ACS Infectious Diseases
Editorial
pubs.acs.org/journal/aidcbc

The Known Unknowns of Emerging Viruses

ZIKA VIRUS RESOURCE PAGE

In light of the ongoing Zika virus epidemic *ACS Infectious Diseases* has assembled a resource page (http://connect.acspubs.org/ZIKA) that brings together recent content published by the American Chemical Society on Zika virus, flaviviruses, and other mosquito-borne emerging viruses.

FROM ONE OUTBREAK TO THE NEXT

On April 6, 2016, the White House announced that it would be shifting $589 million in funds earmarked for Ebola to assist in the fight against Zika virus. Less than 12 months ago on May 9, 2015, the World Health Organization (WHO) declared the West African country of Liberia to be Ebola-free. Liberia had reported the highest number of Ebola virus disease-related fatalities during the outbreak with peak numbers of 300−400 cases per week in August and September of 2014. Although Ebola continued to spread in the neighboring countries of Sierra Leone and Guinea, an end to the outbreak seemed in sight, concerns regarding global spread of the virus abated, and media attention shifted from Ebola to including Chikungunya virus and now to Zika virus. In January 2016, WHO issued a statement that the Ebola outbreak had come to an end, wherein it was declared that all transmission chains in all three affected African countries had been broken. However, since the first declaration of an Ebola-free Liberia, and the subsequent declaration of an end to the Ebola outbreak across West Africa, intermittent infections have continued to be reported throughout the region.[1]

A great deal of information was gleaned from this devastating outbreak as the scientific community rallied to contain the virus, improve diagnostics, establish treatment protocols, develop therapeutics and vaccines, and better understand Ebola virus pathogenesis.[2,3] Indeed, critical insights into Ebola virus disease gathered during this outbreak have fundamentally changed the way we view the virus and manage those who become infected.[2] For example, the identification of Ebola virus persistence within sperm for extended periods (months) after it had been cleared from the blood presents a new threat of continued spread through sexual transmission.[4] Nonetheless, as cases become sparse, we are left with a number of fundamental questions. Despite reports of successful clinical trials for Ebola-targeted vaccines, we cannot truly ascertain efficacy in the absence of the outbreak. Similarly, although a handful of individuals recovered from disease following extensive clinical management and treatment with ZMapp, we cannot say for certain whether their survival was due to ZMapp or the high level of supportive clinical care they received.[2] Long-term sequelae has been reported in survivors of Ebola infection; however, no comprehensive studies have been conducted so we have yet to fully understand the long-term physiological ramifications of patients infected during the outbreak.[5] Furthermore, after years of searching, we still do not definitively know the natural reservoir for the virus. What we do know is that Ebola virus will continue to resurface.

The story behind the rise of Zika virus is distinctly different from that of Ebola. Where Ebola had long been recognized, not only by the infectious disease community but by the general population, as a terrifying and deadly disease, few had ever heard of Zika virus prior to the current outbreak in the Americas. Due to the generally mild symptoms associated with Zika infections and limited geographic distribution, Zika was considered of little interest or concern by the scientific community. In fact, a search of PubMed for papers published prior to 2013 returns only 144 results. Despite there being a lack of concerted effort in Zika virus research prior to the current epidemic, we do have a good understanding of natural transmission via mosquito vectors. In the African jungle, Zika is circulated among nonhuman primates by the *Aedes africanus* species of mosquito and has now been transmitted to humans in urban areas by *Aedes aegypti*.[6] In contrast to Ebola, where spread from natural reservoir to humans is poorly understood, understanding this key piece of information about the transmission of Zika virus allows for experts to more effectively model potential spread of the disease. Furthermore, as Zika is closely related to other well-studied flaviviruses, including dengue, yellow fever, and West Nile virus, the wealth of knowledge for these viruses can potentially be translated to Zika. There is of course caution to be had with such translation of knowledge as the current epidemic has brought forth a number of key distinctions between Zika and other flaviviruses. Most notably, evidence suggests Zika has the ability to cross the placenta in pregnant women, causing debilitating microcephaly in developing fetuses.[7,8] It has also demonstrated the capacity for sexual transmission and long-term sequelae including Guillain-Barré syndrome.[6] More and more questions are arising as the Zika epidemic continues. How will prior Zika infection affect future dengue infection or vice versa? What is the causal relationship between Zika infection and microcephaly? Does the virus mutate over time? What are the long-term social and economic implications? How far will Zika spread? Can we develop an effective vaccine or antiviral agent? Once again, the scientific community is rallying to answer these unknowns.

Although Ebola and Zika are distinctly different in many respects, there are a number of parallels to draw between the recent Ebola outbreak and the current Zika epidemic from a research perspective. Research on emerging viruses such as Ebola and Zika is generally not viewed as a priority until a demonstrated global threat materializes. With research dollars being spread thin, a majority of scientists focus their efforts on diseases that are established and pose sustained problems for public health. This leaves a small minority of researchers to study a large number emerging pathogens. In addition, it has become particularly apparent from the emergence of Ebola and Zika that we often know so little about emerging diseases that we do not even know what research questions to ask. There are so many facets of these diseases that are poorly understood.

Received: April 28, 2016
Published: May 13, 2016

DOI: 10.1021/acsinfecdis.6b00072
ACS Infect. Dis. 2016, 2, 310−311

Thus, we have a small number of researchers tasked with answering an infinite number of questions. Ultimately, we will never know which pathogens will in fact emerge as global threat and so we will continue to act in a reactionary manner; nonetheless, what we now know about Ebola and Zika we cannot unknow. As a scientific community, we have the responsibility to continue to pursue these known unknowns after the outbreaks subside.

At *ACS Infectious Diseases*, we hope to serve as a future platform for basic research that will continue to address these important questions. Although the solid basic science to adequately address these questions takes time and we will continue to publish this work as it evolves, we also hope to assist the research community by making any current resources available in a timely manner by making Zika and related content openly available at http://connect.acspubs.org/ZIKA. We hope this resource will serve the scientific community to make further advances in the ongoing fight against Zika virus.

Courtney C. Aldrich, Editor-in-Chief

AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

REFERENCES

(1) WHO Statement (April 2016). New positive case of Ebola virus disease confirmed in Liberia; retrieved from http://www.who.int/mediacentre/news/statements/2016/liberia-ebola/en/.

(2) Mendoza, E. J., Qui, X., and Kobinger, G. P. (2016) Progression of Ebola Therapeutics During the 2014−2015 Outbreak. *Trends Mol. Med. 22*, 164−73. DOI: 10.1016/j.molmed.2015.12.005.

(3) Amarasinghe, G. K., and Basler, C. F. (2015) Filovirus pathogenesis and immune evasion: insights from Ebola virus and Marburg virus. *Nat. Rev. Microbiol.13*, 663−76. DOI: 10.1038/nrmicro3524.

(4) Mate, S. E., Kugelman, J. R., Nyenswah, T. G., Ladner, J. T., Wiley, M. R., Cordier-Lassalle, T., Christie, A., Schroth, G. P., Gross, S. M., Davies-Wayne, G. J., Shinde, S. A., Murugan, R., Sieh, S. B., Badio, M., Fakoli, L., Taweh, F., de Wit, E., van Doremalen, N., Munster, V. J., Pettitt, J., Prieto, K., Humrighouse, B. W., Ströher, U., DiClaro, J. W., Hensley, L. E., Schoepp, R. J., Safronetz, D., Fair, J., Kuhn, J. H., Blackley, D. J., Laney, A. S., Williams, D. E., Lo, T., Gasasira, A., Nichol, S. T., Formenty, P., Kateh, F. N., De Cock, K. M., Bolay, F., Sanchez-Lockhart, M., and Palacios, G. (2015) Molecular Evidence of Sexual Transmission of Ebola Virus. *N. Engl. J. Med.* 373, 2448−245. DOI: 10.1056/NEJMoa1509773.

(5) Vetter, P., Kaiser, L., Schibler, M., Ciglenecki, I., and Bausch, D. G. (2016) Sequelae of Ebola virus disease: the emergency within the emergency. *Lancet Infect. Dis.* DOI: 10.1016/S1473-3099(16)00077-3.

(6) Fauci, A. S., and Morens, D. M. (2016) Zika Virus in the Americas — Yet Another Arbovirus Threat. *N. Engl. J. Med.* 374, 601−604. DOI: 10.1056/NEJMp1600297.

(7) Calvet, G., Aguiar, R. S., Melo, A. S., Sampaio, S. A., de Filippis, I., Fabri, A., Araujo, E. S., de Sequeira, P. C., de Mendonça, M. C., de Oliveira, L., Tschoeke, D. A., Schrago, C. G., Thompson, F. L., Brasil, P., Dos Santos, F. B., Nogueira, R. M., Tanuri, A., and de Filippis, A. M. (2016) Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. DOI: 10.1016/S1473-3099(16)00095-5.

(8) Petersen, L. R., Jamieson, D. J., Powers, A. M., and Honein, M. A. (2016) Zika Virus. *N. Engl. J. Med.* DOI: 10.1056/NEJMra1602113.

DOI: 10.1021/acsinfecdis.6b00072
ACS Infect. Dis. 2016, 2, 310−311