HUMAN VACCINES & IMMUNOTHERAPEUTICS
2021, VOL. 17, NO. 3, 904–908
https://doi.org/10.1080/21645515.2020.1796428

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COMMENTARY

Zika virus—an update on the current efforts for vaccine development

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ABSTRACT

In 2015, the world witnessed the resurgence and global spread of Zika virus (ZIKV). This arbovirus infection is associated with Guillain-Barré syndrome in adults and with devastating congenital malformations during pregnancy. Despite scientific efforts, the development of a vaccine capable of inducing long-term protection has been challenging. Without a safe and efficacious licensed vaccine, control of virus transmission is based on vector control, but this strategy has been shown to be inefficient. An effective and protective vaccine relies on several requirements, which include: (i) induction of specific immune response against immunodominant antigens; (ii) selection of adjuvant-antigen formulation; and (iii) assessment of safety, effectiveness, and long-term protection. In this commentary, we provide a brief overview about the current efforts for the development of an efficacious ZIKV vaccine, covering the most important preclinical trials up to the formulations that are now being evaluated in clinical trials.

ARTICLE HISTORY
Received 23 June 2020
Accepted 9 July 2020

KEYWORDS
Zika virus; vaccine; clinical trials

Zika virus (ZIKV) is a mosquito-borne flavivirus first isolated from a *rhesus* macaque in 1947.[1] Before 2015, ZIKV infection was reported in a few countries and associated mostly with a mild disease. Thenceforth, ZIKV outbreaks spread across more than 80 countries, and the disease has been associated with severe complications.[2] Although ZIKV shares many structural features with other flavivirus such as dengue virus (DENV), its ability to cause congenital malformations during pregnancy[3], and rare neurological disorders in adults, such as Guillain-Barré syndrome,[4] makes this virus uniquely dreadful. Given the effectiveness of some vaccines against flaviviruses like yellow fever virus (YFV) and Japanese encephalitis virus (JEV), the pursuit of an effective vaccine candidate against ZIKV is attainable and has been the subject of intensive research. Currently, there are several ongoing clinical trials (Phases I and II) to develop a vaccine to prevent ZIKV infection (Table 1) using different strategies (Figure 1).

DNA-based vaccine formulations are one of the most promising candidates tested in humans due to their ability to induce humoral and cellular immune responses, low cost, high stability, and safety profile,[5] without infection or replication capacity. Since ZIKV outbreaks, researchers have evaluated the immunogenicity and protection profiles of different DNA-based vaccines encoding E and prM-E proteins.[6] In preclinical studies, constructs encoding the full-length *prM-E* sequence showed to be the most promising candidates to induce neutralizing antibodies, T-cell immunity, and protection in mice[6,7] and nonhuman primates.[8] Passive transfer of antibodies induced by DNA vaccines provided sterile protection in a lethal challenge model.[9] Recently, we showed that a recombinant protein and a plasmid DNA based on the ZIKV E protein induced a robust humoral and polyfunctional $CD4^+$ T cell response.[10] In order to increase the immunogenicity of DNA vaccines, several strategies have been described,[11] such as the use of *in vivo* electroporation, combination with adjuvants, and heterologous prime-boost immunization.[12] Inovio Pharmaceuticals developed the first ZIKV DNA vaccine candidate (GLS-5700) tested in clinical trials (NCT02809443 and NCT02887482). GLS-5700 was administered via intradermal injection followed by electroporation, and 62% of the volunteers developed neutralizing antibodies against ZIKV after receiving three doses of the vaccine candidate.[13]

Other two DNA vaccines are being tested in humans: VRC5283 and VRC5288, developed by the Vaccine Research Center[14] of the National Institute of Allergy and Infectious Diseases (NIAID). Unlike GLS-5700, modifications have been made to improve protein-expression and subviral particle release from transduced cells. To create the VRC5283 vaccine, the ZIKV *prM* signal sequence was replaced with the analogous region of JEV. In VRC5288, besides the modification in the signal sequence, the carboxyterminal stem-anchor region of ZIKV protein E was also exchanged to the equivalent JEV sequence.[15] Both vaccine-formulations elicited high titers of neutralizing antibodies that protected mice and nonhuman primates after challenge.[15] For this reason, both DNA vaccines were selected for immunogenicity and safety evaluation in humans (NCT02840487 and NCT02996461). Recent functional analysis revealed that despite the capacity to induce neutralizing antibodies, the ability to bind to the mature virion better predicts vaccine-induced protection and should be considered to assay new candidates.[16] VRC5283 was shown to be safe, well-tolerated and induced T-cell immune response and neutralizing antibodies,[14] moving forward to a Phase II clinical trial (NCT03110770).

Another promising, low-cost, and safe vaccine approach is based on non-replicating mRNA. The main advantage is that

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Table 1. ZIKV-vaccine candidates in clinical trial.

Vaccine strategy	Candidate name	Antigen	Sponsor	Status	Phase I	Phase II	References
DNA	GLS-5700	*prM-E*	GeneOne Life Science, Inc./ Inovio Pharmaceuticals vio	Completed	NCT02809443	NCT03110770	13
	VRC5283		NIAID/VRC	Completed	NCT02996461		14,15
	VRC5288			Completed	NCT02840487		14
mRNA	mRNA-1325	*prM-E*	Moderna Therapeutics	Completed	NCT03014089		21
	mRNA-1893			Active, not recruiting	NCT04064905		23
				Completed or	NCT02963909		
	ZPIV		NIAID/WRAIR/BIDMC	Active, not recruiting*	NCT02952833		6,8,24
					NCT02937233		
					NCT03008122		
Whole inactivated	PIZV (TAK-426)	Virus	Takeda Pharmaceuticals	Active, not recruiting	NCT03343626		26
	BBV121		Bharat Biotech International	Completed	CTRI/2017/05/008539		27
	VLA1601		Valneva Austria GmbH/Emergent Biosolutions	Completed	NCT03425149		-
Live attenuated	rZIKV/D4130-713	Virus	NIAID	Completed	NCT03611946		30,31
	MV-ZIKA		Themis Bioscience GmbH	Completed	NCT02996890		38
Viral vectored	MV-ZIKA RSP			Recruiting	NCT04033068		38
	ChAdOx1 Zika	*prM-E*	University of Oxford	Recruiting	NCT04015648		34

*Only NCT03008122 is active, not recruiting.

the mRNA vaccine can be directly translated in the cytoplasm upon cell transfection, contrary to a DNA vaccine which needs to enter the nucleus to start transcription.[17] In recent years, lipid-encapsulated or naked forms of sequence-optimized mRNA candidates elicit potent immunity against several pathogens and cancer.[18–21] A single dose of lipid-nanoparticle-encapsulated mRNA encoding *prM- E*-induced potent neutralizing antibodies and protected mice and nonhuman primates from viremia.[21] Similarly, other encapsulated mRNA vaccine-conferred neutralizing antibodies and consequently sterilizing immunity in mice. This engineered vaccine encodes mutations into the conserved fusion-loop epitope in the *E* sequence that reduces the production of antibodies enhancing DENV infection.[22] Two mRNA vaccine candidates for ZIKV developed by Moderna Therapeutics are being tested in Phase I clinical trials, named mRNA-1325 (NCT03014089) and mRNA-1893 (NCT04064905). In preclinical trials, mRNA-1893 protected against ZIKV transmission during pregnancy in mice.[23]

Efforts to develop a whole inactivated virus vaccine against the ZIKV vaccine began immediately after the 2015 outbreak. This platform has been successfully developed against other flaviviruses such as Tick-borne encephalitis virus (TBEV) and JEV. The first preclinical studies using a purified inactivated ZIKV vaccine (named as ZPIV) were described by Larocca et al.[6] A single dose of formalin-inactivated ZIKV vaccine, adjuvanted with aluminum hydroxide, protected mice from different ZIKV challenge strains (Brazil and Puerto Rico ZIKV isolates).[6] In addition, an extra dose of the ZPIV vaccine was also effective in rhesus macaques,[8] and afforded robust protection even after 1 year of vaccination.[24] The safety and immunogenicity evaluation of this vaccine candidate conducted by NIAID/WRAIR/BIDMC was confirmed in three clinical trials (NCT02963909, NCT02952833 and NCT02937233). Fourth trial in an endemic area is still ongoing (NCT03008122).

In a collaboration between WRAIR and Sanofi Pasteur, the vaccine was optimized using Pasteur's experience in flavivirus vaccine development. A modified and optimized ZIKV-vaccine (ZPIV-SP) showed improved immunogenicity compared with the first-generation vaccine in mice,[25] supporting advancement of the ZPIV-SP candidate toward clinical development. Other formalin-inactivated ZIKV candidates were developed by Takeda Pharmaceuticals, Valneva Austria GmbH/Emergent BioSolutions and Bharat Biotech, Hyderabad (NCT03343626, NCT03425149, and CTRI/2017/05/008539, respectively). In preclinical trials, TAK-426 (alum-adjuvanted PIZV) by Takeda Pharmaceuticals induced high levels of neutralizing antibodies that were able to confer passive protection to naive mice against lethal challenge.[26] Similarly, an alum-adjuvanted inactivated-vaccine (BBV121. Bharat Biotech) conferred protection against Asian and African ZIKV strains in immunodeficient mice.[27]

First-generation live-attenuated vaccines (LAV) against other flavivirus diseases, like YFV and JEV, have also been evaluated as potential ZIKV-vaccine candidates. There are few ways to reduce the virulence of the pathogen for vaccine production – differently from that used for the 17D YF vaccine, genetic manipulation of the viral genome has been used for ZIKV attenuation. Strategies are based on the removal of specific carbohydrate

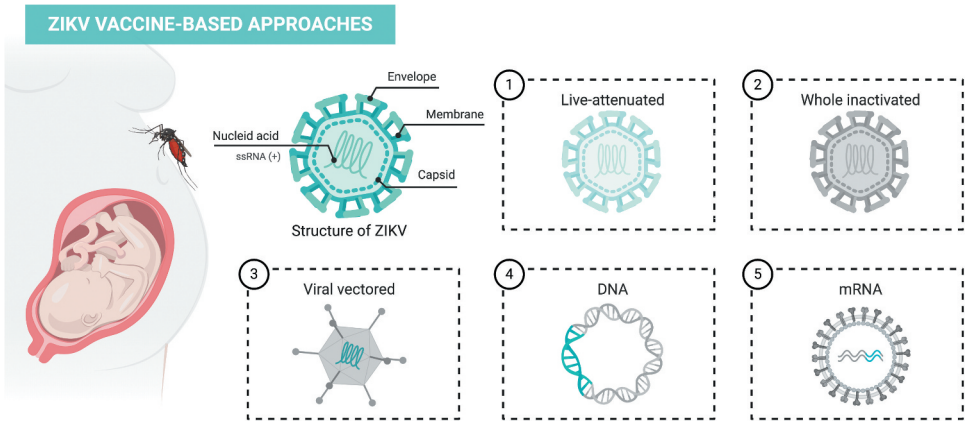

Figure 1. ZIKV vaccine-based approaches. **(1)** Live-attenuated vaccine: in this approach, the virus is attenuated by different methods and loses its effectivity to replicate and promote disease. The live-attenuated virus induces a potent immune response, but despite of being active the virus in the formulation is not able to induce sickness in an immunocompetent individual. The attenuated vaccine usually guarantees long-term protection and only requires a single dose, for example, in the widely described YF vaccine. **(2)** Whole inactivated: the virus becomes noninfectious using chemical agents such as formalin, β-propiolactone or heat; therefore, the virus is unable to cause disease nor to infect the cells or replicate. **(3)** Viral vector: viral vectors are genetically engineered viruses without pathogenicity, that retains their capacity to infect host cells but not causing any disease. Through genetic engineering techniques, it is possible to add antigens of interest into the genetic material of the virus. There are many viral vectors like adenovirus and vaccinia virus. **(4)** DNA vaccine: this vaccine is based on delivery of genes encoding a specific antigen that is subsequently transcribed and translated in proteins by host cells. Furthermore, DNA vaccines are able to induce cellular and humoral immune responses safely, with low cost and are easily manufactured. **(5)** mRNA: as DNA vaccines, the strategy of vaccination with mRNA can induce a potent cellular and humoral immune responses. Figure created with BioRender.com.

addition sites, site-directed deletions on 3′-UTR region or production of chimeric-attenuated flaviviruses that encode the ZIKV *prM* and *E* sequences.[28] A ZIKV- 3′UTR-LAV candidate induced protective immunity in mice and rhesus macaques, also preventing pregnancy transmission and testis damage in mice.[29] Similarly, a single-dose of plasmid-launched live-attenuated ZIKV vaccine-induced seroconversion, T-cell immune response, and sterile immunity in mice.[30]

Furthermore, a chimeric-attenuated vaccine swapping the *prM-E* sequence between DENV-2 and ZIKV into DENV-2 backbone or into ZIKV backbone was highly immunogenic and prevented viral infection by DENV-2 or ZIKV after challenge, respectively.[31] Another chimeric-attenuated candidate using ZIKV *prM-E* in a DENV-4 backbone has been developed by NIAID, and recently completed a Phase 1 trial (NCT03611946). Different viral vectors that express ZIKV genes have been tested as a delivery platform in pursuit to develop an effective ZIKV-vaccine. Adenovirus-based vaccine vectors have been tested in preclinical settings and demonstrated high immunogenic potential.[32–36] A single-shot of a rhesus adenovirus serotype 52 vector vaccine candidate expressing the ZIKV *prM-E* elicited neutralizing antibodies and long-term protection against viral challenge in rhesus monkeys.[8,24] A replication-deficient chimpanzee adenoviral (ChAdOx1) ZIKV-vaccine candidate also provided protection and long-lasting anti-envelope immunity in mice, and will be next evaluated in a clinical trial (NCT04015648).[34] Other strategies using a vaccinia-based construct against both ZIKV and Chikungunya virus (CHIKV) induced neutralizing antibodies in mice and protected against viremia and arthritis or fetal/placental infection and testis damage after CHIKV or ZIKV challenges, respectively.[35] Furthermore, a vesicular stomatitis virus (VSV) vector expressing ZIKV *prM-E* induced strong cellular and humoral immune responses that protected mice from lethal challenge.[37] Preclinical evaluation with a measles virus-based vaccine candidate expressing the ZIKV *prM-E* reduced plasma viremia and ZIKV load in distinct organs, preventing fetal infection during pregnancy.[38] Now, two measles-based ZIKV-vaccine candidates developed by Themis Bioscience have been tested in Phase I clinical trial (NCT02996890 and NCT04033068).

Until now, substantial breakthroughs have been achieved toward the development of vaccine platforms to prevent ZIKV infection and effectively limit congenital syndrome. Without an effective-licensed ZIKV-vaccine, we are still susceptible to another epidemic equal or even worse than the 2015 outbreak, reminding that we are still dealing with the consequences of children born with neurological problems from the previous outbreak.

For this reason, the pursuit of a safe, effective, and long-term immunogenic vaccine against ZIKV continues.

Acknowledgments

The authors want to thank Prof. Silvia Beatriz Boscardin for the critical reading of the manuscript. JSA received fellowship from CAPES; VASL received fellowship from FAPESP (grant number 2018/05320-7); ERF received fellowship from AFIP and DSR received fellowship from CNPq.

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

Funding

This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico; Fundação de Amparo à Pesquisa do Estado de São Paulo [2017/17471-7].

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