HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2018 May 22.

Published in final edited form as:

Curr Opin Pediatr. 2017 February ; 29(1): 114–121. doi:10.1097/MOP.0000000000000441.

Potential for Treatment and a Zika Virus Vaccine

Natalie Quanquin[1], **Lulan Wang**[2,3], and **Genhong Cheng**[1,3,*]

[1]Department of Microbiology, Immunology and Molecular Genetics University of California, Los Angeles, CA 90095, USA

[2]Molecular Biology Interdepartmental Program, University of California, Los Angeles, CA 90095, USA

[3]Center of System Medicine, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing; Suzhou Institute of Systems, Suzhou, Jiangsu, China

Abstract

Purpose of Review—Zika virus (ZIKV) has only recently been exposed as a significant public health threat, and much of our limited knowledge of its pathogenesis and triggered immune responses were discovered in only the last few years. There are currently no ZIKV-specific therapeutics or vaccines available. This review seeks to bring the reader up-to-date with the latest developments in finding a way to combat this emerging infectious disease.

Recent findings—Current strategies used for developing ZIKV vaccines or treatments follow proven methods used against other flaviviruses. Unfortunately, ZIKV carries many unique challenges, such as the need to target drugs and vaccines towards immunocompromised populations (pregnant mothers and fetuses), the risk of stimulating harmful immune responses (either autoimmune or antibody-dependent enhancement of infection in those with previous flavivirus exposure), frequently silent infection that may delay treatment and increase risk of transmission to others, and multiple routes of transmission (arthropod vector, sexual, bloodborne, and potentially other body fluids).

Summary—Current medical recommendations are directed towards resolving symptoms and not the actual infection; however, ZIKV treatments and vaccines are in development. Vector control and travel restrictions to endemic areas may remain our only available interventions for some time.

Keywords

Zika virus; vaccine; treatment

*Correspondence to: **Genhong Cheng**, Department of Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, CA 90095, USA. Phone: 310-825-8896, Fax: 310-206-3865, gcheng@mednet.ucla.edu.

The authors confirm that there are no known conflicts of interest associated with this publication.

INTRODUCTION

Although Zika virus (ZIKV) was first discovered in 1947, it garnered little attention until this last decade due to an association with only mild symptoms and less than 20 reported human cases [1*]. However, at some point during its migration from Africa to Asia and subsequently the Pacific Islands, the virus mutated [2*, 3*, 4], changing the manifestations of its infection. Not only has it become more pathogenic, causing Guillain-Barré syndrome (GBS) and congenital malformations, but it has acquired (or perhaps we are simply just now uncovering) alternate routes of transmission not seen in any other mosquito-borne virus [1*, 5**]. These concerning developments have stirred public frenzy towards finding a means of halting the spread of this pandemic, as well as treatments to preserve the health of unborn children at risk of neurologic devastation [6*]. This review will highlight the key advancements made over the last 18 months in creating a ZIKV vaccine and in finding therapeutic options that neutralize or suppress virus replication and therefore counter its damaging effects.

The Foundations for building a ZIKV Vaccine

Fear over the potential global transmission of ZIKV is reminiscent of the public response to the Ebola virus (EBOV) outbreak in West Africa in 2014. However, unlike the high levels of morbidity and mortality associated with hemorrhagic fever viruses such as EBOV, ZIKV infection is symptomatic in only twenty percent of non-congenital cases, few of which even require hospitalization [1*]. As a category A bioterrorism agent, EBOV had the benefit of funding and years of former research by the U.S. defense department, enabling the rapid development and production of a vaccine within a year of the outbreak [7*]. By contrast, there have been very few studies on ZIKV infection prior to its appearance in the Yap Islands of Micronesia in 2007, and in French Polynesia in 2013 when it first became associated with GBS cases [5**, 6*]. It was only after a link between ZIKV maternal infection and adverse congenital outcomes was suspected [5**] that research in this field exploded. President Obama called for increased funding towards ZIKV research, particularly vaccine development, some of which was necessarily re-appropriated from money originally intended to combat EBOV [8].

While we are faced with the challenge of creating a vaccine for a virus whose pathogenesis and host immune response we are only beginning to understand, we have the benefit of previous advancements made towards the study of related flaviviruses [9*]. Members of this genus all have linear, positive-sense nonsegmented RNA genomes inside enveloped capsids. The viruses are predominantly transmitted by either ticks or mosquitos, with a propensity to cause either neurologic or hemorrhagic disease. As the route of transmission is by insect bite to the skin with initial propagation in local keratinocytes, fibroblasts, and immature dendritic cells [10**], many flavivirus vaccines are administered subcutaneously to target those same cells. The first discovered and approved for human use is the 17D strain of yellow fever virus, which accumulated multiple stable and attenuating mutations throughout its genome after serial passaging *in vitro*. Researchers have also used 17D as a backbone to create chimeric vaccine strains for other flaviviruses, including Japanese encephalitis virus (JEV), DENV, West Nile and St. Louis encephalitis viruses, although only the first two have

finished clinical trials and been approved for use in certain countries [11*, 12*, 13]. These recombinant vaccines replace the genes encoding the envelope (E) and pre-membrane (PrM) proteins of 17D with the ones from their respective viruses (the DENV vaccine includes genes for the 4 most common serotypes) [14*]. E is the surface antigen thought to be the predominant target of neutralizing antibody responses to flaviviruses. Other recombinant live DENV vaccines still in clinical trials include one that instead uses an attenuated DENV2 serotype virus as the backbone for the other three serotypes [15], and one comprised of four attenuated DENV strains [16]. An advantage of live attenuated vaccines is that they can induce long-lasting protective immune responses, similar to infection with the original virus. Such a strategy could be used for a ZIKV vaccine, although it is not yet known whether ZIKV infection results in life-long immunity, nor whether distinct serotypes will emerge [3*]. Unfortunately, live vaccines also require more rigorous safety testing, as they can be dangerous to immunocompromised hosts, such as pregnant women and their fetuses (ironically, the population we are most interested in protecting from ZIKV). Despite the promising results of the current DENV vaccine [14*], it still took over two decades of testing to win approval for human use [14*, 16, 17].

Other approaches to flavivirus immunization have also been tested in humans, such as intramuscular injection with purified formalin-inactivated tick-borne encephalitis virus, JEV or DENV, or with recombinant subunits of the DENV E and nonstructural protein 1 (NS1) proteins [11*, 17–19]. The NS1 of flaviviruses contains highly conserved areas within a secreted hexamer form that is involved in immune evasion, and has been targeted in other vaccines [20*]. Although less immunogenic than live viruses, inactivated and subunit vaccines can be tailored to deliver precise amounts of antigen, without the risk of live viruses in a multi-subtype formulation interfering with one another (a potential explanation for why the DENV tetravalent attenuated vaccine is not as effective against certain serotypes) [19]. Simultaneous immunization against all serotypes is important in preventing hemorrhagic complications that can arise in natural DENV infection when memory immune responses to one serotype later aggravate the disease caused by a different serotype [18]. Although this phenomenon is not well understood, antibody-dependent enhancement (ADE) of disease is a potential mechanism [19]. As ZIKV and DENV are closely related, there is a possibility that ZIKV infection in a population previously exposed to DENV or its vaccine may result in exacerbated disease [1*, 21**]. This has actually been proposed as a possible explanation for the GBS seen in 42 ZIKV-infected patients in French Polynesia, when DENV1 and 3 subtypes were also circulating [5**, 22*, 23*]. It is possible that a future ZIKV vaccine will therefore require co-administration with DENV vaccines to prevent ADE complications, however further study on this association is first warranted. It is also possible that the existing immunity to related flaviviruses in endemic regions will impact the effectiveness of a ZIKV vaccine, potentially boosting immunity, but also perhaps interfering with immunization [1*].

ZIKV Vaccines in Development

The WHO conducted an analysis in March 2016 of all publically declared commercial, government and academic-led projects directed at ZIKV interventions, including vaccines (Table 1) [24**]. The list comprises multiple strategies, including vaccines using purified

inactivated virus, nucleic acids, protein subunits, VLPs, and live recombinant attenuated viruses. However, most were still in the preclinical stages of development at the time of that posting, and Phase 1 clinical studies were not expected to begin until the end of 2016 [25*]. One factor potentially complicating vaccine studies is the lack of good animal models of ZIKV infection. Mice and other rodents are often the first subjects used to test vaccine effectiveness, as their immune responses have been well characterized and closely resemble those of humans. However, mice were found not to not show overt signs of ZIKV infection unless they were deficient in genes of the interferon (IFN) signaling pathway [26**, 27**] or tyrosine kinases [28*], which could confound the interpretation of protection studies. One group was able to induce ZIKV-neutralizing antibodies in susceptible mice after immunization with inactivated ZIKV virus or a DNA plasmid encoding the ZIKV prM-E proteins [29**]. To show that E-specific antibody titers also represent key immunologic correlates of protection in non-human primates, they immunized rhesus monkeys with either the purified inactivated vaccine (PIV), the DNA plasmid, or a recombinant rhesus adenovirus serotype 52 virus expressing those prM-E [30**]. While the adenovirus vaccine induced the strongest response, all three protected monkeys from subsequent ZIKV challenge, and the authors expected to begin clinical trials with the PIV in late 2016. Promising results have also been shown by others using the E protein as an adenovirus-delivered or subunit vaccine [32*], and with a ZIKV DNA vaccine [33**] To date, no other groups have published their preliminary findings, however the prevailing opinion among experts is that ZIKV vaccines will take several years to pass safety screening before being available for general distribution [1*, 6*]. While live attenuated vaccines may be the most immunogenic, other platforms will likely prove safer for pregnant women, an important high risk population.

Currently Recommended Medical Interventions

Similar to other flavivirus infections, there are currently no virus-specific therapeutic interventions against ZIKV. After a 3–14 day incubation period, the infection remains asymptomatic in 80 percent of patients, while the remainder have an array of symptoms that can include low grade fever, maculopapular rash, myalgia, arthralgia, and conjunctivitis [6*]. Antihistamines can be used for pruritis, and fever and pain can be alleviated by acetaminophen (aspirin is not recommended in children due to risk of Reye's syndrome, and other nonsteroidal anti-inflammatory drugs can provoke hemorrhagic complications in cases of misdiagnosed DENV infection) [31*]. Symptoms are self-limited and usually resolve in 2–7 days, however a small subgroup of patients can progress to more serious complications, such as GBS. These would require hospitalization for monitoring and possible mechanical ventilation, intravenous immunoglobulin, and electrophoresis [23*]. Pregnant mothers with suspected ZIKV infection are recommended to undergo ZIKV rRT-PCR testing if the symptoms or exposure occurred within the previous 2 weeks (during which ZIKV is detectable in the blood, potentially up to 10 weeks) [34]. IgM testing is to be done first if the infection occurred after this period (IgG may give false positives due to cross-reactivity with other flaviviruses), but results should still be confirmed with PCR, DENV IgM, and/or PRNT [35**]. If there is a possibility of infection, serial fetal ultrasounds are recommended to detect possible congenital malformations, including microcephaly, cerebral calcifications,

and brain atrophy [6*]. Children born with suspected congenital ZIKV syndrome are advised to be tested for ZIKV infection, as well as ophthalmologic exams, hearing screens, and periodic neurodevelopmental assessments [36**].

Preventative measures involve limiting exposure to mosquito vectors through restricted travel to endemic areas, protective clothing, insect repellants, and staying within air-conditioned environments. Blood banks have already begun screening for ZIKV contamination. As the virus has been sexually transmitted from asymptomatic hosts, can be detected in semen up to 6 months after infection, and can replicate within the female vaginal tract, correct and consistent condom use is strongly recommended during oral, vaginal or rectal intercourse with anyone who is living in or has recently traveled to a ZIKV endemic region [1*, 37*].

Potential future ZIKV therapeutics

Although there are currently no treatments available against ZIKV, an improved understanding of its pathophysiology points us to potential drug targets. The viral envelope binds to multiple surface receptors on several host cell types to mediate entry, after which it replicates and induces autophagy to enhance its propagation [10**]. Type I interferons (IFN-I) can block viral replication and cell autophagy [10**, 38*], and mice deficient in the IFN receptor (IFNAR) have been found to be particularly sensitive to ZIKV infection [26**, 27**]. Interferon-induced proteins such as IFITM-1 and -3 have been shown to inhibit ZIKV replication and modulate its cytotoxicity [39*]. In addition, broad-spectrum antivirals such as ranpirnase and ribavirin, and antimalarials with antiviral properties such as chloroquine and amodiaquine, have been tested against flaviviruses and shown limited effectiveness [24**, 31*]. Most of these drugs are listed by the WHO as currently under investigation for ZIKV therapy (Table 2). In addition, 3-Methyladenine (3-MA), an inhibitor of autophagosome formation, was shown *in vitro* to reduce ZIKV copy numbers in infected fibroblasts [10**]. EGCG, a polyphenol found in green tea that has broad antiviral properties, was also found to inhibit ZIKV entry into cultured cells [40]. While these studies are preliminary, they demonstrate that progress is being made towards a cure, which could potentially be attainable long before a ZIKV vaccine.

Passive immunization could be considered for ZIKV treatment or short-term protection during high-risk periods of exposure [24**, 31*]. Polyclonal serum from immune donors was used in EBOV-infected patients during that recent outbreak. Although its effectiveness was unclear, given the present lack of alternatives, convalescent serum could represent a relatively safe option for use during pregnancy to accelerate ZIKV clearance and potentially reduce vertical transmission [24**]. Virus-specific monoclonal antibodies (mAbs) are an improvement to this approach, and have shown promise in animal models against other flaviviruses. Progress has been made in testing mAbs from ZIKV-infected donors and screening them for cross-reactivity with DENV, and promising candidates have already shown protection in mice [41**, 42]. While mAb development uses a more straightforward strategy than vaccines, given ZIKV's propensity to induce adverse antibody reactions such as ADE and GBS, rigorous testing will still be necessary [23*].

Therapies specifically aimed at stopping the teratogenic effects of ZIKV are difficult to study, given that the mechanisms by which the virus crosses the placenta and causes fetal neuronal tissue destruction have only just been elucidated. Experiments in mice have shown that ZIKV infects cortical progenitor cells, inducing apoptosis and autophagy that leads to microcephaly [28**]. A screen of ~6000 compounds for ZIKV inhibition in infected neuronal cells identified emricasan, niclosamide, and PHA-690509 as promising products [43*]. A study examining how ZIKV interacts with host receptor TIm1 for cell entry found that duramycin can block this process, resulting in reduced infection of placental cells *in vitro* [44*]. Although mouse models of ZIKV-induced microcephaly exist for which these drugs could be tested, screening for safety and effectiveness in pregnant women will likely take years. The target populations will most likely be women of child bearing age and their partners who are at risk in endemic areas or who plan to travel to endemic areas.

CONCLUSION

We must rely on lessons learned from related flaviviruses to quickly design new therapeutic and prophylactic ZIKV interventions. Three vaccines have already shown promise in monkeys, and many more are in development. ZIKV antivirals are still in early testing, although monoclonal antibodies have worked for other infections and could be easier to screen and produce. Each endeavor has the added challenge of proving safety in pregnant women, and accounting for possible ZIKV induction of adverse antibody responses leading to GBS and potentially ADE in populations with preexisting flavivirus immunity. Therefore, immunizations and treatments against ZIKV will require prolonged testing.

Acknowledgments

This work was supported by: 1. The NIH R01 AI069120, AI056154 and AI078389 and T32 AI089398-07 grants; 2. The Ministry of Science and Technology of China grants 2015ZX09102023 and 2015CB910501; 3. The National Natural Science Foundation of China grants 81590765 and 31470273; 4. The Institutional Research Fund for Thousand Talents Program at the Chinese Academy of Medical Sciences. 5. The National Key Plan for Scientific Research and Development of China (2016YFD0500300).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

*1. Lazear HM, Diamond MS. Zika Virus: New Clinical Syndromes and Its Emergence in the Western Hemisphere. J Virol. 2016; 90(10):4864–75. This is a comprehensive review of ZIKV's history and new developments. The authors, experts in arboviruses and immunology, also discuss issues in ZIKV vaccine development and adverse antibody responses. [PubMed: 26962217]

*2. Wang L, Valderramos SG, Wu A, et al. From Mosquitos to Humans: Genetic Evolution of Zika Virus. Cell Host Microbe. 2016; 19(5):561–5. This article analyzes the genetic changes ZIKV has accumulated over time and their potential effects on virulence and fitness. [PubMed: 27091703]

*3. Ye Q, Liu ZY, Han JF, Jiang T, et al. Genomic characterization and phylogenetic analysis of Zika virus circulating in the Americas. Infect Genet Evol. 2016; 43:43–9. This study compares the

ZIKV genome with other arboviruses and notes regions of conservation and immunogenicity important for vaccine development. [PubMed: 27156653]

4. Faye O, Freire CC, Iamarino A, et al. Molecular evolution of Zika virus during its emergence in the 20(th) century. PLoS Negl Trop Dis. 2014; 8(1):e2636. [PubMed: 24421913]

**5. World Health Organization. Zika Situation Report Neurological Syndrome and Congenital Anomalies. World Health Organization; 2016. 05 February Report. This was the initial announcement by the WHO acknowleding the association between ZIKV infection and congenital microcephaly. This significantly raised international concern and spurred new ZIKV funding and research.

*6. Focosi D, Maggi F, Pistello M. Zika Virus: Implications for Public Health. Clin Infect Dis. 2016; 63(2):227–33. This review discusses ZIKV transmission risks and current measures for prevention. [PubMed: 27048745]

*7. Hoyt K, Hatchett R. Preparing for the next Zika. Nat Biotechnol. 2016; 34(4):384–6. This commentary discusses the obstacles of rapid vaccine development in response to recent pandemics. [PubMed: 27054989]

8. Gostin LO, Hodge JG Jr. Is the United States Prepared for a Major Zika Virus Outbreak? JAMA. 2016; 315(22):2395–6. [PubMed: 27074330]

*9. Tripp RA, Ross TM. Development of a Zika vaccine. Expert Rev Vaccines. 2016; 15(9):1083–5. This editorial discusses previous successes in flavivirus immunizations, proposing those same avenues for ZIKV. [PubMed: 27212079]

**10. Hamel R, Dejarnac O, Wichit S, et al. Biology of Zika Virus Infection in Human Skin Cells. J Virol. 2015; 89(17):8880–96. This paper reveals breakthrough findings in the mechanisms of ZIKV cellular infection. It also tests the effectiveness of antivirals and autophagy inhibitors on ZIKV infection in cultured cells. [PubMed: 26085147]

*11. Weaver SC, Costa F, Garcia-Blanco MA, et al. Zika virus: History, emergence, biology, and prospects for control. Antiviral Res. 2016; 130:69–80. This lengthy review summarizes the gaps in our preparedness against ZIKV and points out issues of concern for drug and vaccine development. [PubMed: 26996139]

*12. Leibovitch EC, Jacobson S. Vaccinations for Neuroinfectious Disease: A Global Health Priority. Neurotherapeutics. 2016; 13(3):562–70. This article discusses the successes and challenges of vaccination against a large variety of different neurological infections,. [PubMed: 27365085]

13. Monath TP, McCarthy K, Bedford P, et al. Clinical proof of principle for ChimeriVax: recombinant live, attenuated vaccines against flavivirus infections. Vaccine. 2002; 20(7–8):1004–18. [PubMed: 11803060]

*14. Wilder-Smith A, Yoon IK. Edging closer towards the goal of a dengue vaccine. Expert Rev Vaccines. 2016; 15(4):433–5. This editorial objectively outlines the successes and limitiations of the currently approved live attenuated chimeric DENV vaccine. This vaccine is a model being pursued for ZIKV, to which DENV is closely related. [PubMed: 26881780]

15. Osorio JE, Velez ID, Thomson C, et al. Safety and immunogenicity of a recombinant live attenuated tetravalent dengue vaccine (DENVax) in flavivirus-naive healthy adults in Colombia: a randomised, placebo-controlled, phase 1 study. Lancet Infect Dis. 2014; 14(9):830–8. [PubMed: 25087476]

16. Durbin AP, Kirkpatrick BD, Pierce KK, et al. A 12-Month-Interval Dosing Study in Adults Indicates That a Single Dose of the National Institute of Allergy and Infectious Diseases Tetravalent Dengue Vaccine Induces a Robust Neutralizing Antibody Response. J Infect Dis. 2016; 214(6):832–5. [PubMed: 26908742]

17. Schwartz LM, Halloran ME, Durbin AP, Longini IM Jr. The dengue vaccine pipeline: Implications for the future of dengue control. Vaccine. 2015; 33(29):3293–8. [PubMed: 25989449]

18. Coller BA, Clements DE, Bett AJ, et al. The development of recombinant subunit envelope-based vaccines to protect against dengue virus induced disease. Vaccine. 2011; 29(42):7267–75. [PubMed: 21777637]

19. Fernandez S, Thomas SJ, De La Barrera R, et al. An adjuvanted, tetravalent dengue virus purified inactivated vaccine candidate induces long-lasting and protective antibody responses against

dengue challenge in rhesus macaques. Am J Trop Med Hyg. 2015; 92(4):698–708. [PubMed: 25646261]

*20. Rastogi M, Sharma N, Singh SK. Flavivirus NS1: a multifaceted enigmatic viral protein. Virol J. 2016; 13:131. This review describes the roles of NS1 in flavivirus cell invasion and immune evasion, and its importance as a vaccine target. [PubMed: 27473856]

**21. Dejnirattisai W, Supasa P, Wongwiwat W, et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. Nat Immunol. 2016; 17(9):1102–8. This study supports the feared possibility that DENV and ZIKV crossreactive antibodies can lead to enhanced disease. Exposure of ZIKV to human sera with antibodies to DENV was able to augment the infection of cultured cells. [PubMed: 27339099]

*22. Garcia EYE, Nishino E, Millot V, et al. Zika virus infection: global update on epidemiology and potentially associated clinical manifestations. Wkly Epidemiol Rec. 2016; 91(7):73–81. This report by the WHO describes the rise of GBS seen in ZIKV cases around the world. [PubMed: 26897760]

*23. Malone RW, Homan J, Callahan MV, et al. Zika Virus: Medical Countermeasure Development Challenges. PLoS Negl Trop Dis. 2016; 10(3):e0004530. This review descibes interventions in development against ZIKV and related flaviviruses, and their limitations. [PubMed: 26934531]

**24. World Health Organization. Current Zika Product Pipeline. World Health Organization; 2016. 03 March Report. This report by the WHO lists the status of vaccines and drugs in development from multiple projects worldwide. The list was only current as of March 2016, but we have updated it in tables 1 and 2 of this review.

*25. Fauci AS, Morens DM. Zika Virus in the Americas--Yet Another Arbovirus Threat. N Engl J Med. 2016; 374(7):601–4. This review characterizes the ZIKV pandemic compared to those of other arboviruses and discusses the urgency of finding a vaccine. [PubMed: 26761185]

**26. Lazear Helen M, Govero J, Smith Amber M, et al. A Mouse Model of Zika Virus Pathogenesis. Cell Host & Microbe. 2016 This study was the second to describe an animal model for ZIKV infection with contemporary viruses. It used several mutant strains of mice to characterize the importance of IFN signaling.

**27. Aliota MT, Caine EA, Walker EC, et al. Correction: Characterization of Lethal Zika Virus Infection in AG129 Mice. PLoS Negl Trop Dis. 2016; 10(5):e0004750. This breakthrough study was the first to describe an animal model for studying infection with contemporary ZIKV strains. It also characterized the pathology seen in these mice. [PubMed: 27214379]

**28. Cugola FR, Fernandes IR, Russo FB, et al. The Brazilian Zika virus strain causes birth defects in experimental models. Nature. 2016; 534(7606):267–71. This study presented a mouse model for congenital ZIKV infection, and described the pathology seen. In addition, they characterized the ZIKV infection of human brain organoids. [PubMed: 27279226]

**29. Larocca RA, Abbink P, Peron JP, et al. Vaccine protection against Zika virus from Brazil. Nature. 2016; 536(7617):474–8. This is the first publication that details the findings of a ZIKV vaccine in mice. Both a PIV and DNA plasmid vaccine were tested and individually conferred full protection to mice, which was noted to be antibody and not T cell-mediated. [PubMed: 27355570]

**30. Abbink P, Larocca RA, De La Barrera RA, et al. Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys. Science. 2016 This article describes the subsequent immunization of monkeys with the vaccines from [29], as well as an adenovirus-delivered live ZIKV vaccine. All three were individually able to confer full protection in this model, a promising step towards proving efficacy in humans.

*31. Fellner C. Zika Virus: Anatomy of a Global Health Crisis. P T. 2016; 41(4):242–53. This review focuses on the current interventions against ZIKV and the ones in development. [PubMed: 27069344]

**32. Kim E, Erdos G, Huang S, et al. Preventative Vaccines for Zika Virus Outbreak: Preliminary Evaluation. EBioMedicine. 2016 This study shows promising results for an E protein subunit vaccine, either through direct injection or using an adenovirus vector. The vaccines both protected adult mice against challenge, and when given to pregnent female mice, their newborns had less weight loss and neurological morbidity than unvaccinated controls upon ZIKV challenge.

**33. Dowd KA, Ko SY, Morabito KM, et al. Rapid development of a DNA vaccine for Zika virus. Science. 2016; 354(6309):237–240. This article found that injection of mice and nonhuman primates with a DNA vaccine encoding the premembrane and envelope proteins of ZIKV could induce protection. They also defined the levels of neutralizing antibody induction and corresponding reduction in viremia with this vaccine. [PubMed: 27708058]

34. Driggers RW, Ho CY, Korhonen EM, et al. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. N Engl J Med. 2016; 374(22):2142–51. [PubMed: 27028667]

**35. Oduyebo T, Igbinosa I, Petersen EE, et al. Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure - United States, July 2016. MMWR Morb Mortal Wkly Rep. 2016; 65(29):739–44. This report describes the updated CDC guidelines outlining the screening and care of pregnant women at risk of ZIKV infection and transmission to the fetus. [PubMed: 27467820]

**36. Russell K, Oliver SE, Lewis L, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection - United States, August 2016. MMWR Morb Mortal Wkly Rep. 2016; 65(33):870–8. This report by the CDC describes the recommended screening and management of children with suspected congenital ZIKV infection. [PubMed: 27559830]

*37. Brooks JT, Friedman A, Kachur RE, et al. Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus - United States, July 2016. MMWR Morb Mortal Wkly Rep. 2016; 65(29):745–7. This report describes the known cases, risks, and necessary preventative practices for ZIKV sexual transmission. [PubMed: 27466758]

*38. Grant A, Ponia SS, Tripathi S, et al. Zika Virus Targets Human STAT2 to Inhibit Type I Interferon Signaling. Cell Host Microbe. 2016; 19(6):882–90. This article describes how ZIKV NS5 interacts with human STAT2 to interfere with IFN signaling. The fact that it doesn't interact with mouse STAT2 could explain why immune competant mice do not experience ZIKV disease. [PubMed: 27212660]

*39. Savidis G, Perreira JM, Portmann JM, et al. The IFITMs Inhibit Zika Virus Replication. Cell Rep. 2016; 15(11):2323–30. The mutation studies in this article demonstrate the importance of specific interferon-stimulated genes in preventing ZIKV infection, and suggests that enhancing their effects could be a means of protection against ZIKV. [PubMed: 27268505]

40. Carneiro BM, Batista MN, Braga AC, et al. The green tea molecule EGCG inhibits Zika virus entry. Virology. 2016; 496:215–8. [PubMed: 27344138]

**41. Stettler K, Beltramello M, Espinosa DA, et al. Specificity, cross-reactivity, and function of antibodies elicited by Zika virus infection. Science. 2016; 353(6301):823–6. This study characterizes the epitopes that generate cross-reactive antibodies between DENV and ZIKV. One particular antibody was also shown to protect mice against ZIKV infection. [PubMed: 27417494]

*42. Swanstrom JA, Plante JA, Plante KS, et al. Dengue Virus Envelope Dimer Epitope Monoclonal Antibodies Isolated from Dengue Patients Are Protective against Zika Virus. MBio. 2016; 7(4):e01123–16. This study examines cross-protective antibodies between DENV- and ZIKV-infected patients, and identifies mAbs to the envelope dimer epitope I as particularly promising. [PubMed: 27435464]

*43. Xu M, Lee EM, Wen Z, et al. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. Nat Med. 2016 This article indentifies promising ZIKV drugs from a screen of over 6000 compounds for antiviral or neuroprotective properties. These drugs showed efficacy in ZIKV-infected human neural cells.

*44. Tabata T, Petitt M, Puerta-Guardo H, et al. Zika Virus Targets Different Primary Human Placental Cells, Suggesting Two Routes for Vertical Transmission. Cell Host Microbe. 2016; 20(2):155–66. The results of this study suggest that ZIKV can infect the fetus through both a placental and a paraplacental route, based on the cell types permissive to infection in vitro. Duramycin was also shown to prevent ZIKV infection of these cells. [PubMed: 27443522]

Key Points

- Zika virus (ZIKV) is an emerging global public health threat, with no treatments or vaccines currently available.
- Our understanding of ZIKV is founded on limited research from only the last few years, therefore medical intervention strategies currently draw on knowledge of related flavivirus infections.
- The developing fetus is most at risk of ZIKV complications, therefore women of child bearing age and their partners who are at risk by living in endemic areas or by travel, as well as pregnant women must be targeted for treatments and vaccines; however this presents challenges for ensuring both efficacy and safety in this immunocompromised population.
- Gaps in our ZIKV knowledge base, animal model limitations, and concern for adverse immune responses and teratogenic effects, all pose challenges to drug developers, and could prolong the wait before a ZIKV vaccine or treatment becomes available.

Curr Opin Pediatr. Author manuscript; available in PMC 2018 May 22.

Table 1

ZIKV Vaccines in Development

Clinical Trial Phase I

Company	Base	Technologies	Start date	End date*	Status and timelines**	Collaboration
Bharat	India	Inactivated; VLP with prM/E	2017+	2018	Preclinical work completed	
Bio-Manguinhos/Fiocruz	Brazil	Inactivated; YF17D chimeric; VLP; DNA			Preclinical work initiated	Under consideration
Butantan	Brazil	Live dengue recombinant; Inactivated			Preclinical work initiated	US NIH
GeoVax	U.S.	MVA expressing VLP; VLP			Preclinical work initiated	University of Georgia
GlaxoSmithKline	U.K	Self-amplifying mRNA (SAM); Inactivated			Preclinical work initiated	US NIH
Harvard University	U.S.	VSV vectored			Preclinical work initiated	
Hawaii Biotech	U.S.	Recombinant proteins			Preclinical work initiated	
Jenner Institute	U.K	Chimpanzee adenovirus vectored			Preclinical work initiated	
InOvio/GeneOne	U.S./Korea	DNA (GLS-5700)	Jul 2016	Nov 2016	Phase 1: active	Université Laval; UPenn
Institut Pasteur	France	Lentivirus vectored; measles vectored			Preclinical work initiated	Themis
Moderna	U.S	mRNA vaccine			Preclinical work initiated	US DHHS; US BARDA
NewLink	U.S.	Inactivated			Preclinical work initiated	Merck
Novavax	U.S.	E protein nanoparticles			Preclinical work initiated	
PaxVax	U.S	Inactivated			Preclinical work initiated	
Protein Sciences	U.S	Recombinant E protein			Preclinical work initiated	
Replikins	U.S.	Synthetic replilink peptides			Preclinical work initiated	
Sanofi Pasteur	France	Live attenuated (ChimeriVax)	2016+	2017	Preclinical work completed	WRAIR
Sanofi Pasteur	France	Inactiviated	2018+	2019	Preclinical work initiated	WRAIR; US BARDA
SLU vaccine center	U.S.	Inactivated (ZPIV)	Nov 2016	Nov 2017	Preclinical work completed	
Takeda	Japan	Inactivated			Preclinical work initiated	US BARDA
Themis Bioscience	Austria	Measles vectored			Preclinical work initiated	Institut Pasteur
US CDC	U.S.	DNA plasmid expressing VLP; live recombinant adenovirus			Preclinical work initiated	
US NIAID	U.S.	DNA (VRC-ZKADNA085-00-VP)	Jul 2016	Dec 2017	Phase 1; recuiting	Various
US NIAID	U.S.	Live attenuated; Live recombinant VSV			Preclinical work initiated	Various
UTMB/Instituto Butantan	U.S./Brazil	Live attenuated			Preclinical work initiated	

Clinical Trial Phase I

Company	Base	Technologies	Start date	End date*	Status and timelines**	Collaboration
Valneva	France	Inactivated			Preclinical work initiated	

In addition, the following institutions have communicated about their active consideration of the field or have committed planning/discovery stage activities: CureVac, Johnson & Johnson, Oxford University, Pfizer, Profectus Biosciences, Sementis, Sinergium.

+ Estimated start date of clinical trials,

* Estimated Primary Completion Date,

** Preclinical work refers to animal studies, Table modified from[24].

Table 2

Potential ZIKV Therapeutics

Therapeutic	In vivo activity against ZIKV or other flaviviruses	In vitro data (Effective concentration, specificity index, cell type)	Safety/ Use in pregnant women	Availability/ Feasibility
Amodiaquine	unknown	DENV EC90=2.7uM, SI ~10 in BHK-21 cells	unlikely teratogenic; occasional agranulocytosis, neutropenia, hepatotoxicity SAE in long-term use in some CYP2C8 gene variants	common antimalarial; possible benefit against EBOV
Chloroquine	DENV: no decrease in adult viremia	DENV: 0.5 ug/ml in Vero cells. No effect in C6/36 cells	Safe	common antimalarial
Ribavirin	DENV: not effective in NHPs; YF: increased hamster survival	ZIKV: EC50 = 140 ug/ml Vero, SI >55; DENV: EC50 = 20 ug/ml Vero, SI >400; YF: EC50=42ug/ml Vero, SI = 174	Teratogenic	readily available; broad use antiviral
Interferon a	JEV: no effect in infants	JEV: EC50=4.8 IU/ml Vero; ZIKV: EC50= 34 IU/ml Vero		efficacy against hepatitis viruses
BCX4430 (Biocryst, USA)	YF: increased hamster survival	YF: EC50=8.3 ug/ml Vero SI = ~5; DENV: EC50=13ug/ml; WNV:EC50=16ug/ml	Phase I safety completed, no information on teratogenicity	
GS-5734 (Gilead, USA)	EBOV: reduced mortality and pathology in infected NHPs	EBOV: inhibits viral replication in multiple human cell types; ZIKV: under investigation	Phase I safety completed, no information on teratogenicity	
NITD008	DENV2: decreased viremia/ mortality in mice	DENV: EC50 = 3uM; WNV: EC50=5 uM; YF: EC50=3uM	no human safety data	likely long time to human safety data
Monoclonal antibodies	ZIKV: complete protection in mice		likely safe but possible antibody-mediated pathology	cost and other considerations limit widespread use
Emricasan		Protected cultured human neural cells from ZIKV-induced cell death	Phase II for liver protection from HCV showed no SAE; teratogenicity unknown	being studied for protection from hepatitis C virus (HCV) liver pathology
Niclosamide		Inhibited JEV replication in BHK21 cells; inhibited ZIKV replication in human neural cells	Pregnancy category B	common teniacide
PHA-690509		Inhibited ZIKV replication in cultured human neural cells	Teratogenicity unknown	was in phase I trials for cancer therapy
Duramycin		DENV, WNV: reduced infection in A549 and Vero; ZIKV: reduced infection in multiple placental cell types	hemolytic at high concentrations; teratogenicity unknown	aerosolized form in clinical trials for cystic fibrosis
3-Methyladenine (3-MA)		reduced ZIKV viral copies in infected skin fibroblast cell line	Teratogenicity unknown	authophagy inhibitor; used in chemotherapy studies
EGCG		inhibited ZIKV infection of Vero cells	crosses placenta but no teratogenic effects seen in rats	controversial antiviral/ dietary supplement; poor bioavailability

Therapeutic	In vivo activity against ZIKV or other flaviviruses	In vitro data (Effective concentration, specificity index, cell type)	Safety/ Use in pregnant women	Availability/ Feasibility
Ranpirnase	EBOV: decreased viremia/ mortality in mice	inhibited infections of Vero cells with EBOV and undisclosed cells with ZIKV	Was in phase III for mesothelioma, no information on teratogenicity	induces apoptosis in malignant cells; inhibits papillomaviruses

Table modified from [24], with additional entries from [10, 31, 38, 39, 40, 41] abbreviations not used in text: SAE = serious adverse event; NHP = nonhuman primate.