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Risk Assessment: Emergence and Vector-borne Transmission of Zika Virus in Québec

SCIENTIFIC ADVISORY

Québec

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Direction des risques biologiques et de la santé au travail

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[1] Note: Two of the authors of this paper, Anne-Marie Lowe and Louise Normandin, are also members of the Comité scientifique sur les zoonoses et l'adaptation aux changements climatiques.

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Glossary

Climate: Synthesis of weather conditions in a given area, characterized by long-term statistics (mean values, variances, probabilities of extreme values, etc.) of the meteorological elements in that area[2] [1].

Risk assessment: The process of determining a hazard's probability and consequences within a defined time period and population, and, consequently, the risk that hazard poses to the population [2].

Exotic disease: A disease for which no virus circulation has been detected in the environment, either in a vector or host [3].

Health threat: The presence within the population of a biological, chemical or physical agent that may cause an epidemic if it is not controlled according to the *Public Health Act*. As a rule, it equates a significant health risk [4].

Risk levels: A risk may be categorized according to a "risk level," defined as a degree of intensity (low, moderate, high, etc.) assigned to a risk based on an assessment of the probability and significance (severity and magnitude) of its consequences. The risk level may be assessed using a risk matrix, which is a two-dimensional graph (probability and consequences). The risk level should ideally be accompanied by an estimate reliability assessment, based on the quality of evidence [4].

Extrinsic incubation period: The time required for a mosquito to be able to transmit a virus at a given temperature [5].

Probability: The estimated onset level of negative health consequences. This estimate may be quantitative (e.g., percentage, possible number of cases) or qualitative (e.g., very unlikely, likely, almost certain). The overall probability of a health risk is estimated by considering the probabilities associated with the various stages of the chain of risks, specifically: the probability of hazard onset, the probability of hazard exposure and the probability of observing a hazard's negative effects on an exposed population's health [4].

Risk: The negative consequences on a population's health and the probability of observing these consequences following exposure to a hazardous agent [4].

Thermal threshold: Minimum incubation temperature required for virus development within a vector host [6].

[2] Original source cited by Ouranos: International Meteorological Vocabulary, WMO - No. 182 (climate).

List of acronyms and abbreviations

Ae.	*Aedes*
CDC	Centers for Disease Control and Prevention (US)
CHIKV	Chikungunya virus
CI	Confidence interval
Cx.	*Culex*
ECDC	European Centre for Disease Prevention and Control
EIP	Extrinsic incubation period
GBS	Guillain-Barré syndrome
INSPQ	Institut national de santé publique du Québec
km	kilometre
LSPQ	Laboratoire de santé publique du Québec
MSSS	Ministère de la Santé et des Services sociaux
ND	Notifiable disease
PAHO	Pan American Health Organization
PHAC	Public Health Agency of Canada
RCPs	Representative Concentration Pathways
Real-time PCR	Real-time polymerase chain reaction
RNA	Ribonucleic acid
SERCMI	Surveillance, évaluation du risque et contrôle des maladies infectieuses
SOD	Symptom onset date
SSR	Socio-sanitary region [health region]
US	United States
WHO	World Health Organization
WNV	West Nile virus

Highlights

- Zika virus emerged in the Americas in 2015 and has since expanded its geographical range significantly. Currently, the virus is transmitted locally in 35 countries of the Caribbean, Central America and South America.
- Zika virus infection is benign: 70 to 80% of patients have no symptoms, whereas 20% have a fever and rash accompanied by arthralgia and myalgia, conjunctivitis, headache, retro-orbital pain and fatigue.
- Zika virus infection can cause neurological complications, including Guillain-Barré syndrome.
- Zika virus infection during pregnancy causes congenital defects, including newborn microcephaly.
- Zika virus infection is transmitted by mosquitoes of the genus *Aedes*: in America, *Ae. aegypti* is the primary vector and *Ae. albopictus* is a potential vector. These vectors are currently absent in Québec.
- Zika virus needs a threshold temperature between 22°C and 26°C for 15 days for replication in *Ae. aegypti*, and above 27°C for one week for replication in *Ae. albopictus*. Québec's current summer temperatures are unlikely to allow for an extrinsic incubation period.
- Therefore, the current risk of vector-borne transmission of Zika virus in Québec is negligible.
- The medium-term risk of Zika virus emergence and vector-borne transmission in Québec is assessed as low. However, the presence of favourable conditions warrants concerns about long-term Zika virus emergence and vector-borne transmission for the following reasons:
  - Since humans are reservoirs of the virus, travellers coming from countries where Zika virus is endemic could carry it to Québec by airplane;
  - Established populations of the *Ae. albopictus* mosquito vector have been documented in American states bordering Québec;
  - The southern Québec climate could be favourable to *Ae. albopictus* introduction;
  - There is a possibility for a point-source introduction of adult mosquito vectors and Zika virus in the province.
- The Institut national de santé publique du Québec (INSPQ) [Québec's public health institute] is continuing scientific monitoring of the topics and additional questions raised in this risk assessment.
- Recommendations are to:
  - Develop a plan for sustainable entomological surveillance that would expand entomological surveillance objectives;
  - Add Zika virus infection to the notifiable diseases list and to the human case surveillance lists of doctors and laboratories;
  - Conduct studies on the capacity of *Ae. albopictus* to survive in the southern Québec climate.

Summary

The first cases of Zika virus infection in the Americas were documented in 2014, on Easter Island. In 2015, it was introduced on the continent (South America) in Brazil. Subsequently, the epidemic quickly spread to other countries in South America, Central America and in the Caribbean islands.

Zika virus infection is benign: 70 to 80% of patients have no symptoms whereas 20% have a fever and rash accompanied by arthralgia and myalgia, conjunctivitis, headache, retro-orbital pain and fatigue.

On February 1, 2016, the World Health Organization declared that the increased cases of microcephaly and other neurological disorders documented in Brazil constituted a Public Health Emergency of International Concern mainly because the situation was unexpected and knowledge on the topic was lacking.

It has now been confirmed that Zika virus infection complications can result in Guillain-Barré syndrome and cause congenital defects during pregnancy, which manifest as microcephaly in newborns.

Zika virus transmission vectors are insects belonging to the Culicidae (mosquito) family. After a blood meal on an animal or human host carrying the virus, females acquire the virus, which then replicates and may be transmitted to an animal reservoir. Where transmission in the Americas is concerned, there is no known animal reservoir; however, high viremia in infected humans makes them the primary reservoirs in urban environments.

Temperature is the most frequently investigated and quantified factor affecting vector-borne zoonosis transmission given its impact on vectors survival and virus dynamics. In the Americas, the main competent vector for transmitting Zika virus is *Ae. aegypti. Ae. albopictus* also has this potential. Unlike *Ae. aegypti*, *Ae. albopictus* has, in recent decades, been able to significantly increase its distribution area and invade most continents. Hence, there are currently *Ae. albopictus* species strains from tropical and temperate regions.

Although some more temperate regions are unfavourable to the establishment of Zika virus mosquito-vector populations, accidental discovery of seasonal populations in these regions must not be ruled out. The United States Centers for Disease Control and Prevention (CDC) estimates that the potential distribution of *Ae. albopictus* extends into the Québec-adjacent US states of Vermont, New York and New Hampshire. The current entomological surveillance data in Québec does not allow for extensive identification of the composition of mosquito populations outside urban areas.

The time required for a mosquito to transmit Zika virus (or any other vector-borne virus) is defined by the extrinsic incubation period (EIP), based on a given temperature. Knowledge on the extrinsic incubation period for Zika virus is sparse, as few studies have been conducted on this virus to date. The time required for a mosquito vector to transmit Zika virus is likely between 7 and 15 days at temperatures between 22°C and 29°C. The threshold temperature for Zika virus is currently unknown, but based on available information, it is likely about 25°C.

Québec's current summer temperatures are unlikely to satisfy the extrinsic incubation period for Zika virus, assuming that this period requires 7 to 15 days at a constant temperature above 22°C. Throughout July and August 2004–2015, the highest reported mean temperature was 26.3°C (in the Montérégie health region: 16.9°C minimum, 36.0°C maximum, 3.3°C standard deviation).

In addition to the influence of temperature, there is a mutation risk among Zika virus vectors and in the virus itself, as seen in the Chikungunya and West Nile viruses. Such mutations could support the development of these organisms at our latitude, the maintenance of a zoonotic cycle and an epidemic capability.

It has been hypothesized that *Aedes* species other than *Ae. aegypti*, *Ae. albopictus* and other mosquito genera could be Zika virus vectors in the Americas. One such example is *Culex*.

Other modes of Zika virus transmission have been documented: sexual, transplacental, perinatal, breast feeding and blood transfusion.

In Québec, the Institut national de santé publique du Québec has scientifically documented the risk of Zika virus emergence and vector-borne transmission by conducting scientific surveillance and a rapid risk assessment through its Surveillance, évaluation du risque et contrôle des maladies infectieuses unit.

The question and scope of the risk assessment have been defined as follows: What is the current, medium- and long-term probability for the Québec population (including pregnant women) to be exposed to Zika virus transmission through a mosquito-vector bite? Among an infected population, this risk could potentially result in mild symptoms or neurological disorders, such as Guillain-Barré syndrome, or congenital defects in the fetuses or newborns of infected pregnant women (microcephaly and other congenital defects).

Based on the knowledge of mosquito vectors and Québec climatic conditions at the date of publication of this scientific advisory, the risk of Zika virus vector-borne transmission in Québec is negligible. This is mainly due to the absence of established populations of mosquito-vector species and the current climate, which is unfavourable to emergence and amplification of the virus.

The medium-term risk of Zika virus emergence and transmission in Québec is assessed as low. However, there are favourable conditions that warrant concerns about Zika virus emergence and vector-borne transmission over the long-term: 1) one of the mosquito species, *Ae. albopictus,* has adapted to temperate temperatures and has in recent years significantly expanded its geographical range up to the northeastern US states bordering Québec; 2) conservative climate models predict that the projected climate for a 2011 to 2040 timeline would allow *Ae. albopictus* introduction in southern Québec; and, 3) the threshold temperature of approximately 25°C could be sustained for the duration of the virus's incubation period in southern Québec as a result of climate change.

Added to these favourable conditions are the potential mutations that could adapt the virus to native vectors in Québec or to lower threshold temperature conditions. Such changes could accelerate the introduction and transmission of the virus.

The risk of acquiring the disease is nevertheless present for members of the Québec population who travel to countries with documented local transmission or who have unprotected sex with an infected male (transmission via sperm). Recommendations have been issued by other bodies, including the Comité consultatif québécois en santé des voyageurs (CCQSV) [Québec's travel health advisory board] of the Institut national de santé publique du Québec and the ministère de la Santé et des Services sociaux du Québec (MSSS) [Québec's ministry of health and social services].

It will be important to learn more about the composition of mosquito populations in southern Québec, and in particular, to detect the *Ae. albopictus* strain adapted to temperate regions. The results of future research on the Zika virus vector competence of mosquito species native to Canada will help modulate risk. Studies on the virus will also make it possible to detect the occurrence of mutations that would increase its capacity to spread.

1 Introduction

1.1 Background

Zika virus (ZIKV) is an arbovirus transmitted to humans through the bite of mosquitoes of the genus *Aedes*. Cases of human-to-human transmission have also been reported (sexual transmission) [7, 8]. ZIKV belongs to the Flavivirus genus, as do the dengue virus and West Nile virus (WNV). ZIKV infections are asymptomatic in 70% to 80% of cases. When infection cases are symptomatic, the symptoms are usually mild and last from two to seven days. They are mainly characterized by fever, joint pain, headaches, conjunctivitis, and rashes. These symptoms are similar to those caused by dengue virus [7].

Discovered in Uganda in 1947, ZIKV has caused outbreaks in Africa and Asia. It spread next to the Pacific, on the Micronesian island of Yap (2007) [9], in French Polynesia (2013) [10], and on other Pacific Islands (2012 to 2014) [11]. In 2014, autochthonous transmission was documented on Easter Island (Chile) and in May 2015, transmission of the virus was confirmed in Brazil [12]. Since then, it has caused epidemics in the Americas [7].

In August 2015, Brazil's public health authorities reported an increased number of Guillain-Barré syndrome (GBS) cases. In October 2015, an unusually high number of microcephaly cases were reported in Brazil's northeastern states [13]. Confronted with the magnitude of the situation, on February 1, 2016, the World Health Organization (WHO) declared that the increased cases of microcephaly and other neurological disorders constituted a Public Health Emergency of International Concern [14] mainly because the situation was unexpected and knowledge on the topic was lacking [15].

Since October 2015, Brazil has reported 7 150 suspected cases of microcephaly or other congenital deformities of the central nervous system in regions where the virus has spread; among these, 1 168 cases were associated with congenital infections [16]. Scientific evidence was collected for months and there is now a scientific consensus on the causal link between ZIKV and cases of microcephaly and GBS [16, 17, 18].

ZIKA infection is spreading rapidly throughout countries in the Americas where mosquito-vector populations are established. On April 28, 2016, autochthonous transmissions were identified in 35 countries in the Americas and the Caribbean [19]. Cases acquired abroad were also reported in Canada, including Québec, among others.

1.2 Québec's response

Within this context, several stakeholders in the Québec public health network have mobilized to join the international fight against the ZIKV infection epidemic:

1) **Monitoring**: The Laboratoire de santé publique du Québec (LSPQ) [Québec's public health laboratory] of the Institut national de santé publique du Québec (INSPQ) [Québec's national public health institute] reports people infected with ZIKV to regional public health authorities, which in turn contact these people to document the manifestations of the disease and where it was acquired; the Bureau de surveillance et de vigie (BSV) [Bureau of surveillance and vigilance] of the ministère de la Santé et des Services sociaux (MSSS) [Québec's ministry of health and social services] declares cases to the Public Health Agency of Canada (PHAC), which in turn reports them to the Pan American Health Organization (PAHO).

2) **Prevention recommendations for travellers to countries with local transmission**: The INSPQ's Comité consultatif québécois sur la santé des voyageurs (CCQSV) [Québec's travel health advisory board] publishes ZIKV information bulletins that include recommendations to the public health network and travel health network on sharing information with travellers at risk of being exposed to the virus.
3) **Prevention among the vulnerable population (pregnant women) and clinical management of cases**: The MSSS's Direction générale des services de santé et médecine universitaire [General directorate of health services and academic medicine] has enlisted the collaboration of medical consultants from the Centre hospitalier universitaire (CHU) Sainte-Justine to develop recommendations aimed at practitioners who have clientele vulnerable to ZIKV.
4) **Prevention of blood transfusion transmission**: Héma-Québec has added a new eligibility criterion for blood donors, imposing a 21-day waiting period before travellers who have stayed at a destination other than the continental United States or Europe can donate blood. This measure is intended to prevent the risk of ZIKV and similar viruses, such as dengue virus and Chikungunya virus (CHIKV).

On November 27, 2015, the INSPQ's LSPQ issued a notice to the heads of microbiology laboratories, medical microbiologists-infectologists and laboratory technical coordinators to raise awareness on ZIKV emergence in the Americas [20].

On January 21, 2016, at an INSPQ meeting of the Comité scientifique sur les zoonoses et l'adaptation aux changements climatiques (CSZACC) [Scientific committee on zoonoses and climate change adaptation], and the Surveillance, évaluation de risque et contrôle de maladie infectieuses (SERCMI) [Infectious disease monitoring, risk assessment and control] of the Direction des risques biologiques et de la santé au travail (DRBST) [Directorate of biological hazards and occupational health] presented the MSSS with a progress report on the troublesome epidemiological situation which showed an increased incidence of cases of microcephaly and other neurological complications associated with ZIKV infections in Brazil. Exercising its decisional support function for Québec public health authorities, the SERCMI unit responded with twofold action by first developing a scientific monitoring program to collect clinical and epidemiological data (including a scientific monitoring brief to inform decision makers) and following up with the development of a risk assessment process.

The objective of this risk assessment process is to answer one of the four questions[3] identified by PHAC to assess the risk posed by ZIKV [21]: What is the risk of ZIKV emergence and vector-borne transmission?

In 2014, at the MSSS's request, the INSPQ published a scientific advisory on assessing the potential emergence and vector-borne transmission of CHIKV in Québec [22]. Some of the information contained in the publication was used by public health authorities to compile a brief assessment of the risk posed by ZIKV since the two arboviruses have the same vector-borne mode of transmission and the same primary vectors (content details are in section 3.2 of this document). However, the unique aspects of ZIKV infection justify a separate risk assessment. Section 3.1 provides detailed information on ZIKV infection and section 3.3 describes other modes of transmission.

[3] The other three questions are: What are the risks of microcephaly and other neurological disorders associated with ZIKV infection? What is the risk of ZIKV infection for travellers to countries with local transmission? and What is the risk of sexual and blood-based transmission?

The present scientific advisory therefore describes the approach adopted, the available evidence on ZIKV hazards and hazard exposure (modes of virus transmission), and risk assessment results.

This risk assessment is part of a global approach to public health risk management.

2 Methodology

A rapid risk assessment is recommended when an acute event has already been reported and decisions to take action must be made quickly. The assessment may be conducted more than once during the same event, depending on how the situation progresses [2].

The risk assessment approach applied in this scientific advisory is based on two complementary methodologies. On one hand are the approaches not specifically focused on arbovirus risk assessment, such as INSPQ's *Cadre de référence sur la gestion des risques en santé publique au Québec* [Public health risk management in Québec: terms of reference] [4] and WHO's *Rapid Risk Assessment of Acute Public Health Events* manual [2]. On the other hand are approaches specifically focused on arbovirus risk assessment, such as those used by the US Centers for Disease Control and Prevention (CDC) [23] and an ad hoc expert group from INSPQ's SERCMI unit [3].

The following steps are guided by these approaches.

2.1 Collect data to present a situation overview

The rapid risk assessment draws on the results of a broad review of the literature to collect data on ZIKV infection (virus characteristics, available laboratory tests, symptoms, potential complications and epidemiology in the Americas), as well as on data on vector-borne transmission and other modes of transmission (sexual, blood transfusion, transplacental, perinatal and breast milk).

The PubMed database, reference material from grey literature and some international health organizations' websites were consulted (e.g., WHO, PAHO, CDC, European Centre for Disease Prevention and Control [ECDC] and PHAC). Research included articles published in English and French. Since there is little literature on ZIKV, the search key used was "Zika."

Scientific monitoring was also established using the same documentary sources and search key to supplement the information as the situation progressed.

This information made it possible to present a situation overview to guide the next steps, described in section 3.

2.2 Set up an expert group

The situation overview guided the selection of group experts. Experts were selected so as to combine multidisciplinary and complementary expertise on infectious diseases transmitted by mosquitoes and on risk assessment, and to leverage knowledge in the specific area of ZIKV infection epidemics. Appendix 1 lists the expert group members' areas of expertise, names and mandate.

2.3 Assess risk based on the question and its scope

The purpose of the risk assessment is to estimate the health consequences for a population exposed to a health hazard and the probability of observing these consequences. It also identifies the agent (if not already known), sources and causes [4].

First, the risk statement was defined. This risk statement is based on these specific elements: population, environment/location, time, event, agent, source, circumstances of the exposure and consequences [4]. Table 2 (section 4) shows information that is specific to the ZIKV epidemic and that clarifies the risk statement.

Based on the question and scope, the risk assessment is divided into four steps:

1) Identify the effects,
2) Estimate the exposure,
3) Analyze the context,
4) Estimate the risk.

First, these four steps were used to document ZIKV infection symptoms and complications. The hazard (ZIKV) exposure assessment involved a qualitative estimation of the population's probability of exposure to the bites of infected mosquitoes. Based on the knowledge of mosquito vectors and Québec climatic conditions at publication of this scientific advisory, it was determined that there could be a present and future (medium- and long-term) probability of exposure. Groups with potential for exposure and groups likely to acquire the infection and develop related complications were identified. Information about the presence and introduction of mosquito vectors of ZIKV in Québec was documented. Lastly, the epidemiological background was analyzed.

To complete the present risk assessment, it was considered sufficient to exclusively consider the ecological and epidemiological evidence and use only hazard and exposure indicators. This approach therefore did not consider vulnerability or response-capacity indicators.[4]

The approach to the rapid risk assessment of vector-borne infectious disease outbreaks uses CDC guidelines on arbovirus surveillance programs [23]. Some documented information is included to support the approach, specifically on these questions:

- Mosquito populations: are vectors present?
- Mosquito viral infection rates: is localized viral activity observed?
- The risk to humans: is there vector activity in populated areas?

CDC risk categories for mosquito-borne arbovirus disease outbreaks are reproduced in Table 3 (section 4).

[4] In its technical reports on the ZIKV risk assessment for African and European regions, WHO attributed a risk to each country in these regions so as to compare them. Its approaches included the countries' vulnerability and response-capacity indicators [24, 25].

Also applied is the approach developed by an ad hoc expert group from INSPQ's SERCMI unit for analyzing the risk of pathogen introduction in Québec [3]. This 2013 research work provides practical vector-borne disease surveillance models, specifically for the introduction and establishment of new invasive vectors and exotic pathogens, and vector-borne diseases from the United States or Central America that spread with the natural movement of vectors or animal hosts. The expert group identified seven variables[5] to support the risk analysis of pathogen introduction in Québec and added an eighth variable for the purposes of this work:

1) Humans are reservoirs,
2) Endemicity in a country with a high number of travellers flying to Québec,
3) Endemicity in the United States,
4) Endemicity in US states bordering Québec,
5) Potential bird reservoir,
6) Circulation of the pathogen in a temperate-cold zone,
7) Presence of potential reservoirs in Québec,
8) Presence of potential vectors in Québec.

These eight variables have been taken into account to assess the future (medium- and long-term) emergence and transmission risk of ZIKV in Québec (Table 4, section 4).

[5] These variables were applied to developing a model for prioritizing the list of human-relevant mosquito-borne diseases among travellers in terms of emergence and scale. ZIKV infection was included but was not at that time a high-priority exotic vector disease of interest for humans. The model did not take into account the severity and relative impact of the disease.

3 Overview of the infection, vector-borne transmission and other modes of transmission

3.1 ZIKV infection

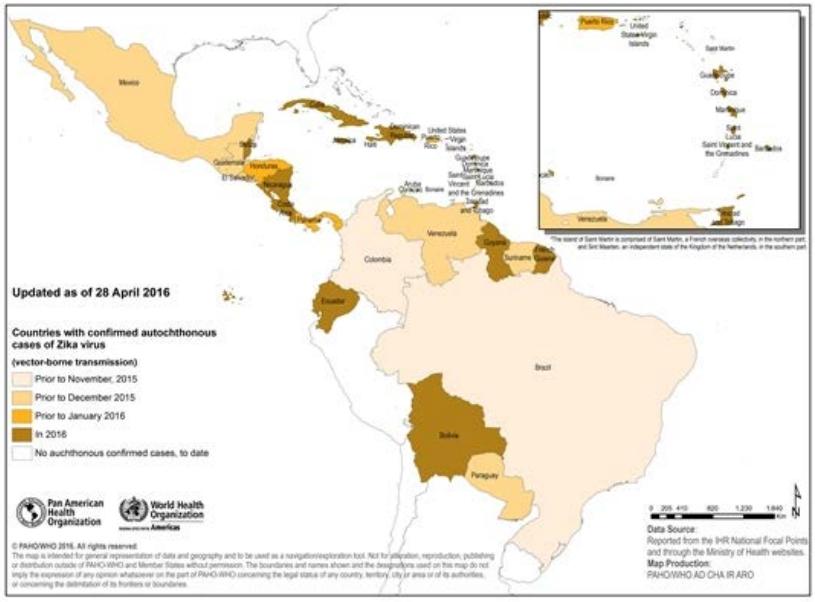
The evidence in this section documents the public health hazard posed by ZIKV.

3.1.1 Emergence of ZIKV in the Americas

ZIKV was first isolated in a rhesus monkey during a 1947 study on yellow fever in Uganda's Zika forest [26]. It was subsequently identified in humans in 1952 in Uganda and Tanzania. Phylogenetic analyses show three lineages: West African, African and East Asian [27, 28]. The four outbreaks of ZIKV infection (Micronesian island of Yap in 2007, French Polynesia in 2013, New Caledonia in 2014 and Brazil in 2015) are of the Asian lineage and occurred in geographic areas where the virus had never circulated, that is, in immunologically naïve populations [29].

In May 2015, the first cases of fever and rash symptoms were detected in the northeastern states of Brazil. The Brazilian Ministry of health informed the international community of autochthonous circulation of ZIKV in its territory. During epidemiological week 13 (ending April 2, 2016), a total of 91 387 probable cases were documented in that country, resulting in an incidence rate of 44.7 cases per 100 000 people [19]. Subsequently, the epidemic quickly spread to other countries in South America, Central America and in the Caribbean islands (Figure 1).

Figure 1 Countries and territories in the Americas with confirmed autochthonous (vector-borne) ZIKV cases, 2015 to 2016 (April 28, 2016)



Taken from "Regional Zika Epidemiological update (Americas), 28 April 2016." Pan American Health Organization. Washington, D.C.: Copyright © PAHO, 2016. Reproduced with the permission of the Pan American Health Organization.

The CDC analyzed the genome of the virus found in people infected in Guatemala and Puerto Rico. The results of these studies demonstrate that the genetic sequences of the virus found in these individuals are of the Asian lineage and are closely related to the strains recently isolated in Brazil (2015) and French Polynesia (2013) [28].

The ZIKV attack rates estimated by various studies illustrate the ease with which the virus can spread and infect humans in immunologically naïve populations. A retrospective study of seroprevalence and surveillance data on the 2013 outbreak in French Polynesia has helped estimate the ZIKV attack rate at 66% (95% CI: 62 to 70%) [30]. On the Micronesian island of Yap, the attack rate of the 2007 outbreak has been estimated at 73% (95% CI: 68 to 77%) [31]. By way of comparison, seroprevalence studies have helped assess the CHIKV attack rate at 63% on Grande Comore Island [32] and at 75% within Kenya's Lamu Island population [33]. However, when only symptomatic cases were analyzed in an immunologically naïve population (children aged between 2 and 14 years in Nicaragua), the attack rate was lower, at 2.9% (95% CI: 2.3 to 3.4%) [34].

3.1.2 CHARACTERISTICS OF THE VIRUS

ZIKV is a flavivirus of the arbovirus group. It is transmitted by the bite of mosquitoes, as is dengue virus, WNV and yellow fever virus. It is a single-stranded RNA enveloped virus. The mechanism of infection of human epithelial cells was studied *in vitro* using a strain of the virus isolated from a human case in the French Polynesian outbreak [35]. More specifically, this study showed that human dermal fibroblasts, epidermal keratinocytes, and immature dendritic cells are permissive to ZIKV infection. To establish a link between ZIKV infection and its associated neurological problems, researchers have demonstrated that a strain of ZIKV (MR766) can infect human neural progenitor cells. The same study revealed that ZIKV interferes with the cycle of neural progenitor cells and significantly increases cell death [36].

3.1.3 SYMPTOMS AND COMPLICATIONS

Whereas the clinical presentation associated with ZIKV initially seemed benign (rash, low-grade fever, conjunctivitis, fatigue, arthralgia, retro-orbital pain) with positive progression, two types of more severe neurological complications have been associated with the infection: central nervous system malformations in the fetus or infant (mainly microcephaly) and GBS. The accumulation of evidence through recent studies has established a causal link between ZIKV infection and microcephaly cases and GBS (see Appendix 2 for further details on these two complications). ZIKV has therefore been added to the list of infections with potential neurological consequences.

In January 2016, CDC reported that Brazil had declared approximately 40 times more microcephaly cases than the country's baseline prevalence of approximately 0.2% among the neonatal population [37]. By retrospectively analyzing data on the 2013 to 2014 French Polynesian outbreak, Cauchemez et al. calculated that a woman infected with ZIKV during the first trimester of pregnancy had a 1% risk of giving birth to a microcephalic infant (95/10 000 infected women) [30]. To compare, microcephaly incidence is usually 2/10 000 births, which is 50 times lower [30]. Microcephaly cases may have other infectious etiologies, such as congenital infection caused by cytomegalovirus, rubella virus, herpes simplex virus or the *Toxoplasma gondii* parasite. Genetic, environmental and social factors, and teratogens are also on the list of factors that can induce microcephaly syndrome.

Ocular lesions are a third type of complication in microcephalic newborns (see Appendix 3 for details).

3.1.4 SURVEILLANCE

ZIKV infection cases are monitored under the provisions of the PAHO International Health Regulations, which has called upon countries in the Americas to cooperate in reporting cases. Contrary to the United States [38], Québec has not designated ZIKV infection a notifiable disease (ND).[6]

The Canadian Congenital Anomalies Surveillance Network relies on hospitalization data from the Canadian Institute for Health Information. These surveillance data include microcephaly cases but do not as yet include Québec data. In Québec, the MED-ECHO database records identified cases (Julie Soucy, personal communication, February 23, 2016).

3.1.4.1 Laboratory testing and case reporting

Given the similar symptoms caused by dengue virus, CHIKV and ZIKV, and their co-endemicity, laboratory testing is needed to establish a definitive diagnosis.

CDC and PHAC have issued recommendations for ZIKV laboratory diagnostic testing. They recommend that diagnostic testing be based on the clinical context (acute or convalescent phase). LSPQ adapted these recommendations on April 20, 2016 [39].

Laboratory tests are reserved for:

- Symptomatic persons who have returned from areas where ZIKV is endemic;
- Asymptomatic pregnant women who have returned from areas where ZIKV is endemic;
- Babies with microcephaly whose mother has travelled to an area where ZIKV is endemic.

The types of recommended tests are:

- Based on the symptom onset date (SOD) and the sample collection date:
  - Acute phase (≤ 14 days SOD): virus detection (RNA genome);
  - Convalescent phase (≤ 7 days SOD): antibody detection (IgM and PRINT);
  - Asymptomatic pregnant woman (≥ 4 weeks after return from travel): antibody detection (IgM and PRINT).

The performance characteristics of serological testing are unknown when used for screening asymptomatic pregnant women. The attending physician must consequently help the patient understand the limitations of these tests and the long delays associated with confirmatory testing.

Based on the Public Health Emergency of International Concern declaration and the International Health Regulation criteria, PHAC recommends that all laboratory-confirmed cases be declared to provincial and federal public health authorities [40].

[6] In its published scientific advisory on assessing the potential emergence and vector-borne transmission of CHIKV in Québec, the INSPQ recommended designating CHIKV and dengue virus NDs [22].

3.1.4.2 Infection cases in Québec

On May 2, 2016, the MSSS's BSV reported 16 cases of ZIKV infection acquired during travel to countries in the Americas with local transmission (Brazil: 1 case; Colombia: 2 cases; El Salvador: 2 cases; Haiti: 7 cases; Martinique: 3 cases; and Nicaragua: 1 case) (Marie-Andrée Leblanc, personal communication, May 2, 2016). Prior to this, no ZIKV infection case had been reported in Québec or acquired locally in Québec.

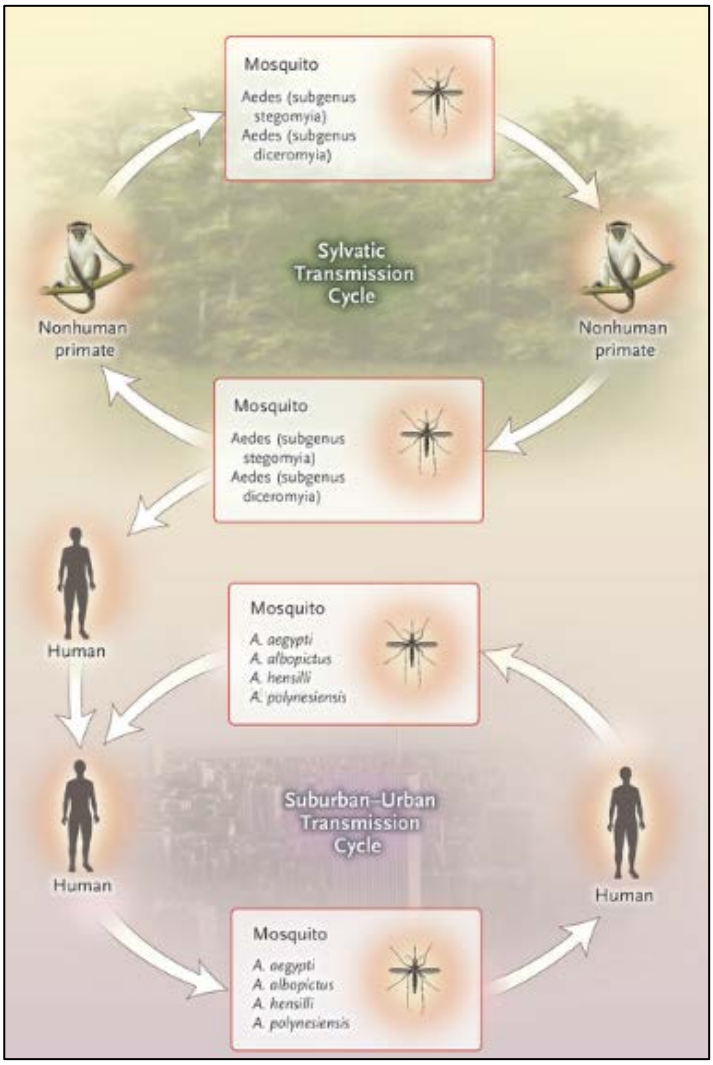
3.2 Vector-borne transmission of ZIKV

The evidence in this section documents hazard exposure and context, and more specifically, vector-borne exposure to ZIKV. Although this risk assessment applies solely to vector-borne transmission, it was decided to include a brief documentation of the other modes of ZIKV transmission as part of the situation overview (section 3.3).

ZIKV transmission vectors are the Culicidae (mosquito) family of the order diptera. After a blood meal on an animal or human host carrying the virus, females acquire the virus, which then replicates and may be transmitted to an animal or human reservoir [41].

The natural cycle of ZIKV in Africa involves vector mosquitoes and vertebrate hosts, especially African primates [42, 41]. In Asia, a sylvatic transmission cycle has not yet been identified [43]. Figure 2 illustrates ZIKV sylvatic and urban transmission cycles [43]. Other sources have identified anti-Zika antibodies in some mammals, such as zebras and elephants [44, 45], and rodents in Pakistan. Where transmission in the Americas is concerned, there is no known animal reservoir [7]; however, high viremia in infected humans makes them the primary reservoirs in urban environments [43].

Figure 2 ZIKV Transmission Cycle



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Factors linked to the vector-borne transmission risk of ZIKV are a function of vector competence and distribution, which is dependent on climatic conditions favourable to vector development. Information about the introduction of a new pathogen or a new invasive vector is therefore essential in assessing the risk of introduction of this exotic disease in Québec [3].

A new pathogen can be introduced in Québec by an infected vector, animal or human via air, sea or land transportation. Pathogens also travel naturally via migratory birds and the northward return of animals or vectors from the United States. To detect the presence of a new pathogen or invasive vector in an area, it is necessary to know the broad environmental conditions that promote circulation of pathogens within the area of interest [3].

Because of their geographic location, infrastructure or climatic conditions, some areas are more at risk of introduction and emergence of vector-borne diseases. The receptivity of an area corresponds to the environmental conditions that favour a pathogen's transmission. The entry of a new pathogen or vector also depends on area vulnerability, in other words, the proximity of areas where an arbovirus is present, the frequent influx of infected individuals or groups, or the influx of infected arthropods. Areas vulnerable to the introduction of a vector or new pathogen are entry points into the area. They include ports, airports, train stations, border stations and warehouses that store imported goods (used tires, plants, etc.) [3].

Between May and July, 2012, more than 64 000 travellers arrived in Canada, mainly through Toronto and Montréal airports, from countries with documented established populations of ZIKV mosquito-vector species (the Caribbean and South America for example) [46].

3.2.1 CLIMATE IMPACT ON CURRENT VECTOR DISTRIBUTION

Several *Aedes* species have been involved in the transmission of ZIKV. This virus has been isolated from *Ae. africanus*, *Ae. apicoargenteus, Ae. luteocephalus, Ae. aegypti, Ae. vitattus* and *Ae. furcifer*. *Ae. hensilii* was the predominant mosquito species present on the island of Yap during the ZIKV outbreak in 2007, but the virus was never detected in this species during the outbreak [8, 47]. The capability of *Ae. aegypti* to transmit ZIKV to mice and monkeys in the laboratory has been demonstrated [48, 49].

Ae. aegypti appears to be the primary vector in Asia, was the suspected primary vector in the French Polynesian outbreak [8] and appears to be the primary competent vector for ZIKV transmission in the Americas [50, 51, 11]. The fact that *Ae. aegypti* feeds primarily on humans, often bites multiple humans in a single blood meal, has an almost imperceptible bite, and shares its environment with human habitation gives it high vectorial capacity [43].

The role played by *Ae. albopictus* in a 2007 outbreak in Gabon, its wide distribution in the United States, combined with ZIKV's lack of restriction to a specific *Aedes* species indicate that *Ae. albopictus* could serve as a vector in the US [8]. PAHO recently reported the first detection, in the Americas, of ZIKV in this species (captured in the environment in the Mexican state of San Luis Potosi) [52]. This hypothesis is supported by the results of a study by Chouin-Carneiro et al., who show that strains of *Ae. aegypti* and *Ae. albopictus* involved in the transmission of the ZIKV in different countries of the Americas could have similar transmission potential. An unusual fact is that the ability of these vectors to transmit the virus under laboratory conditions was unexpectedly lower than initially believed; this suggests that other factors (e.g., large immunologically naïve population for ZIKV and the high densities of human-biting mosquitoes) are contributing to the rapid spread of ZIKV during the current epidemic in the Americas [53].

Ae. albopictus is found in urban and natural areas. Its ability to colonize artificial sites in inhabited places, including tires and containers in peridomestic environments, has promoted its establishment near humans [54]. This mosquito is the world's most invasive species [55, 54]: it is established on several continents, including North America as far up as northeastern United States. Wherever *Ae. albopictus* is established, it can act as an additional endemic virus vector of dengue virus, CHIKV, WNV and eastern equine encephalitis virus [56, 54].

Temperature is the most frequently investigated and quantified factor affecting vector-borne transmission of infectious disease given its impact on vector survival and virus dynamics [57]. Unlike *Ae. aegypti*, *Ae. albopictus* has in recent decades been able to significantly increase its distribution area and invade most continents. Evolutionary responses associated with various colonized habitats

have modified the genetic characteristics of *Ae. albopictus*, allowing it to adapt to varied weather patterns. Hence, there are now different strains of *Ae. albopictus* species: tropical and temperate [58, 59, 60].

Here is what characterizes the different strains:

- **Tropical region strain**: absence of diapause; develops continuously; higher requirement in terms of development temperature, which limits its geographic distribution.
- **Temperate region strain**: presence of diapause (winter dormancy) in the egg stage when the temperature and photoperiod reach a certain threshold; desiccation-resistant eggs, favouring the accidental transport of this species.

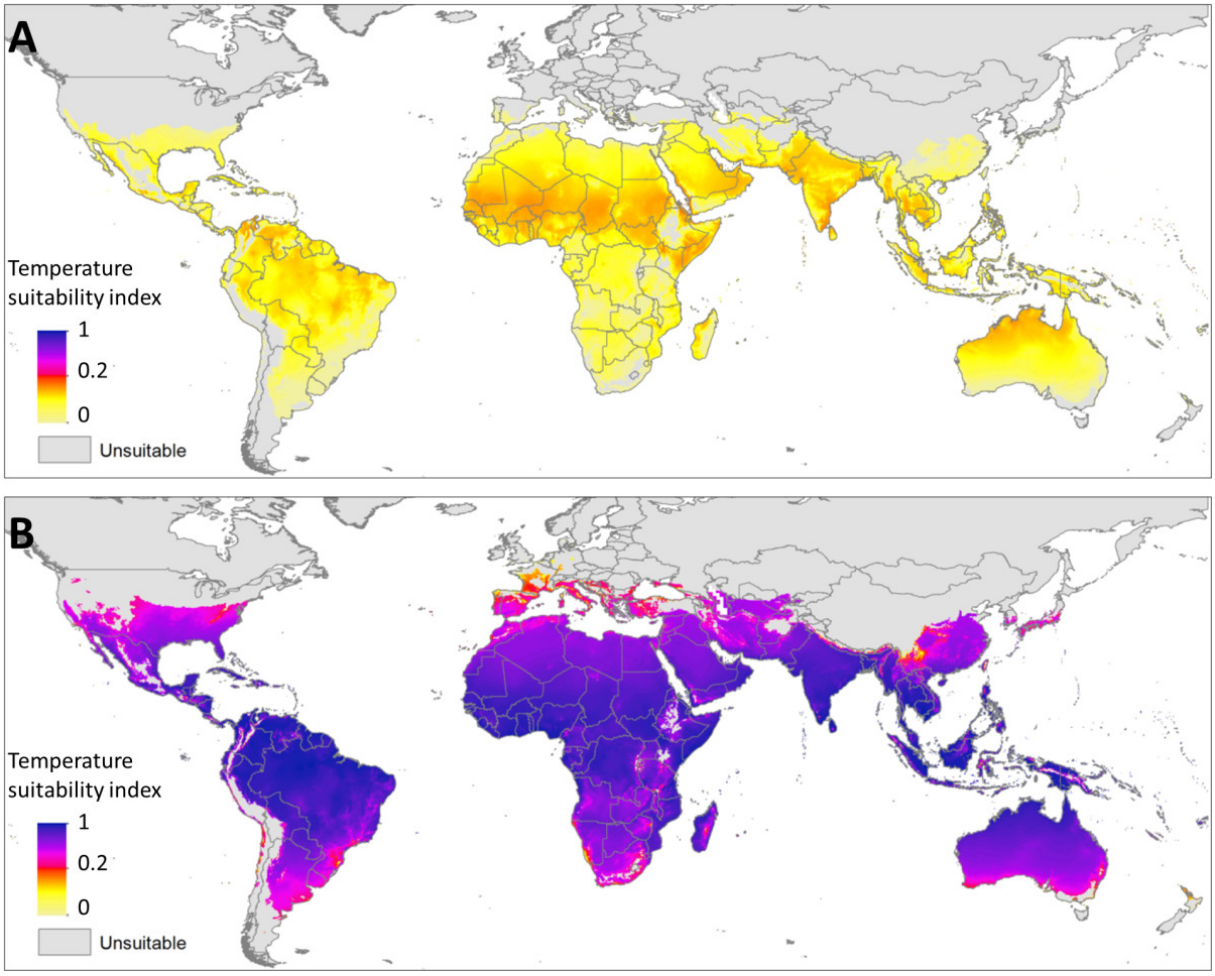
This species has thus adapted to temperate environments through its cold-tolerant eggs in diapause (at temperatures unfavourable to adult survival); this in turn promotes the international spread of this mosquito species [57, 54, 43, 61]. Egg survival of the temperate strain of *Ae. albopictus* at winter temperatures in Indiana (US) has been demonstrated [62]. In this study, 78% of the eggs of the temperate strain survived in tires between November 4, 1990, and April 28, 1991, at temperatures between 28°C and –19°C. The authors observed that neither the absolute minimum temperature nor the mean temperature between January and February correlated to the winter survival of the *Ae. albopictus* temperate strain. They also proposed the hypothesis that snow could play an insulating role promoting egg survival from winter to winter [62]. On the other hand, a study in northeastern Connecticut (US) described the introduction of *Ae. albopictus* specimens in a tire recycling plant; despite their seasonal establishment (between August and October) in the adjoining woodlands, this species did not survive winter to allow establishment [63].

No information is available on the egg survival capacity of *Ae. albopictus* at Québec winter temperatures. However, for December to February of 1971 to 2000, the Ouranos consortium recorded a mean temperature of –9.5°C (1.6°C standard deviation) in southern Québec [64]. Among all southern Québec regions, Outaouais was found to hold the lowest mean temperature, recorded between 2004 and 2015. The mean temperature for this period was –4°C, with a –25.6°C minimum, 17.9°C maximum and 6.5°C standard deviation (Germain Lebel, personal communication, April 7, 2016). Moreover, Trudel et al. reported that a constant temperature of 0°C maintained in the duff under a 120-cm snow cover throughout January and February 1998 (Saguenay region, Québec) allowed fir coneworm eggs (*Dioryctria abietivorella*) to survive cold Québec winters [65]. It is therefore not unlikely that, under an adequate snow cover, diapausing eggs of the temperate strain of *Ae. albopictus* could survive winter temperatures in Québec.

In Canada, *Ae. albopictus* adult specimens were captured in Ontario in the summers of 2005 and 2012 [66]; as well, near Québec's Montréal–Trudeau airport, two specimens were caught during CDC's epidemiological week 34 and two more, during week 37, in August 2005, [22]. However, adult survivorship during the winter months, based on the current climatic conditions at Québec latitudes, would be unlikely given that it is known to fail at temperatures below 9°C [57, 67].

Temperate *Ae. albopictus* is the sole strain currently found at the northernmost latitudes in North America. A study conducted in Japan reported that this species' distribution lies south of the geographic areas where the mean annual temperature is above 11°C and the mean January temperature is above –2°C [68], which is not the case in Québec. Figure 3 shows the areas in the Americas where the temperature is currently favourable to *Ae. aegypti* and *Ae. albopictus* population development. The conclusions indicate that Québec is not one of the targeted areas [57].

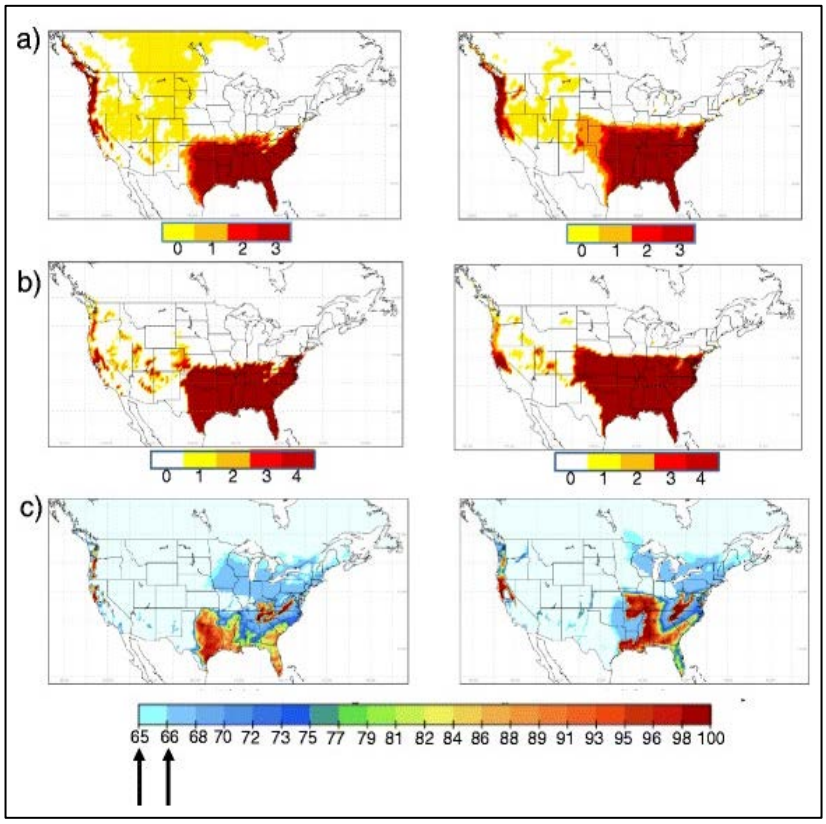
Figure 3 Comparative temperature suitability of *Ae. aegypti* (A) and *Ae. albopictus* (B)



This figure is being used with the permission of Oliver J. Brady. Taken from the article "Global Temperature Constraints on *Ae. aegypti* and *Ae. albopictus* Persistence and Competence for Dengue Virus Transmission" by Oliver J. Brady, N. Golding, D.M. Pigott et al. *Parasites & Vectors*. July 22, 2014. Vol. 7, No. 338 [57]. This article is published by BioMed Central Ltd and distributed under the terms of the Creative Commons Attribution License that allows unrestricted use.

On the other hand, Ogden et al. modelled the risk of *Ae. albopictus* expanding its geographic range; they used more complex indicators of the species' survival based on current and projected climatic data (temperature, precipitation and winter survival capacity). The least conservative scenario indicates that the current climate (taking into account 1989 to 2010 climatic data) would be favourable to temperate *Ae. albopictus* establishment northward into the regions of the Atlantic coast, southern Ontario, Québec and the Maritimes (Figure 4, maps c) [54].

Figure 4 Predictions of current climate suitability for *Ae.* albopictus



Legend
The left column maps are based on observed climate data for 1989 to 2010. The right column maps are the CanRCM4 model output for the same time period.
Maps a) are based on the OW indicator (overwintering conditions), maps b) are based on the OWAT indicator (overwintering conditions combined with annual air temperature), and maps c) are based on the SIG indicator (linear index of precipitation and air temperature suitability expressed through a sigmoidal function). The colour scale shows the value for each indicator, and for SIG, the cut off at 66.69% and 64.64% is indicated by the arrows. For maps a), the climate of low suitability for *Ae. albopictus* is indicated by yellow areas (where January temperature is below 0°C and annual precipitation is below 500 mm) and white areas (where January temperature is below 0°C or annual precipitation is below 500 mm) (51).

This figure is used with the permission of Nicholas H. Ogden. Taken from the article "Recent and Projected Future Climatic Suitability of North America for the Asian Tiger Mosquito *Aedes albopictus*" by Nicholas H. Ogden, R. Milka, C. Caminade, et al. *Parasites & Vectors*. December 2, 2014. Vol. 2, No. 7 [54]. This article is published by BioMed Central Ltd and distributed under the terms of the Creative Commons Attribution License that allows unrestricted use.

The most conservative projections of the final northern limits of *Ae. albopictus* distribution for 2041 to 2070 produced by this study include southern Ontario, Québec and the Maritimes. Meanwhile, the least conservative scenarios predict a much greater range expansion for 2011 to 2040 and 2041 to 2070, extending up to 1 000 km into Canada [54].

Although the establishment of ZIKV mosquito-vector populations in the more temperate regions is questionable, accidental discovery of seasonal populations there, as reported by Andreades in the Connecticut (US) study, must not be ruled out [63]. Monaghan et al. underline the significance of this type of population in a study that maps US states (mainly southern) with established *Ae. aegypti* and *Ae. albopictus* populations, and locations where these vectors can be found accidentally and seasonally, even though there may not necessarily be established populations. This seasonality varies according to local meteorological conditions, and thus can provide one measure of the potential for ZIKV transmission. According to these authors, cities along the US eastern coast (the northernmost being New York) could be at risk of vector-borne transmission of ZIKV, given the summer presence of *Ae. aegypti* populations and the high number of travellers flying in from countries in Central America and the Caribbean [69].

Accidental importation of *Ae. albopictus* mosquitoes has been documented in Europe, specifically in the Netherlands, Italy and Germany. In the Netherlands, this type of introduction did not lead to the establishment of this mosquito population [70]; however, it appears that current climatic conditions could favour the winter survival of diapausing eggs of the temperate strain, which points to this country's vulnerability to the establishment of this vector [71]. Such a situation occurred in Italy, where *Ae. albopictus* colonized nearly all regions [67] and in southwestern Germany, where established populations were found in 2015 [72].

Entomological surveillance data for the United States theoretically define the northern limit for populations of the *Ae. albopictus* strain from temperate regions and *Ae. aegypti*. CDC estimates that the potential distribution of *Ae. albopictus* extends into the following Québec-adjacent US states: Vermont, New York and New Hampshire [73]. However, it is important to note that this surveillance is not systematic in space and time, and this can produce false negatives [54]. For example, although counties north of New York City have no routine entomological surveillance, documentation shows that adult *Ae. albopictus* mosquitoes are occasionally captured there during summer months (Richard Falco, personal communication, March 19, 2016).

In Québec, an extensive identification of the composition of mosquito populations cannot be done with current entomological surveillance data, which was conducted solely within the framework of the 2013 to 2015 government response plans designed to protect the public against WNV [74]. Entomological data derived from this framework showed that, in 2015, the species group *Culex pipiens/restuans* represented 9.9% of a total catch of 169 073 mosquitoes. The *Ae. ultimum* species represented 58.0% of catches. Other species of the genera *Aedes (Ae. vexans, Ae. japonicus and Ae. cinereus)* and *Ochlerotatus* represented 16.8% of catches, whereas the other specimens (15.2%) were species of other genera (mainly *Coquillettidia*, *Anopheles*, *Culex* and *Culiseta*) [75].

An INSPQ ad hoc expert group has identified *Ae. albopictus* as the main exotic invasive vector to consider in Québec [3]. Using this information, the assessment of the relative probability of introduction of certain pathogenic agents could be refined. Nonetheless, this information would not be useful in predicting whether these vectors or local vectors are competent for ZIKV.

3.2.2 VECTOR COMPETENCE

As presented in the previous section, ZIKV transmission in a given area's population first requires the presence of competent vectors. Ideally, for efficient virus transmission from a mosquito vector to a vertebrate host, a number of factors must be satisfied [76]. Where it concerns the mosquito host, its vector competence is considered to be unique and characteristic to each virus-vector pair [77]. Suitable environmental conditions must be present at the time of these events.

The time required for a mosquito to transmit ZIKV, as well as any other vector-borne virus, is defined by the extrinsic incubation period (EIP), based on a given temperature. If this incubation temperature is too low, the viral cycle is interrupted and the virus remains in a dormant state inside the vector [5].

Knowledge on the EIP for mosquito vectors of ZIKV is sparse as few studies have been conducted on this virus to date. In a 1956 laboratory study, Boorman et al. observed that the EIP of the ZIKV in *Ae. aegypti* mosquitoes is greater than 15 days when the ambient temperature varies between 22°C and 26°C [48, 78]. Other more recent laboratory studies kept *Ae. albopictus* and *Ae. aegypti* females at constant temperatures of 27°C to 29°C, respectively, to complete the EIP within a week [79, 49]. Chouin-Carneiro et al. recently evaluated the vector competence of *Ae. aegypti* and *Ae. albopictus* mosquitoes species found in the Caribbean (Martinique, Guadeloupe), North America (southern United States) and South America (Brazil, French Guiana) for the Asian genotype of the ZIKV currently

circulating. They estimate that a 14-day EIP is required for *Ae. albopictus* to transmit ZIKV at a constant temperature of 28°C (±1°C) without specifying whether the strain is from temperate or tropical regions [53]. Thus, the time a mosquito requires to transmit ZIKV is likely between 7 and 15 days at temperatures between 22°C and 29°C. The threshold temperature for ZIKV is currently unknown, but based on available information, it is likely around 25°C (expert opinion). This estimate may be conservative given that the temperature threshold conducive to CHIKV outbreaks is set at 20°C [54, 80, 81].

Québec's current summer temperatures are unlikely to allow for ZIKV's EIP, assuming that this period requires 7 to 15 days at a constant temperature above 22°C. In fact, throughout July and August 2004 to 2015, the highest mean temperature, 26.3°C, was reported in the Montérégie region (16.9°C minimum, 36.0°C maximum, 3.3°C standard deviation) (Table 1).

Table 1 Mean, minimum and maximum temperatures from 2004 to 2015 for some health regions (socio-sanitary regions - SSRs) in southern Québec

Health regions	Mean temperature (°C)	Minimum temperature (°C)	Maximum temperature (°C)	Standard deviation (°C)
Outaouais (SSR-07)	25.2	13.9	36.3	3.7
Estrie (SSR-05)	25.2	14.0	33.3	3.4
Montréal (SSR-06)	26.0	17.1	35.0	3.2
Montérégie (SSR-16)	26.3	16.9	36.0	3.3

Heat waves are periods during which the three-day moving mean of the maximum and minimum temperatures observed at reference meteorological stations reach extreme heat thresholds as defined by the Institut national de la recherche scientifique [National institute of scientific research] and the INSPQ [82]. Threshold temperatures used to define an extreme heat wave vary from one health region to another. For example, in Montréal and Montérégie, the minimum threshold for extreme heat is 20°C and the maximum, is 33°C. Over the past five years, 37 heat waves were reported in Québec. The Outaouais recorded the highest number of extreme heat waves (eight) between May and September 2010 to 2015 (minimum threshold: 18°C, maximum threshold: 31°C) (Germain Lebel, personal communication, April 7, 2016). In other words, there is only a very low probability that the temperature could remain above a minimum threshold of 22°C for several consecutive days (e.g., between 7 and 15 days).

However, various climatic scenarios project that, by 2020, southern Québec will see a mean June to August temperature increase of +1.0°C to +1.8°C (RCP 4.5) and +1.0°C to +2.0°C (RCP 8.5). The summary of the values observed in southern Québec for 1971 to 2000 indicates that the June to August mean temperature was 17.6°C (0.8°C standard deviation). Various climatic scenarios project values of +1.6°C to +3.3°C (RCP 4.5) and +2.2°C to +4.5°C (RCP 8.5) by 2050. In addition, large increases are projected for the duration of heat waves and the frequency of hot nights (minimum temperature > 20°C) [64]. This could promote the conditions required for successful long-term ZIKV EIP in Québec.

In addition to the influence of temperature, there exists a risk that ZIKV vectors and the virus itself might mutate, thus facilitating the development of these organisms at our latitude, the maintenance of a zoonotic cycle and epidemic capabilities [8]. A study on the molecular evolution of ZIKV uncovered several sites in the viral genome nucleus that are under strong negative selection pressures, suggesting a potential for mutations [83]. In fact, since its introduction in North America in

1999, WNV underwent evolutionary pressure to adapt to environmental conditions; in 2001, a mutation shortened the EIP of mosquito vectors for WNV from 8 to 5 days [84]. This has promoted the introduction of this vector-borne disease in North America. In addition, a mutation in the envelope gene (A226V) of CHKV increases the vector competence of *Ae. albopictus* for this virus, allowing it to spread and replicate more efficiently in this new vector [85].

Lastly, it has been hypothesized that *Aedes* species other than *Ae. aegypti*, *Ae. albopictus* and other mosquito genera could become ZIKV vectors in the Americas. The presence of ZIKV has already been reported in a *Culex* species (*Cx. perfuscus*) captured in an agricultural area of Senegal [86]. A study is underway in Brazil on the vector competence for ZIKV of the *Cx. quinquefasciatus* mosquito, which is 20 times more common than *Ae. aegypti* in that country. The study has already demonstrated the capacity of the mosquito's salivary glands for infection and spread of the virus [87]. The question was also raised in Canada, about whether native mosquitoes are a competent vector for ZIKV, including mosquitoes capable of transmitting other flaviviruses (e.g., *Culex pipiens/restuans, Ae. vexans, Ae. japonicus*). Studies on this subject are currently underway (Fiona Hunter, personal communication, February 24, 2016). Study results will resonate with Québec, where these mosquito species are present.

3.3 Other ZIKV transmission modes

3.3.1 Sexual transmission

Information on potential sexual transmission of ZIKV is based on a few transmission cases from men to their partners [78, 88, 89]. The first case of sexual transmission was reported in 2008 in the United States. After returning home from Senegal, a scientist transmitted ZIKV to his wife, who had not travelled. The virus was not present in the United States [78]. Recently, a person was infected by the virus after sexual contact with the person's spouse, who had acquired the infection during a trip to Venezuela (first known case of local acquisition of ZIKV during this epidemic) [90]. Several cases have been documented since then. CDC stated that these new infection cases suggest that sexual transmission may be a more likely means of transmission for ZIKV than previously considered and it issued a Health Alert Network Advisory [91].

Moreover, during the ZIKV outbreak in French Polynesia, the ZIKV genome was isolated from an infected individual's semen more than two weeks after symptoms had subsided. This individual showed signs of hematospermia [92]. Recently, the semen of an individual experiencing fever and rash symptoms tested positive for ZIKV 62 days after the onset of symptoms. These data indicate prolonged presence of ZIKV in semen, which in turn could indicate a prolonged potential for its sexual transmission [93]. To date, there is no documented data on sexual transmission of the virus from asymptomatic cases [95].

3.3.2 Blood transfusion

ZIKV through a blood transfusion is likely to occur given that other, related flaviviruses are transmitted through this hematogenous route [43]. Furthermore, during the ZIKV outbreak in French Polynesia, 42 out of 1 505 blood donors (2.8%) tested positive for ZIKV [96]. These donors were asymptomatic at the time of the blood donation. Brazil recently reported a confirmed case of ZIKV infection transmitted by blood transfused from an asymptomatic donor [21].

3.3.3 TRANSPLACENTAL AND PERINATAL

An increasing number of studies show the potential for ZIKV transmission from pregnant mother to fetus. The presence of ZIKV RNA in the amniotic fluid of mothers with foetuses exhibiting congenital brain defects (detected by ultrasound) has been demonstrated [97, 98, 99]. RNA and antigens of the virus have been identified in the tissues of the brain and in the placenta of newborns presenting with microcephaly and dying shortly after birth, and in tissues from miscarriages [100, 99]. Perinatal transmission of ZIKV was documented for the first time by Besnard et al. during the French Polynesian ZIKV outbreak. During this epidemic, two cases of perinatal transmission were described. These transmissions to newborns probably occurred by transplacental transmission or during delivery [101].

3.3.4 BREAST MILK

During the outbreak in French Polynesia, the viral genome of ZIKV was detected in breast milk samples from two mothers with documented perinatal transmission [101]. This raises the probability of the virus being transmitted during breastfeeding. Even though investigations have failed to isolate the virus in breast milk, the authors consider that ZIKV transmission must be considered given that transmission through breast milk has been documented for dengue virus [102] and WNV [103]. CDC has reported that to date, there have been no reported cases of ZIKV infection in breastfeeding infants [104].

4 Risk assessment

4.1 Clarification of the question and scope of the risk assessment

From the onset of this process, the question and scope of this assessment have been clearly defined. Based on the available evidence, it was agreed to limit the question to the emergence and vector-borne transmission of ZIKV in Québec.

The scope of the risk assessment was established based on the factors shown in Table 2, which are adapted from the INSPQ's risk management framework.

Table 2 Factors that clarify the scope of the risk assessment

Factors	Specific information on the threat and context assessed
Population	Québec population, with specific focus on the vulnerable population (women who are pregnant or of childbearing age).
Environment, location	All Québec regions, with specific focus on the southern regions of the province (bordering the northeastern US states).
Time	Current, medium- and long-term risk.
Pathogen	ZIKV.
Event	Periodic seasonal emergence and vector-borne transmission of the virus.
Source	Infected mosquito vectors.
Exposure circumstances	Seasonal point-source introduction emergence: virus introduction by human cases infected in countries where there is transmission; virus introduction by infected mosquitoes having travelled in tires, by airplane; presence of local mosquito species with competence for the virus; migration or introduction of vector species. Vector-borne transmission: exposure through the bites of mosquito-vector species that are local or introduced and established; establishment of viral replication cycles.
Consequences	Asymptomatic infection (80% of cases), symptomatic infection (20% of cases), potential neurological complications in the infected person (GBS) or in the fetus or newborn (microcephaly and other congenital defects).

More precisely, the question and scope of the risk assessment have been defined as follows:

What is the current, medium- and long-term probability of the Québec population’s (including women who are pregnant or of childbearing age) exposure to ZIKV transmission through a mosquito-vector bite? Among an infected population, this risk could potentially result in mild symptoms or more severe neurological disorders, such as GBS, or congenital defects in the fetuses or newborns of infected pregnant women (microcephaly and other congenital defects).

4.2 Current risk of vector-borne transmission of ZIKV in Québec

Given that humans in urban environments are a reservoir of ZIKV, the current risk of vector-borne transmission of ZIKV essentially depends on the presence of potential mosquito vectors of the virus and their capacity to transmit the virus (i.e., the vector competence, population density, preferred bloodmeal hosts, bite rate and population survival of these mosquitoes) [105].

The characterization of the current risk of ZIKV transmission in Québec is based on the ecological data in section 3, which have made it possible to answer the following questions in terms of probability:

1) Are the species of mosquito vectors of ZIKV present in North America also present in Québec (*i.e., Ae. aegypti* and the *Ae. albopictus* strain from temperate regions)?

The entomological data available in Québec do not cover reporting established populations, and documenting the seasonal presence of mosquito species known to be vectors of ZIKV, such as *Ae. aegypti* and *Ae. albopictus*.

CDC estimates that the distribution of *Ae albopictus* extends midway into the following Québec-adjacent US states: Vermont, New York and New Hampshire.

The geographical distribution of *Ae. aegypti* tends to be less northern, which is less concerning for Québec.

Entomological surveillance is not conducted continuously in space and time in Québec-adjacent US states, thus raising the hypothesis of a false negative in entomological surveillance data. Given the present context in which the entomological surveillance is conducted in Québec (e.g., government response plans designed to protect the public against WNV), whether these mosquitoes are present at the border cannot be established.

The presence of *Ae. albopictus* adult specimens was documented in 2005 at the Montréal–Trudeau airport, confirming the species' potential for introduction by airplane and highlighting its ability to survive during the hottest months of the year.

However, adults cannot survive at temperatures below 9°C. The temperature data available for southern Québec indicate that between December and February (1971 to 2000), the mean temperature was –9.5°C (1.6°C standard deviation). Of all the southern Québec regions, Outaouais was found to hold the lowest mean temperature recorded between 2004 and 2015; that is, –4°C (–25.6°C minimum, 17.9°C maximum, 6.5°C standard deviation). Winter temperatures are significantly lower than the survival threshold for temperate *Ae. albopictus* adults.

Given the hypothesis that an insulating snow cover allows *Ae. albopictus* eggs to survive, and the demonstrated constant temperature of 0°C in the duff under a 120-cm snow cover (January to February 1998), there is a theoretical probability that any eggs laid in Québec could survive; however, more information is required.

Based on this information, the expert group estimates the following:

- Adult specimens of *Ae. aegypti* or *Ae. albopictus* are likely to be accidentally introduced in Québec and survive summer;
- It is very unlikely that the *Ae. aegypti* species currently has the ability to establish itself seasonally in Québec;
- It is unlikely that the *Ae. aegypti* strain from temperate regions currently has the ability to establish itself seasonally in Québec;
- The expert group cannot determine the probability of successful egg overwintering for the *Ae. albopictus* strain from temperate regions;
- It is very unlikely that established populations of the temperate strain of *Ae. albopictus* are currently present in Québec.

2) Do mosquitoes native to Québec currently have vector competence for ZIKV?

It has been hypothesized that *Aedes* species other than *Ae. aegypti* and other common mosquito genera, particularly *Culex*, could be ZIKV vectors.

ZIKV was detected in *Cx. perfuscus* in Senegal.

Cx. quinquefasciatis, a *Culex* species present in Brazil, has infection capacity for ZIKV and can spread it through its salivary glands.

Mosquito species with flavivirus transmission competence are present in Québec (*Cx. pipiens/restuans, Ae. ultimum*).

The ZIKV vector competence of *Culex* species and other mosquito species native to Québec (e.g.. *Ae. japonicus*) is unknown.

Given the little information available, the expert group:

- Cannot determine the probability of mosquitoes native to Québec having vector competence for ZIKV.

3) Is the current Québec climate favourable to a successful EIP for ZIKV mosquito vectors present in North America?

Available evidence shows that the EIP for ZIKV is between 7 and 15 days at temperatures between 22°C and 29°C.

The threshold temperature for ZIKV is currently unknown but is probably about 25°C (expert opinion).

Extreme heat waves in Québec are typified by periodic three-day-long projected temperatures that remain above 18°C to 20°C overnight and rise to 31°C to 33°C in daytime.

However, for a successful EIP, ZIKV needs its threshold temperature to remain constant for a sufficient number of consecutive degree-days.

Based on this information, the expert group estimates the following:

- Although the temperature in southern Québec may rise beyond the estimated threshold temperature for Zika, it is very unlikely that, in the event of seasonal and accidental presence of temperate *Ae. albopictus*, the current Québec climate will facilitate this mosquito's EIP to allow sufficient amplification and transmission of the virus in Québec.

Answers to these three questions provide updated information pertaining to the CDC risk categories for mosquito-borne arbovirus disease outbreaks (Table 3). The probability of an outbreak of arboviruses implies mosquito-borne transmission.

Table 3 CDC risk categories for mosquito-borne arbovirus disease outbreaks

Category	Probability of outbreak	Definition
0	Negligible or none*	Absence of mosquito populations; climate unfavourable to virus emergence (threshold temperature too high, EIP difficult to attain, even in summer).
1	Remote	Seasonal (spring, summer, or fall); adult vectors active but not abundant; ambient temperature not satisfactory for viral development in vectors.
2	Possible	Focal abundance of adult vectors; temperature adequate for extrinsic incubation; seroconversion in sentinel hosts.
3	Probable	Abundant adult vectors in most areas; multiple virus isolations from enzootic hosts or a confirmed human or equine case; optimal conditions for extrinsic incubation and vector survival; these phenomena occur early in the normal season for viral activity.
4	Outbreak in progress	Multiple confirmed cases in humans.

* The expert group considers the terms "negligible" and "none" synonymous; however, to clearly explain this risk assessment's results, the term "negligible" alone will define Category 0.

Source: Moore, C. G., et al., 1993. Guidelines for Arbovirus Surveillance Programs in the United States, Centers for Disease Control.

The evidence and the expert group's current knowledge are limited by Québec's lack of documentation on the North American presence of established mosquito-vector populations (i.e., *Ae. aegypti* and *Ae. albopictus*); thus, the current probability of a ZIKV outbreak in Québec is categorized as 0 or "negligible." Consequently, the current risk of vector-borne transmission of ZIKV in Québec is negligible.

4.3 The medium- and long-term risk of ZIKV emergence and vector-borne transmission in Québec

In terms of the medium- and long-term emergence of ZIKV in Québec, this risk assessment identifies a periodic seasonal emergence occurring during the hottest months of the year, rather than an emergence leading to endemicity.

ZIKV introduction in Québec may occur through accidental importation of infected mosquitoes or through the arrival of viremic humans. The characterization of the current emergence and transmission risk of ZIKV in Québec is based mainly on ecological and epidemiological data, which have made it possible to answer the following questions in terms of probability:

1) What is the medium- and long-term risk of ZIKV mosquito-vector introduction in Québec?

Adult specimens of *Ae. albopictus* have already been periodically introduced in Québec by airplane and captured at the Montréal–Trudeau airport, which highlights their capacity to survive during Québec's warmer months.

A large number of travellers arrive at the Montréal-Trudeau airport in summer from countries where the presence of established populations of ZIKV mosquito-vector species has been documented (such as the Caribbean and South America). Mosquito vectors can thus be introduced this way.

Established populations of the temperate *Ae. albopictus* strain have been documented in the US states bordering southern Québec. This introduces the probability of introduction by land, through such activities as trucking.

Climatic models predict that the geographical limit for *Ae. albopictus* survival could reach southern Québec in the medium-term, specifically, in the coming decades (2011 to 2040).

Southern Québec may currently be an area vulnerable to the introduction of mosquito species with vector competence for ZIKV.

Based on this knowledge, the expert group estimates the following:

- ZIKV mosquito vectors are likely to be introduced in Québec not only by airplane, but by sea and land routes as well.

2) What is the medium- and long-term risk of ZIKV mosquito-vector population establishment in Québec?

The *Ae. aegypti* species is not adapted to temperate climates.

The temperate strain of *Ae. albopictus* is acclimated to colder temperatures.

Temperate *Ae. albopictus* eggs are dormant in winter. Their survival in Québec winter conditions is unknown. Given the hypothesis that an insulating snow cover allows *Ae. albopictus* eggs to survive, and the demonstrated constant temperature of 0°C in the duff under 120 cm of snow (January to February 1998), there is a theoretical probability that any eggs laid in Québec could survive.

Egg survival could generate a potential to produce subsequent generations the next summer, as reported in some European countries.

Based on the climate from 1981 to 2010, some climatic models predict that the current climate could accommodate the establishment of *Ae. albopictus* as far northward as southern Québec.

Based on this information, the expert group estimates the following:

- It is very unlikely that *Ae. aegypti* will establish in southern Québec in the medium- and long-term;
- It is unlikely that temperate *Ae. albopictus* will establish in southern Québec in the medium- and long-term;
- But it is more likely that a temporary population of temperate *Ae. albopictus* will establish in summer months with observed temperatures above 9°C;
- These findings could vary in a context of climate change and potential vector acclimation.

3) What is the probability that mosquitoes native to Québec will develop vector competence for ZIKV?

The competence of Québec-native mosquito vectors for ZIKV is unknown; this includes those capable of transmitting other flaviviruses.

However, the ZIKV transmission capacity of some mosquito species native to and established in Québec could change as a result of mutations in their genome, or in the virus itself.

Given the little available information and the uncertainly surrounding the subject:

- The expert group cannot determine the probability that Québec-native mosquitoes will develop vector competence for ZIKV.

4) What is the medium- and long-term probability of ZIKV introduction in Québec?

The risk of ZIKV introduction depends on some of the factors presented in Table 4. This table describes ZIKV-specific information showing that the probability of ZIKV introduction in Québec is increased by humans functioning as reservoirs and by ZIKV endemicity in countries from which numerous travellers fly into Québec.

Table 4 A 2013 INSPQ expert group identified variables substantiating a pathogen-introduction risk analysis for Québec, and ZIKV-specific information

Variables	ZIKV-specific information
1) Humans are reservoirs	**Yes**
2) Endemicity in a country with a high number of travellers flying to Québec	**Yes** (the Caribbean, Central America, South America)
3) Endemicity in the US	Puerto Rico (geographically located in Central America)
4) Endemicity in US states bordering Québec	No
5) Potential bird reservoir	Unknown
6) Circulation of the pathogen in a temperate-cold zone	No
7) Presence of potential reservoirs in Québec	Unknown
8) Genotype and viral genome evolution	ZIKV in America is of the Asian lineage. It is phylogenetically similar to the strains isolated during the 2013 to 2014 French Polynesian epidemic. To date, no mutations have been described in ZIKV strains in America.

Supplementary to Table 4, the answer to question 4) was supported by factors presented in the situation overview.

Surveillance of ZIKV human infection cases reveals that the virus has already been introduced in Québec by travellers infected during trips to countries with transmission.

There is currently no data documenting the introduction of the virus to Québec through infected mosquitoes travelling in tires or airplanes. However, *Ae. albopictus* adult specimens were captured at the Montréal–Trudeau airport 2005, which indicates that periodic introduction of ZIKV in this way is probable.

Based on this information, the expert group estimates the following:

- Periodic and accidental ZIKV introduction is likely to occur in Québec in the medium- and long-term through infected travellers and infected mosquitoes;
- It is very unlikely that the virus, if introduced periodically and accidentally, will amplify sufficiently in human reservoirs to sustain medium- and long-term vector transmission.

5) What is the probability that the medium- and long-term Québec climate will favour a successful EIP for mosquito vectors?

EIP for ZIKV is between 7 and 15 days at temperatures between 22°C and 29°C.

The threshold temperature for ZIKV is currently unknown but may be around 25°C (expert opinion).

For June to August of 1971 to 2000, the mean temperature in southern Québec was 17.6°C (0.8°C standard deviation).

Throughout July and August 2004 to 2015, the highest mean temperature, 26.3°C, was reported in the Montérégie region (16.9°C minimum, 36.0°C maximum, 3.3°C standard deviation).

Canadian climatic models provide a good idea of the future climate. They predict an increase in Québec's temperatures for all seasons. Various climatic scenarios project that, by 2020, June to August in southern Québec will see a mean temperature increase of +1.0°C to +1.8°C (RCP 4.5) and +1.0°C to +2.0°C (RCP 8.5); in addition, they project that, by 2050, this increase will be +1.6°C to +3.3°C (RCP 4.5) and +2.2°C to +4.5°C (RCP 8.5).

Large increases are projected for the duration of heat waves and the frequency of hot nights (whose minimum temperature is greater than 20°C).

Climatic simulations do not predict whether future temperatures will accommodate successful EIP should there be a presence of mosquito species competent for ZIKV and a reservoir amplifying the virus.

Mutations could occur in the ZIKV genome and diminish its EIP, just as they have in WNV.

Based on this information, the expert group estimates the following:

- In the event of seasonal and accidental presence of temperate *Ae. albopictus* in Québec, along with a reservoir amplifying the virus, the medium-term (e.g., 2020) Québec climate is very unlikely to favour the EIP of this mosquito to allow sufficient amplification and transmission of the virus in Québec;
- In the event of seasonal and accidental presence of temperate *Ae. albopictus* in Québec, along with a reservoir amplifying the virus, the long-term (e.g., 2050) Québec climate is unlikely to favour the EIP of this mosquito to allow sufficient amplification and transmission of the virus in Québec.

Based on this information, the expert group estimates that, according to the CDC categories shown in Table 3, the probability of a ZIKV outbreak in the medium-term is "remote." In this case, the medium-term risk of ZIKV emergence and vector-borne transmission in Québec is low.

However, some conditions in Québec are favourable to ZIKV emergence and vector-borne transmission: humans functioning as reservoirs, ZIKV endemicity in countries from where numerous travellers fly into Québec, established populations of *Ae. albopictus* mosquito vectors documented in Québec-adjacent US states, the southern Québec climate being potentially favourable to *Ae. albopictus* introduction, and probable point-source introduction of *Ae. albopictus* adult specimens and ZIKV. Although Canadian climatic models predict an increase in Québec temperatures for all seasons, it is not possible to predict the long-term risk of ZIKV emergence and vector-borne transmission in Québec.

4.4 Risk perception

Although the current risk of vector-borne transmission of ZIKV in Québec is deemed negligible, and the medium-term risk of ZIKV emergence and vector-borne transmission in Québec is termed low, some unique aspects of the epidemiological situation heighten the perception of risk, mainly because of the magnitude of the consequences:

- In most cases, ZIKV infection is benign; however, severe complications can occur and create a significant burden for infected persons, their families, society and healthcare in the affected countries. These include:
  - A significant number of congenital defects (including microcephaly) associated with ZIKV infection in pregnant women can potentially impact society and long-term healthcare. These complications affect the risk perception of the population and healthcare providers.
  - Anyone infected by ZIKV can present neurological complications, including GBS. Despite this, the burden these complications create for the society and healthcare of affected countries is low.
- Most of Québec's population has never been exposed to ZIKV and therefore has not developed immunity to it. Introduction of the virus in this type of population could result in an infection spread of major epidemic proportions.

Sustained transmission of ZIKV in Québec is unlikely. It is difficult to estimate the impact this transmission could have on the number of microcephaly cases during a French-Polynesian–type outbreak. Nevertheless, it might be edifying to make a projection based on available data about Québec's total births to compare the impact of ZIKV congenital infections with that of common neonatal diseases or neurological defects.

Should Québec have an attack rate similar to the 73% attack rate reported on the Micronesian island of Yap, or the 66% attack rate modeled by Cauchemez et al., the impact among the general population would be significant solely in terms of the number of infected individuals, since most cases would not develop symptoms. The proportion of fetal defects estimated by Cauchemez et al. for pregnant women infected with ZIKV is 1%. Brazil reported approximately 40 times more microcephaly cases than its baseline prevalence, which represents approximately 0.2% in the neonatal population. Québec's approximate 0.04% baseline for neonatal microcephaly cases (Nathalie Auger, personal communication, May 12, 2016) means it has about 36 microcephalic infants born per year (there were 87 700 total births in 2014); the proximate 0.2% to 0.66% rate of congenital

defects caused by ZIKV infection during an epidemic would mean 175 to 578 Québec newborns with neurological defects per year.

This same exercise can be conducted to estimate the impact of sustained ZIKV transmission on Québec's number of GBS cases during a French-Polynesian–type outbreak.

For 2015, 1 708 GBS cases were reported throughout Brazil, representing a 19% increase from 2014, which had 1 439 reported cases of GBS [106]. An INSPQ study covering the period from October 13, 2009, to March 31, 2010, showed that the incidence rate of GBS level 1 to 3 cases among the Québec population aged 6 months or older was 1.96/100 000 person-years; the rate was 2.29/100 000 person-years when including level 4 cases [107]. A 19% increase would give a rate of 2.73/100 000 person-years (GBS level 1 to 4), making the estimated baseline number rise from 188 to 224 (population of Québec in 2014: 8.215 million).

This information represents a scenario where ZIKV vector-borne transmission is possible, although unlikely. It would also be important to examine this information with regard to ZIKV sexual transmission, which could be the source of a local spread of infection. However, these considerations extend beyond the objectives this scientific advisory.

5 Conclusion and recommendations

The risk assessment results are specific to the population situation and climate condition of Québec. In Québec, the current risk of vector-borne transmission of ZIKV is negligible, whereas the medium-term risk of ZIKV emergence and vector-borne transmission is low.

To date, various public health organizations have published risk assessment results on ZIKV infection and vector-borne transmission: these include PHAC (target population: Canada) [21], Public Health Ontario (target population: Ontario) [108], Public Health England (target population: United Kingdom) [109], ECDC (target populations: European Union countries) [110] and WHO (target populations: Africa and Europe) [24, 25]. The risk assessment results showed in the present scientific advisory are consistent with those targeting other regions of the world with Québec-like climates and presence (or absence) of ZIKV mosquito-vector species: these regions include the rest of Canada (very low risk), Ontario (low risk) and the United Kingdom (very low risk) [21, 108, 109].

Vector-borne transmission of ZIKV requires conditions favourable to vector competence development and the EIP of the virus. The rapid spread of ZIKV may also be attributable to other contributing factors, such as an immunologically naïve population for ZIKV and high densities of human-biting mosquitoes [53].

The presence of favourable conditions warrants concerns about long-term ZIKV emergence and vector-borne transmission:

1) One of the mosquito species, *Ae. albopictus*, has adapted to temperate temperatures and has, in recent years, significantly expanded its geographical range as far north as the northeastern US states bordering Québec.
2) Climate models qualified as conservative predict that the projected climate for a 2011 to 2040 timeline would accommodate *Ae. albopictus* introduction in southern Québec.
3) The estimated threshold temperature of 25°C could be maintained throughout the virus incubation period in southern Québec as a result of climate change.

In addition, the virus could mutate to adapt to native vectors in Québec or to lower threshold temperatures. Such changes could accelerate the introduction and transmission of the virus.

The risk of contracting the disease is nevertheless present for Québec travellers visiting countries where local transmission is documented or through an infected man's sperm during unprotected sex. Recommendations have been issued by other bodies, including the INSPQ's CCQSV and the MSSS [111, 112].

The main limitation on this risk assessment is the heterogeneity of entomological surveillance knowledge in Québec, in neighbouring provinces and in US states. It will therefore be important to learn more about the composition of mosquito populations in southern Québec, in particular to detect the *Ae. albopictus* strain from temperate regions. Future research results on the ZIKV vector competence of mosquito species native to Canada will also help modulate risk. Studies on the virus will also detect the occurrence of possible mutations that would increase its ability to spread.

In these circumstances, the following actions are recommended:

1) Develop a medium- and long-term sustainable plan for entomological surveillance that would expand its objectives[7] in order to document mosquito species established in southern Québec. Entomological stations could be located at entry points to Québec (e.g., airports and ports) and in southern Québec communities. Repeating this ongoing surveillance would document any increase in the number of individual specimens captured or any population establishment.
2) Implement Recommendation 3 of the scientific advisory entitled *Évaluation de l'émergence possible du virus Chikungunya et du risque de transmission vectorielle au Québec* [Assessment of the potential emergence and vector-borne transmission risk of *Chikungunya virus* in Québec] and add ZIKV to it: ("The INSPQ recommends adding CHIK virus and dengue virus infection to the list of notifiable diseases, and to the human case surveillance lists of doctors and laboratories, in order to better monitor the progression of these two vector-borne diseases" [translation]).
3) Maintain the scientific monitoring implemented for the purposes of this risk assessment with special attention on publishing the results of the work conducted by two Canadian research teams (the Fiona Hunter team of Ontario's Brock University, and the Robbin Lindsay team of the National Microbiology Laboratory): this will increase knowledge about the vector competence of Canadian native species currently involved in the transmission of other flaviviruses, including *Ae. japonicus*, a new species introduced in Canada.
4) Conduct studies that would increase local knowledge on topics such the ability of *Ae. albopictus* to survive the southern Québec climate, with a specific focus on egg survival under snow cover.

This rapid risk assessment may be updated as dictated by the progression of the situation.

[7] The 2016 entomological surveillance plan published by INSPQ at MSSS's request includes the objective of documenting the *Ae. albopictus* mosquito species in areas at risk of introduction, with a specific focus on southern Québec (Louise Normandin, personal communication, May 16, 2016).

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Appendix 1

The expert group's areas of expertise and mandate

The expert group's areas of expertise and mandate

Areas of expertise represented in the group:

- Entomology (Richard Trudel);
- Public health (including the infection risk assessment) (Anne Fortin, Anne-Marie Lowe and Louise Normandin);
- Microbiology-infectology (Christian Renaud);
- Microbiology and laboratory diagnostic tests (Christian Therrien).

The general mandate of the expert group is to support the SERCMI unit in its risk assessment of the emergence and vector-borne transmission of ZIKV in Québec.

The specific mandate of the expert group is to:

- Review the scientific evidence substantiating the scientific advisory entitled *Évaluation de l'émergence possible du virus Chikungunya et du risque de transmission vectorielle au Québec*;
- Draw upon the group members' respective expertise to shed light on other risk situations of concern associated with ZIKV infection;
- Conduct a literature review;
- Conduct the risk assessment;
- Offer guidelines and lines of thinking based on the rapid risk assessment of this scientific advisory;
- Draft, comment on or update this scientific advisory.

Expert consultations took place on February 4, 11 and 25, and May 10, in 2016. The expert group enlisted the collaboration of a CCQSV medical consultant and an expert from PHAC's National Microbiology Laboratory. A draft version of this document was circulated to an INSPQ communications professional, the INSPQ's DRBST director and the INSPQ's CSZACC core team members to gather their comments. The final version of this scientific advisory has been reviewed by the above-mentioned experts.

Appendix 2

Causal link between microcephaly and ZIKV infection

Causal link between microcephaly and ZIKV infection

Past evidence establishing a causal link between microcephaly and ZIKV infection

Until late October 2015, ZIKV had not been described as responsible for microcephaly or other congenital defects. The 2007 epidemic on the island of Yap, described above, was located in a sparsely populated territory (7 391 inhabitants) and the number of ZIKV cases was limited to 49 confirmed cases and 59 probable cases [31].

In October 2015, the Brazilian Ministry of Health reported an unusual increase in microcephaly[8] cases among newborns in the state of Pernambuco, located in northeastern Brazil. From the beginning of the year until November 11, 2015, 141 microcephaly cases were detected in this state, whereas the annual average was 10 cases. A similar situation was also observed in the states of Paraíba, Rio Grande do Norte and Piaui. This increase in microcephaly cases in northeastern Brazil was reported in an epidemiological alert issued by WHO/PAHO on November 17, 2015 [13].

After the Brazilian alert, health authorities in French Polynesia performed a retrospective analysis of 2014 and 2015 births to investigate the country's own 2013 to 2014 Zika outbreak. It reported that the annual cases of central nervous system defects in fetuses and infants had increased from 1 to 17 cases. The various central nervous system defects observed in 12 of the 17 cases included microcephaly, destruction of the brain structure, cerebellar hypoplasia, agenesis of the corpus callosum, and ventriculomegaly >10 mm in the first trimester. These results led to medical terminations of pregnancy in 9 cases [113].

On February 26, 2016, the Brazilian Ministry of Health reported 5 640 suspected cases microcephaly or central nervous system defects potentially linked to congenital infection, including 120 deaths. Of these 5 079 suspected cases, 462 were confirmed cases of microcephaly of unknown etiology, including 41 cases which were laboratory-confirmed as having ZIKV infection. It was established that 765 of these suspected cases did not have microcephaly, whereas 3 852 cases remained under investigation [114]. By comparison, between 2001 and 2014, an annual average of 163 cases was reported in Brazil [19]. Brazil's Ministry of Health reports indicated a 20-fold increase in newborn microcephaly cases, indicating a possible association between congenital microcephaly and ZIKV infection during pregnancy [115].

The increased number of microcephaly, embryopathy and fetopathy cases observed in Brazil and French Polynesia temporally coincided with these two countries' ZIKV outbreaks.

In November 2015, ZIKV RNA was identified by reverse transcription polymerase chain reaction (RT-PCR) in samples of the amniotic fluid of two pregnant women whose fetuses had been diagnosed with microcephaly through prenatal ultrasound [98]. ZIKV RNA was also identified in many body tissues, including the brain of a microcephalic infant who died during the immediate postnatal period, and placental tissue from an early abortion [100]. These findings triggered new alerts addressing a possible association between microcephaly and ZIKV infection by ECDC [115] and PAHO [116].

Schuler-Faccini et al. [37] reported that the Brazilian Ministry of Health established a task force to investigate the possible association of microcephaly with ZIKV infection during pregnancy, a registry for new cases of microcephaly, and pregnancy outcomes among women suspected to have had ZIKV infection during pregnancy. The authors mention that, among a group of 35 microcephalic

[8] Head circumference two standard deviations below the mean, in accordance with the WHO standard Q02.

infants born between August and October 2015 and reported to the registry, the mothers of all 35 had lived in or visited ZIKV-affected areas during their pregnancies. Overall, 26 (74%) mothers of infants with microcephaly reported a rash during the first (n = 21) or second (n = 5) trimester. Twenty-five (71%) infants had severe microcephaly, 17 (49%) had at least one neurological defect and, among 27 infants who underwent neuroimaging studies, all had defects. Moreover, widespread brain calcifications were noted.

Evidence of a link between ZIKV infection and microcephaly was subsequently described. Viral RNA and antigens were detected in the brains of two newborns with microcephaly who died within hours of birth. Only the brain tissue was tested positive by RT-PCR. Histopathological changes were limited to the brain and included parenchymal calcifications and cell degeneration and necrosis [100]. A case study published by Slovenian researchers reinforces the thesis of a causal link between microcephaly and ZIKV infection. ZIKV was found in the brain tissue of a fetus whose mother had been infected by the virus in the 13th week of pregnancy. Ultrasound examinations performed in weeks 14 and 20 of gestation produced normal results. The examination done at 29 weeks showed the first signs of central nervous system defects. An ultrasound at 32 weeks confirmed an intrauterine growth retardation and microcephaly with brain and placental calcifications. After the medical termination of pregnancy, RT-PCR analysis by indirect immunofluorescence, RT-PCR and electronic microscopy revealed that the virus was present in the fetus's brain but absent from any other organ, suggesting a strong neurotropism of the virus. Moreover, a complete genome of ZIKV found in the brain was sequenced [117].

On February 26, 2016, CDC published an advisory on the cases of pregnant women living in the United States and infected by ZIKV. Nine patients who developed symptoms following a trip in an endemic area were identified, six of whom were exposed to the virus during the first trimester. Among these six patients, outcomes included two early pregnancy losses, two elective pregnancy terminations, one delivery of a newborn with microcephaly and one ongoing pregnancy. Among the pregnant women exposed during the second or third trimester, two infants were born without any sign of defects, and one pregnancy was ongoing [99].

The causal link between ZIKV infection during pregnancy and microcephaly was consequently confirmed by CDC on April 13, 2016 [18, 17].

Past evidence establishing a causal link between GBS and ZIKV infection

In November 2013, GBS cases were observed in the 2013 to 2014 ZIKV infection epidemic in French Polynesia during concurrent circulation of dengue virus and ZIKV. Specifically, a woman developed paresthesia of the four limb extremities, muscular weakness, tetraparesis predominant in the lower limbs, diffuse myalgia and bilateral but asymmetric facial palsy. These symptoms had been preceded, seven days before, by myalgia, fever, cutaneous rash and conjunctivitis, evoking ZIKV infection [118].

During this epidemic, 42 GBS cases occurred over a period of four months, whereas French Polynesia usually records an average of only five GBS cases per year. Of these cases, 37 presented clear ZIKV infection profiles (ECDC, November 24) [119]. This spatio-temporal association—described for the first time—between ZIKV infection cases and the frequency of GBS-type neurological complications suggested that ZIKV was the cause of these complications [119]. A case-control study was subsequently conducted on 42 GBS cases. Study results reinforced the causality between ZIKV infection, proven by serologic markers, and the GBS. During the French Polynesian epidemic, the risk of developing GBS was estimated at 2.4 cases for every 10 000 ZIKV infection cases [120].

In July 2015, Brazilian health authorities diagnosed neurological syndromes in 76 patients with a recent history of ZIKV infection. Among these patients, 55% (42) were diagnosed with GBS, of which 62% (26/42) had presented symptoms consistent with ZIKV. Five patients had other neurological syndromes, 4 were discarded and 25 remained under investigation [116, 110]. For 2015, 1 708 GBS cases were reported throughout Brazil, representing a 19% increase from 2014, which had 1 439 reported cases of GBS [16].

During the course of the epidemics that have continued since October 2015, eight countries or territories[9] reported an increase in the number of GBS cases with at least one GBS case that has been laboratory confirmed for ZIKV infection. Five countries or territories[10] reported no increase in GBS incidence, but reported at least one GBS case with laboratory-confirmed ZIKV infection.

CDC has conducted studies to assess the link between GBS and ZIKV [121].

[9] Brazil, Colombia, Dominican Republic, El Salvador, French Polynesia, Honduras, Suriname and Venezuela.

[10] French Guinea, Haiti, Martinique, Panama and Puerto Rico.

Appendix 3

Other complications

Other complications (ocular lesions and neurological or autoimmune complications)

In addition to microcephaly and central nervous system defects, in January 2016, Ventura et al. [122, 123] reported the first documented cases of ocular lesions in microcephalic infants born to mothers infected with ZIKV during the first or the second trimester of their pregnancies. In 10 assessed microcephalic infants, ocular lesions included macular abnormalities in 15 eyes (75%) and optic nerve abnormalities in 9 eyes (45%). No ophthalmic lesions were reported among mothers, who reported no ocular symptoms during pregnancy [123].

A second study assessed a series of ocular lesion cases observed in microcephalic infants and associated with intrauterine ZIKV infection. In this case series, 23 of 29 mothers (80%) reported signs and symptoms associated with ZIKV infection during pregnancy. Of 29 children examined (58 eyes), ocular abnormalities were present in 17 eyes (29.3%) of 10 children (35%) of which 7 had bilateral abnormalities. The most common ocular lesions were focal pigment mottling of the retina and chorioretinal atrophy in 11 of the 17 eyes with abnormalities (64.7%), followed by optic nerve abnormalities in 8 eyes (47.1%) [124].

In February 2016, Jampol and Goldstein (2016) stated that congenital ZIKV infections were not yet well described and that it was still difficult to know whether ocular lesions occur in the absence of microcephaly [125].

By analogy with observations on WNV (also a flavivirus) it has been reported that ophthalmic abnormalities may be possible given that chorioretinal scars have been documented during the intrauterine transmission of the virus [126]. Since then, causality has been confirmed between ZIKV infection during pregnancy and microcephaly and vision problems as well [127].

Furthermore, during the French Polynesian epidemic, about 30 individuals were hospitalized for neurological or autoimmune complications, possibly related to an earlier ZIKV infection. These cases included encephalitis, meningoencephalitis, immune thrombocytopenic purpura, optic neuritis and myelitis [119]. Further, another study showed that the virus caused meningoencephalitis in an 81-year-old patient. The virus was detected in the cerebrospinal fluid by RT-PCR [128].

In Guadeloupe, a study showed that ZIKV caused acute myelitis in a previously healthy 15-year old patient, based on the virus's presence in the cerebrospinal fluid 9 days after symptom onset. The authors stated that this case strengthens the hypothesis that the virus is neurotropic in character [129].

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