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SUPPLEMENT ARTICLE

Pandemic Zika: A Formidable Challenge to Medicine and Public Health

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> *Not a single year passes without [which]…we can tell the world: here is a new disease!*
>
> Rudolf Virchow [1]

It has been 150 years since the noted German physician-scientist and public health advocate Rudolf Virchow made his prescient observation about new diseases. Since then, the world has seen a dizzying succession of newly emerging and reemerging infectious diseases that have changed the landscape of medical practice and of biomedical research [2].

The Zika pandemic was first recognized in 2013 and is still unfolding in alarming and unprecedented ways. Because of the pandemic's uniqueness and the insidious ability of Zika virus to harm unborn children, the pandemic has captured the attention of infectious disease researchers and practitioners of clinical and public health medicine around the world, as well as the attention of allied colleagues working in entomology, vector control, informatics, teratology, immunology, and a host of other disciplines [3–5].

Zika virus has now spread to >80 countries or territories [5], including 50 in the Americas and the Caribbean, causing millions of infections. An enormous body of information about Zika has rapidly accumulated and the scientific community is now energetically organizing and translating new data into control and prevention approaches.

In this issue of the *Journal*, we review what we have learned so far and how we may best apply it to blunt Zika's alarming progress. Eighteen expert groups discuss multiple aspects of the Zika pandemic, including its history, epidemiology, virology, vector characteristics, immunology, teratology, and vaccinology. Our collective goal is to stimulate thought and discussion so we can more effectively work together in pursuit of preventing Zika infections, developing treatments for those affected, and ending the pandemic.

Among the many important aspects of the Zika pandemic covered in these reviews, its history, epidemiology, and vector biology are of fundamental interest [4–8]. Zika virus was first thought of as an almost completely inconsequential virus that had smoldered at a low level in remote African/Asian sylvatic cycles for decades, if not centuries. Zika virus then suddenly and unexpectedly surged, and the virus was spread around the world by a nonsylvatic-vector mosquito, the globally ubiquitous *Aedes aegypti*.

This is the same mosquito that also has transmitted yellow fever, dengue, and chikungunya viruses around the world. *A. aegypti* is intensely anthropophilic (preferring blood meals from human beings as opposed to other animal hosts). While human travel and population growth and crowding clearly have played an important role in Zika's emergence, these factors alone seem insufficient to explain its sudden pandemicity, since the virus has apparently long persisted in populous and mobile urbanized Asian/Southeast Asian countries with hyperabundant *A. aegypti* mosquitoes [4]. It is conceivable that one or more viral mutation occurred to facilitate viral spread. This remains a critically important research question. Preliminary data show no evidence for phenotypic changes related to human pathogenic or transmissibility properties of the virus [9] and fortunately no evidence of viral evolution that would hinder diagnostic detection [10]. However, surprising preliminary evidence is consistent with the new (Asian lineage–derived) pandemic strain causing earlier and more-frequent viral infection of mosquito salivary glands [11, 12].

Most pandemic Zika cases appear to have been acquired from *A. aegypti*, a tenacious mosquito vector intimately associated with human dwellings and extremely difficult to eliminate or even control effectively. Some evidence also suggests that at least 3 other *Aedes* species have also vectored Zika outbreaks. This is of great concern not only because of the global abundance of 2 of these mosquitoes (*Aedes albopictus* and *Aedes polynesiensis*), but because of the possibility that Zika virus may be able to adapt to become more efficiently transmitted by new vectors, as has been seen with the chikungunya alphavirus [13]. This would

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have alarming implications for enhanced Zika virus spread and more broadly for the possibility of emergence of other diseases via enhanced vector capacity. In addition to vector transmission, Zika virus also is transmitted from mothers to fetuses and infants, via sexual transmission, via laboratory accident, and possibly through blood transfusion and organ transplantation [7]. These realities greatly complicate public health control efforts.

Understanding the pathogenesis and natural history of Zika virus infection has been facilitated by decades of research with flaviviruses [14]. However, despite its genetic similarity to the other 58 flaviviruses (including its close cousins, the 4 dengue viruses), Zika virus has some unique or at least uncommon phenotypic properties. These include the ability to cause congenital infections and marked teratogenicity; to be simultaneously viscerotropic and neurotropic, causing not only dengue-like febrile illnesses, but also neurologic conditions, such as Guillain-Barré syndrome and encephalitis [15]; to transmit sexually; and to persist for long periods in multiple sites of the body.

Furthermore, some studies have suggested that preexisting flavivirus immunity (eg, from prior dengue virus infection) might potentiate Zika [16] via antibody-dependent infection enhancement in some circumstances [17], while other research has countered this view [18]. Regardless, the serologic and immune responses to Zika virus in the background of high population immunity to related flaviviruses is complex and raises difficult questions about diagnosis and pathogenesis [10, 19]. Whether this proves to be the case, the serologic and immune responses to Zika virus in the background of high population immunity to related flaviviruses is complex and raises difficult questions about diagnosis and pathogenesis [10, 19].

The emergence of Zika virus has shown it to be among the most unique and least understood of flaviviruses, necessitating intensive experimental study to determine how it causes disease. As with most flaviviruses, small-animal models of Zika virus infection and disease have been problematic, but considerable progress has nonetheless been made, including important new information bearing on teratogenicity and vaccine design strategy [20]. Moreover, exciting nonhuman primate work is yielding insights into the natural history not only of typical infection, but also of placentally acquired infection of fetuses [21].

Unquestionably, the most disturbing aspect of the Zika pandemic is the secondary pandemic of Zika-associated microcephaly and many other birth defects (congenital Zika syndrome), as well as fetal losses that have affected a large but still unknown percentage of women infected with Zika virus during pregnancy [22]. A large body of experimental work, including epidemiological and clinical studies being conducted in South and Central America, represents the first time that an epidemic of a human teratogenic/fetal infectious disease has been intensively investigated in real time.

These efforts are critically important because of the unfolding tragedy of the loss of thousands of babies and the birth of thousands more who will be incapacitated, sometimes severely, throughout their lifetimes. To make matters worse, it is suspected that many infected babies born in apparent health will manifest delayed effects of intrauterine Zika virus infection as they grow into infancy, toddler age, and early school age. The epidemic of congenital Zika syndrome represents not only a profound medical tragedy, but a societal challenge, as well: thousands of parents and caregivers will need financial, medical, and social support for decades to come. In this regard, it is worth reflecting upon and studying the rubella epidemic of the mid 1960s, when tens of thousands of babies were born with congenital rubella syndrome in the United States [23], the deadliest epidemic of infectious birth defects ever documented. Study of this rubella epidemic and the ongoing occurrences of other congenital infections, such as cytomegalovirus infection, have made clear the importance of understanding Zika through large-scale prospective epidemiologic studies, such as those now underway in the Americas.

Effective antiviral therapy for Zika virus infection is still an unrealized goal, but numerous compounds, including repurposed drugs that are already in use, as well as antiviral antibodies, are being examined in preclinical studies [23]. Because the most important clinical application of an anti-Zika drug would be treatment of infected pregnant women and infected fetuses, unprecedented challenges are now being considered [24].

Another critically important research goal is the development of a preventive Zika vaccine [25, 26]. Almost a century of work on flavivirus vaccines (going back to the 1920s) [27] has provided us with several viable vaccine approaches and platforms, including those using other flavivirus proteins, and could readily be switched to Zika virus proteins. At least 7 different Zika vaccines are currently (in late 2017) in clinical trials, with ≥40 more in preclinical development [25, 26]. Zika vaccine trials face significant challenges, including the fact that the Zika pandemic is waning in many areas and that flavivirus outbreaks normally appear sporadically and unexpectedly. Furthermore, it is unknown which of several possible vaccination strategies is optimal, eg, inducing sterilizing immunity in vulnerable individuals, protecting pregnant women by vaccine induction of population herd immunity, or vaccinating children to induce partial population immunity [25]. In addition, as noted above, serious questions about vaccine-associated immunologically enhanced disease remain unanswered.

Finally, it is important that we not assume that pandemic Zika is a one-time crisis that can be met, controlled, and then forgotten or relegated to historical review. Over the past 4 decades, we have seen the dawn of a new infectious disease era in which mostly quiescent arboviruses have begun to aggressively emerge and reemerge around the globe, including dengue virus, West Nile virus, and chikungunya virus. All the tropical world and much of the temperate world is now at risk and is likely to remain at risk for the foreseeable future. How we deal with the Zika pandemic is likely to become a roadmap for

future challenges. This issue of the *Journal* outlines some of the important thoroughfares on that roadmap and will hopefully contribute to the difficult journey ahead.

Notes

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