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RESEARCH AND POLICY

Once and future epidemics: Zika virus emerging

IN A COMPLEX WORLD, VIRUSES REPRESENT ISLANDS OF BIOLOGICAL SIMPLICITY. The genomes of RNA viruses typically measure one-millionth the size of the human genome and encode only a handful of proteins. Despite their genetic economy, microbes nonetheless cause global pandemics that bring untold human suffering. In aggregate, their medical, social, and economic impacts have been devastating (*1*, *2*). Zika virus represents the latest emerging pathogen to sound the global alarm. Whereas this infection is benign in most people, it is putatively associated with two uncommon diseases: microcephaly in newborn babies and Guillain-Barré syndrome. The recent outbreak has raised numerous questions about (i) our scientific understanding of the pathogen, (ii) how to respond to outbreaks, and (iii) how to implement the public policies and infrastructure that can protect us against future infectious threats.

ZIKA VIRUS EMERGENCE

The history of Zika virus infection has been well documented (*3*, *4*). First recognized in nonhuman primates living in the Zika forest of Uganda in 1947, this flavivirus posed little medical concern. Infection in humans is largely asymptomic and in one of five cases induces a mild self-limited illness that resolves in days. Previous outbreaks were confined to limited areas of Africa and Asia, but since 2007, Zika has spread rapidly through the Pacific to the tropical and subtropical Americas.

In large measure, the rapid spread of Zika can be attributed to its zoonotic life cycle and transmission by the *Aedes aegyptae* mosquito, the same vector that transmits dengue and chikungunya viruses. Zika's association, in certain geographical areas, with coexistent dengue and chikungunya infections in humans has raised questions about the potential roles of these other viruses as cofactors for the more serious complications of Zika. Because of genetic and serological cross-reactivity between dengue and Zika, more precise and rapid diagnostics as well as rigorous epidemiological investigations are needed to clarify the contributions of various pathogens and other environmental cofactors to Zika disease pathology.

Zika infections remain associated with microcephaly in the Americas and Guillain-Barré syndrome in French Polynesia and South America. Although Zika virus has been identified in a handful of cases in fetuses with microcephaly, this association does not demonstrate causality (*5*). Further epidemiological study and the development of relevant animal models to establish Koch's postulates for Zika virus relative to microcephaly would help to clarify the connection. Likewise, for Guillain-Barré syndrome, the background rates of the disease are not known, and the impact of Zika infection is not fully understood. The role of other contributing factors requires further examination in this syndrome. Needless to say, the association and lack of alternative explanations is concerning, and it is prudent to avoid exposure to the virus and expedite the development of countermeasures to prevent and treat infection.

ACCELERATING COUNTERMEASURES

In any emerging outbreak, the first priority is to accelerate the development of medicines already known to be safe in humans with known on-target efficacy. It is also useful to search for repurposed drugs that can be rapidly tested in clinical trials. The next priority is to advance vaccines and other antiviral therapies with efficacy to prevent and cure, respectively, Zika infection in relevant animal models. In the case of Zika virus, because infection is self-limited and short in duration, treatment with antiviral drugs would be challenging and impractical. Therefore, effective preventive measures such as vaccines remain a priority. But because vaccine development is lengthy, the question remains as to whether one can be generated and tested for efficacy before the current outbreak subsides. For these reasons, efforts to reduce transmission through mosquito vector control also merit attention, along with an objective assessment of their efficacy.

PHOTOS: SANOFI

Expediting vaccine development

A vaccine has shown efficacy against dengue, a related flavivirus (*6*, *7*). Zika shows ~60% genetic similarity with dengue viruses, and some diagnostic tests and antibodies do not readily distinguish between the two. It is important to determine whether this quadrivalent dengue vaccine, Dengvaxia, can cross-protect against Zika virus. Careful surveillance, sequence analysis, case control studies of microcephaly in Brazil (where the dengue vaccine is now being deployed), and cross-neutralization analyses in the laboratory will be informative.

Should cross-protection not be observed, as might be expected, the dengue vaccine does provide a readily adaptable platform for the development of a Zika vaccine. Dengvaxia is derived from the yellow fever vaccine virus and is made chimeric with selected dengue genes. An analogous approach can be taken with Zika. Because Zika chimeric virus seed lots could be generated and the manufacturing experience and infrastructure are available, it might be possible to prepare pilot vaccine lots and scale industrial production more readily to meet demand. Because of the concerns related to Zika replication during pregnancy and to Guillain-Barré syndrome, it may be preferable to use inactivated, adjuvanted virus rather than the attenuated virus as is present in Dengvaxia. In parallel, other approaches merit investigation: Gene-based vaccination has led to protective immune responses against West Nile—another related flavivirus—both in human studies and in animals. Because DNA and, more recently, RNA vaccines have shown promise and can be relatively readily produced, they offer viable alternatives to the chimeric Zika flavivirus vaccine.

Immunotherapies and antivirals for prevention

Although the use of antivirals during acute infection represents a challenge, such therapies could be used for prevention if they are safe and effective. Whereas it is difficult to develop a small-molecule drug candidate rapidly, it is now possible to isolate and produce monoclonal antibodies (mAb) relatively quickly. Although it will take longer to produce reasonable quantities of mAbs relative to small molecules, this approach merits further investigation and might prove complementary to vaccination.

Accelerating clinical trials

It is important to provide medicines to infected individuals with the utmost speed; however, it is also essential to demonstrate clinical safety and efficacy before a candidate vaccine is used widely. To perform successful clinical trials, substantial challenges loom. First, because the disease spreads rapidly and likely will confer substantial herd immunity, the development and release of clinical lots in endemic regions must be streamlined so that trials can start quickly. Because standard lot release testing often takes 6 months, background safety data on the vaccine platform might provide a rationale for accelerating this process in populations at risk while the disease remains prevalent. As witnessed during Ebola and West Nile virus outbreaks, it is difficult to provide vaccine candidates in time to establish efficacy in an outbreak setting. Once this window of opportunity has passed, it might not arise again for decades.

GLOBAL PREPAREDNESS

Numerous thoughtful calls have been made for global action to defend against emerging pathogens, and more aggressive action is needed to preempt their uncontrolled spread (*1*, *2*). The fundamental problem comes from the lack of sustained investment and support for developing and testing medicines that can be made available in advance of the outbreaks. The biopharmaceutical industry has a singular and critical role to play in the response, but it cannot solve this problem alone. Progress can be achieved only if government, academic, regulatory, and industry partners work collaboratively to solve the scientific, clinical trial, safety, manufacturing, and public health challenges facing vaccine success.

Globally, the current systems of response to outbreaks are ill defined, with little accountability, little organization, and few resources to avert emerging crises. To improve this situation, five elements require attention: (i) sustained public support and commitment of political leadership to empower effective and coordinated international responses; (ii) global champions with fiscal resources supporting the effort (specifically, the finance ministers of countries whose public health and economic stability are threatened); (iii) adequate public health infrastructure, regulatory harmonization, and manufacturing capacity; (iv) public-private partnerships to maximize resources and treatment and prevention approaches; and (v) sustained investment in scientific, clinical, and manufacturing capabilities to foster more effective and adaptive solutions. Transformative innovation in vaccine

design, immune monitoring, and production technology can help to advance more effective, timely, and affordable medicines.

Improved protection requires that political will, economic resources, diagnostic technology, manufacturing capacity, clinical infrastructure, and health care delivery systems come together to ensure that measures are applied reproducibly, systematically, and with local flexibility. Progress toward developing an effective countermeasure strategy has been alarmingly slow. As Zika, Ebola, and chikungunya have taught us, it is increasingly likely that changes in vector characteristics, globalization, and climatic changes are converging on a world at increasing risk of further outbreaks from known viruses such as Marburg and Lhassa. Greater focus on epidemiological surveillance coupled with a proactive strategy to develop rapidly testable therapies during the outbreaks are necessary to protect our world. A combined preclinical, regulatory, and early safety-testing pathway for treatments in patients that is responsive to emergent threats, along with a scale-up of manufacturing capabilities, are essential to global preparedness. The need for a globally coordinated system to protect against global health threats remains urgent.

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