



Zika virus and severe microcephaly in Canada



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Congenital microcephaly

Microcephaly is an anomaly of the central nervous system where an infant's head is smaller than the head of other children of the same age and sex. Severe microcephaly is a more serious, extreme form of microcephaly where a baby's head is significantly smaller than expected.¹ Microcephaly (including severe microcephaly) results from abnormal brain development *in utero*, or during early infancy. There are many known causes of microcephaly, including genetic disorders, exposures to known drugs or toxins, hypoxic injury, and congenital infections. A wide variety of outcomes are associated with microcephaly. Many affected children experience developmental and intellectual delays, ranging from mild to severe. Children with microcephaly also present with a constellation of other health concerns, often requiring intensive, significant, and life-long medical, educational, and social supports.²

Prevalence of microcephaly in Canada

Given the relationship of microcephaly to a child's developmental trajectory, microcephaly is of clinical and public health importance. Microcephaly is currently monitored through the Public Health Agency of Canada's Canadian Congenital Anomalies Surveillance System (CCASS). CCASS cannot distinguish between microcephaly and severe microcephaly; however, recent CCASS data shows that the incidence of all microcephaly in Canada (excluding Quebec) in 2013 was 6.6 per 10,000 births (a total of 198 cases annually).³ In the United States, during a similar time period, estimated rates of all microcephaly cases varied from 2.1 per 10,000 births in Utah to 14.6 per 10,000 births in Texas.⁴ International jurisdictions reported rates of all microcephaly ranging from 3.11 per 10,000 births in the United Kingdom to 3.8 per 10,000 births in Australia.⁴

The National Birth Defects Prevention Network recommends that severe congenital microcephaly cases include infants with a head circumference at birth (or at delivery for stillbirths and elective terminations) less than 2 standard deviations below the reference population mean.⁵ The diagnostic criteria are based on sex-specific growth parameters defined by the World Health Organization. In Canada, variability exists between jurisdictions and health care providers on how severe microcephaly is defined,

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with most opting for a less than the 3rd percentile definition. However, most diagnostic criteria are similar and are considered comparable.

Link between Zika virus infection and microcephaly

The Zika virus, from the family *Flaviviridae*, is primarily contracted through the bite of an *Aedes aegypti* or *Aedes albopictus* mosquito. Infection through sexual contact with an infected partner and through blood, cell, and tissue transfusions has been documented.¹ During pregnancy, the virus may be transmitted to the fetus transplacentally and may result in a range of congenital anomalies. There has been a recent increase in microcephaly cases reported globally linked to an outbreak of the Zika virus, with over 30 countries now reporting cases of congenital Zika syndrome.⁶ Previous research suggested that the risk of Zika-associated microcephaly was highest in the first trimester. Newer evidence indicates a significant risk of Zika-associated congenital anomalies exists following transplacental infection in all trimesters.⁷⁻⁸ While cases have been documented primarily in countries where Zika outbreaks have occurred, given the modes of transmission of the Zika virus and acknowledging the global travel patterns of Canadians, it is critical to monitor for potential Zika virus-related cases of microcephaly in Canada.

While evidence suggests that congenital Zika syndrome (CZS) cases may present with a broad spectrum of central nervous system and other disorders,⁹⁻¹¹ CZS is typically characterized by the presence of severe microcephaly, including cranial disproportions, redundant scalp with roughness, hypertonia, irritability, and epileptic seizures.¹¹ Additionally, there are reported cases of abnormal cortical development including cerebral hypoplasia, diffuse cerebral calcifications, and cerebral atrophy.^{6, 11-12} Auditory and visual anomalies, such as central hearing loss, focal retinal pigment epithelium changes, and chorio-retinal atrophy have been reported.^{6, 11-12} Joint impairments in newborns include manifestations of arthropathy which can range from a club foot to severe malformations (arthrogryposis) of the hands and feet. While the link is less understood, there has also been an increase in the observed number of spontaneous abortions and fetal deaths among potentially infected Zika patients.⁹ Information is sparse on long-term medical and developmental outcomes for infants with CZS. Based on previous data concerning severe microcephaly², development among these children is likely to be impaired.

A recent review provided a synthesis of five clinical features to aid clinicians in differentiating congenital Zika syndrome from other congenital infections: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia with symptoms of extrapyramidal involvement.¹² Recognition of these signs and symptoms among at-risk patients may aid clinicians in identifying CZS to ensure appropriate and timely evaluation and management of these infants.

Canadian clinical guidelines for screening infants at risk of congenital Zika syndrome

To ensure successful surveillance and management of congenital Zika syndrome, it is imperative that standardized operational procedures are followed. Guidelines for the investigation of infants with congenital Zika syndrome, including severe microcephaly, were developed by the Canadian Paediatric Society and are summarized below:

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Group	Screening Protocol
<p>Infants born to mothers with potential exposure to Zika virus (ZIKV) during pregnancy</p>	<ul style="list-style-type: none"> • Infants born to women with confirmed or suspected ZIKV infection in pregnancy, or those with microcephaly, intracranial calcifications, or other symptoms of congenital ZIKV infection in whom the mother had potential exposure to the virus, should be tested. • Testing should include ZIKV serology, polymerase chain reaction (PCR) of blood and urine from mother and child, and PCR of placenta. Document timing of potential ZIKV exposure on requisition to ensure the correct serologic test is conducted. • Perform ultrasound and MRI of the head on a non-urgent basis. • Discuss with paediatric infectious disease (ID) physician for differential (may consider testing child +/- mother for cytomegalovirus, toxoplasmosis, rubella, lymphocytic choriomeningitis virus +/- others)
<p>Infants born to mothers with ZIKV testing negative</p>	<ul style="list-style-type: none"> • If maternal ZIKV testing is negative then congenital ZIKV infection is excluded. • Pursue other testing as directed by paediatric ID physician.
<p>Infants with suspected or confirmed congenital ZIKV infection</p>	<ul style="list-style-type: none"> • If ZIKV serology is positive or indeterminate or ZIKV PCR is positive from any specimen then the interpretation of results must be done in consultation with a paediatric ID physician. • If results are inconclusive, send placenta for pathology and ZIKV PCR (plus testing for other potential pathogens). • Detection of ZIKV by PCR from any specimen from the child is diagnostic of congenital ZIKV infection (unless the child travelled to a ZIKV-endemic country in the preceding two weeks). • Detection of ZIKV by PCR from the placenta or from any maternal specimen is highly suggestive of congenital ZIKV infection (unless the mother has post-partum travel to a ZIKV-endemic country in the preceding two weeks). • ZIKV IgM from the child is highly suggestive of congenital ZIKV (unless the child has travelled to a ZIKV-endemic country) but cross reaction with other viruses may occur. Confirmatory serology (a plaque reduction neutralization test [PRNT] assay) may confirm that they are ZIKV antibodies. • A positive PRNT test can be from passive maternal antibodies but if it remains positive beyond 18 months of age and the child has not travelled to a ZIKV-endemic country, the child has congenital ZIKV infection. • Follow-up advice regarding children with congenital ZIKV infection can be found at: https://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w • Consult a paediatric neurologist. Request ophthalmic and audiologic assessments on all possible or proven cases of congenital infection with any pathogen (with repeat audiologic assessment annually until age 6 years, even if initial testing was normal).

Table adapted from: Robinson JL. Zika virus: What does a physician caring for children in Canada need to know? *Paediatric Child Health* 2017; 22(1):48-51



Conclusion

An increase in prevalence of the Zika virus and the emergence of its association with microcephaly highlights the need for awareness and surveillance, as well as a standardized approach to screening, management, and treatment. Clinicians should refer to the CPS Practice Point on Zika virus (available online at <http://www.cps.ca/en/documents/position/Zika-virus>) to ensure timely and appropriate management of potentially infected mothers and their infants.

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Quiz

1. **The clinical definition for severe microcephaly includes:**
 - a) Head circumference less than the 5th percentile, according to Centers for Disease Control and Prevention (CDC) growth charts
 - b) Head circumference less than the 5th percentile, according to either the CDC or World Health Organization growth charts
 - c) Head circumference less than 2 standard deviations below the population mean
 - d) Head circumference less than 3 standard deviations below the population mean

2. **A 9-week old baby boy presents for a routine visit. He has severe microcephaly. His mother travelled extensively in South America during her first and second trimesters of her pregnancy. She was never tested for Zika. Which of the following are true?**
 - a) This infant should be tested for possible link to Zika virus, including ZIKV PCR.
 - b) This infant should undergo a head ultrasound.
 - c) This infant's care should be discussed with an infectious disease specialist.
 - d) All of the above.

3. **Which of the following is not a documented mechanism in which Zika virus is contracted?**
 - a) Through the bite of an infected mosquito
 - b) Through sexual contact with an infected partner
 - c) Through blood, cell, and/or tissue transfer
 - d) Through ingestion of contaminated food and/or water

4. **Which of the following is not a documented feature of congenital Zika syndrome?**
 - a) Distal arthrogryposis
 - b) Thrombocytopenia
 - c) Intracranial subcortical calcifications
 - d) Retinal anomalies

5. **You are called to the delivery room following the delivery of a full-term newborn with severe microcephaly. Travel history includes a trip to a Zika-endemic area four months prior to birth. Which of the following statements is true?**
 - a) Congenital Zika syndrome is unlikely, given the potential exposure to ZIKV was not in the first trimester.
 - b) ZIKV testing on the infant includes both serology and ZIKV PCR on both blood and urine.
 - c) ZIKV PCR testing should be performed on the placenta or the mother, but not both.
 - d) A head ultrasound and brain MRI should be obtained urgently.