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Vaccination strategies against Zika virus

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The epidemic emergence of Zika virus (ZIKV) in 2015–2016 has been associated with congenital malformations and neurological sequela. Current efforts to develop a ZIKV vaccine build on technologies that successfully reduced infection or disease burden against closely related flaviviruses or other RNA viruses. Subunit-based (DNA plasmid and modified mRNA), viral vectored (adeno- and measles viruses) and inactivated viral vaccines are already advancing to clinical trials in humans after successful mouse and non-human primate studies. Among the greatest challenges for the rapid implementation of immunogenic and protective ZIKV vaccines will be addressing the potential for exacerbating Dengue virus infection or causing Guillain–Barré syndrome through production of cross-reactive immunity targeting related viral or host proteins. Here, we review vaccine strategies under development for ZIKV and the issues surrounding their usage.

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Introduction

Historically, Zika virus (ZIKV) infection caused a mild, self-limiting febrile illness that was associated with conjunctivitis, rash, headache, myalgia, and arthralgia [1]. However, during the recent epidemics in Asia and the Americas, more severe and unusual clinical consequences have been observed. Infection of fetuses during pregnancy, particularly during the first trimester, has been associated with placental insufficiency and congenital malformations including cerebral calcifications, microcephaly, and miscarriage [2,3•,4–6]. In adults, ZIKV infection is linked to an increased incidence of Guillain–Barré syndrome (GBS), an autoimmune disease characterized by ascending paralysis and polyneuropathy [7] that occurs during the acute phase of ZIKV infection or shortly afterward [8–10].

ZIKV was identified in 1947 from a sentinel Rhesus monkey in the Zika Forest of Uganda [11,12]. Prior to 2007, seroprevalence studies in Asia and Africa suggested ZIKV infections occurred periodically without evidence of severe disease [1,13]. Contemporary outbreaks of ZIKV arose in 2007 on Yap Island in the Federated States of Micronesia followed by an epidemic in French Polynesia in 2013 [14]; these events were associated with a high prevalence of infection, with greater than 11% of people on the islands presenting with ZIKV-associated symptoms [7,14]. A study in French Polynesia of patients diagnosed with GBS during the outbreak found that all had neutralizing antibodies against ZIKV compared to 56% of patients presenting to hospitals with non-febrile illnesses [7]. The next ZIKV outbreak began in late 2014 in northeastern Brazil, which was followed by a rapid spread to many other countries in the Americas in 2015 and 2016, including locally-transmitted infections in Florida and Texas in the United States [15–17]. Associated with the ZIKV epidemic were cases of GBS and congenital defects that correlated temporally with the growing number of infections [9]. *Aedes aegypti* and *Aedes albopictus* mosquitoes have tested positive for ZIKV and are believed to be primary agents of transmission [18,19]. In addition to mosquito vectors, sexual transmission of ZIKV was established from male-to-female [20,21] and subsequently from male-to-male and female-to-male [22,23]. Diagnostic studies have confirmed viral RNA in semen, sperm, and vaginal secretions of symptomatic patients up to 6 months following the onset of symptoms [24–26].

ZIKV belongs to the Flavivirus genus of the *Flaviviridae* family of positive-stranded, enveloped RNA viruses. ZIKV has an ~11 kb RNA genome and one open reading frame. Translation of infectious viral RNA in the cytoplasm generates a polyprotein that is cleaved into three structural proteins (capsid (C), pre-membrane/membrane (prM/M), and envelope (E)) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). ZIKV strains are classified into two genetic lineages, African and Asian/American. As the African lineage shows greater divergence [27], some studies have divided them into two African subtypes [28]. The

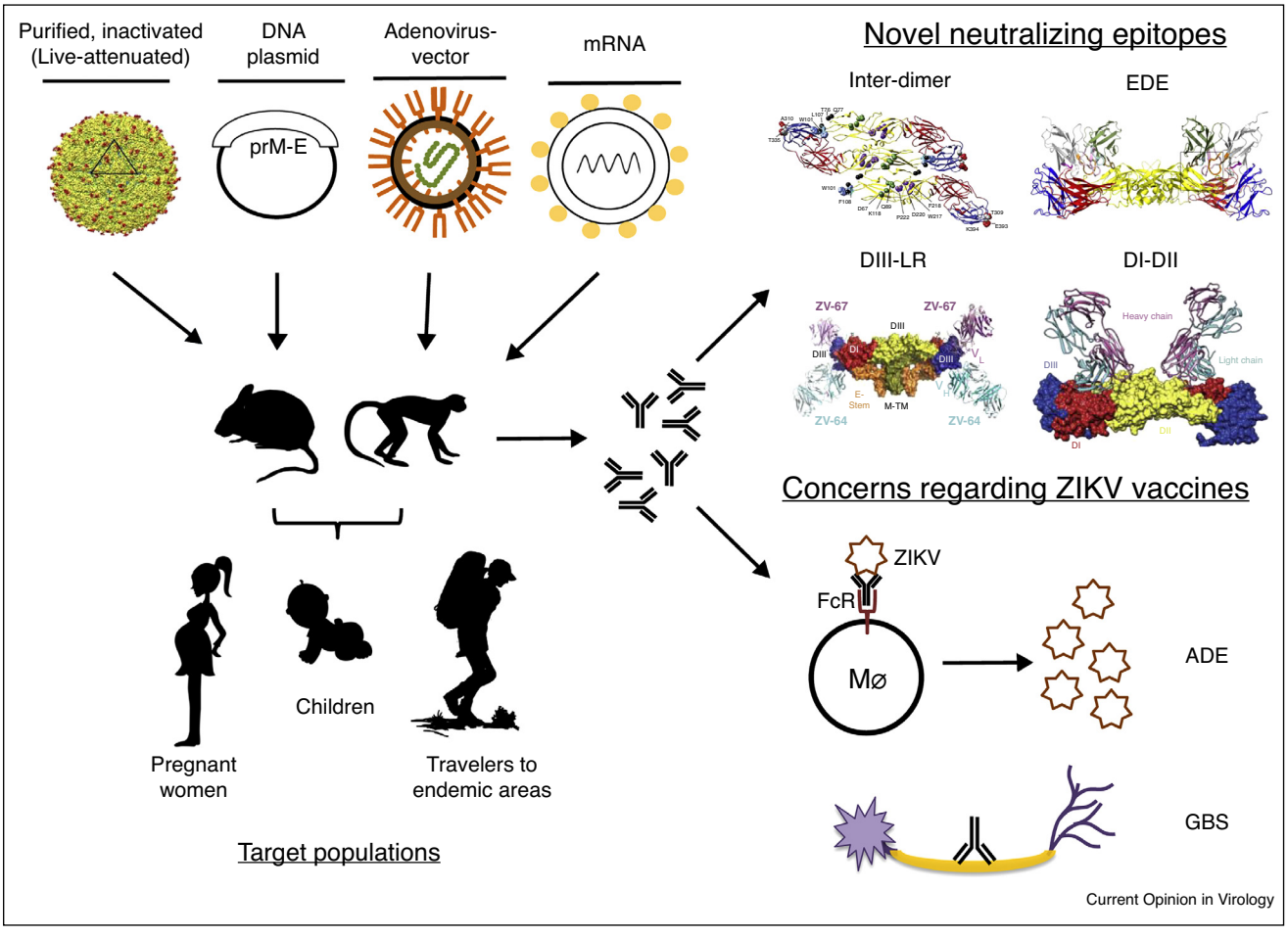
existence of multiple lineages, however, does not impact antibody neutralization significantly and thus, ZIKV has been classified as a single serotype [29]. ZIKV is related genetically to several pathogens that cause disease globally including Dengue (DENV), yellow fever (YFV), West Nile (WNV), Japanese encephalitis (JEV), and tick-borne encephalitis (TBEV) viruses. Of these viruses, ZIKV is most closely related to the four serotypes of DENV and shares 54–59% amino acid identity across the viral E protein [30••]. The sequence similarity between ZIKV and DENV poses unique issues for diagnosis and vaccination, and has implications for disease pathogenesis due to antibody cross-reactivity [30••,31,32,33•].

Studies on related flaviviruses have shown that antibody responses against the viral E protein can serve as correlates of protection in animals and humans [34–38]. The historical efficacy of the YFV, TBEV, and JEV vaccines in preventing infection and epidemics suggests that an effective vaccine targeting all strains of ZIKV should be feasible, especially given the limited (~3–5%) amino acid variability between E proteins of the two lineages [27]. In terms of prioritization, pre-pubescent children and men and women of child-bearing age living within or traveling to endemic areas might be priority recipients in a ZIKV vaccination campaign (Figure 1) [39].

ZIKV vaccine epitope targets of humoral immunity

The ZIKV E protein is composed of three ectodomains (DI, DII, and DIII), which are displayed on the surface of

Figure 1



ZIKV vaccine candidates, targets, and challenges.
(*Left*) Current platforms entering Phase 1 clinical trials in humans include purified, inactivated virus (adapted from Ref. [97]), DNA plasmid, adenovirus-vectored, and modified mRNA vaccines, all of which have demonstrated pre-clinical efficacy in mice and non-human primates. The primary target populations are indicated. (*Right*, *top*) Structural analysis of monoclonal antibodies derived from infected mice and human subjects identified protective epitopes for vaccine targeting: Inter-dimer (adapted from Ref. [32••]), Intra-dimer (EDE) (adapted from Ref. [51]), DIII-LR (adapted from Ref. [47]), and DI-DII (adapted from Ref. [33•]). (*Right*, *bottom*) Concerns for ZIKV vaccine development and deployment include immune-mediated enhancement (ADE) of DENV infection and Guillain–Barré syndrome (GBS) due to the possible induction of autoreactive antibodies and/or T cells (latter not shown).