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EMERGENCY PLANNING

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The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

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EMERGENCY PLANNING

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Federal, provincial and territorial public health response plan for biological events

R McNeill[1], J Topping[1]* on behalf of the FPT Response Plan Task Group

Abstract

The *Federal/Provincial/Territorial (FPT) Public Health Response Plan for Biological Events* was developed for the Public Health Network Council (PHNC). This plan outlines how the national response to public health events caused by biological agents will be conducted and coordinated, with a focus on implementation of responses led by senior-level FPT public health decision-makers. The plan was developed by an expert task group and was approved by PHNC in October, 2017. The plan describes roles, responsibilities and authorities of FPT governments for public health and emergency management, a concept of operations outlining four scalable response levels and a governance structure that aims to facilitate an efficient, timely, evidence-informed and consistent approach across jurisdictions. Improving effective engagement amongst public health, health care delivery and health emergency management authorities is a key objective of the plan.

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Introduction

Emerging infections, and other biological events, happen regularly in Canada and around the world, and require a coordinated health and public health response. Previous public health responses at a national level in Canada have addressed many hazards, ranging from epidemics of novel respiratory pathogens (e.g., SARS and H1N1 pandemics), to emerging infections, such as international and travel-related public health threats (e.g., Zika and Ebola), food-borne illness outbreaks, significant vaccine supply issues and the current opioid crisis.

Health planners have learned a great deal from previous experiences. The 2009 H1N1 pandemic revealed that coordination of decision-making and information sharing at the federal/provincial/territorial (FPT) level was often complex, challenging and time consuming; for example, multiple levels of government provided similar, but not identical, advice and recommendations regarding clinical guidelines for front-line health professionals and these differences led to confusion about whose advice to follow (1).

Lessons learned have demonstrated the need for a nimble, flexible FPT governance structure that can be applied consistently, in whole or in part, to a range of public health scenarios. They also demonstrated the need to clarify roles and responsibilities, as well as decision-making and approval processes, at various levels of government within the health sector. To address these issues, FPT Deputy Ministers of Health agreed that improvements to the FPT governance structure developed during H1N1 should continue, with the understanding that they would need to be flexible enough to adapt to different types of urgent situations, while respecting various responsibilities and authorities.

Public health in Canada is a shared responsibility among municipal, provincial, territorial and federal governments. Significant public health events, including public health emergencies, require coordination between all levels of government and a consistent approach across jurisdictions. Consensus on response strategies at a national level is desirable, recognizing that some or all jurisdictions involved (e.g., local, FPT governments and others) may choose to implement actions dependent on the legislative frameworks and circumstances of the event. It was with this goal of facilitating collaboration and decision-making between multiple authorities and levels of government, that the *FPT Public Health Response Plan for Biological Events* was developed.

Legislation requires all jurisdictions in Canada have plans that set out the steps to be taken in the event of an emergency. These plans identify linkages and channels of communication to other ministries, programs and agencies of the government and contribute to a coordinated, system-wide approach to emergency management. In addition, the FPT health sector has in place well established hazard-specific tools that are routinely used to effectively plan and manage public health events. A feature of the *FPT Public Health Response Plan for Biological Events* is that it is intended to complement and, where appropriate, be used in conjunction with existing mechanisms. For example, the *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (CPIP)* provides pan-Canadian planning guidance for pandemic influenza (2).

In a pandemic, it is expected the CPIP will inform the technical aspects of the response while the *FPT Public Health Response Plan for Biological Events* will provide the overall governance structure that will support decision-making. The objective of this paper is to provide a high level summary of the *FPT Public Health Response Plan for Biological Events*.

Key features of the plan

The plan is made up of a main body and various supporting appendices. The main body includes two key components: the concept of operations and the FPT governance structure. It also addresses health care sector engagement, describes how the governance structure will be supported and how it will interact with both federal and PT operations centres. The appendices include the guiding principles used in the development of the plan, a summary of key FPT roles and responsibilities for public health and emergency management and the Terms of Reference for the various groups within the governance structure.

Concept of operations

The concept of operations describes the steps that are taken from the initial notification of a public health event leading to the activation of the plan to the eventual de-escalation of the response. It describes how notification of public health events are made to the Public Health Agency of Canada (PHAC), and how response needs are assessed by technical experts and decision-makers. The concept of operations also describes four response levels to facilitate scaling of response activities as needed. Examples of scenarios where these response levels may be applied are given below.

- **Routine:** There is a need for information sharing regarding a public health event between an affected jurisdiction and other FPT or international authorities (e.g., outbreak of measles in a single jurisdiction).
- **Heightened:** There is a need for a routine public health response involving one or more jurisdictions (e.g., a food-borne outbreak occurring in multiple jurisdictions).
- **Escalated:** A coordinated response is required for a public health event that has potential implications for the Canadian health care system (e.g., outbreak due to a highly antibiotic-resistant bacterium).
- **Emergency:** A national response is required for an event in Canada causing significant illness and has the potential for rapid spread (e.g., a novel influenza virus is spreading efficiently between humans).

Governance structure

The governance structure is designed to streamline response processes, provide clarity on roles/responsibilities, facilitate a high degree of situational awareness and centralize risk management and task delegation. It is modelled on the 'day-to-day' governance structures of the Public Health Network Council and is made up of a Special Advisory Committee (SAC) and three main response streams (technical, logistical and communications) each led by advisory committees/working groups. The governance structure, through the SAC, reports to and is accountable to the FPT Conference of Deputy Ministers of Health (CDMH).

Special Advisory Committee

The SAC has a mandate to provide advice to the CDMH pertaining to the coordination, public health policy and technical content on matters related to the response to a significant public health event. As such, SAC is the main decision-making body of the governance and the main forum for approval of products developed by the governance such as recommendations, guidance documents, protocols and communication products. The SAC is composed of the members of the Pan-Canadian Public Health Network Council and the Council of Chief Medical Officers of Health (CCMOH).

Technical Advisory Committee

The Technical Advisory Committee (TAC) is largely focused on the characteristics of the public health event and what needs to be done from a technical, public health perspective to achieve the response objectives. Under TAC, task groups will be established to address public health response functions (e.g., surveillance, laboratory and medical countermeasures) and to provide technical input into products such as communications material aimed at informing media, health professionals and the public on the most current information available at the time. The TAC will develop products such as epidemiological reports, guidance on public health measures, and recommendations on the type of medical countermeasures (e.g., medications/antivirals or vaccines) to be used. The TAC will be co-chaired by the co-chairs of the Communicable and Infectious Disease Steering Committee (CID-SC).

Public Health Network Communications Group

The Public Health Network Communication Group (PHN CG) supports consistent and coordinated public communications by providing a mechanism by which FPT governments work together on common messaging. It provides a forum to share news releases and media material, conduct technical and media briefings, and direct Canadians on where to seek the most current information and guidance. Once the plan is activated, communication related response activities will be coordinated through the PHN CG, thus enabling FPT governments to align their communication strategies.

Logistics Advisory Committee

The Logistics Advisory Committee (LAC) will be largely focused on how the response activities will be implemented in order to achieve the response objectives. As with the TAC, under the LAC, task groups may be established to address specific logistical response issues. For example, LAC is responsible for engaging with the health care delivery sector and for establishing task groups as required to ensure this sector is represented in the governance. The LAC would develop products such as funding agreements, mutual aid agreements and recommendations regarding acquiring resources (e.g., vaccines or other medical countermeasures). The LAC is co-chaired by the co-chairs of the Public Health Infrastructure Steering Committee (PHI-SC).

Health care delivery engagement

Decisions of interest to health care clinicians are expected to be made at various fora in the governance structure. For example, the LAC may activate a Health Care Delivery Engagement Task Group to respond to requests by the SAC for products such as guidance documents. Task group members would include federal representatives and multidisciplinary experts, and provincial/territorial representatives that would also provide their perspective and expertise, including clinical expertise. The Task Group would engage non-governmental organizations, research communities and other stakeholders in the area of health care delivery. It would also coordinate with external expert organizations, such as the Association of Medical Microbiology and Infectious Disease (AMMI) Canada, to foster linkages between public health technical and response products and health care related products such as clinical care guidelines. The TAC would also establish task groups in this same fashion to help inform development of technical guidance and recommendations including those aimed at health professionals.

Health care delivery is further represented at a strategic level by SAC members who act as informal liaisons to the health care sector within their respective jurisdictions, and provide their unique jurisdictional views to SAC to ensure that the full continuum of the health sector is considered in response planning. Complementary to this, at the operational level, the health emergency management directors of provincial/territorial ministries of health may assume various roles within the governance structure and would act as liaisons to health care delivery within their jurisdiction as well.

Governance support

SAC Secretariat

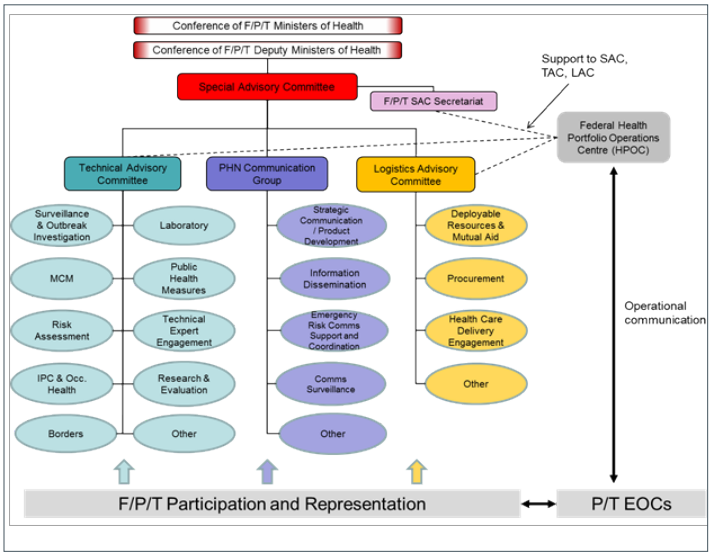
The SAC Secretariat supports the SAC and the response streams by assuming multiple coordination functions. It is responsible for rapid centralized analysis of issues and response needs, prioritization and distribution of tasks. Specifically the SAC Secretariat, with direction from SAC co-chairs, will identify what type of product/action is required, task this to the appropriate groups (TAC, LAC or Communications) within the governance structure and monitor progress.

Another key activity of the SAC Secretariat is to consider the integration of analysis and evidence across the response streams, including policy implications on decisions related to a public health event. An example of when this would occur is if SAC requested a single product that includes technical recommendations, logistical issues and a communication response—such as a vaccine response strategy. In order to support effective decision-making by SAC, there is a need to ensure that all evidence is considered in a holistic manner, informed by the co-chairs of the relevant response streams.

Health Portfolio Operations Centre

Figure 1 outlines the FPT governance structure and illustrates the operational communications between the federal Health Portfolio Operations Centre (HPOC) and provincial/territorial Emergency Operations Centres (EOCs). The HPOC serves as the Health Portfolio focal point for the coordination of response activities to significant public health events of national interest within the Health Portfolio's mandate, and acts as the point of contact for operational communications with other government departments and internationally. When the plan is activated, the HPOC provides support to the governance structure and participates in its groups as required.

Figure 1: FPT governance structure and its relation to FPT operation centres



Abbreviations: Comms, Communications; EOCs, Emergency Operations Centres; F/P/T, Federal provincial territorial; IPC&Occ Health, Infection Prevention Control and Occupational Health; LAC, Logistics Advisory Committee; MCM, Medical Counter-measures; PHN, Public Health Network; SAC, Special Advisory Committee; TAC, Technical Advisory Committee

Discussion

The *FPT Public Health Response Plan for Biological Events*, as all response plans, is an evergreen document. The need for revision will be guided by after action reviews following the response to a real or simulated event requiring implementation of the plan, in whole or in part. The revision of the plan may also include recommendations for the development of new event-specific Annexes as required, to further support implementation of the plan. Implementation will also be supported by training and exercises to familiarize various stakeholders with roles and responsibilities under the plan, and to identify areas for further improvement.

Conclusion

The *FPT Public Health Response Plan for Biological Events* is an important new tool that will help to support inter-jurisdictional collaboration, information-sharing and decision-making between and amongst various jurisdictions. It represents a continuing commitment on behalf of FPT governments to work collaboratively to ensure Canada is ready to respond to public health events and prepared to protect the health of Canadians.

Conflict of interest

None.

Acknowledgements

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Canadian Pandemic Influenza Preparedness: Health sector planning guidance

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Abstract

Pandemic preparedness requires a multifaceted approach with collaboration from all levels of government. The *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* (CPIP) is a guidance document that outlines key health sector preparedness activities designed to ensure Canada is ready to respond to the next influenza pandemic. This article outlines Canada's approach to pandemic influenza preparedness as described in the CPIP Main Body. Canada's pandemic influenza preparedness planning takes place within a network of legislated requirements and emergency frameworks at provincial/territorial, federal and international levels. The plan includes several guiding principles, including collaboration among governments and stakeholders, evidence-based decision-making, proportionality and flexibility in tailoring responses to the situation, the adoption of a precautionary approach, the use of established practices and systems and the explicit incorporation of ethical principles in all decisions and decision-making processes. The roles and responsibilities of the federal and provincial/territorial governments is identified and three planning tools are provided: planning assumptions rooted in evidence; multiple scenarios to support decision-making; and descriptive terms such as the start, peak and end of pandemic wave rather than phase terminology to provide triggers for action. Overall, the CPIP Main Body sets out a scalable, coordinated risk management approach to an influenza pandemic. This is an evergreen document that will be updated regularly.

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Introduction

Influenza pandemics are infrequent occurrences that emerge when a novel influenza A virus with sustained human-to-human transmission causes widespread human illness. Governments must make advance preparations to respond to an influenza pandemic, as it is impossible to predict when a pandemic may occur, or how severe it will be.

This article summarizes the main body of Canada's pandemic influenza planning approach, as set out in the *Canadian Pandemic Influenza Preparedness (CPIP): Planning Guidance for the Health Sector* (1). The CPIP provides guidance to the federal, provincial and territorial (FPT) jurisdictions that are responsible for preparing for and responding to an influenza pandemic, and is aimed primarily at FPT ministries of health and other ministries that have health responsibilities. It is not a pandemic response plan in itself.

Effective collaboration among all FPT governments is necessary in the planning and delivery of response activities. Accordingly, the CPIP describes how the FPT "jurisdictions will work together to ensure a coordinated and consistent health sector approach to pandemic preparedness and response" (1). The strategy and guidance described in the CPIP main body were approved by the Pan-Canadian Public Health Network (PHN) Council (2) and the Conference of FPT Deputy Ministers of Health, and it is anticipated that FPT planning will align with the strategic direction of the CPIP.

Since the CPIP is built as much as possible on existing health sector functions and structures, such as surveillance and control measures, it supports all-hazards response plans that apply to any type of public health emergency.

The updated plan

The CPIP provides planning guidance for the health sector for pan-Canadian influenza preparedness and response. It is intended to minimize illness and overall deaths, and to minimize societal disruption from an influenza pandemic.

New aspects of the CPIP include:

- guiding principles and approaches, such as the consideration of ethics and Canada's diversity,
- the adoption of a risk management approach, with updated planning assumptions, and
- planning tools to assist provinces/territories in developing their own plans.

Some elements in the updated CPIP reflect lessons that were learned in the 2009 H1N1 influenza pandemic (3). For example, due to the high demand for some response elements, such as surveillance activities and critical care medical equipment, it was recommended that surveillance systems and epidemiology capacity and links with primary care providers, be strengthened. As a result of the variation in timing and intensity of pandemic waves, greater scalability and adaptability of response measures have been incorporated, with a set of triggers for action that identify the pandemic conditions at which certain responses should be activated and deactivated.

The main body describes the background and rationale for pandemic influenza preparedness planning in general and for the approach taken in the Canadian context in particular. This broad strategic guidance is complemented by a set of technical annexes that provide more detailed guidance and advice specific to many of the key functional elements of pandemic preparedness and response, while also incorporating the broader strategic principles of the main body. Annexes for three key response functions, surveillance, laboratory services and vaccines, have recently been updated to reflect lessons learned from the 2009 H1N1 pandemic.

This article is the second in a series; providing an update on the different sections of the CPIP. Additional articles on the laboratory strategy and surveillance strategy annexes follow later in this issue of the CCDR (4,5). The first article in the series was a summary of the CPIP's *Vaccine Annex* (6).

Context for planning

Legislation and emergency frameworks

Canada's pandemic influenza preparedness planning takes place within a network of legislated requirements and emergency frameworks at provincial/territorial, federal and international levels. The federal government's preparedness plans for public health emergencies are part of the broader emergency management system that is managed by Public Safety Canada (7), and there is also a system of FPT health emergency plans. Canada also collaborates with several international partners to ensure regional preparedness for an influenza pandemic under agreements such as the Pandemic Influenza Preparedness Framework (World Health Assembly) (8) and the North American Plan for Animal and Pandemic Influenza (NAPAPI) (9) with Mexico and the United States.

Other planning considerations

The updated CPIP was prepared with consideration of the diversity of Canada, which reflects the geographic size and variability of the country, and the ethnic, language, religious, cultural and lifestyle diversity of the population. Examples of planning considerations include the presence of many small, remote and isolated communities across the country that are less well served by health and other services and the many individuals and groups who are more vulnerable to health emergencies; for example, those who are physically or mentally disabled, are low income or are homeless.

These factors are of particular relevance to pandemic preparedness and response, primarily through the need to support a response that is flexible to local conditions and to the needs of specific or vulnerable people. Ethical principles are explicit in the updated CPIP; guiding decisions that are based on the health and interests of a population rather than on clinical ethics that are based on the interests of individuals. This orientation implies a need to encourage a sense of solidarity within a community and reciprocity with those who may require greater support.

Guiding principles

The updated CPIP is underpinned by a set of guiding principles. These include collaboration among governments and stakeholders, evidence-based decision-making and proportionality and flexibility in tailoring responses to the situation. Three more general approaches are also applied: in the adoption of a precautionary or protective approach, particularly in the early stages when uncertainties are high; the use of established practices and systems, rather than attempting to adopt new approaches during an emergency; and the explicit incorporation of ethical principles in all decisions and decision-making processes.

Guidance for preparedness and response

Coordination of roles and responsibilities

Preparedness and response to an influenza pandemic require a whole-of-government approach to ensure the commitment of all necessary resources to minimize health, societal and economic impacts, and these contributions must be coordinated. The health sector pandemic preparedness activities that are described in the CPIP require the participation of international and FPT levels of government; furthermore, many operational functions are carried out by a range of professional disciplines within and beyond the health sector, such as health practitioners, international regulators, vaccine manufacturers and non-governmental organizations. The delineation of the responsibilities of the FPT governments for these functions, and the mechanisms for their collaboration, are major aspects of preparedness described in the CPIP.

Internationally, the World Health Organization (WHO) conducts global risk assessments, makes the declaration of a public health emergency of international concern, selects the pandemic vaccine strain and determines the switch from seasonal to pandemic vaccine production. Liaison with this and other international organizations in pandemic management is a federal government responsibility.

The coordination of a pan-Canadian response requires collective infrastructure and coordinated activities; for example, the federal government is responsible for the regulatory aspects of testing and approvals for influenza vaccines and antiviral medications, for negotiating with manufacturers and establishing contracts for the FPT purchase of influenza vaccines and antiviral medications, and for maintenance and mobilization of medical supplies in the National Emergency Strategic Stockpile (NESS) and by

facilitating the acquisition of additional supplies (10). The PTs are responsible for the purchasing, distribution and administration of vaccines and antiviral medications within their jurisdictions.

Risk management approach

The updated CPIP introduces a risk management approach to decision-making to manage the uncertainties that are inherent in preparedness planning for pandemic influenza. Risk management is a systematic approach to setting the best course of action in an uncertain environment by identifying, assessing, acting on and communicating risks. This approach is supported by the CPIP principles of evidence-based decision-making, proportionality and flexibility, and a precautionary/protective approach in uncertain conditions.

Tools for pandemic preparedness planning

Given the large number of variables that are involved in influenza pandemic planning, comprehensive risk management is challenging. The updated CPIP contains three broad planning tools: planning assumptions; pandemic planning scenarios; and planning phases and triggers for action.

Planning assumptions are hypothetical assumptions rooted in evidence, which serve as a guide to manage uncertainty and provide a useful framework for planning phases. As a pandemic unfolds, emerging evidence will replace the assumptions and be used to guide the response.

To help with risk identification, multiple scenarios have been defined to support planning and evidence-informed decision-making. Planning scenarios provide a starting point to think through implications and risks that would be associated with pandemics of varying population impacts, from low to high.

Descriptive terms for planning phases, such as the start, peak and end of a pandemic wave, are defined in the CPIP. Previously, the WHO's phase terminology (interpandemic, alert, pandemic, transition) was used to describe pandemic activity in the country or in a jurisdiction within Canada. Triggers for action provide guidance for initiation of FPT activities and for their modification and cessation. Pandemic response should be appropriate to the local situation to ensure PT, or regional/local level response is appropriate to the situation.

Assessment and evaluation

Preparing for and responding to a pandemic is a complex process that requires the coordinated efforts of all levels of government in collaboration with stakeholders. To ensure pandemic plans (or all-hazards plans, according to the jurisdiction) are comprehensive and effective, jurisdictions should assess their level of preparedness, test their plans regularly, and evaluate their pandemic response.

Discussion

The updated CPIP responds to several challenges that are inherent in planning influenza pandemic preparedness and response in Canada, which include not only the uncertainties that are inherent in influenza pandemics but also the scale, diversity and jurisdictional divisions in Canada.

The CPIP addresses the uncertainties of pandemic influenza, through a risk management approach that is scalable to different pandemic impact levels (low, moderate and high) and to changing impacts throughout the progress of a pandemic. This approach also provides the flexibility that is needed for decision makers to tailor a response to the needs and capacities of different regions in Canada, adjusting to regional variations in timing and intensity of pandemic impact, as well as to diverse communities and populations.

While flexibility is needed to allow different jurisdictions to tailor their plans and pandemic response activities to regional needs and conditions, shared objectives and a consistent approach are also needed to enable the jurisdictions to collaborate on delivering response activities. To provide consistency in the approach to pandemic planning among FPT jurisdictions and to aid in collaboration among response partners, the CPIP articulates a set of principles and a consideration of ethics and of the diverse and vulnerable populations in Canada with which pandemic plans must align. More operationally, collaboration among jurisdictions and between jurisdictional levels is critical to the effective response to a pandemic. The CPIP provide a delineation of roles and responsibilities for preparedness and response activities nationally, and define a process for interaction and communication between and among jurisdictions. These collaborative roles, structures and processes form a major part of pandemic preparedness in Canada.

The broad principles and considerations, risk management approach and structures and processes for collaboration that are set out in the CPIP are carried through into the more detailed guidance that has been developed for the response components.

Conclusion

The CPIP is an evergreen document that will be updated regularly with new information, legislative changes/agreements or best practices as required. A more comprehensive and fulsome review of the CPIP and its technical annexes will occur every five years to ensure the document is up-to-date and meeting the needs of FPT governments, health professionals and stakeholders. The Main Body will undergo its next full review in 2019.

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Canada's Pandemic Influenza Preparedness: Laboratory strategy

B Henry[1,2] on behalf of the Canadian Pandemic Influenza Preparedness (CPIP) Task Group*

Abstract

The *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* (CPIP) is a guidance document that outlines key health sector preparedness activities designed to ensure Canada is ready to respond to the next influenza pandemic. This article outlines Canada's pandemic influenza laboratory strategy as described in the CPIP *Laboratory Annex*. Laboratory identification and characterization of an influenza pandemic virus is critical to detect the pandemic, develop a vaccine, detect antiviral resistance and inform surveillance functions such as monitoring the geographic spread of the disease. Key elements of the laboratory response will include ensuring there are adequate resources for all activities. Pre-analytical activities include the appropriate collection, transport to the laboratory, triaging and preparation of specimens. Analytical activities refer to the different testing methods for the detection of influenza, including maintaining the ability to culture influenza virus for genetic and antigenic characterization. Post-analytic activities include ensuring front-line and provincial public health laboratories work together to make data and specimens available for surveillance purposes. In the inter-pandemic period, it is important to develop the infrastructure, protocols and processes to enable rapid-response research during a pandemic. This is an evergreen document that will be updated regularly.

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Introduction

The ability to detect an influenza pandemic, as well as the development of a vaccine to protect the population and reduce pandemic spread, and to detect antiviral resistance which would limit the effectiveness of Canada's antiviral stockpile, depend on the identification and characterization of the novel virus that is involved. Laboratories perform this role through tests designed to distinguish a novel influenza strain from seasonal influenza and other respiratory viruses. These laboratory data are used to inform surveillance functions such as monitoring the geographic spread of disease and the impact of interventions.

Canada's pandemic influenza laboratory strategy is described in the Laboratory Annex (1) to Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (CPIP) (2). It is informed by laboratory experience gained during the 2009 H1N1 pandemic, which made clear the importance of effective communication and coordination among all laboratory tiers and their counterparts throughout the duration of the pandemic response. This technical guidance document describes a scalable approach to the delivery of laboratory services in a pandemic, with triggers for action and other tools providing the flexibility needed to tailor laboratory activities to increased and variable demands for testing. It is directed toward clinical laboratory professionals in Canadian national, provincial and hospital laboratories, and to clinicians, epidemiologists and other stakeholders whose responsibilities intersect with those of these laboratories as well as interested others. This article summarizes the recently updated Laboratory Annex (1) of the CPIP. Summaries of the health sector planning guidance and surveillance strategy are also included in this issue of the *Canada Communicable Disease Report* (CCDR) (3,4).

Canada's pandemic influenza laboratory strategy

Objectives

Laboratory testing for the influenza virus in a pandemic has two broad purposes: population-based surveillance and diagnostic testing. Population-based surveillance involves detection and identification of the novel virus and differentiation from common strains, and includes determination of antiviral susceptibility and strain characterization that can be used to identify potential vaccine mismatch. Although diagnostic testing of patients with influenza-like illness (ILI) may not be indicated for the clinical management of people with uncomplicated ILI, testing will have a role in community-based surveillance of outbreaks, as well as timely diagnosis of hospitalized and high-risk patients to inform treatment and management of exposed contacts.

Canadian context

Laboratories accredited to perform the analytical activities required in a pandemic are maintained by federal and provincial jurisdictions—these include the federal National Microbiology Laboratory (NML), provincial public health laboratories (PPHLs) and front-line hospital laboratories. Collaboration, supported by a clear designation of roles and appropriate structures and processes, is necessary among laboratories in all jurisdictions to enable the rapid determination and delivery of public health response measures during a pandemic.

The Public Health Agency of Canada (PHAC), through the NML, is responsible for coordinating national laboratory surveillance and for reporting laboratory results internationally to the World Health Organization (WHO) and its partners. The NML plays a significant role in supporting PPHLs through specific laboratory functions such as genetic and antigenic characterization of seasonal and novel influenza strains and phenotypic antiviral susceptibility testing, as well as providing information and support to PPHLs to develop and validate diagnostic assays for new strains for decentralized use. PPHLs carry out primary detection assays and are responsible for having the capability to detect the emergence of a potential novel subtype. They provide a supportive role to front line laboratories and submit viral samples, patient specimens and limited epidemiological information to the NML through established surveillance systems. Front-line laboratories' responsibilities during a pandemic include testing to identify influenza in patient specimens and submitting diagnostic specimens to the PPHL for further characterization.

Collaboration will be required to respond to uneven demand and capacity for testing in different regions of the country. Due to Canada's size and geographic population distribution, it is likely that a pandemic will affect different regions at different times and with varying severity, so that laboratories in more affected regions will experience a greater demand for testing. Testing is also more challenging in remote and isolated communities and requires collaboration between jurisdictions; for example, laboratories in British Columbia and Alberta carry out testing for the Territories, requiring logistical preparation for sample collection and transportation.

Key elements of the laboratory response

Pre-analytical activities

Pre-analytical activities are those that must be followed to ensure appropriate collection of specimens and their transport to the laboratory for testing. Different types of specimens and collection methods are often used to optimize the detection of influenza in patients with more severe disease. Transportation conditions and timing are important considerations for maintaining specimen integrity.

During the 2009 influenza pandemic, many laboratories underestimated the pre-analytic pressures associated with an increase in testing demand. Strategies are required to ensure adequate resources will be available to address this demand, such as increasing resources for accessioning specimens received by the laboratory (e.g., receiving, sorting, logging into the laboratory information system, labelling and processing). There should be a process in place in advance for triaging specimens during periods of high demand. Laboratories should also develop a process for aliquoting (dividing or apportioning) of specimens to allow for retesting a sample or submitting a sample to the NML as needed.

Analytical activities

There are several different testing methods available for the detection of influenza, each with specific time for results, sensitivities, ability to characterize subtypes, throughput and cost. The most widely recommended tests for detecting and characterizing influenza are nucleic acid amplification tests (NAAT), because of their performance, automation and scalability. Direct immunefluorescence assays (DFA) and indirect immune-fluorescence assays (IFA) methods can be used for detecting influenza A, but are not sufficient for subtyping and are less sensitive than NAAT methods. Although rapid influenza detection tests (RIDT), which are based on antigen detection, can provide results within 30 minutes, they cannot subtype and their poor sensitivity limits their usefulness in the management of individual patients; however, RIDT may be useful for monitoring outbreaks, or as an option for timely detection of influenza in remote communities. If antigen-based RIDT are used, the test limitations must be clearly understood by the end user. More rapid NAAT are becoming available; however, their performance in detecting novel viruses and their influence on patient outcomes requires further study. Serology tests are labour-intensive and not used routinely for diagnosis, but have been useful for epidemiologic and immunologic research.

Maintaining the ability to culture influenza virus is important as viral isolates are required for genetic and antigenic characterization, for monitoring of antigenic drift and for phenotypic antiviral resistance (AVR) testing; however, it is expected that novel influenza viruses will be risk group 3 pathogens that will restrict this activity to PPHLs with the appropriate containment level 3 laboratory licence. Ongoing genetic and antigenic characterization and antiviral resistance testing are an important part of routine surveillance. In addition, phenotypic and genotypic testing for antiviral resistance is also done through targeted testing of specimens from patients who are suspected of having a resistant virus. AVR testing informs guidelines for the use of antivirals, and can be an important adjunct in the clinical management of individual patients.

During an influenza pandemic, other respiratory viruses (such as parainfluenza or rhinovirus) can circulate in the population and cause significant illness. To ensure that morbidity and mortality are correctly attributed to the pandemic influenza, it is important to maintain some testing for other respiratory viruses even as resources become more limited.

Post-analytical activities

It is important to ensure front-line laboratories and PPHLs work together to make data and specimens available for surveillance purposes. If elevated testing demands require changes in laboratory testing methods, these changes need to be communicated to clinicians and other users of laboratory data, and their impact on surveillance or patient care made clear. A communication strategy should be developed during

seasonal influenza, to ensure that a process and infrastructure are in place to develop and disseminate messages in a pandemic. Laboratories also need to plan for archiving, storing and removing the large number of specimens that will be processed during a pandemic.

Quality assurance and quality control

Participation in influenza proficiency programs is essential for all laboratories performing influenza diagnostic work, and quality control activities should continue as a pandemic evolves. The NML provides proficiency panels assessing the performance of tests at PPHLs and other laboratories, and also transfers sequence information on influenza viruses to the PPHLs to ensure that the tests used to identify the novel subtype are effective. If, as occurred in the 2009 pandemic, a novel virus requires new testing protocols, PPHLs and the NML will work together to validate the accuracy of new methods or of commercially available assays.

Biosafety considerations

Laboratories need to observe biosafety protocols to prevent exposure to a novel virus in the laboratory when samples are tested. The Centre for Biosecurity at PHAC will provide guidance on the way that specimens of a novel virus should be handled; guidance will be updated as further knowledge is gained about the virus (5).

Integration of laboratory functions with other CPIP components

Laboratories and public health decision makers should work together in the interpandemic period to ensure an awareness and understanding of laboratory functions, including the unique requirements associated with influenza detection in a pandemic, and the important role of the laboratory in the response to a pandemic. In addition, data sharing between laboratories and between Provinces/Territories and PHAC during a pandemic is critical. Data-sharing agreements should be in place before a pandemic to facilitate data transfer and must include intellectual property, copyright and other publication issues.

There are several key linkages and interrelationships with laboratory activities that contribute to an effective and coordinated pandemic response. To ensure the comparability and correct interpretation of data, epidemiologists must understand the details of laboratory testing (e.g., testing algorithms, sensitivity and specificity of the tests used); just as laboratories need to understand which data the epidemiologists need for risk assessments and analysis of pandemic progression. The use of existing surveillance infrastructure for seasonal influenza and other respiratory viruses and the development of data sharing agreements during the interpandemic period provide optimized surveillance capacity in a pandemic (6). Laboratories should communicate changes made to laboratory testing practices, including changes in collection requirements and test performance to clinicians and other end users so that clinicians understand how changes may influence and limit patient management. Community planners must collaborate with laboratory experts and Provinces/Territories to develop new ways of providing testing in First Nations' or other remote and isolated communities and of communicating information among partners. Geographic location and weather conditions may be important considerations in planning the transport of specimens to a laboratory, as these specimens are both time- and temperature-sensitive. Finally, laboratories should put in place the necessary processes to communicate with vendors to rapidly access supplies of commercial assays and reagents to support the laboratory response.

Research needs

In the inter-pandemic period, it is important to develop the infrastructure, protocols and processes to enable rapid-response research during a pandemic to help address knowledge gaps about influenza prevention, treatment and control strategies. In light of their role in supporting such research, laboratories should be involved in this advanced planning. Laboratories should also undertake advanced planning for the infrastructure they would require to support such research. Preparation for research should be encouraged through rapidly-conducted influenza studies during interpandemic influenza seasons.

Discussion

The CPIP laboratory strategy uses testing algorithms and collaborative and data-sharing arrangements that form the seasonal influenza testing and surveillance system, and has been updated to incorporate lessons learned in the 2009 H1N1 pandemic. Challenges remain, however, and are noted as suggestions for improvements in preparedness that laboratories in all jurisdictions should consider during the interpandemic periods.

A primary challenge is the anticipated increase in demand for testing in a pandemic—which could be more than ten-fold over peak seasonal demand. Plans should be developed in the interpandemic period to manage this demand and include those relating to operational functions such as policies for hiring and training staff to meet increased demand, consideration of the processing of high volumes of specimens and plans to meet demands for laboratory supplies. Front-line laboratories should use this period to strengthen their diagnostic capacity, while Provinces/Territories should utilize the criteria established by PPHLs to prioritize testing, so that reporting at the national level is consistent.

Communication strategies could also be strengthened during the interpandemic period, to enable more timely exchange of data, particularly with respect to greater coordination between PPHLs and front-line laboratories in the communication of surveillance data. Linkages within the Canadian Public Health Laboratory network (CPHLN) (7) and similar groups, as well as support for ongoing meetings, should be maintained throughout the interpandemic periods to facilitate the CPHLN's ongoing effectiveness in coordinating the national response to testing, as it did during the 2009 pandemic (8).

The CPHLN continues to monitor developments in laboratory contributions to pandemic influenza preparedness and response. The CPHLN, in consultation with the Pandemic Influenza Laboratory Preparedness Network (PILPN), review laboratory

protocols to ensure Canadian laboratories are able to detect a new influenza virus if it appears in the country. CPHLN also oversees reviews of the *CPIP Laboratory Annex* and incorporates any new developments that arise.

Conclusion

Laboratory testing is a critical function in a response to an influenza pandemic, contributing to both epidemiological surveillance work and to clinical support of affected individuals. It benefits from the systems and structures that are used and refined each year with seasonal influenza and other respiratory viruses, but will need to anticipate and scale activities to meet the needs of a pandemic.

Authors' statement

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Canada's Pandemic Influenza Preparedness: Surveillance strategy

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Abstract

The *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* (CPIP) is a guidance document that outlines key health sector preparedness activities designed to ensure Canada is ready to respond to the next influenza pandemic. This article outlines Canada's pandemic influenza surveillance strategy as described in the CPIP *Surveillance Annex*. The strategy builds on the surveillance activities used for seasonal influenza and incorporates lessons learned from the 2009 H1N1 pandemic, including improved information sharing, improved electronic links among Federal/Provinical/Territorial (FPT) partners and improved surveillance for Indigenous communities. Key elements of the surveillance strategy include early detection and investigation of a novel influenza virus through the reporting of cases or clusters of severe acute respiratory infections and laboratory detections of novel influenza viruses. Community-based surveillance will provide information on clinical severity, age groups affected and risk factors associated with severe disease. Severe outcome surveillance will capture data on hospitalizations and deaths. Laboratory surveillance will include weekly reports of respiratory virus detections. The response activities are adaptable to the demands of different levels of pandemic activity and impact, supported by a set of triggers for the activation and deactivation. Surveillance will be linked with other response components, such as communications, research, assessment and evaluation. This is an evergreen document that will be updated regularly.

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Introduction

Public health surveillance, the systematic collection and analysis of health data needed for planning, implementing and evaluating public health measures, is a key function in an influenza pandemic (1). Timely surveillance data provide information on the impact of the novel virus and the spread of the pandemic through different regions and populations, informing decisions on pandemic control elements such as the use of vaccines and other interventions.

Canada's pandemic surveillance strategy, described in the *Surveillance Annex* (2) to the broader *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* (CPIP) (3), provides technical advice and operational guidance for federal, provincial and territorial (FPT) ministries of health and other participants in surveillance activities, such as health professionals and laboratories. It describes surveillance activities that are carried out collaboratively by all FPT jurisdictions, coordinated at the national level by the Public Health Agency of Canada (PHAC). The response activities are adaptable to the demands of different levels of pandemic activity and impact, supported by a set of triggers for the activation and deactivation of specific surveillance activities at different stages of a pandemic.

The surveillance strategy incorporates a number of lessons learned about the surveillance function in the 2009 H1N1 influenza pandemic. These lessons include improved information sharing among federal and provincial and territorial (PT) partners, a more integrated national surveillance system with improved electronic links among partners and improved surveillance systems for First Nations, Métis and Inuit communities. This article summarizes the recently updated *Surveillance Annex* of the CPIP (2).

Objectives

In support of the broader CPIP goals of minimizing serious illness and overall deaths and societal disruption, the objectives of the surveillance strategy are to provide timely and high-quality information to:

- Determine when and where influenza activity is occurring and who is being affected
- Determine and monitor underlying risk conditions associated with severe disease
- Describe clinical patterns of disease
- Assess and monitor the relative impact of the pandemic
- Detect changes in the antigenic and genetic character of the pandemic virus and its susceptibility to antiviral medications
- Support the implementation of interventions and the evaluation of their impact.

Canadian context

Pandemic surveillance involves both epidemiologic and laboratory components and is built on the FPT surveillance systems that are already in place for seasonal influenza, taking advantage of existing and practised processes and linkages among jurisdictional and international public health entities. Seasonal surveillance systems include FluWatch, Canada's national influenza surveillance system, as well as the Immunization Monitoring Program ACTive (IMPACT), the Serious Outcomes Surveillance (SOS) Network and the Sentinel Practitioners Surveillance Network (SPSN). However, as seasonal surveillance systems do not provide data on the full spectrum of disease, pandemic surveillance can be augmented by special studies that focus on certain geographic regions, communities, or vulnerable groups within the population to obtain data on symptomatic individuals who do not seek health care and asymptomatically infected persons.

There are a number of uncertainties and variabilities associated with pandemic influenza that require specific surveillance capabilities and activities. As the timing and specific characteristics of a pandemic are not known in advance, pandemic surveillance must be scalable to different levels of impacts, and adaptable to changing conditions. Flexibility and adaptability are also necessary to respond appropriately to the variable conditions in different regions of Canada; due to Canada's size and the fact that pandemic conditions (e.g., intensity, timing and strain dominance) can differ by region. The geographic and sociocultural diversity in Canada's populations also requires flexibility to tailor surveillance activities to the needs and capacities of different regions and populations. Finally, surveillance activities during a pandemic must take into account ethical considerations, such as data confidentiality, to guard against unintentional stigmatization, and legal considerations, such as data-sharing agreements, to facilitate reporting requirements.

Key elements in the surveillance strategy

Early detection and investigation

Early detection and investigation of a novel influenza virus may occur through detection of signal events, such as cases or clusters of severe acute respiratory infections (SARI) and laboratory detections of novel influenza viruses; therefore, participation of hospitals in SARI surveillance is important for detecting novel viruses. When a novel virus is confirmed by laboratory testing and virus subtyping, local public health authorities will conduct case and contact investigations, with FPT support as required. In turn, PTs should report cases to PHAC within 24 hours to enable reporting to the World Health Organization (WHO) as required by the *International Health Regulations* (4).

Community-based surveillance

Community-based pandemic surveillance provides information on the occurrence of influenza illness, including data on clinical severity, age groups affected and risk factors associated with severe disease. This surveillance also provides data on the progress of the pandemic, enabling local authorities to plan response needs. Community-based surveillance is based on the seasonal FluWatch surveillance system, consisting of regular PT reporting of influenza activity levels and outbreaks of influenza-like-illnesses (ILI) to monitor geographic spread and trends over time, as well as syndromic surveillance, such as patient consultations for ILI, calls to PT telehealth systems and data on antiviral prescriptions and sales of over-the-counter medications relevant to influenza and ILI.

Severe outcomes surveillance

Severe outcomes surveillance (SOS), which captures data on severe outcomes, such as hospitalizations, intensive care unit admissions and deaths forms, is an important component of pandemic influenza surveillance. Data from SOS helps quantify the impact upon the health care system, identify high-risk conditions for prioritization of vaccines and antiviral recommendations, assess the effectiveness of the vaccine, and determine the need for additional public health measures. Seasonal SOS is provided through reports of hospitalizations and deaths from some PTs, as well as from IMPACT, a pediatric hospital-based surveillance network, and the SOS Network, a sentinel influenza network of hospitals that reports detailed case-based information on adult hospitalizations and deaths.

Laboratory surveillance

Laboratory surveillance includes routine weekly reports of respiratory virus detections, including the number of positive tests for influenza by type and subtype. These data are reported to FluWatch through the sentinel-laboratory-based Respiratory Virus Detection Surveillance System (RVDSS) (5) and also to the Global Influenza Surveillance and Response System through the WHO's FluNet (6). Public Health Laboratories (PHLs) also follow a protocol to submit a proportion of virus samples and patient specimens, which the National Microbiology Laboratory (NML) tests for strain characterization and antiviral resistance, to inform the ongoing immunization program or antiviral strategy during a pandemic. Guidance on the conduct of these laboratory functions by federal, provincial and front-line laboratories is provided in the *Laboratory Annex* (7) and is also summarized elsewhere in this issue of the *Canada Communicable Disease Report* (CCDR) (8).

Special studies

Routine seasonal influenza surveillance may not provide all the information that authorities need in a pandemic to understand the novel virus and determine the most appropriate interventions. Special studies may be required to gather information on community transmission and rates of infection and illness among specific populations. Planning for these studies needs to be in place in advance to enable rapid implementation in a pandemic. The Public Health Agency of Canada (PHAC) is a participant in the Consortium for Standardization of Influenza Seroepidemiology (CONSISE), an international initiative to develop a standardized approach to influenza studies and comprehensive influenza investigation protocols for pandemic studies (9).

Modelling

Mathematical modelling, coordinated by PHAC in partnership with academics and public health agencies, can help support pandemic decision-making by helping predict the anticipated impact of a pandemic, the interventions that might be effective, and whether subsequent waves of disease may occur.

There are challenges in the use of surveillance data for modelling, including data quality and national representativeness. These challenges should be addressed during the interpandemic period by strengthening linkages between public health and modellers, developing data-sharing protocols, and establishing data standards and reporting requirements for modelling.

Data collection, reporting and analysis

Data collection and reporting rely on information generated by a number of sources. The PHAC receives and analyzes surveillance data collected by the PTs and from the NML, and reports key information back to PTs and internationally to the WHO. All epidemiological and clinical data need to be analyzed in a timely manner to assess the characteristics and impact of the pandemic. To enable these analyses during a pandemic, key epidemiological and clinical parameters should be characterized in advance.

The 2009 H1N1 pandemic identified the need to improve the consistency of information captured in national influenza surveillance, as well as the need for formal FPT data-sharing agreements, electronic linkages to facilitate timely transfer of surveillance data, and sufficient human resources for data analysis and interpretation. There are ongoing FPT efforts to strengthen national influenza surveillance to address these issues.

Integration with other response components

Many surveillance activities are conducted in interaction with other components of the influenza response. These other components include the laboratory response, which is described in the *Laboratory Annex* (7) and in the summary of the laboratory strategy in this issue of CCDR (8).

Recommendations on the use of vaccines and on vaccine prioritization require epidemiological information and analysis of risk factors for severe disease. These activities and others, including monitoring of influenza strain and vaccine effectiveness, are detailed in the *Vaccine Annex* (10,11). Surveillance data also support decisions on other interventions, such as the use of antivirals, and decisions on public health measures are based on epidemiological characteristics, while clinical care is influenced by information produced by early assessments of the impact of the pandemic.

Wild birds are the natural reservoir for the influenza virus. As such, surveillance on wildlife, poultry and other livestock is important to better understand influenza virus evolution and to assess pandemic threats. Formal linkages between public health and animal health authorities at the federal and PT levels are needed to strengthen surveillance activities and information sharing.

Another critical component of pandemic influenza response that relies on information provided by surveillance activities is communication with the public and with health care providers. A risk communication plan should be developed, on the basis of information produced by risk assessments; detailed guidance on this activity is provided in the *Communications Annex* (12).

Research

Prior to a pandemic, it is important to develop data standards and minimum data reporting requirements to facilitate the generation of consistent, high-quality data for epidemiological and modelling research conducted during a pandemic. In addition, it is important to undertake pre-planning activities, such as developing detailed protocols with pre-approval by the appropriate regulatory and research ethics boards to allow quick implementation of research projects during a pandemic.

Assessment and evaluation

Routine seasonal influenza surveillance offers an opportunity for practice and for piloting and evaluating new surveillance strategies. In addition, after a pandemic, surveillance programs should be evaluated in each jurisdiction and comparisons made to identify lessons learned and best practices.

Discussion

A major principle underpinning the surveillance strategy is the value of using existing Canadian structures and networks in place for seasonal influenza as the basis for pandemic surveillance activities. Improvements in the surveillance system are still needed, however, including consistency of information capture, FPT data-sharing agreements, and electronic links for transferring data. As much of this work as possible should be done in advance. Work to standardize data collection and improve data transfer should be conducted in the interpandemic period, and where possible integrated into the seasonal influenza surveillance system, which will enhance pandemic surveillance capabilities. Consistency in reporting can be improved through the development of standard reporting templates and timelines to be used by PTs and PHAC; these will be enabled by improvements in infrastructure such as electronic databases, immunization registries in all jurisdictions, and secure electronic or web-based reporting mechanisms.

Seasonal influenza surveillance is conducted every year and provides an opportunity for an evaluation of existing strategies and arrangements, and to trial new activities. Periodic outbreaks are additional opportunities for the testing of coordinated and rapid response, including rapid deployment and reporting of research studies. Guidelines and indicators for evaluating surveillance systems have been produced by the WHO (13) and the US Centers for Disease Control and Prevention (CDC) (14) and are available for use to assist with this activity.

Conclusion

The surveillance strategy guides FPT governments in developing their plans and ensuring their capacity to fulfill their roles and collaborate effectively with other jurisdictions in an influenza pandemic. As with other components of the CPIP, it is an evergreen strategy, and the state of preparedness of the surveillance system is subject to ongoing evaluation, with improvements and updates incorporated as appropriate.

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Travel-related Zika virus cases in Canada: October 2015–June 2017

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Abstract

Background: Zika virus (ZIKV) is an emerging mosquito-borne disease that can cause severe birth defects if contracted congenitally. Since late 2015, there has been a large increase in the number of travel-related cases of Zika virus infection in Canada.

Objective: The objective of this study was to describe the epidemiology of travel-related Zika cases in Canada from October 2015 to June 2017 and review them in the context of the international outbreak in the Americas.

Methods: Zika virus infections were confirmed by polymerase chain reaction (PCR) detection of viral RNA and/or the serological identification of ZIKV-specific antibodies in serum. Cases of ZIKV infection were identified by provincial and territorial health authorities, and reported on a regular basis to the Public Health Agency of Canada (PHAC). Case information requested included date of illness onset, age category, sex, pregnancy status, and location(s) and dates of travel. Estimates for the monthly number of Canadians travelling outside of Canada to other countries in the Americas were obtained from Statistics Canada and the International Air Transport Association (IATA). Data to produce the epidemic curves of autochthonous cases for each region of the Americas were extracted from country-specific epidemic curves on the Pan American Health Organization website.

Results: As of June 7, 2017, 513 laboratory confirmed cases and two Zika-related birth/fetal anomalies were reported across all 10 provinces. Illness in Canadian travellers generally coincided with outbreak intensity in the country of exposure rather than travel volume. There has been no evidence of autochthonous (local) transmission in Canada. Currently, cases are on the decline both in Canada and internationally.

Conclusion: The surge in Canadian ZIKV infections in 2016 was directly related to the incursion and spread of ZIKV into the Americas. Although cases are now on the decline worldwide, it remains to be seen whether a resurgence of cases in previously affected or new areas will occur. Both outbreak intensity and seasonality of ZIKV transmission should be monitored over time in order to inform the timing of public health education campaigns, as some may turn out to be more effective in the off-peak travel season when the risk of disease transmission may be higher. Ongoing education and awareness among travellers, particularly for pregnant women and those planning pregnancies, is still indicated.

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Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus primarily transmitted to humans by Aedes species mosquitoes. First identified in 1947 in the Zika forest of Uganda (1,2), ZIKV was largely confined for over fifty years to a relatively narrow equatorial belt running from Asia to Africa (3). In 2007, the first major outbreak of ZIKV was reported on the island of Yap (Micronesia) (4), followed by several outbreaks on islands and archipelagos in the Pacific region, including a large outbreak in French Polynesia in 2013 (5,6). Zika virus was first reported in Brazil in 2015 and has since emerged across Central and South America, the Caribbean and Mexico. Concurrent with this outbreak was an alarming increase in cases of babies with microcephaly and other neurological disorders born to ZIKV-infected mothers. As a result, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on February 1, 2016, requesting international response and collaboration (7).

Zika virus is predominately spread through the bite of an infected mosquito; however, it can also spread via vertical intrauterine, and sexual and blood-borne transmission routes

(8-14). Only an estimated 20% of those infected with ZIKV will develop symptoms (4). If symptoms do occur, they typically develop within three to seven days (maximum 14 days) following infection and include low-grade fever, arthritis/arthralgia, maculo-papular rash, conjunctivitis, myalgia and other non-specific flu-like symptoms (4,15). Infection may go unrecognized or be misdiagnosed as dengue, chikungunya or other viral infections causing fever and rash. Rarely, neurologic complications such as Guillain-Barré syndrome have been reported (16).

Of greatest concern is the serious effects ZIKV infection can have on a developing fetus, resulting in a spectrum of congenital anomalies known as congenital Zika syndrome (CZS). Brain abnormalities and microcephaly are commonly reported (17,18) but CZS is also known to include arthrogryposis (reduced mobility of multiple joints due to contractures), dysphagia (difficulty swallowing), auditory deficits, visual impairment and other anomalies (19). Reports from the United States Zika Pregnancy Registry found that an estimated 5% (95% confidence interval [CI] = 4%–7%) of completed pregnancies with laboratory evidence of possible recent ZIKV infection (i.e., recent flavivirus exposure) had a fetus or infant with evidence of CZS. The proportion increased to 10% (95% CI = 7%–14) when restricted to pregnancies with laboratory-confirmed ZIKV infection and 15% (95% CI = 8%–26%) of fetuses/infants of completed pregnancies with confirmed ZIKV infection in the first trimester (17). Both symptomatic and asymptomatic infections during pregnancy seem to result in similar percentages of birth defects (17,18).

Prior to 2015, only one laboratory-confirmed case of ZIKV infection had ever been reported in Canada—in a traveller returning from Thailand (20). In December 2015, Canada reported its first travel-associated case linked to the outbreak in the Americas (21). To date, no local transmission has been reported, as the primary mosquito vectors—*Aedes aegypti* and *Aedes albopictus*—are not established here. Although local transmission via mosquitoes in Canada is unlikely, Canadians make an estimated 7.3 million visits to the Caribbean, Central and South America and Mexico annually and also travel in significant numbers to the Asia-Pacific and African regions where ZIKV continues to circulate (22). As of June 29, 2017, there were 56 countries or areas reporting new introduction or re-introduction of ZIKV since 2015 and an additional 20 that reported ZIKV prior to 2015 with ongoing transmission (23). A number of countries are reporting a downward trend in cases; however, there are still some countries experiencing increases (24). The persistence and recirculation of ZIKV as immunity builds and wanes in affected populations, along with seasonal changes in vector activity, is largely unknown and is of ongoing concern (25). The Government of Canada has responded to the spread of ZIKV by issuing a travel health notice with recommendations for pregnant women and those planning a pregnancy to avoid travel to countries with ongoing ZIKV outbreaks (26). In addition, *Canadian Recommendations on Prevention and Treatment of Zika virus* were developed by Canada's Committee to Advise on Tropical Medicine and Travel (CATMAT) to inform Canadian health care practitioners on the health risks related to ZIKV and recommendations on how to mitigate these risks (27).

Following the declaration of a PHEIC by the WHO, Canadian federal, provincial and territorial partners agreed to national reporting of ZIKV cases on a temporary basis to:

- Fulfill International Health Regulation (IHR) reporting requests
- Maintain situational awareness of the context in Canada, including the assessment of where Canadians are being infected and the likely mode of transmission
- Assess and inform the level of risk to the Canadian public where possible
- Contribute to the international body of knowledge on ZIKV

This article describes the epidemiology of travel-related ZIKV cases in Canada from October 2015 to June 2017 and reviews them in the context of the international outbreak in the Americas.

Methods

Laboratory diagnosis

Confirmation of ZIKV infections is primarily carried out by two testing methodologies: polymerase chain reaction (PCR) detection of viral RNA in serum and/or urine samples and the serological identification of ZIKV specific antibodies in serum (27-29). Acute samples of serum and urine (collected within two weeks of symptom onset) are the most appropriate specimens for PCR testing since viremia is quite transient and the virus is usually present for only a brief period of time in these samples. Enzyme-linked immunosorbent assay (ELISA) is the primary serological screening test to identify possible exposures or cases of infection through the detection of viral IgM and IgG antibodies. However, due to cross reactivity with other related viruses, such as dengue, a plaque reduction neutralization assay must also be performed to identify ZIKV-specific antibodies in samples that are positive by ELISA procedures. Antibodies to ZIKV usually develop within three to four weeks after exposure and can be detected for several months (IgM) or years (neutralizing IgG). In certain cases, individuals may have been previously exposed to other flaviviruses through mosquito bites or vaccination (e.g., yellow fever, Japanese encephalitis virus vaccines), which can lead to further complications when interpreting serological results. Significant serum neutralization titres to both dengue and ZIKV may be identified in samples from certain individuals (e.g., secondary flavivirus infections), which result in the documentation of these cases as "flavivirus exposures" with no definitive identification of the infecting virus.

Initially, all laboratory testing was conducted at the National Microbiology Laboratory (NML); however, public health laboratories in British Columbia, Alberta, Ontario and Quebec have adopted PCR testing in their respective jurisdictions. Testing efforts focus primarily on pregnant women and symptomatic travellers. Serological testing is currently performed at the NML; however, sensitive commercial IgM and IgG ELISAs are now available and will allow for some provincial laboratories to include screening assays as part of their diagnostic capability.

Epidemiology

A case was defined as a resident of Canada with laboratory confirmation of ZIKV infection by one or more of the following, with or without clinical evidence: 1) isolation of virus from, or detection of specific viral antigen or nucleic acid from an

appropriate clinical specimen; or 2) viral IgM antibodies against ZIKV in an appropriate clinical specimen and the identification of confirmatory virus-specific neutralizing antibodies in the same or a later specimen, or a demonstrated seroconversion or diagnostic rise (four-fold or greater change) in virus-specific neutralizing antibody titers in paired sera.

Cases of ZIKV infection were identified by provincial and territorial health authorities, and reported on a regular basis to the Public Health Agency of Canada (PHAC). Case information requested included date of illness onset, age category, sex, pregnancy status and location(s) and dates of travel.

The date of exposure for cases was estimated using the return travel date or onset of illness less seven days if return date was not available. Cases that travelled to multiple countries or those with neither dates available were not assigned an exposure date. Status of the outbreak in the country of travel was determined for each case by the epidemic curve for the country at the time of their exposure. The "outbreak period" or time period of "high activity" for each country was designated as the time from when cases first increased substantially (often tripled or more) from the initial number of reported cases, to the time when the number of cases returned to a level similar to the initial reported case numbers. The time before the first outbreak period was designated as "low activity" or "early in the outbreak". All other time periods, whether in between outbreak waves, or late in the outbreak, were considered "low activity" time periods.

Estimates for the monthly number of Canadians travelling outside of Canada to other countries in the Americas were obtained from two sources: yearly counts of travellers to specific countries and regions were obtained from the International Travel Survey, Statistics Canada, 2015 (22); and monthly traveller counts for the Americas in 2015 and 2016 were obtained using passenger-level ticket sales data from the International Air Transport Association (IATA). The IATA data comprise the full route itineraries of travellers, including their initial airport of embarkation, final airport destination and, where applicable, connecting airports. These data account for an estimated 90% of all trips on commercial flights worldwide, while the remaining 10% are modelled using airline market intelligence. Numbers for 2017 were estimated using an average of the monthly values in 2015 and 2016.

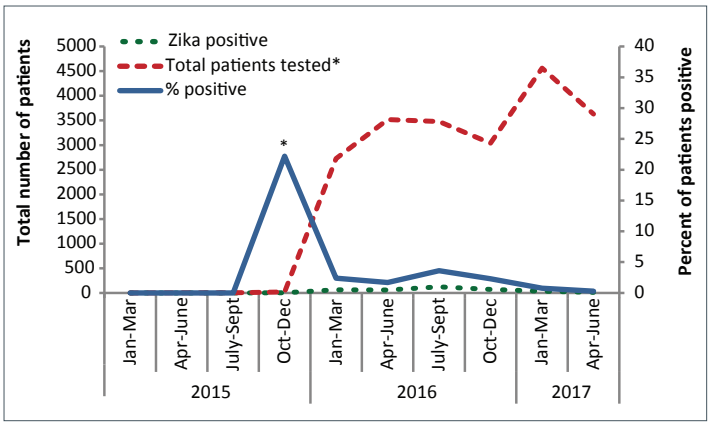
Data to produce the epidemic curves of autochthonous cases for each region of the Americas were extracted from country-specific epidemic curves on the Pan American Health Organization (PAHO) website using the WebPlotDigitizer tool (24). The countries used in the estimates were as follows:

- North America: Mexico
- Caribbean: Anguilla, Antigua and Barbuda, Aruba, Barbados, Curaçao, Dominica, Dominican Republic, Bonaire, Saint Eustatius, Saba, Cayman Islands, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Montserrat, Puerto Rico, Saint Barthelemy, Saint Kitts and Nevis, Saint Martin, Saint Vincent and the Grenadines, Saint Maarten, U.S. Virgin Islands, St. Thomas, St. Croix, St. John, Trinidad and Tobago, Turks and Caicos
- Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama
- South America: Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Paraguay, Peru, Suriname and Venezuela

Results

Between May 2015 and June 7, 2017, over 22,000 samples were tested by the National Microbiology Laboratory. The number of samples received each week increased dramatically around week six (February 7–13, 2016). Since that time, testing levels have remained high with an average of 320 samples being submitted on a weekly basis (Range: 165-500 samples weekly), despite the number of positive samples decreasing (**Figure 1).**

Figure 1: Number and percentage of Zika positive patients tested by the National Microbiology Laboratory, Canada, January 2015–June 2017[a]



[a] From October to December 2015, 18 samples were tested; of those four (22%) were positive

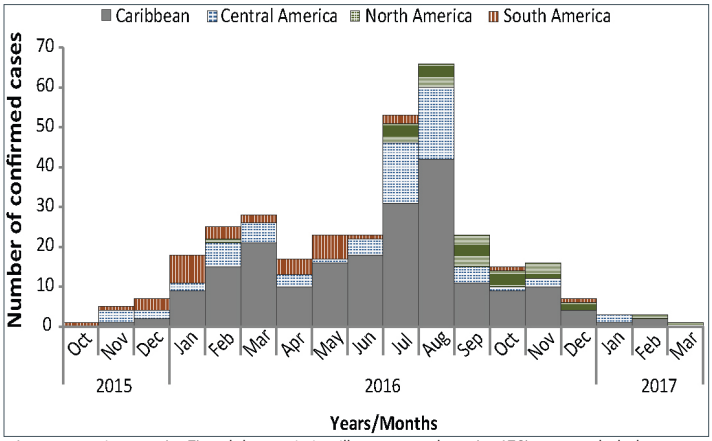
As of June 7, 2017, there have been 513 confirmed cases of ZIKV across all 10 provinces. Information on transmission mode was available for 512 cases and, of these, 507 (99%) acquired ZIKV infection while travelling to affected regions. An additional three cases with no history of travel were infected through sexual contact with an infected traveller. Two (n=2) cases of maternal-fetal transmission were reported. Fifty-five percent (55%) of cases were between the age of 20–44 years, and 64% were female (**Table 1).**

Table 1: Confirmed cases by age category and sex, Canada, October 2015–June 2017

Age (years)	Female	Male	Unknown	Total (% of Total)
Newborn-1	2	0	0	2 (<1%)
1-19	13	9	0	22 (4%)
20-44	195	86	0	281 (55%)
45-64	96	69	6	171 (33%)
>64	20	17	0	37 (7%)
Total (% of Total)	326 (64%)	181 (35%)	6 (1%)	513 (100%)

Of those with information available (n=499), 99% (n=492) reported symptoms prior to testing. Dates of illness onset ranged from October 12, 2015–March 30, 2017, with a peak noted in July and August 2016 (**Figure 2**). There were 35 pregnancies reported among Zika-infected women; however pregnancy outcomes were not collected routinely so only limited data were available. Of the four reported pregnancy outcomes, two of the infants had no apparent anomalies at birth and two of the fetuses/infants had Zika-related anomalies.

Figure 2: Number of confirmed travel-associated Zika virus cases by month of symptom onset and region of travel, Canada, October 2015–June 2017 (n=334)[a]



[a] Asymptomatic cases (n=7) and those missing illness onset dates (n=172) were excluded

Overall, 66% of Canadian travellers were infected while visiting the Caribbean, 19% in Central America, 10% in North America (Mexico) and 6% in South America (**Appendix 1).**

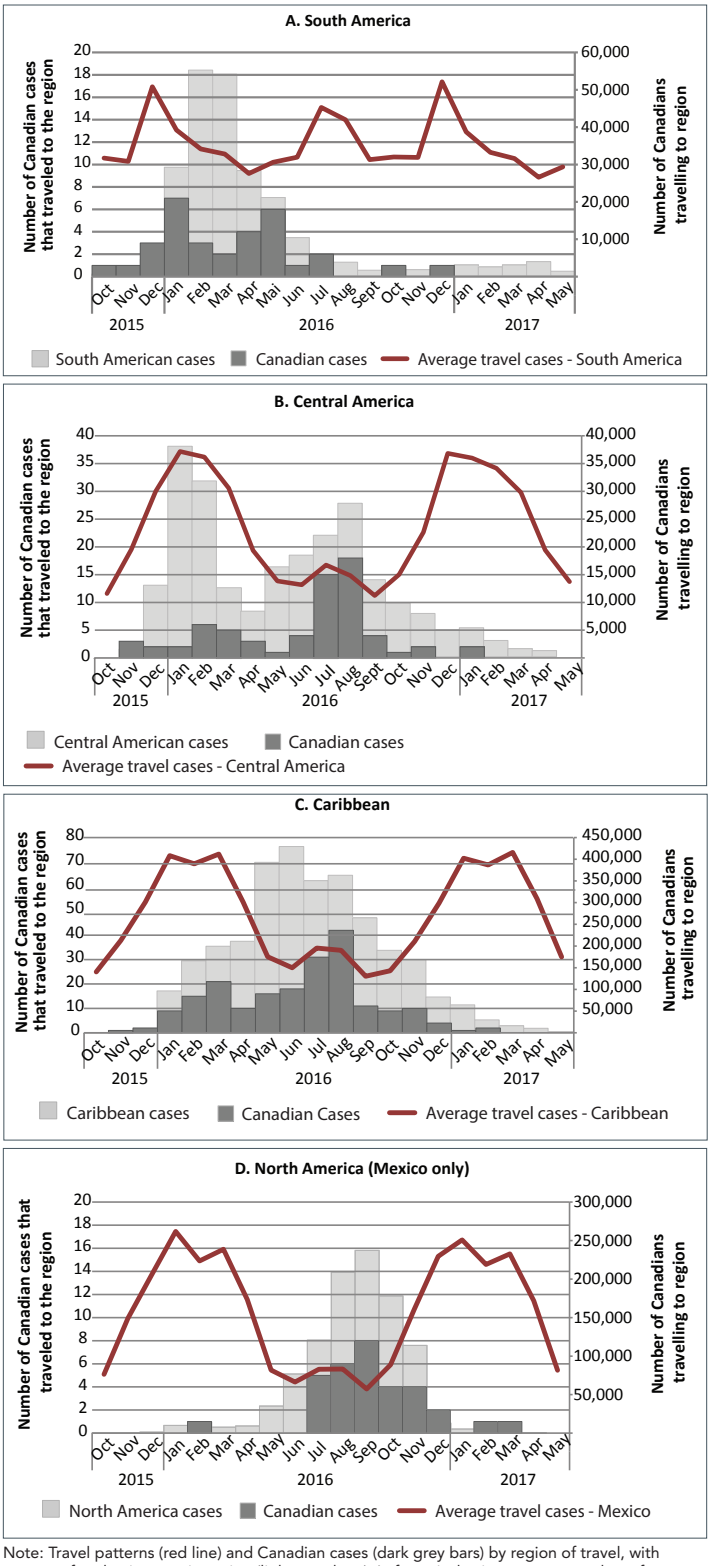
Most (83%) of the cases travelled to their destination countries when the country was reporting high numbers of cases (i.e., during the "outbreak" period); however, there were a few cases who travelled to countries before those countries reported their first case (2%), or in periods of lower activity (16%) (**Table 2**).

Table 2: Timing of travel in relation to Zika virus outbreak status in country of travel: Canada, 2015–2017

Status of outbreak in country of travel	Number of cases	% of total cases
Prior to notification of first case	5	2
Low activity: early in the outbreak	16	6
High activity: during the main outbreak period	240	83
Low activity: late in the outbreak or in between outbreak waves	28	10
Total	289	100

The pattern of travel-associated cases observed, by region, appears to more closely coincide with Zika transmission activity in the region, rather than number of individuals travelling from Canada (**Figure 3).**

Figure 3: Monthly travel patterns and Canadian Zika virus cases by region of travel



Note: Travel patterns (red line) and Canadian cases (dark grey bars) by region of travel, with pattern of endemic cases in region (light grey bars). Left vertical axis represent number of Canadian cases, right vertical axis represents the estimated number of individuals travelling from Canada to the region based on IATA monthly traveller data. For the estimated endemic cases per region, the pattern from the regional epidemic curve is shown, with no scaling

Discussion

From October 2015 to June 2017, there were 507 confirmed cases of travel-related ZIKV and three cases of sexual transmission in Canada. Sixty-four percent of cases were female and, of those, 11% were pregnant. Finding a higher proportion of infected women than men is consistent with other international reports and likely reflects a testing and reporting bias rather than biological differences in susceptibility or exposure (30). Outcome information was available for only four pregnancies; two fetuses/infants had Zika-related anomalies while two did not have any apparent anomalies.

Despite the decline in number of cases in the past few months in returning travellers, the volume of laboratory testing remains high, reflecting the ongoing level of concern amongst pregnant couples and those planning pregnancies. There continues to be a significant number of pregnant 'worried well'; those who travelled to an at-risk region, did not develop symptoms but were tested. Given that both symptomatic and asymptomatic infections seem to result in similar percentages of birth defects, the concern is understandable. As infection rates continue to decline, there is a very low pre-test probability when testing asymptomatic individuals, which limits the value of testing. As a result, testing guidelines do not routinely recommend testing of asymptomatic pregnant women with no ongoing risk (i.e., travellers) (31). Several testing procedures for case identification are available; however, antibody cross reactivity between ZIKV and related viruses such as dengue can complicate diagnosis when using serological platforms. As well, individuals who have previously been exposed to related flaviviruses may exhibit serological responses that confound test interpretation. As a result some ZIKV exposures cannot be confirmed by immunoassays and are documented as "flavivirus infections". In these cases, physicians should be aware that a ZIKV exposure may still have occurred.

Almost all cases in Canada were travel-associated, and there is no evidence of autochthonous (local) transmission to date. Data suggests that sexual transmission alone is not likely to independently sustain an outbreak (30), and ongoing transmission is unlikely in the absence of tropical/subtropical *Aedes* spp. (32). The primary mosquito vectors—*Aedes aegypti* and *Aedes albopictus*—are not established in Canada and current research suggests that Canadian mosquito species are not competent hosts. Further, the risk of autochthonous transmission via the establishment of *Aedes albopictus*, given current climatic conditions, is predicted to be very low.

Illness in Canadian travellers generally coincided with outbreak intensity in the country of exposure rather than travel volume. It has been previously reported that the risk to travellers varies with the force of transmission cycles in the countries they are visiting, and that travellers as a group are not highly protected from infection in affected countries by virtue of their traveller status (32). The peak in cases recorded in July and August of 2016 was due to increases in cases exposed in Central America and the Caribbean, and to some extent from Mexico, but at a time when travel to these destinations are typically at their seasonal lows. Climatic factors such as temperature, humidity and precipitation have been shown to affect vector abundance, and ultimately level of disease transmission for diseases such dengue and chikungunya (33), resulting in seasonal trends in transmission favouring the warmer, wetter months. Both outbreak intensity and seasonality of ZIKV transmission should be monitored over time in order to inform the timing of public health education campaigns, as some may turn out be more effective in the 'off-peak' travel season when, despite lower absolute travel volumes, the risk of disease transmission may be higher.

Limitations

There are several limitations worth noting when interpreting the results. The laboratory testing results presented here only account for a subset of the testing done in Canada. Although NML initially conducted all ZIKV testing, as the outbreak progressed, three provinces adopted PCR testing for ZIKV in their respective jurisdictions. Findings reported here underestimate the total volume of ZIKV testing conducted in Canada.

Secondly, illness onset dates were not available for a number of cases, and were therefore excluded from the epidemic curve. To determine the impact of excluding these cases, a comparison was made between those with available information and those without. Estimated onset dates were generated for those missing onset dates using the PCR confirmation date, accounting for average testing and reporting delays. Based on this analysis, there was some variability in the timing of the cases with missing onset dates; however, this timing coincided with the peaks of the epidemic curve. While excluding these cases resulted in a slight attenuation of the peaks, the general shape of the curve remained the same, and no other meaningful changes were noted.

Pregnancy outcomes were not collected routinely as part of national reporting; therefore the very small subset of cases reported here should be interpreted with caution. More reliable estimates of the impact of ZIKV on pregnancy can be found elsewhere in the international literature.

Conclusion

Since late 2015, there was a significant increase in travel-associated ZIKV cases in Canada. Given that ZIKV can present like other viral diseases, and that many people only experience mild symptoms or no symptoms at all, this is likely a significant underestimate of the total travel-associated cases returning to Canada as a result of this international outbreak in the Americas. Cases in Canada and internationally are now on the decline; however, it is likely that cases will continue to be reported. The impact of seasonality and population immunity on the persistence of the virus in the Americas, and more broadly, is unknown. It is important to continue monitoring outbreak intensity and seasonality of ZIKV transmission in endemic countries in order to inform the timing of public health education campaigns, as some may turn out be more effective in the 'off-peak' travel season when, despite lower absolute travel volumes, the risk of disease transmission may be higher.

Zika virus is the third example of a recent arbovirus emerging into the Western Hemisphere with significant impact on human health (West Nile virus, chikungunya). Ongoing national and international collaboration is needed to prepare for and respond to these emerging diseases. Further application of new diagnostic platforms such as commercial screening ELISAs will enhance and expand laboratory testing capacity in Canada.

The PHAC and CATMAT recommend that pregnant women and those planning a pregnancy should postpone travel to areas

where ZIKV transmission is ongoing (27,34). Patients with clinical symptoms consistent with ZIKV and pregnant women or couples planning pregnancies, who have recently returned from travelling to countries where the virus is circulating, should see their health care provider to discuss their situation and risk. Health care providers should continue to educate their patients about the risks for, and measures to prevent, ZIKV infection and other mosquito-borne infections.

Authors' statement

JT- Conceptualization, Methodology, Analysis, Interpretation, Writing original draft, review and editing
LV- Conceptualization, Methodology, Analysis, Interpretation, Writing original draft (parts) and review
MD- Conceptualization, Investigation, Interpretation, Writing – original draft (parts) and review
HW- Investigation, Analysis, Writing – review
EP- Investigation, Writing original draft (parts) and review
SC- Investigation, Writing original draft and review
JG- Investigation, Conceptualization, Writing original draft (parts) and review
MG- Methodology, Analysis, Writing original draft (parts) and review
KK- Methodology, Analysis, Writing original draft (parts) and review
PAB- Conceptualization, Writing original draft, review and editing

Conflict of interest

None.

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Appendix 1: Zika infection in Canadian travellers, by region and country of travel, May 2015 – June 2017 (N=493[a])

Region	Country/area of travel	n	Estimated Canadian travellers (May 2015–June 2017)[b]	Estimated infection rate (per 100,000 travellers)	Total # of travel cases per region	Percent of travel cases per region	Estimated total travellers to region	Estimated infection rate per 100,000 travellers to region
Caribbean	Antigua and Barbuda	4	102, 917	3.89	322	65.71	2,897,083	1.11
	Bahamas	3	454,583	0.66				
	Barbados	53	394,375	13.44				
	Bonaire, Saint Eustatius and Saba	4	-	-				
	British Virgin Islands	4	52,083	7.68				
	Caribbean (unspecified)	12	-	-				
	Curacao	15	-	-				
	Dominican Republic	40	1,014,167	3.94				
	Grenada	10	25,208	39.67				
	Guadeloupe	5	46,042	10.86				
	Haiti	19	82,500	-				
	Jamaica	78	461,042	16.92				
	Martinique	7	9,792	71.49				
	Saint Lucia	8	88,958	8.99				
	Saint Martin/ Saint Maarten	17	17,292	98.31				
	Saint Vincent and the Grenadines	8	17,708	45.18				
	Trinidad and Tobago	35	130,417	26.84				
North America	Mexico	47	4,012,292	1.17	47	9.59	4,012,292	1.17
Central America (unspecified)	Central America	8	-	-	76	15.51	780,000	9.74
	Costa Rica	15	362,708	4.14				
	El Salvador	9	85,208	10.56				
	Guatemala	10	58,333	17.14				
	Honduras	4	138,750	2.88				
	Nicaragua	29	62,083	46.71				
	Panama	1	72,917	1.37				
South America	Belize	1	198125	0.50	45	9.18	1,082,798	4.16
	Brazil	4	203333	1.97				
	Columbia	17	187,083	9.09				
	Ecuador	3	71,250	4.21				
	Guyana	14	135,000	10.37				
	Peru	1	274,792	0.36				
	Venezuela	5	13,125	38.10				
Other	Philippines	1	-	-	3		-	-
	Thailand	1	-	-				
	Vietnam	1	-	-				
TOTAL		**493**	**n/a**	**n/a**	**493**	**100**	**8,772,083**	**5.59**

Abbreviations: "-", data not available; N, number of cases; n/a, not applicable
[a] Cases who travelled to more than one region (n=14) were excluded
[b] Data source: International Travel Survey—Statistics Canada, 2015 data was adjusted to reflect estimated numbers over 25 months (May 1, 2015–June 1, 2017) (22)

EDITORIAL

Zika virus: Where to from here?

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Abstract

After the waves of reported cases of infection with Zika virus swept across the Americas in 2015–16, the overall transmission of the virus in the Western Hemisphere declined in 2017. Between June 8 and August 31, 2017, only 16 new cases of Zika virus infection, all travel-related, were reported in Canada. This represents an 88% reduction in the cases recorded during the same time frame in 2016. Herd immunity undoubtedly constrains the transmission of the virus in endemic regions. However, while most countries in the Americas are no longer observing continuous transmission in the form of sustained increases over time, some areas are experiencing a notable resurgence. Zika virus, in the wake of dengue, West Nile and chikungunya, has become one of the globalized emerging infections—proliferating beyond previously restricted geographic zones. Zika virus is no longer deemed a global health crisis but the virus' unique potential to cause neurological anomalies in fetuses remains a significant concern.

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After the waves of reported cases of infection with Zika virus swept across the Americas in 2015–16, the overall transmission of the virus in the Western Hemisphere declined in 2017, likely due to a combination of herd immunity and enhanced mosquito-control campaigns. The decrease in Zika virus transmission was reflected in the concomitant reduction in number of travel-related Zika cases reported by health authorities including the Public Health Agency of Canada (1), the Centers for Disease Control Prevention (2), the European Centre for Disease Prevention and Control (3,4) and the Pan American Health Organization (5).

Between June 8 and August 31, 2017, only 16 new cases of Zika virus infection, all travel-related, were reported in Canada. This represents an 88% reduction in the cases recorded during the same time frame in 2016. In the continental United States of America (USA), 225 travel-related Zika infections were reported as of October 11, 2017, compared to a total of 5,259 infections in travelers returning from affected regions in 2016 (2). Cases related to locally-acquired vector-borne transmission on the mainland USA also decreased notably: one locally-acquired mosquito borne infection was reported in 2017 (provisional data) versus 225 vector-borne endemic cases in 2016 (2). Similarly, surveillance data from countries in the European Union and European Economic Area (EU/EEA) exhibited a steep decline in the number of confirmed cases in travelers returning from the Caribbean, Central and South America in the latter part of 2016 and into 2017 (3). As of August 29, 2017, no locally-acquired cases by vector-borne transmission were detected in EU/EEA member states (5). The absence of *Aedes aegypti*, restricted distribution of the European *Aedes albopictus* and current environmental conditions limit the risk of transmission of Zika virus in the European Union (3,4).

Herd immunity undoubtedly constrains the transmission of the virus in endemic regions; however, transmissibility of the Zika virus, like other vector-borne disease, is associated with spatial heterogeneity (regional variations in mosquito concentrations), driven by seasonal changes in *Aedes* abundance and local temperatures that affect vector competence (i.e., the ability of this mosquito to acquire, maintain and transmit the Zika virus). The characteristics of the exposed population (e.g., housing and other socioeconomic factors) further determine the fraction of the population exposed to the vector (6). The complex interactions of these variables contribute to a decline or increase in infection rates relative to the immune status of the host population.

While most countries in the Americas are no longer observing continuous transmission in the form of sustained increases over time, some areas are experiencing a notable resurgence of autochthonous cases and new geographical places where infection is transmitted (7). Approximately 50% of the confirmed cases in Mexico reported between January and August 2017 occurred in three geographical areas where previously only minimal activity had been documented (5). In the early months of this year, Ecuador reported an increase in Zika virus cases in 2017, resulting in a distinctive second wave after the number of cases declined in mid-2016 (8). In Peru, a surge of infections resulted in 800 cases reported to Pan American Health Organization (PAHO) at the peak of the outbreak in March 2017, a four-fold increase over the peak in 2016 (9). Argentina reported sporadic Zika cases in 2016, followed by an increasing trend of confirmed cases in 2017 between January (26 cases) and April (63 cases). By August 31, 2017, Argentina had confirmed 276 cases of Zika virus to PAHO (10).

Zika virus has been present in Africa for over 60 years. In Asia, the virus was first discovered in 1966 and is known to have been circulating in Cambodia, the Republic of Laos and Vietnam prior to 2015. In Southeast Asia, only Singapore experienced an epidemic of Zika virus (11). Outbreaks of equivalent magnitude to that seen in the Americas were not detected across either continent, despite the globalization of travel, the presence

of permissive mosquito vectors and favourable ecological conditions for transmission. Although evidence from a recent study in Singapore indicated that Zika virus can be easily introduced into a region with good baseline vector control, it is yet unknown whether Asia is at risk of a major Zika epidemic (11).

Zika virus, in the wake of dengue, West Nile and chikungunya, has become one of the globalized emerging infections—proliferating beyond previously restricted geographic zones. Zika virus is no longer deemed a global health crisis but the virus' unique potential to cause neurological anomalies in fetuses remains a significant concern. While the risk to Canadians is predominantly related to travel to affected areas, the potential impact of climate change on invasive mosquito species inclusion and establishment in Canada needs to be informed by ongoing surveillance and research.

Conflict of interest

None.

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Canadian recommendations for laboratory interpretation of multiple or extensive drug resistance in clinical isolates of Enterobacteriaceae, *Acinetobacter* species and *Pseudomonas aeruginosa*

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Abstract

The goal of this document was to provide Canadian laboratories with a framework for consistent reporting and monitoring of multidrug resistant organisms (MDRO) and extensively drug resistant organisms (XDRO) for common gram-negative pathogens. This is the final edition of the interim recommendations, which were modified after one year of broad consultative review. This edition represents a consensus of peer-reviewed information and was co-authored by the Canadian Public Health Laboratory Network and the Canadian Association of Clinical Microbiology and Infectious Diseases. There are two main recommendations. The first recommendation provides standardized definitions for MDRO and XDRO for gram-negative organisms in clinical specimens. These definitions were limited to antibiotics that are commonly tested clinically and, to reduce ambiguity, resistance (rather than non-susceptibility) was used to calculate drug resistance status. The second recommendation identifies the use of standardized laboratory reporting of organisms identified as MDRO or XDRO. Through the broad consultation, which included public health and infection prevention and control colleagues, these definitions are ready to be applied for policy development. Both authoring organizations intend to review these recommendations regularly as antibiotic resistance testing evolves in Canada.

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Introduction

These recommendations were produced under the auspices and authority of the Canadian Public Health Laboratory Network (CPHLN) and the Canadian Association of Clinical Microbiology and Infectious Diseases (CACMID). They represent a consensus of peer-reviewed information and expert opinion on the most appropriate ways to define and report multidrug resistant phenotypes in common gram-negative pathogens. They build on previous interim recommendations (1) and underwent broad consultation with local, national, and international stakeholders. These recommendations are intended for use in Canadian non-veterinary clinical microbiology laboratories, and will enable standardized reporting in provincial and national surveillance programs.

Background

Antimicrobial resistance is a growing concern for human health as bacterial pathogens continue to accumulate genetic alterations conferring resistance to the antimicrobials used to treat human infections. Most concerning is the acquisition of multiple resistance traits within individual pathogens, which can greatly limit or entirely eliminate the arsenal of effective treatment options, thereby leading to poor clinical outcomes. In Canada, we have observed these highly resistant strains in Enterobacteriaceae, *Acinetobacter* spp. and *Pseudomonas aeruginosa* (2-4).

The goal of this document is to provide Canadian laboratories with a framework for consistent reporting and monitoring of multidrug resistant organisms (MDRO) and extensively drug resistant organisms (XDRO). There was a need to standardize the classification of organisms that are resistant to multiple antimicrobials in order to consistently and accurately share information locally, nationally and internationally with the medical community, public health authorities and policy makers. Additionally, classification as 'multidrug resistant' may be an actionable finding within hospital infection prevention and control programs.

The need for standardized categorization of antimicrobial resistance was recognized in 2012 by Magiorakos et al. (5), who proposed interim international definitions in selected gram-positive and gram-negative organisms. Those definitions have not yet led to revised or definitive guidelines. The recommendations in this document are based on the interim definitions proposed by Magiorakos et al. for gram-negative organisms, with modifications to better reflect the Canadian context and take into account Canadian stakeholder input. See **Appendix A** for more information on the methodology for developing the final recommendations as well as a description of the modifications and their justifications. **Table 1** identifies the broad provincial, national, and international consultations that were conducted with the interim recommendations.

Table 1: Provincial, national and international organizations consulted on the interim guidelines

Level of consultation	Organization
Provincial	British Columbia Association of Medical Microbiologists (BCAMM)
	Diagnostic Services Manitoba Medical and Clinical Microbiologists
	Provincial (Ontario) Infectious Diseases Advisory Committee (PIDAC)
	GNB infection control committee of Comité sur les infections nosocomiales du Québec (CINQ)
	Provincial (PEI) Infection Control and Prevention Advisory Committee (PICPAC)
	Microbiologists, infection diseases physicians, and the public health office (New Brunswick)
	Microbiologists and Public Health Office (Nova Scotia)
	Microbiologists and Public Health Office (Newfoundland)
National	Association of Medical Microbiology and Infectious Disease (AMMI) Canada
	Infection Prevention and Control Canada (IPCC)
	Canadian College of Microbiologists (CCM)
	Public Health Networks Task Groups on AMR Surveillance and AMR Infection Control
	Canadian Association of Clinical Microbiology and Infectious Diseases (CACMID)
	Microbiology Scientific Committee of the Institute of Quality Management in Health Care (IQMH)
International	Public Health England
	Pan American Health Organization
	Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)

Abbreviation: GNB, gram-negative bacilli

Over time, as new antimicrobials become available and currently used antimicrobials lose effectiveness or are no longer available, these definitions will require revision. The recommendations stated herein are considered final and will be reviewed every three years.

Recommendations for antimicrobial susceptibility testing

1. A resistant interpretation of an isolate can be determined using disk diffusion, broth microdilution or agar dilution following Clinical and Laboratory Standards Institute (CLSI) guidelines for susceptibility testing and interpretation of Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp (6).

For data harmonization, emphasis is placed on minimum inhibitory concentration (MIC) and phenotypic methods rather than expert rules providing interpretative criteria. A Health Canada- or Federal Drug Administration (FDA)- approved automated method or gradient diffusion strips can also be used for the generation of antimicrobial susceptibility data.

2. Current CLSI M100 breakpoints should be used to determine antimicrobial susceptibility of isolates (6).

Some laboratories may routinely use other breakpoint interpretations (e.g., FDA, European Committee on Antimicrobial Susceptibility Testing (EUCAST)) that differ from CLSI recommendations. Laboratories using non-CLSI breakpoints, including those using unmodified FDA-approved automated instruments, should disclose this information in their reports to provincial public health laboratories.

3. Certain species of Enterobacteriaceae should not be tested for particular antimicrobial agents because of intrinsic resistance.

Refer to the appendices of CLSI M100 (6) or EUCAST Expert Rules (7).

Definitions

These recommendations are intended to be applied only to isolates from clinical/diagnostic specimens; however, infection prevention and control programs may choose to apply these MDRO/XDRO definitions in their antimicrobial resistant organism control activities. When reporting MDRO/XDRO isolates that are part of an asymptomatic surveillance program (e.g., inpatient admission screening), it should be clearly indicated in the laboratory report that the MDRO/XDRO classification refers to colonization or carriage status only in order to avoid unnecessary treatment.

In the following definitions, criteria using the term 'OR' should be interpreted as follows: if an isolate is resistant to either of the antimicrobial agents listed, it should be considered resistant to that criterion for the purposes of these definitions.

Enterobacteriaceae definitions

An isolate should be considered a MDRO if it is resistant to **THREE OR FOUR** of the **SIX** antimicrobial groups listed below:

- Tobramycin **OR** gentamicin (see exceptions for Serratia spp. in Table 2)
- Piperacillin-tazobactam
- Imipenem **OR** meropenem (see exceptions for Proteus spp. in Table 2)
- Cefotaxime **OR** ceftriaxone **OR** ceftazidime
- Ciprofloxacin
- Trimethoprim-sulfamethoxazole

An isolate should be considered an XDRO if it is resistant to **FIVE OR SIX** of the **SIX** antimicrobial groups listed above.

Acinetobacter spp. or *P. aeruginosa* definitions

There are no final recommendations for MDRO definitions for *Acinetobacter* spp. or *P. aeruginosa*. The previous interim recommendations for *Acinetobacter* spp. or *P. aeruginosa* MDRO status should be disregarded at this time (1).

An isolate should be considered an XDRO if it is resistant to **ALL** of the **FIVE** antimicrobial groups listed below:

- Ciprofloxacin
- Piperacillin-tazobactam (For *P. aeruginosa* can substitute piperacillin)
- Ceftazidime
- Imipenem OR meropenem
- Tobramycin

Table 2 provides a summary of the definitions for determining whether select gram-negative organisms are MDRO/XDRO.

Reference laboratories notification

The provincial public health laboratory should be notified of XDROs as defined above. Unlike the interim recommendations, sending of isolates is NOT requested. Referral of clinical isolates to reference laboratories should continue to occur as clinically necessary. Provincial public health laboratories will collaborate on notification and particular privacy concerns in each province. Include the following information when reporting:

- Age of patient
- Gender of patient
- Type of clinical specimen (blood, respiratory, skin/soft tissue or urine)
- Date of collection
- Antimicrobial susceptibility testing results from submitting laboratory

Method and interpretive criteria used for antimicrobial susceptibility testing, as described in the recommendations above.

If multiple clinical isolates of the same species and susceptibility pattern are recovered from the same patient, report the isolate from the most invasive site where possible. Only one isolate of each XDRO should be reported per patient per year to the provincial laboratory.

The provincial public health laboratory as defined in **Appendix B** will report all of the data to the National Microbiology Laboratory (NML). The NML will compile and enable distribution of national surveillance reports to contributing laboratories and provincial public health authorities on an annual basis.

Table 2: Definitions for the determination of MDRO/XDRO in select organisms

MDRO		XDRO	
Definition	Antimicrobial groups	Definition	Antimicrobial groups
Enterobacteriaceae			
Resistance to THREE OR FOUR of the SIX antimicrobial groups	Tobramycin OR[a] gentamicin[b]	Resistance to FIVE OR SIX of the antimicrobial groups	Tobramycin OR gentamicin
	Piperacillin-tazobactam		Piperacillin-tazobactam
	Imipenem OR meropenem[c]		Imipenem OR meropenem
	Cefotaxime OR ceftriaxone OR ceftazidime		Cefotaxime OR ceftriaxone OR ceftazidime
	Ciprofloxacin		Ciprofloxacin
	Trimethoprim-sulfamethoxazole		Trimethoprim-sulfamethoxazole
Organisms: *Pseudomonas aeruginosa* OR *Acinetobacter* species			
Not applicable	Not applicable	Resistance to ALL FIVE antimicrobial groups	Ciprofloxacin
			Piperacillin-tazobactam[d]
			Ceftazidime
			Imipenem OR meropenem
			Tobramycin

Abbreviations: MDRO, multidrug resistant organisms; XDRO, extensively drug resistant organisms
[a] The term 'OR' should be interpreted as follows: if an isolate is resistant to either antimicrobial agent listed, it should be considered resistant to that criterion for the purposes of these definitions
[b] Resistance in *Serratia* spp. should only consider gentamicin susceptibility testing results
[c] Resistance in *Proteus* spp. should only consider meropenem susceptibility testing results
[d] Resistance in *P. aeruginosa* may include piperacillin-tazobactam OR piperacillin. For all Acinetobacter spp. piperacillin-tazobactam must be used

Conflict of Interest

None.

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Appendix A: Methodology for developing the final recommendations

The article published by Magiorakos et al. (5) was used as the main reference for the development of these Canadian recommendations. Drs. German and Mulvey developed the initial framework for the document, which was reviewed by the Canadian Public Health Laboratory Network (CPHLN) Antimicrobial Resistance (AMR) Working Group members and invited collaborators. Two main considerations were discussed by the working group members: the formulation of a recommendation that focused on antimicrobial drugs commonly used in Canada; and the creation of a document that would be easy to use by frontline laboratories, which predominantly utilize automated methods for generating antimicrobial susceptibility data.

Three rounds of discussion and document revision took place with the working group. This included discussion and suggestions from the Communicable and Infectious Disease Steering Committee (CIDSC) AMR Task Group from the Pan-Canadian Public Health Network. The final draft recommendations were reviewed by the CPHLN Executive.

Major variation with recommendations in this document as compared to Magiorakos et al. (5) was as follows:

- The working group decided to focus on gram-negative isolates to keep the recommendations straightforward and achievable. It was decided that recommendations for gram-positive organisms would be addressed in a future document.
- The pan-drug resistant organisms (PDRO) nomenclature was eliminated in these revised recommendations as all potential antimicrobials are not tested routinely by clinical microbiology laboratories.
- Although the definition of MDRO in gram-negative organisms is an important consideration given the treatment complications that can be associated with these infections, it was decided at a provincial and national level to voluntarily report only XDRO isolates and use the identification of an MDRO as a screening test to direct further testing and reporting of resistant isolates.
- A great deal of discussion focused on the value of using the definition of resistance, as defined by CLSI, rather than that of non-susceptibility, as proposed by Magiorakos et al. (5). It was decided to use the CLSI definition of resistance based on the main arguments put forward, which were: front-line laboratories may have difficulty analyzing 'intermediate resistance' data in the context of MDRO/XDRO; and there were concerns about the reporting of these organisms in relation to public health. A stringent definition of resistance was determined to be the most feasible solution.
- It was noted that laboratories may have to use FDA breakpoints, which may differ from the CLSI breakpoints. It was requested in the recommendations that these differences be noted in the report to the local provincial public health laboratory.
- The exhaustive list of antimicrobial agents in the article by Magiorakos et al. (5) was simplified to reflect the antimicrobial agents commonly used and available in Canada.
- Ertapenem was removed as a marker for carbapenem resistance in Enterobacteriaceae. The specificity of ertapenem to detect acquired resistance is lower than that of meropenem and imipenem, and ertapenem-resistant isolates may be treated successfully by other carbapenems.
- The tetracyclines were removed from the list of antimicrobials to be considered as they are not frequently tested in frontline laboratories, nor are they commonly used to treat serious infections.
- The Canadian recommendations requested additional clinical information that was not included in the article by Magiorakos et al. (5).
- Nitrofurantoin and fosfomycin were removed from definitions as they do not represent currently accepted treatment options available for all infections, specifically invasive and more serious infections.

A broad provincial, national, international consultation process was conducted with the interim recommendations (Table 1). Feedback to the interim document led to the creation of several revisions. Since CACMID provided astute feedback of the interim document and would provide more front line clinical laboratory perspective they were invited to co-author the final recommendations. A task group was organized by CACMID. The recommendations were presented in near final form to the Annual 2017 CACMID general meeting. Further opportunities were provide for input from attendees. The final document was approved by the CACMID Board, the CPHLN AMR working group and the CPHLN Laboratory Council.

Appendix B: Reference laboratory contact information

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Human cases of West Nile virus in Canada, 2017

Source: Public Health Agency of Canada. **Surveillance of West Nile virus**. http://healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/west-nile-nil-occidental/surveillance-eng.php

During the West Nile virus (WNv) season from mid-April to October, Canada conducts ongoing human case surveillance across the country. Monitoring West Nile virus nationally is a joint effort between the Government of Canada and its partners, including provincial and territorial ministries of health, First Nations authorities and blood supply agencies.

The Government of Canada relies on the provinces and territories to report the number of West Nile virus cases. To accurately reflect the annual occurrence of WNv cases in Canada, health professionals need to remain vigilant in diagnosing WNv, and reporting cases to their public health regional authorities. See source for case definitions.

West Nile virus clinical cases in Canada, as of October 21, 2017

Province/Territory	Total number of clinical cases
Newfoundland and Labrador	0
Prince Edward Island	0
Nova Scotia	0
New Brunswick	0
Quebec	14
Ontario	148
Manitoba	4
Saskatchewan	0
Alberta	7
British Columbia	0
Yukon	0
North West Territories	0
Nunavut	0
Canada	173

In 2017, there were a total of 173 clinical cases and six asymptomatic infections reported as of October 21, 2017. These numbers may change slightly as provincial or territorial public health organizations can sometimes retroactively identify cases. Surveillance detects only a portion of West Nile virus cases in Canada; the true number is likely greater.

Overall, this summer has recorded the highest number of cases since 2012 in Canada, with most (94%) being reported in the central region (ON and QC). The heavy rainfall in spring, long and warm summer in the region was favorable to mosquito abundance and increased the risk of human exposure.

How many human cases of West Nile virus are reported annually?

Year	Number of human cases
2007	2215
2008	36
2009	13
2010	5
2011	101
2012	428
2013	115
2014	21
2015	80
2016	100
2017	173

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Lidiya Tsegaye

and any others who we may have inadvertently missed.

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