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Zika virus vaccines: immune response, current status, and future challenges

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Zika virus (ZIKV) is the most recent mosquito-transmitted virus to cause a global health crisis following its entrance into a naïve population in the Western Hemisphere. Once the ZIKV outbreak began investigators rapidly established small and large animal models of pathogenesis, developed a number candidate vaccines using different platforms, and defined mechanisms of protection. In this review, we characterize the adaptive immune response elicited by ZIKV infections and vaccines, the status of ongoing clinical trials in humans, and discuss future challenges within the field.

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Introduction

Zika virus (ZIKV) is an enveloped, positive-sense single stranded RNA virus within the Flavivirus genus of the *Flaviviridae*. This family encompasses a number of globally relevant viruses that have been targeted for vaccine development including yellow fever (YFV) [1], Japanese encephalitis (JEV) [2], Dengue (DENV) [3], West Nile (WNV) [4], and tick-borne encephalitis (TBEV) viruses [5]. The RNA genome of these viruses encodes for a single open reading frame, which is translated as a polyprotein and cleaved by viral and cellular proteases to generate the three structural proteins (capsid (C), pre-membrane (prM), and envelope (E)) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Neutralizing antibodies elicited upon infection or vaccination predominantly target the E protein on the surface of the viral particle [6,7]. Prior to 2007, ZIKV was a relatively obscure virus and associated with mild febrile illness in a small number of human cases. In 2007, the virus spread to the Pacific Islands where it caused large outbreaks. ZIKV entered northeastern Brazil in 2013 [8] and spread over the following two years throughout Central and South America, and into parts of North America, including the United States. From 2015 to January 2018, more than 800 000 documented and suspected human cases of ZIKV were reported [9]. In addition to an explosion of new human cases, the outbreak was associated with congenital defects in the context of infection of pregnant women, which resulted in publicized cases of microcephaly [10] and other birth defects [11]. In adults, ZIKV also has been linked to an increased incidence of Guillain–Barré syndrome [12–14], an autoimmune, neurological disorder characterized by ascending muscle weakness. The emergence of ZIKV into a new geographical niche along with novel viral-associated diseases prompted the call for medical countermeasures. In response, several vaccine platforms have been developed rapidly including mRNA, DNA, virus-vectored, live-attenuated viruses, and inactivated viral particles, and are described in recent reviews [15–17]. Here, we discuss the adaptive immune responses to vaccination in the context of animal models, the preliminary data from human clinical trials (Table 1), and the possible challenges facing the field (Figure 1).

Adaptive immune responses to ZIKV infection and vaccination

The success of a viral vaccine depends on its ability to induce durable adaptive B and T cell responses that inhibit viral replication and dissemination. The observation that a primary ZIKV infection in rhesus macaques inhibited secondary challenge with a homologous or heterologous virus [18–20] suggests that anti-ZIKV adaptive immunity can be protective. Many of the current suite of anti-ZIKV vaccines induce high levels of neutralizing antibody and antiviral $CD4^+$ and $CD8^+$ T cell responses. Antibody alone is sufficient for protection, as passive transfer of IgG from purified formalin-inactivated virus (PIV) vaccinated non-human primates (NHPs) into naïve recipient mice or NHPs inhibited ZIKV viremia upon challenge [21]. Similarly, passive transfer of sera isolated from humans vaccinated with PIV or a DNA vaccine encoding the prM-E viral genes

Table 1

ZIKV vaccines in clinical trials

Vaccine	Platform	Sponsors	Clinical Trials	Status	References
mRNA-1325	mRNA encoding prM-E	Moderna Therapeutics BARDA[a]	NCT03014089	Phase I/II	Richner *et al.* [28•] Richner *et al.* [57]
GLS-5700	DNA encoding prM-E	GeneOne Life Sciences Inovio Pharmaceuticals	NCT02809443 NCT02887482	Phase I Phase I	Tebas *et al.* [23••] Muthumani *et al.* [40]
VRC5288	DNA encoding prM-E (Chimeric ZIKV-JEV)	NIAID[b]	NCT02840487	Phase I	Gaudinski *et al.* [27••] Dowd *et al.* [26]
VRC5283	DNA encoding prM-E (ZIKV)	NIAID	NCT02996461 NCT03110770	Phase I Phase II	Gaudinski *et al.* [27••] Dowd *et al.* [26]
ZPIV	Purified inactivated virus	NIAID WRAIR[c]	NCT02963909 NCT02952833 NCT02937233 NCT03008122	Phase I Phase I Phase I Phase I	Modjarrad *et al.* [22••] Larocca *et al.* [41] Abbink *et al.* [21]
VLA1601	Purified inactivated virus	ValNeva Emergent BioSolutions	NCT03425149	Phase I	
TAK-426	Purified inactivated virus	Takeda BARDA	NCT03343626	Phase I	
MV-ZIKA	Measles-vectored	Themis Biosciences	NCT02996890	Phase I	

[a] BARDA = Biomedical Advanced Research & Development Authority.
[b] NIAID = National Institute of Allergy & Infectious Diseases.
[c] WRAIR = Walter Reed Army Institute of Research.

blocked viremia [22••] and protected immunodeficient mice [23••]. Defining the threshold neutralization titer required for vaccine immunity is critical for determining a correlate of protection. A threshold neutralizing titer in serum of approximately 1/100 [21,24•,25] to 1/1000 [26] inhibited viremia following viral challenge after vaccination of NHPs. In human clinical trials, three doses of a DNA vaccine encoding for prM-E, or two doses of the PIV vaccine achieved mean titers above this 1/100 threshold [22••,27••]. Notwithstanding these results, the level of neutralizing antibody required for sterilizing immunity is much higher. In immunodeficient mice, the neutralizing antibody titer that prevented virus detection in serum or susceptible tissues and an anamnestic immune response was greater than 1/10 000 [28•]. A key question remains as to whether sterilizing immunity is required to prevent seeding of the placenta and vertical transmission.

Characterization of the circulating plasmablasts and memory B cells from ZIKV-infected human patients has helped to define epitope targets on the E protein of strongly neutralizing and protective mAbs [29–33]. Antibodies elicited against the lateral ridge epitope in domain III, quaternary epitopes spanning domains I, II, and III across the E protein dimer (EDE mAbs), and sites within domains I or II were highly neutralizing [30–35]. In contrast, other highly cross-reactive antibodies that targeted the conserved fusion loop in domain II were poorly neutralizing and could lead to antibody-dependent enhancement of infection (ADE, see below) [29,36]. Likely, different vaccine platforms induce antibodies and memory B cells with unique epitope specificity, which may have implications for protective activity and cross-reactivity. A structural correlate of antibody protection is an important goal where mapping epitopes of vaccine-induced polyclonal antibodies can be related to long-term efficacy.

In addition to B-cell mediated immunity, T cells also contribute to protection against ZIKV infection. Polyfunctional antiviral $CD4^+$ and $CD8^+$ T cells can be detected after ZIKV infection in mice, NHPs, and humans [19,37–40], with many of the immunodominant epitopes within the structural genes (E, prM, and C) [37]. In susceptible mouse models, the absence of $CD8^+$ T cells led to increased viral burden and mortality, and adoptive transfer of T cells from infected mice limited viral infection in a $CD8^+$ T cell deficient host [38,39]. Vaccines also induce antiviral T cell responses. Vaccination of mice with DNA or mRNA vaccines encoding for prM-E or vaccination of NHPs with PIV, DNA, or adenovirus-vectored vaccines induced antiviral $CD4^+$ and $CD8^+$ T cells [21,25,40,41]. However, depletion of $CD4^+$ and/or $CD8^+$ T cells in mice that were immunized with a DNA vaccine had no effect on protective immunity [41], suggesting that while T cells contribute to the adaptive immune response, they may not be absolutely necessary for protection. In preliminary data from human clinical trials with DNA vaccines, anti-E $CD4^+$ and $CD8^+$ cytokine-secreting cells were detected following peptide stimulation [27••].