Zika virus: What does a physician caring for children in Canada need to know?

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Abstract
Zika virus (ZIKV) was recently recognized to be teratogenic. The diagnosis of congenital ZIKV syndrome should be considered in children with unexplained microcephaly, intracranial calcifications, ventriculomegaly or major structural central nervous system abnormalities. Management is evolving but suggestions are provided for children with findings compatible with congenital infection and for those born to women with potential exposure during pregnancy.

Key words: Congenital infection, Microcephaly, Teratogen, Zika virus

EPIDEMIOLOGY
Zika virus (ZIKV) is an RNA virus and member of the flavivirus family, which includes West Nile, dengue, Japanese encephalitis, St. Louis encephalitis and yellow fever viruses. ZIKV was first detected in monkeys in 1947 in the Zika Forest, Uganda. A small number of human cases with nonspecific features were documented in Africa and Asia over the subsequent 60 years [1]. Then, in 2007, ZIKV infected an estimated 73% of the population of Yap Island in the South Pacific [2]. Outbreaks were subsequently recognized in 2013 to 2014 in French Polynesia, the Cook Islands, New Caledonia, and Easter Island [2]. ZIKV was detected in Brazil in 2015 [2] but may have been present there since 2013 [3]. During 2016, locally acquired cases have been documented in most countries in South America and the Caribbean, Mexico, and the USA (in Florida and Texas only, as of March 1, 2017) (see www.cdc.gov/zika/geo/index.html).

ZIKV is spread by the bite of Aedes aegypti mosquitoes and less commonly Aedes albopictus, neither of which is known to be established in Canada (see https://elifesciences.org/content/4/e08347 for maps of worldwide Aedes distribution). Because patients are commonly asymptomatic yet viremic, it is not surprising that transmission via blood products occurs. ZIKV has been detected in semen for ≥181 days [4] and in female genital secretions for up to 3 weeks [5]; male-to-female, female-to-male and male-to-male sexual transmission have been documented (www.cdc.gov/zika/hc-providers/clinical-guidance/sexualtransmission.html).

CLINICAL FEATURES
The estimated incubation period is 3 to 12 days. Most infections (75% to 80%) are asymptomatic. Common features of symptomatic infections are maculopapular rash (typically pruritic, starting proximally and spreading to the limbs, with associated edema), low-grade fever, arthralgias (especially of small joints in the hands and feet), myalgias, headache and nonpurulent conjunctivitis. Recovery is usually complete within 3 to 14 days. Features overlap with disease caused by dengue and chikungunya viruses, which are transmitted by the same mosquitoes.

A small number of cases have had unusual features, including myelitis or encephalitis (with detection of ZIKV in cerebrospinal fluid [CSF]) [6], hearing loss, genitourinary symptoms, hematospermia, hypotension [2], thrombotic thrombocytopenia [7] and death [6-8].

Guillain-Barré syndrome (GBS) has been associated with ZIKV infection, with an estimated incidence of 0.24/1000 total cases in French Polynesia [9] and 1.73/1000 symptomatic cases in the USA and US territories as of November 16, 2016 [10]. Onset is median only 7 days following initial ZIKV symptoms, with paresthesias and facial palsy possibly being more
common than usual [11]. It is not clear whether any cases have occurred in children.

**CONGENITAL ZIKV SYNDROME (Czs)**

ZIKV is neurotropic in mice when injected into the peritoneum [12], but was not suspected to be teratogenic in humans until an unusual cluster of microcephaly was noted in Brazil in 2015. It appears that CZS cases commonly have severe microcephaly, cerebral atrophy, abnormal cortical development, callosal hypoplasia and diffuse subcortical calcifications [13][14]. Microcephaly with normal brain imaging was described in 0 of 11 [13] and 16 of 27 cases [14]; interpretation of these discordant results is not clear. Head circumference can be normal with ventriculomegaly [13]. Infants with severe microcephaly from CZS have redundant scalp consistent with fetal brain disruption sequence. Abnormal fetal tone can result in clubfoot or fetal akinesia deformation sequence (arthrogryposis); the latter was described in 3 of 11 proven [13] and 7 of 104 possible cases [19]. Microphthalmia, cataracts, and retinal abnormalities have been described in a small number of CZS cases [13][19]. Sensorineural hearing loss was documented in 5 of 70 cases (7%) [17]. Intratraumatic growth retardation is common.

A recent review article summarized the features of CZS that distinguish it from other congenital infections as follows: [11] 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 and symptoms of extrapyramidal involvement [18]. There are no consistent reports of congenital abnormalities outside of the central nervous system (CNS). Congenital ZIKV infection without CNS involvement undoubtedly occurs but has not been described to date [19]; presumably such cases would be labelled “congenital ZIKV infection,” rather than CZS.

Strong evidence that ZIKV causes CZS emerged from a case-controlled study where ZIKV was detected in the amniotic fluid and/or brain/CSF of fetuses and infants in 13 of 32 cases and 0 of 62 controls [14]. It is surprising that 60 years elapsed between the first detection of ZIKV in humans and the recognition that it is teratogenic. One possible explanation for the sudden explosion of cases of CZS is that recent outbreaks are Asian-lineage ZIKV, while the original cases were African-lineage ZIKV. The Asian lineage generates higher level viremia and therefore may more readily infect a population and cross the placenta [20]. Another theory is that “antibody-mediated enhancement” caused by ZIKV interacting with pre-existing dengue virus antibodies, which are common in Brazilians, led to teratogenicity [21].

The incidence and risk of CZS with ZIKV infection during pregnancy are unknown. Most, but not all mothers of infants with CZS recalled a rash during pregnancy [13][19]. Microcephaly occurred in an estimated 0.76% to 1.27% of infants born to women with first trimester ZIKV in French Polynesia [22]. A study from Brazil estimated 1% to 13% risk, depending on the ZIKV infection rate and the degree of overreporting of microcephaly [23]. More alarming data reported abnormal in-utero ultrasounds in 13 of 45 cases of ZIKV during pregnancy in Brazil (29%) [24]. CZS has been described mainly with first trimester infection but also with second and third trimester infection [13][19]. There are two reports of subependymal cysts and lenticulostriate vasculopathy (findings suggestive of injury to the developing brain) on postnatal ultrasound following maternal infection at 36 weeks gestation; one of the infants affected had ZIKV detected in urine [25].

Perinatal transmission appears to be benign. It was documented in two infants; one had a rash and the other was asymptomatic [26].

**DIAGNOSIS**

Diagnosis is by:

1. Serology (IgM or IgG or neutralizing antibody) or
2. Detection of ZIKV RNA by polymerase reaction (PCR) testing.

IgM becomes positive about 7 days following symptom onset, with IgG appearing about 3 days later [27]. IgG presumably persists indefinitely. It is estimated that IgM persists 3 months [27]. Both IgM and IgG can cross-react with other flaviviruses and therefore must be confirmed to be ZIKV antibodies by a plaque reduction neutralization test (PRNT). If PRNT titres for both dengue and ZIKV are identified, the result will be assessed as “indeterminate.” Current testing in Canada consists only of IgM with PRNT done when IgM is positive or when IgM is negative but the requisition clarifies that exposure is remote.

PCR testing on blood is usually only positive during the first 4 days of symptoms [27]. However, viremia persisted for ≥71 days in one pregnant woman [28] and ≥67 days in CZS [29], possibly because fetuses have prolonged viremia from immature immune systems; ZIKV crosses the placenta, yielding persistent maternal
viremia. PCR on urine is usually positive on days 2 through 9 following symptom onset [27]. See Figures 1 and 2 for guidance on testing in different scenarios or with positive laboratory results.

Figure 1. Investigating infants or children with features suggestive of congenital Zika syndrome.

Child born from 2016 on with unexplained microcephaly (present at birth or detected later), intracranial calcifications, ventriculomegaly, or major structural CNS abnormalities AND maternal history of: i) travel to a ZIKV-endemic country during pregnancy OR ii) sexual contact during pregnancy with a male who travelled to a ZIKV-endemic country in the preceding 6 months.

Request:
- ZIKV serology and blood and urine for ZIKV PCR on mother and child as soon as possible (it is unclear up to what age they may be positive) – document timing of potential ZIKV exposure on requisition to ensure correct serologic test is run
- That the placenta be saved
- U/S and MRI of the head on a non-urgent basis.

Discuss with a paediatric ID physician (may consider testing child +/- mother for CMV, toxoplasmosis, rubella and LCMV +/- others, depending on the history and findings).

All ZIKV testing is negative

Congenital ZIKV infection is excluded. Pursue other testing as directed by paediatric ID physician.

ZIKV serology is positive or indeterminate or ZIKV PCR is positive from any specimen

Discuss interpretation of ZIKV serology and PCR results 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 2 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 2 weeks).
- ZIKV IgM from the child is highly suggestive of congenital ZIKV (unless the child has travelled to a ZIKV-endemic country) but crossreaction with other viruses may occur. Confirmatory serology (a 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).

1Negative maternal ZIKV serology more than 4 weeks after exposure rules out ZIKV infection and congenital ZIKV infection. However, since one may wait weeks for results, sending specimens for PCR and testing the child simultaneously is advised. Assuming that the child has not travelled to a ZIKV-endemic country, they should only have positive ZIKV serology if the mother tests positive. Discuss with an ID physician or microbiologist if results are positive only from the child.

CMV cytomegalovirus; CNS central nervous system; CSF cerebrospinal fluid; ID infectious diseases; IgM Immune globulin; LCMV lymphocytic choriomeningitis virus; MRI magnetic resonance imaging; PCR polymerase chain reaction; PRNT plaque reduction neutralization test; U/S ultrasound; ZIKV Zika virus
Figure 2. Management of infants born to women with potential exposure to ZIKV during pregnancy.

1. Infant born to mother with potential exposure to ZIKV during pregnancy

2. Request ZIKV serology on mother. If potential exposure was in the previous 4 weeks, also send maternal blood and urine for ZIKV PCR.

   - Maternal ZIKV testing negative
     - Congenital ZIKV infection is excluded
     - Infant has normal head circumference and normal neurological exam.

   - Maternal ZIKV serology positive or indeterminate or mother had positive ZIKV PCR from any specimen.
     - Infant has abnormal neurological exam without microcephaly
     - Infant has microcephaly

   - Request ZIKV IgM and blood and urine for ZIKV PCR and ultrasound of the head.
     - Head imaging normal or shows minor abnormalities
       - Normal head growth and neurodevelopment
       - See Figure 1 for interpretation of ZIKV serology and PCR results. Optimal follow-up of children with asymptomatic congenital ZIKV is not known. Late-onset hearing loss is described with congenital rubella and CMV, so consider annual audioligic follow-up until age 6 years.
     - Head imaging shows intracranial calcifications, ventriculomegaly or major structural brain abnormalities.
       - Concerns regarding head growth or neurodevelopment
       - See Figure 1 for interpretation of ZIKV serology and PCR results. Arrange MRI of head (if not already done), audiologic and ophthalmologic assessments.

   - Request ZIKV IgM and blood and urine for ZIKV PCR and MRI of the head.
   - Follow algorithm in Figure 1
Delayed onset of hearing loss is well described in infants with congenital rubella or cytomegalovirus who are asymptomatic at birth; there may also be late sequelae with congenital ZIKV infection. Therefore, all women with potential ZIKV exposure during pregnancy should be identified. When the exposure is noted only after delivery, ZIKV serology should be requested on the mother or infant. The algorithm in Figure 2 is followed when results are positive or indeterminate.

Testing is generally not advised for asymptomatic or symptomatic children with exposure to ZIKV after birth, unless they require hospitalization. However, when considering testing a febrile traveller for arboviruses, add ZIKV if appropriate. Travel history should be ascertained from all children with GBS.

**PREVENTION**

There is no treatment for ZIKV infections. Several vaccines are in development and may be licensed as early as 2018. Travellers to areas with ZIKV should use personal protective measures (i.e., bed nets, appropriate clothing and mosquito repellents) to prevent mosquito bites day and night, both inside and outside (See www.cps.ca/documents/position/preventing-mosquito-and-tick-bites and www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-3/index-eng.php). Those who are or may become pregnant and their sexual partners should avoid travel to affected areas, where practical (https://travel.gc.ca/travelling/advisories).

Although ZIKV RNA has been detected in breast milk, the virus is not thought to be infectious. However, some experts advise caution with breastfeeding during acute ZIKV infection. There was a case of transmission from a dying elderly man with very high grade viremia to his son [10], but nonsexual person-to-person transmission appears to be rare. However, routine infection control precautions always apply. Pending more data on transmission, pregnant women should employ meticulous hand hygiene when they have direct contact with infants with congenital ZIKV infection. For more detail (particularly about adults), see www.phac-aspc.gc.ca/publicat/ccdr-rmtc/16vol42/dr-rm42-5/ar-01-eng.php?id=zika_virus_16_phac_catmat.

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**References**


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