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1 ZIKA VIRUS INFECTION: AN UPDATE

2

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8

9 **Abstract**

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

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

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21 **1. Introduction**

22 Zika virus (ZIKV) is an emerging mosquito-borne Flavivirus, belonging to the *Flaviviridae*
23 family. ZIKV contains a positive single-stranded RNA encoding a polyprotein precursor that
24 is processed by cellular and viral proteases to yield its three structural proteins: the capsid (C),
25 the precursor of membrane (prM) and the envelop (E) proteins, as well as seven non-structural
26 protein: NS1 to NS5. ZIKV was discovered following scientific research on the enzootic
27 cycle of the Yellow fever virus and other unknown arboviruses in the Zika forest of Uganda.
28 The first case of human ZIKV infection has been reported in Uganda in 1952 [1] and the virus
29 was later isolated from humans in South East Asia [2]. Viral pathology was associated with a
30 few sporadic cases in tropical Africa and the south of Asia until 2007 when the number of
31 human cases of ZIKV infection unexpectedly increased, initially in Micronesia, then in
32 Pacific Ocean Island to finally reach the South American continent in 2015. Although the
33 reasons for the sudden emergence of the virus are not clear, several hypotheses can be put
34 forward. Many factors may determine the emergence of arboviruses, such as the actual
35 climate change, which affects the distribution of vectors, viral mutation frequency leading to
36 an increasing virulence, as well as changes in anthropological behaviour resulting in increased
37 host-pathogen interactions. ZIKV entry in Brazil from Pacific countries [3,4] has been linked
38 to two major social events, the World cup soccer game and the World Sprint Championships
39 [5] that were held in this country in 2014. At present, three different major lineages of ZIKV,
40 belonging to African, Asian and Brazilian strains, have been characterized according to
41 phylogenetic investigations. While Asian and Brazilian strains show low nucleotidics
42 differences, mutations have been highlighted between Asian strain and African strain.
43 Moreover, *in vitro* and *in vivo* studies revealed differential infection outcome, particularly
44 between the African and Asian/Brazilian strains, suggesting that the African strain seems to
45 be more virulent and to cause more cellular damage than the Asian/Brazilian strain [6–8].

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

48

49 **2. Epidemiology**

50 **2.1 Geographic distribution**

51 Despite its broad geographical distribution, human infections with ZIKV have remained
52 sporadic and limited to small-scale epidemics for decades, until 2007 when a large epidemic
53 was reported on Yap Island with nearly 75% of the population being infected with the virus
54 [9]. Moreover, an outbreak of a syndrome due to ZIKV fever has been reported in French
55 Polynesia, associated with ZIKV-infection-related neurological and an unexpected increase in
56 the incidence of Guillain Barré syndrome by 20 fold [10]. Subsequently, several cases of
57 ZIKV infection in New Caledonia, Easter Island and the Cook Islands have been described
58 indicating a rapid spreading of the virus in the Pacific [3]. The ZIKV epidemic in 2015 has
59 been the start of an international public health emergency when the virus reaches the
60 American continent, with 33 countries reporting autochthonous transmission of ZIKV
61 infection and an increase in the incidence of cases of microcephaly and/or Guillain-Barré
62 syndrome. Moreover, ZIKV infection has also been associated with imported cases, notably in
63 Europe [11], indicating a rapid world-wide spread of the virus. On February 2016, the WHO
64 started to issue monthly reports on the situation of the ZIKV epidemy. On March 2017, the
65 WHO published the last report following the ZIKV outbreaks establishing a total of 61 areas
66 with ongoing virus transmission: 13 countries with evidence of person to person virus
67 transmission: 31 countries reporting neurological disorders associated with ZIKV infection
68 (microcephally, congenital malformations ...) and 23 countries reporting an increased
69 incidence of Guillain-Barré in ZIKV-infected patients (situation report, 10 March 2017,
70 WHO). During this period an estimate of 400 000 to 1.5 million cases of ZIKV infection have
71 been reported in these countries. Since 2017, the number of cases declined, although the virus

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

83

84 **2.2 Transmission and vector control**

85 The main mode of ZIKV transmission occurs via the female mosquito bite during blood
86 feeding, although the human to human transmission route, among which perinatal
87 transmission [14], sexual transmission [15,16] and breast milk feeding [17–19] has been
88 described as well. Many different species of *Aedes* mosquito can account for the transmission
89 of ZIKV, including *Ae.aegypti* and *albopictus* [20,21]. Nevertheless, the competence of this
90 two *Aedes* genus seems to be variable according to geographic sites and the viral strain it has
91 been infected with [22,23]. The *Aedes* genus is dispersed in predominantly tropical areas on
92 three continents (Asia, Africa, America), but shows increased spreading, particularly in North
93 America, Europe and China [24], which highlights the importance to develop efficient tools to
94 control the spread of the vectors. Strategies to contain and reduce the development of
95 mosquito populations have already been established to limit arbovirus propagation (**Figure**
96 **1**). To this aim, the WHO promotes a combination of methods, such as individual and
97 household protection (clothing, air-conditioning, repellents, net ...), procedures to limit

98 backwater and the safe use of insecticides. However, these methods are not sufficient to halt
99 vector-borne disease spread and there is a real need for innovative, efficacious, approaches.
100 Recently, the Worldwide Insecticide resistance Network (WIN) [25] symposium
101 (<https://www.winsingapore2018.com/>) has provided an overview of the alternative methods
102 currently under development for the control of arbovirus vectors [26–28]. Amongst these new
103 tools feature novel larvicides (entomopathogenic Ascomycetes fungi, pyroproxifen,
104 autodissemination), classical and biotechnology-based sterile insect techniques, spatial
105 repellents, insect traps, attractive targeted sugar baits, insecticide-treated materials and gene
106 drives (ex : CRISPR-Cas like system C2c2). Moreover, an emerging method showing
107 impressive results to prevent arbovirus propagation is the use of the bacterial *Wolbachia*
108 genus to either eliminate *Ae.aegypti* mosquito (mosquito population suppression) [29,30] or
109 restrict the arbovirus infection (i.e. mosquito population replacement) [31]. In fact, it has
110 been shown that the endosymbiotic bacterium *Wolbachia*, naturally present in up to 40% of
111 all arthropods [32] is able to block the transmission of many human pathogens in mosquitoes,
112 such as CHIKV, DENV and Plasmodium [33,34], by cytoplasmic incompatibility [35]. More
113 recently, several experimental studies showed that the wMel *Wolbachia* strain is able to also
114 restrict ZIKV infection in *Ae. aegypti* [36–38]. Nevertheless these methods show efficacy
115 limits and ethical issues and need to also integrate a sustainable, effective, community-based,
116 locally adapted vector control management to reduce the burden of *Aedes*-transmitted disease
117 [27].

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

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

126

127 **3. Pathogenicity of ZIKV in humans**

128 **3.1 Symptoms of Zika virus infection**

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

148 [10,39,47,48]. GBS is an auto-immune disease associated with aberrant inflammation that
149 targets peripheral nerves and leading to muscle weakness and paralysis [49]. It is
150 hypothesized that the production of neutralizing antibodies against ZIKV target peripheral
151 nerve glycolipids, thereby inducing injuries of myelin or axonal membranes that leads to
152 inflammatory demyelinating polyneuropathy [49–51]. Further research is needed to better
153 characterized the immune response mechanism involved in the GBS development associated
154 with ZIKV infection.

155

156 **3.2 Zika virus permissiveness and replication**

157 The epidemic of Zika in Brazil has been followed by an exceptional effort from the scientific
158 community to identify the key biological factors associated with the pathogenicity of the virus
159 and to help the health system to contain the epidemic. ZIKV infection studies using patients
160 samples, *in vivo* and *in vitro* models [52,53] allowed to characterized different tissue and cell
161 lines permissive to infection. ZIKV has been detected in placenta, brain, eye, testis, uterus,
162 vagina and body fluids (blood, tears, saliva, semen, cervical mucus and urine) in human [54],
163 but also in liver, spleen, lung, kidney, heart and muscle in various animal models [55–59].
164 Moreover, *in vitro* studies characterized a broad range of cell lines showing differential
165 susceptibility to ZIKV infection, providing new tools to study its pathogenesis [60,61].
166 Interestingly, cell lines derived from the placenta or genital tract are susceptible to infection
167 with ZIKV, but not with other while other flaviviruses, such as DENV [61] which could
168 explain the association of ZIKV with congenital disorders. In addition, ZIKV was found to
169 replicate in human testicular tissue and male germ cells and furthermore persisted in semen
170 [62,63] resulting in a high risk of sexual transmission. More precisely, a recent study
171 investigating ZIKV dissemination in the male reproductive tract proposed a model in which
172 ZIKV infects the testis through the hematogenous route, whereas infection of the epididymis

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

194

195 **3.3 Innate immune response to ZIKV**

196 ZIKV infection induces innate and adaptative responses by infected cells. First, viral RNA
197 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 I (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 gestational 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 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

223 type I interferon in human lung epithelial cells [93,94]. More recently, the FXMRP protein,
224 identified as restricted factor of ZIKV, has been shown to be antagonized by ZIKV sfRNA
225 [95].

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

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

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

249

250 4. Treatment and vaccine perspectives

251 4.1 Antiviral molecules

252 Currently, no vaccines or antiviral treatments have been approved to cure ZIKV infection and
253 patients' care is mainly focused on treating their symptoms. The main challenge is to develop
254 treatment for ZIKV infection that can be administrated to pregnant women. Nevertheless,
255 hundreds of compounds are currently tested *in silico* for their capacity to interfere with the
256 replicative life cycle of ZIKV, but only few have been shown to inhibit ZIKV infection *in*
257 *vitro* and need further testing *in vivo* as well as in clinical trials (**Table 1**) (**Figure 1**) [105–
258 107]. Some molecules, called Direct Acting Agents have the potential to directly act on viral
259 function by inhibiting both early and late stages of replication. Another antiviral strategy is to
260 block viral entry by inhibiting the attachment, endocytosis and fusion of the virus in the cell.
261 Several molecules show encouraging *in vitro* results such as duramycin and suramin that may
262 prevent attachment to host receptors mediating flavivirus entry into the cell [108–110] and
263 nanchangmycin that seems to block clathrine-mediated endocytosis of ZIKV [111].
264 Nevertheless, no *in vivo* studies have been published so far that sustain their efficacy. *In vivo*
265 experiments demonstrated that two inhibitors of ZIKV entry, a synthetic peptide inhibitor, Z2,
266 interfered with vertical transmission of ZIKV in pregnant mice [112] and Cholesterol-25-
267 hydroxylase, a natural interferon stimulated gene, responsible for cholesterol oxydation
268 inhibiting ZIKV uptake, are protective against ZIKV symptoms and microcephaly [113].
269 These molecules need now to be tested in clinical trials. Another strategy consists in the
270 targeting of the NS2B-NS3 viral protease protein which allows the cleavage of the different
271 viral proteins from the polyprotein. Therefore Novobiocin, lopinavir-ritonavir and

272 Bromocriptine, among other molecules, show a significant effect on ZIKV infection and cell
273 death *in vitro* or *in silico*, via the inhibition of protease activity [114,115]. Another targeted
274 viral protein is NS5 RdRp whose polymerase activity is crucial for the replication of the virus.
275 One of the promising molecules is the Sofosbuvir a class B FDA-approved compound that has
276 already been tested to treat Hepatitis C virus infections. Importantly, animal studies have not
277 demonstrated a risk to use it during pregnancy. The efficacy of Sofosbuvir to inhibit ZIKV
278 infection has been demonstrated *in vitro* in neural progenitor cells, brain organoids,
279 neuroepithelial stem cells and *in vivo* in mice [91,116–118]. Other viral protein are targeted to
280 identify new potential drugs, such as NS3 helicase (Ivermectin and Resveratrol) and NS5
281 methyltransferase for which compounds have shown antiviral activity against other
282 flaviviruses and therefore will need to be tested on ZIKV infection [107]. Many other
283 compounds which show a conserved efficacy among flaviviruses could represent a potential
284 target for ZIKV and need to be tested as well. Several other molecules that are currently under
285 development are tested to counteract undesirable cell effects that could be induced by the
286 virus. For example, Emericansan has been shown to reduce cellular apoptosis by inhibiting
287 caspase-3 activity, whereas several nucleoside analogues are able to reduce cytopathic effects
288 and cell death after ZIKV infection [119]. Moreover, some modulators of lipid metabolism
289 such as Imipramine, an FDA approved drug, inhibits ZIKV replication and viral production,
290 in human skin fibroblasts, probably through interference with intracellular cholesterol
291 transport [120]. More recently, Taguwa et al. highlighted the interest to target the cellular
292 protein Hsp70, essential for flavivirus replication for antiviral strategy. They showed that
293 Hsp70 inhibitor, significantly reduced ZIKV replication in cells, associated with reducing
294 pathogenicity in mice and low cytotoxicity effect. Furthermore Hsp70 inhibitors present a low
295 risk of drug resistance makes them new attractive antivirals against ZIKV infection [121].
296 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

322 [64]. In summary, remarkable efforts have been undertaken to develop an effective vaccine
323 against ZIKV infection and a list of potential candidates has been identified of which several
324 have reached phase II in clinical trials.

325 5. Conclusion

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

339

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743

744 LEGENDS

745 **Figure 1. Strategies to control ZIKV infection in humans**

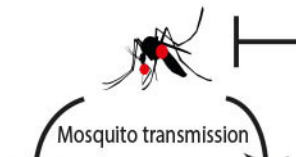
746 Innovative strategies to limit ZIKV transmission through the control and the reduction of *Aedes*
747 mosquito populations (1); the production of antiviral drugs able to inhibit ZIKV infection in humans
748 (2) and the development of efficient ZIKV vaccines to counteract ZIKV epidemy propagation (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

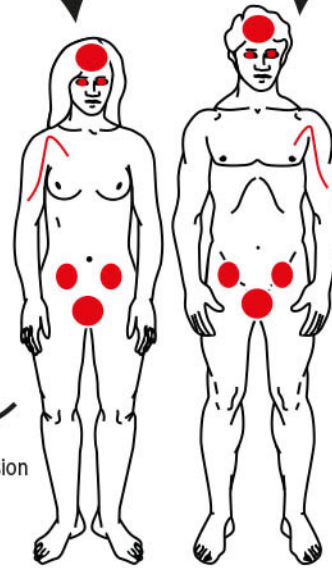


3- Vaccines

- Inactivated virus
- Nucleic acid vaccines
- Adenovirus-based vaccines



Vertical transmission



Sexual transmission

2-Treatments

1- Attachment

- Suramin
- Duramycin
- AXL
- Other receptors ?

2- Entry

- Nanchangmycin
- 25HC
- Z2

3- replication

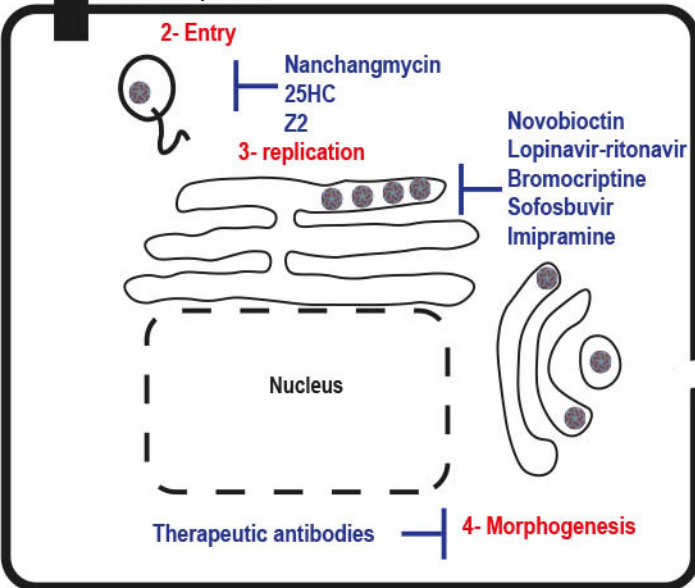
- Novobiocin
- Lopinavir-ritonavir
- Bromocriptine
- Sofosbuvir
- Imipramine

Nucleus

Therapeutic antibodies

4- Morphogenesis

Virions



Treatment	Target	system of validation	reference
Duramycin	viral entry	<i>in vitro</i>	104-106
Suramin	viral entry	<i>in vitro</i>	104-106
Nanchangmycin	viral entry	<i>in vitro</i>	107
Z2	viral entry	<i>in vitro/in vivo</i>	108
25HC	viral entry	<i>in vitro/in vivo</i>	109
Novobiocin	NS2B-NS3	<i>in silico/in vitro</i>	110
Lopinavir-ritonavir	NS2B-NS3	<i>in silico/in vitro</i>	110
Bromocriptine	NS2B-NS3	<i>in vitro</i>	111
Sofosbuvir	NS5 RdRp	<i>in silico/in vitro</i>	89,104-106
Emricasan	caspase 3	<i>in vitro</i>	115
Imipramine	cholesterol transport	<i>in vitro</i>	116
therapeutics antibodies	E	<i>in vitro/in vivo</i>	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