Public Health Ontario | Santé publique Ontario

PARTNERS FOR HEALTH | PARTENAIRES POUR LA SANTÉ

Rapid risk assessment: Zika virus

August 12, 2016

Summary

Event information summary:

Zika virus (ZIKV) infection is a mosquito-borne illness that is usually mild and resolves without treatment. This outbreak was first documented in Brazil in early 2015. Since then, ZIKV infection has spread rapidly throughout Central and South America and the Caribbean, with local transmission recently documented in two counties in Florida. The World Health Organization (WHO) has concluded that ZIKV is a causative agent of congenital malformations and neurological complications.

As of August 11, 2016, the Public Health Agency of Canada (PHAC) has reported 205 cases of travel-associated ZIKV infection in Canada, with two cases of sexual transmission and two cases of fetal infection. As of August 9, 2016, the Ontario Ministry of Health and Long-Term Care (MOHLTC) reported 117 cases of travel-associated ZIKV infection in Ontario, with two cases of locally transmitted infection via sexual transmission. Currently, Ontario has the third highest case count of ZIKV infections, behind Florida (322 cases) and New York State/City (530), as reported by the Centers for Disease Control and Prevention (CDC) in Canada and the USA. Ontario's high case could be due to relatively high travel volumes to endemic regions of the Americas, greater public or clinician awareness in the province, or other factors.

Risk assessment summary:

Assessing the risk of infection to individual Ontarians who travel to areas where transmission of ZIKV is occurring continues to be challenging, but overall is considered low to moderate depending on the area to which the individual travels, the extent to which mosquito control measures are taking place and/or personal protective practices are used. Given the number of Ontarians who travel to endemic areas, the likelihood of continued imported cases remains high.

The risk to residents in Ontario who are non-travellers is extremely low, except in cases where sexual transmission or fetal/perinatal transmission could occur. Public Health Ontario's (PHO) level of confidence in the existing primary literature, grey literature and expert opinion is moderate, given the rapidly emerging situation in the Americas. We expect ZIKV will continue to spread throughout the

Americas, especially where competent vectors are present and where conditions are conducive to transmission.

Summary risk level: Low

Likelihood of transmission: High risk of imported cases, low risk of local transmission through sexual contact or fetal/perinatal transmission.

Severity of impact: Very low on a population level; high in cases of congenital infections and neurological complications such as Guillain-Barre Syndrome.

Request information

Source and date of initial request:

Brian Schwartz, chief, Communicable Diseases, Emergency Preparedness and Response (CDEPR), and Lisa Fortuna, director, CDEPR, requested a Zika virus RRA on January 21, 2016.

Source and date of update requests:

On March 4, 2016, the PHO internal response team (Appendix A) assessed the triggers required for updating the RRA and determined that there was sufficient new evidence to update the RRA. Triggers met:

- Causal linkage established between ZIKV and microcephaly/congenital abnormalities (increasing risk of severe disease to travellers).
- Causal linkage established between ZIKV and GBS (increasing risk of severe disease in travellers).

On April 27, 2016, the PHO internal response team assessed the triggers required for updating the RRA and determined that there was sufficient new evidence to update the RRA. Trigger met:

- Further evidence of sexual transmission (increasing risk of local transmission).

On July 29, 2016, the PHO internal response team assessed the triggers required for updating the RRA and determined that there was sufficient new evidence to update the RRA. Triggers met:

- Demonstrated asymptomatic sexual transmission (increasing risk of local transmission).
- Demonstrated female-to-male sexual transmission (increasing risk of local transmission).
- Demonstrated vector-borne transmission of ZIKV in the US (increasing the risk of infection for travellers by increasing the geographical area affected by local transmission of ZIKV).

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Background

Event information

Given the rapid emergence and spread of Zika virus (ZIKV) infection in the Americas, initial reports of potential links with congenital malformations and neurological complications, and the possibility of imported cases in Ontario, PHO was asked to provide a rapid risk assessment (RRA) of ZIKV on January 29, 2016. The RRA would ultimately inform public health policy and health care system planning, as well as provide responses to inquiries from stakeholders and the public. Given new evidence for vector-borne transmission in the USA and demonstration of female-to-male sexual transmission, PHO has conducted a third update of the RRA, reflecting the latest science available.

This review considers published materials from national and international agencies such as the WHO, the Pan American Health Organization (PAHO), the European Centre for Disease Control (ECDC), CDC and PHAC. Given an RRA involves a quick and timely situational assessment, formal systematic review and quality assessment procedures were not conducted.

MEDLINE, Embase, BIOSIS, Scopus and PubMed were searched for new Zika-related literature by daily search alerts. An initial Ovid MEDLINE search strategy was a simple keyword search for “zika” or “zikv” in title and abstract, as the MeSH terms “Zika Virus Infection” and “Zika Virus” had not yet been created. Subsequent Ovid MEDLINE search strategies were update to capture records indexed with the new MeSH terms. The final MEDLINE strategy, as well as the strategies for the additional databases, was as follows:

Ovid MEDLINE, Embase, BIOSIS

#	Searches
1	(zika or zikv).mp,hw.

Scopus

#	Searches
1	TITLE-ABS-KEY (zika OR zikv)

PubMed

#	Searches
1	zika[all fields] OR zikv[all fields]

On January 28, 2016, the WHO Director-General, Dr. Margaret Chan, announced the convening of an International Health Regulations Emergency Committee on ZIKV in response to the observed increase in neurological disorders and neonatal malformations. The Committee met on February 1, 2016, and determined that the cluster of microcephaly cases and other neurological disorders associated with Zika

virus infection constituted a Public Health Emergency of International Concern (PHEIC), a decision reaffirmed in subsequent meetings.

On February 19, 2016, Ontario's Chief Medical Officer of Health issued a statement concerning Ontario's first confirmed case of ZIKV infection in a returning traveller from South America. On April 25, 2016, Canada's Chief Public Health Officer and Ontario's Chief Medical Officer of Health issued a joint statement on Canada's first positive case of sexually-transmitted ZIKV infection.

On July 29, 2016, the Florida Department of Health reported the first occurrence of local, mosquito-borne ZIKV transmission in the continental USA.

Disease background

Overview

ZIKV is a mosquito-borne virus discovered in 1947 in the Zika Forest of Uganda.[1] Zika virus is a flavivirus closely related to other mosquito-borne flaviviruses such as dengue virus (DENV) and West Nile virus (WNV). In the past, outbreaks of ZIKV disease have been reported in parts of Asia, Africa and Pacific islands.

As of August 9, 2016, 117 cases of travel-related and two non-travel related (sexual transmission) cases of ZIKV infection have been reported in Ontario (Ontario provincial case reporting). As ZIKV spreads in the Americas, and awareness increases on the part of Ontario physicians, we expect the number of travel and non-travel related cases identified in Ontario to increase.

Transmission

Zika virus infection is primarily a mosquito-borne disease transmitted through the yellow fever mosquito, *Aedes aegypti*, and the Asian tiger mosquito, *Ae. albopictus*.[2] Transmission may occur through unprotected sexual contact. There are documented cases of transmission from males to females and males to males, and there is a case report suggesting that transmission may occur from females to males.[3-5] The potential for transmission by breast milk, saliva and urine requires further study and no documented cases of transmission have been reported to date from any of these routes.

Imported cases of ZIKV infection have been diagnosed in Ontarians returning from travel to countries where ZIKV is circulating. However, local mosquito-borne transmission in Ontario is unlikely as *Ae. aegypti* and *Ae. albopictus* mosquitoes are not native to Ontario and the province's mosquito species have not been found to be competent vectors for ZIKV.

Zika virus is circulating in an expanding number of countries in the Americas. Zika virus will continue to spread throughout areas of this region that have competent vectors (in Canada, competent mosquito vectors are not present) as the majority of the population has not been exposed to ZIKV and therefore lacks immunity. The proclivity of *Ae. aegypti* to blood feed primarily on humans and its ability to proliferate in urban areas partially explains the rapid spread of ZIKV in the Americas. In addition, the

similarity of ZIKV infection symptoms to dengue fever and chikungunya infection has likely meant that cases of ZIKV have gone unrecognized for some time, allowing the virus to spread undetected. While the ZIKV outbreak in the Americas was thought initially to be aided by mass gathering events such as the 2014 World Cup held in Brazil,[2,6] research has now identified retrospective ZIKV infections in Haiti in December 2014, indicating that ZIKV was present in that country prior to the outbreak in Brazil.[7]

Given the evolving understanding of ZIKV transmission in the Americas, readers are urged to refer CDC's "Areas with Zika" for the latest list of affected countries.

Disease severity

Zika virus infection is a mild illness that generally resolves within 2–7 days; 75–80 per cent of people infected with ZIKV display no symptoms.[8] The incubation period for ZIKV is from three to 12 days, with symptoms that can include fever, joint and muscle pain, skin rash that is frequently itchy, conjunctivitis and headache that can last from three to seven days.

There is sufficient evidence to conclude that ZIKV infection during pregnancy is a cause of microcephaly and other birth defects. Evidence strongly suggests Guillain-Barre Syndrome (GBS) is associated with ZIKV infection as well. Evidence of other complications is emerging.

Prevention and treatment

There is no vaccine or antiviral therapy for ZIKV, and treatment options are supportive in nature, including pain management and fluids to prevent dehydration. Non-steroidal anti-inflammatory drugs should be avoided until DENV infection has been ruled out due to the risk of bleeding (as well as being avoided in all pregnant patients).

PHAC has issued Travel Health Notice concerning ZIKV. Recommendations include:

- "Pregnant women and those planning a pregnancy should avoid travel to countries with ongoing Zika virus outbreaks. If travel cannot be avoided or postponed strict mosquito bite prevention measures should be followed due to the association between Zika virus infection and increased risk of serious health effects on their unborn baby."
- "Travellers returning from countries with ongoing Zika virus outbreaks:
    - For pregnant women, if you develop symptoms that could be consistent with Zika virus infection, you should consult a health care provider.
    - For women planning a pregnancy, it is strongly recommended that you wait at least 2 months before trying to conceive to ensure that any possible Zika virus infection has cleared your body.
    - For men, Zika virus can persist for an extended period of time in the semen of infected men, therefore, it is strongly recommended that: 1) if you have a pregnant partner, you should use condoms or avoid having sex for the duration of the pregnancy; 2) you and

your partner wait to conceive for 6 months by using a condom or by avoiding having sex; and 3) you should consider using condoms or avoid having sex with any partner for 6 months."

All travellers to affected countries are advised to practice appropriate personal protection measures against mosquito bites, especially during mid-morning and late afternoon when mosquitos are most active. The Committee to Advise on Tropical Medicine and Travel (CATMAT) has provided recommendations for personal protection:

- use insect repellant
- wear light colored clothing to cover exposed skin
- use physical barriers such as screens
- remove or empty containers with standing water to eliminate mosquito breeding sites

CATMAT also recommends that individuals with symptoms of ZIKV infection after returning from travel in Central and South America and the Caribbean consult their health care provider.

Human health risk assessment

Assessing likelihood of transmission

Is human exposure and vector transmission likely within Ontario?

The primary vectors of ZIKV in the Americas are the yellow fever mosquito, *Ae. aegypti* and the Asian tiger mosquito, *Aedes albopictus*, two species that do not occur in Ontario. The relatively cooler temperatures of Ontario cannot support the establishment and spread of these vector mosquito species in the province. On rare occasions *Ae. albopictus* has been detected in Ontario.[9] These exceptional findings of *Ae. albopictus* are due to adventitious insects likely entering via cross-border vehicular traffic and trade. No established populations of *Ae. albopictus* have been detected in Ontario, with the closest established, over-wintering populations occurring in southern New York State and Ohio.[10] The current distribution of *Ae. albopictus* is south of areas with annual mean temperatures higher than 11°C and mean temperatures of the coldest month, January, higher than -2°C.[11] In Windsor, Ontario, the annual mean temperature is 9.4°C with a mean January temperature of -4.5°C; in St. Catharines, Ontario, the annual mean temperature is 8.8°C with a mean January temperature of -4.1°C (eldoradocountyweather).

Determining that a mosquito species is a vector (or at least potentially could serve as a vector) of a specific pathogen depends upon meeting four criteria:

- Potential vector feeds on infected vertebrate hosts (i.e., humans).
- Demonstration of a spatiotemporal association between the potential vector's activity and infection in hosts.
- Detection of the pathogen in potential vectors in the field.
- Demonstration of transmission of the pathogen to a host by the potential vector under controlled experimental conditions.[12]

For mosquito species present in the Americas, only *Ae. aegypti* and *Ae. albopictus* have met these criteria to be designated as vectors of ZIKV.[13-17] A recent study indicated *Ae. aegypti* and *Ae. albopictus* populations in the Americas are not highly competent vectors of ZIKV (*Ae. aegypti* more competent than *Ae. albopictus*), suggesting that the rapid expansion of the current outbreak is likely due to a large immune-naïve human population and relatively high densities of vectors with high human biting rates.[18] During a recent outbreak in Chiapas, Mexico, 5 out of 55 *Ae. aegypti* pools collected around patient homes were positive for ZIKV; however, *Culex quinquefasciatus* (southern house mosquito) was the second most abundant mosquito during these collections yet no pools were positive for ZIKV.[19] The Chiapas, Mexico research is the first study in the Americas to document *Ae. aegypti* as the primary vector during a ZIKV outbreak. On April 21, 2016, PAHO reported the first detection in the Americas of ZIKV in field-collected mosquitoes, when *Ae. albopictus* collected from San Luis Potosi State in central Mexico tested positive for ZIKV during an outbreak in that state.[20]

Laboratory research conducted in Brazil indicates *Cx. quinquefasciatus* is a competent vector of ZIKV; however, this research is yet to be peer-reviewed and published. In addition, the Oswaldo Cruz Foundation (Fiocruz) in Brazil reported that three out of 80 pools of *Cx. quinquefasciatus* collected in Recife, Brazil were positive for ZIKV. Further research is required to determine the extent to which *Cx. quinquefasciatus* contributes to the ZIKV transmission in the Americas. *Culex quinquefasciatus* is not present in Ontario and is a tropical/sub-tropical species present in the southern US. *Culex pipiens* (the northern house mosquito, related to *Cx. quinquefasciatus*) is a common mosquito in Ontario and the primary vector of WNV. Laboratory investigations into *Cx. pipiens* and another species that occurs in Ontario, *Aedes triseriatus* (eastern treehole mosquito), demonstrate that these species are not competent vectors of ZIKV.[21] Currently, vector competence studies are underway on other Ontario mosquito species at Brock University in St. Catharines, Ontario.[22]

Potential reservoirs of ZIKV are unknown, but presumed to be humans.[23] Zika virus infection has been documented in several monkey and ape species, including sentinel rhesus monkeys in Africa and orangutans in Southeast Asia.[24,25] In the Americas, there have been reports of ZIKV RNA detection in non-human primates in northeastern Brazil (marmosets, capuchin monkeys) and western Ecuador (howler monkey); however, whether or not these primates serve as reservoirs is unknown.[20] Zika virus antibodies have been detected in bats, birds, cattle, goats, horses, rodents and sheep; however, their role as reservoirs has not been investigated and, in most cases, positive serology may not indicate prior Zika virus infection due to potential cross-reactivity with related flaviviruses.[24,26] Without efficient reservoirs, modelling research indicates that the ZIKV outbreak in the Americas will end in approximately three years (with absence of large-scale outbreaks for another 10 years or more), due to increasing herd immunity in the human population.[27]

In conclusion, the risk of local vector-borne transmission of, and exposure to, ZIKV in Ontario is low, with a moderate degree of confidence in the evidence.

Is human exposure likely among Ontarians who travel to affected countries?

The introduction and relatively rapid spread of ZIKV throughout much of South America, Central America and the Caribbean, as well as the recent detection of local transmission in southern Florida presents a threat to Ontarians travelling to these regions. The highest risk of exposure and infection will be in areas where vector mosquitoes are present. *Aedes aegypti* is primarily an urban species; however, *Ae. albopictus* can be found in both urban and rural areas. In general, risk of exposure is variable and depends on travel destination, the extent of local mosquito management and a traveller's personal protective behaviours.

Currently, the evidence points to *Ae. aegypti* as the primary vector in the Americas; therefore, this risk assessment will focus on travel to regions where this vector is present and where conditions are conducive to ZIKV transmission. In parts of Brazil, for example, *Ae. aegypti* populations are relatively large, due in part to the concentration of litter (which serves as immature mosquito habitat) and the collection of drinking water by the public (due to water shortages and poor water supply infrastructure)

in highly urbanized areas.[28] This situation is particularly in the northeastern portion of Brazil where intense transmission of ZIKV occurred. Risk of infection in Ontario travellers is likely higher in densely populated urban areas, where *Ae. aegypti* are abundant.

Currently, there is uncertainty in the geographical range of ZIKV transmission in Central and South America, the Caribbean and the US. The variable risk of exposure in rural, urban or resort areas is unknown. If *Ae. aegypti* is the principal vector, then risk will largely be centered on urban areas of the Americas; however, if *Ae. albopictus* is involved, then the risk of exposure/transmission will be much broader. In addition, integrated vector management activities to reduce vector populations are highly variable, with inter- and intra-country differences. Caribbean resorts visited by Ontarians generally apply insecticides to control biting mosquito populations; therefore, risk of ZIKV exposure in resorts is assumed lower than urban, untreated areas outside of resorts. Risk of ZIKV transmission is also very low in areas above 2000m above sea level.[29] The CDC has developed mosquito surveillance, management guidance and a phased, risk-based response for states based on the presence of *Ae. aegypti* and *Ae. albopictus*.[30] In the USA, *Ae. aegypti* distribution is largely limited to long-standing populations in Arizona, California, Florida and Texas; a subterranean population is established in the Washington, DC area.[10]

On July 29, 2016, the Florida Department of Health and the CDC reported four vector-borne ZIKV infections in Broward and Miami-Dade counties in southeastern Florida, the first cases of vector-borne transmission of ZIKV infections in the USA. As of August 2, 2016, the CDC is advising that pregnant women not travel to the Wynwood neighbourhood of Miami and that pregnant women living in the affected area take special precautions. After interviewing Wynwood residents, additional cases of ZIKV infection where identified and intensive education and mosquito management programs initiated. It is possible that this risk area will increase in size as public health officials conduct further surveillance and additional vector-borne cases identified.

Risk of ZIKV infection for travellers to affected areas is also seasonally dependent. In the USA, *Ae. aegypti* abundance is the greatest during the warmest months of the year; in particular, from July through September in the southeastern USA (Florida) and southern Texas where mosquito populations are established.[31] By contrast, in Buenos Aires, Argentina, abundance and activity is higher from February through March;[32] San Miguel de Tucumán, Northwestern Argentina (December–March);[33] Sao Paulo, Brazil (November–May);[34] Rio de Janeiro, Brazil (January–February);[35] Manaus, Brazil (December–March);[36] and Trinidad and Tobago (May–October).[37] Given the variability in *Ae. aegypti* seasonality throughout the Americas, risk of ZIKV infection to Ontarians will likewise vary with season of travel.

Overall, the likelihood of a ZIKV infection in an Ontarian traveller during travel is low, noting that assigning a low risk is dependent upon numerous factors and that risk is highly variable with high degrees of uncertainty.

Are there secondary modes of transmission?

As with most mosquito-borne viruses, secondary modes of transmission are rare; however, with ZIKV, these secondary modes of transmission are more common. The structure of ZIKV and its relatively

higher thermal stability offer possible explanations for its survival in the normally harsh conditions of saliva, semen and urine, and in the case of semen, virus survival leads to increased risk of sexual transmission.[38] Zika virus RNA has been detected in saliva up to 29 days post onset of symptoms; in semen up to 93 days; and in urine up to 80 days.[39-46] While detected in saliva and urine, transmission of ZIKV via these bodily fluids remains undocumented. The isolation of infectious ZIKV from these various clinical samples has occurred less often than detection via PCR. Infectious ZIKV particles are present for a shorter time in semen, with one description of detection of infectious virus 24 days post symptom onset; however, a sexually transmitted infection 32 to 41 days post symptom onset has been reported. Infectious virus has also been detected in saliva (six days) and in urine (four to six days).[5,39,47,48]

Fetal/perinatal transmission

Fetal/perinatal transmission occurs with ZIKV, with intrauterine transmission or transmission occurring during delivery.[49-55] The incidence of asymptomatic transmission during pregnancy is under investigation. The Instituto Nacional de Salud, Columbia, has reported cases of asymptomatic pregnant females in Columbia giving birth to infants with microcephaly. In addition, researchers have detected ZIKV in breast milk; however, there is no documentation of transmission via breast milk.[23,49,56] While ZIKV has been detected in breast milk, the WHO states that the benefits of breastfeeding outweigh potential risks of ZIKV infection in newborns and that newborns be fed according to normal infant feeding recommendations.[57] A recent report suggests that a pregnant woman may have ZIKV RNA present in serum five weeks post onset of symptoms; however, the presence of ZIKV for a prolonged period may be due to concurrent fetal infection.[58] In addition, a study of ZIKV-infected pregnant women in the USA revealed that ZIKV RNA was present in serum up 46 days post illness onset in symptomatic women, and 53 days for a single asymptomatic woman.[59] The risk of fetal ZIKV infection via fetal/perinatal transmission is low with low confidence in the current evidence.

Sexual transmission

At the beginning of the outbreak in the Americas researchers thought the risk of sexual transmission was low, given that there were only sporadic case reports.[60,61] Ongoing research indicates that sexual transmission is more common than initially suspected and studies document ZIKV RNA in semen 93 days after illness onset (in some cases with high viral loads).[45,46,61-65] Most cases of sexual transmission are male-to-female; however, male-to-male transmission and one case of presumed female-to-male sexual transmission has been documented.[4] Both vaginal and anal sex are potential modes of sexual transmission.[66,67] While sexual transmission has been documented, the incidence of sexual transmission from asymptomatic males is unquantified, with one case of male-to-female transmission, 21 to 36 days post exposure, from an asymptomatic male being reported in a French couple returning from Martinique.[68] A study of imported Zika cases in China (with travel history to Venezuela) revealed an asymptomatic individual with a viremia as high as in symptomatic patients.[69] The risk of male-to-female or male-to-male transmission is high, with moderate confidence in the current evidence.

In July 2016, the CDC reported the first instance of female-to-male transmission in New York; however, this mode of transmission requires further study and description, given increasing evidence of viral shedding in vaginal fluids.[70] In Guadeloupe, ZIKV has been reported in the female genital tract (genital

swab, endocervical swab and cervical mucus were all positive for ZIKV RNA) of a ZIKV-infected patient; cervical mucus was positive 11 days post symptom onset.[71] The authors of the Guadeloupe research raise the possibility that infected females can act as chronic ZIKV carriers; however, further research will help clarify the risk of chronic, asymptomatic carriers to sexual partners.[71] Following the first report of female-to-male transmission, the CDC expanded its existing recommendations on the prevention of sexual transmission to cover all pregnant couples, including pregnant women with female sex partners.[3] In addition, the CDC extended the period for women to avoid pregnancy after a Zika infection to six months due to the risk of chronic shedding. The risk of female-to-male transmission is low, with low confidence in the current evidence.

Transmission via blood and organ products

Research conducted in French Polynesia during a recent outbreak demonstrated the possibility for asymptomatic blood donors to be PCR-positive for ZIKV.[65,72] There has been reports from Brazil of probable ZIKV infection via blood transfusion.[73] The risk of exposure in Ontario from blood and organ products is very low (see "Blood and organ products" section below), with moderate confidence in the current evidence.

Zoonotic transmission

There is a single report of a Zika case acquiring infection from the bite of an infected monkey in Bali, Indonesia.[7] This mode of transmission is rare for ZIKV and other flaviviruses; therefore, the risk of exposure from animal bites (in endemic regions) is very low, with low confidence in the current evidence.

Occupational exposure

While undocumented for ZIKV, there is a possibility of health care-associated (including laboratory workers) exposures to infectious bodily fluids, as is the case with similar flaviviruses such as WNV.[75,76] As of June 15, 2016, the CDC reported one case of laboratory-acquired ZIKV infection in the USA. The risk of occupational exposure (in Ontario or in endemic regions) is very low, with moderate confidence in the current evidence.

Is the population susceptible?

The majority of Ontarians have no immunity to ZIKV, and are thus highly susceptible to ZIKV infection. There is no evidence that certain parts of the population Zika virus and immunocompromised patients (e.g., pregnancy status, sex, age) are more at risk of infection.[77] Public Health England has produced guidance on Zika virus and immunocompromised patients, noting that evidence for ZIKV infection in immunocompromised or immunosuppressed people is limited and impact expected to be similar to other flaviviruses. Public Health England's practical advice for immunocompromised patients: "Since risks are likely to vary according to the immunosuppression or immunocompromise involved, travel advice will need to be tailored to the individual, with the strongest recommendations being made for severely immunocompromised patients (as per Green Book definitions)." The risk of exposure (Ontario travellers), regardless of portion of population is considered low, with low confidence in the literature.

Is the agent likely to cause severe disease?

Of those exposed to a ZIKV-infectious mosquito bite, approximately 75 per cent will become infected, of whom approximately 75–80 per cent of people will have asymptomatic infections.[78-80] A yet unknown fraction of these infected individuals may develop neurological complications such as encephalitis, meningitis or acute flaccid paralysis, similar to some other flavivirus infections.[1,20,81-83] A case of acute myelitis was reported in a ZIKV infection patient from Guadeloupe, with ZIKV detected in the cerebrospinal fluid, consistent with the neurotropic nature of ZIKV.[84] Current evidence suggests that ZIKV is both cytotoxic and neurotropic, targeting neural cells in the fetus and suggesting a risk of severe neurological complications post ZIKV infection.[58,85-89] Currently, a full characterization of risk factors associated with ZIKV infection are pending; therefore, uncertainty surrounds the understanding as to which subsets of the population are at increased risk of infection or serious complications. As with other arboviruses such as WNV, one expects that people with underlying medical conditions (cardiovascular disease or cancer) and/or immunocompromised are at a higher risk of severe disease.[81] Recent research indicates that people with prior DENV infection may experience more severe clinical disease when infected with ZIKV, through the process of antibody-dependent enhancement, although these lab-based results have not yet been documented in human cases of ZIKV infection.[82,90]

Guillain-Barré syndrome (GBS)

Evidence for a causal link between ZIKV infection and GBS has been established. Guillain-Barré syndrome has been associated with ZIKV outbreaks in French Polynesia (2013–14), with a 20-fold increase in GBS.[91] A recent case-control study of ZIKV infections in French Polynesia provides support for a causal link between ZIKV and GBS.[92] The study in French Polynesia matched 42 patients with GBS to control groups (n=98) with no GBS; 88 per cent of GBS group patients had serological evidence of ZIKV exposure, while 36 per cent of control group had serological evidence of ZIKV exposure. The estimated risk of GBS was 24 per 100,000.[92] In another study of the French Polynesia outbreak, the attributable risk of GBS was 0.39 per 1000 person-years, a 21-fold increase in GBS compared to pre-outbreak period.[93] As of July 29, 2016, PAHO reported increases in GBS associated with ZIKV infection in Brazil, Columbia, Dominican Republic, El Salvador, French Guiana, Guadeloupe, Haiti, Honduras, Jamaica, Martinique, Panama, Paraguay, Puerto Rico, Suriname and Venezuela. The risk of GBS in Ontario travellers to affected countries is low, with a low confidence in the current evidence.

Mortality

Rates of hospitalization and mortality from ZIKV infection are low.[79] A fatal case of ZIKV infection was reported in a patient with sickle cell disease in Columbia.[94] In addition, 139 fatal cases have been reported in Brazil (most in northeast provinces), all in neonates.[95] Fatalities have been reported in Columbia, where four of the deceased patients had underlying medical conditions (i.e., type 2 diabetes, leukemia, liver disease).[96] The risk of death in Ontario travellers with ZIKV infection is very low, with a low confidence in the current evidence.

Congenital abnormalities

Evidence for a causal link between ZIKV and congenital abnormalities (e.g., microcephaly) has been increasing since of the start of the ZIKV outbreak in the Americas. Early in the outbreak, the link between ZIKV and congenital abnormalities was based primarily on spatial and temporal associations of the increased prevalence of microcephaly. Since then, several studies have strengthened the causal link between ZIKV and congenital abnormalities, accompanied by evidence of ZIKV infection in multiple birth products and the central nervous system tissues of aborted fetuses. In addition, hearing loss has been noted in a ZIKV-infected and microcephalic newborn in Brazil; however, further studies are required to determine if the prevalence of this congenital abnormality.[102]

A preliminary study of 88 pregnant women with ZIKV-like symptoms from Rio de Janeiro, Brazil, indicated 82 per cent (n=72) of patients had a mild infection (maculopapular rash, conjunctivitis, lymphadenopathy); of those positive (n=42) and who had ultrasounds performed, 29 per cent (12/42) had abnormal fetal ultrasounds.[53] Two fetuses died, five had abnormal growth (with or without microcephaly), seven had CNS lesions and seven had abnormal amniotic fluid volume or circulation. This study provides evidence to support a causal link between ZIKV infection in pregnant women and congenital abnormalities and that relatively mild infection in pregnant women can lead to serious fetal/neonatal outcomes. A case series of 29 pregnant women from Salvador, Brazil, reported on the association of ZIKV infection with bilateral macular and perimacular lesions as well as optic nerve abnormalities in children born with microcephaly.[52] In another report, children with microcephaly in Brazil also showed signs of macular and optic nerve abnormalities.[103,104]

In March 2016, a Brazilian study investigated the link between 574 cases of microcephaly and ZIKV.[105] ZIKV transmission was laboratory-confirmed by RT-PCR in 15 of the 19 states studied; among these 15 states, the overall microcephaly birth prevalence was 2.8 (CI = 1.86–4.05) per 10,000 live births, compared with 0.60 (CI = 0.22–1.31) in the four states without laboratory-confirmed ZIKV transmission ($p<0.001$). The overall microcephaly birth prevalence in the 12 states reporting microcephaly was 4.6 per 10,000 live births (CI = 4.19–5.05); the highest prevalence rates were reported in Pernambuco (14.6; CI = 12.33–17.17) and Paraíba (10.8; CI = 8.86–13.04).

A study of pregnant women in the US with ZIKV infection further adds to the evidence of adverse birth outcomes.[106] Of nine confirmed cases, two had early miscarriages, two chose elective terminations of their pregnancies, two pregnancies resulted in live births of healthy children, two were progressing normally and one live birth was diagnosed with microcephaly. Furthermore, brain histological examinations of five fetuses (two newborns that died, a two-month old baby and two fetuses that spontaneously aborted) with microcephaly were positive for ZIKV through RT-PCR.[51] A case report of a pregnant female form Salvador, Brazil, indicates a possible link between ZIKV and hydrops fetalis and fetal demise.[107] Using a monkey cell line as a model, researchers have demonstrated ZIKV efficiently infects human neural progenitor cells, indicating the neurotropic behaviour of ZIKV.[86] Additional research shows that ZIKV specifically targets human brain cells and hinders normal development of nerve cells.[108]

Currently, there is growing evidence documenting that infection during the first or second trimester is associated with the development of congenital abnormalities. A study of the ZIKV outbreak and microcephaly in French Polynesia indicated a higher risk of microcephaly resulting from ZIKV infection during the first trimester.[101] Further investigation of ZIKV-infected pregnant women in French Polynesia and Brazil indicates an increased risk of congenital abnormalities if infection occurred in the first trimester.[109] In Columbia, researchers followed 11,944 pregnant women with ZIKV infection; there was no risk of congenital abnormalities if a woman was infected during the third trimester.[55] In a study of 1,501 live births in Brazil, probable Zika cases, when compared to discarded cases (cases that did not meet case definition), were more likely to have smaller head circumferences and higher first-week mortality; congenital abnormalities were more common if a maternal rash occurred earlier in preganacy.[54] As of July 29, 2016, PAHO has reported ZIKV-associated congenital abnormalities from Brazil, Columbia, El Salvador, French Guiana, Martinique, Panama, Puerto Rico and the USA.

The evidence for a causal link between ZIKV and congenital abnormalities has been rigorously evaluated using established criteria for assessing potential teratogens.[110] The published literature supports a causal link between ZIKV and congenital abnormalities; therefore, the ability of ZIKV to cause serious disease (in Ontario travellers, fetus/newborn) in this instance is moderate, with moderate confidence in the current evidence.

Other

Recently, there have been reports of severe thrombocytopenia in ZIKV-infected individuals.[96,111-113] One case was reported from the Netherlands in a returning traveller from Suriname, with possible concomitant or previous DENV infection.[112] A study of 683 Zika cases in Puerto Rico identified nine cases with thrombocytopenia (blood platelets levels <100,000 cells/mm^3).[114] A study of two cases in Puerto Rico indicated that the severe thrombocytopenia is immune-mediated.[115] Further research is needed to determine if ZIKV is the direct cause of thrombocytopenia, or if co-infection with DENV contributed to the severe outcome.

Will a significant proportion of the population be affected?

There is low risk of infection (via sexual transmission, through fetal/perinatal transmission or through exposure to contaminated blood/blood products or other virus-containing body fluids) in Ontarians who do not travel to affected areas. There is a very low risk of ZIKV exposure for a significant proportion of Ontarians that travel to affected areas.

Are effective treatments and/or control measures available?

There is no vaccine or specific treatment for ZIKV infections, especially antivirals. To our knowledge, there are no antivirals available or in development to combat ZIKV infections. Treatment is primarily supportive; i.e., fluids to prevent dehydration, routine medications for pain and fever (with the exception of non-steroidal anti-inflammatories in pregnant women). When caring for suspected or confirmed ZIKV cases, as with any other patient, health care workers should employ routine practices

and follow infection prevention and control guidance provided by the Provincial Infectious Diseases Advisory Committee including the appropriate use of personal protective equipment.[116]

Research is starting to identify target mechanisms for treatment in humans. Type III interferons (from primary human trophoblasts) are capable of preventing ZIKV infection across the placenta, offering potential therapeutic options to limit replication of ZIKV or spread.[117] Zika virus and DENV share common epitopes that can be targeted by neutralizing antibodies, indicating a potential immunotherapeutic therapy for those infected with ZIKV or the potential for using DENV vaccines as a tool to induce cross-protection to ZIKV.[118] Researchers showed that a viral polymerase inhibitor (7-deaza-2'-C-methyladenosine; 7DMA) reduces viremia and reduces morbidity and mortality in ZIKV-infected mice.[119]

Given the rapidly evolving situation, advice and guidance surrounding pregnant women and couples planning to become pregnant are updated as needed. As new evidence emerges, CATMAT will be updating their recommendations appropriately.

Personal protection

Travel alerts in Canada recommend travellers take appropriate personal protective measures when visiting areas affected by ZIKV. Preventive measures, as proposed by CATMAT, consist primarily of personal protection against mosquito bites during travel.[120] There is uncertainty surrounding the adherence to mosquito avoidance advice as proposed by CATMAT and others in Ontario travellers. In the case of malaria, it is well known that adherence to personal protective advice is poor.[121,122] Several reviews have examined preventive measures, including protective measures for pregnant women.[123,124] Laboratory investigations show that nitrile and latex gloves are protective.[125]

Blood and organ products

Canadian Blood Services screens potential donors, with deferral of donations for those with a travel history to affected regions: "Donors who have travelled to locations outside of Canada, the continental U.S. and Europe must wait 21 days after their return home before donating blood." In addition, if required, there are methods available to inactivate ZIKV in donated plasma.[126] A study has determined that disinfectants (i.e., dimethyl sulfoxide, ethanol, glutaraldehyde, hypochlorite, incidin, isopropanol, paraformaldehyde) readily kill ZIKV.[125]

Prevention for pregnant women

The Public Health Agency of Canada advises in its latest Travel Health Notice: "Pregnant women and those planning a pregnancy should avoid travel to countries with ongoing Zika virus outbreaks. If travel cannot be avoided or postponed strict mosquito bite prevention measures should be followed due to the association between Zika virus infection and increased risk of serious health effects on their unborn baby." On August 1, 2016, PHAC updated its Travel Health Notice: "The Public Health Agency of Canada recommends that pregnant women and those planning a pregnancy avoid travel to the area in South Florida (see CDC map) and countries with reported mosquito-borne Zika virus." The American Congress

of Obstetricians and Gynecologists has supported the CDC advice for pregnant women, similar to PHAC's and the Society of Obstetricians and Gynaecologists of Canada's (SOGC; April 25, 2016) advice.

Currently, CATMAT advises the following "For pregnant women and those planning a pregnancy who choose to travel to areas with ZIKV transmission or for whom travel cannot be avoided, use of PPM (personal protective measures) against insect bites is strongly advised. Based on current information on the incubation period and duration of viremia, and the unclear duration of viral persistence in tissues, women wishing to become pregnant should wait at least two months after their return from an area currently considered to have suitable conditions for sustained and high levels of ZIKV transmission before trying to conceive."[120]

For men who have travelled to areas where Zika virus is circulating, and countries where the virus has the potential to circulate: "It is strongly recommended that, if you have a pregnant partner, you should use condoms for the duration of the pregnancy. It is strongly recommended that you and your partner wait to conceive for six months by using a condom. It is recommended that you should consider using condoms with any partner for six months."[127]

The SOGC has produced advice for clinicians in Canada. In addition, a recent review has provided an overview of clinical considerations when caring for women potentially exposed to ZIKV.[128]

Will there be impact to resources and services?

Currently, the level of impact on PHO resources and services is low to moderate; however, this may change as the situation progresses. Given the potential for microcephaly and other severe disease manifestations, the number of samples sent to the PHO laboratory for testing would likely be higher than for similar imported arboviral infections such as dengue fever and chikungunya. PHO has developed a ZIKV webpage that includes a Testing Information Sheet for health care professionals and a Fact Sheet for our stakeholders. PHO will update these resources as appropriate and as the science on ZIKV develops.

If there are substantial numbers of ZIKV infections identified in Ontario, especially with severe pregnancy or other complications, there may be additional demands/stresses on the broader health care system. In particular, there would be increased need for specialized care for affected pregnant females and infants born with congenital abnormalities, or specialized care for patients with neurological or autoimmune complications.

Summary risk level: Low

Likelihood of transmission: High risk of imported cases, low risk of local transmission through sexual contact or fetal/perinatal transmission.

Severity of impact: Very low on a population level, high in cases of congenital infections and neurological complications.

Guidance and future considerations

What changes might we anticipate to affect the level of risk?

The level of risk for Ontario travellers could change under certain circumstances. Currently, *Ae. aegypti* is the considered the principal vector throughout the Americas where local transmission is occurring; it is currently unclear if *Ae. albopictus* or other mosquito species are involved in transmission in these areas. With increased documentation of ZIKV transmission by *Ae. albopictus* larger geographic areas of the Americas, especially the Eastern USA, will be affected.

The level of risk for non-travellers would change if Ontario mosquito species were identified as competent vectors of ZIKV. Currently, the established vectors in ZIKV-affected areas do not have closely related species present in Ontario.[129] In addition, increased incidence of ZIKV infection via secondary modes of transmission will increase risk of local transmission (e.g., sexual transmission).

How would a change in case fatality rate affect the risk assumptions?

Fatality from ZIKV infection is rare. If case fatality rates were to rise, then we would reassess our risk assumptions.

What changes in the etiologic agent would trigger a re-assessment?

Recent research on several isolates of ZIKV indicates that recombination events have occurred in the recent evolutionary history of the virus. These recombination events have led to the loss and gain (in some isolates) of the N-linked glycosylation site in the E protein, genes responsible for mosquito cell infectivity.[130] These recombination events are assumed responsible for transmission to humans in anthropophilic mosquito vectors and in one case, the transmission in sylvatic cycles in zoophilic mosquito vectors. A study of 41 isolates from the Americas of the ZIKV Asian lineage indicate a relatively high degree of sequence variation; these variations are proposed to have caused changes to the prM gene (a membrane precursor, structural gene) coding a protein vital to virulence and increased fitness (e.g., virus replication speed).[131] The potential for continued recombination events is possible, potentially changing the suite of potential vectors in the Americas. For example, the A226V substitution in the E1 envelope glycoprotein of chikungunya virus allowed the virus to use *Ae. albopictus* as a vector during a 2005–06 outbreak in La Réunion Island (Indian Ocean).[132]

What changes in the clinical or epidemiological profile of ZIKV would trigger a re-assessment?

The primary changes in the clinical or epidemiological profile of ZIKV that would trigger a potential reassessment includes:

1) Demonstration* of a chronic carrier state in convalescing or asymptomatic individuals (increasing risk of local transmission in Ontario and in endemic regions).

2) Demonstrated transmission via breast milk, saliva or urine (increasing risk of local transmission in Ontario and in endemic regions).

3) Demonstration* of birds or other wildlife as reservoirs of ZIKV (increasing risk of local transmission in endemic regions).

4) Demonstrated* transmission by *Ae. albopictus* in the Americas (increasing the risk of infection for travellers by increasing the geographical area affected by ZIKV; e.g., eastern USA).

5) Demonstrated* vector competence of non-*Aedes* or other mosquito species to transmit ZIKV, e.g., *Culex* species (increasing the risk of infection for travellers by increasing the geographical area affected by ZIKV or increasing risks of local transmission in Ontario).

6) Demonstrated* vector competence of Ontario mosquito species for ZIKV or demonstrated* vector-transmission of ZIKV in Ontario (increasing risk of local transmission in Ontario).

***Demonstrated/demonstration** refers to evidence as reported in the peer-reviewed literature (using appropriate sample sizes and methodologies) and/or corroboration from reports from government agencies or expert opinion.

Interpretation and conclusions

The risk of transmission to Ontarians, either as travellers or non-travellers, is low and the potential impact to Ontarians is low. Given the low risk for transmission and impact, the summary risk is low. Since the situation in the Americas has emerged rapidly, the level of confidence surrounding the primary literature, the grey literature and expert opinion is moderate. Overall, the primary literature on clinical and epidemiological aspects of ZIKV in the Americas is limited, although it is increasing in both quantity and quality. In addition, there are no comparable outbreaks (e.g., arboviruses with potential serious congenital disease outcomes) from which to draw experience.

We expect continued spread of ZIKV throughout the Americas, especially where competent vectors are present and where conditions are conducive to transmission (e.g., climate, immature habitats, urban areas). As new evidence emerges, PHO will update the RRA as appropriate to inform decision-making.

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Appendix A: Internal response team and consulted experts

Lisa Fortuna, Director, Communicable Disease, Emergency Preparedness and Response (CDEPR)

Nicole Helsberg, Senior Communications Advisor, Communications

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Mark P. Nelder, Senior Program Specialist, EZVBD

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Beata Pach, Manager, Library Services

Georgina Ralevski, Manager, Quality Assurance and Customer Service, PHOL

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