



Potential Research Priorities to Inform Public Health and Medical Practice for Domestic Zika Virus: Workshop in Brief

DETAILS

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Potential Research Priorities to Inform Public Health and Medical Practice for Domestic Zika Virus—Workshop in Brief

Given the recent rapid spread of Zika virus (ZIKV) throughout the Americas and the presence of its vector mosquito species within parts of the United States, RADM Nicole Lurie, Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS), determined an urgent need for additional research to better characterize ZIKV, especially those issues related to the means of transmission and infection during pregnancy.

At the request of Lurie, the National Academies of Sciences, Engineering, and Medicine convened a 1-day public workshop on February 16, 2016, to discuss and explore key factors¹ associated with ZIKV, a single-stranded RNA virus of the Flaviviridae family transmitted to humans primarily through the bite of an infected *Aedes* species mosquito, and its emergence in the United States.

Victor Dzau² described and framed the threat posed by the spread of ZIKV in the context of increasingly frequent emerging infectious diseases. ZIKV is endemic to parts of Africa, spread to Asia, and recently moved to South and Central America, and the Caribbean.³ In the Americas, ZIKV first emerged in Brazil in 2015 and has since spread rapidly, with local transmission in at least 26 countries in South and Central America, Mexico, and the Caribbean, including the U.S. Virgin Islands and Puerto Rico. Although only an estimated one in five people infected with ZIKV develop signs or symptoms, said Dzau, and symptoms that do present are usually quite mild (e.g., conjunctivitis, fever, rash, joint pain), there is concern about infections having severe consequences: in pregnant women, the possibility of microcephaly⁴ and other severe neurodevelopmental birth defects and, in adults, the possibility of Guillain-Barré Syndrome (GBS).⁵ Given the widespread range of the vector and the consequences of ZIKV infection to pregnant women and children, said Dzau, a global response is imperative. The emergence of this outbreak, as well as others in the past decade, illustrates the need to create a global health risk framework⁶—a global architecture to reduce, mitigate, and respond to the next global health crisis—and to identify the leaders, roles, and resources necessary for a timely and coordinated response.

¹ The response to the spread of ZIKV is a rapidly evolving situation involving many aspects of importance. Some aspects were not discussed during this workshop. Their exclusion does not diminish their importance.

² Victor J. Dzau, M.D., is the president of the National Academy of Medicine.

³ For information about the areas of active ZIKV transmission, see <http://www.cdc.gov/zika/geo/index.html> (accessed February 24, 2016).

⁴ Microcephaly is a condition where a baby is born with a small head or the head stops growing after birth.

⁵ Guillain-Barré Syndrome is a neurologic disease that manifests with weakness or paralysis.

⁶ For more information, see *The Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Crises* at <http://www.nap.edu/catalog/21891> (accessed February 24, 2016).

Following Dzau's remarks, Mary Wilson⁷ provided an overview of the workshop objectives, which included discussing: (1) key factors to reduce the likelihood of local transmission of ZIKV in the United States; (2) areas of insufficient knowledge related to the key factors and prevention strategies; (3) potential research priorities of specific concern (e.g., establishing causality or the absence of causality between ZIKV and microcephaly); and (4) critical communication needs of evidence-based information for public health officials, providers, and the general public regarding the level of risk and associated risk factors; transmissibility of the virus; associated health consequences; and the measures and strategies that should be taken to minimize the number of infections and prevent the spread of ZIKV in the United States.

In her charge to the workshop participants, Lurie emphasized the need for conducting research during catastrophic events that can inform and improve responses in real time and for future disasters. She added that disaster science should be conducted in a timely manner, while also not affecting the response in progress, and requires an infrastructure to rapidly identify research priorities and galvanize activity. In this context, she charged the participants to explore potential research priorities to inform public health and medical practice arising as a result of the emergence of ZIKV in the United States (see Box 1 for the full statement of task).

BOX 1 **Statement of Task**

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will organize a 1-day workshop that will explore potential research priorities arising as a result of the emergence of ZIKV in the United States. The workshop will focus primarily on basic science and research questions of specific concern to affected and potentially affected United States communities. The workshop will help inform future research that could be conducted under real-world conditions (i.e., during an event) that would provide public health officials and the general public with additional accurate information about virus transmission, mitigation of health risks, and appropriate measures to prevent the spread of disease. Specific topics that may be addressed in this workshop include:

- Epidemiologic characteristics of ZIKV transmission, for example,
 - Virus vectors
 - Transmission
 - Natural reservoirs
- Basics of disease pathogenesis, for example,
 - Development of relevant animal models
 - Sites of virus replication and consequences of infection
 - Mechanism of transplacental transmission
 - Neurotropism
 - Virus strains, evolution and determinants of virulence
 - Role of the immune response in disease and virus clearance or persistence
 - Cross reactivity with other flaviviruses and the role of prior infection with or vaccination for yellow fever and dengue
- Clinical management and public health intervention, for example,
 - Risk factors for developing clinical disease (symptoms, neurologic complications, fetal infection)
 - Diagnosis
 - Potential for therapeutic intervention
 - Modeling the effects of vector control and/or vaccination

The ad hoc committee will develop the agenda for the workshop session, select and invite speakers and discussants, and moderate the discussions. A Workshop in Brief summary will be prepared by a designated rapporteur in accordance with institutional guidelines, based on the presentations and discussions held during the workshop.

⁷ Mary E. Wilson, M.D., is an adjunct professor of global health and population at the Harvard School of Public Health.

AN EMERGING INFECTIOUS DISEASE: ZIKA VIRUS UPDATE

Discussions began with reviewing what is known about the epidemiological characteristics; vectors and reservoirs; disease pathogenesis and consequences of infections; clinical management and public health interventions; and prevention strategies associated with the further emergence of ZIKV within the United States.

Epidemiological Characteristics

Ronald Rosenberg⁸ and Marcos Espinal⁹ discussed what is known about the origin, spread and epidemiology of ZIKV; the nature and incidence of resulting complications; the role of travelers in transporting the virus; non-vector modes of transmission; and disease surveillance. Sharing the chronology of the spread of the virus, Rosenberg commented on the surprising epidemic of ZIKV infection on Yap Island in 2007, followed by an apparent disappearance for 6 years, and the reemergence of the virus in French Polynesia in 2013. ZIKV then made a very rapid appearance on Easter Island. It was no surprise that it eventually turned up in South America, he said, as it essentially followed the same course as Chikungunya virus (CHIKV) 1 year earlier. Adding to these remarks, Espinal provided an overview of the ZIKV outbreak in Latin America and the Caribbean, indicating that the peak of the epidemic curve for this outbreak has not yet been seen and could result in 2 or 3 million cases in the Americas.

Rosenberg commented that while ZIKV is not new, and though it shares many similarities to other flaviviruses, there is much that is unknown about this virus. It is not known, he said, whether the virus has mutated in a way that facilitated this explosive epidemic. Importantly, without further investigation it will be difficult to determine the risk factors for symptomatic infection, the level of infectivity of asymptomatic people, and the causal relationships between ZIKV in pregnant women and adverse outcomes like microcephaly in infants, or subsequent GBS in infected adults.

Virus Vectors and Reservoirs

Scott Weaver¹⁰ and Thomas Monath¹¹ reviewed vector distribution and vector control strategies associated with ZIKV; potential reservoir hosts; and weather and other climate effects on the virus. Weaver highlighted three hypotheses explaining the recent outbreak in the Americas. First, he said, it is possible ZIKV underwent some sort of adaptive evolution, similar to the mutations of CHIKV, to enhance its infectivity within the mosquitoes transmitting the viruses in these recent outbreaks. Weaver's second hypothesis is that ZIKV mutated to increase rates of viral replication in human hosts, leading to higher levels of viremia and facilitating uptake and spread via mosquito vectors. This perhaps increased efficiency of humans or improved replication that leads to higher levels of human viremia, which would also facilitate more efficient circulation and spread of the virus. The last hypothesis is that nothing at all has changed, Weaver noted, and the rapid spread of ZIKV in the Americas is not due to viral mutations but instead a consequence of its introduction into areas in which nearly all people are immunologically naïve and therefore susceptible to active infection and transmission. That introduction may have, for the first time, increased the risk of virus dispersing around the world in infected travelers and its establishment in the Americas.

Monath noted that temperature and rainfall are typically the most important factors limiting or contributing to arbovirus transmission, as it prolongs mosquito survivorship and shortens the extrinsic incubation period.¹² Both are linked to a changing climate and El Niño, though empirical linkage between these factors and incidence of ZIKV has not yet been established. He added that with warming climates in the Americas, the northern expansion of ZIKV-transmitting mosquitoes is likely and southern California, southern Florida, and southern Texas are areas of concern within the United States. Monath further commented that there is some evidence for the persistence of ZIKV in person-to-person transmission, congenitally and via transfusion and transplantation, but that little is known about the risk of transmission via sexual intercourse. Not much is known about the viremia levels for ZIKV, and data are needed to accurately assess the potential for vector-borne transmission and blood contamination transmission. He also added that not enough is known about the potential for alternative vectors or hosts in the context of ZIKV transmission and because there are no longer ongoing field studies in place, similar to research conducted by the Rockefeller Foundation from the 1940s to the 1970s, "we are at risk of not knowing what we don't know." Monath set forth a number of uncertainties with regard to the

⁸ Ron Rosenberg, Sc.D., is an epidemiologist in the Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention.

⁹ Marcos A. Espinal, Dr.P.H., M.D., M.P.H., is currently the director of the Department of Communicable Diseases and Health Analysis at the Pan American Health Organization.

¹⁰ Scott Weaver, Ph.D., M.S., is director of the University of Texas Medical Branch Institute for Human Infections and Immunity and the Scientific Director of the Galveston National Laboratory.

¹¹ Thomas P. Monath, M.D., is a chief science officer and chief operating officer of BioProtection Systems/NewLink Genetics Corp.

¹² Extrinsic incubation period is the time required for the development of a disease agent in a vector, from the time of uptake of the agent to the time when the vector is infective.

ability of ZIKV to become persistently established in the Americas, including maintenance of human–mosquito infectious cycles; persistence of ZIKV as a reservoir in human hosts; development of sylvatic cycles (e.g., New World primates or mammals serving as alternate hosts); vertical transmission (passage from mature mosquitoes to their ova); and alternate vectors in addition to *Aedes aegypti* and *albopictus*.

Continuing in the vein of uncertainties, Weaver and Monath highlighted a number of important potential research priorities, including learning more about the role of asymptotically infected people as amplifying hosts for mosquito transmission, the contribution of human-to-human transmission, the potential for an enzootic cycle in primates or other vertebrates in the Americas, and interactions between ZIKV and heterologous flaviviruses.

Further commenting on the areas of research pertaining to the vector, Weaver discussed the *Aedes aegypti* and certain properties of its ecology and behavior that make it the perfect vector of ZIKV. It is highly domesticated and can reproduce in small containers of water including tires, discarded plastic containers, and water capture and storage containers in many parts of the world where there is no domestic water service. He added that only female *Aedes aegypti* bite people and tend to bite during the day time and more than once during a single reproductive cycle. More importantly, he noted, it preferentially bites people even when it has the opportunity to bite domesticated animals and over several days after being infected viral levels are amplified. As possible control strategies, Weaver offered: (1) space spraying, rather than outdoor spraying, as a more effective method in reducing *Aedes aegypti* population indoors; (2) perifocal control around diagnosed cases to control the initiation of the cycle after an importation; and (3) targeted source reduction to eliminate the larvae habits of *Aedes aegypti* around houses, in sewers, or other locations to reduce populations and suppress transmission.

Disease Pathogenesis and Consequences of Infection

Richard Kuhn,¹³ Michael Diamond,¹⁴ and William Britt¹⁵ explored what is known and unknown in the areas of viral genetics, evolution, structure, and replication of the virus; the disease pathogenesis and associated complications and immune responses; issues of virus clearance and persistence; and the need for animal models to study ZIKV. Kuhn offered a number of unanswered questions about how the specific ZIKV structure impacts the pathogenesis of ZIKV infection and disease. First, to what extent is the structure of ZIKV heterogenic (in contrast to dengue)? Second, how do ZIKV surface proteins influence infectivity and immunity? Lastly, how does the structure of ZIKV influence receptor interactions and govern virus tropism?

Diamond discussed ZIKV disease pathogenesis, focusing particularly on where pathogenesis of ZIKV is similar to and different from other flavivirus infections. Highlighting a number of areas where additional research is needed, he stressed that animal models of infection and disease pathogenesis with circulating strains (i.e., in mouse and nonhuman primate models) are needed to better understand pathogenesis as well as risks for GBS and maternal–fetal transmission. Specifically, he noted that it is urgent to know how in utero transmission is occurring, whether pre-existing dengue immunity affects ZIKV immunity and the basis for GBS in the context of ZIKV with or without prior dengue infection. He added that longitudinal studies to follow where the virus goes in the body and the nature of the virus-induced injury are also essential to understanding how the disease manifests in humans.

Adding to these comments, Britt reviewed mechanisms for transmission and diseases in congenital viral infections and drew comparisons among rubella, cytomegalovirus (CMV), and ZIKV. He noted that much is still unknown about fetal transmissions because the three systems are involved simultaneously—the pregnant woman, the placenta, and the fetus—and it is difficult to study one system in isolation from the other two. He added that infection of the fetus occurs via the placenta and can lead to fetal thrombotic vasculopathy and loss of placental function, which interrupts the nutrient and oxygen supply to the fetus. This can result in a wide spectrum of health outcomes, including microcephaly, neurodevelopmental delays, seizures, and sensory deficits. In terms of research priorities, Britt suggested generating comprehensive and definitive natural history studies of congenital and prenatal ZIKV infections. Echoing Diamond's comments, Britt also stressed the importance of developing informative animal model systems to study the virus that recapitulate key aspects of human infections.

¹³ Richard Kuhn, Ph.D., is a professor and head in the Department of Biological Sciences and director of the Purdue Institute for Inflammation, Immunology, and Infectious Diseases at Purdue University.

¹⁴ Michael Diamond, M.D., Ph.D., is a professor of medicine, molecular microbiology, pathology, and immunology at the Washington University School of Medicine and the co-director of the Midwest Regional Center for Excellence in Biodefense and Emerging Infectious Disease Research.

¹⁵ William R. Britt, M.D., is a professor of pediatrics in the Division of Infectious Diseases at the University of Alabama at Birmingham School of Medicine and an attending physician at the Children's Hospital of Alabama and the University Hospital of the University of Alabama.

Clinical Management and Public Health Interventions

Laura Elizabeth Riley¹⁶ and Albert Ko¹⁷ reviewed the spectrum of disease in adults, children, and infants; the evidence for microcephaly and other congenital anomalies; diagnostic strategies; cross reactivity; clinical management of the virus; management of potential maternal–fetal and sexual transmission of the virus; and potential prevention strategies. Riley commented on the Centers for Disease Control and Prevention’s (CDC’s) *Interim Guidelines for Pregnant Women During a Zika Virus Outbreak—United States, 2016* (January 2016).¹⁸ She noted gaps in the evidence base used in the development of the guidelines and that research would be helpful to better understand cross reactivity and performance of the serologic test and other diagnostics for ZIKV,¹⁹ the incidence of maternal–fetal transmission by trimester, at what point in utero abnormalities such as microcephaly become apparent, and how often ultrasounds should be repeated. Riley also discussed the possible causal relationship between ZIKV and other adverse outcomes aside from microcephaly that affect both pregnant women and infants. Adding to these comments, Ko highlighted that viral shedding²⁰ post-infection may be prolonged for ZIKV (15 days in urine and 62 days in semen). He noted that the association with GBS needs to be confirmed in studies that can control for possible confounding by CHIKV and other infections. Studies that assess a broader range of possible post-infectious neurological outcomes, such as isolated sensory disturbances and encephalitis, would also be helpful. He also suggested that better diagnostic tools for acute, intrauterine, and past infections need to be developed.

POTENTIAL RESEARCH PRIORITY AREAS

During breakout sessions, individual workshop participants discussed areas of insufficient knowledge and potential research priorities in the following four focus areas: (1) epidemiological characteristics; (2) virus vectors and reservoirs; (3) disease pathogenesis and consequences of infection; and (4) clinical management and public health interventions. When workshop attendees reconvened in the afternoon, breakout session facilitators presented the research priority areas discussed during each session.

Epidemiological Characteristics

Discussants Sonja Rasmussen²¹ and Rosenberg discussed several areas of insufficient knowledge related to the epidemiological characteristics of ZIKV and associated diseases. Participant discussion centered on six potential research priority areas: (1) better understanding of birth defects; (2) the development of better diagnostic tools; (3) improved and accurate risk communication; (4) understanding other (human-to-human) modes of transmission; (5) enhancement of surveillance for ZIKV incident cases, birth defects, and GBS; and (6) data sharing.

Rasmussen began the discussion by highlighting the broad range of questions that have surfaced about the connection between ZIKV and pregnancy, including what factors affect maternal–fetal transmission, how often is the virus transmitted to the fetus, and under what conditions does microcephaly or other neuro anomalies occur, as well as the question of whether or not a mother being symptomatic with the virus is relevant to fetal transmission. Adding to this, Rosenberg emphasized the importance of having diagnostic tools for data collection, and a few participants noted the difficulty in responding to the ZIKV outbreak without more reliable data on which to base interventions. A few participants raised concerns with sharing data as it evolves, including balancing a desire to disseminate information rapidly versus preserving the publication and commercial value and viability of research efforts. Also noted by participants were the perceived differences in how and when governments and researchers from different countries share information during an evolving public health event. Another participant noted that sharing data and counting cases across borders requires a common language to be effective.

Discussion leader Andrew Pavia²² pointed out the need for communication to support the rapid debunking of myths or hastily drawn conclusions. Discussions within this vein covered a broad array of issues, including message fatigue, messaging to reach risk groups within the population, as well as expanding messages to better communicate

¹⁶ Laura Elizabeth Riley, M.D., is the director of obstetrics and gynecology infectious disease at Massachusetts General Hospital.

¹⁷ Albert Icksang Ko, M.D., is a professor and chair of the Department of Epidemiology of Microbial Diseases at the Yale School of Public Health and collaborating researcher at the Oswaldo Cruz Foundation, Brazilian Ministry of Health.

¹⁸ For more information on the interim guidelines for health care providers, see <http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6502e1.pdf> (accessed February 24, 2016).

¹⁹ For more information on the serologic test and other diagnostics for ZIKV, see <http://www.cdc.gov/zika/pdfs/denvchikvzikh-testing-algorithm.pdf> (accessed February 24, 2016).

²⁰ Process that occurs when a virus is present in bodily fluids and can thereby be transmitted to another person.

²¹ Sonja Rasmussen is the director of the Division of Public Health Information and Dissemination, Center for Surveillance, Epidemiology, and Laboratory Services, Office of Public Health Scientific Services, CDC.

²² Andrew Pavia, M.D., FAAP, FIDSA, is the George and Esther Gross Presidential professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah and director of Hospital Epidemiology at Primary Children’s Medical Center.

the role men play in transmitting ZIKV. While there was limited time for the discussion of other modes of human-to-human transmission, Pavia advocated that better understanding the risk of such transmission—including through semen, saliva, and urine—should be a priority. Other participants echoed the idea that other potential transmission modes might expand the focus to include different aspects of risk and response, such as sperm banks and a potential risk to families of service members returning from deployment in infected areas.

Pavia presented potential research priority areas discussed during the breakout session about the epidemiological characteristics of ZIKV that could be addressed now to inform public health and medical practice.

Virus Vectors and Reservoirs

Discussants Stephen Higgs²³ and Thomas Scott²⁴ gave presentations on vector transmission cycles, vector control, mosquito ecology, and the role that mathematical and simulation modeling can play in better understanding this virus. Participant discussion centered on six potential research priority areas: (1) human infection and the role of asymptomatic cases in disease transmission; (2) vector and host biology and ecology; (3) efficacy of current vector control technologies; (4) the role of vertical transmission; (5) research and development, data sharing and governance; and (6) the need for basic research to inform long-term preparedness.

A recurring issue raised by a few participants concerned the contribution of potential modes of human-to-human transmission, specifically sexual transmission and congenital transmission, in the current outbreak or in future sites of potential spread. Many participants noted that data are needed to better assess the various modes of human-to-human transmission, differences in the viremia levels in asymptomatic patients compared to symptomatic patients, and when, within the continuum of the disease, humans transmit ZIKV.

Adding to this, some participants discussed the role of asymptotically infected people as amplifying hosts for mosquito transmission and the interactions between ZIKV and other related viruses,²⁵ as well as the role of immunity and cross protection. Another recurring topic raised by a number of participants was vertical transmission²⁶ within the mosquito population, which typically could stabilize the virus and allow it to survive through cold and dry seasons. However, Monath said, very little is known about this mode in the context of ZIKV. Weaver added that it is difficult to address this experimentally. A few participants discussed the potential for ZIKV to establish an enzootic cycle²⁷ in primates or other vertebrates in the Americas, similar to that of yellow fever, and added that if enzootic circulation were to become established, there may be long-term impact on human disease. In response to this, some participants noted that an appropriate surveillance system for ZIKV and enzootic infection in humans and primates in the Americas could be useful in monitoring for this type of circulation.

Several participants commented on the paucity of data on *Aedes aegypti* and *Aedes albopictus* distribution in the United States and noted the need to track mosquitoes to better understand blood-feeding behavior. The potential of other vectors to transmit ZIKV is concerning, said Weaver, and vector competency studies could be conducted in the laboratory to determine the susceptibility of vectors within the United States. Many participants noted the difficulty in controlling *Aedes aegypti* populations and that past vector control methods were not evaluated to determine public health impact and whether they reduce human infection and disease. Richard Reithinger²⁸ stated that there are many lessons to be taken from successful malaria eradication campaigns. Communities and individual homeowners must take personal responsibility for eliminating *Aedes aegypti* from the property, said Weaver; however, these community-based programs on their own will not be sustainable in controlling the disease spread.

In terms of research and development of vector control technologies and tools, various participants discussed numerous new approaches that could be employed. One participant noted that a central governance mechanism would be useful in prioritizing technologies for research, development, and efficacy trials. Some participants also highlighted the need for models, which could help determine the magnitude of risk for mosquito borne transmission in the United

²³ Stephen Higgs, Ph.D., FRES, FASTMH, is the director of the Biosecurity Research Institute and associate vice president for Research, university distinguished professor, Diagnostic Medicine and Pathobiology, Kansas State University.

²⁴ Thomas Scott is a distinguished professor and the director of the Vector-Borne Disease Laboratory, Department of Entomology and Nematology, University of California, Davis.

²⁵ Relevant arboviruses include the flaviviruses yellow fever, dengue, Japanese encephalitis, and West Nile and the alphavirus CHIKV.

²⁶ Arthropod-borne viruses (arboviruses) are mainly transmitted horizontally among vertebrate hosts by blood-feeding invertebrate vectors, but can also be transmitted vertically in the vector from an infected female to its offspring. Vertical transmission (VT) is considered a possible mechanism for the persistence of arboviruses during periods unfavorable for horizontal transmission, but the extent and epidemiological significance of this phenomenon have remained controversial.

²⁷ Most arboviruses are zoonotic (diseases that can be passed between animals and humans) and have a maintenance enzootic cycle involving birds, rodents, or nonhuman primates as reservoir hosts.

²⁸ Richard Reithinger, Ph.D., M.Sc., is the vice president of RTI International's Global Health Division.

States. To prepare for other emerging viruses, Weaver suggested that efforts be focused on looking at the similarities across the structural biology of viruses, rather than a matrix based approach where characteristics of every virus are looked at discretely, which is an overwhelming task.

David Lakey²⁹ presented potential research priority areas discussed during the breakout session about ZIKV vectors and reservoirs that could be addressed now to inform public health and medical practice.

Disease Pathogenesis and Consequences of Infection

Discussants Kristen Bernard³⁰ and Nikos Vasilakis³¹ highlighted what is known and unknown about ZIKV pathogenesis. Participant discussion centered on three potential research priority areas: (1) developing a comprehensive understanding of the molecular characteristics of the ZIKV; (2) identifying appropriate animal models to examine disease pathogenesis and host responses; and (3) accelerating human clinical research to understand ZIKV pathophysiology, immune responses, susceptibilities, and persistence.

Multiple participants noted the significant gap in the molecular understanding of ZIKV including the lack of information about the viral structure and tropism, cell receptor binding sites, and the cellular consequences following infection. Some participants highlighted specific research questions such as evaluating Zika viral evolution using sequence homology³² between earlier ZIKV strains and current cases in Central and South America and exploring the implications of resultant changes in ZIKV proteins for nervous system infectivity, antibody evasion, and glycan attachment.

Many participants mentioned a concern with the lack of animal models currently available to study ZIKV, and a few participants suggested a number of potential animal models, including rat, ferret, guinea pig, knockout mice, and nonhuman primates (e.g., baboons, macaques), might be informative in studying disease pathogenesis and transmission. Building on this concern, numerous participants highlighted the importance of establishing animal models to serve multiple purposes (e.g., disease pathogenesis, transmission, and vaccine and antiviral countermeasure development), and sharing this information to speed progress in understanding ZIKV and potential approaches to intervene. Several participants noted that it is critical to study ZIKV in humans in the countries most affected and highlighted the importance of establishing a coordinated and well-resourced research approach to ZIKV, which would include the efficient sharing of biospecimens across international borders, availability of rapid funding announcements, better communication among scientists about the types of research being conducted, and the availability of datasets.

Diane Griffin³³ presented potential research priority areas discussed during the breakout session about disease pathogenesis and consequences of infection that could be addressed now to inform public health and medical practice.

Clinical Management and Public Health Interventions

Discussants George Saade³⁴ and Stephen Whitehead³⁵ discussed clinical management and potential prevention strategies. Participant discussion centered on six potential research priority areas: (1) establishing causality, (2) managing pregnancy, (3) clinical assessment, (4) managing travel, (5) vaccines and pharmaceuticals, and (6) facilitating research and public health practice.

Conversations initially focused on establishing causality, particularly in regard to maternal–fetal transmission, including biological plausibility for the relationship, the role of the placenta in transmission, the ease by which the virus moves across the placenta to cause an in utero infection, and neuropathological evidence that the virus is actually causing the damage suspected.

Management of pregnancy was also raised as a concern by several participants, particularly in terms of the evidentiary basis for the interim guidelines for health care providers. Research on risk communication was also suggested by

²⁹ David L. Lakey, M.D., is the associate vice chancellor for Population Health for the University of Texas System and the Senior Vice President for Population Health and Isadore Roosth distinguished professor at the University of Texas Health Science Center in Tyler.

³⁰ Kristen A. Bernard, Ph.D., D.V.M., M.S., is an associate professor of virology in the Department of Pathobiological Sciences, University of Wisconsin–Madison.

³¹ Nikos Vasilakis, Ph.D., is an associate professor at the Department of Pathology and Center of Biodefense and Emerging Infectious Diseases at the University of Texas Medical Branch.

³² The degree of similarity between sequences of amino acids that can serve as a potential indicator of the genetic relatedness between the organisms.

³³ Diane E. Griffin, M.D., Ph.D., is a university distinguished service professor and Alfred and Jill Sommer chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health.

³⁴ George Saade, M.D., is a professor of obstetrics and gynecology, professor of cell biology, director of the Perinatal Research Division, chief of obstetrics and maternal–fetal medicine and the Jennie Sealy Smith distinguished chair in obstetrics and gynecology at the University of Texas Medical Branch.

³⁵ Stephen Whitehead, M.S., Ph.D., is currently a senior associate scientist in the Laboratory of Infectious Diseases at the National Institutes of Health.

many participants, specifically on how to communicate risk to those who might become pregnant or who have traveled or have a sexual partner who has traveled to an area of transmission.

Numerous participants raised concerns with clinical assessment and diagnostic tests for ZIKV, particularly the sensitivity, specificity, and predictive value of the tests, as well as how to interpret results. Some also commented on the extent and duration of infection in semen, blood, and breast milk, and subsequent evidence-based recommendations regarding human contact with such fluids or the handling of infected fluids. As with many outbreaks of infectious disease in a global society, concerns with the management of travel were also raised by some participants. Questions mentioned by individual participants focused on the evidence base for advice provided to returning travelers, possible stigmatization of ZIKV transmission areas, and how to best identify cohorts of people who travel frequently who might be recruited into surveillance or epidemiology studies to better understand ZIKV transmission.

While vaccines and pharmaceuticals were mentioned as obvious strategies for public health management or for treatment clinically, some participants noted that there are no current vaccine candidates in development, making rapid development a challenge. GBS was also discussed, as there have been news reports that ZIKV-specific intravenous immunoglobulin (IVIG) products are in development. Participants noted that there is uncertainty surrounding these treatments for these populations and the need for possible clinical studies.

Various participants also explored a number of items focused on facilitating research and public health practice, including the shipment of samples across borders, availability and appropriateness of personal protection equipment, improving data sharing and availability, and coordinating research networks. The importance of pre-positioning a standardized consent study, protocols, and other disaster science resources that might be applicable in future outbreaks was also highlighted by some participants, echoing remarks by Lurie in her initial charge to participants. Lastly, Dan Hanfling³⁶ noted the opportunity this outbreak affords to improving long-term preparedness and the engagement of the health system and communities.

Lynn Goldman³⁷ presented potential research priority areas discussed during the breakout session about clinical management and public health interventions that could be addressed now to inform public health and medical practice.

³⁶ Dan Hanfling, M.D., is a contributing scholar at the University of Pittsburgh Medical Center, Center for Health Security, clinical professor of Emergency Medicine at The George Washington University, and adjunct faculty at the George Mason University School of Public Policy.

³⁷ Lynn R. Goldman, M.D., M.S., M.P.H., a pediatrician and an epidemiologist, is the Michael and Lori Milken dean of The George Washington University Milken Institute School of Public Health.

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