence of specific cell surface receptors which allow the entry of the virus in the cells. Several entry receptors have already been identified to facilitate ZIKV infection, including the innate immune receptor DC-SIGN, TIM-1 and TAM receptors (transmembrane protein TYRO-3, AXL and MER) in human skin cells, endothelial cells, neural and retinal progenitor cells, highlighting a unique tropism among flaviviruses [60,42,71–75]. More recently, high-throughput fitness profiling of ZIKV E protein has shown that N-linked glycosylation enhances ZIKV infection in mammalian cell line following interaction with DC-SIGN [76]. Several studies in experimental mouse models have also shown that TAM receptors, in particularly AXL, are determinant, although not essential, for ZIKV infection [77,78]. Further investigations are still needed to clarify the role of each of each of these receptors and to identify any additional key entry factors that could represent an potential new therapeutic target.

3.3 Innate immune response to ZIKV

ZIKV infection induces innate and adaptative responses by infected cells. First, viral RNA sensors activate TLR receptors, in particularly TLR3 and TLR7, as well as the RIG-like

198 receptors MDA5 and RIG-I, leading to the production of type 1 (IFN-β) and type III (IFN-
199 λ) interferons. The latter will then bind their respective receptors to induce the activation of
200 the JAK/STAT signaling pathway leading to the production of interferon-stimulated genes,
201 such as ISG15, OAS2, MX1, and IFIT, as well as inflammatory chemokines, like CCL5 and
202 CXCL10 [42,79]. Moreover, recent reports have also highlighted the importance of IFITM1
203 and IFITM3, members of the family of interferon-inducible transmembrane proteins, in the
204 inhibition of ZIKV replication [80,81] and the prevention of ZIKV-induced cell death [81].
205 The importance of IFN signaling pathway has been highlighted by the development of ZIKV-
206 induced pathology in mice deficient in the expression of type I and II IFN receptors or
207 STAT2 that was not observed in immunocompetent mice [56,58,53,82]. Moreover, IFN-λ has
208 been shown to be particularly protective against ZIKV infection in the female reproductive
209 tract [83] and in the maternal decidua and placenta associated with its production at later
210 gestationnel stages during pregnancy [84,85]. Therefore, differential innate immune response
211 profiles according to cell type and cell differentiation state associated with immunological
212 maturation could be related to variable susceptibility to ZIKV infection [83–85] (Ferraris et
213 al., unpublished data).
214 ZIKV, as many other viruses, is able to counteract anti-viral immune responses through the
215 interaction of viral proteins with proteins of cellular signalling. In particular, ZIKV is able to
216 impair IFNs signaling pathways [86] by preventing STAT1 phosphorylation [87], inducing
217 JAK1 and STAT2 proteasomal degradation through its interaction with the NS2B-NS3
218 protease [88] and and NS5 [89], respectively . Moreover, the NS2B-NS3 protease complex is
219 also able to target the human STING protein [90] whereas NS1 and NS4B reduce IFN-β
220 production by disrupting phospho-TBK1 in human brain cells [91].
221 ZIKV sfRNA, a subgenomic viral RNA, is also involved in viral interference with innate
222 immune responses [92], since it has been reported to antagonize RIG-I mediated induction of

type I interferon in human lung epithelial cells [93,94]. More recently, the FXMRP protein, identified as rectricted factor of ZIKV, has been shown to be antagonized by ZIKV sfRNA [95].

The immune response is essential to fight infection but can also be associated with pathogenesis by inducing auto-immune disease. Within this context, it has been shown that ZIKV can induce exacerbated neuro-inflammation associated with NPC depletion in human organoids, notably through the activation of TLR3 [96] and production of cytokines [97]. Moreover, the production of non-neutralizing antibodies that induce a process called Antibody-Dependent Enhancement during a primary infection against DENV can facilitate the infection by another flavivirus through the cross-reactivity with the Fcγ receptor [98]. Because of the important ZIKV outbreak in countries where DENV is known to be epidemic, many studies have been performed to evaluate this cross-reactivity between both viruses [99]. However, the results remain controversial, whereas some studies found that prior DENV infection was associated with lower risk to develop ZIKV infection symptoms [100,101], other *in vitro* and *in vivo* studies reported opposite obversations [98,102,103]. This phenomenon seems to be dependent on the virus strain and host immune response, and needs to be taken in account in the development of an anti-ZIKV vaccine [104].

Since the ZIKV outbreak in 2015 an exceptional effort has been made to develop fundamental research aimed to improve our knowledge about the biology of this flavivirus, including its tropism, morphogenesis and antiviral responses. These studies have been essential to better understand the infection and to implement novel approaches for treatment and the development of vaccines. These advances notwithstanding, continued investigations are still needed to understand the molecular mechansims underlying the capacity of the virus to cross the placental and blood-brain barrier, unlike other flaviviruses, as well as the differences

between the various ZIKV strains and the impact of co-infection with other arboviruses on viral pathogenicity.

4. Treatment and vaccine perspectives

4.1 Antiviral molecules

Currently, no vaccines or antiviral treatments have been approved to cure ZIKV infection and patients' care is mainly focused on treating their symptoms. The main challenge is to develop treatment for ZIKV infection that can be administrated to pregnant women. Nevertheless, hundreds of compounds are currently tested *in silico* for their capacity to interfere with the replicative life cycle of ZIKV, but only few have been shown to inhibit ZIKV infection *in vitro* and need further testing *in vivo* as well as in clinical trials (**Table 1**) (**Figure 1**) [105–107]. Some molecules, called Direct Acting Agents have the potential to directly act on viral function by inhibiting both early and late stages of replication. Another antiviral strategy is to block viral entry by inhibiting the attachment, endocytosis and fusion of the virus in the cell. Several molecules show encouraging *in vitro* results such as duramycin and suramin that may prevent attachment to host receptors mediating flavivirus entry into the cell [108–110] and nanchangmycin that seems to block clathrine-mediated endocytosis of ZIKV [111]. Nevertheless, no *in vivo* studies have been published so far that sustain their efficacy. *In vivo* experiments demonstrated that two inhibitors of ZIKV entry, a synthetic peptide inhibitor, Z2, interfered with vertical transmission of ZIKV in pregnant mice [112] and Cholesterol-25-hydroxylase, a natural interferon stimulated gene, responsible for cholesterol oxydation inhibiting ZIKV uptake, are protective against ZIKV symptoms and microcephaly [113]. These molecules need now to be tested in clinical trials. Another strategy consists in the targeting of the NS2B-NS3 viral protease protein which allows the cleavage of the different viral proteins from the polyprotein. Therefore Novobioctin, lopinavir-ritonavir and

Bromocriptine, among other molecules, show a significant effect on ZIKV infection and cell death *in vitro* or *in silico, via* the inhibition of protease activity [114,115]. Another targeted viral protein is NS5 RdRp whose polymerase activity is crucial for the replication of the virus. One of the promising molecules is the Sofosbuvir a class B FDA-approved compound that has already been tested to treat Hepatitis C virus infections. Importantly, animal studies have not demonstrated a risk to use it during pregnancy. The efficacy of Sofosbuvir to inhibit ZIKV infection has been demonstrated in vitro in neural progenitor cells, brain organoids, neuroepithelial stem cells and *in vivo* in mice [91,116–118]. Other viral protein are targeted to identify new potential drugs, such as NS3 helicase (Ivermectin and Resveratrol) and NS5 methyltransferase for which compounds have shown antiviral activity against other flaviviruses and therefore will need to be tested on ZIKV infection [107]. Many other compounds which show a conserved efficacy among flaviviruses could represent a potential target for ZIKV and need to be tested as well. Several other molecules that are currently under development are tested to counteract undesirable cell effects that could be induced by the virus. For example, Emricansan has been shown to reduce cellular apoptosis by inhibiting caspase-3 activity, whereas several nucleoside analogues are able to reduce cytopathic effects and cell death after ZIKV infection [119]. Moreover, some modulators of lipid metabolism such as Imipramine, an FDA approved drug, inhibits ZIKV replication and viral production, in human skin fibroblasts, probably through interference with intracellular cholesterol transport [120]. More recently, Taguwa et al. highlighted the interest to target the cellular protein Hsp70, essential for flavivirus replication for antiviral strategy. They showed that Hsp70 inhibitor, significantly reduced ZIKV replication in cells, associated with reducing pathogenicity in mice and low cytotoxicity effect. Furthemore Hsp70 inhibitors present a low risk of drug resistance makes them new attractive antivirals against ZIKV infection [121]. Finally, therapeutic antibodies could be also an alternative since the results of several studies

297 have shown that neutralizing antibodies targeting ZIKV can prevent viral replication,
298 microcephally and fetal disease in mice [122–124].
299
300 **4.2 Vaccines**
301 Following the sudden outbreak of ZIKV infection in Brazil, the international health care
302 system has called for the development of candidate vaccines against the virus. One of the
303 important challenge of ZIKV vaccine development is to produce a low cost and safe vaccine
304 to be inoculated in pregnant women, particularly in low-ressource countries where viral
305 outbreaks occur. Several mouse and rhesus monkey models have been established in the
306 framework of ZIKV vaccine development [58,53,125,126]. Most models used to study ZIKV
307 vaccine efficacy are knockout mice (129, C57BL/6, Balbc, Swiss…) with deficiencies in IFN
308 type I (IFN-α and -β) or II (IFN-γ) receptors which have the particularity to reproduce several
309 characteristics of ZIKV pathogenesis, such as fever, neurological disorders on newborn
310 mouse and lethality. Many vaccine subtypes and strategies are under development and
311 vaccine candidates are currently tested for their non-toxicity and efficacy, although only a few
312 are currently in phase I or II clinical trials (**Table 1**) (**Figure 1**) [125,127,128]. Among the
313 more promising vaccines in clinical trials there is a ZIKV-purified inactivated virus (ZPIV)
314 which was found to confer long-term protection in monkeys [129,130] and several nucleic
315 acid vaccines targeting the prM and E proteins that provide complete protection against viral
316 challenges in both mice and non human primates [129–134] as well as an adenovirus-based
317 vaccine targeting the prM and E protein of ZIKV with a complete long-term protection in
318 monkeys [129,135]. Additional vaccines are also being investigated but are still in the process
319 of preclinical development [125,127,128,136]. Also, fundamental research has higlighted a
320 new and very interesting strategy, pertaining to as an miRNA co-targeting approach for a live
321 virus vaccine that might result in improved genetic stability and restricted virus replication

[64]. In summary, remarkable efforts have been undertaken to develop an effective vaccine against ZIKV infection and a list of potential candidates has been identified of which several have reached phase II in clinical trials.

5. Conclusion

Three years after the beginning of the ZIKV outbreak in Brazil, the virus is still subject to intense medical research. Many investigations have allowed to better understand the biology of the infection leading to the establishment of vector control strategies and the development of drugs and vaccines that are currently tested in clinical trials in a remarkably short time following the outbreak (**Figure 1**). Nevertheless, most of the challenges such as vector control, diagnostics and patients care need to be improved in order to better control ZIKV spread. The symptomatic consequences of the co-circulation of ZIKV with other arboviruses such as DENV and CHIKV are still poorly characterized. However, since both viruses use the same vector it is important to continue to put a main effort in strategies of vector control. The latest ZIKV outbreak also highlights the importance to develop better tools to survey the ciculation of arboviruses in general and prevent the emergence of new ones. *In fine*, lessons from ZIKV outbreak have to be integrated to be prepared to adequately respond to the emergence of the next generation of arboviruses already circulating in the vector [137].

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References :

[1] Moore DL, Causey OR, Carey DE, Reddy S, Cooke AR, Akinkugbe FM, et al. Arthropod-borne viral infections of man in Nigeria, 1964-1970. Ann Trop Med Parasitol 1975;69:49–64.

[2] Darwish MA, Hoogstraal H, Roberts TJ, Ghazi R, Amer T. A sero-epidemiological survey for Bunyaviridae and certain other arboviruses in Pakistan. Trans R Soc Trop Med Hyg 1983;77:446–50.

[3] Musso D, Nilles EJ, Cao-Lormeau V-M. Rapid spread of emerging Zika virus in the Pacific area. Clin Microbiol Infect 2014;20:O595-596. doi:10.1111/1469-0691.12707.

[4] Weaver SC, Costa F, Garcia-Blanco MA, Ko AI, Ribeiro GS, Saade G, et al. Zika virus: History, emergence, biology, and prospects for control. Antiviral Res 2016;130:69–80. doi:10.1016/j.antiviral.2016.03.010.

[5] Zanluca C, Melo VCA de, Mosimann ALP, Santos GIV dos, Santos CND dos, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Memórias Do Instituto Oswaldo Cruz 2015;110:569–72. doi:10.1590/0074-02760150192.

[6] Anfasa F, Siegers JY, van der Kroeg M, Mumtaz N, Stalin Raj V, de Vrij FMS, et al. Phenotypic Differences between Asian and African Lineage Zika Viruses in Human Neural Progenitor Cells. MSphere 2017;2. doi:10.1128/mSphere.00292-17.

[7] Simonin Y, van Riel D, Van de Perre P, Rockx B, Salinas S. Differential virulence between Asian and African lineages of Zika virus. PLOS Neglected Tropical Diseases 2017;11:e0005821. doi:10.1371/journal.pntd.0005821.

[8] Hamel R, Ferraris P, Wichit S, Diop F, Talignani L, Pompon J, et al. African and Asian Zika virus strains differentially induce early antiviral responses in primary human astrocytes. Infection, Genetics and Evolution 2017;49:134–7. doi:10.1016/j.meegid.2017.01.015.

[9] Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika Virus Outbreak on Yap Island, Federated States of Micronesia. New England Journal of Medicine 2009;360:2536–43. doi:10.1056/NEJMoa0805715.

[10] Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome--case report, French Polynesia, December 2013. Euro Surveill 2014;19.

[11] Zammarchi L, Tappe D, Fortuna C, Remoli ME, Günther S, Venturi G, et al. Zika virus infection in a traveller returning to Europe from Brazil, March 2015. Euro Surveill 2015;20.

[12] Lo D, Park B. Modeling the spread of the Zika virus using topological data analysis. PLOS ONE 2018;13:e0192120. doi:10.1371/journal.pone.0192120.

[13] O'Reilly KM, Lowe R, Edmunds WJ, Mayaud P, Kucharski A, Eggo RM, et al. Projecting the end of the Zika virus epidemic in Latin America: a modelling analysis. BMC Medicine 2018;16. doi:10.1186/s12916-018-1158-8.

[14] Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill 2014;19.

[15] D'Ortenzio E, Matheron S, Yazdanpanah Y, de Lamballerie X, Hubert B, Piorkowski G, et al. Evidence of Sexual Transmission of Zika Virus. N Engl J Med 2016;374:2195–8. doi:10.1056/NEJMc1604449.
[16] Sakkas H, Bozidis P, Giannakopoulos X, Sofikitis N, Papadopoulou C. An Update on Sexual Transmission of Zika Virus. Pathogens 2018;7:66. doi:10.3390/pathogens7030066.
[17] Blohm GM, Lednicky JA, Márquez M, White SK, Loeb JC, Pacheco CA, et al. Evidence for Mother-to-Child Transmission of Zika Virus Through Breast Milk. Clinical Infectious Diseases 2018;66:1120–1. doi:10.1093/cid/cix968.
[18] Mann TZ, Haddad LB, Williams TR, Hills SL, Read JS, Dee DL, et al. Breast milk transmission of flaviviruses in the context of Zika virus: A systematic review. Paediatric and Perinatal Epidemiology 2018;32:358–68. doi:10.1111/ppe.12478.
[19] Colt S, Garcia-Casal MN, Peña-Rosas JP, Finkelstein JL, Rayco-Solon P, Weise Prinzo ZC, et al. Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: A systematic review. PLOS Neglected Tropical Diseases 2017;11:e0005528. doi:10.1371/journal.pntd.0005528.
[20] Grard G, Caron M, Mombo IM, Nkoghe D, Mboui Ondo S, Jiolle D, et al. Zika Virus in Gabon (Central Africa) – 2007: A New Threat from Aedes albopictus? PLoS Neglected Tropical Diseases 2014;8:e2681. doi:10.1371/journal.pntd.0002681.
[21] Boyer S, Calvez E, Chouin-Carneiro T, Diallo D, Failloux A-B. An overview of mosquito vectors of Zika virus. Microbes and Infection 2018. doi:10.1016/j.micinf.2018.01.006.
[22] Chouin-Carneiro T, Vega-Rua A, Vazeille M, Yebakima A, Girod R, Goindin D, et al. Differential Susceptibilities of Aedes aegypti and Aedes albopictus from the Americas to Zika Virus. PLoS Negl Trop Dis 2016;10:e0004543. doi:10.1371/journal.pntd.0004543.
[23] Garcia-Luna SM, Weger-Lucarelli J, Rückert C, Murrieta RA, Young MC, Byas AD, et al. Variation in competence for ZIKV transmission by Aedes aegypti and Aedes albopictus in Mexico. PLOS Neglected Tropical Diseases 2018;12:e0006599. doi:10.1371/journal.pntd.0006599.
[24] Kraemer MUG, Sinka ME, Duda KA, Mylne AQN, Shearer FM, Barker CM, et al. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus. Elife 2015;4:e08347. doi:10.7554/eLife.08347.
[25] Corbel V, Achee NL, Chandre F, Coulibaly MB, Dusfour I, Fonseca DM, et al. Tracking Insecticide Resistance in Mosquito Vectors of Arboviruses: The Worldwide Insecticide resistance Network (WIN). PLOS Neglected Tropical Diseases 2016;10:e0005054. doi:10.1371/journal.pntd.0005054.
[26] Achee NL, Grieco JP, Vatandoost H, Seixas G, Pinto J, NG LC, et al. Alternative Strategies for Arbovirus Control. PLOS Neglected Tropical Diseases 2018.
[27] Roiz D, Wilson AL, Scott TW, Fonseca DM, Jourdain F, Müller P, et al. Integrated Aedes management for the control of Aedes-borne diseases. PLOS Neglected Tropical Diseases 2018;12:e0006845. doi:10.1371/journal.pntd.0006845.
[28] Singh RK, Dhama K, Khandia R, Munjal A, Karthik K, Tiwari R, et al. Prevention and Control Strategies to Counter Zika Virus, a Special Focus on Intervention Approaches against Vector Mosquitoes—Current Updates. Frontiers in Microbiology 2018;9. doi:10.3389/fmicb.2018.00087.
[29] Mains JW, Brelsfoard CL, Rose RI, Dobson SL. Female Adult Aedes albopictus Suppression by Wolbachia-Infected Male Mosquitoes. Scientific Reports 2016;6. doi:10.1038/srep33846.
[30] Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe I, Johnson PH, Muzzi F, et al. Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission. Nature 2011;476:454–7. doi:10.1038/nature10356.
[31] Flores HA, O'Neill SL. Controlling vector-borne diseases by releasing modified mosquitoes. Nature Reviews Microbiology 2018;16:508–18. doi:10.1038/s41579-018-0025-0.
[32] Zug R, Hammerstein P. Still a Host of Hosts for Wolbachia: Analysis of Recent Data Suggests That 40% of Terrestrial Arthropod Species Are Infected. PLoS ONE 2012;7:e38544. doi:10.1371/journal.pone.0038544.

[33] Bian G, Joshi D, Dong Y, Lu P, Zhou G, Pan X, et al. Wolbachia Invades Anopheles stephensi Populations and Induces Refractoriness to Plasmodium Infection. Science 2013;340:748–51. doi:10.1126/science.1236192.
[34] Moreira LA, Iturbe-Ormaetxe I, Jeffery JA, Lu G, Pyke AT, Hedges LM, et al. A Wolbachia Symbiont in Aedes aegypti Limits Infection with Dengue, Chikungunya, and Plasmodium. Cell 2009;139:1268–78. doi:10.1016/j.cell.2009.11.042.
[35] Werren JH, Baldo L, Clark ME. Wolbachia: master manipulators of invertebrate biology. Nature Reviews Microbiology 2008;6:741–51. doi:10.1038/nrmicro1969.
[36] Dutra HLC, Rocha MN, Dias FBS, Mansur SB, Caragata EP, Moreira LA. Wolbachia Blocks Currently Circulating Zika Virus Isolates in Brazilian Aedes aegypti Mosquitoes. Cell Host & Microbe 2016;19:771–4. doi:10.1016/j.chom.2016.04.021.
[37] Schultz MJ, Isern S, Michael SF, Corley RB, Connor JH, Frydman HM. Variable Inhibition of Zika Virus Replication by Different Wolbachia Strains in Mosquito Cell Cultures. Journal of Virology 2017;91. doi:10.1128/JVI.00339-17.
[38] Schultz MJ, Tan AL, Gray CN, Isern S, Michael SF, Frydman HM, et al. *Wolbachia w* Stri Blocks Zika Virus Growth at Two Independent Stages of Viral Replication. MBio 2018;9. doi:10.1128/mBio.00738-18.
[39] Cao-Lormeau V-M, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 2016;387:1531–9. doi:10.1016/S0140-6736(16)00562-6.
[40] Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. New England Journal of Medicine 2016;374:951–8. doi:10.1056/NEJMoa1600651.
[41] Baud D, Gubler DJ, Schaub B, Lanteri MC, Musso D. An update on Zika virus infection. The Lancet 2017;390:2099–109. doi:10.1016/S0140-6736(17)31450-2.
[42] Hamel R, Liégeois F, Wichit S, Pompon J, Diop F, Talignani L, et al. Zika virus: epidemiology, clinical features and host-virus interactions. Microbes and Infection 2016;18:441–9. doi:10.1016/j.micinf.2016.03.009.
[43] Brasil P, Pereira JP, Moreira ME, Ribeiro Nogueira RM, Damasceno L, Wakimoto M, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro. N Engl J Med 2016;375:2321–34. doi:10.1056/NEJMoa1602412.
[44] de Fatima Vasco Aragao M, van der Linden V, Brainer-Lima AM, Coeli RR, Rocha MA, Sobral da Silva P, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. BMJ 2016;353:i1901. doi:10.1136/bmj.i1901.
[45] Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. The Lancet 2016;387:2125–32. doi:10.1016/S0140-6736(16)00651-6.
[46] Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S, et al. Zika Virus Associated with Meningoencephalitis. New England Journal of Medicine 2016;374:1595–6. doi:10.1056/NEJMc1602964.
[47] Brasil P, Sequeira PC, Freitas AD, Zogbi HE, Calvet GA, de Souza RV, et al. Guillain-Barré syndrome associated with Zika virus infection. Lancet 2016;387:1482. doi:10.1016/S0140-6736(16)30058-7.
[48] Barbi L, Coelho AVC, Alencar LCA de, Crovella S. Prevalence of Guillain-Barré syndrome among Zika virus infected cases: a systematic review and meta-analysis. The Brazilian Journal of Infectious Diseases 2018;22:137–41. doi:10.1016/j.bjid.2018.02.005.
[49] Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. The Lancet 2016;388:717–27. doi:10.1016/S0140-6736(16)00339-1.
[50] Lynch RM, Mantus G, Encinales L, Pacheco N, Li G, Porras A, et al. Augmented Zika and Dengue Neutralizing Antibodies Are Associated With Guillain-Barré Syndrome. The Journal of Infectious Diseases 2019;219:26–30. doi:10.1093/infdis/jiy466.

494 [51] Chang AY, Lynch R, Martins K, Encinales L, Cadena Bonfanti AÁ, Pacheco N, et al. Long-term
495 clinical outcomes of Zika-associated Guillain-Barré syndrome. Emerging Microbes & Infections
496 2018;7. doi:10.1038/s41426-018-0151-9.
497 [52] Pena LJ, Miranda Guarines K, Duarte Silva AJ, Sales Leal LR, Mendes Félix D, Silva A, et al. In
498 vitro and in vivo models for studying Zika virus biology. Journal of General Virology
499 2018;99:1529–50. doi:10.1099/jgv.0.001153.
500 [53] Morrison TE, Diamond MS. Animal Models of Zika Virus Infection, Pathogenesis, and Immunity.
501 Journal of Virology 2017;91. doi:10.1128/JVI.00009-17.
502 [54] Miner JJ, Diamond MS. Zika Virus Pathogenesis and Tissue Tropism. Cell Host Microbe
503 2017;21:134–42. doi:10.1016/j.chom.2017.01.004.
504 [55] Dowall SD, Graham VA, Rayner E, Atkinson B, Hall G, Watson RJ, et al. A Susceptible Mouse
505 Model for Zika Virus Infection. PLOS Neglected Tropical Diseases 2016;10:e0004658.
506 doi:10.1371/journal.pntd.0004658.
507 [56] Rossi SL, Tesh RB, Azar SR, Muruato AE, Hanley KA, Auguste AJ, et al. Characterization of a
508 Novel Murine Model to Study Zika Virus. Am J Trop Med Hyg 2016;94:1362–9.
509 doi:10.4269/ajtmh.16-0111.
510 [57] Dowall SD, Graham VA, Rayner E, Hunter L, Atkinson B, Pearson G, et al. Lineage-dependent
511 differences in the disease progression of Zika virus infection in type-I interferon receptor
512 knockout (A129) mice. PLOS Neglected Tropical Diseases 2017;11:e0005704.
513 doi:10.1371/journal.pntd.0005704.
514 [58] Lazear HM, Govero J, Smith AM, Platt DJ, Fernandez E, Miner JJ, et al. A Mouse Model of Zika
515 Virus Pathogenesis. Cell Host Microbe 2016;19:720–30. doi:10.1016/j.chom.2016.03.010.
516 [59] Coffey LL, Keesler RI, Pesavento PA, Woolard K, Singapuri A, Watanabe J, et al. Intraamniotic
517 Zika virus inoculation of pregnant rhesus macaques produces fetal neurologic disease. Nature
518 Communications 2018;9. doi:10.1038/s41467-018-04777-6.
519 [60] Hamel R, Dejarnac O, Wichit S, Ekchariyawat P, Neyret A, Luplertlop N, et al. Biology of Zika
520 Virus Infection in Human Skin Cells. Journal of Virology 2015;89:8880–96.
521 doi:10.1128/JVI.00354-15.
522 [61] Chan JF-W, Yip CC-Y, Tsang JO-L, Tee K-M, Cai J-P, Chik KK-H, et al. Differential cell line
523 susceptibility to the emerging Zika virus: implications for disease pathogenesis, non-vector-
524 borne human transmission and animal reservoirs. Emerging Microbes & Infections 2016;5:e93–
525 e93. doi:10.1038/emi.2016.99.
526 [62] Matusali G, Houzet L, Satie A-P, Mahé D, Aubry F, Couderc T, et al. Zika virus infects human
527 testicular tissue and germ cells. Journal of Clinical Investigation 2018;128:4697–710.
528 doi:10.1172/JCI121735.
529 [63] Robinson CL, Chong ACN, Ashbrook AW, Jeng G, Jin J, Chen H, et al. Male germ cells support
530 long-term propagation of Zika virus. Nat Commun 2018;9:2090. doi:10.1038/s41467-018-
531 04444-w.
532 [64] Tsetsarkin KA, Maximova OA, Liu G, Kenney H, Teterina N, Bloom ME, et al. Routes of Zika virus
533 dissemination in the testis and epididymis of immunodeficient mice. Nature Communications
534 2018;9. doi:10.1038/s41467-018-07782-x.
535 [65] Tang H, Hammack C, Ogden SC, Wen Z, Qian X, Li Y, et al. Zika Virus Infects Human Cortical
536 Neural Progenitors and Attenuates Their Growth. Cell Stem Cell 2016;18:587–90.
537 doi:10.1016/j.stem.2016.02.016.
538 [66] Li C, Xu D, Ye Q, Hong S, Jiang Y, Liu X, et al. Zika Virus Disrupts Neural Progenitor Development
539 and Leads to Microcephaly in Mice. Cell Stem Cell 2016;19:120–6.
540 doi:10.1016/j.stem.2016.04.017.
541 [67] Li H, Saucedo-Cuevas L, Regla-Nava JA, Chai G, Sheets N, Tang W, et al. Zika Virus Infects Neural
542 Progenitors in the Adult Mouse Brain and Alters Proliferation. Cell Stem Cell 2016.
543 doi:10.1016/j.stem.2016.08.005.

[68] Wu K-Y, Zuo G-L, Li X-F, Ye Q, Deng Y-Q, Huang X-Y, et al. Vertical transmission of Zika virus targeting the radial glial cells affects cortex development of offspring mice. Cell Res 2016;26:645–54. doi:10.1038/cr.2016.58.
[69] Pierson TC, Diamond MS. The emergence of Zika virus and its new clinical syndromes. Nature 2018;560:573–81. doi:10.1038/s41586-018-0446-y.
[70] Merfeld E, Ben-Avi L, Kennon M, Cerveny KL. Potential mechanisms of Zika-linked microcephaly: Zika-linked microcephaly. Wiley Interdisciplinary Reviews: Developmental Biology 2017;6:e273. doi:10.1002/wdev.273.
[71] Meertens L, Labeau A, Dejarnac O, Cipriani S, Sinigaglia L, Bonnet-Madin L, et al. Axl Mediates ZIKA Virus Entry in Human Glial Cells and Modulates Innate Immune Responses. Cell Reports 2017;18:324–33. doi:10.1016/j.celrep.2016.12.045.
[72] Richard AS, Shim B-S, Kwon Y-C, Zhang R, Otsuka Y, Schmitt K, et al. AXL-dependent infection of human fetal endothelial cells distinguishes Zika virus from other pathogenic flaviviruses. Proc Natl Acad Sci USA 2017;114:2024–9. doi:10.1073/pnas.1620558114.
[73] Chen J, Yang Y-F, Yang Y, Zou P, Chen J, He Y, et al. AXL promotes Zika virus infection in astrocytes by antagonizing type I interferon signalling. Nat Microbiol 2018;3:302–9. doi:10.1038/s41564-017-0092-4.
[74] Laureti M, Narayanan D, Rodriguez-Andres J, Fazakerley JK, Kedzierski L. Flavivirus Receptors: Diversity, Identity, and Cell Entry. Frontiers in Immunology 2018;9. doi:10.3389/fimmu.2018.02180.
[75] Lee I, Bos S, Li G, Wang S, Gadea G, Desprès P, et al. Probing Molecular Insights into Zika Virus–Host Interactions. Viruses 2018;10:233. doi:10.3390/v10050233.
[76] Gong D, Zhang T-H, Zhao D, Du Y, Chapa TJ, Shi Y, et al. High-Throughput Fitness Profiling of Zika Virus E Protein Reveals Different Roles for Glycosylation during Infection of Mammalian and Mosquito Cells. IScience 2018;1:97–111. doi:10.1016/j.isci.2018.02.005.
[77] Wang Z-Y, Wang Z, Zhen Z-D, Feng K-H, Guo J, Gao N, et al. Axl is not an indispensable factor for Zika virus infection in mice. J Gen Virol 2017;98:2061–8. doi:10.1099/jgv.0.000886.
[78] Wells MF, Salick MR, Wiskow O, Ho DJ, Worringer KA, Ihry RJ, et al. Genetic Ablation of AXL Does Not Protect Human Neural Progenitor Cells and Cerebral Organoids from Zika Virus Infection. Cell Stem Cell 2016;19:703–8. doi:10.1016/j.stem.2016.11.011.
[79] Frumence E, Roche M, Krejbich-Trotot P, El-Kalamouni C, Nativel B, Rondeau P, et al. The South Pacific epidemic strain of Zika virus replicates efficiently in human epithelial A549 cells leading to IFN-β production and apoptosis induction. Virology 2016;493:217–26. doi:10.1016/j.virol.2016.03.006.
[80] Savidis G, Perreira JM, Portmann JM, Meraner P, Guo Z, Green S, et al. The IFITMs Inhibit Zika Virus Replication. Cell Reports 2016;15:2323–30. doi:10.1016/j.celrep.2016.05.074.
[81] Monel B, Compton AA, Bruel T, Amraoui S, Burlaud-Gaillard J, Roy N, et al. Zika virus induces massive cytoplasmic vacuolization and paraptosis-like death in infected cells. The EMBO Journal 2017;36:1653–68. doi:10.15252/embj.201695597.
[82] Tripathi S, Balasubramaniam VRMT, Brown JA, Mena I, Grant A, Bardina SV, et al. A novel Zika virus mouse model reveals strain specific differences in virus pathogenesis and host inflammatory immune responses. PLOS Pathogens 2017;13:e1006258. doi:10.1371/journal.ppat.1006258.
[83] Caine EA, Scheaffer SM, Arora N, Zaitsev K, Artyomov MN, Coyne CB, et al. Interferon lambda protects the female reproductive tract against Zika virus infection. Nature Communications 2019;10. doi:10.1038/s41467-018-07993-2.
[84] Bayer A, Lennemann NJ, Ouyang Y, Bramley JC, Morosky S, Marques ETDA, et al. Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection. Cell Host & Microbe 2016;19:705–12. doi:10.1016/j.chom.2016.03.008.
[85] Jagger BW, Miner JJ, Cao B, Arora N, Smith AM, Kovacs A, et al. Gestational Stage and IFN-λ Signaling Regulate ZIKV Infection In Utero. Cell Host & Microbe 2017;22:366-376.e3. doi:10.1016/j.chom.2017.08.012.

[86] Kumar A, Hou S, Airo AM, Limonta D, Mancinelli V, Branton W, et al. Zika virus inhibits type-I interferon production and downstream signaling. EMBO Reports 2016;17:1766–75. doi:10.15252/embr.201642627.
[87] Bowen JR, Quicke KM, Maddur MS, O'Neal JT, McDonald CE, Fedorova NB, et al. Zika Virus Antagonizes Type I Interferon Responses during Infection of Human Dendritic Cells. PLOS Pathogens 2017;13:e1006164. doi:10.1371/journal.ppat.1006164.
[88] Xia H, Luo H, Shan C, Muruato AE, Nunes BTD, Medeiros DBA, et al. An evolutionary NS1 mutation enhances Zika virus evasion of host interferon induction. Nature Communications 2018;9. doi:10.1038/s41467-017-02816-2.
[89] Grant A, Ponia SS, Tripathi S, Balasubramaniam V, Miorin L, Sourisseau M, et al. Zika Virus Targets Human STAT2 to Inhibit Type I Interferon Signaling. Cell Host Microbe 2016;19:882–90. doi:10.1016/j.chom.2016.05.009.
[90] Ding Q, Gaska JM, Douam F, Wei L, Kim D, Balev M, et al. Species-specific disruption of STING-dependent antiviral cellular defenses by the Zika virus NS2B3 protease. Proceedings of the National Academy of Sciences 2018;115:E6310–8. doi:10.1073/pnas.1803406115.
[91] Onorati M, Li Z, Liu F, Sousa AMM, Nakagawa N, Li M, et al. Zika Virus Disrupts Phospho-TBK1 Localization and Mitosis in Human Neuroepithelial Stem Cells and Radial Glia. Cell Rep 2016;16:2576–92. doi:10.1016/j.celrep.2016.08.038.
[92] Göertz GP, Abbo SR, Fros JJ, Pijlman GP. Functional RNA during Zika virus infection. Virus Research 2017. doi:10.1016/j.virusres.2017.08.015.
[93] Akiyama BM, Laurence HM, Massey AR, Costantino DA, Xie X, Yang Y, et al. Zika virus produces noncoding RNAs using a multi-pseudoknot structure that confounds a cellular exonuclease. Science 2016;354:1148–52. doi:10.1126/science.aah3963.
[94] Donald CL, Brennan B, Cumberworth SL, Rezelj VV, Clark JJ, Cordeiro MT, et al. Full Genome Sequence and sfRNA Interferon Antagonist Activity of Zika Virus from Recife, Brazil. PLOS Neglected Tropical Diseases 2016;10:e0005048. doi:10.1371/journal.pntd.0005048.
[95] Soto-Acosta R, Xie X, Shan C, Baker CK, Shi P-Y, Rossi SL, et al. Fragile X mental retardation protein is a Zika virus restriction factor that is antagonized by subgenomic flaviviral RNA. ELife 2018;7. doi:10.7554/eLife.39023.
[96] Dang J, Tiwari SK, Lichinchi G, Qin Y, Patil VS, Eroshkin AM, et al. Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3. Cell Stem Cell 2016;19:258–65. doi:10.1016/j.stem.2016.04.014.
[97] Azevedo RSS, de Sousa JR, Araujo MTF, Martins Filho AJ, de Alcantara BN, Araujo FMC, et al. In situ immune response and mechanisms of cell damage in central nervous system of fatal cases microcephaly by Zika virus. Sci Rep 2018;8:1. doi:10.1038/s41598-017-17765-5.
[98] Halstead SB. Dengue Antibody-Dependent Enhancement: Knowns and Unknowns. Microbiol Spectr 2014;2. doi:10.1128/microbiolspec.AID-0022-2014.
[99] Priyamvada L, Quicke KM, Hudson WH, Onlamoon N, Sewatanon J, Edupuganti S, et al. Human antibody responses after dengue virus infection are highly cross-reactive to Zika virus. Proceedings of the National Academy of Sciences 2016;113:7852–7. doi:10.1073/pnas.1607931113.
[100] Regla-Nava JA, Elong Ngono A, Viramontes KM, Huynh A-T, Wang Y-T, Nguyen A-VT, et al. Cross-reactive Dengue virus-specific CD8+ T cells protect against Zika virus during pregnancy. Nature Communications 2018;9. doi:10.1038/s41467-018-05458-0.
[101] Gordon A, Gresh L, Ojeda S, Katzelnick LC, Sanchez N, Mercado JC, et al. Prior dengue virus infection and risk of Zika: A pediatric cohort in Nicaragua. PLOS Medicine 2019;16:e1002726. doi:10.1371/journal.pmed.1002726.
[102] Pantoja P, Pérez-Guzmán EX, Rodríguez IV, White LJ, González O, Serrano C, et al. Zika virus pathogenesis in rhesus macaques is unaffected by pre-existing immunity to dengue virus. Nature Communications 2017;8:15674. doi:10.1038/ncomms15674.

[103] Fowler AM, Tang WW, Young MP, Mamidi A, Viramontes KM, McCauley MD, et al. Maternally Acquired Zika Antibodies Enhance Dengue Disease Severity in Mice. Cell Host & Microbe 2018;24:743-750.e5. doi:10.1016/j.chom.2018.09.015.
[104] Rey FA, Stiasny K, Vaney M, Dellarole M, Heinz FX. The bright and the dark side of human antibody responses to flaviviruses: lessons for vaccine design. EMBO Reports 2018;19:206–24. doi:10.15252/embr.201745302.
[105] Saiz J-C, Oya N, Blázquez A-B, Escribano-Romero E, Martín-Acebes M. Host-Directed Antivirals: A Realistic Alternative to Fight Zika Virus. Viruses 2018;10:453. doi:10.3390/v10090453.
[106] da Silva S, Oliveira Silva Martins D, Jardim A. A Review of the Ongoing Research on Zika Virus Treatment. Viruses 2018;10:255. doi:10.3390/v10050255.
[107] Abrams RPM, Solis J, Nath A. Therapeutic Approaches for Zika Virus Infection of the Nervous System. Neurotherapeutics 2017;14:1027–48. doi:10.1007/s13311-017-0575-2.
[108] Tabata T, Petitt M, Puerta-Guardo H, Michlmayr D, Wang C, Fang-Hoover J, et al. Zika Virus Targets Different Primary Human Placental Cells, Suggesting Two Routes for Vertical Transmission. Cell Host & Microbe 2016;20:155–66. doi:10.1016/j.chom.2016.07.002.
[109] Albulescu IC, Kovacikova K, Tas A, Snijder EJ, van Hemert MJ. Suramin inhibits Zika virus replication by interfering with virus attachment and release of infectious particles. Antiviral Res 2017;143:230–6. doi:10.1016/j.antiviral.2017.04.016.
[110] Tan CW, Sam I-C, Chong WL, Lee VS, Chan YF. Polysulfonate suramin inhibits Zika virus infection. Antiviral Res 2017;143:186–94. doi:10.1016/j.antiviral.2017.04.017.
[111] Rausch K, Hackett BA, Weinbren NL, Reeder SM, Sadovsky Y, Hunter CA, et al. Screening Bioactives Reveals Nanchangmycin as a Broad Spectrum Antiviral Active against Zika Virus. Cell Reports 2017;18:804–15. doi:10.1016/j.celrep.2016.12.068.
[112] Yu Y, Deng Y-Q, Zou P, Wang Q, Dai Y, Yu F, et al. A peptide-based viral inactivator inhibits Zika virus infection in pregnant mice and fetuses. Nature Communications 2017;8:15672. doi:10.1038/ncomms15672.
[113] Li C, Deng Y-Q, Wang S, Ma F, Aliyari R, Huang X-Y, et al. 25-Hydroxycholesterol Protects Host against Zika Virus Infection and Its Associated Microcephaly in a Mouse Model. Immunity 2017;46:446–56. doi:10.1016/j.immuni.2017.02.012.
[114] Yuan S, Chan JF-W, den-Haan H, Chik KK-H, Zhang AJ, Chan CC-S, et al. Structure-based discovery of clinically approved drugs as Zika virus NS2B-NS3 protease inhibitors that potently inhibit Zika virus infection in vitro and in vivo. Antiviral Research 2017;145:33–43. doi:10.1016/j.antiviral.2017.07.007.
[115] Chan JF-W, Chik KK-H, Yuan S, Yip CC-Y, Zhu Z, Tee K-M, et al. Novel antiviral activity and mechanism of bromocriptine as a Zika virus NS2B-NS3 protease inhibitor. Antiviral Res 2017;141:29–37. doi:10.1016/j.antiviral.2017.02.002.
[116] Sacramento CQ, de Melo GR, de Freitas CS, Rocha N, Hoelz LVB, Miranda M, et al. The clinically approved antiviral drug sofosbuvir inhibits Zika virus replication. Scientific Reports 2017;7. doi:10.1038/srep40920.
[117] Bullard-Feibelman KM, Govero J, Zhu Z, Salazar V, Veselinovic M, Diamond MS, et al. The FDA-approved drug sofosbuvir inhibits Zika virus infection. Antiviral Res 2017;137:134–40. doi:10.1016/j.antiviral.2016.11.023.
[118] Ferreira AC, Zaverucha-do-Valle C, Reis PA, Barbosa-Lima G, Vieira YR, Mattos M, et al. Sofosbuvir protects Zika virus-infected mice from mortality, preventing short- and long-term sequelae. Sci Rep 2017;7:9409. doi:10.1038/s41598-017-09797-8.
[119] Xu M, Lee EM, Wen Z, Cheng Y, Huang W-K, Qian X, et al. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. Nature Medicine 2016;22:1101–7. doi:10.1038/nm.4184.
[120] Wichit S, Hamel R, Bernard E, Talignani L, Diop F, Ferraris P, et al. Imipramine Inhibits Chikungunya Virus Replication in Human Skin Fibroblasts through Interference with Intracellular Cholesterol Trafficking. Scientific Reports 2017;7. doi:10.1038/s41598-017-03316-5.

[121] Taguwa S, Yeh M-T, Rainbolt TK, Nayak A, Shao H, Gestwicki JE, et al. Zika Virus Dependence on Host Hsp70 Provides a Protective Strategy against Infection and Disease. Cell Rep 2019;26:906-920.e3. doi:10.1016/j.celrep.2018.12.095.
[122] Wang S, Hong S, Deng Y-Q, Ye Q, Zhao L-Z, Zhang F-C, et al. Transfer of convalescent serum to pregnant mice prevents Zika virus infection and microcephaly in offspring. Cell Research 2017;27:158–60. doi:10.1038/cr.2016.144.
[123] Sapparapu G, Fernandez E, Kose N, Bin Cao, Fox JM, Bombardi RG, et al. Neutralizing human antibodies prevent Zika virus replication and fetal disease in mice. Nature 2016;540:443–7. doi:10.1038/nature20564.
[124] Wang J, Bardelli M, Espinosa DA, Pedotti M, Ng T-S, Bianchi S, et al. A Human Bi-specific Antibody against Zika Virus with High Therapeutic Potential. Cell 2017;171:229-241.e15. doi:10.1016/j.cell.2017.09.002.
[125] Poland GA, Kennedy RB, Ovsyannikova IG, Palacios R, Ho PL, Kalil J. Development of vaccines against Zika virus. The Lancet Infectious Diseases 2018;18:e211–9. doi:10.1016/S1473-3099(18)30063-X.
[126] Dudley DM, Aliota MT, Mohr EL, Weiler AM, Lehrer-Brey G, Weisgrau KL, et al. A rhesus macaque model of Asian-lineage Zika virus infection. Nature Communications 2016;7. doi:10.1038/ncomms12204.
[127] Abbink P, Stephenson KE, Barouch DH. Zika virus vaccines. Nature Reviews Microbiology 2018;16:594–600. doi:10.1038/s41579-018-0039-7.
[128] Masmejan S, Baud D, Musso D, Panchaud A. Zika virus, vaccines, and antiviral strategies. Expert Review of Anti-Infective Therapy 2018;16:471–83. doi:10.1080/14787210.2018.1483239.
[129] Abbink P, Larocca RA, De La Barrera RA, Bricault CA, Moseley ET, Boyd M, et al. Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys. Science 2016;353:1129–32. doi:10.1126/science.aah6157.
[130] Larocca RA, Abbink P, Peron JPS, de A. Zanotto PM, Iampietro MJ, Badamchi-Zadeh A, et al. Vaccine protection against Zika virus from Brazil. Nature 2016;536:474–8. doi:10.1038/nature18952.
[131] Abbasi J. Zika Vaccine Enters Clinical Trials. JAMA 2016;316:1249. doi:10.1001/jama.2016.12760.
[132] Dowd KA, Ko S-Y, Morabito KM, Yang ES, Pelc RS, DeMaso CR, et al. Rapid development of a DNA vaccine for Zika virus. Science 2016;354:237–40. doi:10.1126/science.aai9137.
[133] Pardi N, Hogan MJ, Pelc RS, Muramatsu H, Andersen H, DeMaso CR, et al. Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination. Nature 2017;543:248–51. doi:10.1038/nature21428.
[134] Dyer O. Trials of Zika vaccine are set to begin in North America. BMJ 2016:i3588. doi:10.1136/bmj.i3588.
[135] Xu K, Song Y, Dai L, Zhang Y, Lu X, Xie Y, et al. Recombinant Chimpanzee Adenovirus Vaccine AdC7-M/E Protects against Zika Virus Infection and Testis Damage. Journal of Virology 2018;92. doi:10.1128/JVI.01722-17.
[136] Durbin A. Vaccine Development for Zika Virus—Timelines and Strategies. Seminars in Reproductive Medicine 2016;34:299–304. doi:10.1055/s-0036-1592070.
[137] Venter M. Assessing the zoonotic potential of arboviruses of African origin. Current Opinion in Virology 2018;28:74–84. doi:10.1016/j.coviro.2017.11.004.

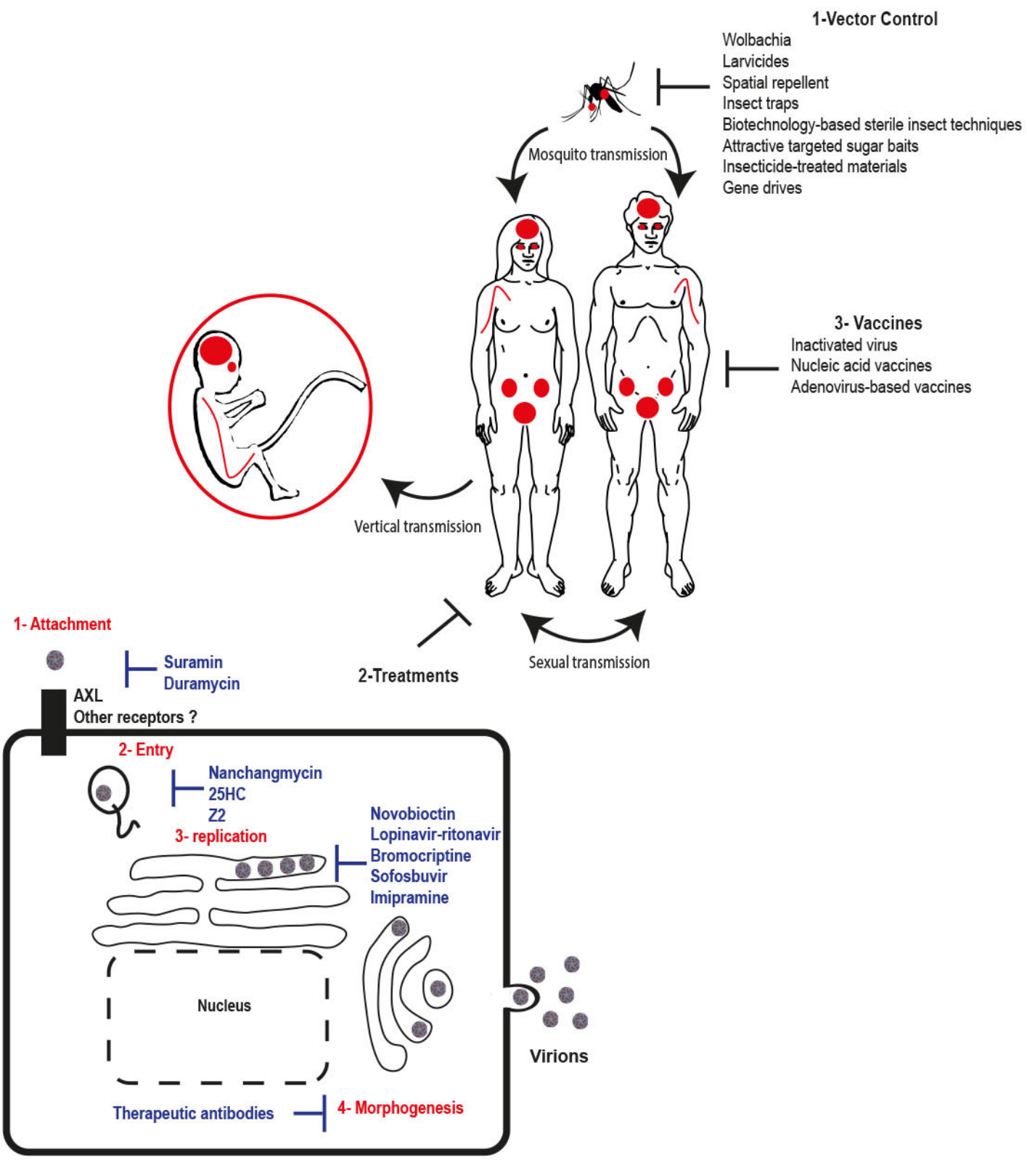
LEGENDS

Figure 1. Strategies to control ZIKV infection in humans

746 Innovative strategies to limit ZIKV transmission through the control and the reduction of *Aedes*
747 mosquito populations (1); the production of antiviral drugs able to inhibit ZIKV infection in humans
748 (2) and the development of efficient ZIKV vaccines to counteract ZIKV epidemy propagation (3). Red
749 spots represent organs from which ZIKV has been isolated.

750 **Table 1. Promising ZIKV antiviral drugs and vaccines**

751


1-Vector Control
Wolbachia
Larvicides
Spatial repellent
Insect traps
Biotechnology-based sterile insect techniques
Attractive targeted sugar baits
Insecticide-treated materials
Gene drives
Mosquito transmission
3- Vaccines
Inactivated virus
Nucleic acid vaccines
Adenovirus-based vaccines
Vertical transmission
2-Treatments
Sexual transmission
1- Attachment
Suramin
Duramycin
AXL
Other receptors ?
2- Entry
Nanchangmycin
25HC
Z2
3- replication
Novobioctin
Lopinavir-ritonavir
Bromocriptine
Sofosbuvir
Imipramine
Nucleus
Virions
Therapeutic antibodies
4- Morphogenesis

Treatment	Target	system of validation	reference
Duramycin	viral entry	*in vitro*	104-106
Suramin	viral entry	*in vitro*	104-106
Nanchangmycin	viral entry	*in vitro*	107
Z2	viral entry	*in vitro/in vivo*	108
25HC	viral entry	*in vitro/in vivo*	109
Novobioctin	NS2B-NS3	*in silico/in vitro*	110
Lopinavir-ritonavir	NS2B-NS3	*in silico/in vitro*	110
Bromocriptine	NS2B-NS3	*in vitro*	111
Sofosbuvir	NS5 RdRp	*in silico/in vitro*	89,104-106
Emricasan	caspase 3	*in vitro*	115
Imipramine	cholesterol transport	*in vitro*	116
therapeutics antibodies	E	*in vitro/in vivo*	117-119
Vaccine	**target**	**clinal trial**	**reference**
inactivated virus	prM & E	phase I	122.125
nucleic acid vaccine	prM & E	phase I/II	122-129
adenovirus-based vaccine	prM & E	phase I	124,130