



Congenital Zika syndrome (CZS) in infants in Canada

Principal investigators

Shaun Morris, MD, Division of Infectious Diseases, Hospital for Sick Children; 555 University Avenue, Toronto ON M5G 1X8; tel.: 416-813 6625; fax: 416-813-8404; shaun.morris@sickkids.ca

Marianna Ofner, PhD, Public Health Agency of Canada; tel.: 416-886-0404; marianna.ofner@phac-aspc.gc.ca

Alex Demarsh, PhD (c), Public Health Agency of Canada, 130 Colonnade Rd., Ottawa ON K1A 0K9; tel.: 613-668-4082; alex.demarsh@phac-aspc.gc.ca

Co-investigators

Ari Bitnun, MD, The Hospital for Sick Children, Toronto

Steven Miller, MD, Hospital for Sick Children

Charlotte Moore Hepburn, MD, Hospital for Sick Children

Chantal Nelson, PhD, Public Health Agency of Canada

Joanne Tataryn, DVM, MSc, Public Health Agency of Canada

Background

Zika virus is primarily transmitted to humans via the bite of an infected *Aedes* mosquito, but can also be transmitted following unprotected sexual contact and, very rarely, via blood and other body fluids. The majority of people infected with Zika virus are asymptomatic or develop mild illness; however, Zika virus has been shown to be neurotropic, particularly to the developing fetus, causing severe neurologic disease that manifests in infants. In October 2015, an increased incidence of microcephaly was noted in northeastern Brazil and further investigations noted an increase in other neurological disorders among newborns born to mothers with Zika virus infection. In February 2016, the World Health Organization (WHO) declared the Zika virus-related cluster of microcephaly and other neurologic disorders to be a public health emergency of international concern.

The spatiotemporal association of cases of microcephaly with the Zika virus outbreak and the evidence emerging from epidemiologic studies have led to a strong scientific consensus that Zika virus is implicated in congenital abnormalities¹⁻³. Drawing on the example of other maternal viruses that are known to affect the fetus in utero (e.g., cytomegalovirus, toxoplasmosis, rubella), it is possible that various degrees of cognitive, developmental, and sensory abnormalities may arise in infants who appear healthy at birth⁴⁻⁷.

A wide range of congenital abnormalities have been described in infants born to Zika virus-infected mothers. In addition to microcephaly, other manifestations

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include craniofacial disproportion, spasticity, seizures, irritability, and brainstem dysfunction, including feeding difficulties, ocular abnormalities, and findings on neuroimaging such as calcifications, cortical disorders, and ventriculomegaly^{2-3, 8-9}. Similarly, some babies have neurological abnormalities with a normal head circumference⁴.

As a result of the spectrum of clinical manifestations and abnormalities seen in infants born to Zika virus-infected mothers, the term congenital Zika syndrome (CZS) has been developed. The range of abnormalities observed and the likely causal relationship with Zika virus infection suggest a new congenital syndrome. WHO, with other countries, is trying to map and analyze the clinical manifestations encompassing the neurological, hearing, visual, and other abnormalities. With longer follow-up of affected children, the scope of the syndrome will likely expand, as further information becomes available.

Recognizing that Canadians frequently travel to warmer climates and that Zika virus-infected mothers have already been identified in Canada, several surveillance systems are being established in Canada. There is a need to rapidly identify and assess infants born to Zika virus-infected mothers in Canada who are manifesting clinical signs and symptoms of congenital and neurological deficits.

Conducting a Canadian Paediatric Surveillance Program (CPSP) study on CZS is highly responsive, timely, and relevant to an emerging public health issue that has received significant international attention and concern. Moreover, data collected will provide valuable clinical and epidemiologic information about the frequency and clinical manifestations of CZS in Canada.

Methods

Paediatricians and paediatric subspecialists will be asked to report all new cases meeting the case definition on a monthly basis. For each new case reported, participants will be asked to complete a detailed questionnaire.

There is currently a CPSP study underway examining the incidence and epidemiology of severe microcephaly in Canada. For cases of severe microcephaly suspected to be associated with Zika virus, CPSP participants will be asked to report using both the severe microcephaly questionnaire AND the CZS questionnaire. There is cross-representation of principal and co-investigators on the research teams to ensure that all cases are appropriately identified and analyzed.

Case definition

Report any infant less than 12 months of age who presents with the following criteria:



Congenital Zika syndrome in infants in Canada (continued)

- Microcephaly, defined as head circumference less than two standard deviations for gestational age and sex according to the standardized reference percentile*

OR

- Other congenital anomalies and malformations consistent with congenital Zika syndrome including malformations of the central nervous system, such as intracranial calcifications, structural brain or eye abnormalities, or other congenital central nervous system-related abnormalities (not explained by another etiology[†])

AND

- A maternal history that includes an epidemiologic linkage[‡] to Zika virus OR a positive or inconclusive Zika virus laboratory test

OR

- An infant with a positive or inconclusive Zika virus laboratory test

* *If there is a case of severe microcephaly suspected to be associated with Zika virus then a questionnaire for the severe microcephaly study and the congenital Zika syndrome study should be completed (i.e., if the case meets both case definitions).*

[†] *Other etiologies that should be considered include other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus, varicella zoster, parvovirus B19, and herpes simplex virus. An assessment of potential genetic and other teratogenic causes of the congenital anomalies should also be considered.*

[‡] *Epidemiological linkage means: travelled to, or resided in, an area with active Zika virus transmission during her pregnancy; OR had unprotected sex during pregnancy with a partner who resided in, or traveled to, an area with active Zika virus transmission.*

Objectives

- 1) Estimate the minimal incidence of CZS in Canada
- 2) Describe the current epidemiology (including place, mode, and timing of acquisition of maternal infection) of CZS in Canada
- 3) Understand the clinical range of findings for infants identified with CZS

Duration

March 2017 to February 2019

Expected number of cases

The incidence of CZD in Canada will likely be very low. The research team expects there to be approximately 30 to 50 pregnant women with laboratory-confirmed Zika virus per year in Canada. Assuming a maximum of 50 percent of infants born to infected mothers will have CZS (likely a very high estimate), it is expected that fewer than 50 cases of infants with some signs and symptoms consistent with CZS will be identified in the two years of this study.



Ethics approval

The Hospital for Sick Children Research Ethics Board
Health Canada and the Public Health Agency of Canada's Research Ethics Board

Analysis and publication

An interim analysis of data will be completed annually to prepare a study summary report (at the end of year one and year two, and at the conclusion of the study) for inclusion in the *CPSP Annual Results* publication. Final results will be published in peer-reviewed journals and will be presented at national and international conferences.

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