is a critical global health goal. The development of a safe and effective Zika vaccine is an important component of a long-term solution. Carefully executed evaluation of candidate Zika vaccines, coupled with thoughtful planning for eventual use and deployment, will be essential to durable control of Zika virus infections.

An audio interview with Anthony Fauci is available at NEJM.org

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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,[1,2] 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, governments, and industry. Current knowledge gaps related to the properties, epidemiology, and pathology of ZIKV increase the complexity of vaccine development (see Table 1), 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.[3] This starting age would align with WHO recommendations[3] 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,

Table 1. Current Knowledge of Zika Virus (ZIKV) Epidemiology and Related Questions for Vaccine Development.*

Variable	Knowns	Unknowns	Questions for Vaccine Development
Time	First human case in Nigeria: 1952 First epidemic in Yap: 2007 First severe manifestations in French Polynesia: 2013	Dynamics of epidemics: frequency, intensity, duration, seasonality Establishment of risks and drivers of endemicity	Should it be used for routine immunization or for outbreak control? Should it be stockpiled? What is the shelf-life? When will clinical trials be undertaken to show vaccine efficacy?
Places	Continuing mosquito-borne transmission in 61 countries and territories (as of June 30, 2016)	Risk of current or prior strains spreading to Africa and Asia	Will vaccine be used in areas with ongoing ZIKV activities or for prevention in areas not experiencing an outbreak?
People	Mild disease: all ages at risk; both sexes at risk, but slight preponderance of women Severe manifestations: ZCS affecting mother and fetus; inapparent ZCS at birth; ZCS from asymptomatic mothers	Mild disease: Age groups at higher risk for clinical disease Severe manifestations: extent of ZCS and neurologic disorders; effect on number of abortions; breadth of populations at risk	Who is the target group for vaccination: Women of childbearing age only? Women and men of all ages? Teenagers prior to childbearing age? Is vaccine aimed at preventing disease or infection? What is the effect of Guillain–Barré syndrome pathophysiology on vaccine development?
Virus strains	African and Asian lineages Cocirculation and coinfections with other arboviruses	Risk and effect of transmission of Asian lineage to other places Effect on symptoms of coinfections or sequential infections by cocirculating arboviruses	Can any virus strain be used for candidate vaccine, or only Asian-lineage strains? Will ZIKV be prevalent each year, like dengue, or sporadic, like West Nile virus?
Transmission	Aedes mosquitoes Maternofetal Sexual (male–female and male–male) Blood donation Solid organ transplants	Other genera of mosquitoes capable of carrying virus Transmission rates of ZCS in symptomatic and asymptomatic mothers Risk during second and third trimesters of pregnancy Breast milk	Is vaccine aimed at preventing mosquito-borne disease or at transmission by other routes?
Epidemiologic indicators	In certain places: ratio of symptomatic to asymptomatic infection; incidence of clinical disease	Incidence rates of clinical disease by age Incidence rates of severe manifestations by age Case fatality rates Seroprevalence rates	Where will clinical trials be undertaken to show vaccine efficacy?

* ZCS denotes ZIKV congenital syndrome.

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Table 2. Zika Virus (ZIKV) Vaccine Challenges.*

Action and Challenge	Solutions for Accelerating Research, Development, and Licensure
Defining a target product profile	
Unknown severe disease incidence; unknown spectrum of ZCS	Early commitments to epidemiologic and natural history studies
Diverse cocirculating flaviviruses	Early inclusion of trial subjects with range of prior flavivirus exposure Efforts to find serologic assay able to distinguish prior exposure
Planning and executing preclinical and clinical studies	
Translating preclinical studies to clinical trials	Preclinical and clinical studies conducted in parallel
Long clinical development pathway	Broader and expanded early clinical studies Adaptive trial designs
Clinical trial design and completion if outbreak subsides or becomes sporadic	Field epidemiologic studies across multiple regions Modeling to predict epidemiologic situation
Relevant and measurable clinical end points	Establishing mild disease as a primary end point and rarer outcomes as secondary end points or focus of postlicensure studies
Unknown full spectrum of ZCS	Prospectively designed studies to confirm incidence of long-term sequelae not detected at birth
Incidence and cause of ZIKV-related GBS	Studies to elucidate pathology and incidence Clinical study end points related to GBS
Theoretical concerns about disease enhancement	Use animal models to test whether in vitro studies translate to in vivo If animal models suggest disease enhancement, use field studies to evaluate theory
Vaccine production and scale-up	
Process development and scale-up	Manufacturing processes and analytic capabilities developed before knowing a vaccine is successful
Capacity in time for licensure	Early investment in manufacturing capacity
Licensing strategy	
Requirement for efficacy trials	Preclinical and natural history studies to identify immune correlate or surrogate of protection; demonstrating effectiveness postlicensure Epidemiologic studies performed early to inform design
Seeking innovative registration pathways	Early engagement with regulatory agencies Address registration procedures for emergency or conditional use

* GBS denotes Guillain–Barré syndrome.

and contributions of different transmission modes to the overall epidemiology, helping to define routine immunization strategies. However, they won't provide information in the short term. Developers of first-generation vaccine candidates will need to measure performance against historical data and experiences with licensed flavivirus vaccines.

Preclinical development investigates vaccine safety, immunogenicity, and potential efficacy in animal models. Zika's interaction with other flaviviruses, role in pregnancy, and neurologic effects must be explored, and researchers are studying mouse and nonhuman primate ZIKV disease models in an effort to do so. Models in which sexual transmission (intravaginal challenges), maternofetal infection, and ZCS are reproduced will allow vaccine developers to assess the potential for preventing or attenuating infection or disease, the safety of vaccination during pregnancy, and the ability to protect the fetus or newborn from ZCS; there is no animal model for Guillain–Barré syndrome (GBS) that would permit the exploration of neurologic disease and the immune responses (to vaccine or infection) driving these outcomes.

It's important to elucidate how cocirculating flaviviruses may interact and affect a Zika vaccine's

performance. The vaccine performance profile may differ in flavivirus-immune and nonimmune recipients. Mechanisms of immune enhancement and the potential association with severe Zika outcomes are being explored in vitro and in animal models. However, human field studies in a setting with cocirculating flaviviruses would be more informative and definitive.

Demonstrating a vaccine's safety and clinical benefit during an epidemic is a key challenge. Before clinical testing, regulators must ensure volunteer safety by assessing the manufacturing process and supporting preclinical data and clinical plans. Many vaccine candidates fail to transition from preclinical to clinical testing because of a lack of sound manufacturing capabilities. Accelerating the production process for Zika vaccine requires numerous early development activities to occur in parallel with clinical evaluation.

Early-phase clinical studies primarily assess safety, but Zika's characteristics necessitate expanded early-phase studies, including assessment of age ranges associated with childbearing potential, volunteers with and without previous flavivirus exposure, and measurement of the longevity of the immune response. Adjuvants may be tested in early phases in efforts to optimize immune responses, but will further complicate clinical studies and potentially delay licensure.

Demonstrating efficacy will require careful planning and substantial resources. First, the relevant clinical end point and its measurability in a reasonably powered and sized study will need to be determined. Historical data indicate that clinical disease develops in approximately 20% of people infected with ZIKV, but this disease is overwhelmingly of a mild phenotype. The current epidemic has been associated with ZCS and GBS, which may be easier to detect but probably have low incidences and will require complex evaluations in order to confirm causal relationships. Additional data are needed to clarify the true incidence of these outcomes; current estimates are that the risk of ZCS after infection during the first trimester of pregnancy ranges from 0.88 to 13.2%[4] and that there are 0.24 GBS cases per 1000 ZIKV infections.[5] Developers must decide whether to design studies to detect mild disease or increase sample sizes to identify rarer outcomes. Mild disease could also be the primary end point, with rare outcomes as secondary end points collected over time. Alternatively, rarer outcomes could be assessed during postlicensure studies.

During clinical trials, adverse events of special interest, such as GBS, have to be prospectively defined, and any cases detected must be monitored. However, rare events will also probably require postlicensure assessment as part of a risk-management plan to address causality. If ZIKV transmission is highly seasonal, herd immunity reduces transmission, or epidemics occur sporadically, the window for conducting a clinical end-point efficacy trial during the current epidemic may be narrow. The field requires more epidemiologic information to properly design advanced clinical trials (see Table 1).

Demonstrating a vaccine's safety and clinical benefit during an epidemic is a key challenge. Before clinical testing, regulators must ensure volunteer safety by assessing the manufacturing process and supporting preclinical data and clinical plans.

Quickly advancing from small-scale manufacturing to levels required to support advanced trials or deploy vaccine in settings where disease is endemic requires substantial expertise and resources. Technical requirements may make scale-up problematic, delaying advanced development and licensure. Annual production of 100 million doses, a projected requirement, would be challenging even for the manufacturers of most licensed vaccines. Transferring technology from one organization to another, scaling up manufacturing, and securing approvals to use the vaccine could take years.

Regulatory and licensing strategies are guided by the TPP and the data generated to support the vaccine's intended use. Regulato-

ry agencies will pay particular attention to preclinical safety and toxicity studies and assessments of unexpected adverse events during clinical trials and after licensure. The case for licensure may be established through traditional clinical efficacy trials, but declining case counts or an urgent need for intervention may necessitate a different pathway. Alternatives include using efficacy data from studies in animals combined with human immunogenicity data or bridging to an as-yet-undefined immune correlate of protection. Human challenge studies have been proposed in order to augment information from efficacy trials, assist in exploring immune correlates of protection, or generate efficacy data if natural transmission substantially declines. In the absence of a clear understanding of the frequency of adverse neurologic outcomes or the persistence of ZIKV in biologic fluids, however, human ZIKV challenge is ethically complex.

Other flavivirus vaccines have been licensed, including those against yellow fever (live attenuated), Japanese encephalitis (inactivated, live chimeric, live attenuated), tickborne encephalitis (inactivated), and dengue (live chimeric). Some have validated surrogates of protection, and all are based on neutralizing antibody. A neutralizing antibody titer of 1 in 10 is the surrogate of protection for the Japanese and tickborne encephalitis vaccines; for yellow fever, the titer is between 1 in 10 and 1 in 50. Preclinical ZIKV studies suggest that a titer of 1 in 10 for mice and approximately 1 in 100 for nonhuman primates protected against ZIKV challenge.[1,2] If these figures translate to humans, developing a ZIKV vaccine is very feasible.

The time required to develop a safe, efficacious ZIKV vaccine will be determined by prior experience with the selected technology, the continuation of outbreaks, and the required scale-up of manufacturing. Ultimately, developing, licensing, and deploying a vaccine capable of affecting the current epidemic will require seamless coordination among developers, regulatory agencies, the WHO, and national health authorities, along with a robust monetary commitment from governments and funding agencies.

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Predicting the Future — Big Data, Machine Learning, and Clinical Medicine

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By now, it's almost old news: big data will transform medicine. It's essential to remember, however, that data by themselves are useless. To be useful, data must be analyzed, interpreted, and acted on. Thus, it is algorithms — not data sets — that will prove transformative. We believe, therefore, that attention has to shift to new statistical tools from the field of machine learning that will be critical for anyone practicing medicine in the 21st century.

First, it's important to understand what machine learning is not. Most computer-based algorithms in medicine are "expert systems" — rule sets encoding knowledge on a given topic, which are applied to draw conclusions