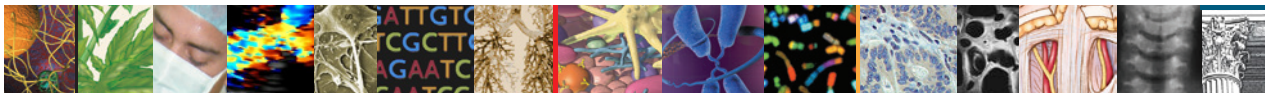

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The Zika Challenge

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"There are many viruses that have similar characteristics to dengue, yellow fever, and Zika that have the potential to emerge. We don't know why Zika emerged now. But we know how to develop surveillance systems that will allow us to pick these viruses up if they start to move as Zika has." This starting point was outlined by tropical medicine expert Duane Gubler at a World Health Organization (WHO) meeting in Geneva in early March. Gubler has spent his career studying tropical infectious diseases with an emphasis on dengue virus (DENV), a flavivirus closely related to Zika virus (ZIKV).[1] His introductory presentation at the international meeting about the ZIKV challenge emphasized the complexity of the flavivirus–host relationship and the inevitability, thanks to urbanization and globalization, of emergence and spread of viruses that were previously confined to small, remote geographic areas.

To prevent and control ZIKV infection in humans, we must understand the virus and its vectors, the modes of transmission between mosquitoes and vertebrates and among humans, and the natural history of ZIKV disease. The main challenge today is that most of this knowledge is lacking. Of the 313 articles on Zika identified by a recent PubMed search, only 25 were published between 1952, when the virus was discovered, and 2009, when the first outbreak outside Africa and Asia was reported in the *Journal*[2]; 225 were published in 2016.

The WHO meeting, which involved 130 experts from 27 countries, allowed specialists in virology, immunology, epidemiology, neurology, and entomology to meet with product developers, regulators, funders, and policy experts to exchange insights, identify knowledge gaps, and agree on a plan for accelerating product development and evaluation in the hope of controlling the rapid spread of ZIKV infection in Brazil and elsewhere.

Transfer of knowledge about other flaviviruses such as dengue, yellow fever, chikungunya, Japanese encephalitis, and West Nile is essential. The human immune response to flaviviruses is complex. It can be both protective and pathogenic, and there are cross-reactions among different viruses and serotypes. These facts have implications for our understanding of clinical manifestations, for diagnosis, and for possible prevention through vaccination. For example, a primary infection with one of the four DENV serotypes probably provides lifelong protection against that serotype, but a secondary infection with a different serotype is a major risk factor for severe disease. Nevertheless, the majority of secondary DENV infections are asymptomatic or result in only mild disease. The immune mechanisms underlying pro-

tection (in most cases) and severe disease (in some) are not well understood.

It is also unclear whether a previous infection with or vaccination against one flavivirus might mediate antibody-dependent enhancement of a secondary severe infection. There is not much evidence to support this possibility — but then there's not much relevant evidence altogether. We need research to clarify the best way to provide protection and to prevent serious consequences of ZIKV and other flaviviruses that were previously unknown. Until recently, ZIKV was believed to cause only mild disease, which it still does in the majority of cases. The main concern today is the growing body of evidence that Zika virus infection results in severe neurologic complications[3-5] — Guillain–Barré syndrome in infected patients and microcephaly in unborn babies — combined with the very rapid spread of the virus.

Gaining a better understanding of the clinical spectrum and associated illness, development of diagnostics, and countermeasures such as vaccines and vector control were the main issues discussed at the Geneva meeting. A correct diagnosis is key but is complicated by several factors. Laboratory evidence of recent chikungunya, DENV, or ZIKV infection is obtained by testing serum for viral nucleic acid or virus-specific IgM and IgG antibodies. During the first 7 days of illness, viral RNA can often be identified in serum, and reverse-transcriptase polymerase chain reaction (RT-PCR) is the preferred test. Since viremia decreases over time, however, negative RT-PCR results 5 to 7 days after symptom onset do not rule out flavivirus infection, and serologic testing should be performed. But serologic cross-reactivity between flaviviruses means that current IgM-antibody assays cannot reliably distinguish between ZIKV and DENV infections. Therefore, an IgM-positive result on an enzyme-linked immunosorbent assay for dengue or Zika IgM should be considered indicative of a recent flavivirus infection. In patients who have received yellow fever or Japanese encephalitis vaccine or have previously been infected with another flavivirus, cross-reactive antibodies may make it difficult to determine which flavivirus is causing the current illness.

Perhaps the most surprising information presented at the WHO meeting was that there's no evidence that any recent vector-control interventions, including massive spraying of insecticides, have had any significant effect on dengue transmission. There are also major gaps in knowledge regarding the role of various mosquito species in transmission of flaviviruses in general and of ZIKV in particular. Experts also stressed the need for greater rigor in evaluating novel biologic and genetic approaches to vector control in which mosquitoes are modified in various ways (by means of infection with wolbachia bacteria or recombinant or irradiation technology).

Although vaccines may come too late for countries currently affected by the ZIKV epidemic, the development of a vaccine that can, above all, protect pregnant women and their babies remains an imperative for countries where the epidemic is expected to arrive in the foreseeable future. The goal would be to allow for medium-to-long-term control of ZIKV, analogous in some ways to the control of rubella.

All ZIKV-vaccine projects are at very early stages, but experience with licensed vaccines against various flaviviruses suggests that development of a ZIKV vaccine is technologically feasible. Effective vaccines against yellow fever and Japanese encephalitis have been available for decades, though vaccines against DENV have proved more difficult to produce and much less successful — probably because of the more complex immune response and four serotypes. In spite of this, there is now a licensed DENV vaccine.

We currently lack major basic tools for ZIKV-vaccine development, including reliable animal models, reference reagents, and assays. Experts also cautioned against drawing too many conclusions from existing flavivirus vaccines and raised two major concerns: the possibilities both of positive or negative interference with preexisting flavivirus immunity and of vaccine-induced Guillain–Barré syndrome. Identification of correlates of protection against ZIKV will be important to help with vaccine development, and we need to understand whether and how prior exposure to related viruses would affect the immune response to a ZIKV vaccine. In addition, animal models are needed to elucidate Zika's pathogenesis and complications, especially to help scientists assess the possible reproductive toxicity of candidate vaccines. These critical questions need to be answered if a safe vaccine is to be developed.

Participants in the WHO meeting considered a draft target-product profile for an emergency-use vaccine, although major questions

remain regarding vaccine evaluation and clinical end points, among other important issues. Such a profile from the WHO will help to orient and guide those who will consult and build consensus on regulatory and policy requirements for evaluation and registration of a ZIKV vaccine. The current draft focuses on approaches using non–live vaccine, such as inactivated vaccines, since such approaches will raise fewer specific safety concerns related to potential use during pregnancy.

A major problem both for clinical monitoring of ZIKV disease and for product development is the lack of standardized diagnostic tools. There is a need for increased access to samples and reference materials for disease monitoring, clinical research, and facilitation of product development. It will also be necessary to get rapid feedback from basic research (e.g., on virus mutations) to support product development and evaluation efforts. Data from ongoing research on animal models and assays should be shared in due course and should serve as the basis for developing reference protocols for key assays.

Many lessons learned from the response to the recent Ebola outbreak have helped in the response to the ZIKV outbreak. Most important, there is general agreement on the need for international collaboration on regulatory issues, research, and data sharing. For example, major regulatory agencies (such as Brazil's Agência Nacional de Vigilância Sanitária, the U.S. Food and Drug Administration, and the European Medicines Agency) have committed to prioritizing the expedited evaluation of Zika products and will proactively reach out to product developers to provide advice on regulatory issues. Regulators have also initiated collaborations and are sharing their experiences with each other.

Another major advance over the Ebola response has been the speed with which data are being shared — for example, through the real-time posting of data from pathogenesis experiments in nonhuman primates. The December 2015 statement from the International Committee of Medical Journal Editors clarifying that prepublication dissemination of critical information will not prejudice later journal publication related to ZIKV or future public health emergencies has been helpful. Similarly, a February 2016 statement on open data sharing in ZIKV has been transformative in signaling that funders expect proactive data sharing. ZIKV provides a case study of the need for expedited research to answer basic questions, which will allow for development of control measures.

We are working in a new area with many unknowns. But as the WHO meeting showed, there is ample experience and expertise from work with other viruses and vectors — ranging from basic science to field work and surveillance — to guide clinical practice, research, and product development. It is critical that we collaborate rather than compete to find answers to the questions that worry millions of women of child-bearing age in areas where ZIKV is spreading rapidly and may become endemic.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article was published on March 30, 2016, at NEJM.org.

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DOI: 10.1056/NEJMp1603734