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SUPPLEMENT ARTICLE

Zika Virus and Future Research Directions

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There was a dramatic upsurge in research activity after the recognition of Zika virus (ZIKV) transmission in South America in 2015 and its causal relationship to devastating anomalies in newborn infants. Progress in this area required a community of arbovirologists poised to refocus their research efforts and rapidly characterize the features of ZIKV transmission and infection through diverse multidisciplinary collaborations. Significant gaps remain in our knowledge of the natural history of ZIKV infection, its effects on neurodevelopment, modes and risk of transmission, and its interrelationship with other arbovirus infections. Development of effective countermeasures, such as therapeutics and an effective vaccine, are also research priorities. Lessons learned from our research response to ZIKV may help public health officials plan for the next emerging infectious disease threat.

The last 18 months have witnessed one of the most rapid and coordinated research responses against an emerging disease to date. Zika virus, a pathogen that has been known since 1947 but poorly studied until recently because it was believed to only cause a mild infection, has rapidly become the object of intense investigation by the international research community since the link between infection and severe congenital disease was announced by Brazilian authorities in November 2015. According to PubMed, the total number of ZIKV-related publications skyrocketed from 117 in 2015 to 3253 in August of 2017. This supplement summarizes the tremendous progress that has been made since 2015 to elucidate the biology of this virus, its various disease manifestations in humans and animals, the diverse routes by which it is transmitted, and the role of various mosquito vectors in the recent outbreaks. In addition, several efforts have been initiated to develop new diagnostics, therapeutics, vaccines, and vector control strategies to better detect, treat, and prevent this important infection. There are 3 factors that contributed to the rapid progress in ZIKV research: (1) the availability of dedicated funding for ZIKV research; (2) the prior existence of both flavivirologists and maternal-child health researchers who were poised to tackle this new public health challenge; and (3) the high level of coordination and collaboration between different research agencies worldwide.

Despite the significant progress, many significant questions remain to be addressed to accelerate the development of effective ZIKV countermeasures and increase our preparedness against this significant public health threat. Some of the most pressing scientific gaps that need to be addressed to advance the field are summarized below.

Keywords. priorities; research directions; Zika.

ZIKA VIRUS INFECTION: NATURAL HISTORY AND MECHANISMS OF PATHOGENESIS

It was the stunning observation that intrauterine exposure to Zika virus (ZIKV) infection caused congenital microcephaly in infants that led to the declaration of a public health emergency in areas where ZIKV transmission was occurring. The causal link between ZIKV exposure and abnormal brain development became established early in the 2015–16 Brazil epidemic through case-control studies of pregnant women and further bolstered by evidence from studies in animal models [1, 2]. The impact of ZIKV on the neurodevelopment in utero raises the possibility that more subtle neurodevelopment abnormalities may occur if there is ZIKV exposure peri- or postpartum. Any impact of ZIKV exposure in utero or early life on a child's neurodevelopment will only be fully understood through carefully designed prospective cohort studies. Observational cohorts comprised of exposed and unexposed infants in regions where there is ZIKV transmission that incorporate neurologic testing, developmental milestones, and cognitive outcomes through school age will further our understanding in this area.

In a minority of cases, ZIKV infection is characterized by clinically significant neurologic disease, most prominently Guillain-Barrè syndrome (GBS) [3]. The pathophysiology of GBS occurring as a parainfectious syndrome with ZIKV is not well understood and represents a significant knowledge gap that could have important implications for vaccine development, especially if GBS after ZIKV infection is immune-mediated. Animal models that recapitulate this neurologic disease in humans are required to test appropriate countermeasures, such as vaccines, antiviral molecules, or monoclonal antibodies.

Natural history studies that measure ZIKV infectiousness in various body fluids is also an important area for research focus to inform public health interventions to control transmission and allow for the evaluation of experimental therapeutics. Men with ZIKV infection may shed ZIKV ribonucleic acid (RNA) in semen for up to 6 months after initial infection [4, 5], and asymptomatic

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blood donors testing positive for ZIKV RNA appear to shed ZIKV in semen at rates similar to those identified with clinical illness [6]. Duration of shedding in female genital secretions and in breast milk are also unknown, but these have implications for controlling epidemic spread. The potential role of pre-existing immunity to flaviviruses in ZIKV pathogenesis is another area of research that needs to be further developed to explore possible links between congenital Zika syndrome (CZS) and neurological disease severity and existing immunity to flaviviruses. In contrast, it will be important to understand whether exposure to ZIKV will change the course of disease to subsequent flavivirus infections such as dengue. This information will better inform vaccine developers and public health authorities on the potential risks of introducing Zika vaccine in flavivirus-endemic areas.

FORECASTING ZIKA VIRUS EPIDEMIC SPREAD

Epidemiologic models that predict ZIKV transmission in advance of appearance of clinical cases will be important to planning an effective public health response. However, accurately forecasting the epidemic spread of other flaviviruses has proven to be a formidable challenge and ZIKV is likely to be similar [7]. West Nile virus, Chikungunya virus, and yellow fever virus epidemics have all demonstrated sporadic and unpredictable patterns of spread [8–13]. Infectious disease epidemic modelers have identified some factors predictive of ZIKV transmission: mosquito density, temperature, rainfall conditions, management of standing water, and human population density are all variables that contribute to a model's accuracy. Among flaviviruses, ZIKV is perhaps unique in its capacity for sexual transmission. This contributes to a greater probability of further spread within a population once introduced through the bite of a mosquito vector. As a sexually transmitted infection, the rate of ZIKV spread is thus likely to be influenced by the demographic structure and sexual mixing within a population [14], adding additional complexity to constructing models that accurately predict the next ZIKV epidemic.

In addition to managing public health resources, accurate forecasting of the next epidemic foci is crucial for executing the evaluation of ZIKV vaccines and therapeutics in clinical trials. The required enrollment for a vaccine trial designed to test the efficacy of a candidate vaccine, for example, will vary widely based upon the event rate (incidence of ZIKV infection) among the enrolled participants. Incidence may be very high when ZIKV is first introduced into a naive population, and then wane the next year. The time necessary to complete a vaccine trial requires brisk enrollment at sites with consistently high incidence. A moving epidemic may necessitate opening and closing research sites as the ZIKV epidemiology changes, leading to delays in bringing a vaccine to the commercial market.

ANTIVIRALS AND DIAGNOSTICS

Zika virus infections usually follow a mild course in terms of symptoms. Therefore, the clinical indication for an anti-ZIKV product—either a small molecule or an antibody—that targets ZIKV replication would not likely be symptomatic ZIKV illness. Rather, preventing CZS in utero would be the highest clinical priority. A rational path for testing anti-ZIKV compounds clinically would focus first on demonstrating safety in healthy adults, then testing in ZIKV-exposed pregnant women to prevent CZS. Given the need to minimize teratogenicity, anti-ZIKV monoclonal antibodies may be a more attractive option than small molecule antivirals for the maternal population. A ZIKV therapeutic might also be useful for the treatment of infants born to ZIKV-infected mothers to lower their viral loads, prevent further damage to their central nervous system, and improve their clinical and developmental outcomes. Improved outcomes have been demonstrated in infants with congenital cytomegalovirus infection, providing a rationale for considering similar testing in ZIKV-infected infants [15].

Zika virus RNA is present in semen for up to 6 months after initial ZIKV infection [4, 5]. Based upon this observation, treating men recovering from ZIKV infection with anti-ZIKV drugs or antibodies to reduce infectiousness to sex partners will also be a priority for ZIKV clinical research. Ultimately, if such strategies prove safe and efficacious, pre- and postexposure prophylaxis for ZIKV-exposed women and male sex partners may limit the risk and devastation of CZS.

As the ZIKV epidemic wanes, it will become increasingly difficult to evaluate the efficacy of therapeutic interventions in infected patients. Therefore, it is important to continue developing immune-competent animal models that recapitulate ZIKV pathogenesis and allow for the evaluation of interventions to prevent CZS [16, 17]. A safe and ethically acceptable controlled human infection model could also be useful to evaluate the effect of ZIKV therapeutics on mild clinical disease and viremia in healthy, nonpregnant adults [18].

The evaluation of experimental ZIKV therapeutics hinges on the availability of rapid, specific, and point-of-care ZIKV diagnostics for different populations that might benefit from a ZIKV therapeutic: pregnant women, infants, and men of reproductive age. Substantial progress has been made in the last 2 years in the development of new molecular diagnostics for ZIKV [3]. Additional research will be needed to convert these diagnostic platforms to rapid, point-of-care testing that can be applied clinically.

Improved serological diagnostics that are sensitive and specific for ZIKV are also urgently needed to be able to diagnose recent and past ZIKV infections and differentiate them from other arboviral infections with similar clinical manifestations (especially dengue and CHIKV). Such improved tests would allow public health laboratories to identify more easily pregnant women that have been infected and greatly facilitate ZIKV epidemiology, natural history, and interventional clinical studies.

VECTOR CONTROL

Developing and testing preventative vaccines and drug therapies is the standard research approach to combating an infectious

disease epidemic. Vector control through pesticides or larvicides is also standard public health practice in limiting mosquito-borne diseases. A challenge arising with the use of current insecticides and larvicides is the rapid development of resistance in mosquitos. An understanding of the molecular mechanism of acquiring resistance will inform the development of the next generation of insecticidal and larvicidal compounds and increase our armamentarium of tools to control ZIKV epidemics. A more detailed understanding of the physiology of vector olfaction might help identify new targets for the development of novel strategies to alter the mosquito olfactory sense and their biting behavior.

Novel technologies in vector manipulation are attractive for public health, especially when they can be applied to several species of mosquitos, because this could result in the control of several mosquito-borne diseases at the same time (eg, ZIKV, dengue, and malaria). Ongoing field studies of *Aedes aegypti* and *Aedes albopictus* altered with endosymbiotic bacterium such as *Wolbachia* sp should help us better understand the effect of manipulated mosquitos on ZIKV epidemic transmission and measure their persistence, fitness, and ecological impact in natural settings [19]. Finally, we will need to better understand the competence of different mosquito vectors for transmitting ZIKV to target the development and implementation of vector-control strategies to the most important mosquito species.

VACCINE DEVELOPMENT

Several efforts to develop ZIKV vaccines were rapidly initiated in response to the recent ZIKV outbreaks, and some of these candidates are currently being evaluated in Phase I and Phase II clinical trials [20]. Because the current ZIKV epidemic is waning, it is unclear whether sufficient ZIKV infections will occur in endemic regions to support efficacy evaluation in traditional Phase III clinical trials. In light of this, it will be very important to learn as much as possible from the immune responses to vaccines in ZIKV-endemic areas and, if sufficient infections occur in the current Phase II study, to elucidate what immunological responses correlate with protection from disease and/or viremia. Natural history studies in endemic countries and studies in well characterized animal models can also advance our understanding of ZIKV immunological correlates of protection. A common endpoint for large efficacy trials of vaccines is the prevention of virologically confirmed symptomatic infection [21]. Because 80% of ZIKV infections are asymptomatic [22], efficacy trials must enroll a very large number of people to reach statistical significance. If a valid surrogate endpoint could be used in efficacy trials (eg, prevention or reduction of viremia), the size of trials could be drastically reduced making them more feasible and less costly. Longitudinal cohort studies in pregnant women should be leveraged to determine the correlation between the level/timing of maternal viremia and the risk of infection and congenital disease in infants. If such a surrogate marker (maternal viremia) was validated and accepted by regulatory authorities, vaccine developers could use it as an endpoint for efficacy in vaccine trials, allowing for more efficient accumulation of clinical trial endpoints. Safe, controlled human infections studies may also allow us to elucidate the correlates of immunological protection in well controlled experimental settings and provide a tool to vaccine developers to select the most promising vaccine candidates to put forward into larger-scale clinical trials.

Despite the remarkable scientific progress that has been made in the last 18 months, it will be challenging to maintain the continued interest by the scientific community, international research funders, and the pharmaceutical industry, as the ZIKV epidemic wanes. Research investments are always made with hopes for long-term benefits. The full benefits of discovery and development are often reaped decades after the initial investments, when technological advances and accrued knowledge bring new interventions. It will be critical to sustain research efforts on ZIKV to fully capitalize on the recent scientific advances and bring new vaccines and other interventions to the market to protect the global community from future outbreaks.

CONCLUSIONS

Zika virus provides a perfect example for re-emerging infections. It came into the public consciousness—seemingly out of nowhere—spreading rapidly and causing a new disease (congenital ZIKV syndrome). The early research response required a robust multidisciplinary effort of virologists, epidemiologists, maternal-fetal clinicians, neurologists, entomologists, bioethicists, and vaccinologists, all working collaboratively. The dramatic events associated with the recent reemergence of ZIKV and the cases of microcephaly in infants remind us, once again, of the importance of supporting and maintaining robust biomedical research programs to prepare for the next inevitable and yet unknown infectious disease threat.

Notes

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