Literature Review

The Zika virus in the United States: A comprehensive review

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ABSTRACT

Background: With a series of outbreaks spanning the globe, the Zika virus has transitioned, in a short time, from an obscure virus to a public health emergency. Locally transmitted Zika has reached the United States, leading to increased concern regarding further transmission and the potential impact on public health.

Methods: The present study was conducted to examine the propagation and effects of Zika in the United States by reviewing published literature regarding Zika in conjunction with updates from the Centers for Disease Control and Prevention. To gauge the regional response, including prevention and control efforts, interviews were conducted with public health and mosquito control officials.

Results: Exposure to Zika may be through vectors, sexual activity with an infected partner, or congenitally to the unborn fetus. Regardless of the mode of transmission, Zika infection may result in serious neurological consequences in adults and especially in fetuses.

Conclusions: Prevention of Zika infection is key to successful control of the virus. Vector control and surveillance as well as personal protection from virus exposure are necessary to avoid the potentially devastating effects of the virus. In an effort to prevent further spread, public health authorities are implementing strategies for public education, prevention, and containment.

Key words: Zika virus, Guillain-Barré syndrome, microcephaly, *Aedes aegypti*, vector control

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INTRODUCTION

In a short time, the Zika virus has moved from a relatively obscure virus to a cause of international concern. Zika virus was first isolated in 1947 in the Zika Forest of Uganda during a yellow fever surveillance project (Dick, 1952). Since its discovery, Zika has remained relatively benign, causing only sporadic, isolated cases. In 2007, this changed as Zika re-emerged, causing epidemic outbreaks in various islands of the Pacific (Duffy et al., 2009; Ioos et al., 2014). In the Americas, February 2015 marked the beginning of a Zika pandemic that has sparked international alarm. The outbreak began in Brazil and quickly spread throughout South America and the Caribbean. A high incidence of neurological effects among Zika-infected adults and fetuses led to a call for action to combat further spread of the virus. Across the United States (US), hundreds of travel-related and multiple sexually transmitted cases have been reported (ECDPC, 2015; CDC: Case counts in the US, 2016). In July 2016, cases identified in Florida marked the first local transmission of Zika in the continental US (CDC: Case Counts in the US, 2016; CDC: FL investigation, 2016). Relative to these outbreaks, this review examines the propagation and potential effects of the Zika virus in the US, including responses by front-line public health authorities to prevent transmission of the virus and to initiate protocols for preparedness in the event of an outbreak.

METHODS

This review was conducted by assessing published literature regarding the Zika virus as well as current and updated guidance from the Centers for Disease Control and Prevention (CDC) via its website. In addition, unstructured interviews were conducted with the administrator and lead epidemiologist at the Georgia Department of Public Health, Coastal District, to investigate regional response protocols and prevention efforts. Further, the director and the lead entomologist of Chatham County Mosquito Control were interviewed and were joined in the field to examine vector control and surveillance efforts currently underway.

RESULTS

Exposure

Although the Zika virus can be transmitted in various ways, the primary route is via mosquito vectors. During this vector transmission of Zika, the virus in the saliva of an infected female mosquito is transferred into the skin of a human during a blood meal. The virus is deposited in the epidermis and dermis of the host, infecting several cell types that provide a haven for viral replication and allow dissemination throughout the body (Hamel et al., 2015). Although Zika may be transmitted by several mosquito species, in the Americas, *Aedes aegypti*, commonly known as the yellow fever mosquito, appears to serve as the main vector (Tilak et al., 2016). *A. aegypti* is primarily an urban mosquito, meaning that it prefers a habitat in close contact with humans. The mosquito typically dwells around or in homes, increasing the chances of viral transmission. Females deposit their eggs in small, stagnant bodies of water, preferring household containers. Since adult *A. aegypti* mosquitoes are relatively poor fliers, they tend to dwell relatively close to their hatch site if a food source is available, making them a persistent nuisance once established around a home. In recent years, the distribution of *A. aegypti* in the US has declined, mainly due to the arrival of the more competitive *A. albopictus* species. Although some populations are still present in the southern US, great numbers of *A. aegypti* are primarily found only in Florida and regions along the Gulf Coast (Zettel & Kaufman, 2013; CDC: Dengue entomology and ecology, 2016; Heusel & Moulis, communication). Despite the wider distribution of *A. albopictus*, this species is a less efficient vector of Zika and less likely to cause a major outbreak (Chouin-Carneiro et al., 2016; Hotez, 2016).

In addition to vector transmission, Zika can be transmitted by other means, leading to increased concern regarding control of the virus. Sexually transmitted cases have been reported across the US (CDC: Case counts in the US, 2016). Zika viral RNA has been detected in semen up to 93 days after the patient's symptomatic period of illness, indicating possible transmission to a sexual partner months after infection (Musso, Roche, Robin et al., 2015; Atkinson et al., 2016; Brooks et al., 2016; Mansuy et al., 2016). A case of probable sexual transmission from an infected female to her male sexual partner has also been reported (Davidson et al., 2016; Moreira et al., 2016). In Brazil, there has been probable transmission of Zika by transfusion of blood products from an infected donor (Barjas-Castro et al., 2016). The possibility of transmission of Zika by transfusion has been suspected, as other related viruses have been transmitted in this manner (Lanteri et al., 2016; Musso, Stamer et al., 2016).

Although up to ninety percent of individuals infected with Zika will be asymptomatic, those developing symptoms generally suffer mild flu-like symptoms of short duration that may be accompanied by a maculopapular rash (Duffy et al., 2009; Ioos et al., 2014; CDC: Zika virus symptoms, 2016; Musso & Gubler, 2016). In addition, Zika-infected individuals may be at a greater risk for development of Guillain-Barré syndrome (GBS). After the epidemics in the Pacific and Brazil, an unusually high incidence of new cases of GBS was reported for Zika-infected individuals (Arujo et al., 2016; Musso & Gubler, 2016; Silva & Souza, 2016). GBS is an acute-onset, autoimmune-mediated peripheral polyneuropathy that can result subsequent to a variety of infections or as a result of idiopathic causes. The exact mechanism of GBS in the context of Zika infection is unclear, but it has been hypothesized that, during viral replication, the virus may incorporate host gangliosides into its makeup, eliciting an immune response that cross-reacts with normal gangliosides of the host causing self-reactivity against the peripheral nervous system. The resulting demyelination causes disruption in neural signaling and potential axonal degradation (Anaya et al., 2016; Cao-Lormeau et al., 2016). In severe cases, muscle weakness and dysfunction, which are commonly experienced, may compromise breathing (Cao-Lormeau et al., 2016, Musso & Gubler, 2016).

Vertical transmission of Zika from an infected mother to her fetus during pregnancy has been linked to congenital fetal Zika infections. Recent evidence, derived with animal models, has suggested that the virus is transmitted to the fetus across the placenta. Although the exact mechanism by which the virus crosses the placental membrane is uncertain, it has been hypothesized that the virus crosses from the maternal bloodstream in the chorionic villi to the placenta, where it is amplified before spreading into the fetal circulation and moving to infect neural progenitor cells (NPCs) (Miner et al., 2016; Quicke et al., 2016; Silva & Souza, 2016; Wu et al., 2016).

Congenital Zika infection of the developing fetus may result in serious neurological defects, including microcephaly, along with other developmental anomalies primarily affecting the central nervous system (Driggers et al., 2016; Hazin et al., 2016; Kleber et al., 2016; Mlakar et al., 2016; Musso & Gubler, 2016; Silva & Souza, 2016). In the US, as of July 2016, there have been at least twelve newborns with congenital birth defects due to Zika, with more cases likely to follow (CDC: Outcomes of pregnancies, 2016). It is thought that the Zika virus is associated more with a disruption in neural development, rather than neural destruction (Hazin et al., 2016). Cortical NPCs, which would normally develop into the cerebral cortex, are a key target for the virus. Infection of these cell populations with Zika results in dysregulation of the cell cycle and in attenuation of neural development (Cugola et al., 2016; Li et al., 2016; Tang et al., 2016). In Zika-infected fetuses, ocular abnormalities, intrauterine growth restriction, and fetal demise have also been reported (Brasil et al., 2016; de Miranda et al., 2016; de Paula Freitas et al., 2016; Mlakar et al., 2016; Sarno et al., 2016).

DISCUSSION

Prevention

With the potential of a major Zika outbreak in the continental US, many state and local agencies have stepped up efforts to prevent spread of the virus. As the primary route of transmission is via mosquito vectors, many of these efforts are centered on mosquito control. Effective control, however, is often challenging. In most areas of the US, mosquito control is dealt with on a local level with funding and organization provided by local governments. This can cause discontinuities across a region or state, as many areas lack professional mosquito control entities or may be poorly funded.

Effective and efficient mosquito control is dependent upon mosquito surveillance programs, which allow for identification of the specific mosquito species and their population numbers in a particular area. This information can ensure that mosquitoes, especially those that may serve as disease vectors, can be targeted by control efforts. Information collected from surveillance may affect the type and amount of pesticide applied, the method and time of application, and area in which it is applied. In areas that lack a professional mosquito agency, mosquito surveillance is often nonexistent (Heusel & Moulis, communication).

In preparation for the Zika threat, some states have taken a proactive approach to address the lack of surveillance. The Georgia Department of Public Health (GDPH), for example, has hired new environmental health employees to conduct surveillance in areas of the state where it is lacking. This surveillance primarily follows *A. albopictus* and *A. aegypti*, the two known vectors of Zika in the US (Heusel & Moulis, communication; McCall & Thornton, communication). Surveillance is conducted using specially designed traps, such as the widely used Biogents Sentinel® trap, that target both of these *Aedes* species (Cornel et al., 2016; Heusel & Moulis, communication). Once identified, the species may be targeted by a combination of adulticides and larvicides. Since both *A. albopictus* and *A. aegypti* usually dwell in close vicinity to homes and breed in household containers, pesticide applications that target these areas is essential for effective control (Rios & Maruniak, 2011; Zettel & Kaufman, 2013; CDC: Surveillance and control, 2016; Heusel & Moulis, communication). In many areas, aerial application may be beneficial, as this approach is not limited by roadway access. This method, however, may not be effective in treating container-breeding sites in congested urban areas (Heusel & Moulis, communication).

Controlling the vectors of Zika depends heavily upon public involvement to help eliminate mosquito-breeding sites around homes. In response, public health officials urge the public to become involved in the control effort. To spread awareness, the GDPH has instituted a public education campaign known as “Tip and Toss.” The campaign urges citizens to be involved in reducing mosquito-breeding sources around their homes by emptying or eliminating water-holding containers (GDPH: Tip ‘n toss, 2016; Rey & Connelly, 2016; McCall &

Thornton, communication). Involvement of entire communities is essential for the success of such programs. Unfortunately, in some cases, there may be residents who are reluctant or refuse to participate. This allows mosquito-breeding sources to remain on properties and may undermine the community effort (Petersen et al., 2016; Heusel & Moulis, communication). In addition to eliminating breeding sites, authorities are striving to increase public awareness concerning ways to prevent mosquito bites through public outreach campaigns and strategically placed informational signage, such as in airports. To prevent mosquito bites, officials advise wearing, while outdoors, lightweight clothing that covers exposed areas of skin and recommend, if outdoors for long periods, treating clothing with permethrin to deter mosquitoes (DeRaedt et al., 2015; CDC: Zika virus prevent mosquito bites, 2016; GDPH: Zika virus awareness campaign, 2016; McCall & Thornton, communication). Perhaps the most effective way to prevent mosquito bites is to apply an effective insect repellant before going outdoors. The most recommended personal repellants are those containing DEET (20-30%), although others containing picardin, Bayrepel, icardin, and IR3535 are also approved by the Environmental Protection Agency and CDC (CDC: Zika virus prevent mosquito bites, 2016; GDPH: Zika virus awareness campaign, 2016). For those seeking a natural alternative to synthetics, repellants containing oil of lemon eucalyptus are effective (CDC: Zika virus prevent mosquito bites, 2016).

In addition to preventing mosquito bites, care should be taken to prevent sexual transmission of Zika. All sexual couples in which one or both partners live in areas of ongoing local transmission or have traveled to these areas should take precautions before engaging in any form of sexual activity. This is especially important for pregnant women and women who are planning to become pregnant. Due to the longevity of Zika particles in semen and their unknown duration in vaginal fluids, the CDC currently recommends that, for at least six months after the symptomatic infection (or suspected infection) of a partner, couples utilize barriers before any type of intercourse. For couples in which neither has experienced symptoms, barriers are suggested for at least eight weeks after travel to an area of local transmission. Couples living in an area of ongoing transmission should use barriers as long as there is Zika reported in their area. Pregnant women with a partner who has traveled to or lives in a Zika area should utilize barriers throughout the duration of pregnancy or abstain from sexual activity to prevent potential infection of the mother and fetus (Brooks et al., 2016; CDC: Zika virus protect yourself during sex, 2016).

The discovery, in Brazil, of probable Zika virus transmission by blood transfusions has prompted a federal effort to protect the US blood supply. To prevent the distribution of infected blood products, the Food and Drug Administration (FDA) has issued guidelines for blood collection centers, including immediate testing of all donated blood products collected in the US (FDA: FDA advises testing, 2016). Testing may be conducted on individual blood donations by use of a newly developed nucleic acid test. Donated plasma and apheresis platelets may be treated with pathogen reduction technology (Kuehnert et al., 2016).

Containment

While prevention of Zika infection is the goal, rapid identification and containment after an infection occurs is essential to prevent an isolated outbreak from developing into an epidemic. With the arrival of Zika to the continental US, federal, state, and local authorities have prepared containment plans in the event that an outbreak does occur. The first, and perhaps the most important, step after an infection is an accurate and timely diagnosis, which is largely dependent on healthcare providers. Upon examining a patient with suspected Zika infection, providers are directed to notify the Department of Public Health immediately (CDC: Interim CDC Zika response plan, 2016; McCall & Thornton, communication). Despite the fact that molecular and serological testing has been made available to state public health laboratories, accurate diagnosis of Zika infection is difficult. Testing may not yield a correct result depending on the time of sampling and the high degree of cross reactivity between related viruses. In many cases, a series of tests requiring considerable time, especially for laboratories with large test loads, must be conducted to reach a definitive result of infection status (CDC: Revised diagnostic testing, 2016; Musso & Gubler, 2016; Plourde & Bloch, 2016; McCall & Thornton, communication).

In the state of Georgia, once a suspected case is reported, the GDPH contacts the patient as soon as possible, even if results of Zika testing are still pending. The GDPH advises patients on methods to prevent further local transmission, including avoidance of unprotected sexual contact and prevention of mosquito bites, which could spread the virus to others. The GDPH (or local mosquito control entities) may also conduct a home visit and mosquito surveillance around the index case site. If the area is conducive to mosquito breeding, public authorities may intervene to reduce the risk of transmission from the index case (CDC: Interim CDC Zika response plan, 2016; Ndeffo-Mbah et al., 2016; Heusel & Moulis, communication; McCall & Thornton, communication). The GDPH also distributes educational materials throughout the surrounding area, warning the residents of possible Zika transmission and outlining steps to protect themselves (GDPH: Zika virus awareness campaign, 2016; McCall & Thornton, communication). The CDC, also notified in the case of potential local transmission, offers support to local authorities. If needed, the CDC activates emergency response teams to aid in surveillance, vector control, communications, and technical support at the scene (CDC: Interim CDC Zika response plan, 2016).

Future outlook

No specific treatment or vaccine for Zika infection currently exists, but researchers are working to develop these life-saving interventions. Investigators and public health authorities are hopeful that a Zika vaccine is attainable, as vaccines have been developed for other flaviviruses (Dowd et al., 2016). Several experimental vaccines have already entered phase I clinical trials or are scheduled to begin soon, including bacterial DNA-based vaccines and a more traditional vaccine containing inactivated virus (Inovio, 2016; NIH, 2016; Pellerin, 2016). A recent study with murine models has found both DNA-based and inactivated viral vaccines to be effective and shows promise for use in humans (Larocca et al., 2016).

Despite rapid development and advancement to clinical trials, an approved vaccine for Zika could still be years away. Investigational vaccines must be vetted for safety and effectiveness through rigorous clinical testing before being considered for FDA approval. The complex approval process may take up to two years. Vaccine applications granted priority status, such as Zika is likely to receive, may undergo expedited review but can still take several months to receive approval (Marshall & Baylor, 2011; Pickering & Walton, 2013; Singh & Mehta, 2016).

CONCLUSIONS

The Zika virus has recently emerged onto the world stage, causing epidemic outbreaks circumventing the globe. With the arrival of Zika transmission to the US, public health authorities and healthcare providers are preparing for new outbreaks. Controlling mosquito vectors and protecting people from exposure through possible routes of transmission are key to successful prevention. These efforts are of paramount importance to prevent possible infection of adults and developing fetuses. With an effective vaccine possibly years away and no specific treatment for Zika infection, prevention and containment must be initiated immediately to avoid the potentially devastating neurological effects, including GBS in adults and microcephaly in developing fetuses.

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