Considerations for Developing a Zika Virus Vaccine

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The rapid spread of Zika virus through the Americas and its devastating consequences for pregnant women and infants have precipitated an international, multisectoral response. Current prevention strategies focus on mosquito control, protection of the blood supply, barrier protection during sex, and other forms of contraception. When this explosive epidemic abates, Zika virus could remain endemic in many countries, where the risk to pregnant women, the general public, and travelers will persist. Therefore, a safe and effective vaccine is essential.

Development of a safe, effective Zika vaccine should be feasible. Vaccines against related flaviviruses, such as yellow fever and Japanese encephalitis, have been developed and deployed, and Zika infection appears to generate protective immunity in nonhuman primates. Scientific feasibility, however, does not ensure successful development. An efficient development pathway must be delineated, including the optimal ways to evaluate the safety, immunogenicity, and effectiveness of vaccine candidates for intended target populations.

The primary goal of Zika vaccination is to prevent infection and protect against serious sequelae of the virus, particularly fetal congenital anomalies following in utero infection; however, given the relatively low frequency of these events in relation to the total number of infections, generating evidence of efficacy against these sequelae in prelicensure trials may not be feasible within a reasonable time frame. Demonstrating that vaccination averts congenital anomalies will most likely require postlicensure studies.

Prevention of congenital anomalies through vaccination of women during pregnancy faces several challenges. First, to protect the developing fetus, one must achieve protective immunity before the time of peak vulnerability, which is probably during the first and early second trimesters (although complications resulting from infections later in pregnancy have been reported). Furthermore, many women are unaware of their pregnancies until well into the first trimester. Although replicating live-virus vaccines may be protective after a single dose, these are generally not good candidates for vaccines administered during pregnancy. Inactivated, recombinant subunit, and other nonreplicating vaccines, more appropriate for use during pregnancy, usually require multiple doses to achieve protec-

N ENGL J MED 375;13  NEJM.ORG  SEPTEMBER 29, 2016

The New England Journal of Medicine
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tive immunity, thereby delaying effective immunity beyond the window of peak vulnerability for the fetus.

Second, vaccine safety and immunogenicity are generally established in nonpregnant adults before vaccination of pregnant women is considered — a standard practice that delays vaccine use in the latter population until some assurances of safety are provided. Hence, it is likely that vaccinating women of childbearing age (and men in order to prevent sexual transmission) would be the optimal initial public health strategy. In the longer term, it may be advisable to vaccinate pediatric populations, well before their first sexual contact. Here, the experience with rubella is instructive: protection of pregnant women was achieved through broad vaccination of young children. Adoption of this strategy would depend on the durability of protection offered by a Zika vaccine.

In approaching clinical development of Zika vaccines, investigators should adopt the most efficient methods for generating high-quality data on safety, immunogenicity, and efficacy. There are several reasons to favor randomized, controlled trials (RCTs) for this purpose. First, regional and temporal variability in Zika incidence due to differences in vector density and infection rates complicate the use of non-RCT trial designs. Second, specific aspects of the pathogenesis of Zika virus and other flavivirus diseases raise potential safety concerns that can best be assessed through direct comparison with a simultaneously enrolled control population. Concerns include the risk of vaccine-associated Guillain–Barré syndrome, the potential for neurotropism with live-attenuated vaccines, and the theoretical risk of antibody-dependent enhancement of Zika virus replication in persons who have previously been infected with or vaccinated against a flavivirus. RCTs offer the most reliable means of obtaining an early assessment of these potential complications.

In conducting clinical trials, we envision three potential strategies (see diagram). The relative merit of each plan depends largely on disease incidence and the resultant likelihood of generating reliable data on safety and efficacy. Regardless of the strategy used, affected communities must be actively engaged in trial design and execution to ensure that their concerns are reflected in all aspects of clinical evaluation.

Strategy 1 would use a traditional vaccine-development approach, in which phase 1 and phase 2 studies assess safety and immunogenicity, including the effect of prior flavivirus exposure on responses to Zika vaccines (e.g., in dengue-endemic regions). Investigators could adopt one of two end points for evaluation of efficacy in phase 2b or phase 3 studies. The first would be symptomatic infection alone (confirmed by polymerase chain reaction, which can distinguish Zika virus from circulating arboviruses such as chikungunya and flaviviruses such as dengue that cross-react serologically with Zika [Strategy 1a]). The second would be a combination of symptomatic and asymptomatic infections (Strategy 1b), which would require active surveillance, most likely through the regular collection of urine or blood, since an estimated 80% of infections are asymptomatic. The advantage of this approach is that it would facilitate efficacy evaluation using a smaller sample size. Moreover, demonstrating protection against asymptomatic infection may be important if such infection is shown to be associated with congenital disease.

In Strategy 2, human challenge studies would be conducted after phase 1 and 2 studies. This approach could prove a viable alternative to Strategy 1 if the incidence of Zika disease drops to low levels before large vaccine efficacy studies can be initiated.

Although this approach could permit efficient assessment of vaccine efficacy, it would require careful and specific ethical review in which the risk to volunteers is weighed against the potential public health benefit. Risks could in-
Pathways for Clinical Evaluation of Zika Vaccine Candidates.

Strategies 1a and 1b would require high infection rates in trial communities in order to accumulate sufficient infection end points. Strategy 1a would use incidence of confirmed symptomatic infection as a primary end point, relying on report of symptoms and diagnostic confirmation. This approach would not capture asymptomatic infections. Strategy 1b would capture both asymptomatic and symptomatic infections. Strategies 2 and 3 could be used if the incidence of infection falls substantially, rendering Strategies 1a and 1b infeasible to pursue. In these cases, human challenge (Strategy 2) and animal models (Strategy 3) could provide evidence of vaccine efficacy.

Initially, neurologic sequelae and sex-specific concerns: for male and female vaccinees, the risk of sexual transmission to partners (and thus the risk to any resulting pregnancy); for female vaccinees, the risk of inadvertent or unrecognized pregnancy. Some of these issues could be managed through subject selection and counseling. Until the risks of neurologic sequelae are well understood, the prospect of conducting human challenge studies should be approached with caution.

Challenge studies might also identify immunologic markers that could be used as surrogate end points to support accelerated approval of vaccine candidates. Vaccines approved through this pathway are subject to the additional requirement of postlicensure study to verify clinical benefit.

Strategy 3 would apply only in situations in which human efficacy studies are not feasible (e.g., if the incidence drops dramatically). In this scenario, developers could rely on the Food and Drug Administration Animal Rule, under which licensure would be based on adequate and well-controlled efficacy studies in animals coupled with the evaluation of safety and immunogenicity studies in humans. Reliance on Strategy 3 would require more thorough characterization of animal models and protective immune responses.

Finally, since there are several vaccine candidates in various stages of development, it will be challenging to efficiently identify the most promising candidates. One solution is for public institutions to consider supporting trials evaluating multiple candidates over time against a common control group. The selection of candidates for inclusion would be based on preclinical and early clinical data and other considerations (e.g., manufacturing timelines).

Given the effects of Zika infection, especially on the developing fetus, control of the Zika epidemic...
Fast-Track Zika Vaccine Development — Is It Possible?

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Studies have demonstrated that various Zika virus (ZIKV) vaccine constructs generate protective immune responses in mice and nonhuman primates, and two DNA ZIKV vaccine candidates have entered phase 1 human safety testing (ClinicalTrials.gov numbers, NCT01099852 and NCT02840487). ZIKV vaccine development is advancing rapidly thanks to collaborations among academia, government, and industry. Current knowledge gaps related to the properties, epidemiology, and pathology of ZIKV increase the complexity of vaccine development, but historical success in developing other flavivirus vaccines encourages optimism.

An ongoing epidemic in the Americas and the impact of ZIKV congenital syndrome (ZCS) necessitate rapid development of a safe, efficacious vaccine. As Ebola vaccine-development efforts taught us, conducting sequential, iterative preclinical studies followed by phase escalating human trials is suboptimal in an ongoing outbreak. Preclinical studies of ZIKV vaccine candidates need to continue in parallel with human trials, informing their design and the evolving target product profile (TPP), including dose level and schedule, delivery method, and primary vaccinee population. Newly minted ZIKV vaccinologists need to determine which questions will inform development plans (see Table 2).

Defining the TPP of a vaccine for emergency or conditional use has been a complex exercise, and the World Health Organization (WHO) has made a proposal (www.who.int/immunization/research/development/zika/en). Considerations include indications for male and female vaccinees, a short immunization schedule, brisk induction of a protective immune response, an advantageous safety profile, and potential contraindications in pregnancy. Though live or other replicating virus vaccine platforms would probably be less acceptable in emergencies, they might offer advantages for routine immunization, such as long-term protective immunity with minimal dosing. Given the need to protect girls before they reach childbearing age, a TPP should address vaccination starting at 9 years of age and in people of both sexes, given evidence of ZIKV in semen up to 6 months after infection. This starting age would align with WHO recommendations and with the precedent set by human papillomavirus vaccines (target group, girls 9 to 13 years old).

Prospective cohort studies can elucidate infection and disease attack rates, incidence of adverse pregnancy or neurologic outcomes,

Disclosure forms provided by the authors are available at NEJM.org.

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DOI: 10.1056/NEJMp1607762
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