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## Review

## 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 approaches to understand and control ZIKV infection.

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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 nucleotides 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.

## 1. Epidemiology

## 1.1. 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

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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 worldwide spread of the virus. On February 2016, the WHO started to issue monthly reports on the situation of the ZIKV epidemic. 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 (microcephaly, 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 developed 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 epidemic.

## 1.2. Transmission and vector control

The main mode of ZIKV transmission occurs via the female mosquito 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 mosquito populations have already been established to limit arbovirus propagation (Fig. 1). To this aim, the WHO promotes a combination of methods, such as individual and household protection (clothing, air-conditioning, 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]. Amongst 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

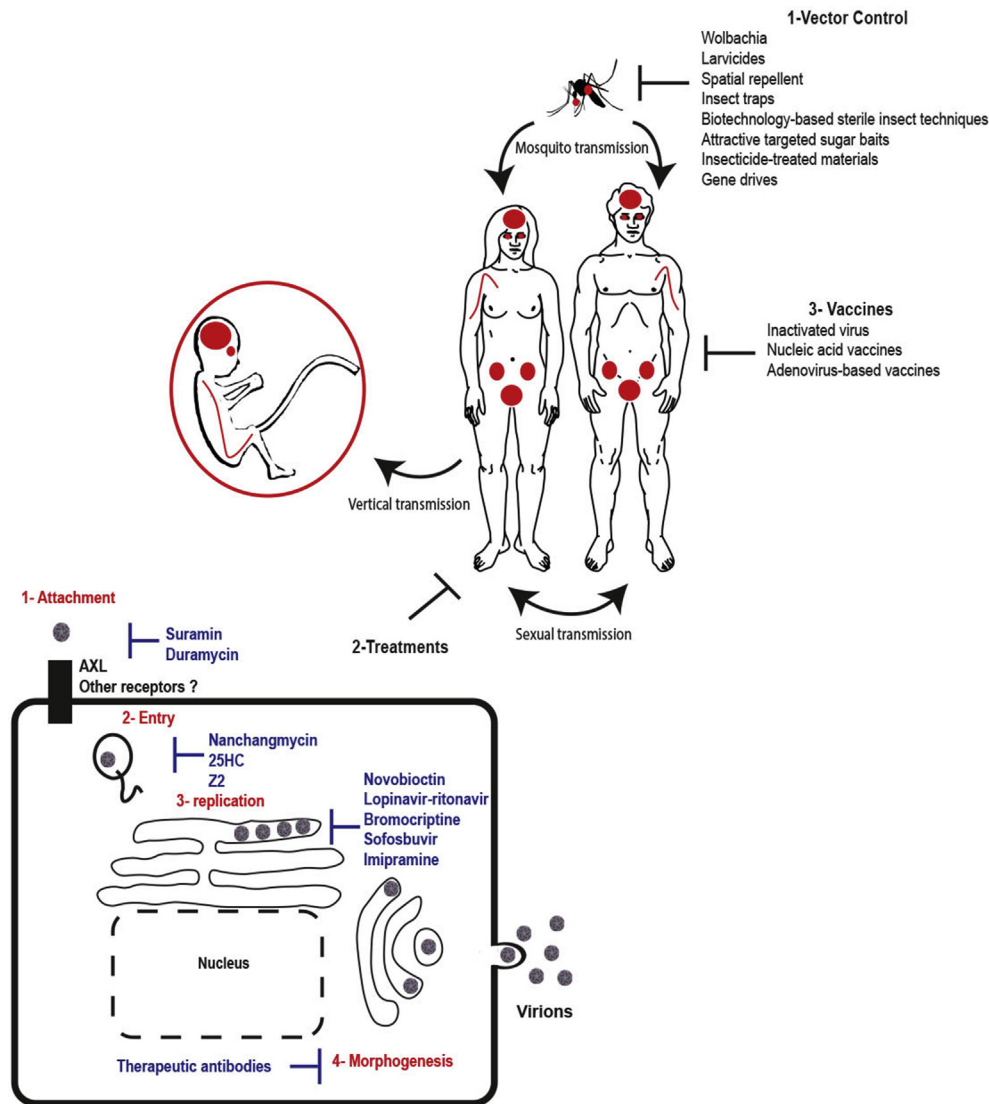
materials and gene drives (ex: CRISPR-Cas like system C2c2). Moreover, an emerging method showing impressive results to prevent arbovirus propagation is the use of the bacterial *Wolbachia* genus to either eliminate *Ae.aegypti* mosquito (mosquito population suppression) [29,30] or restrict the arbovirus infection (i.e. mosquito 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 is 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.

## 2. Pathogenicity of ZIKV in humans

### 2.1. Symptoms of Zika virus infection

The sudden emergence of ZIKV has rapidly become a major public health due to the severe symptoms developed 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-borne 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



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

to better characterized the immune response mechanism involved in the GBS development associated with ZIKV infection.

## 2.2. 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 different 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 these receptors and to identify any additional key entry factors that could represent a potential new therapeutic target.

### 2.3. Innate immune response to ZIKV

ZIKV infection induces innate and adaptive responses by infected cells. First, viral RNA sensors activate TLR receptors, in particularly TLR3 and TLR7, as well as the RIG-I-like receptors MDA5 and RIG-I, leading to the production of type I (IFN- $\beta$ ) and type III (IFN- $\lambda$ ) interferons. The latter will then bind their respective receptors to induce the activation of the JAK/STAT signaling pathway leading to the production of interferon-stimulated genes, such as ISG15, OAS2, MX1, and IFIT, as well as inflammatory chemokines, like CCL5 and CXCL10 [42,79]. Moreover, recent reports have also highlighted the importance of IFITM1 and IFITM3, members of the family of interferon-inducible transmembrane proteins, in the inhibition of ZIKV replication [80,81] and the prevention of ZIKV-induced cell death [81]. The importance of IFN signaling pathway has been highlighted by the development of ZIKV-induced pathology in mice deficient in the expression of type I and II IFN receptors or STAT2 that was not observed in immunocompetent mice [56,58,53,82]. Moreover, IFN- $\lambda$  has been shown to be particularly protective against ZIKV infection in the female reproductive tract [83] and in the maternal decidua and placenta associated with its production at later gestational stages during pregnancy [84,85]. Therefore, differential innate immune response profiles according to cell type and cell differentiation state associated with immunological maturation could be related to variable susceptibility to ZIKV infection [83–85] (Ferraris et al., unpublished data).

ZIKV, as many other viruses, is able to counteract anti-viral immune responses through the interaction of viral proteins with proteins of cellular signalling. In particular, ZIKV is able to impair IFNs signaling pathways [86] by preventing STAT1 phosphorylation [87], inducing JAK1 and STAT2 proteasomal degradation through its interaction with the NS2B-NS3 protease [88] and NS5 [89], respectively. Moreover, the NS2B-NS3 protease complex is also able to target the human STING protein [90] whereas NS1 and NS4B reduce IFN- $\beta$  production by disrupting phospho-TBK1 in human brain cells [91].

ZIKV sRNA, a subgenomic viral RNA, is also involved in viral interference with innate 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 restricted factor of ZIKV, has been shown to be antagonized by ZIKV sRNA [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 Fc $\gamma$  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 observations [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 mechanisms 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.

## 3. Treatment and vaccine perspectives

### 3.1. 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 administered 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) (Fig. 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 clathrin-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 oxidation 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 Novobiocin, 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



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

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
therapeutic antibodies	E	<i>in vitro/in vivo</i>	117–119
Vaccine	target	clinical 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

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, Emricasan 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. Furthermore 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 have shown that neutralizing antibodies targeting ZIKV can prevent viral replication, microcephaly and fetal disease in mice [122–124].

### 3.2. Vaccines

Following the sudden outbreak of ZIKV infection in Brazil, the international health care system has called for the development of candidate vaccines against the virus. One of the important challenge of ZIKV vaccine development is to produce a low cost and safe vaccine to be inoculated in pregnant women, particularly in low-resource countries where viral outbreaks occur. Several mouse and rhesus monkey models have been established in the framework of ZIKV vaccine development [58,53,125,126]. Most models used to study ZIKV vaccine efficacy are knockout mice (129, C57BL/6, Balbc, Swiss...) with deficiencies in IFN type I (IFN- $\alpha$  and - $\beta$ ) or II (IFN- $\gamma$ ) receptors which have the particularity to reproduce several

characteristics of ZIKV pathogenesis, such as fever, neurological disorders on newborn mouse and lethality. Many vaccine subtypes and strategies are under development and vaccine candidates are currently tested for their non-toxicity and efficacy, although only a few are currently in phase I or II clinical trials (Table 1) (Fig. 1) [125,127,128]. Among the more promising vaccines in clinical trials there is a ZIKV-purified inactivated virus (ZPIV) which was found to confer long-term protection in monkeys [129,130] and several nucleic acid vaccines targeting the prM and E proteins that provide complete protection against viral challenges in both mice and non human primates [129–134] as well as an adenovirus-based vaccine targeting the prM and E protein of ZIKV with a complete long-term protection in monkeys [129,135]. Additional vaccines are also being investigated but are still in the process of preclinical development [125,127,128,136]. Also, fundamental research has highlighted a new and very interesting strategy, pertaining to as an miRNA co-targeting approach for a live 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.

### 4. 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 (Fig. 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 circulation 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].

### Conflict of interest

There is no conflict of interest.

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