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SUPPLEMENT ARTICLE

Zika Virus Vaccine Development

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The emergence of Zika virus in Brazil and its association with microcephaly and Guillain-Barré syndrome led to accelerated vaccine development efforts. Based on prior flavivirus vaccine development programs, knowledge of flavivirus particle structure, definition of E dimers as the key antigenic target, and deep understanding of neutralizing mechanisms, multiple vaccine strategies have advanced to the stage of clinical evaluation with unprecedented speed. These include nucleic acid (DNA and messenger RNA), whole-inactivated virus, live-attenuated or chimeric virus, and protein or viruslike particle vaccines. Within a year from the declaration by the World Health Organization of Zika virus as a Public Health Emergency of International Concern, multiple vaccine candidates entered clinical trials, now totaling 7 products with an additional 40-plus candidate vaccines in preclinical development. The rapid progress in vaccine development demonstrates the capacity of governments, public health organizations, and the scientific community to respond to pandemic threats when sufficient prior knowledge exists, emergency funding is made available, and interagency cooperation is achieved and serves as a paradigm for preparing for future emerging infectious diseases.

Key words: Zika virus; vaccine development; DNA; mRNA; whole-inactivated; live-attenuated; chimeric.

Zika virus (ZIKV) was first identified in 1947 from a sentinel Rhesus macaque in the Ziika Forest near Entebbe Uganda. It has caused sporadic human outbreaks in Africa and Southeast Asia since that time [1]. However, the large outbreak of ZIKV in the Western hemisphere and association of ZIKV infection in pregnant women with congenital disease including microcephaly thrust the relatively unknown ZIKV into the spotlight and created an imperative for vaccine development [2, 3]. ZIKV first garnered international attention in 2007 when it caused an outbreak in the Yap islands estimated to have infected 75% of the population within 4 months [4]. This was followed by a 2013 outbreak in French Polynesia where approximately 8750 persons were suspected to have been infected with ZIKV, with 383 laboratory-confirmed cases [2]. In 2014 and 2015, a syndrome of fever and rash was recognized by Brazilian physicians, designated *doenca misteriosa* (mystery disease), and diagnosed in mid-2015. During that time, a striking increase in cases of microcephaly and Guillain-Barré syndrome (GBS) was temporally associated with ZIKV infections [3, 5]. The observations in Brazil sparked a retrospective analysis of the French Polynesian outbreak that showed a temporal association of microcephaly and GBS with ZIKV infection consistent with findings in Brazil [2, 4]. No cases of GBS or microcephaly were identified in Yap, but this is probably due to the small population size and relatively low incidence rates for GBS and microcephaly.

ZIKV typically causes an asymptomatic or mild illness in healthy adults that may include headache, fever, rash, nonpurulent conjunctivitis, and joint and muscle pain. The rate of mild symptomatic illness has been reported to be approximately 20% [4, 6]. The primary clinical concern for ZIKV infection is for the fetus when infected in utero which can lead to miscarriages and congenital ZIKV syndrome (CZS). Although an increase in cases of microcephaly has received the most attention, there is evidence that ZIKV infection can cause a range of adverse outcomes during pregnancy consequent to direct infection of the central nervous system causing visual, auditory, sensory, motor, and cognitive defects [3, 7–10]. In addition to CZS, the recent outbreaks of ZIKV have been associated with GBS estimated to occur in approximately 0.24 cases per 1000 infections [11, 12].

CLINICAL DEVELOPMENT STRATEGY

Rationale for ZIKV Vaccine Development

Although models predict that the ZIKV epidemic will wane in Central and South America and the Caribbean over the next few years, ZIKV will likely become endemic following the course of other arboviral diseases that have accompanied the invasive *Aedes aegypti* mosquito to the Western hemisphere. Thus, there will continue to be a risk of ZIKV transmission and danger of CZS if pregnant women are infected. This risk is amplified because, unlike prior flavivirus infections, ZIKV can be sexually transmitted to a pregnant woman through the semen of an infected male partner, even during the early convalescent phase of infection. Therefore, to protect the fetus from ZIKV infection, women of childbearing age would need to be immunized before pregnancy to prevent infection, and their male partners would need to be immunized to reduce the likelihood of transmission to pregnant women. Even in the absence of an active outbreak, the threat of unsafe pregnancies in all women in endemic regions or exposure of travelers to endemic regions merits the effort to achieve a high rate of ZIKV immunity in the general population.

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This is unlike the goal of most licensed vaccines, for which the main objective is to protect the vaccinee from disease.

Although the full spectrum of disease in adults has not been fully defined, and there may ultimately be some direct clinical benefit to vaccinated individuals, without CZS there would be little motivation for vaccine development. This is most like the ongoing rationale for rubella vaccination. Rubella also causes a mild symptomatic illness in adults but is a cause of serious congenital disease when pregnant women are infected, leading to miscarriage, stillbirths, and birth defects. Congenital rubella can cause cataracts, hearing impairment, developmental delays, and congenital heart disease. In 1969, when rubella vaccines were first licensed, vaccine campaigns targeted school-aged children, rather than women of childbearing age owing to concerns about the safety of administering a live-attenuated vaccine to pregnant women. Since that time and the inclusion of the rubella vaccine in the childhood vaccination schedule, congenital rubella syndrome has nearly disappeared from the Western hemisphere, and virtually all cases are imported [13]. Unfortunately, there are still >100 000 cases of congenital rubella syndrome globally even though an effective vaccine has been available for half a century. A similar vaccine approach has been proposed to combat congenital cytomegalovirus infection.

History of Flavivirus Vaccines

ZIKV is an arbovirus from the Flaviviridae family. Vaccine development efforts for ZIKV have been substantially informed by the prior development of efficacious vaccines against related flaiviviruses including yellow fever virus (YFV), tick-borne encephalitis virus (TBEV), Japanese encephalitis virus (JEV) and dengue virus (DENV). Killed or whole-inactivated virus vaccines against TBEV and JEV have been available for various strains since the 1930s [14, 15]. Live-attenuated YFV vaccines have also been available for several decades [16]. These flavivirus vaccines are highly immunogenic, with approximately 85%–90% of vaccinees generating robust immune responses, and in subjects with detectable neutralizing antibody (>1:10 Plaque Reduction Neutralization Titer ($PRNT_{50}$) or Focus Reduction Neutralization Titer ($FRNT_{50}$)) there is protection from severe disease.

DENV vaccines have been much more challenging. DENV comprises 4 distinct serotypes and severe disease requiring hospitalization occurs in approximately 1% of primary infections. When persons are subsequently infected with a heterologous DENV serotype, approximately 2%–3% have severe disease, and there is a concern that this is mediated by antibody-dependent enhancement of infection. This is a phenomenon in which antibodies from the prior exposure are sufficient to bind but not neutralize the secondary virus and facilitate entry into FcR-bearing cells, thereby amplifying viral replication [17]. In addition, the neutralizing correlate of protection is estimated to be 1:100 or greater for DENV, well above the level needed to protect against other flaviviruses. Nevertheless, recent progress has been made in advanced development of vaccines against DENV. The most advanced concepts use live-attenuated chimeric viruses.

The first approved DENV vaccine (Dengavaxia) was approved in 2015 in Mexico and expresses the prM and E proteins of DENV1-4 in the context of a YFV backbone [18, 19]. Other approaches currently in efficacy field trials use the DENV4 or DENV2 backbones to express prM-E sequences from the other serotypes [20–23].

Vaccine Target Populations and Rationale

Ultimately, the goal will be to establish ZIKV immunity in children before they reach childbearing age. This would include vaccinating both girls and boys to provide full immunity to women and their male partners before pregnancy. When a vaccine becomes available, it may be distributed to several successive groups. First, women of childbearing age planning to become pregnant and their male partners with exposure to endemic regions should be immunized. Subsequently, women of childbearing age and their partners without regard to pregnancy plans. When those considered at risk for fetal transmission of ZIKV are immunized, the vaccine could be used in the younger general population.

Although vaccines should be safe for pregnancy, vaccination before pregnancy is important because the risks of CZS and miscarriage are highest in the first trimester. Many women will not know that they are pregnant until late in the first trimester, and vaccine-induced immunity may take several additional weeks to peak, leaving the fetus vulnerable to infection during a critical phase of development. In addition, some vaccines such as live-attenuated vaccines or those requiring potent adjuvants may pose safety risks for pregnant women. Although it is ideal to vaccinate women before they become pregnant, vaccination of the woman and her male partner during pregnancy may be reasonable, depending on the type of vaccine being considered. This may provide some protection against ZIKV infection later in pregnancy, and women who are pregnant often become pregnant again in the next 2 years; vaccination during pregnancy would help protect against CZS in subsequent pregnancies.

VACCINE DESIGN AND IMMUNOLOGICAL GOALS

Vaccine Delivery Approaches

Within 1.5 years of the announcement by the World Health Organization (WHO) declaring ZIKV a Public Health Emergency of International Concern, there are more than 40 vaccine candidates in preclinical development (http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/). Seven vaccine candidates are being evaluated in phase 1 clinical trials in the United States, Puerto Rico, Austria, and India, and 1 candidate has entered phase 2b evaluation in the United States and endemic sites in the Northern and Southern hemispheres (Table 1). There is a substantial amount of preclinical data suggesting induction of effective immunity will be possible. However, a number of questions remain about

the level and type of immunity needed to protect the fetus from viremia and whether reduction or absolute prevention of viremia will be required. This may become clearer as additional data from natural history studies accumulate.

Completely preventing viremia would be an ambitious goal for vaccine efficacy and may be dependent on the sensitivity of the measurement tools. Prevention of viremia as measured by quantitative polymerase chain reaction assays depends on the assay's limit of detection, which is currently in the range of about 0.05 plaque-forming units/mL equivalents or 50–100 genome copies/mL. Measuring postchallenge anamnestic serological responses may be a more sensitive test of whether a low level of replication occurred.

The overall importance of $CD8^+$ T cells in rapid clearance of viremia and protection of the fetus is not well understood at this point. There is evidence from animal models that such cells may contribute to both viral clearance and pathology in DENV and WNV infection [24, 25]. For ZIKV the role of $CD8^+$ T cells in human infection is unknown. However, mouse models suggest a protective role for T cells in ZIKV infection, including reduction of viral loads, weight loss, mortality and ZIKV-induced weight loss in wild-type and immunodeficient mice [26, 27]. Interestingly, cross-reactive DENV-specific $CD8^+$ T cells were found to be protective against ZIKV in mouse models [28]. If it turns out that $CD8^+$ T cells are important for vaccine effectiveness and protection of the fetus, gene-based nucleic acid and vector approaches and live-attenuated virus or chimeric viruses may have advantages because of their capacity to elicit $CD8^+$ T-cell responses, whereas whole-inactivated and protein-based approaches would be very limited in this regard. Most current approaches for flavivirus vaccines are based on the induction of neutralizing antibody, which has been shown to be the major correlate of protection [29–31].

Durability of effective vaccine-induced antibody-mediated immunity will be a major factor in matching the vaccine approach to the appropriate target population. For example, if vaccine-induced immunity is relatively short-lived, that vaccine approach may be useful for only outbreak intervention, travelers, women and their partners contemplating pregnancy, or postpartum immunization of women and their partners based on the significant probability of another pregnancy within a few years. Approaches meant for adolescents and even more so for childhood vaccination will need to have long-lived protection to minimize the need for repeated booster immunizations. Gene-based antigen delivery approaches, particularly nucleic acid approaches such as DNA or messenger RNA (mRNA) can be rapidly developed and manufactured, and they have preexisting safety and toxicology data to support expedited regulatory approval.

Although the durability and potency of these approaches need more study, nucleic acid approaches provide the potential for testing multiple design variants and possibility of obtaining efficacy data before a new outbreak wanes [32, 33]. Delivery of vaccine antigens by gene-based vectors also provides flexibility for modifying antigen designs and is more likely to induce primary immunity with a single dose than nucleic acid delivery. However, gene-based vectors generally have a longer manufacturing and regulatory process and more issues to consider involving safety and preexisting immunity. Development of whole-inactivated and live-attenuated virus vaccines is a slower process owing to the high level of process development needed to produce large amounts of virus and the increased safety analysis inherent in a process involving live virus. Production of recombinant protein subunit vaccines requires significant process development, and though such vaccines would be likely to have a favorable safety profile, the durability of primary immune responses is uncertain. The likely need for adjuvants in the formulation of protein-based subunit vaccines will add safety concerns and additional time to the development process.

Antigen Design

Preclinical ZIKV vaccine studies have shown that protection was correlated with serum neutralizing activity, and passive antibody transfer studies have demonstrated protection in mice and nonhuman primates (NHPs) against ZIKV challenge, supporting the role of neutralizing antibody in protection against ZIKV [34–36]. Therefore, most efforts are focused on producing vaccine antigens that induce effective antibody responses. Fortunately, unlike DENV, all ZIKV strains seem to be a single serotype, including African strains from the 1950s, suggesting that a single vaccine antigen should generate protective cross-reactive antibodies against infection by all strains of ZIKV [37]. E is the envelope protein and the target of neutralizing antibodies. It exists as an antiparallel dimer on the virion surface. It is supported by the M (matrix) protein, which begins as a precursor protein (prM) and undergoes furin cleavage during assembly and maturation, losing the amino terminal fragment (pr) [38]. Therefore, most vaccines have focused on the display of E in the context of a whole virus or a subviral particle through the expression of prM and E.

The conformation of the E antigen will determine whether quaternary epitopes are preserved. Antibodies targeting quaternary epitopes are thought to be important for neutralizing mature virus particles where pr has been fully cleaved and the E dimers are in the down position [38–41]. Maintaining the integrity of the virus particle may also be important for avoiding responses to the fusion loop that are more likely to be cross-reactive with other flaviviruses and generally have poor seroprotective activity [42–44]. Whole virus vaccines have the potential advantages of maintaining a more authentic virus particle conformation, which could induce high-quality neutralizing antibodies compared with subunit approaches, as long as the inactivation process does not destroy epitopes. Viruslike particles vaccines, including those generated by gene-based vaccines, are smaller

than whole virus and adopt a T = 1 rather than a T = 3 structural organization, which may affect the display of E protein on the surface [45]. Whole virus vaccines also have a larger antigenic content beyond prM and E, including capsid and nonstructural proteins. This may improve the breadth of T-cell responses, but it will also induce antibodies without functional neutralizing activity, which may compete or interfere with more protective antibodies. Because the basis of the GBS associated with about 1 in 5000 ZIKV infections is not defined, limiting the antigen content to key neutralizing targets may have advantages.

ZIKV CANDIDATE VACCINES

Nucleic Acid Vaccines

The most rapid approach to vaccine development for ZIKV has been nucleic acid platforms that use plasmid DNA or mRNA encoding prM-E genes from recent or consensus ZIKV strains. This strategy is based on the idea that expression of prM-E proteins will lead to the production of subviral particles from transduced cells. Three DNA plasmid vaccines against ZIKV are currently in phase 1 clinical trials. The first ZIKV vaccine to enter clinical evaluation was a DNA vaccine developed by Inovio Pharmaceuticals. This DNA vaccine (GLS-5700) is based on a consensus prM-E sequence derived from African and more recent Asian/American strains and was shown to be immunogenic in mice and NHP studies when administered by electroporation. Passive transfer of vaccine-induced serum into interferon (IFN) α/β receptor knockout mice ($IFNAR^{-/-}$) (A129) demonstrated that antibody levels correlated with protection, although both humoral and cellular immune responses were generated [34]. GLS-5700 is currently being evaluated in 2 phase 1 clinical trials. One in flavivirus-naive individuals (NCT02809443 started 26 July 2016) and the other in flavivirus-immune subjects (NCT02887482 began in August 2016).

The Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, is currently evaluating 2 DNA vaccine candidates, VRC5288 and VRC5283. The first clinical candidate, VRC5288, expresses a codon-modified ZIKV/JEV chimeric prM-E based on the sequence of French Polynesian and early Brazilian ZIKV isolates. It was designed with the final 98 amino acids of the E protein (comprising the transmembrane and stem domains) from JEV swapped with the corresponding regions from ZIKV E protein. This candidate is being evaluated in 80 subjects at 3 sites within the United States (NCT 02840487; begun 2 August 2016)). The VRC is also evaluating a second candidate plasmid vaccine, VRC5283, which expresses the full ZIKV prM-E sequence in a 45-subject phase 1 clinical trial that began in the United States in December 2016 (NCT02996461). Enrollment has been completed in both phase 1 studies, and both trials are in follow up.

In March 2017, the second vaccine candidate, VRC5283, has advanced into a phase 2 clinical trial (NCT03110770). The first part of the phase 2 clinical trial (part A) will further assess the safety and immunogenicity of VRC5283 in 90 subjects at 2 sites in the United States and will evaluate dose and delivery approaches. The second part of the phase 2 clinical trail (part B) began in July 2017 in sites selected by modeling the likely progression of the ZIKV epidemic in the Western hemisphere. Both of these vaccines were immunogenic in mice and NHPs, and 2 doses of DNA vaccine prevented viremia in 17 of 18 rhesus macaques after ZIKV challenge [33]. Protection was correlated with serum neutralizing activity. A single dose of the VRC5288 plasmid did not prevent viremia, but viremia was significantly reduced compared with unvaccinated controls [33].

Recent advances in the use of modified nucleotides, amplicons, and improved formulations has improved the stability, delivery, and immunogenicity of mRNA vaccines, making them appealing platforms for vaccine development against emerging infectious diseases. Unlike DNA, which needs to reach the nucleus to initiate transcription, mRNA needs only to gain access to the cytoplasm, where it can be directly translated.

Two distinct mRNA vaccine approaches have been applied to ZIKV. The first is based on the use of modified nucleotides and codon optimization that increases stability and diminishes detection by intracellular innate immune sensors, resulting in higher magnitude and duration of vaccine antigen production [46–48]. Pardi et al used such an approach coupled with intradermal delivery of mRNA formulated in lipid nanoparticles and demonstrated that immunocompetent mice and NHPs could be protected from ZIKV viremia with a single dose of mRNA encoding prM-E from a French Polynesian strain of ZIKV [49]. Moderna Therapeutics has taken a similar ZIKV vaccine (mRNA-1325) based on the Micronesia 2007 ZIKV strain encapsulated in a lipid nanoparticle into a phase 1/2 clinical trial (NTC03014089). Intramuscular administration of 2 doses of mRNA-1325 vaccine was efficacious in immunocompetent mice treated with IFN-α/β antibody before ZIKV challenge and immunodeficient mice lacking the IFN-α/β and IFN-γ receptors (AG129) [50]. A second mRNA vaccine approach is self-amplifying mRNA, based on alphavirus amplicons and initially developed by Novartis [45]. This technology differs from the modified mRNA approach because it rapidly produces a large amount of transcripts and vaccine antigen and significant activation of innate sensors, and is thereby "self-adjuvanted." GlaxoSmithKline is developing a ZIKV vaccine in collaboration with the VRC, using GSK's self-amplifying mRNA technology platform. Preclinical evaluation of 2 lead mRNA candidates is ongoing.

Whole-Inactivated Virus Vaccines

Whole inactivated virus vaccines have been effectively used for other flaviviruses including YFV, JEV, and TBEV [51]. In this tradition, whole-inactivated ZIKV vaccines are being pursued by several groups. Bharat Biotechnologies, based in Hyderabad India, initiated development of a whole-inactivated ZIKV vaccine

after the outbreak in French Polynesia in 2013, well before ZIKV reached Brazil. That product, which protected 100% of vaccinated immunodeficient AG129 (IFNα/β receptor and IFN-γ receptor knockout) after 2 doses, is now in phase 1 clinical evaluation [52].

ZIKV purified inactivated virus (ZPIV) is also under development by the Walter Reed Army Institute of Research based on its previous experience with a JEV vaccine [53]. ZPIV, which is inactivated by formalin treatment, elicited robust neutralizing antibody responses and protected against ZIKV infection in rhesus macaques and immunocompetent mice [35, 36]. The safety and immunogenicity of ZPIV is currently being assessed in 4 phase 1 clinical trials in flavivirus-naive and flavivirus-immune populations (NTC02963909 and NCT03008122) and in collaboration with St Louis University (NCT02952833) and Beth Israel Deaconess Medical Center (NCT02937233). Biomedical Advanced Research and Development Authority (BARDA) has also supported Takeda Pharmaceutical and Sanofi Pasteur to develop whole-inactivated virus ZIKV vaccines.

Live-Attenuated and Chimeric Viral Vaccines

The 17D YF vaccine has demonstrated live-attenuated vaccines to be a promising approach for generating long-lasting flavivirus immunity. Although the YFV 17D vaccine was attenuated by passage through mouse and chicken tissue, the approaches being developed for ZIKV vaccination use more deliberate methods. One live-attenuated vaccine approach uses site-directed mutagenesis of the 3'UTR to attenuate a Cambodian strain (FSS13025) of ZIKV. This attenuated vaccine induced sterilizing protection in A129 mice (IFN-α/β receptor knockout) and NHPs [54] and prevented fetal transmission and testis damage in IFN-alpha/beta receptor blocking antibody treated C57BL/6 mice [55]. Codagenix has also announced generation of a ZIKV vaccine based on codon deoptimization technology. Chimeric vaccines are another version of live-attenuated vaccines but use partial sequences from other flaviviruses. Building on a 4-component DENV vaccine currently in phase 3 advanced clinical evaluation [21], the Laboratory of Infectious Diseases of the NIAID is developing a chimeric ZIKV vaccine that expresses the ZIKV prM-E genes in the context of an attenuated DENV2 backbone, to be used in conjunction with the tetravalent chimeric DENV product built on the DENV4 backbone.

Other Vector-Based and Subunit Vaccines

Another vaccine approach has involved vector-based approaches that express ZIKV genes in the context of replication-competent or replication-defective viral vectors. Themis Biosciences produced a recombinant measles vector that expresses the prM-E proteins of ZIKV virus and started phase 1 clinical evaluation (NCT02996890) in April 2017. Preclinicial studies of a rhesus adenovirus serotype 52 vaccine that expresses the M and E proteins from ZIKV showed protection from 2 strains of ZIKV with only a single dose [36]. Additional approaches using an MVA vector expressing NS1 (Geovax) and a VSV vector expressing prM-E (Harvard) are also in development, but studies have not been published to date.

Another approach to ZIKV vaccination uses an in vitro produced viruslike particle or protein subunits. Similar to nucleic acid– or gene-based vector vaccines, viruslike particle approaches take advantage of the fact that the prM-E proteins are sufficient to produce viruslike particles. However, these subviral particles are generated in vitro and purified for use as a protein-based vaccine. This strategy is being pursued by a number of companies including VBI Vaccines, NewLinksGenetics, and PaxVax. Because the E dimer has been defined as the antigenic target for neutralizing antibodies, there are also some efforts to use soluble E proteins as vaccine antigens. Peptide vaccines, designed to induce antibodies to specific epitopes, are also being explored in preclinical studies.

FUTURE FLAVIVIRUS THREATS AND CONSIDERATIONS FOR ADVANCED PREPARATION

Vaccine development for ZIKV virus was built on decades of research and vaccine development for JEV, TBEV, YFV and DENV. Knowledge of the atomic level structure of flavivirus E dimers and overall virion structure combined with understanding mechanisms of neutralization and other aspects of flavivirus biology and immunology was leveraged to rapidly develop ZIKV vaccines and advance candidate vaccines into efficacy evaluation with unprecedented speed. Importantly, the US Department of Health and Human Services made emergency funding available for vaccine development in August 2016 by diverting $81 million from other National Institutes of Health and BARDA projects. Congress eventually supplemented this funding by an additional $1.1 billion in September 2016. Therefore, the response did require delay of some other programs, and despite the funding efforts, the incidence of new ZIKV infections is waning in many areas and may complicate the evaluation of vaccine efficacy in field trials. Alternative paths to licensure may therefore be needed. In the future, it would be preferable to have preassigned budgets available for emergency responses.

The ZIKV vaccine development effort was in part a response to the World Health Organization declaration of a Public Health Emergency of International Concern for the second time in 2 years. The apparent acceleration of emerging infections with pandemic potential suggests that we should be more proactive in preparing for future threats by expanding work on basic aspects of viral structure, immunology, and pathogenesis relevant to the production of vaccines and therapeutics. The technologies are available to produce a catalogue of information and reagents for flaviviruses and other viruses with potential to infect humans before the next outbreak.

Table 1. ZIKV Vaccine Candidates in Clinical Development

Vaccine Strategy	Platform	Sponsor	Candidate Name	Immunogen	Phase 1	Phase 2
Nucleic acid	DNA	GeneOne Life Sciences	GLS-5700	prME	June 2016: NCT0280944;3 August 2016: NCT02887482	
		VRC/NIAID	VRC5288	prME	August 2016: NCT02840487	
		VRC/NIAID	VRC5283	prME	December 2016: NCT02996461	2a—March 2017; 2b—July 2017: NCT03110770
	mRNA	Moderna Therapeutics	mRNA-1325	prME	Phase 1/2—December 2016: NCT03014089	
Whole inactivated	Formalin inactivated	WRAIR/BIDMC	ZPIV	Whole virus	November 2016: NCT02963909; October 2016: NCT0295283; October 2016: NCT02937233; February 2017: NCT03008122	
		Bharat Biotech International	Purified inactivated ZIKV	Whole virus	May 2017	
Vector based	Measles virus vector	Themis Bioscience	MV-Zika	prME	April 2017: NCT02996890	

Abbreviations: BIDMC, Beth Israel Deaconess Medical Center; NIAID, National Institute of Allergy and Infectious Diseases; VRC, Vaccine Research Center; WRAIR, Walter Reed Army Institute of Research; ZIKV, Zika virus; ZPIV, ZIKV purified inactivated virus.

Notes

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