

Zika Virus: Prospects for the Development of Vaccine and Antiviral Agents

Sita Awasthi*

Infectious Disease Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

The recent Zika virus (ZIKV) outbreaks of 2013 in French Polynesia and of 2015 in South and Central America are associated with Guillain-Barré syndrome (GBS) and microcephaly in infants born to the infected mother. Over 4500 new cases of microcephaly, a 20-fold increase in the number of cases in Brazil by early 2016 pressed World Health Organization to declare a public health emergency. In this article, a brief introduction to the recent ZIKV outbreaks and the prospects for the development of vaccines and antiviral agents are discussed.

Keywords: Zika virus; Flavivirus; *Aedes aegypti* mosquitoes; Microcephaly; Chikungunya virus

Editorial

Zika virus (ZIKV) is a member of the flavivirus family, which also includes dengue virus (DENV), Yellow Fever Virus (YFV), West Nile Virus (WNV), Japanese Encephalitis Virus (JEV), Tick-borne Encephalitis Virus (TBEV) and Chikungunya virus (CHIKV). ZIKV was first discovered in Uganda in 1947 and since then there are only a handful of reports of ZIKV outbreaks worldwide. ZIKV circulated in regions of Southeast Asia and Africa, but did not trigger a large outbreak. In 2007 and 2013 outbreaks were reported in Yap Island and Micronesia and in French Polynesia respectively. In May 2015, first confirmed ZIKV infection was reported in Brazil [1,2]. Since then ZIKV virus transmission is reported in countries and territories in Central and South America, Caribbean Islands, Puerto Rico and the U.S. Virgin Islands [3]. While many states in main land United States reported ZIKV infection, none is acquired locally by a ZIKV infected mosquito bites. About 193 travel related cases, including a case of sexual transmission from a returning traveler is reported in main land US (Figure 1). In contrast United States territories have reported 173 ZIKV infections acquired via infected mosquito bites as of March 2016.

The ZIKV is primarily transmitted to humans through the bite of infected *Aedes aegypti* mosquitoes. The virus may also be transmitted from an infected pregnant woman to her baby during pregnancy or, rarely, around the time of birth. Spread of the ZIKV through blood transfusion and sexual contact are reported [4]. Most people who are infected with ZIKV remain asymptomatic, about 20 percent of infected people show mild illness that includes symptoms like fever, rash, joint pain and conjunctivitis, and lasts a week or two. In French Polynesia following ZIKV outbreak of 2013, there have been reports of Guillain-Barré syndrome (GBS) [5]. The GBS is a rare autoimmune disorder in which damaged nerve cells cause muscle weakness and, sometimes, paralysis. Most people do regain the muscle strength from GBS, but in rare cases it leads to permanent nerve damage or death. While it is not scientifically proven that ZIKV infection causes GBS, a strong association exists. During the ZIKV outbreak of 2015, Brazil reported a 20-fold increase in the number of infants born with microcephaly. A total of 4500 cases of microcephaly have been reported by early 2016 by Ministry of health, Brazil [6,7]. So far only a handful of cases have confirmed the presence of ZIKV by RTPCR, full length viral sequence and electron micrographs in fetal brain following termination of pregnancy due to microcephaly at the request of the mothers [8,9]. Microcephaly is a condition when infant is born with abnormally

small head with incomplete brain development [10]. The unanticipated connection between ZIKV and microcephaly, and the lack of prevention or treatment strategies for ZIKV infection in pregnant women have raised the anxiety among couples of childbearing age in the ZIKV prevalent area. Public health agencies in some countries have issued recommendations for pregnancy delay. In the United States, the Center of Disease Control (CDC) has recommended the use of condoms for men and increase prenatal surveillance of pregnant women who have travelled to the ZIKV affected areas [4,11-13]. While connection between ZIKV and microcephaly is not scientifically proven yet, biomedical research community and funding agencies across the globe joining forces to ramp up the research on the basic understanding of ZIKV infection, transmission, treatment, its association with GBS and microcephaly, and the vaccine development.

Vaccine development against ZIKV

In 2015 ZIKV outbreak, approximately 2 million people are reported to be infected in multiple countries [6]. Currently there are no antivirals or vaccine available to combat the infections or disease. Vaccinations against other flavivirus such as YFV, JEV and TBEV infection have been effective in reducing the disease caused by these viruses. Recently, a vaccine against DENV (tetraivalent live attenuated viral vaccine) successfully ended phase III trial, and made its way to Brazil, Philippines and Mexico [14]. Vaccine Research Center (VRC), National Institute of Allergy and Infectious Disease (NIAID) is actively working on developing vaccine candidates to prevent ZIKV infection based on the vaccine platform for other flaviviruses, including a DNA-plasmid based vaccine that uses a strategy similar to an investigational flavivirus vaccine for WNV and found to be safe and immunogenic in a phase I clinical trial; a live-attenuated investigational ZIKV vaccine building on a similar vaccine approach for DENV; and a ZIKV vaccine that uses a genetically engineered version of vesicular stomatitis virus (VSV –an animal virus) and was investigated for Ebola vaccine by

***Corresponding author:** Sita Awasthi, Infectious Disease Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, 522F Johnson Pavilion, 3610 Hamilton Walk, PA 19104-6073, USA, Tel: 215-573-8422; Fax: 215-349-5111; E-mail: sawasthi@mail.med.upenn.edu

Received March 16, 2016; **Accepted** March 21, 2016; **Published** March 27, 2016

Citation: Awasthi S (2016) Zika Virus: Prospects for the Development of Vaccine and Antiviral Agents. J Antivir Antiretrovir 8: LXI-LXIII. doi:10.4172/jaa.1000e130

Copyright: © 2016 Awasthi S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

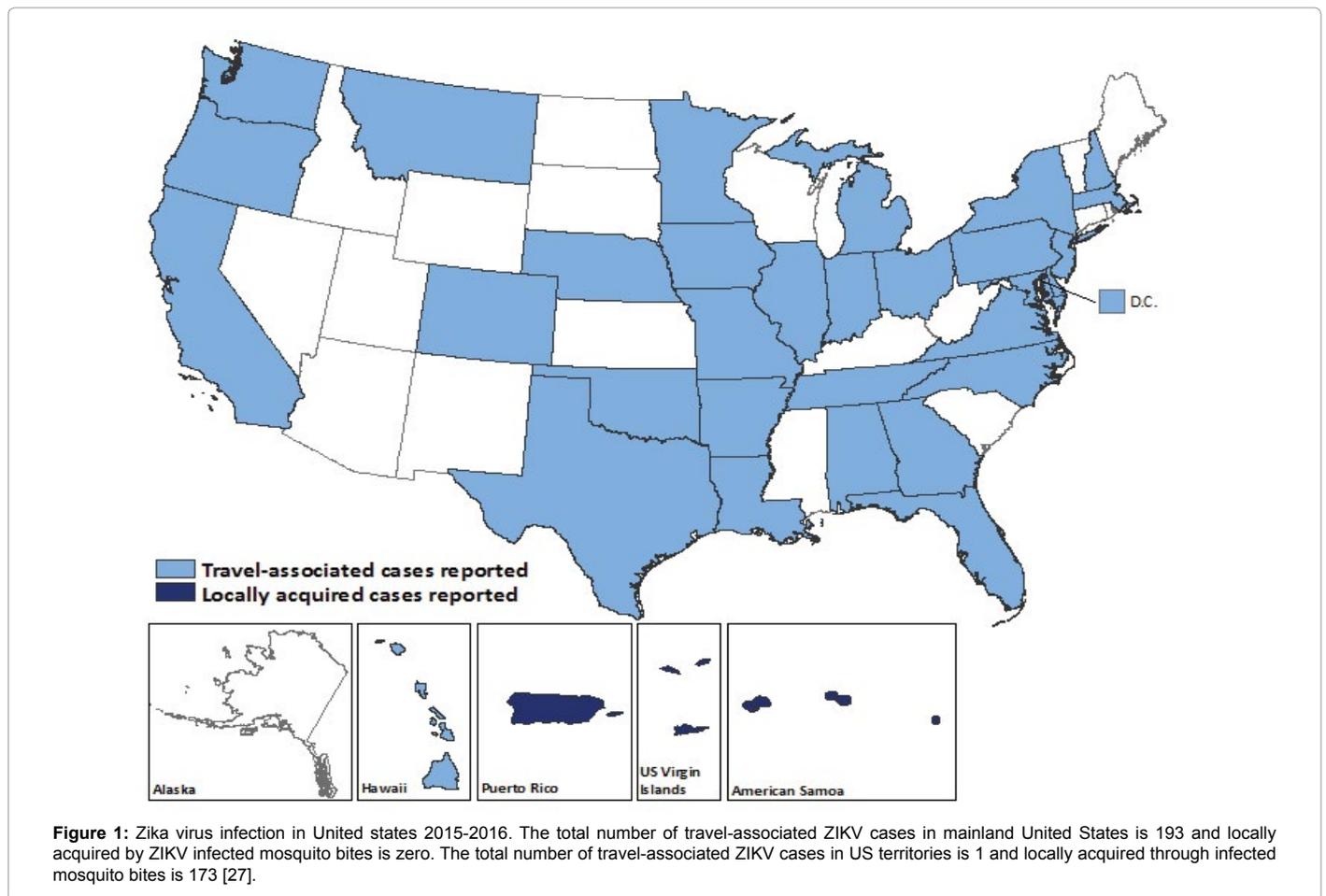


Figure 1: Zika virus infection in United states 2015-2016. The total number of travel-associated ZIKV cases in mainland United States is 193 and locally acquired by ZIKV infected mosquito bites is zero. The total number of travel-associated ZIKV cases in US territories is 1 and locally acquired through infected mosquito bites is 173 [27].

NIAID. These vaccine approaches are at an early stage with plans to evaluate the ZIKV vaccine candidates in tissue culture and animal models. Considering the low strain diversity among ZIKV strains, it may be possible to develop a single vaccine that is effective against all circulating strains of ZIKV [15].

In absence of well-established animal models for assessment of protective immune response and efficacy of vaccine against ZIKV infection is another challenge scientific community phasing. In a recently study by O'Connor and Osorio, ZIKV infection is assessed in Indian rhesus macaques and showed that the viral RNA copies are detected in blood, saliva and urine samples by RTPCR for up to 10 days post-subcutaneous infection. An occasion surge in viral RNA copies after 10 days is noted [16]. There are couple at reports on ZIKV infection of CNS in mice are published. Mice and rhesus studies suggest that both animals are permissive to ZIKV infection, whether it mimics human infection and develops microcephaly or GBS is not examined [17,18]. For a successful ZIKV vaccine, assessment of pre-existing immunity to other flaviviruses is an important issue. The immune response to other flavivirus infections or vaccines could obstruct or promote protective immunity of ZIKV vaccine by boosting the cross-reactivity immunity to other flaviviruses. The pre-clinical studies in animal model and early phase clinical trial will determine immunogenicity in naïve subjects, and subjects with pre-existing immunity to ZIKV or other flavivirus infections or vaccinations.

Development of antivirals and therapeutics

Currently no drug screening studies are reported for ZIKV. Other common flavivirus infections like dengue fever and yellow fever are frequent in some geographical regions, and antiviral drugs are not used commonly to manage symptoms. The fluid therapy has become the key in dengue management, and applied based on the severity of disease. In modern medicine ribavirin, glycyrrhizin and 6-azauridine are reported to have cytostatic and inhibitory effects on the dengue virus [19]. An adenosine analog is another promising drug studied for flavivirus. The chemical 'NITD008' is the best example [20]. The use of computational biology, bioinformatics and high-throughput screening was helpful in searching new antiviral drug for dengue [21]. The high throughput screen helps identify and understand the molecular structure of virus for prediction of binding to the newly developed drug candidates. For example, screening of a combinatorial library of peptidomimetic inhibitors of dengue virus NS2B-NS3 protease [22]. It is only logical to screen these drugs for ZIKV. The drug discovery targets for ZIKV are NS3 (protease and helicase activity), NS5 (RNA-dependent RNA polymerase and methyltransferase activities) and E protein (fusion activity) [23]. Like other flavivirus, ZIKV could also develop resistance strains swiftly following treatment with drug that targets single gene; therefore, use of combination drugs with multiple targets will prove to be a valuable strategy. Immunotherapy using passive transfer of immune IgG and use of human monoclonal antibody (neutralizing) are also viable options for treatment [24,25].

Since an effective ZIKV vaccine is decades away, the development of treatment to limit ZIKV disease is of prime significance. To expedite the treatment plan for ZIKV, National Institute of health (NIH) is funding research to develop drug-screening programs for existing antiviral drugs other flaviviruses, such as DENV, WNV, YFV and JEV, and to create tests that could examine drug compounds for potential antiviral activity against ZIKV. NIH is also evaluating antivirals with activity against hepatitis C, which is not a flavivirus, but is closely related to ZIKV. The overarching goal is to develop a broad-spectrum antiviral drug that could be used to treat a variety of flaviviruses, including ZIKV. If the ZIKV and microcephaly connection is founded, the challenge will be to design new drug trials in pregnant women, the group is rarely included in clinical trials.

Social and behavioral modifications to control ZIKV: In the absence of antivirals and vaccine to combat ZIKV, vector control is a practical strategy to limit new ZIKV infections. The common-sense approach includes removing standing water that serves as breeding ground, insecticide and larvicide application, use of long sleeve clothing, mosquito net, and bug sprays. Such social and behavioral adjustments to avoid mosquito exposure may protect population against other mosquito-borne diseases. Possible option to introduce genetically modified or sterile mosquitoes into the ZIKV epidemic site is also considered [26]. The association between ZIKV infection and microcephaly, and the lack measures to prevent or treat ZIKV in pregnant women, has compelled public health authorities in some countries to recommend use of contraceptives and pregnancy delays [4].

Addendum

Right before the publication of this editorial, a retrospective data analysis of Zika virus outbreak 2013, in French Polynesia was published online on thetancet.com suggesting that the ZIKV infection in the first trimester of pregnancy is associated with increased risk of microcephaly.

References

- Zanluca C, Melo VC, Mosimann AL, Santos GI, Santos CN, et al. (2015) First report of autochthonous transmission of Zika virus in Brazil. *Mem Inst Oswaldo Cruz* 110: 569-572.
- Campos GS, Bandeira AC, Sardi SI (2015) Zika Virus Outbreak, Bahia, Brazil. *Emerg Infect Dis* 21: 1885-1886.
- Fauci AS, Morens DM (2016) Zika Virus in the Americas—Yet Another Arbovirus Threat. *N Engl J Med* 374: 601-604.
- Hills SL, Russell K, Hennessey M, Williams C, Oster AM, et al. (2016) Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission - Continental United States, 2016. *MMWR Morb Mortal Wkly Rep* 65: 215-216.
- Cao-Lormeau VM, Roche C, Teissier A, Robin E, Berry AL, et al. (2014) Zika virus, French polynesia, South pacific, 2013. *Emerg Infect Dis* 20: 1085-1086.
- Heymann DL, Hodgson A, Sall AA, Freedman DO, Staples JE, et al. (2016) Zika virus and microcephaly: why is this situation a PHEIC? *Lancet* 387: 719-721.
- Victora CG, Schuler-Faccini L, Matijasevich A, Ribeiro E, Pessoa A, et al. (2016) Microcephaly in Brazil: how to interpret reported numbers? *Lancet* 387: 621-624.
- Mlakar J, Korva M, Tul N, Popovi M, Poljak-Prijatelj M, et al. (2016) Zika Virus Associated with Microcephaly. *N Engl J Med* 374: 951-958.
- Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, et al. (2016) Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound in Obstetrics & Gynecology* 47: 6-7.
- Harris SR (2015) Measuring head circumference: Update on infant microcephaly. *Can Fam Physician* 61: 680-684.
- Petersen EE, Staples JE, Meaney-Delman D, Fischer M, Ellington SR, et al. (2016) Interim Guidelines for Pregnant Women During a Zika Virus Outbreak - United States, 2016. *MMWR Morb Mortal Wkly Rep* 65: 30-33.
- Meaney-Delman D, Hills SL, Williams C, Galang RR, Iyengar P, et al. (2016) Zika Virus Infection Among U.S. Pregnant Travelers - August 2015-February 2016. *MMWR Morb Mortal Wkly Rep* 65: 211-214.
- Morens DM, Fauci AS (2016) Zika Virus Infection and Zika-Associated Fetal Infection/Microcephaly, in *Harrison's Principles of Internal Medicine*, New York.
- Villar L, Dayan GH, Arredondo-Garcia JL, Rivera DM, Cunha R, et al. (2015) Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 372: 113-123.
- Faye O, Freire CC, Iamarino A, Faye O, de Oliveira JV, et al. (2014) Molecular evolution of Zika virus during its emergence in the 20(th) century. *PLoS Negl Trop Dis* 8: e2636.
- <https://zika.labkey.com/project/OConnor/ZIKV-001/begin.view>
- Becker R (2016) Missing link: Animal models to study whether Zika causes birth defects. *Nat Med* 22: 225-227.
- Bell TM, Field EJ, Narang HK (1971) Zika virus infection of the central nervous system of mice. *Arch Gesamte Virusforsch* 35: 183-193.
- Crance JM, Scaramozzino N, Jouan A, Garin D (2003) Interferon, ribavirin, 6-azauridine and glycyrrhizin: antiviral compounds active against pathogenic flaviviruses. *Antiviral Res* 58: 73-79.
- Yin Z, Chen YL, Schul W, Wang QY, Gu F, et al. (2009) An adenosine nucleoside inhibitor of dengue virus. *Proc Natl Acad Sci U S A* 106: 20435-20439.
- Che PL, Wang L, Li Q (2009) The development, optimization and validation of an assay for high throughput antiviral drug screening against Dengue virus. *International Journal of Clinical and Experimental Medicine* 2: 363-373.
- Freder V, Miertus S (2010) Design, structure-based focusing and in silico screening of combinatorial library of peptidomimetic inhibitors of Dengue virus NS2B-NS3 protease. *J Comput Aided Mol Des* 24: 195-212.
- Whitehorn J, Yacoub S, Anders KL, Macareo LR, Cassetti MC, et al. (2014) Dengue therapeutics, chemoprophylaxis, and allied tools: state of the art and future directions. *PLoS Negl Trop Dis* 8: e3025.
- Oliphant T, Engle M, Nybakken GE, Doane C, Johnson S, et al. (2005) Development of a humanized monoclonal antibody with therapeutic potential against West Nile virus. *Nat Med* 11: 522-530.
- Dejnirattisai W, Wongwiwat W, Supasa S, Zhang X, Dai X, et al. (2015) A new class of highly potent, broadly neutralizing antibodies isolated from viremic patients infected with dengue virus. *Nat Immunol* 16: 170-177.
- Yakob L, Walker T (2016) Zika virus outbreak in the Americas: the need for novel mosquito control methods. *Lancet Glob Health* 4: e148-149.
- (2016) Zika virus disease in the United States, 2015–2016. Centers for disease control and prevention.