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Reviews of Science for Science Librarians: The Challenge of the Zika Virus: An Emerging Arbovirus Disease

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**Review of Science for Science Librarians:
The Challenge of the Zika Virus: An Emerging Arbovirus
Disease**

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Review of Science for Science Librarians:**The Challenge of the Zika Virus: An Emerging Arbovirus Disease**

In early 2015, the previously obscure Zika virus swept into the Americas, seemingly coming from out of nowhere. With unprecedented speed and intensity, it raced across South and Central America, touching large portions of the population, and leaving in its wake unsettling reports of newborns suffering from devastating neurological disorders. By all accounts, this sub-microscopic particle of miniscule size has somehow managed to take the local, regional, national, and international health authorities, as well as the public at large, entirely by surprise. Where did this virus come from? How is it transmitted? What type of illness does it cause? This paper seeks to answer these questions, and more. Following a brief synopsis of the present-day outbreak, it reviews the virology of the Zika virus, its modes of transmission, the nature of Zika Virus Disease, and current and future research endeavors that seek to increase our understanding of the virus.

History

The Zika virus is one of several emerging mosquito-borne viruses, including dengue, West Nile, and chikungunya, that have recently expanded their reach into the western hemisphere. The Zika virus (ZIKV) was first described in the medical literature as an incidental discovery made in 1947 in rhesus monkeys during a sylvatic yellow fever study in the Zika forest of Uganda (Dick, Kitchen, and Haddock 1952, Imperato 2016). Over the course of the next sixty years, a few small, isolated outbreaks of Zika Virus Disease in humans were reported, primarily in Africa and southeast Asia, together amounting to only 14 cases (Vasconcelos and Calisher

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3 2016). In April 2007, the situation changed dramatically, as the first large-scale outbreak
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5 occurred on the Yap Islands of the Federated States of Micronesia. Nearly three quarters of the
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7 islands' 7391 residents were believed to have been infected, and upwards of 900 people became
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9 ill (Duffy et al. 2009). In 2013-2014, a more extensive outbreak occurred in French Polynesia,
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11 resulting in approximately 28,000 cases (Musso, Nilles, and Cao-Lormeau 2014). From there,
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13 the virus cropped up in the Cook Islands, Easter Island, New Caledonia, the Solomon Islands,
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15 and other Pacific islands (Musso 2015).
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23 **Current Outbreak in the Americas**

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25 In late 2014, the Zika virus first emerged in Brazil (Kleber de Oliveira et al. 2016),
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27 presumably stemming from the 2014 Va'a World Sprint Championship canoe race held in Rio de
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29 Janeiro, which reportedly included participants from ZIKV infected areas of French Polynesia
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31 (Musso 2015, Gautret and Simon 2016). Finding abundant breeding grounds for its mosquito
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33 vector in the densely populated urban environments of Brazil, and an immunologically naïve
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35 host population, the virus was able to spread rapidly northward and westward over the course of
36
37 the next year, reaching Mexico by November 2015 (Gatherer and Kohl 2016), Puerto Rico by
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39 December 2015 (Thomas et al. 2016), and threatening to reach continental United States in 2016.
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41 As of May 05, 2016, locally acquired (autochthonous) vector-borne transmission of the Zika
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43 virus had been confirmed in 38 countries and territories in the Region of the Americas (Pan
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45 American Health Organization 2016b). (Figs. 1 and 2).
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52 <Insert Figures 1 and 2 here>
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55 In the United States, according to the Centers for Disease Control and Prevention (CDC),
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57 153 cases of Zika Virus Disease had been reported as of March 02, 2016; a month later, that
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3 number had jumped to 312; and two months later, 472 cases had been reported, all of which were
4
5 travel-associated. As of May 04, 2016, no autochthonous mosquito-borne cases of ZIKV had
6
7 been documented in the United States. However, in the US territories, the situation was quite the
8
9 reverse. As of May 04, 2016, 661 cases were reported in American Samoa, Puerto Rico, and the
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11 US Virgin Islands, including 3 (0.5%) travel-associated cases and 658 (99.5%) autochthonous
12
13 cases, of which 629 (95.6%) occurred in Puerto Rico (Centers for Disease Control and
14
15 Prevention 2016). The most up to date epidemiological information on the Zika virus outbreak in
16
17 the Americas can be found by consulting the resources listed in Table 1.
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22 <Insert Table 1 here>
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25 The current outbreak is the result of a complex interplay of factors involving
26
27 virus/vector/host relationships, many of which are not yet fully understood. The wide distribution
28
29 of the primary vector *Aedes aegypti*, increased international air travel, and the densely populated
30
31 urban areas of Central and South America with less than optimal sanitation are likely
32
33 contributors (Imperato 2016). The strong El Niño weather pattern and record warm temperatures
34
35 that affected Brazil in the latter half of 2015 may have contributed to the rapid spread of the Zika
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37 virus by providing conditions favorable to its mosquito vector (Paz and Semenza 2016).
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39 Adaptive changes made by the Zika virus making it more pathogenic or better able to be
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41 transmitted by new arthropod vectors may also be contributing factors (Costa et al. 2016).
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48 **Virology**

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50 The Zika Virus (ZIKV) is an **arthropod-borne** virus (“**arbovirus**”) of the family
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52 *Flaviviridae*, genus *Flavivirus*, a group of positive-sense, single-stranded RNA (+ssRNA)
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viruses that includes the dengue, yellow fever, West Nile, and the Japanese encephalitis viruses.

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(Table 2) ZIKV is relatively small, measuring approximately 40 nm (Nierenberg 2016), enveloped, and icosahedral in shape. (Fig 3) It has a non-coding region at the 5° and 3° ends, and a single open reading frame (ORF) that encodes for a polyprotein, which is cleaved post-translationally into multiple structural and non-structural proteins (Faye et al. 2014).

<Insert Fig. 3 here>

<Insert Table 2 here>

Upon injection of the virus into the skin of the human host, a complicated sequence of events occurs at the molecular level, leading to attachment and entry of the virus into target cells, and ultimately hijacking of the host's cellular machinery by the virus for its own replication. Consistent with its primary mode of transmission, human dermal fibroblasts, epidermal keratinocytes, and dendritic cells in the skin have been shown to be highly permissive to infection with ZIKV; additionally, the virus has been found to induce the production of autophagosomes in infected fibroblasts, possibly as a means of promoting viral replication (Hamel et al. 2015). After replication in skin cells, the virus disseminates via the lymphatics and blood stream to other parts of the body, including the CNS, heart, skeletal muscles, and possibly crossing the placenta to reach the developing fetus (Chan et al. 2016). The exact target cells of ZIKV are not yet known, though various studies suggest neurological cells may be chief among them. A 1952 study in mice showed the Zika virus to be highly neurotropic (Dick 1952); an in vitro model indicated that human cortical neural progenitors are readily infected by ZIKV (Tang et al. 2016); and an in vitro model mimicking brain development in the first trimester demonstrated that ZIKV induces cell death in cultured neural stem cells (Garcez et al. 2016).

There are two primary strains of ZIKV, African and Asian. Phylogenetic studies indicate that the strain implicated in the 2015-2016 outbreak in Brazil is essentially identical with the

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3 strain that caused the 2013-2014 French Polynesia outbreak, and is of Asian lineage (Zanluca et
4 al. 2015, Musso 2015).
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10 **Arthropod-borne Transmission**

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12 The principal mode of transmission of ZIKV to humans is through the bite of an infected
13 mosquito. The arthropod vector most frequently implicated in the transmission of ZIKV is the
14 female *Aedes aegypti* mosquito, which also transmits dengue, yellow fever, and chikungunya.
15
16 The *Aedes aegypti* mosquito secured its place in the annals of history when, at the turn of the 20th
17 century, it became the object of intense research by Dr. Carlos Juan Finlay, Dr. Jesse William
18 Lazear, Major Walter Reed, and others in their heroic efforts to conquer yellow fever.
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27 The *Aedes aegypti* mosquito is notable in that it feeds throughout the day, prefers humans
28 as the source of its blood meals, and feeds both indoors and outdoors. Over the millennia, this
29 species of mosquito has adapted to coexist with humans, developing a predilection for breeding
30 in small pools of stagnant water such as those found in artificial containers in and around areas
31 of human habitation (Fauci and Morens 2016). These may include water transport and storage
32 containers, old tires, trash bins, flower pots, and discarded plastic containers, as well as wet areas
33 inside the home. Eggs laid by the *Aedes* mosquito are hardy, being able to survive for as long as
34 a year without water, readily hatching once water becomes available (World Health Organization
35 2016b).
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48 In urban settings, humans develop a sufficiently high level of viremia to enable them to
49 serve as the primary vertebrate host for ZIKV, resulting in an urban transmission cycle. Thus,
50 residents of densely settled, resource-poor regions within the vector's geographic range where
51 indoor and outdoor sanitation may be sub-standard are at risk for ZIKV infections. In Africa and
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3 Asia, ZIKV is believed to be maintained in a sylvatic cycle between mosquito and non-human
4 primates, probably monkeys (Lazear and Diamond 2016, Zanluca and Duarte Dos Santos 2016).
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6 Antibodies to the virus have been detected in various large mammals and rodents, but it is not
7
8 known whether these animals serve as reservoirs (Zanluca and Duarte Dos Santos 2016).
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11
12 In the United States, the geographic range of *Aedes aegypti* extends into the southeastern
13 part of the country, making it feasible that vector-borne autochthonous cases will occur in states
14 such as Florida, Texas, and Louisiana. However, ZIKV is also transmitted by several other *Aedes*
15 species, including *Aedes albopictus* (Chouin-Carneiro et al. 2016), which notably has a more
16 northerly geographic range that extends well into the central and eastern part of the country
17 (Kraemer et al. 2015).
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21 If the ZIKV genome is able to make adaptive changes to improve the effectiveness of the
22 *A. albopictus* mosquito as a vector, as occurred with the chikungunya virus, it could move into
23 areas lacking *A. aegypti*, potentially bringing the virus to much of the US, as well as to Canada,
24 Chile, and parts of Europe and Asia (Gardner, Chen, and Sarkar 2016, Stein 2016, Petersen and
25 Busch 2010). The virus has been recovered from other mosquito genera as well, such as
26 *Anopheles*, *Culex*, and *Mansonia* (Ayres 2016), though again it is not clear whether they are able
27 to serve as competent vectors (Gardner, Chen, and Sarkar 2016).
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46 **Non-arthropod-borne Transmission**

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48 The potential for vertical transmission from mother to child emerged as a major global
49 health concern in the 2015-2016 outbreak due to the observed increase in microcephaly in
50 fetuses/newborns of mothers who had been infected with ZIKV during pregnancy (Kleber de
51 Oliveira et al. 2016). Microcephaly has been traditionally defined as an abnormally small head
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3 that is more than 2 standard deviations (SDs) below the mean for the age and sex of the child
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5 (Weaver 1999). In Brazil, the national live birth registry applied a stricter definition for
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7 microcephaly as being ≥ 3 SDs for age and sex (Kleber de Oliveira et al. 2016).
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10 Temporal and circumstantial evidence has been reported for the transplacental
11
12 transmission of ZIKV and its association with microcephaly. Amniotic fluid from two pregnant
13
14 women in Brazil with past exposure to ZIKV who were diagnosed with fetal microcephaly was
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16 shown to be positive for the Zika virus (Oliveira Melo et al. 2016), and autopsy results of a
17
18 microcephalic fetus of a woman who was presumed to have had a ZIKV infection at 13 weeks'
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20 gestation showed ZIKV in the brain tissues (Mlakar et al. 2016).
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24 The mechanisms by which ZIKV may cause microcephaly and other neurological defects
25
26 are not yet clear. The virus could cross the placental barrier and infect the fetus directly, as
27
28 occurs with rubella and cytomegalovirus (Mor 2016). Alternatively, the virus may induce an
29
30 inflammatory response in the placenta, or it may disrupt the production by the placenta of
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32 particular genes, molecules, or pathways, which in turn may adversely affect fetal brain
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34 development (Adibi et al. 2016, Mor 2016).
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38 Sexual transmission has been confirmed in a small number of cases in the US and
39
40 elsewhere as a result of sexual contact with men returning from travel to Zika-infected areas who
41
42 experienced symptoms consistent with ZIKV Infection (Foy et al. 2011, McCarthy 2016, Oster et
43
44 al. 2016). The semen of a man who contracted a ZIKV infection in the 2013-2014 French
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46 Polynesia outbreak tested positive for the virus on reverse transcriptase polymerase chain
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48 reaction (RT-PCR) two weeks after recovering from the illness (Musso, Roche, Robin, et al.
49
50 2015). In a 2014 travel-associated case in the United Kingdom, semen from a man tested positive
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52 for ZIKV at 27 and 62 days after onset of illness (Atkinson 2016). Both cases raise concerns
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3 about the long-term persistence of ZIKV in semen and a possible post-recovery carrier state. The
4 risk of sexual transmission is of particular concern if the female partner is pregnant, as the virus
5 could possibly be transmitted to the fetus.
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10 Other possible routes of transmission, such as saliva, urine, respiratory droplets, breast
11 milk, vaginal delivery, mucocutaneous exposure, hemodialysis, and organ transplantation, cannot
12 be ruled out (Chan et al. 2016).
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17 Transmission of ZIKV through blood transfusion is a credible risk, given the
18 asymptomatic viremia that occurs early in the infection, the high rate of asymptomatic cases, and
19 the high incidence of infection that occurs among immunologically naïve populations during
20 massive outbreaks (Marano et al. 2015, Petersen and Busch 2010). In the 2013-2014 outbreak in
21 French Polynesia, 2.8% (42/1505) of asymptomatic blood donors tested positive for ZIKV on
22 RT-PCR, and 26.2% (11/42) of those reported a Zika-like illness 3-10 days after donating blood
23 (Musso et al. 2014).
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34 In lieu of a blood donor screening test for ZIKV for use by blood collection centers, the
35 US Food and Drug Administration has issued the following guidelines for blood donations. In
36 areas with no active ZIKV transmission, a 4-week deferral period is recommended for donors
37 deemed to be at risk for Zika infection, and in areas with active transmission, it is recommended
38 that blood and blood products be obtained from outside the region (Marks, Epstein, and Borio
39 2016).
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48 However, in geographically isolated areas, it may be impractical or impossible to obtain
49 blood from another region. Such was the case during the 2013-2014 French Polynesia outbreak,
50 prompting local health authorities to grant permission for use of RT-PCR to screen locally
51 donated blood, coupled with pathogen inactivation for selected blood products (Musso et al.
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3 2014). In the future, it is hoped that pathogen reduction techniques will be developed that could
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5 be applied to all blood products, thereby reducing the need for the battery of expensive screening
6
7 tests currently in use (Marks, Epstein, and Borio 2016).
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10 11 12 **Zika Virus Infections**

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15 In approximately 80% of cases, infection with the Zika virus is asymptomatic or very
16
17 mild, with only about 20% of those infected actually becoming ill (Centers for Disease Control
18
19 and Prevention 2016a). Those who become symptomatic, do so following an incubation period
20
21 of 2-14 days (Chan et al. 2016, Rudolph et al. 2014), with a systemic febrile rash illness similar
22
23 to dengue or chikungunya. The current PAHO/WHO definition for a suspected case of Zika
24
25 Virus Disease is a patient with rash, plus two or more of the following symptoms: fever,
26
27 conjunctivitis, arthralgia, myalgia, and peri-articular edema (Pan American Health Organization
28
29 2016a). Other symptoms that have been reported include headache, fatigue, malaise, chills, retro-
30
31 orbital pain, paresthesia, lymphadenopathy, edema, diarrhea, nausea, vomiting, abdominal pain,
32
33 sore throat, dizziness, and dysuria (Brasil et al. 2016, Chan et al. 2016).
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39 Since fever is not always a presenting symptom, use of the term “Zika Fever” is
40
41 discouraged. In fact, a 2016 report of ZIKV infections in pregnant women in Brazil showed that
42
43 whereas maculopapular rash, conjunctivitis, and lymphadenopathy were clinically significant
44
45 features, fever was present in only 28% of the cases (Brasil et al. 2016). However, other studies
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47 showed higher numbers: in a retrospective study of 2015 data from Brazil, 67% of patients had
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49 fever (Cerbino-Neto J 2016), and a study from Puerto Rico in 2015-2016 showed that 73% had
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51 fever (Thomas et al. 2016).
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Review of Science: Zika Virus

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3 The majority of ZIKV illnesses are self-limiting, with most symptoms resolving within 3-
4
5 7 days. Because of the high rate of asymptomatic infection, non-specific symptomology,
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8 resemblance to other arbovirus infections, and possible co-infections with other endemic viruses
9
10 such as dengue or chikungunya, many cases of ZIKV infection are probably undiagnosed or
11
12 misdiagnosed.
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14 15 16 17 18 **Complications of Zika Virus Infections**

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20 Despite the mild nature of the disease and high rate of asymptomatic cases, Zika virus
21
22 infections are of concern because of their suspected association with microcephaly and other
23
24 neurological abnormalities. In the 2013-2014 outbreak in French Polynesia, perinatal
25
26 transmission, either transplacentally or during delivery, was reported (Besnard et al. 2014), and a
27
28 retrospective analysis of the data suggested that exposure to ZIKV by pregnant women in the
29
30 first trimester was associated with an increased risk of microcephaly (Cauchemez et al. 2016). In
31
32 Nov 2015, a nearly 20-fold increase in the incidence of microcephaly was reported in Brazil,
33
34 with 99.7cases/100,000 live births, versus 5.5 cases/100,000 live births in 2000 (Pan American
35
36 Health Organization 2015). Between Jan 01, 2015 and Jan 07, 2016, a total of 574 cases of
37
38 microcephaly were identified in Brazil, compared with an average of 157 cases per year for the
39
40 years 2000-2014 (Kleber de Oliveira et al. 2016). ZIKV infections contracted during the first
41
42 trimester of pregnancy appear to be associated with an increased risk of microcephaly
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44 (Cauchemez et al. 2016, Kleber de Oliveira et al. 2016), though fetal abnormalities have been
45
46 reported following ZIKV infections during any week of gestation (Brasil et al. 2016).
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3 Along with a small head circumference, congenital microcephaly is characterized by a
4 heterogeneous range of clinical findings, including facial disproportionality, excess skin scalp
5 folds, hypertonia or spasticity, tremors, hearing and visual abnormalities, umbilical hernia,
6 clubfoot, arthrogryposis, and more (Miranda-Filho et al. 2016). Zika virus infections during
7 pregnancy were found to be associated with intrauterine growth restriction, cerebral
8 calcifications, placental insufficiency, and oligo- or anhydramnios (Brasil et al. 2016). In a small
9 study of microcephalic newborns, various ocular defects were found, including optic nerve
10 alterations and macular abnormalities, especially foveal reflex loss (Ventura et al. 2016).
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22 In addition to congenital complications, Zika infections have been associated with an
23 increased incidence of Guillain-Barre Syndrome (GBS), a rare acute inflammatory autoimmune
24 neuritis that is frequently triggered by a preceding viral or bacterial infection (Cao-Lormeau et
25 al. 2016). In the 2013-2014 Zika outbreak in French Polynesia, forty-two cases of Guillain-Barre
26 Syndrome (GBS) were reported, representing a 20-fold increase over the previous four years
27 (Cao-Lormeau et al. 2016, Oehler et al. 2014, World Health Organization 2016c). In the current
28 outbreak, an increased incidence of GBS has been reported in Brazil, El Salvador, Suriname, and
29 Venezuela, and cases of GBS with confirmed ZIKV infection have been reported in Columbia,
30 Dominican Republic, Honduras, Puerto Rico, Haiti, and Martinique (World Health Organization
31 2016c). It is thought that the unusual spike in GBS cases both in French Polynesia and in the
32 Americas may be due to co-infections with dengue and ZIKV, and/or consecutive arbovirus
33 infections (Zika Virus Infection, 2016).
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50 On Feb 01, 2016, the World Health Organization (WHO) declared a Public Health
51 Emergency of International Concern (PHEIC) due to concern over the possibility of an
52 association between ZIKV infections and microcephaly, GBS, and other neurological disorders
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3 (World Health Organization 2016a). On April 07, 2016, the WHO issued a statement saying that
4
5 “Based on a growing body of preliminary research, there is scientific consensus that Zika virus is
6
7 a cause of microcephaly and Guillain-Barré syndrome” (World Health Organization 2016c).
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10 From a societal and sociological standpoint, numerous immediate and long-term
11
12 repercussions of the current ZIKV outbreak are becoming apparent. Counseling will be required
13
14 for pregnant women who contract a ZIKV infection, especially during the first trimester.
15
16 Intensive care treatment for patients struck by Guillain-Barre Syndrome will be crucial, as will
17
18 long-term treatment of newborns with microcephaly and other neurological abnormalities.
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20 Patients will need multidisciplinary support and ongoing medical care, incurring a substantial
21
22 burden to individuals, families, and communities. These factors will have serious long-term
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24 implications for overall health policy, especially in resource-poor regions.
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32 **Laboratory Diagnosis**

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34 Currently, there is no rapid diagnostic test for ZIKV available for routine use in clinical
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36 laboratories or at the point of care. Therefore, diagnosis is often made on the basis of clinical
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38 presentation, travel history, and time spent in an area of active ZIKV transmission, keeping in
39
40 mind that the disease may mimic or coexist with other endemic infections. For confirmation of
41
42 ZIKV infections, the most accurate test currently available is the reverse transcriptase
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44 polymerase chain reaction (RT-PCR), which detects the presence of Zika viral RNA in serum,
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46 plasma, or other body fluids. Several RT-PCR assays have been developed, including one
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48 designed by the CDC that uses “two one-step real-time RT-PCR (rRT-PCR) reactions targeting
49
50 the ZIKV premembrane (prM) and envelope (E) genes, respectively”, as well as other assays that
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52 target various non-structural proteins such as NS1, NS3, and NS5 (Waggoner and Pinsky 2016).
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Other methods for laboratory diagnosis of ZIKV include serologic testing for IgM antibodies using enzyme-linked immunosorbent assays (ELISA), coupled with plaque-reduction neutralization tests (PRNT) to determine neutralizing antibody titers (Duffy et al. 2009). Cross-reactivity with other flaviviruses, especially the dengue virus, with which ZIKV often co-exists, can make interpretation of ELISA test results difficult. This is particularly true when ZIKV is a secondary flavivirus infection, or in populations with background immunity to other flaviviruses (Lanciotti et al. 2008). Nevertheless, in suspected cases of Zika virus infection, a positive ELISA test for Zika IgM antibodies, coupled with sufficiently high PRNT titers and in the absence of other flaviviruses, is considered confirmatory for ZIKV (Pan American Health Organization 2016a).

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The period of viremia with ZIKV infections is believed to be relatively brief, approximately 3-5 days after the onset of symptoms (Waggoner and Pinsky 2016), reflecting the ideal time frame for collecting blood samples for diagnosis of acute ZIKV infections. This can be challenging, given the non-specific nature of the symptoms and lack of a clear onset of illness. However, urine may prove to be a suitable alternative, as the RNA load in urine has been found to be higher than in serum and is detectable for a longer period of time, and, as a laboratory specimen, it is less invasive to collect (Gourinat et al. 2015). Saliva may also prove to be a useful substitute or adjunct for acute phase diagnosis, especially in pediatric patients, as it will sometimes test positive for ZIKV when a concurrent serum sample tests negative (Musso, Roche, Nhan, et al. 2015). In the future, it is hoped that diagnostic tests will be developed that are able to detect multiple arbovirus infections, such as Zika, dengue, and chikungunya, simultaneously (Waggoner and Pinsky 2016).

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3 Laboratory diagnosis may also be obtained through viral culture, though this method is
4 generally reserved for use in research laboratories and public health facilities (Waggoner and
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6
7
8 Pinsky 2016).
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Treatment

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15 Currently, there is no treatment available specifically for ZIKV infections. Therefore,
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17 treatment consists primarily of supportive care, including rest and fluids, plus antihistamines and
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19 acetaminophen for symptom relief. The use of aspirin is not recommended due to the risk of
20
21 bleeding or Reye's Syndrome, nor is the use of other non-steroidal anti-inflammatory drugs
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23 (NSAIDs), as they are contraindicated in cases of dengue or chikungunya, with which Zika
24
25 infections may coexist (Pan American Health Organization 2015).
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Prevention

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34 Since there is currently no vaccine for ZIKV, prevention of ZIKV infections is primarily
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36 focused on averting arthropod-borne transmission of the infectious agent, both through reducing
37
38 the population of mosquitoes, and reducing contact between mosquitoes and humans (World
39
40 Health Organization 2016b). At the individual level, the use of protective clothing and an
41
42 Environmental Protection Agency (EPA)-registered insect repellent, such as DEET, picaridin,
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44 IR3535, oil of lemon eucalyptus, or para-menthane-diol, is recommended (Centers for Disease
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46 Control and Prevention 2016a). For patients who become symptomatic, it is particularly
47
48 important to avoid mosquito bites during the first week of illness to prevent transmission of the
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50 virus to others during the viremic period.
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3 Within the household, small pools of standing water in and around the home should be
4 eliminated to reduce mosquito breeding habitat. Water storage receptacles and artificial
5 containers should be emptied or covered, and bathing, cooking, and laundry areas should be kept
6 as dry as possible. Since the *Aedes* mosquito bites throughout the day, both indoors and out, the
7 installation of securely fitting window and door screens on homes, and the use of bed nets is
8 advised. These measures are especially important for pregnant women, or those who might
9 become pregnant, in order to prevent possible perinatal transmission.
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20 At the community level, aggressive vector control will serve to disrupt the urban
21 transmission cycle between infected humans, the mosquito vector, and susceptible humans.
22 Efforts should be made to reduce the density of mosquitoes in the locality, and during outbreaks,
23 the spraying of insecticides may be advised (World Health Organization 2016b). Public
24 education campaigns conducted in schools, churches, clinics, stores, and businesses in regions of
25 active transmission will help to raise public awareness of the risks and symptoms of ZIKV
26 infections. Health care professionals are advised to remain alert for signs and symptoms of ZIKV
27 infection among their patients, and whenever possible, provide ultrasound and other diagnostics
28 to pregnant women who may have been exposed. Data and information sharing between
29 communities, and enhanced surveillance at the national and international level, will further
30 contribute to the global prevention and control of widespread ZIKV outbreaks.
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47 In response to studies demonstrating the sexual transmission of ZIKV, the CDC has
48 issued an interim guideline for couples in which a man lives in or has recently traveled to an area
49 of active transmission (Oster et al. 2016). In addition, the CDC has issued a number of guidelines
50 directed at specific populations, including pregnant women and pregnant travelers, and health
51 care providers caring for pregnant women and infants and children. Since these guidelines are
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3 subject to revision as more information about ZIKV becomes available, the CDC website
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6 (www.cdc.gov) should be consulted for the most current recommendations.
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10 11 **Future Perspectives**

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15 The two previous large-scale outbreaks of the Zika virus, which occurred in the Yap
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17 Islands in 2007 and French Polynesia in 2013-2014, abated after roughly a year. Though it is too
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19 early to determine whether the current outbreak in the Americas will follow the same pattern, it
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21 is already clear that this event has exacted a heavy toll on the populations it has affected. In spite
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23 of, or perhaps because of, the enormous challenges it has presented, this outbreak has triggered a
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25 dramatic increase in our overall understanding of this emerging disease. Indeed, the number of
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27 scholarly publications published on the Zika virus has multiplied exponentially in the past year,
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29 as the medical and scientific communities struggle to understand this mysterious illness and its
30
31 sequelae. Yet, there remains much to be learned.
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37 Research initiatives are proceeding apace on multiple fronts, both at the basic science and
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39 clinical level, focusing on all aspects of the virus/vector/host triad. The National Science
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41 Foundation recently announced an invitation for research proposals to address the ecological
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43 transmission dynamics of the Zika virus, including the non-human hosts of ZIKV, transmission
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45 rate of ZIKV between vectors/carriers and humans, and the rate of spread of ZIKV worldwide
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47 (National Science Foundation 2016).
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51 The mosquito vector itself has been, and will continue to be, the subject of active
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53 research. Mosquito resistance to insecticides has long been the subject of research in the context
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55 of malaria and other arbovirus diseases, and will have clear implications for ZIKV transmission.
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57 Studies on the effect of global climate change on the lifespan and geographic ranges of vector
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3 mosquitoes, and how these factors will affect the transmission of ZIKV, are also underway.

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5 Recently, a small biotech company, originally launched by Oxford University in 2002, has taken
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7 mosquito research to a whole new level. It has developed a genetically engineered male
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9 mosquito called OX513A that carries a lethal gene which, when mated with female wild
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11 mosquitos, will cause the offspring to die. The company, now owned by biotech giant Intrexon,
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13 has field tested the mosquito in the Cayman Islands, Panama, and Brazil, and hopes to employ it
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15 in Florida in the near future, pending FDA approval (LaMotte 2016).
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20 Complementing these initiatives, the National Institute of Allergy and Infectious Diseases
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22 (NIAID), has invited proposals for projects covering a wide range of basic science and clinical
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24 aspects of ZIKV and Zika Virus Disease (National Institute of Allergy and Infectious Diseases).
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26
27 (Table 3)

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29 <Insert Table 3 here>
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33 Though information gained from each of these research foci will be essential for building
34
35 the overall knowledgebase of Zika, research in three areas in particular is urgently needed. First,
36
37 it is critically important that the mechanism by which the Zika virus causes congenital
38
39 neurological abnormalities be elucidated, in order to prevent the development of devastating
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41 birth defects. Secondly, an affordable, rapid, and reliable diagnostic test for ZIKV for use in
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43 clinical environments is vital to enable the timely and accurate diagnosis of Zika infections.
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45 Finally, the development of a safe and effective vaccine against ZIKV is a clear priority, as it
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47 may well prove to be the world's best hope for conquering this new disease. Yet the
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49 development of a vaccine for any infectious disease is no trivial matter. At best, it can take years,
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51 perhaps decades, to come to fruition. At worst, the efforts will sputter and stall, only to languish
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53 as unfunded, orphan initiatives.
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3 Undaunted, the challenge of developing a ZIKV vaccine has been taken up by multiple
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Undaunted, the challenge of developing a ZIKV vaccine has been taken up by multiple entitles, including universities, pharmaceutical companies, private research institutes, and government bodies, as described in a recent article in *Science* (Cohen 2016). For example, NewLink Genetics of Massachusetts, USA, is working to develop a traditional-style vaccine using an inactivated virus. The advantage of this type of vaccine is that it may be more likely to be approved for use in pregnancy. Researchers at the Butantan Institute of São Paulo, Brazil are investigating use of an attenuated live vaccine made with a technology similar to that used by the NIAID for its dengue vaccine. The technology used by the NIAID for its West Nile vaccine may be yet another option. This involves the insertion of a circular DNA plasmid containing specific ZIKV genes into bacterial cells, resulting in the production of “virus-like particles” that will elicit an immune response similar to that of inactivated vaccines (Cohen 2016).

By passing the need for a bacterial carrier cell altogether, Inovio Pharmaceuticals of Pennsylvania, USA is working to develop a vaccine using simply a plasmid containing Zika virus genes, which would be injected directly into the skin. Though this method can be used to produce a vaccine relatively quickly, in the past, it has been plagued by failure to launch a sufficiently strong immune response. Still another high-tech strategy is to insert the ZIKV genes into the genome of a harmless virus, which is similar to the approach used by GlaxoSmithKline for its recently developed Ebola vaccine (Cohen 2016).

Which of these strategies will eventually emerge as the industry leader(s) is anybody’s guess at this point. The fervent hope of the general public and health authorities alike is that one of them will ultimately be successful in producing a vaccine capable of forestalling the next Zika pandemic.

Conclusion

Though once thought of merely as the source of a mild, unremarkable arboviral disease that was little cause for concern, the Zika virus has proven its ability to wreak havoc on a global scale. The medical and scientific community is still very early in the process of understanding the science of this disease and its clinical sequelae, and much of the information presented herein may already be outdated. As this event unfolds, we are witnessing the creation of medical history before our very eyes and observing the generation of scientific knowledge in real time, with new findings being revealed on almost a daily basis. May the lessons learned carry us forward, ready and prepared to meet the next emerging viral pandemic.

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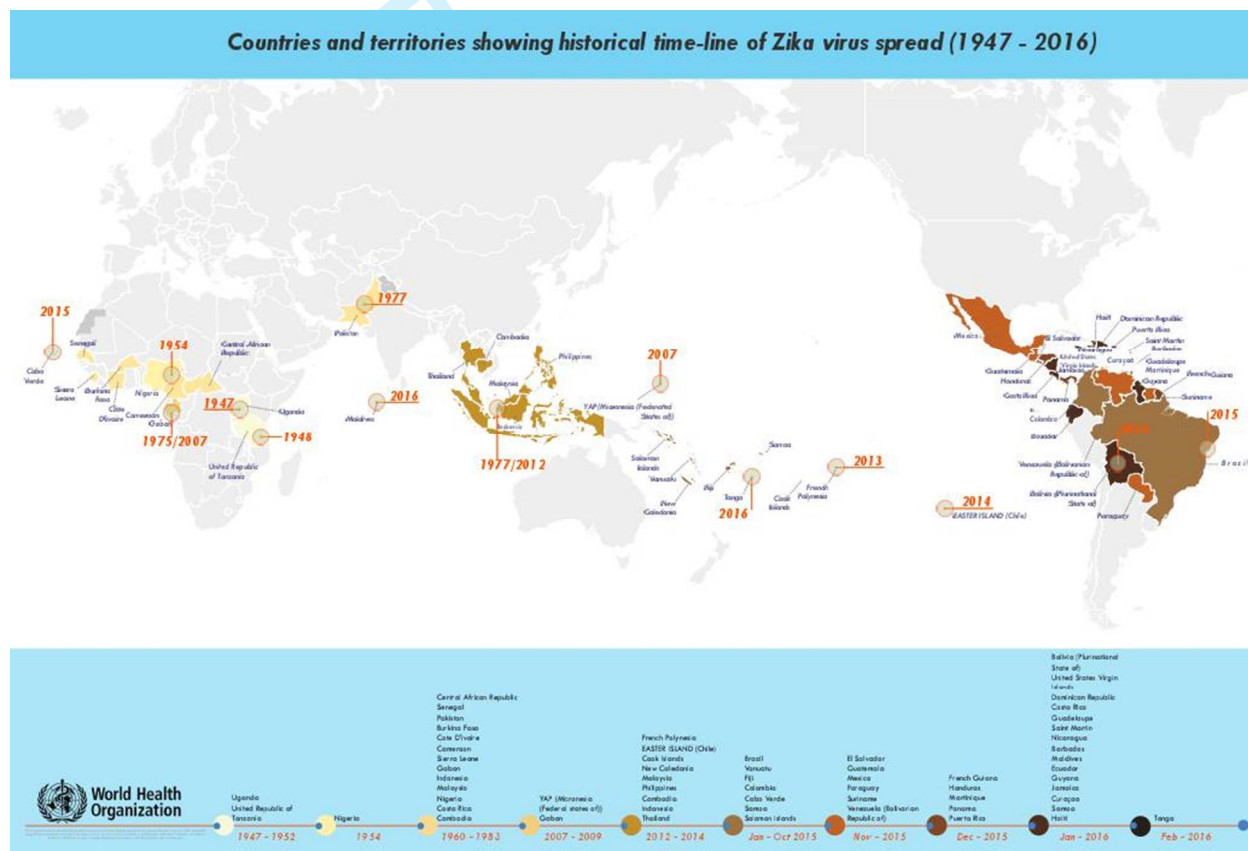
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Figures and Tables

Fig 1. Timeline of global Zika virus spread, 1947-2016. Source: World Health Organization.

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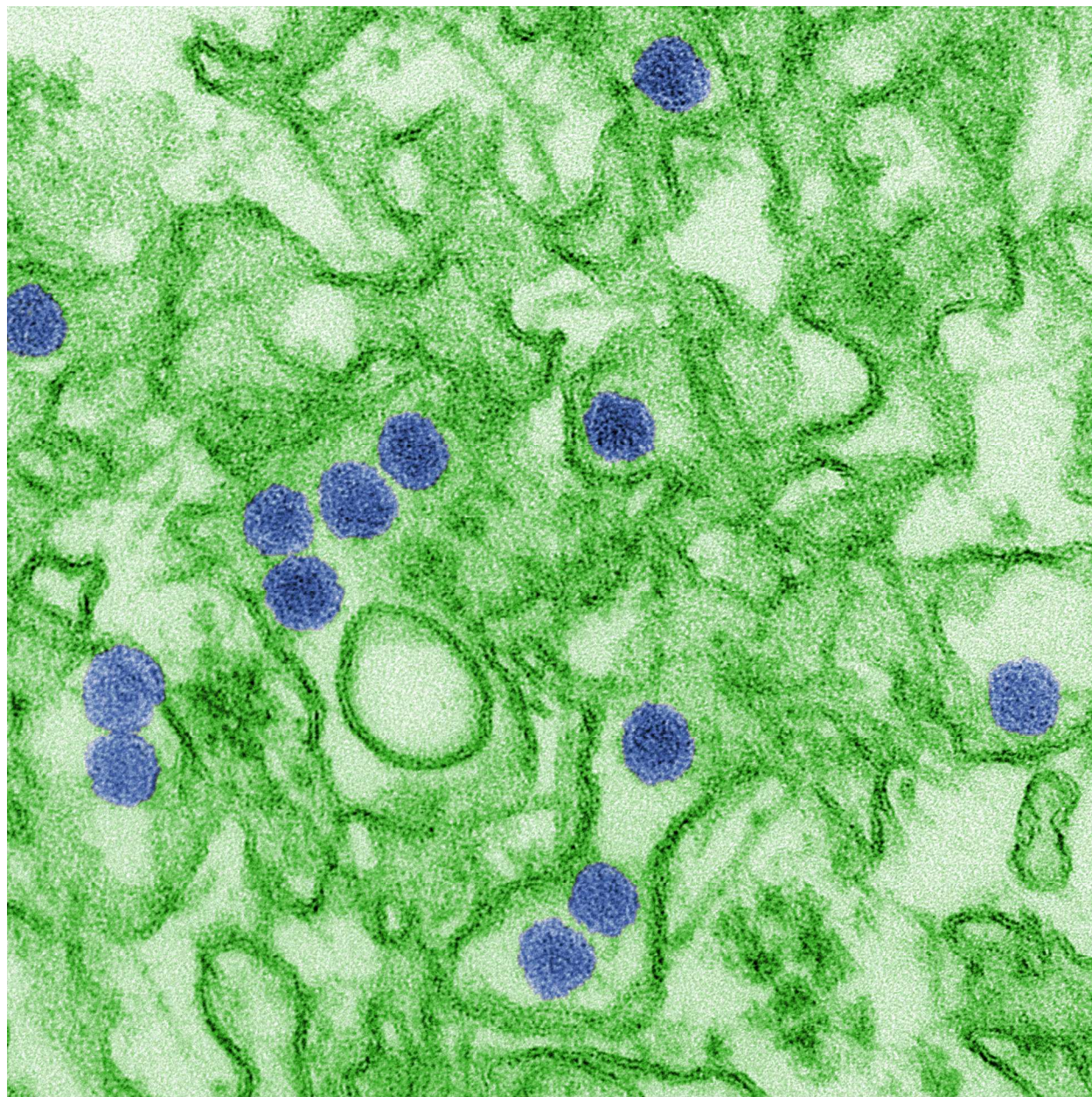
Fig. 2. The distribution of Zika virus in the Americas, 2015-2016. Source: World Health Organization. <http://www.who.int/emergencies/zika-virus/situation-report/7-april-2016/en/> Accessed 04/15/16. Used with permission.



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Fig 3. Transmission electron micrograph (TEM) of the Zika virus. Source: Cynthia Goldsmith, Centers for Disease Control and Prevention (<http://phil.cdc.gov/phil/details.asp?pid=20541>).

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Table 1. Selected websites for clinical, epidemiological, and research information on Zika Virus and Zika Virus outbreaks.

Resource	Description
Centers for Disease Control and Prevention (CDC): Zika Virus http://www.cdc.gov/zika/index.html	Provides comprehensive information on all aspects of Zika Virus, including weekly epidemiologic updates. Operated under the US Department of Health & Human Services.
Disaster Information Management Resource Center (DIMRC): Zika Virus Health Information Resource Guide https://sis.nlm.nih.gov/dimrc/zikavirus.html	Includes an extensive listing of resources on Zika virus outbreaks from US and international sources. The DIMRC is part of the US National Library of Medicine.
European Centre for Disease Prevention and Control (ECDC): Zika Virus Infection http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/Pages/index.aspx	Provides mosquito maps for the EU, risk assessment documents, epidemiological updates, and news. The ECDC is an independent European Union agency.
Health Map: Zika Outbreak http://www.healthmap.org	Features interactive global maps with moveable timelines and links to local, regional, & national news sources. From Boston Children's Hospital, Boston, MA, USA.
MedlinePlus: Zika Virus https://www.nlm.nih.gov/medlineplus/zikavirus.html	Offers high-quality, authoritative information on Zika virus for researchers, healthcare professionals, students, and the general public. From the US National Library of Medicine.
National Institute of Allergy and Infectious Diseases (NIAID): Zika Virus https://www.niaid.nih.gov/topics/Zika/Pages/default.aspx	Contains information and reports on current Zika research. The NIAID is one of the 21 institutes of the US National Institutes of Health.
Pan American Health Organization (PAHO): Zika Virus Infection http://www.paho.org/hq/	Provides information, news and epidemiological updates for the general public and health authorities. PAHO is the regional office of the World Health Organization.
Program for Monitoring Emerging Diseases/ProMed-mail	International forum for rapid reporting of infectious disease

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http://www.promedmail.org/	outbreaks and environmental exposures. From the International Society for Infectious Diseases.
PubMed http://www.ncbi.nlm.nih.gov/pubmed	Provides citations, abstracts, and often the full text, for peer-reviewed journal articles. From the US National Library of Medicine.
World Health Organization (WHO): Zika http://www.who.int/en/	Provides a wealth of resources and publications on Zika virus, including periodic situation reports. The WHO is an agency of the United Nations.

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Table 2. Zika Virus and its taxonomic relatives. Excerpted from: International Committee on Taxonomy of Viruses 2014. <http://www.ictvonline.org/virustaxonomy.asp>. Accessed 04/15/16.

Family: Flaviridae
Genus: Flavivirus (53 species)
Species (Selected):
Dengue Virus
Japanese encephalitis virus
St. Louis encephalitis virus
Tick-borne encephalitis virus
West Nile virus
Yellow fever virus
Zika virus
Family: Togaviridae
Genus: Alphavirus (31 species)
Species (Selected):
Chikungunya virus
Eastern equine encephalitis virus
Sindbis virus
Venezuelan equine encephalitis virus
Western equine encephalitis virus
Genus: Rubivirus (1 species)
Species:
Rubella virus

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Table 3. The National Institute of Allergy and Infectious Diseases' research approach to Zika Virus. Adapted from: National Institute of Allergy and Infectious Diseases

<https://www.niaid.nih.gov/topics/Zika/ResearchApproach/Pages/default.aspx> Accessed 04/16/16.

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In Jan 2016, the NIAID issued a call for Zika-related research proposals in the following areas:

- Development of sensitive, specific, and rapid clinical diagnostic tests for Zika virus
- Development of Zika-specific antivirals, as well as broad spectrum antivirals that would be effective against multiple flaviviruses
- Development and testing of vaccines to protect against Zika virus infection
- Virology research to understand Zika virus infection, replication, pathogenesis, and transmission, as well as the biology of the mosquito vectors
- Development of animal models for the study of the progression of Zika infections in humans
- Studies on the evolution and emergence of Zika virus, including the identification of factors that affect host-range and virulence
- Surveillance studies of the distribution and natural history of Zika virus
- Evaluation of immune responses to Zika and co-existing flaviviruses, especially dengue virus and yellow fever virus

Additionally, in Feb 2016, the National Institutes of Health issued a call for proposals for studies investigating the effect of the Zika virus on reproduction, pregnancy, and the developing fetus.