

Unravelling the Paediatric and Perinatal Zika Virus Epidemic through Population-based Research

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ABSTRACT

Zika virus epidemic now involves 72 countries, worldwide. Transmission is multimodal through mosquito bites and blood and body fluids. Zika virus causes Guillain Barre syndrome and pregnancy complications including perinatal microcephaly. Diagnosis is complicated by subclinical infection in 80%, co-circulation with dengue and chikungunya fevers with similar presentations and cross-reactivity in serological tests. There is no cure, or preventive vaccine. Large population-based studies will help to elucidate ZIKV epidemiology, vertical transmission, risks to the fetus of maternal ZIKV infection and natural history of congenital and non-congenital ZIKV infection as provided by the activities in the “ZIKAction” research consortium in Latin America, Europe and the Caribbean, which was recently funded by the European Commission.

Key words: Caribbean, child, Zika virus, Guillain-Barre syndrome, microcephaly, pregnancy

Desentrañando la Epidemia Pediátrica y Perinatal del Virus del Zika Mediante una Investigación Poblacional

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RESUMEN

En el presente, la epidemia del virus Zika abarca 72 países a nivel mundial. La transmisión es multimodal a través de las picaduras de mosquito, la sangre y los fluidos corporales. El ZIKV causa el síndrome de Guillain-Barré y complicaciones del embarazo, incluyendo la microcefalia perinatal. El diagnóstico se complica por infección subclínica en 80%, y la co-circulación de las fiebres de dengue y chikungunya, con similitud de las manifestaciones y la reactividad en las pruebas serológicas. No existe cura ni vacuna preventiva. Los estudios poblacionales a gran escala ayudarán a dilucidar la epidemiología del ZIKV, su transmisión vertical, y los riesgos que para el feto tienen la infección materna de ZIKV y la historia natural de la infección congénita y no congénita por ZIKV. Un ejemplo de tales estudios es el que ofrecen las actividades del Consorcio de investigación “ZIKAction” en América Latina, Europa y el Caribe recientemente financiado por la Comisión Europea.

Palabras claves: Caribe, niño, virus del Zika, síndrome de Guillain-Barré, microcefalia, embarazo

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INTRODUCTION

Zika virus (ZIKV), an arbovirus of the flavivirus family, has spread explosively through the Americas since it was first identified in Brazil in 2014 (1, 2). As of September 1, 2016, some

72 countries worldwide, are reporting local transmission and territories are reporting mosquito-borne ZIKV transmission since 2007, 69 with reports from 2016 and 55 with a first outbreak since 2015 and 47 of these countries are in the Americas, including the mainland of the United States of America and also the Caribbean [Figure] (1). Over four million cases of ZIKV infection were projected to occur in the Americas this year, when “a public health emergency of international concern” was declared by the World Health Organization on February 1, to elucidate the links between ZIKV and congenital microcephaly and Guillain Barre syndrome (3).

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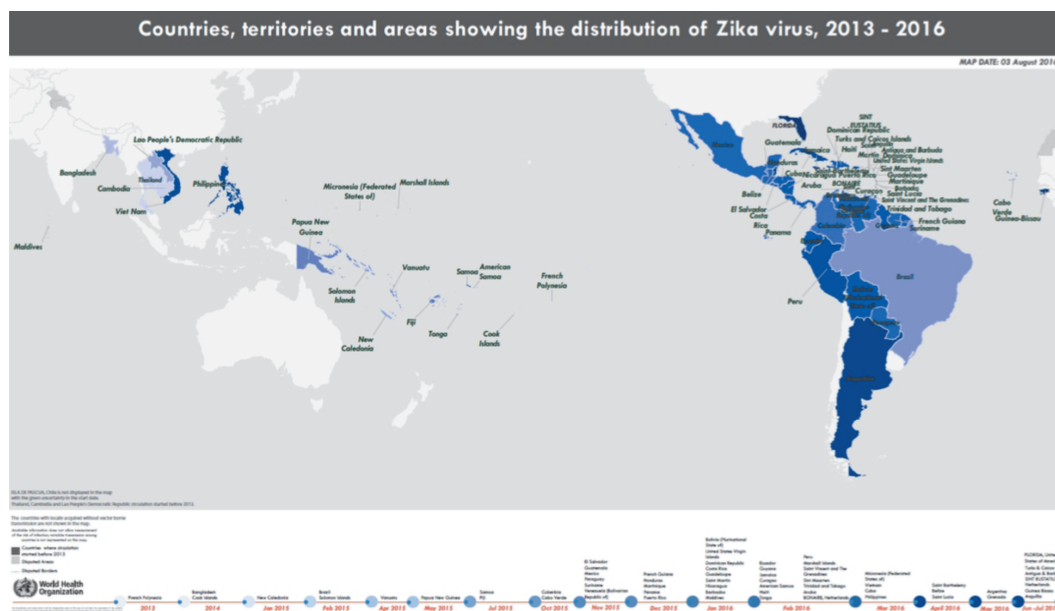


Figure: Countries, territories and areas showing the distribution of Zika virus, 2013–2016.

Zika virus is spread primarily by the bite of the *Aedes aegypti* and less likely from the *Aedes albopictus* mosquitoes, which may also transmit Dengue, Chikungunya and Yellow Fever. However, the common *Culex* mosquito is now being implicated (4). In addition to mosquito transmission, ZIKV can be transmitted vertically from the mother to the fetus, through sexual activity and blood transfusion; although less frequently, exposure to saliva, urine, tears and a laboratory accident have also been implicated (5–12). Attack rates of ZIKV in populations are high, approaching 66% to 73% in the French Polynesian and Yap island epidemics (13, 14). The multiple modes of transmission through mosquito bites and exposure to blood and body fluids, with the possibility of re-infection, means that once the virus enters a population it is likely to become endemic. Further, the co-circulation of ZIKV with other arboviruses, particularly Dengue and Chikungunya, not only presents challenges with respect to the similar clinical presentations and the laboratory diagnostics due to cross-reactivity in serological tests, but may potentially be important in understanding the pathogenesis and epidemiology of ZIKV infection.

Clinical features of ZIKV infection are present in 15–20% of adult cases and are generally mild, comprising primarily a generalized maculo-papular rash, joint and muscle pain, headache, non-purulent conjunctivitis and low grade, or no fever. While the majority, 80–85%, of ZIKV infections are asymptomatic. Treatment is supportive and as yet, there is no vaccine, or recognized therapeutic cure. During the French Polynesia outbreak, the post-infectious neurological complication, notably Guillain-Barre Syndrome was first documented (15). These patients presented with acute motor axonal neuropathy and rapid evolution of their disease. Clinical features include generalized muscle weakness, inability to walk, facial

nerve palsy and increased cerebrospinal fluid proteins; about 30% required ventilator support, which was prolonged. Countries are therefore increasing their intensive care bed capacity to better manage the expected high burden of patients with Guillain-Barre syndrome.

Until reports of an unexpected surge in congenital microcephaly coinciding with the ZIKV outbreak in Brazil started emerging in September 2015, there had been no prior indication of adverse outcomes associated with ZIKV infection in pregnancy, although a subsequent retrospective study in French Polynesia identified microcephaly cases with temporal association with the ZIKV outbreak there (5). Prenatal ZIKV infection has now been conclusively linked as with a cause of adverse pregnancy outcomes, including spontaneous abortions, stillbirths, intrauterine growth retardation, severe microcephaly and other brain lesions (16). Case reports, case series and epidemiologic studies of microcephaly associated with laboratory confirmed ZIKV infections confirm that the timing of “The Congenital ZIKV Syndrome” appears consistent with the “Fetal Brain Disruption Sequence” with microcephaly, redundant scalp skin, eye findings, arthrogryposis and clubfoot (17).

The rare exposure to the rare outcome of microcephaly, has been confirmed in travellers who spent limited time in areas with active ZIKV transmission (18). Zika virus has also been isolated from glial cells and neurons of newborns with microcephaly (19). Estimated risks of severe microcephaly from infants infected primarily in the first trimester range from 1–30% in the French Polynesian and Brazilian epidemics (5–8). A more disturbing recent report from Brazil concerns infants who are exposed to ZIKV in late pregnancy, who are born with a normal head circumference, but later develop microcephaly by six months of age (20).

Once ZIKV enters a population, about 70% of pregnant women would be expected to develop ZIKV infection (13, 14). However, the identification of such women is very difficult. While 20% of cases may be symptomatic and maybe identified by ZIKV polymerase chain reaction testing, the symptoms may be mild, nonspecific and their significance maybe entirely missed (6). The remaining 80% are asymptomatic. In this latter group, the ZIKV serological tests (IgM and IgG) are being explored; however these may be falsely positive for ZIKV in areas of the world, like the Caribbean, where Dengue and Yellow Fever, are also circulating. Neutralizing antibodies may be used in these settings for clarification, but these assays are still very difficult to be used successfully. Similarly, laboratory identification of the ZIKV-infected infant at birth is currently very challenging.

Recommendations for the management of pregnancy in ZIKV endemic areas are still very general (21). All women are being advised to protect themselves from mosquito bites and practice barrier contraceptives during sexual intercourse. Pregnant women are being asked to consult their physicians and to be evaluated for historical exposure to ZIKV infection followed by clinical evaluation, uterine ultrasounds, laboratory and other tests, as appropriate, at every antenatal visit (20). Reproductive health rights should be considered, in addition to the legal, ethical, religious, cultural, political, social, medical and other issues that must be weighed for any interventions, in each country, jurisdiction, or population, regarding the management of ZIKV infection in pregnancy.

Broad preventive measures for the general population include the recommendation to delay pregnancy for at least two months after a ZIKV infection (21). Others have advised women to delay pregnancy for up to two years. However, this may be ineffective as over 50% of all pregnancies maybe unplanned, some 20% of pregnancies may occur in youth, while many others may be forced. Similarly, men are advised to wear a condom during sexual activity for up to six months after possible ZIKV exposure and the virus has been isolated from semen for over 60 days (22). However, most of these suggestions are really impractical. Countries are preparing by educating their populations about Zika V and vector control, stopping the breeding of mosquitoes in stagnant water, while others are releasing the *Wolbachia*-infected *Aedes aegypti* mosquito as a research initiative to eradicate the mosquito.

Important research questions remain to be answered. These may include understanding the full spectrum of birth defects caused by congenital ZIKV infections, clarifying the risks to infants who are born to women who are exposed to ZIKV at different time points before and during pregnancy and identifying the factors that may modify pregnancy outcomes (including previous infection with dengue, or chikungunya fever). Clinical trials of drugs and ZIKV vaccines, similar to the recently developed dengue fever vaccine, are also urgently needed to be rapidly developed, scaled-up for testing in large placebo-controlled human trials and approved for use, to urgently deflect the dreaded complications of ZIKV and espe-

cially, the development of future generations of children, worldwide, with significantly diminished neuro-developmental potential.

These and other important epidemiological questions can be answered through large, multi-country, population-based, research consortia, like “ZIKAction”. This involves several research sites in Europe, Latin America and the Caribbean (including The University of the West Indies) which is led by the Pediatric European Network for Treatment of AIDS and Infectious Diseases (PENTA-ID) Foundation and was recently funded by the European Commission. A better understanding of ZIKV epidemiology, vertical transmission, risks to the fetus of maternal ZIKV infection and natural history of both congenital and non-congenital ZIKV infection provided by the “ZIKAction” activities is needed. This will identify potential interventions to prevent, or to decrease ZIKV acquisition and mitigate infection-induced damage, to inform evidence-based guidelines regarding clinical management of ZIKV infection of various types, to facilitate development of effective and appropriate surveillance systems and public health responses, as well as to provide important real-time information for health care planners and providers and policy-makers.

The University of the West Indies Regional Headquarters, therefore, welcomes wholeheartedly the 60 researchers from Europe, Latin America and the Caribbean who will be meeting in Jamaica for the “ZikAction Kick-Off Research” Conference from Sunday, October 30 to November 1, 2016, even as Jamaica responds simultaneously to its ZIKV epidemic (23).

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