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ZIKA VIRUS: AN EMERGING INFECTIOUS THREAT FOR PREGNANT WOMEN

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ZIKA VIRUS INTRODUCTION

Zika virus (ZIKV) is an emerging arboviral infection, affecting approximately 2 million residents in 45 countries since 2015, and is primarily transmitted by *Aedes aegypti* mosquitoes through a mosquito to human transmission cycle (World Health Organization [WHO], 2016). ZIKV, recently declared by the WHO as a "Public Health Emergency of International Concern" may affect approximately 4 million people by the end of 2016 (WHO, 2016). Two and a half billion individuals reside in regions where the *aedes* mosquitoes commonly circulate and the risk for disease transmission remains high (Institut Pasteur, 2015). The geographical distribution of ZIKV is increasing due to foreign travel and climate change and to date, a total of 107 travel-associated cases were identified in the Continental United States (Centers for Disease Control & Prevention [CDC], 2016). Of the 107 ZIKV cases identified in the Continental United States, 9 were confirmed in pregnant women, of which two (22%) resulted in miscarriages (CDC, 2016).

ZIKV is typically characterized by the following symptoms: rash (90-95%), fever (65-73%), arthralgia (65-70%), and/or non-purulent conjunctivitis (55-63%), occurring approximately 3-12 days after the bite of an infected mosquito (CDC 2016; European Centre for Disease Prevention & Control [ECDC] 2015; Gourinat, O'Connor, Calvez, Goarant, & Dupont-Rouzeyrol, 2015). Most studies have noted that ZIKV typically results in mild symptoms (20% of cases) lasting approximately several days to a week, is asymptomatic in the majority of cases (60-80%), and case-fatality rates remain low (CDC 2016; ECDC 2015; Gourinat et al., 2015). However, during recent ZIKV outbreaks, adverse birth outcomes including: microcephaly (>3,500 cases), spontaneous abortions, and miscarriage has occurred in Brazil, Colombia, and non-endemic ZIKV regions including the United States during the first two trimesters of pregnancy (ECDC 2015; Campos, Bandeira, & Sardi, 2015; Gourinat et al., 2015).

STATEMENT OF THE PROBLEM

This is the first time in history that ZIKV has been associated with the development of adverse birth outcomes and has been linked to perinatal transmission (Vogel 2016). Little is known regarding the natural history, epidemiological transmission patterns, and major risk factors associated with ZIKV (Vogel 2016). Data on the outcomes of pregnancies in ZIKV infected women as well as specific trimesters when pregnant women are at highest risk for developing an adverse birth outcome remains sparse. The purpose of this study is to evaluate potential risk factors associated with development of adverse birth outcomes in pregnant women with a laboratory confirmed diagnosis of ZIKV and gain insight into the development of future interventions, screening guidelines for pregnant women, educational messages targeted towards women of reproductive age, and vaccine development.

EPIDEMIOLOGICAL BACKGROUND OF ZIKV

The first major ZIKV outbreak occurred in the Federated States of Micronesia in 2007 and spread to many countries throughout Oceania (Henry R., 2014; Ioos, Mallet, Goffart, Cardoso, & Herida, 2014; Musso 2015). To date, the largest ZIKV outbreak affecting approximately 30,000 cases was identified in French Polynesia between 2013 through 2014 (ECDC 2015; Henry R., 2014; Ioos et al. 2015; Musso 2015). Since the ZIKV outbreak occurred in French Polynesia, novel epidemics took place in Central & South America and locally transmitted cases were identified in 17 regions of the Americas including: Brazil, Colombia, El Salvador, Mexico, and Puerto Rico (CDC 2015; Pan American Health Organization 2016).

Based on current research, ZIKV is an arboviral infection that disproportionately affects women of reproductive age (Zanluca, Campos Andrade de Melo, Mosimann, Viano dos Santos, Duarte dos Santos, & Luz, 2015). In a study conducted by Zanluca et al. (2015) the characteristics of 8 laboratory confirmed ZIKV patients in Natal, Brazil were analyzed and 7 out of 8 (88%) cases occurred in females with a median age of 39 years old (range: 18-65). Brazil is currently experiencing an ongoing ZIKV outbreak that began in May 2015 and to date, approximately 400,000 to 1.4 million cases have been identified in the country; of these cases approximately 3,900 have been linked to microcephaly in pregnant women (Cha A., 2016; ECDC 2015). As of January 7, 2016, a total of 173 suspected microcephaly cases and 38 deaths involving neonates were reported from pregnant women with a laboratory based confirmation of ZIKV in the Rio de Grande Norte State of Brazil. The following

regions in the state were affected: Natal (56 cases), Mossoro (17 cases), Parnamirim (13 cases), Ceara-Mirim (11 cases), and 73 additional cases were represented from other municipalities (Secretaria de Saude Publica, 2016).

METHODS

A case control study will be used to evaluate potential risk factors and exposures associated with the development of adverse birth outcomes in pregnant women with a laboratory confirmed diagnosis of ZIKV in Brazil. The case control study will be used since it is noted to be a good study design for assessing rare diseases and it can be conducted in a relative short amount of time with few resources needed. Multiple exposures will be measured to explore associations among the risk of developing adverse birth outcomes among ZIKV infected pregnant women including: previous arboviral infection with dengue and/or chikungunya, co-infections with one or more illnesses including: chronic hypertension, diabetes, sexually transmitted diseases (gonorrhea, HIV, syphilis) and/or arboviral diseases (dengue and chikungunya), travel within the past 14 days of illness onset, age at pregnancy, smoking, alcohol and/or drug use during any stage of pregnancy etc. The primary outcome measure for this study is the development of adverse pregnancy outcomes (e.g., microcephaly, death of neonate, etc.) among women infected with ZIKV.

The null hypothesis for this study is: H_0: There will be no difference in exposures among ZIKV infected pregnant women developing adverse birth outcomes and the group of ZIKV infected pregnant women that did not experience any adverse birth outcomes. The alternative hypothesis for this study is**:** H_a: There will be a significant difference in the exposures identified among ZIKV infected pregnant women developing adverse birth outcomes versus ZIKV infected pregnant women that did not have any adverse birth outcomes.

This study will attempt to answer the following research questions:

- What is the likelihood that pregnant women with a confirmed diagnosis of ZIKV will develop an adverse birth outcome?
- Are pregnant ZIKV co-infected women (e.g., diabetes, chronic hypertension, sexually transmitted diseases, and arboviral infections) more likely to develop adverse birth outcomes?
- Are ZIKV pregnant women previously diagnosed with an arboviral infection of dengue and/or chikungunya more likely to develop an adverse pregnancy outcome?

Study Population

The inclusion criteria for this study will include a total of 811 pregnant laboratory confirmed ZIKV patients (211 cases with adverse birth outcomes and 400 controls without any adverse birth outcomes) that were admitted for delivery in one of several health facilities located in the Rio de Grande Norte State of Brazil. Pregnant mothers reporting the following infections during pregnancy: rubella, toxoplasmosis, and cytomegalovirus and exposure to harmful substances including alcohol and/or drug use will be excluded from the study since these exposures are reported to be linked to microcephaly in newborns (CDC, 2016).

A total of 811 structured questionnaires will be administered via telephone by a team of trained epidemiologists from the Brazil Ministry of Health. Prior to beginning this investigation, the research protocol will be submitted for approval to the Brazilian Ethical Committee and the University of South of Florida's Institutional Review Board. The questionnaires will consist of several sections including: participant's demographic information (e.g., geographic location, age, ethnic group, weight and height to determine body mass index, etc.) clinical data (onset date, symptoms, timing of specific symptom development, severe and/or rare complications noted as a result of ZIKV (guillain-barre syndrome), and record of previous yellow fever vaccination. In addition, the questionnaires will inquire whether participants were previously infected with dengue or chikungunya and time period of infection will be noted. The trimester of pregnancy that participants became infected with ZIKV will be recorded as well. In addition, the questionnaire will assess exposures and consist of a section on travel history and inquire about travel to another country or state in Brazil within the past 14 days of illness onset. The risk factor section on the questionnaire will assess exposures including: previous arboviral infection with dengue and/or chikungunya, co-infections with one or more illnesses including: chronic hypertension, diabetes, sexually transmitted diseases (gonorrhea, HIV, syphilis), and arboviral diseases (dengue and chikungunya), travel within the past 14 days of illness onset, and known exposure to pesticides. In addition to administering interviews, patient's medical record abstraction will be performed by study investigators to collect information on clinical symptoms, adverse birth outcomes, illness onset, timing of symptoms, medications used during pregnancy, etc. An odds ratio will be calculated for each exposure to determine the likelihood that a ZIKV infected pregnant mother may develop an adverse birth outcome (Table 1).

Table 1. Co-Infections in ZIKV Infected Pregnant Women and Development of Adverse Birth Outcomes*			
	Pregnant women with ZIKV developing an adverse pregnancy outcome	Pregnant women with ZIKV who did not develop an adverse pregnancy outcome	Total
Exposure (e.g., Co-infections with chronic hypertension, diabetes, sexually transmitted or arboviral diseases)	A (N)	B (N)	=A+B
No Exposure (No co-infections/healthy during time of pregnancy)	C (N)	D (N)	=C+D
TOTAL	**=A+C**	**=B+D**	**=A+B+C+D**

*Adverse Birth Outcomes includes: microcephaly,

CONCLUSION

The study sample used in this study was limited to one particular region in Northeastern Brazil and additional research is needed to determine adverse birth outcomes in pregnant ZIKV infected women residing in other nations. Brazil is unique from other countries in that it represents the world' s leading dengue fever case count, almost half of all malaria cases in Latin America occur in this nation, and there is a large abundance of *aedes* mosquitoes present year round (Lacerda, Mourao, Alexandre, Siqueira, Magalhaes, & Martinez-Esposa, 2012). We can expect to observe an increase in the total number of cases reported world-wide due to a large abundance of aedes mosquito species present (CDC, 2015). ZIKV will most likely follow the same epidemiological cycles found in the rapid spread of both dengue virus and chikungunya and overall incidence rates are expected to increase due to several factors including: climate change, globalization, international travel

& trade, socioeconomics, and viral evolution (Musso, D., Cao-Lormeau, V., & Gubler, D., 2015). The potential for ZIKV to spread throughout the world in non-endemic regions as well as the potential for *aedes* mosquitoes to be infected with all three viruses: ZIKV, dengue, and chikungunya reinforces the ongoing need to develop travel advisories, educating pregnant women to taking necessary precautions to avoid adverse birth outcomes, enhanced educational programs to convey important preventative messages to the public, as well as vaccines and drugs to treat these infections (Musso et al., 2015).

In addition, due to scant literature available on this emergent disease, it is critical to develop future studies to examine potential reservoirs, transmission modes, as well develop a greater understanding of ZIKV's clinical presentation and associated complications. Furthermore, research efforts should evaluate the incidence of maternal-fetal transmission of ZIKV by trimester, risk of developing neurological complications and adverse birth outcomes if pregnant, and investigation of possible transmission routes. Advances in our understanding of potential ZIKV transmission routes, co-infection among ZIKV and other arboviral diseases, high risk groups, and epidemiological distribution of the disease will support the rational development and application of novel interventions including: vaccines, vaccine recommendations for women of reproductive age, targeted public health messaging toward high risk groups, and vector control strategies.

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