CCDR | CANADA COMMUNICABLE DISEASE REPORT

canada.ca/ccdr

October 1, 2020 - Vol. 46 No. 10

# LABORATORY BIOSAFETY



NEXT ISSUE NOVEMBER 5, 2020

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

# CCDR
## CANADA COMMUNICABLE DISEASE REPORT


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The picture on the cover of this issue illustrates various levels of containment from biosafety level 2 to 4. Illustrations provided by the National Microbiology Laboratory of the Public Health Agency of Canada in Winnipeg and adapted by Lyal Saikaly.


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# Laboratory response checklist for infectious disease outbreaks—preparedness and response considerations for emerging threats

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## Abstract

The purpose of the Laboratory Response Checklist for Infectious Disease Outbreaks (the Checklist) is to provide public health laboratories and laboratory networks operating at multiple jurisdictional levels with a useful, adaptable tool to help rapidly identify important outbreak response considerations, particularly when investigating a previously unknown infectious disease threat. The Checklist was developed by the National Microbiology Laboratory of Canada in collaboration with provincial/territorial, national and international laboratory experts, including the Canadian Public Health Laboratory Network, and the Global Health Security Action Group Laboratory Network. While the Checklist was initially designed to reflect lessons learned through National Microbiology Laboratory participation in extended national and international outbreak responses (e.g. Zika virus epidemic [2015–2016], Ebola virus epidemic, West Africa [2014–2016]), the importance of optimizing laboratory response coordination has only been underscored by the ongoing challenges presented by the coronavirus disease 2019 (COVID-19) pandemic response requirements. The Checklist identifies five highly interdependent laboratory response themes, each of which encompasses multiple considerations that may be critical to a coordinated, strategic outbreak response. As such, the comprehensive review of Checklist considerations by responding laboratory organizations may provide a valuable opportunity to quickly detect key response considerations and interdependencies, and mitigate risks with the potential to impact public health action.

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***Suggested citation:*** EisBrenner T, Tipples G, Kuschak T, Gilmour M. Laboratory response checklist for infectious disease outbreaks—preparedness and response considerations for emerging threats. Can Commun Dis Rep 2020:46(10):311–21. https://doi.org/10.14745/ccdr.v46i10a01

***Keywords:*** checklist, COVID-19, Ebola, emerging infectious disease, emergency management, high consequence pathogens, infectious disease, laboratory response, outbreak preparedness, outbreak response, public health laboratory, SARS, SARS-CoV-2, Zika

## Introduction

Infectious disease outbreak response poses unique challenges and considerations for laboratories, particularly when investigating a previously unknown or newly defined infectious disease (1). Through extensive National Microbiology Laboratory (NML) participation in national and international outbreak and pandemic responses, a number of key considerations and lessons learned have been highlighted. These include the potential need for responding laboratories to 1) rapidly develop and deploy novel pathogen-specific diagnostic testing methods, 2) participate in collaborative, iterative development of case definitions and testing criteria to reflect evolving scientific evidence as an outbreak progresses, 3) strategically engage public health partners to optimize response capacity and coordination, and 4) establish information sharing processes and procedures that support timely public health laboratory (PHL) investigation, surveillance, research, public health messaging and action (2). Continually evolving public health genomics and other "omics" approaches present additional challenges, and provide valuable opportunities to further enhance infectious disease response capacity (3,4). Given the complex, outbreak-specific nature of laboratory response considerations, timely and effective coordination can prove challenging in the absence of a strategic and structured approach.

The potential usefulness of a checklist approach to strengthen laboratory preparedness and response coordination was most recently emphasized by extended NML engagement in national and international response efforts, in particular the Ebola virus epidemic in West Africa (2014–2016) and the Zika virus

epidemic (2015–2016) (5–8). Within this context, development of a checklist tool was also considered in alignment with desired outcomes articulated in the *Canadian Public Health Laboratory Network Strategic Plan, 2016–2020*; including "Priority 2: Strengthen coordinated response capacity to address established, emerging and re-emerging infectious disease pathogens and public health threats" (9).

A review of the literature at the time, however, yielded few publicly available references with checklist content related to emerging and high-consequence infectious disease response. Notably, these references either lacked a strong focus on the laboratory component of public health resilience, or did not describe laboratory response considerations independently of organizational, jurisdictional or infectious disease-specific contexts (2,10,11). The recent emergence of the novel coronavirus infectious disease (coronavirus disease 2019, COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has only served to underscore the critical importance of timely and coordinated laboratory response to support public health action (12).

The Laboratory Response Checklist for Infectious Disease Outbreaks (the Checklist) was developed to provide laboratory organizations with a useful, adaptable tool to rapidly identify key outbreak response considerations using a systematic approach, particularly when investigating a previously unknown or a newly defined infectious disease threat. To encompass considerations associated with larger scale, protracted laboratory responses, the Checklist was significantly informed by lessons learned through prior NML response efforts to Ebola, Zika, Severe Acute Respiratory Syndrome (SARS) in 2003, and by continuing COVID-19 response efforts (5–8,13,14). As laboratory-related response roles are expected to differ between organizations and jurisdictional levels, the Checklist content is not intended to be prescriptive. Rather, the Checklist was designed to broadly capture the scope of response considerations that may be relevant at all levels, while supporting content customization to reflect setting-specific requirements. As such, the Checklist is envisioned as a complementary tool to existing laboratory preparedness and response plans and protocols.

## Methods

An NML working group (WG) was convened to inform development of the Checklist tool to support timely coordination of laboratory response efforts. The WG composition included multiple program representatives with prior experience fulfilling NML Emergency Operations Centre (EOC) roles during outbreak response activations (15). The WG members identified requirements and challenges encountered when responding to infectious disease outbreaks and emerging threats both domestically and internationally. Information gathered was used to draft response considerations for a preliminary version of the Checklist. To support implementation by laboratory organizations operating at various jurisdictional levels, the Checklist development was guided by the need to incorporate the following key attributes: adaptability; acceptability; scalability; and ease of use (16).

To enhance adaptability of the Checklist, response considerations were described at a high level using generic, context-neutral terminology wherever possible. This approach was taken to allow users to readily modify content by incorporating preferred, organization and jurisdiction-specific terminology and operational requirements, thereby expanding the potential scope of implementing laboratory organizations and networks at the regional, provincial/territorial/state, national and international levels. The content of proposed response considerations was assessed, and five laboratory response themes were identified to support ease of use. Content within each theme was developed to be scalable, allowing users to expand or edit the scope of the Checklist items in alignment with response activities relevant to the role of the implementing laboratory organization. The resulting Checklist Review Table (**Supplemental I**) is intended to be replicable and adaptable using preferred spreadsheet or database software, offering the ability to flexibly select, sort and monitor the status of flagged items following user. To further support ease of use, a number of approaches to classify, customize and prioritize the Checklist items of interest were developed for user consideration (**Supplemental II**).

The draft Checklist was piloted using a scenario-based tabletop review exercise engaging NML EOC personnel and interjurisdictional laboratory liaison staff. Exercise input was used to refine content and to consider how to best operationalize the Checklist to enhance emergency response protocols. A supplementary NML Response Toolkit capturing laboratory contacts, references and resources specific to the Canadian context was concurrently developed to support NML implementation, and as a model adaptable by others (available upon request). To further verify content acceptability and validity, the Checklist and 'NML Response Toolkit' were distributed for review by federal and provincial/territorial laboratory experts (NML, Canadian Public Health Laboratory Network [CPHLN]), and internationally by the Global Health Security Action Group Laboratory Network. The Checklist was originally distributed in two forms: as a sortable 'Checklist Review Table' (Microsoft Excel 2010) (Supplemental I), and as a conventional 'checkbox' formatted 'Checklist' document (Microsoft Word 2010) (**Supplemental III**). External review input was addressed to produce a final reference version of the Checklist, which was then circulated to NML, CPHLN and Global Health Security Action Group Laboratory Network stakeholders in 2018. Interjurisdictional review indicated that the Checklist was well aligned with previously identified core PHL functions, and with priorities outlined in the *Canadian Public Health Laboratory Network Strategic Plan, 2016–2020* (9,17,18). Content was subsequently updated to produce the current version, which includes COVID-19 laboratory response context.

## The Checklist

The Checklist encompasses five central themes: laboratory investigation; laboratory response capacity and training; laboratory surveillance and data management; interjurisdictional engagement and communication; and research and ethics (Supplementals I and III). Each theme includes multiple considerations identified as having the potential to impact a strategic laboratory response.

### 1. Laboratory investigation

When investigating a new or emerging pathogen, early response considerations include developing, validating, sharing and implementing evidence-based testing protocols and recommendations in close collaboration with interjurisdictional laboratory partners. Establishing standardized laboratory-based case confirmation criteria may also be prioritized to support consistent case reporting and surveillance across impacted jurisdictions (2). The rapid development of testing capacity was a critical consideration from the outset of Canada's national COVID-19 response. In anticipation of the arrival of COVID-19 in Canada, NML worked to develop molecular diagnostic testing methods that were used to successfully confirm the first presumptive-positive COVID-19 case in January 2020. NML continued to provide confirmatory reference testing and quality assurance support to responding provincial and territorial PHL partners to ensure the ongoing accuracy of national case detection (19).

Response efforts may also demand sustained, high-volume front-line screening and/or confirmatory testing in excess of routinely available laboratory capacity. Under these circumstances, implementing testing criteria and triage protocols based upon known risk factors may become a consideration to prioritize laboratory investigations appropriately and to manage limited resources. This was a key NML consideration during its initial domestic response to the Zika epidemic, which posed significant capacity challenges as demand for Zika testing persisted at elevated levels well beyond the initial 2015–2016 response period (6). During early COVID-19 response, Canadian provinces and territories similarly established testing criteria to prioritize testing within existing laboratory capacities. This approach was taken as overwhelming global demands on international supply chains significantly impacted the ability to rapidly secure necessary laboratory supplies, equipment and reagents; including personal protective equipment (PPE), specimen collection swabs, viral transport media, test kits, reagents and testing platforms (20,21).

The Checklist identifies various response considerations with the potential to influence the timely coordination of laboratory investigation, ranging from requirements for specimen collection and transportation, to laboratory testing and result reporting. These considerations include 1) the ability to collect, store and transport specimens to meet specimen acceptance criteria for testing, 2) biosafety, biosecurity and infection control considerations, 3) legislative and regulatory requirements, 4) laboratory testing and case confirmation criteria and 5) triaging protocols for priority testing. Quality control and standardization of testing methods and result reporting processes were considered essential to all aspects of a coordinated laboratory response.

### 2. Laboratory response capacity and training

For responding public health laboratories, an early capacity consideration may be the availability of validated, pathogen-specific front-line screening and confirmatory diagnostic test methods with known performance characteristics. National reference laboratories may be expected to maintain the capability to rapidly develop and validate new test methods when external capacity either does not exist, or may not be reliably available under outbreak circumstances (2). Public health laboratories may also be required to participate in coordinated, interjurisdictional sourcing and ongoing clinical validation of laboratory testing methods, equipment and supplies; particularly when dealing with multiple and/or changing vendors to manage supply chain continuity issues, as during the COVID-19 response (21). Time-sensitive, resource-intense requirements of this nature can place considerable demands on responding scientific and technical staff, as there is a parallel need to maintain routine, mandated program activities.

Laboratory response capacity may be further challenged as personnel are impacted by government-mandated measures implemented to prevent community-level transmission of a newly emerging infectious disease (EID) threat, or by contracting EID-associated illness. As experienced during the COVID-19 response, such measures may include extended periods of self-isolation/quarantine due to confirmed disease, symptomatic illness or potential exposure (case-contact, travel history); as well as "remote work" and alternate work arrangements required to manage child and family-care issues resulting from school closures and other stay-at-home and physical distancing measures (22,23).

Engagement and mobilization of personnel with response-essential skills and expertise may play a pivotal role in addressing surge capacity challenges both internal and external to a responding laboratory organization, as was demonstrated by the NML domestic responses to COVID-19 and Zika, and through the international deployment of mobile laboratory response teams to support on-site Ebola virus testing during the 2014–2016 Ebola epidemic in West Africa (5). NML also deployed mobile laboratory capacity domestically to support testing of recently returned Canadian travellers at quarantine sites during the initial COVID-19 pandemic response.

Depending upon the magnitude and duration of response requirements, decentralization of diagnostic testing and other technology transfer activities may also be prioritized to expand interjurisdictional laboratory capabilities on a temporary or long term basis, and to improve access by remote or isolated

populations (24). During the Canadian domestic responses to Ebola, Zika and, most recently, COVID-19, NML and its provincial PHL counterparts worked collaboratively to support decentralization of front-line laboratory testing within select jurisdictions to improve the distribution of response capabilities where feasible, while maintaining centralized national capacity for reference and confirmatory testing (21,25).

The ability to flexibly address capacity and capability challenges specific to new or EID threats was deemed critical to response efforts. Related considerations include the collaborative identification of laboratory response capabilities with interjurisdictional public health partners, and the dynamic assessment of surge capacity and training requirements to support response-critical activities.

The Checklist highlights various considerations that may be explored if additional surge capacity is required. These include investigating alternate approaches to enhance laboratory test throughput and information sharing, engaging EOC site support for response coordination, and identifying surge capacity personnel with in-demand skillsets through response-focused personnel inventory processes. Surge positions may be cross-trained and mobilized to alternate laboratory sites within or external to the organization, or deployed to the field under the oversight of senior scientific staff as part of a mobile laboratory response team.

## 3. Laboratory surveillance and data management

Laboratory result data are well-recognized as a critical input to support infectious disease-related epidemiological investigations, surveillance and public health action (26,27). NML response activities have emphasized that laboratory investigations are often similarly dependent on the timely availability of epidemiological data to inform test triaging processes, the selection of appropriate diagnostic and confirmatory testing algorithms, and appropriate interpretation of test results. During the domestic response to Zika, the ability to triage and route specimen testing using known risk factors relied on the provision of epidemiological and clinical data as part of the test requisition process (e.g. pregnancy status, travel history and onset date for symptomatic cases). Interjurisdictional linkage of NML test results with cases under investigation was similarly reliant on the provision of appropriate unique identifiers (28).

To support timely, integrated laboratory-based surveillance and data management, early response considerations may include rapid, iterative, consensus-based development of an infectious disease case definition that incorporates laboratory and epidemiological case confirmation criteria relevant within the current outbreak context (24). Integral to this process is the identification of data elements required for laboratory investigation, case confirmation and surveillance efforts. Alignment of confirmation criteria and data element requirements between reporting jurisdictions may warrant consideration to ensure consistent case detection, reporting and surveillance; and comparability of subnational, national and international surveillance data wherever possible. An interrelated surveillance consideration is the ability to rapidly link laboratory results with cases under investigation, and to link confirmed cases with an outbreak or outbreak source. Linkage and data integration may prove challenging when laboratory and epidemiological data elements relevant to case investigations are generated or collected by separate public health jurisdictions.

Laboratory-based surveillance and response activities may be further enhanced by implementing standardized public health genomics approaches and other advanced molecular epidemiology tools to improve pathogen and outbreak detection, characterization, source attribution and transmission pattern identification. Use of whole genome sequencing methods to support real-time, laboratory-based surveillance of select pathogens also offers the promised advantage of unambiguous nomenclature for interjurisdictional comparison purposes (29).

The Checklist outlines a number of considerations that may impact laboratory-based surveillance and data management. A review of data flow requirements may be valuable at the outset of an EID threat response, including the need for standardized approaches to document, monitor and report laboratory investigation results and outbreak summary information to meet the intelligence requirements of various stakeholders (e.g. lab-confirmed case reporting by jurisdiction, percent positive tests versus total tests performed for target groups/populations). It may also be helpful to explore the potential of existing laboratory information management systems, web-based public health informatics and surveillance platforms, and other enabling tools to flexibly meet pathogen-specific surveillance and response requirements. As observed during NML participation in early COVID-19 response activities, desired functions may include timely and secure data collection, linkage and integration; laboratory test result and surveillance indicator reporting, public health alerting and predictive modeling (30–32). For laboratory partners implementing "omics" approaches to enhance outbreak detection and response capabilities, longer term considerations may include operational and infrastructure support requirements for data transfer pipelines and bioinformatics tools used to transmit, acquire, analyze, interpret and report whole genome sequencing and other "omics" results (27,32,33). Interjurisdictional sharing of laboratory-generated surveillance data may also require consideration within the context of relevant legislative and regulatory frameworks and information sharing agreements, in alignment with established jurisdictional and organization-specific public health roles (33–37).

## 4. Interjurisdictional engagement and communication

To support evidence-based development of laboratory guidelines, clinical recommendations, public health surveillance and intervention strategies, it may be important to consider strengthening intelligence-sharing mechanisms with relevant public health partners and interjurisdictional networks (14,38). This may involve exploring alternative collaborative and multi-disciplinary approaches. Within Canada, CPHLN serves a critical function by providing an established, secretariat-supported network of national, provincial and territorial PHL experts to support timely consensus-based interjurisdictional development of response strategies, recommendations and guidelines (9).

NML response efforts have also highlighted the importance of clearly identifying event-specific communication and reporting structures to support effective internal and external routing of requests and information. This includes consistent messaging using "single-window" points of contact for responding programs and task groups within the laboratory organization whenever possible. Such considerations are not unique to laboratory response; the need for clearly articulated leadership roles and communication structures was also identified in an assessment of broader public health resilience considerations related to community-level Ebola virus disease response in the United States (10). To support the routing of time-sensitive external requests, NML has had success with the provision of single-window access to laboratory support via a 24-hour emergency contact number, combined with site-based EOC support to centrally coordinate and direct requests within an incident command system context (15). NML also maintains a public-facing, web-based Guide to Laboratory Services as a reference for external test requisitions (28).

Increased frequency of time-sensitive interjurisdictional engagement and risk communication requirements may pose ongoing challenges to response coordination, particularly when a health event generates significant public concern, media interest and political attention over a prolonged time period. Laboratory subject matter experts responsible for organizational response may also be those most in-demand to address information requests from multiple sources.

As identified in the Checklist, a strategic communication strategy may become crucial to safeguard the valuable time of responding staff, facilitate coordinated stakeholder engagement, and ensure consistent messaging of public health intelligence to meet audience-specific needs. Use of social media tools and other web-based platforms may provide opportunities to improve the accessibility of laboratory guidance to public health professionals, the media and the public.

## 5. Research and ethics

In Canada, active engagement in public health-related research is considered a core PHL function, as the ongoing maintenance of this scientific capacity provides the required foundation for responsive public health action (13,17). As demonstrated during the 2003 SARS coronavirus outbreak response, immediate laboratory-related public health research priorities may include rapid pathogen identification and characterization, including genomic sequencing (39). Launched in response to the 2020 COVID-19 coronavirus pandemic, the Canadian COVID Genomics Network initiative will, with public health laboratory engagement, create a "virus to patient" genomic database through large-scale sequencing of host and viral genomes to support national and international research into viral pathogenicity, evolution and health outcomes; as well as vaccines and therapeutics (40).

Other immediate response priorities may include the development and validation of diagnostic testing methods, and applied biosafety research with a focus on timely knowledge translation. Pathogen transmission and vector competence studies may also be prioritized to help characterize risk and inform prevention strategies. As during the Zika response, this may be particularly relevant when the potential for introduction and sustained transmission of an emerging vector-borne disease has yet to be assessed for non-endemic settings (41).

To reduce morbidity and mortality within at-risk populations, national research priorities may extend to collaborative development and implementation of public health interventions including vaccines and other medical countermeasures, as evidenced by the NML response to Ebola virus disease (42,43). Continuing COVID-19 pandemic response efforts have demonstrated the imperative need to understand the host immune response to infection, which is required to inform laboratory testing strategies to determine individual and population-level immune status (e.g. via seroprevalence studies), as well as therapeutic and vaccine development and implementation strategies (44). In April 2020, the Government of Canada launched the COVID-19 Immunity Task Force, bringing together national experts in academia, hospitals and public health to help address outstanding questions related to COVID-19 immunity, including 1) immune status and duration of immunity post-infection and 2) the scope of population-level immunity to support national epidemic response efforts (45).

When faced with an EID threat, there may be an urgent need to strategically direct public health research activities to bridge important gaps in scientific knowledge and technical capabilities. Levels of research engagement may vary considerably amongst laboratory entities, contingent upon jurisdictional context and mandated public health responsibilities.

As outlined in the Checklist, an early response consideration may be to prioritize collaborative research activities within existing resources and capabilities. Research priorities may include pathogen identification and characterization studies, diagnostic and reference testing method development and validation studies, host and population-level immunity-related research, transmission and vector competency studies, vaccine and other medical countermeasure development and assessment, applied biosafety research and public health surveillance studies. To streamline response coordination, it may also be helpful to clearly differentiate between applied public health research and surveillance activities that are integral to routine laboratory response, and other targeted research activities that will require prior consent and completion of research ethics approval processes.

The EID response task forces and networks may also be convened to pursue high priority, time-sensitive research initiatives, engaging public health laboratory expertise along with other scientific experts in academia, hospitals and the private sector. When collaborative research involves interjurisdictional partners or multi-disciplinary teams, considerations may involve coordinating multiple research ethics board review processes, and addressing issues related to authorship and intellectual property in a manner that supports timely publication to inform public health decision-making.

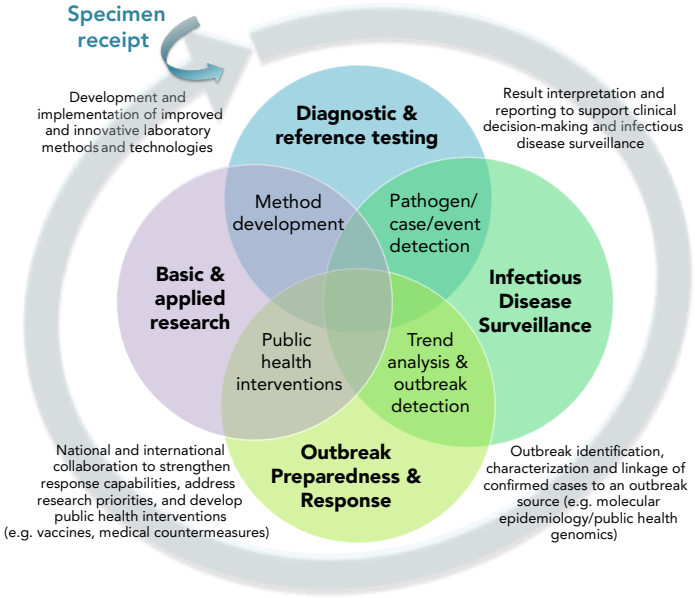
# Discussion

## Interdependence of Public Health Laboratory functions

When assessing and prioritizing laboratory preparedness and response considerations, it is important to note that significant interdependencies exist between key PHL functions, which include the following: diagnostic and reference testing; infectious disease surveillance; outbreak preparedness and response; and basic and applied research (**Figure 1**). At the interface of these cyclic, adjacent PHL functions are highly interrelated EID response requirements. A robust public health response capable of meeting each of these mutually interdependent requirements is reliant upon the available capacity of the PHL system to fulfill each of its core functions.

Figure 1 is a Venn diagram comprised of four overlapping circles, with each circle representing a distinct PHL function, and each area of overlap indicating its interdependency with the immediately adjacent function. The Venn diagram is circumscribed by a circular, clockwise-oriented arrow to indicate the cyclical, ordinal nature of the four functions, beginning with laboratory receipt of a specimen for testing, which is depicted as an external input to the Venn diagram. Interdependencies indicated by areas of overlap between the four public health laboratory functions include laboratory capabilities for the following:

**Figure 1: Interdependencies of Public Health Laboratory response functions**




1. Pathogen, case and event detection, including the interpretation and reporting of test results to support both clinical decision-making and infectious disease surveillance activities
2. Trend analysis and outbreak detection, including disease detection and monitoring activities to support timely outbreak identification, characterization and the linkage of confirmed cases to an outbreak source (e.g. using molecular epidemiology/public health genomics methods)
3. Public health interventions, including national and international collaboration to strengthen response capabilities and advance public health intervention research, including the development of medical countermeasures such as vaccines and other therapeutic approaches
4. Method development, including development and implementation of improved and innovative laboratory methods and technologies

Within the context of interdependent PHL functions, it becomes apparent that individual considerations identified within each of the five Checklist response themes may have important, far-reaching implications for interrelated response activities within the broader public health context. For example, the use of standardized laboratory investigation methods for case detection (Theme 1: Laboratory investigation) may facilitate reliable, well-integrated surveillance mechanisms which, in-turn, allow timely interjurisdictional case and outbreak detection and monitoring (Theme 3: Laboratory surveillance and data management). Public health intelligence generated through high-quality, purpose-based surveillance activities and shared in a timely manner via collaborative expert networks (Theme 4: Interjurisdictional engagement and communication) may then enable the identification of research priorities to inform short and long term preparedness and response efforts

(Theme 5: Research and ethics). Strategic mobilization and training of surge capacity positions may be required to support priority activities across the response continuum (Theme 2: Laboratory response capacity and training).

When operating within resource-constrained environments and under significant time pressures, oversights during the initial planning phase have the potential to impact overall response effectiveness in a variety of ways. Impacts may include a lack of resource allocation to support overlooked laboratory response priorities, delays or disruptions to the sharing of scientific intelligence or the acquisition and distribution of materiel and biologicals, the absence of appropriate laboratory representation at key decision-making tables and other downstream challenges. The importance of rapid funding mechanisms was highlighted by the World Health Organization following the response to Ebola in West Africa, as "disease outbreaks often move faster than the money allocated to respond to them" (46).

A particular challenge may be the ability to maintain routinely mandated activities in parallel with the demands of evolving laboratory response efforts, and may require careful assessment of workforce surge capacity and prioritization of activities. For example, internal reallocation of highly-trained staff from existing programs to meet immediate surge response requirements may create significant operational gaps throughout the organization that must also be addressed to maintain overall public health response capacity. On a long term basis, gaps in expertise may cumulatively impact laboratory capacity over the course of multiple, sequential and/or concurrent response efforts. Such capacity shortfalls may not easily be remedied using short term approaches in the face of an emerging threat. This effect was observed by NML shortly after the commencement of COVID-19 response activities, and has been an ongoing consideration associated with prior extended infectious disease responses. While first identified as an issue in the 2003 Naylor Report which detailed lessons learned in the wake of Canada's public health response to the SARS pandemic, the potential impacts of more recent, post-2014 shortfalls in public health expertise and resources on overall public health response capacity in Canada were again emphasized by Dr. David Butler-Jones on February 3, 2020; just days after the World Health Organization declared the novel 2019–nCoV coronavirus outbreak to be a Public Health Emergency of International Concern on January 30, 2020 (13,47,48).

## Checklist implementation—additional considerations

The multifaceted, interdependent nature of laboratory response considerations poses various challenges to high-level coordination efforts. In the absence of a strategic approach, there is a real risk that not all considerations relevant to the response context will be identified for action in a timely manner.

In the Canadian setting, as in others, numerous guidance documents exist to provide in-depth, pathogen and disease-specific response recommendations. These range from the standardized testing methods, operating procedures and outbreak response protocols used within laboratory environments, to emergency planning and response guidelines used both organizationally and by interjurisdictional laboratory networks (28,49–51). Jurisdiction-specific legislative and regulatory requirements define the parameters within which laboratory response activities are conducted to support biosafety, biosecurity and privacy of information; while other regulations and multi-lateral information sharing agreements (e.g. Multi-Lateral Information Sharing Agreement [MLISA]) set-out disease-specific requirements and principles for interjurisdictional information sharing to support timely surveillance and outbreak response (34,35,52,53).

Operationally, the purpose of the Checklist is to serve a complementary function relative to other, more prescriptive, context-specific laboratory guidance documents. Implementation of a flexible, non-prescriptive Checklist tool is proposed as a means to facilitate overall response coordination by quickly identifying and prioritizing relevant considerations across multiple response themes.

While the Checklist was designed for ease of use in its current reference form, it is recognized that not all Checklist considerations may be relevant or within the normal scope of response activities for a given laboratory entity (e.g. targeted research, development of medical counter-measures). As such, additional customization of Checklist content and terminology to reflect site-specific laboratory roles and responsibilities may optimize overall usefulness. Functionality may be further enhanced by developing supplementary appendices to capture important jurisdiction-specific references and resources, and to help direct further action regarding any considerations identified as relevant during a given Checklist review process.

Implementing organizations and networks may also wish to consider preferred approaches to engage participants in the Checklist review process, including the balance of subject matter expert and working-level representation needed to reflect the scope of potential response activities. It may be helpful to identify operational triggers that might prompt a formal Checklist review, recognizing that such triggers may vary under outbreak and inter-outbreak circumstances, and may be internal or external to the responding organization. For example, comprehensive Checklist review may be considered an immediate organizational priority when responding to infectious disease threats for which response protocols have yet to be developed. Alternately, review may be initiated in response to a relevant external trigger, such as the identification of a potentially high-consequence EID threat, or the formal declaration of a Public Health Emergency of International Concern by the World Health Organization (36).

Checklist implementation may be considered operationally within the context of existing Emergency Management Program planning tools to enhance mitigation, preparedness, response and recovery functions in alignment with the four phases of emergency management (15). For example, a Checklist review process may be initiated in the event that response efforts require centrally coordinated surge support, including formal activation of an EOC associated with the laboratory organization. Review by a subject matter expert group representative of programs engaged in, or potentially impacted by, response activities may be initiated and coordinated by laboratory management or via the EOC. High-level considerations, gaps and proposed action items relevant to the current response may be documented using the electronic version of the Checklist tool, then distributed for follow-up in alignment with the incident command system currently in effect (15). Operationally, a quality-controlled, evergreen Checklist document may be centrally maintained for use as a planning reference during outbreak and inter-outbreak periods.

Whereas each Checklist review process may identify numerous relevant considerations, it may only be feasible to act on a subset of time-sensitive considerations in the midst of a response, while deferring others for future action during an inter-outbreak period. It should also be considered that once the initial response to an EID threat concludes, mandated laboratory responsibilities may not return to their preoutbreak baseline on an immediate or long term basis. As new tests are incorporated into routine laboratory test menus, and testing levels remain elevated to support ongoing case detection and surveillance, each subsequent EID response has the potential to cumulatively impact baseline laboratory activities such that additional resources are required to sustain inter-outbreak activities at "new normal" levels. Periodic review of Checklist considerations during inter-outbreak periods may help to identify resulting operational gaps and inform longer term efforts to strengthen laboratory response capabilities.

### Limitations

The Checklist content primarily reflects the perspectives and experiences of Canadian and international PHL stakeholders directly involved in the development and review process. While considerations for laboratory organizations operating at local and regional levels (e.g. hospital laboratories and front-line diagnostic laboratories) may differ in focus and scope, they remain highly relevant to the overall responsiveness of the PHL ecosystem. An overarching limitation associated with the Checklist initiative is the extent to which the Checklist will be implemented and used as intended by laboratory organizations and networks involved in public health response.

### Conclusion

When faced with an EID threat, effective laboratory response requires the time-sensitive coordination of multiple interdependent activities to support public health action. Preliminary input suggests that the Checklist may serve as a useful tool to rapidly and systematically identify key response considerations; highlight operational requirements and gaps and inform strategic planning, prioritization and decision-making to mitigate risk.

A primary objective of the Checklist initiative was to ensure the broad availability of a reference version that can be used in its current form, or adapted by implementing laboratory entities to enhance setting-specific relevance. Post-implementation, the Checklist is intended to serve as a "living document" that can be updated to reflect evolving roles, considerations and lessons learned through future laboratory response efforts.

Checklist implementation, customization, routine review and updating within the context of existing emergency management frameworks may provide an opportunity to further strengthen laboratory outbreak preparedness and response capabilities, and inform the development of long term public health resilience. Going forward, any future assessment of Checklist usefulness across implementing organizations and jurisdictions will need to take these factors into account.

## Authors' statement

Authorship contributions are as follows:
TE — Conceptualization, content development (Checklist tool, Appendices, Figure illustration), writing, review and editing
GT — Conceptualization, review and editing
TK — Conceptualization, review and editing
MG — Conceptualization, review and editing

### Competing interests

The authors have no competing interests.

## Acknowledgements

All individuals, organizations and networks involved in preliminary technical discussion, development and review of the Checklist document are gratefully acknowledged for their contributions, including the following:

**National Microbiology Laboratory (NML):** S Beddome, Dr. C Corbett, K Gordon, S Guercio, C Jorowski, L Kearney, K Keith, C Ouellette, S Radons Arneson, C Yoshida, R Cole (Laboratory Liaison Technical Officer [LLTO], Manitoba [MB]), K Cronin (LLTO, Ontario [ON]), R DePaulo (LLTO, Saskatchewan [SK]), LA Jalbert (LLTO, New Brunswick [NB]), K Macdonald (LLTO, British Columbia [BC]), C Phillips (LLTO, Nova Scotia [NS]), L Wong (LLTO, Alberta [AB])

**Canadian Public Health Laboratory Network (CPHLN):** Dr. M Gilmour (Federal Co-Chair, NML), Dr. P Van Caeseele (Provincial Co-Chair, Cadham Provincial Laboratory, Winnipeg, MB), Dr. T Kuschak (NML, CPHLN Secretariat), Dr. M Krajden (BC Centre for Disease Control Public Health Laboratory, Vancouver, BC), Y Chang (BC Centre for Disease Control Public Health Laboratory, Vancouver, BC), Dr. G Tipples (Alberta Provincial Laboratory for Public Health, Alberta Precision Laboratories, Edmonton, AB), Dr. P Levett (Roy Romanow Provincial Laboratory, Regina, SK), Dr.F Jamieson (Public Health Ontario Laboratories, Toronto, ON), Dr. J Longtin (Laboratoire de santé publique du Québec, Ste-Anne-de-Bellevue, Québec [QC]), Dr. G German (Health Prince Edward Island [PEI], Charlottetown, PEI), Dr. D Haldane (Queen Elizabeth II Health Science Centre, Halifax, NS), Dr. G Zahariadis (Newfoundland and Labrador [NL] Public Health Laboratory, St. John's, NL), Dr. R Garceau (Centre hospitalier universitaire Dr-Georges-L.-Dumont, Moncton, NB)

**Global Health Security Action Group (GHSAG) Laboratory Network:** Dr. M Gilmour (Co-Chair, Winnipeg, MB, Canada), Dr. JA Diaz Quiñonez (Co-Chair, Mexico City, Mexico), Dr. T Kuschak (Secretariat Lead, Winnipeg, MB, Canada), Dr. A Nitsche (Berlin, Germany), A Roberts (London, United Kingdom), Dr. A Di Caro (Rome, Italy), C Chadwick (Washington DC, United States), Dr. M Saijo (Tokyo, Japan), Dr. MW Shaw (Atlanta, United States)

## Funding

Support for this work was provided by the Public Health Agency of Canada.

## Supplemental material

Supplemental materials for this article are available online.

Supplemental I: Laboratory response checklist for infectious disease outbreaks (https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2020-46/issue-10-oct-1-2020/ccdrv46i10a01s1s2-eng.xlsx)

Supplemental II: Laboratory response checklist for infectious disease outbreaks—use recommendations (https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2020-46/issue-10-oct-1-2020/ccdrv46i10a01s1s2-eng.xlsx)

Supplemental III: Laboratory response checklist for infectious disease outbreaks (https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2020-46/issue-10-oct-1-2020/ccdrv46i10a01s3-eng.pdf)

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# Canadian Public Health Laboratory Network: Prioritized support for northern, remote and isolated communities in Canada

Respiratory Virus Infections Working Group[1]

***Suggested citation:*** Respiratory Virus Infections Working Group. Canadian Public Health Laboratory Network: Prioritized support for northern, remote and isolated communities in Canada. Can Commun Dis Rep 2020;46(10):322–3. https://doi.org/10.14745/ccdr.v46i10a02
***Keywords:*** COVID-19, Canada, point-of-care testing

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## Statement on the distribution of COVID-19 point-of-care supplies—August 26, 2020

In the spirit of Truth and Reconciliation, and in an effort to ensure equitable healthcare access, the Canadian Public Health Laboratory Network (CPHLN) advocates for the prioritized distribution of point-of-care supplies to northern, remote and isolated (NRI) communities. These communities have significantly greater proportions of First Nations, Metis and Inuit peoples than communities in southern Canada and often experience obstacles related to rapid access to conventional health care, such as diagnostic testing services, and to linkage to care. On-site services may not be available and challenges with specimen transport can lead to increased turnaround time and delays in diagnosis/treatment for affected individuals. These delays may then lead to further challenges in contact tracing and implementation of effective public health measures to contain transmission networks.

There are only a limited number of near-care or point-of-care (POC) testing options currently approved in Canada for detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Testing equipment and supplies are severely limited, leading to delays in testing. Current data demonstrate that most transmissions occur in the first five days of illness and, as such, delays in diagnostic turnaround times maximize the potential for spread of SARS-CoV-2. As a result, it is critical to prioritize the distribution of SARS-CoV-2 POC testing supplies to areas where they will have the greatest public health impact, including NRI communities throughout Canada.

The only option for SARS-CoV-2 POC testing currently available in Canada for use outside a laboratory is the Xpert® Xpress SARS-CoV-2 assay, which operates on the GeneXpert® system (Cepheid, Sunnyvale California, United States). The Xpert Xpress SARS-CoV-2 assay has a rapid turnaround time (approximately 50 minutes) with an option for Early Assay Termination as early as 30 minutes for positive specimens. As the GeneXpert system is used to test for many common infections, more than 200 instruments are already distributed across Canada, primarily in urban centres in the south. Urban centres also have access to centralized, laboratory-based testing, with high-throughput commercial or laboratory-developed tests.

Centralized laboratory-based testing is unavailable or difficult to access for NRI communities. To date, 61 POC devices and more than 9,100 tests have been distributed to remote communities and current allocations of tests remain limited. As such, it is essential to develop a coordinated approach for test distribution to ensure that NRI communities receive appropriate supplies to provide adequate diagnostic support.

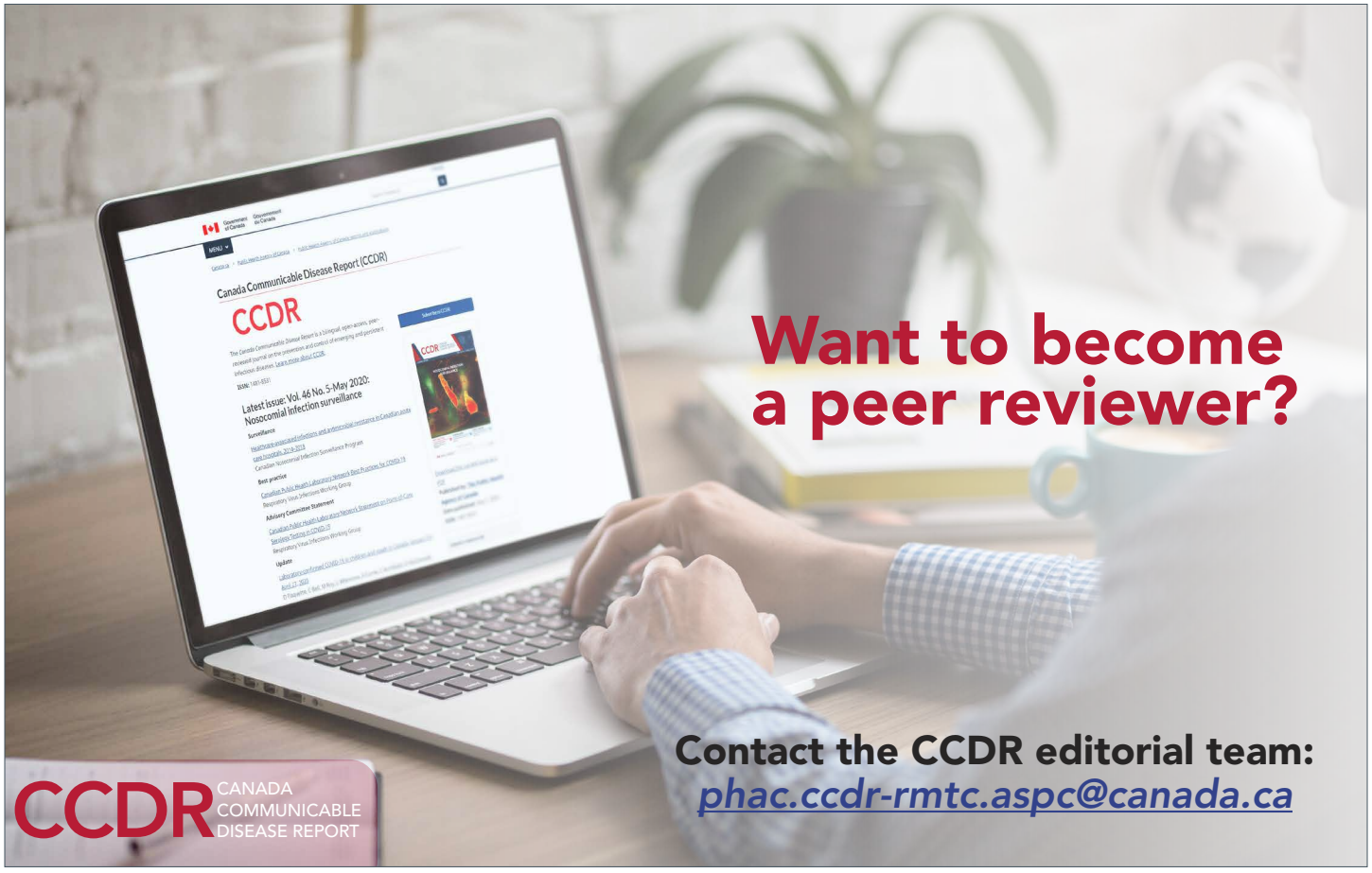
Because they do not have timely access to centralized laboratory-based testing, some NRI communities have turnaround times for POC SARS-CoV-2 testing that can extend beyond 7–10 days. In addition, risk factors for severe COVID-19 cases are prevalent within NRI communities, including diabetes and heart disease. Thus, there is concern that the spread of COVID-19 within and between these communities will stress the existing healthcare system. The allocation of Canada's limited resources should be guided by ethical principles. In this case, equitable and fair distribution of resources in accordance to the principle of justice is paramount in addressing the needs, vulnerabilities and consequent health inequities experienced by those living in NRI communities.

**It is the position of CPHLN that specific, dedicated support should be provided for NRI communities. Provincial and territorial health authorities that have access to conventional, laboratory-based diagnostic testing options are encouraged**

**to prioritize near-care/POC equipment and testing supplies to NRI communities.** While recognizing that each jurisdiction is unique, CPHLN recommends that provinces and territories develop a coordinated approach to deploy a significant proportion of their Xpert Xpress SARS-CoV-2 assay supply to NRI communities.

## Key points from this statement

- The Xpert Xpress SARS-CoV-2 assay POC testing supplies are critically low across Canada.
- The majority of these POC testing supplies are being utilized in urban centres where other testing options are available.
- Because of these supply shortages, it can take up to 7–10 days to receive a SARS-CoV-2 test result in NRI communities.
- Diseases that are associated with severe COVID-19 infection, such as diabetes and heart disease, are prevalent in NRI communities.
- The POC testing supplies should be prioritized for the vulnerable NRI communities who lack equitable access to conventional testing services and where they will have the greatest impact on public health.
- Starting immediately, until there is an increase in the allocation of supplies to Canada, health authorities should consider redeploying a significant proportion of Xpert Xpress SARS-CoV-2 assay testing supplies to NRI communities to support the current and future pandemic waves.
- This prioritization of POC SARS-CoV-2 testing is in respect of the principle of justice, thereby ensuring equitable distribution of resources according to need and promoting well-being for those who otherwise lack equivalent options for rapid diagnostic services.



# Summary of the NACI Supplemental Statement on Mammalian Cell Culture-Based Influenza Vaccines

Angela Sinilaite[1], Ian Gemmill[2,3], Robyn Harrison[4,5] on behalf of the National Advisory Committee on Immunization (NACI)*

## Abstract

**Background:** Mammalian cell culture-based technology is an innovative technique for influenza vaccine manufacturing that may be a valuable alternative to overcome some of the problems and vulnerabilities associated with conventional egg-based influenza vaccine production. Flucelvax® Quad (Seqirus, Inc.) is the first and only mammalian cell culture-based quadrivalent inactivated, subunit influenza vaccine (IIV4-cc) authorized for adult and pediatric use in Canada. The National Advisory Committee on Immunization (NACI) has not previously made a recommendation on cell culture-based influenza vaccines in any population.

**Objective:** To review the available evidence for the efficacy, effectiveness, immunogenicity, and safety of IIV4-cc, and to summarize the NACI recommendation regarding the use of Flucelvax Quad in Canada in adults and children.

**Methods:** A systematic literature review on the vaccine efficacy, effectiveness, immunogenicity and safety of IIV4-cc in persons four years of age and older was performed. The systematic review's methodology was specified *a priori* in a written protocol. The NACI evidence-based process was used to assess the quality of eligible studies, summarize and analyze the findings, and develop a recommendation regarding the use of Flucelvax Quad in adults and children. The proposed recommendation was then considered and approved by NACI in light of the available evidence.

**Results:** Thirteen eligible studies were included in the evidence synthesis. In the four observational studies that assessed vaccine effectiveness of IIV4-cc, there were some data indicating potentially improved protection against influenza compared to conventional egg-based quadrivalent inactivated influenza vaccines (IIV4) or trivalent inactivated influenza vaccine (IIV3), particularly against A(H3N2) virus infection. There was also some evidence that IIV4-cc may be more effective than egg-based trivalent or quadrivalent influenza vaccines against non-laboratory confirmed influenza-related outcomes, but there is insufficient evidence for laboratory-confirmed outcomes. Two randomized controlled trials assessed the immunogenicity and safety of IIV4-cc compared with mammalian cell culture-based trivalent inactivated, subunit influenza vaccine (IIV3-cc). The IIV4-cc was well-tolerated and the reported solicited local and systemic adverse events were generally mild to moderate in intensity, self-limited and did not precipitate sequelae. One clinical review of cases and six peer-reviewed randomized controlled trials (four in adults and two in children) that reported on the safety of IIV3-cc were included in the review. The evidence on immunogenicity and safety was consistent across these studies and showed that there was no significant difference in adults and children four years of age and older who had received IIV3-cc or an egg-based IIV3.

**Conclusion:** NACI concluded that there is fair evidence (Grade B Evidence) that Flucelvax Quad is effective, safe, and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults and children nine years of age and older. NACI recommends that Flucelvax Quad may be considered among the IIV4 offered to adults and children nine years of age and older (Discretionary NACI Recommendation).

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***Suggested citation:*** Sinilaite A, Gemmill I, Harrison R, on behalf of the National Advisory Committee on Immunization (NACI). Summary of the NACI Supplemental Statement on Mammalian Cell Culture-Based Influenza Vaccines. Can Commun Dis Rep 2020;46(10):324–32. https://doi.org/10.14745/ccdr.v46i10a03
***Keywords:*** National Advisory Committee on Immunization, NACI, mammalian, cell culture, MDCK, influenza vaccine

## Introduction

Influenza vaccine production using mammalian cell culture-based technology is an innovative technique that may offer enhanced manufacturing scalability, sterility, timeliness and flexibility and, thus, may be a valuable alternative to overcome some of the problems and vulnerabilities associated with conventional egg-based production (1–4). Influenza A(H3N2) viruses can undergo changes that decrease antigenic relatedness to wild-type, circulating viruses when they are grown in eggs, and that certain egg-adaptive mutations may negatively affect the immunogenicity, efficacy and effectiveness of standard egg-based influenza vaccines, especially during influenza A(H3N2)-dominant seasons (4–10). Cell culture-based influenza vaccines, solely derived from cell culture-based candidate vaccine viruses (CVVs), are insulated from such egg-adaptive changes and have the potential to provide enhanced protection in some seasons compared to standard egg-based influenza vaccines (1,4,5). Flucelvax Quad (Seqirus, Inc.) is the first and only available mammalian cell culture-based quadrivalent inactivated, subunit influenza vaccine (IIV4-cc) to be authorized for use in Canada in adults and children nine years of age and older (11). Since the vaccine first became available, the Flucelvax quadrivalent formulation (licensed as Flucelvax Quadrivalent or Flucelvax® Tetra in other jurisdictions) has been prepared from viruses propagated in mammalian cell lines (proprietary 33016-PF Madin-Darby Canine Kidney [MDCK] cell lines) adapted to grow freely in suspension in culture medium. However, prior to the 2019–2020 influenza season, some of the CVVs provided to the manufacturer had been originally derived in eggs. The Flucelvax quadrivalent formulation for the 2019–2020 influenza season was the first to be manufactured using CVVs for all four influenza viruses that were derived solely from mammalian cell lines from the initial virus isolation through to the full manufacture of the vaccine, making the vaccine egg-free (2).

The National Advisory Committee on Immunization (NACI) has not previously made a recommendation on cell culture-based influenza vaccines in any population. The objective of this advisory committee statement is to review the evidence for efficacy, effectiveness, immunogenicity, and safety that is available for Flucelvax Quad, and to provide provincial and territorial health authorities and health care professionals with guidance on its use in adults and children.

## Methods

A systematic literature review on the vaccine efficacy, effectiveness, immunogenicity and safety of IIV4-cc in persons four years of age and older was performed. Mammalian cell culture-based influenza vaccines have been approved for use by the United States (US) Food and Drug Administration in adults and children four years and older since the 2013–2014 influenza season for the last six years and effectiveness, immunogenicity and safety data is currently available for this age group.

The systematic review's methodology was specified *a priori* in a written protocol that included review questions, search strategy, inclusion and exclusion criteria and quality assessment. NACI's Influenza Working Group (IWG) reviewed and approved the protocol. A search strategy based on the objective was developed in consultation with a federal Reference Librarian from the Health Library of Health Canada and the Public Health Agency of Canada. Searches were restricted to primary research studies and case reports published in English or French, in the EMBASE, MEDLINE, Scopus, ProQuest Public Health and ClinicalTrials.gov electronic databases from inception until February 12, 2019. Registered clinical trials and grey literature from international public health authorities and National Immunization Technical Advisory Groups were also considered.

Two reviewers independently screened the titles and abstracts and eligible full-text articles.

Studies were included if they met the following criteria:

1. The study population or subpopulation consisted of individuals four years of age and older
2. Study assessed efficacy and effectiveness, immunogenicity, or safety of Flucelvax Quad or safety of Flucelvax
3. Primary research studies from peer-reviewed scientific literature
4. Case reports and case series
5. Registered clinical trials and grey literature from international public health authorities
6. The study was published in English or French

Studies were excluded if they met one or more of the following criteria:

1. The study did not present data on any of: efficacy, effectiveness, immunogenicity or safety of Flucelvax Quad, or the safety of Flucelvax
2. The study is in a language other than English or French
3. The study is a non-human or *in vitro* study

4. The article is not a primary research study
5. The article is an editorial, opinion, commentary or news report
6. The article is an economic study, clinical practice guidelines, consensus conference or health technology assessment report
7. The article was a doctoral dissertation, master's thesis or conference summary

Flucelvax Quad has overlapping composition with Flucelvax, which is a trivalent cell culture-based influenza vaccine (IIV3-cc) produced using the same MDCK manufacturing platform (12,13). Therefore, studies that assessed the safety of Flucelvax were also included in this literature review *post hoc* to supplement the evidence base for the safety outcome. Specialty trivalent vaccines (i.e. high-dose trivalent inactivated influenza vaccine [IIV3-HD] and adjuvanted trivalent inactivated influenza vaccine [IIV3-adj]) were also added as comparator vaccines *post hoc*, since these comparisons would originally have been excluded as there is currently no comparable quadrivalent formulation of these vaccines.

Data from included studies were extracted into evidence tables using a piloted data abstraction template. The quality (internal validity) of included studies was assessed using criteria outlined by Harris *et al.* (14). Data extraction and quality assessment were completed by one reviewer and verified by a second reviewer. Results from included studies were synthesized narratively and analyzed according to NACI evidence-based process (15) to develop a new recommendation. Following thorough review of the evidence, NACI approved the recommendation.

## Results

The systematic review retrieved 827 unique articles, of which thirteen were retained for data extraction and analysis. Four studies reported on the effectiveness of IIV4-cc. Two peer-reviewed studies (one in adults and one in children) investigated the immunogenicity and safety of IIV4-cc. No studies that assessed the immunogenicity of Flucelvax Quad compared to egg-based IIV (trivalent or quadrivalent) were identified. One clinical review of cases and six peer-reviewed randomized controlled trials (RCTs) (four in adults and two in children) provided evidence for the safety of IIV3-cc. No efficacy studies for IIV4-cc were identified and studies evaluating the efficacy of IIV3-cc were beyond the scope of the systematic review. A flow diagram of the study selection process is presented in **Figure 1**. Key study characteristics are summarized in **Tables 1** and **2**.

**Figure 1: PRISMA flow diagram of the study selection process for the systematic review on the efficacy, effectiveness, immunogenicity and safety of Flucelvax Quad**

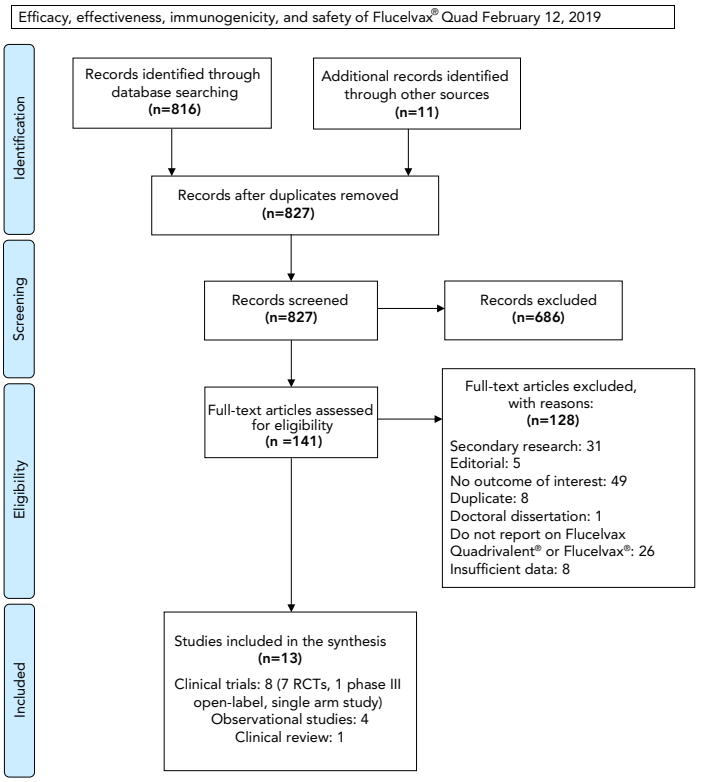


**Table 1: Characteristics of IIV4-cc studies included in the systematic review**

| Study | Design (vaccine) | Study population | Outcomes |
|---|---|---|---|
| DeMarcus *et al.* (2019) | • Test-negative case-control<br>• 2017–2018 influenza season<br>• (IIV4-cc versus egg-based IIV4) | • US DOD healthcare beneficiaries six months–94 years of age<br>• 1,757 cases (laboratory-confirmed):<br>- 531 vaccinated; IIV4-cc (n=192), egg-based IIV4 (n=339)<br>• 2,280 controls:<br>- 977 vaccinated; IIV4-cc (n=314), egg-based IIV4 (n=663) | • VE against laboratory-confirmed influenza<br>• OR for individuals vaccinated with cell-derived vaccine compared to egg-derived vaccine |

**Table 1: Characteristics of IIV4-cc studies included in the systematic review** (*continued*)

| Study | Design (vaccine) | Study population | Outcomes |
|---|---|---|---|
| Izurieta *et al.* (2018) | • Retrospective cohort<br>• 2017–2018 influenza season<br>• (IIV4-cc vs egg-based IIV4-SD, egg-based IIV3-SD, IIV3-adj, IIV3-HD) | • Medicare beneficiaries 65 years of age and older<br>- IIV4-cc (n=653,099)<br>- Egg-based IIV4-SD (n=1,844,745)<br>- Egg-based IIV3-SD (n=8,449,508)<br>- IIV3-adj: (n=1,465,747)<br>- IIV3-HD (n=1,007,082) | • rVE for influenza-related health care interactions |
| Boikos *et al.* (2018)<br>NCT 01992094 | • Retrospective cohort<br>• (IIV4-cc vs egg-based IIV4)<br>• 2017–2018 influenza season | • EMR of US patients four years of age or older<br>- IIV4-cc (n=92,192)<br>- Egg-based IIV4 (n=1,255,983) | • Propensity-score matched rVE against ILI |
| Klein *et al.* (2018) | • Retrospective cohort<br>• 2017–2018 influenza season<br>• (IIV4-cc vs egg-based IIV) | • Kaiser Permanente members 4–64 years of age<br>- IIV4-cc (n=932,874)<br>- Egg-based IIV (n=84,440) | • rVE against laboratory-confirmed influenza A(H3N2)<br>• rVE against all laboratory-confirmed influenza |
| Bart *et al.* (2016) | • RCT<br>• 2013–2014 influenza season<br>• (IIV4-cc vs IIV3-cc) | • Healthy adults 18 years of age and older<br>- IIV4-cc (n=1,335)<br>- IIV3-cc, B/Yam (n=676)<br>- IIV3-cc, B/Vic (n=669) | • GMT ratio 22 days post-vaccination<br>• Seroconversion rate three weeks (day 22) post-vaccination<br>• HI antibody response<br>• Seroprotection rate<br>• Solicited AEs within seven days of vaccination<br>• Unsolicited AEs (day 1–22 post-vaccination) |
| Hartvickson *et al.* (2015)<br>NCT01992107 | • RCT<br>• 2013–2014 influenza season<br>• (IIV4-cc vs IIV3-cc) | • Healthy children 4–18 years of age; stratified into two age cohorts: 4–9 years of age and 9–18 years of age<br>- IIV4-cc (n=1,159)<br>- IIV3-cc, B/Yam (n=593)<br>- IIV3-cc, B/Vic (n=581) | • GMT ratio 22 days post-vaccination<br>• Seroconversion rate three weeks (day 22) post-vaccination with last dose<br>• Seroprotection rate<br>• Solicited AEs within seven days of vaccination<br>• Unsolicited AEs (within 22 days of vaccination) |

Abbreviations: AE, adverse event; EMR, Electronic medical record; GMT, geometric mean titre; HI, hemagglutination inhibition; IIV, inactivated influenza vaccine; IIV3, trivalent inactivated influenza vaccine; IIV3-adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-cc, cell-culture based trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccines; IIV4-cc, cell-culture based quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; ILI, influenza-like illness; NCT, National clinical trial number; OR, odds ratio; RCT, randomized controlled trial; rVE, relative vaccine effectiveness; US DOD, United States Department of Defense; VE, vaccine effectiveness

**Table 2: Characteristics of IIV3-cc studies included in the systematic review**

| Study | Design (vaccine) | Study population | Outcomes |
|---|---|---|---|
| Ambrozaitis *et al.* (2009) | • RCT<br>• 2005–2006 influenza season<br>• (IIV3-cc versus egg-based IIV3) | • Healthy adults 18–60 years of age<br>• IIV3-cc (n=1,028)<br>• Egg-based IIV3 (n=171) | • AEs within seven days of vaccination |
| Szymczakiewicz-Multanowska *et al.* (2009)<br>NCT00492063 | • Phase III, observer blind RCT<br>• 2004–2005 influenza season<br>• (IIV3-cc vs egg-based IIV3) | • Healthy adults 18 years of age and older<br>• IIV3-cc:<br>- 18–60 years of age (n=652)<br>- 61 years of age and older (n=678)<br>• Egg-based IIV3:<br>- 18–60 years of age (n=648)<br>- 61 years of age and older (n=676) | • AEs within seven days of vaccination |
| Nolan *et al.* 2016 | • Phase III, observer blind RCT<br>• 2013–2014 influenza season<br>• (IIV3-cc vs egg-based IIV3) | • Healthy children and adolescents 4–17 years of age<br>• IIV3-cc (n=1,372)<br>• Egg-based IIV3 (n=683) | • AEs within seven days of vaccination |
| Vesikari *et al.* (2012) | • Phase II/III, observer-blind RCT<br>• October 2007–July 2008<br>• (IIV3-cc vs egg-based IIV3) | • Healthy children and adolescents 3–17 years of age<br>• IIV3-cc two doses 3–8 years of age (n=1,599)<br>• IIV3-cc single dose 9–17 years of age (n=652)<br>• Egg-based IIV3 3–8 years of age (n=1,013)<br>• Egg-based IIV3 9–17 years of age (n=316) | • AEs within seven days of vaccination |
| Frey *et al.* (2010)<br>NCT00630331 | • Observer-blind RCT<br>• 2007–2008 influenza season<br>• (IIV3-cc vs egg-based IIV3) | • Healthy adults 18–49 years of age<br>• IIV3-cc (n=3,813)<br>• Egg-based IIV3 (n=3,669)<br>• Placebo (n=3,894) | • AEs within seven days of vaccination |

**Table 2: Characteristics of IIV3-cc studies included in the systematic review** (*continued*)

| Study | Design (vaccine) | Study population | Outcomes |
|---|---|---|---|
| Loebermann *et al.* (2019)<br>NCT01880697 | • Phase III open-label, single-arm, study<br>• 2013–2014 influenza season<br>• (IIV3-cc) | • Healthy adults<br>• IIV3-cc:<br>- 18–60 years age (n=63)<br>- 61 years age and older (n=63) | • AEs following vaccination |
| Moro *et al.* (2015) | • Clinical review of cases identified through VAERS<br>• 2013–2014, 2014–2015 influenza seasons<br>• (IIV3-cc) | • Persons vaccinated with IIV3-cc during July 1, 2013 through March 31, 2015 (reports received by April 30, 2015); excluding non-US reports<br>• Total reports reviewed: n=629<br>• Persons vaccinated with IIV3-cc July 1, 2013–March 31, 2015 (reports received by April 30, 2015); excluding non-US reports<br>• Reports with an AE:<br>- n=309<br>- during 2013–2014 influenza season (n=389)<br>- during 2014–2015 influenza season (n=240) | • AEs following vaccination |

Abbreviations: AE, adverse event; IIV3, trivalent inactivated influenza vaccine; IIV3-cc, cell-culture based trivalent inactivated influenza vaccine; NCT, National clinical trial number; RCT, randomized controlled trial; US, United States; VAERS, Vaccine Adverse Event Reporting System

## Vaccine efficacy and effectiveness

Four observational studies, two peer-reviewed and two not peer-reviewed, were identified that assessed the vaccine effectiveness of IIV4-cc compared to egg-based IIV against laboratory-confirmed influenza infection during the 2017–2018 influenza season in the US (16–19). Of these four studies, two were of good quality (17,18) according to the criteria outlined by Harris *et al.* (14), while the quality of the other two studies (16,19) could not be assessed because they were published as conference abstracts or posters. There were some data indicating that IIV4-cc may offer improved protection against influenza compared with conventional egg-based IIV4 or IIV3, particularly against A(H3N2) virus infection. The IIV4-cc may also be more effective than egg-based trivalent or quadrivalent influenza vaccines against non-laboratory confirmed influenza-related outcomes, including influenza-related health care interactions and influenza-like illness, but there was insufficient evidence for laboratory-confirmed outcomes. Although some data suggests that IIV4-cc may be more effective against laboratory-confirmed influenza A(H3N2) virus infection than egg-based IIV, there was no consistent and statistically significant difference in effectiveness identified for adults or children vaccinated with IIV4-cc compared with egg-based IIV.

## Immunogenicity

Two peer-reviewed studies (20,21) that reported on the immunogenicity and safety of Flucelvax Quadrivalent compared with different IIV3-cc formulations were identified in this review; one study by Bart *et al.* (20) was conducted with adult subjects 18 years of age and older, while the other study by Hartvickson *et al.* (21) focused on pediatric subjects four to 17 years of age. The immunogenicity outcomes assessed by these studies included geometric mean-fold rise in haemagglutination assay (HA) titres (i.e. ratio of post to pre-vaccination geometric mean titre), seroprotection rate (i.e. proportion of participants with HA titres of at least 40 post-vaccination) and seroconversion rate (i.e. proportion of participants with at least a four-fold increase in HA titres post-vaccination, HA titre increase from less than 10 prevaccination to at least 40 post-vaccination, or both). In both studies, IIV4-cc demonstrated non-inferiority, based on geometric mean titre (GMT) ratio and seroconversion rates, and met the threshold for seroprotection for all influenza strains contained in the IIV3-cc vaccines.

The immunogenicity of Flucelvax Quad is further supported by evidence from the clinical development program for Flucelvax that has been licensed in the US, but for which licensure has never been sought in Canada. Flucelvax has demonstrated non-inferiority to standard egg-based IIV3 comparators for hemagglutination inhibition (HI) antibody responses overall to any strain in adults 18 years of age and older and for A(H1N1) and B strains specifically, but not A(H3N2), for persons four to 17 years of age, based on post-vaccination GMT ratios and seroconversion rates (22–25). Notably, IIV3-cc was manufactured using egg-derived CVVs prior to the implementation of manufacturing methods using CVVs solely derived from MDCK cells.

## Safety

Two peer-reviewed studies assessed the safety of Flucelvax Quadrivalent (IIV4-cc) compared with different IIV3-cc formulations; one focused on healthy adults (20) and the other on healthy children four years of age and older (21). The safety outcomes assessed included solicited local and systemic adverse events (AE) from day 1–7 post-vaccination, serious adverse events (SAE) through six months after the last vaccination, and unsolicited AEs from day 1–23 post-vaccination. The reported

solicited local and systemic AE for both adults and children were generally mild to moderate in intensity, self-limited, and did not precipitate sequelae. Serious adverse events were rare and similar in frequency between the quadrivalent and trivalent formulations of the cell culture-based vaccines being compared. No studies that assessed the safety of IIV4-cc compared with egg-based IIV (trivalent or quadrivalent) were identified in this review.

Flucelvax Quadrivalent has been licensed in the US for use in adults and children four years or older in since 2016. Since authorization, no safety signals have been identified through routine pharmacovigilance. One clinical review of cases (26) and six peer-reviewed RCTs (1,27–31) (four in adults and two in children) that reported on the safety of IIV3-cc were included in the review to supplement the evidence base for the safety outcome. The evidence on safety was consistent across studies and showed that there was no significant difference in adults and children four years of age and older who had received the IIV3-cc and egg-based IIV3. Overall, Flucelvax was safe and well tolerated, with local and systemic solicited reactions as well as unsolicited AE and SAE comparable to those typically observed with other injectable egg-derived IIV3. The IIV3-cc also has an established record of safety, and no new safety signals have been identified through routine pharmacovigilance in the US or Europe where the vaccine has been licensed (22,23,25).

## Discussion

Flucelvax Quad is considered effective, immunogenic and safe in adults and children nine years of age and older, and has a comparable immunogenicity and safety profile to 1) egg-based influenza vaccines already licensed in Canada and 2) Flucelvax, which is a trivalent cell culture-based influenza vaccine that has been licensed in the US, but for which licensure has never been sought in Canada. The cell culture-based Flucelvax Quad can also provide broader protection against influenza B viruses when compared with trivalent influenza vaccines. There is a theoretical concern that inactivated influenza vaccines produced in canine kidney cells (MDCK 33016-PF) may cause adverse reactions in individuals with dog allergy. However, evidence from *in vitro* studies on the allergenicity of MDCK cell-based vaccines in individuals with documented allergies associated with dogs, as well as IIV-cc clinical trials and post-market safety surveillance, does not suggest that there is an elevated risk of hypersensitivity reactions as compared with egg-based influenza vaccines (32,33).

Implementation of cell culture-based influenza vaccine technologies and other alternatives to egg-based methods can also enable diversification of vaccine manufacturing platforms to overcome influenza vaccine supply vulnerabilities and improve vaccine-production capacity. Nevertheless, adaptation in cell culture-based influenza vaccines needs to be further investigated given the potential for mutations in the genetic segments of hemagglutinin and neuraminidase surface proteins resulting from serial passaging in MDCK cells (34,35). A more robust, comprehensive and consistent body of evidence, including data on comorbidities, pregnant women, health status, and other potential confounders (36), also needed to evaluate the relative effectiveness and safety of Flucelvax Quad compared with other injectable influenza vaccines. Therefore, ongoing monitoring of vaccine effectiveness, immunogenicity and safety will be important to compare prior and future seasons, across influenza subtypes and overall vaccine effectiveness for each vaccine type.

### Limitations

There are limited peer-reviewed studies currently available on the effectiveness, immunogenicity and safety of IIV4-cc manufactured using fully cell-derived CVVs. All studies that assessed effectiveness were conducted in the US during the same season (2017–2018), which was influenza A(H3N2)-dominant. As influenza seasons can vary widely from year to year, interpretation of the data from these observational studies is limited and further evidence on effectiveness gathered during influenza seasons with different circulating viruses is needed before a conclusion on the relative effectiveness can be made. Two of the observational studies (16,18) evaluating vaccine effectiveness utilized real-world primary care data from the electronic medical records of individual patients. The use of electronic medical record datasets for influenza vaccine effectiveness estimation has not yet been validated and the potential sources of bias and confounding still need to be further investigated. Furthermore, the clinical significance and directness of the evidence provided by influenza-related outcomes, which are surrogate measures of influenza activity, remain uncertain.

### NACI recommendation for individual level decision-making

The following recommendation for Flucelvax Quad supplements NACI's overarching recommendation for influenza vaccination, which is available in the NACI Seasonal Influenza Vaccine Statement. The overarching NACI recommendation for influenza vaccination is that an age appropriate influenza vaccine should be offered annually to anyone six months of age and older (Strong NACI Recommendation), noting product-specific contraindications.

1. **NACI recommends that Flucelvax Quad may be considered among the IIV4 offered to adults and children nine years of age and older (Discretionary NACI Recommendation)**

    - **NACI concludes that there is fair evidence to recommend vaccination of adults and children nine years of age and older with Flucelvax Quad (Grade B Evidence)**

The detailed findings of the literature review, and rationale and relevant considerations for this recommendation can be found in the NACI *Supplemental Statement – Mammalian Cell-Culture Based Influenza Vaccines* (37).

## Conclusion

There is fair evidence that Flucelvax Quad is effective, safe and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults and children nine years of age and older. NACI recommends that Flucelvax Quad may be considered among the IIV4 offered to adults and children nine years of age and older. NACI will continue to monitor the evidence related to cell-culture based influenza vaccines and will update this supplemental statement as needed and as data on Flucelvax Quad from several different influenza seasons accumulates.

## Authors' statement

AS — Writing, original draft, review, editing
IG — Review, editing
RH — Review, editing

The National Advisory Committee on Immunization (NACI) *Canadian Immunization Guide Chapter and Statement on Seasonal Influenza Vaccine 2020–2021: Supplemental Statement – Mammalian Cell-Culture Based Influenza Vaccines* was prepared by A Sinilaite, J Przepiorkowski, K Young, I Gemmill, and R Harrison on behalf of the NACI Influenza Working Group and was approved by NACI.

## Competing interests

None.

# Acknowledgements

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The National Advisory Committee on Immunization acknowledges and appreciates the contribution of A House (CIRID, PHAC), M Laplante (CIRID, PHAC), and K Merucci (Health Library, HC) to this statement.

## Funding

The work of the National Advisory Committee on Immunization is supported by the Public Health Agency of Canada.

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OVERVIEW

# Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry-based identification of security-sensitive bacteria: Considerations for Canadian Bruker users

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## Abstract

**Background:** The use of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) systems for bacterial identification has rapidly become a front line tool for diagnostic laboratories, superseding classical microbiological methods that previously triggered the identification of higher risk pathogens. Unknown Risk Group 3 isolates have been misidentified as less pathogenic species due to spectral library availability, content and quality. Consequently, exposure to higher risk pathogens has been reported within Canadian laboratory staff following the implementation of MALDI-TOF MS. This overview aims to communicate the potential risk to laboratory staff of inaccurate identification of security-sensitive biological agents (SSBA) bacteria and to provide suggestions to mitigate.

**Methods:** Cultures were manipulated in a Biosafety Level 3 laboratory, prepared for MALDI-TOF MS analysis via full chemical extraction and analysed on a Bruker Microflex LT instrument. Data were analyzed with Biotyper software; comparing raw spectra against MS profiles in three libraries: Bruker Taxonomy; Bruker Security-Restricted; and National Microbiology Laboratory (NML) SSBA libraries. Four years of Bruker MALDI-TOF MS data acquired in-house were reviewed.

**Results:** In general, the Bruker MS spectral libraries were less successful in identifying the SSBA bacteria. More successful was the NML library. For example, using a high score cut-off (greater than 2.0), the Bruker SR library was unable to identify 52.8% of our Risk Group 3 agents and near neighbours to the species-level with confidence, whereas the custom NML library was unable to identify only 20.3% of the samples.

**Conclusion:** The last four years of data demonstrated both the importance of library selection and the limitations of the various spectral libraries. Enhanced standard operating procedures are advised to reduce laboratory exposure to SSBAs when using MALDI-TOF MS as a front line identification tool.

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***Suggested citation:*** Antonation KS, Tracz DM, Dreger AD, Corbett CR. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry-based identification of security-sensitive bacteria: Considerations for Canadian Bruker users. Can Commun Dis Rep 2020;46(10):333–8. https://doi.org/10.14745/ccdr.v46i10a04

***Keywords:*** MALDI-TOF mass spectrometry, bacterial pathogens, clinical microbiology laboratory diagnostics, security-sensitive

## Introduction

Within the last decade, clinical microbiology laboratories have moved towards replacing traditional biochemical-based techniques with new matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) systems for bacterial identification (1,2). As a rapid, low-cost, straight-forward, and high-throughput method, MALDI-TOF MS is a powerful tool for bacterial diagnostics and has led to significant cost savings and improved efficiencies in laboratories

(3,4). However, the movement away from classical bacterial testing methods to unilateral use of MALDI-TOF MS presents a very real hazard for clinical laboratories. Despite cautionary tales in the open literature, many clinical laboratories prepare MALDI-TOF MS target plates with live bacterial culture on an open laboratory bench in a Biosafety Level 2 (BSL-2) laboratory area, leading to inadvertent exposure(s) with Risk Group 3 (RG3) agents that may have found their way through the laboratory (5–7).

Within Canada, five exposures to RG3 agents reported within a single nine-month period prompted a root cause investigation of the technology and its use (8). Su *et al*. found that between 2015 and 2017, eight incidents with 39 exposures were reported as a result of misidentification of RG3 bacteria via the use of commercial MALDI-TOF MS systems and associated libraries (8). *Brucella* species, *Francisella tularensis* and *Burkholderia pseudomallei* made up the bulk of these exposures. While the current Association of Public Health Laboratories (APHL) sentinel guidelines clearly define expectations when working with a possible RG3 agent, there are situations where unknown isolates fall into the laboratory workflow that may be RG3. These unknown bacteria can be misidentified as less pathogenic near neighbour species due to 1) the contents of the spectral library supplied with the MS instrument or 2) the quality of the bacterial sample (9–11).

Certainly, many of the security-sensitive bacteria do not have reference spectra in the library supplied with the MS instrument, and in the absence of reference spectra for these species, the tool will either produce no identification (as in the case with *Brucella* spp.) or provide the identity of a closely related organism. We have observed that identification scores provided for a *B. anthracis* misidentified as a *B. cereus* can be quite high (i.e. greater than 2.0; considered high confidence identification), causing no suspicion on the part of the clinician that misidentification has occurred until further testing is complete, prolonging the possible exposure period.

Further, the 2018 *Canada Communicable Disease Report* indicated that some laboratorians did not know which reference library they were using for identification (8). Assuming that this implied a lack of understanding in the content and confidence of the identification library, we re-examined the last four years of MALDI-TOF MS spectra derived from well-characterized or reference strains of security-relevant bacteria and near neighbours that were obtained in-house to bring awareness of the diagnostic sensitivity and specificity of MALDI-TOF MS libraries and considerations for their use. The laboratory at the Public Health Agency of Canada's National Microbiology Laboratory (NML) focusses on security-sensitive biological agents (SSBAs), and is the gatekeeper for the Canadian Laboratory Response Network. As such, we have previously reported on both the safety of MALDI-TOF MS preparation methods and the sensitivity of the libraries for identification of the bacterial SSBAs (12–14). Reviewing the last four years of data demonstrated both the importance of library selection and the limitations of the various libraries.

## Methods

Cultures were manipulated in a Biosafety Level 3 (BSL-3) laboratory, prepared for MALDI-TOF MS analysis via full chemical extractions (70% ethanol-70% formic acid-acetonitrile) and brought to a Bruker Microflex LT instrument (Bruker Daltronics) housed in BSL-2 laboratory, as previously described (13). FlexControl software (version 3.4, build 135) acquired spectra based on 500 individual laser shots of four independent spots per sample.

Data were analyzed with Biotyper software (ver 3.1, build 66), searching raw spectra against bacterial mass spectral profiles (MSP) in the following libraries: 1) the Bruker Taxonomy library (n=5,989 MSPs, not containing SSBAs); 2) the Bruker Security-Restricted (SR) library (n=123 MSPs, containing SSBAs); and 3) a locally-developed NML SSBA library (n=121 MSPs, containing both SSBAs and near neighbour MSPs). In addition, the NML curated library contains high-quality MSPs that exceed the content of the Bruker SR library for *B. anthracis*, *Yersinia pestis*, *F. tularensis* and the *Brucella* species (11).

The top four Biotyper software MSP matches and their associated match score were recorded for each of four spots per bacterial sample to comprise the sample population. This was more representative of the sample distribution than choosing only the top single match per spot. Identification at the "secure genus identification, probable species identification" level (greater than 2.0 match score) was used for all comparative calculations throughout unless detailed otherwise. Diagnostic sensitivity and specificity were calculated for each SSBA against its near neighbour species, based on the greater than 2.0 match score threshold: *B. anthracis* (n=240 sample spots) versus other *B. cereus* complex species (n=256); *Y. pestis* (n=272) vs. *Y. pseudotuberculosis* (n=160); *F. tularensis* (n=528) vs. other *Francisella* (n=48). *Brucella* spp. (n=816) have no near neighbour.

## Results and discussion

Since the standard Bruker Taxonomy library does not contain any highly-pathogenic SSBA entries, the sensitivity for all SSBA samples using only the standard proprietary Bruker library is 0%. Laboratories that have access only to the Bruker library should consider obtaining additional libraries that contain SSBA spectral profiles and/or utilizing enhanced standard operating procedures to recognize a potential exposure threat (as described below). Only clinical laboratories that have access to the specialized Bruker SR library or to the NML SSBA library can identify

highly-pathogenic bacteria with MALDI-TOF MS technology at this time, with varying levels of confidence (as described below).

## *Yersinia pestis*

The MALDI-TOF MS analysis of 17 *Y. pestis* isolates (n=272 total identification results) and 10 *Y. pseudotuberculosis* isolates (n=160 identification results) yielded a sensitivity of 41.9% and specificity of 93.1% using the Bruker Taxonomy and SR library together (**Table 1**). In comparison, improved results for *Y. pestis* identification were obtained when using the NML SSBA library, which yielded a sensitivity of 70.6%.

**Table 1: Sensitivity and specificity values derived from MALDI-TOF MS diagnostic test identification of security-sensitive biological agent bacteria at the National Microbiology Laboratory (2014–2018)**

| SSBA bacteria | Target sample size | Non-target (near neighbour) sample size | Sensitivity of database | | Specificity of database | |
|---|---|---|---|---|---|---|
| | | | Bruker | NML | Bruker | NML |
| *Yersinia pestis* | 272 | 160 | 41.9% | 70.6% | 93.1% | 86.9% |
| *Francisella tularensis* | 528 | 48 | 32.2% | 77.5% | 100.0% | 100.0% |
| *Bacillus anthracis* | 240 | 256 | 86.3% | 90.4% | 80.5% | 98.8% |

Abbreviations: MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NML, National Microbiology Laboratory; SSBA, security-sensitive biological agent
Note: Values were calculated using sample identification results that had a match score of greater than 2.0, reflecting high confidence species-level identification. Sample size is comprised of top four identification results obtained from four spots per isolate

Even with the enhanced SSBA library, 80 of the 272 identification results did not identify *Y. pestis* correctly, but rather produced a *Y. pseudotuberculosis* identification (n=68) or, alternatively, allowed identification only to the genus-level. Indeed, these two species are genetically similar (15,16), which has resulted in the diagnostic misidentification that has been reported in the literature (17) and demonstrated with this data set. However, despite their relatedness, MALDI-TOF MS differentiation can be accomplished via a single biomarker peak at *m/z* 3065, which is associated with the plasmid-encoded protein Pla, as reported by Lasch *et al*. (18). Analysis of representative NML samples determined 65 of the 68 aforementioned *Y. pestis* misidentified as *Y. pseudotuberculosis* did have the *m/z* 3065 peak, which resulted in an increase in sensitivity of 95.6%. No *Y. pseudotuberculosis* spectral profile demonstrated this peak, for a specificity of 100%. Using this peak alone for *Y. pestis* differentiation is superior to both the results seen with the Bruker library and the NML's SSBA library.

Nevertheless, with or without an augmented library, laboratory staff should be aware that a top match of *Y. pseudotuberculosis* could actually indicate the presence of a *Y. pestis* isolate. In addition, small gram-negative isolates with characteristic safety pin staining and "fried egg" colony morphology should immediately cause reversion to BSL-3 practices in a BSL-2 environment and follow APHL sentinel guidelines to rule-out or refer-out.

## *Francisella tularensis*

Analysis of 33 known *F. tularensis* isolates (528 total identification results) determined a sensitivity rate of 32.2% using the Bruker Taxonomy and SR library (Table 1). Again, using the NML SSBA library, sensitivity was higher at 77.5%. Both gave a specificity of 100%; therefore, while a specimen can be falsely negative for *F. tularensis*, a positive identification of *F. tularensis* is certain. This is corroborated by a previous study by Seibold *et al*. (19), which found a Bruker library supplemented with *Francisella* spp. MSPs correctly identified 100% of *Francisella* isolates (n=45) to the species-level. Further, in this review, we found that achieving a secure genus, probable species identification (match score greater than 2.0) for *F. tularensis* was difficult. Many *F. tularensis* isolates were identified as such within the match score range of 1.7–2.0 (i.e. probable genus identification). A much greater percentage of identification results reached the higher confidence species-level score using the NML SSBA library rather than the Bruker SR library (77.5% vs. 32.2% had scores greater than 2.0), and a lesser proportion was unidentifiable entirely (8% vs. 19%), which reflects library reference spectral quality and quantity.

Although *F. tularensis* has no near neighbours that are as close as the *Y. pestis/Y. pseudotuberculosis* relationship, any *Francisella* genus-level identification using MALDI-TOF MS should cause immediate concern, especially when considered with the morphological observation of tiny gram-negative bacilli that are slow growing and show preference to media supplemented with cysteine.

## *Bacillus anthracis*

When comparing cultures of the *Bacillus cereus* complex, MALDI-TOF MS showed high sensitivity for detecting *B. anthracis*, but the Bruker libraries provided lower specificity than the NML's SSBA library (Table 1). Analysis of 15 known *B. anthracis* isolates (n=240 results) and 16 non-*B. anthracis*/*B. cereus* complex species (n=256 results) found both the Bruker SR library and the NML SSBA library had high sensitivity (86.3% and 90.4%, respectively), but the Bruker library was markedly lower in specificity than NML (80.5% and 98.8%, respectively). Both false positives and false negatives are possible, even with an augmented library, and an identification of any member of the *B. cereus* complex should stimulate awareness. Laboratories should also be aware of distinguishing features of *B. anthracis*: large (10 µM) gram positive, spore forming rods that exhibit ground glass colonies that are non-hemolytic and catalase positive. *B. cereus biovar anthracis* isolates have exhibited motility, thereby eliminating this characteristic as a tool for rule-out (20).

## *Brucella* species

The standard Bruker taxonomy library does not contain *Brucella* spp., and the Bruker SR library contains only *B. melitensis*. Thus, the sensitivity was 0% for non-*B. melitensis* species of *Brucella* (*B. abortus*, *B. canis*, *B. ovis*, *B. suis*). The Bruker SR library test sensitivity for *B. melitensis* (n=560) was 83.2%, with notably no other possible *Brucella* matches in that library. More informatively, *Brucella* spp. isolates were correctly-identified at the genus-level in 99.6% instances with the SR library and 100% with the NML-SSBA library. The power of the NML enhanced library is within species-level identification; here, individual *Brucella* species were identified (**Table 2**) with varied levels of sensitivity (48.8% to 88.4%), but with higher levels of specificity (82.8% to 99.3%). Ferreira *et al*. tested *Brucella* strains (n=131) against a MALDI-TOF MS library supplemented with *Brucella* MSPs, and found 100% correlation at a genus-level, but varying degrees of species-level identification (e.g. *B. abortus* at 82.4%, *B. melitensis* at 10.7%) (21). Using a custom-made MALDI-TOF library of 18 unique *Brucella* genotypes, Lista *et al*. correctly identified 98% of *Brucella* isolates (n=152) to the species-level (22). Other studies report MALDI-TOF MS species-level identification of *Brucella* isolates at an accuracy of 92% (23) and 97% (24).

**Table 2: MALDI-TOF MS identification of *Brucella* species with the National Microbiology Laboratory-developed SSBA library**

| *Brucella* species | Sensitivity (%) | Specificity (%) |
|---|---|---|
| *B. melitensis* | 88.4 | 82.8 |
| *B. abortus* | 53.1 | 96.0 |
| *B. canis* | 56.3 | 90.5 |
| *B. ovis* | 56.3 | 99.3 |
| *B. suis* | 48.8 | 98.4 |

Abbreviations: MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; SSBA, security-sensitive biological agent
Note: The proprietary Bruker library only contains *B. melitensis* profiles and no other *Brucella* species

Augmenting a MALDI-TOF MS library with *Brucella* spp. spectra would be the most appreciable gain for clinical laboratories due to the lack of near neighbours, and consequently, no identification or near neighbour trigger provided by the device. Regardless, labs should be aware of tiny gram-negative coccobacilli that stain weakly, grow slowly on chocolate media, and produce small, glistening colonies.

## Conclusion

An understanding of the device library limitations and the application of enhanced standard operating procedures are key requirements for clinical laboratories using MALDI-TOF MS as their primary bacterial identification method. Previous studies have cited the importance of supplementing proprietary libraries with local, in-house developed profiles for bacterial identification (9,11,25,26) and our data supports this for the Bruker MALDI-TOF MS. Custom MALDI-TOF MS libraries improve identifications, thereby limiting misidentification of high consequence SSBA and subsequent laboratory exposures and incorrect diagnosis. Comparing the overall sensitivity of the Bruker MALDI-TOF MS to identify security-sensitive bacteria (e.g. *B. anthracis*, *Y. pestis* or *F. tularensis*), using the different libraries, we found an improvement from 47.2% (Bruker Taxonomy and SR library) to 79.7% (NML SSBA library, inclusive of the *Y. pestis* biomarker peak analysis). If we disregard the rigid cut-off (using only match scores greater than 2.0) these values increase to 75% and 92.9%, respectively. This observation agrees with the results of Lasch *et al*. (10) who found, through an international ring-trial proficiency test panel, that identification results improved from 77% with a standard library and to 93.5% with the Robert Koch Institute supplementary library (10). Importantly, in-house libraries can be created if strains are available, which in the case of SSBA regulated pathogens is quite difficult. In Canada, SSBA work is limited, as only 0.2% of all regulated work involves activities with SSBAs, including both bacterial and viral RG3 and Risk Group 4 work (27). Thus, the distribution of the NML SSBA library to our Canadian public health laboratory partners is an important aspect of risk reduction.

Overall, MALDI-TOF MS is a powerful tool for signalling the presence of highly-pathogenic SSBA bacteria, but it is not a magic bullet. Diagnostic laboratories must consider augmentation of current practices with enhanced practices incorporating older tools such as Gram staining and colony morphology recognition, or moving sample preparation into a biological safety cabinet. The APHL recommendations state that sentinel laboratories should use the tube extraction method with filtration for suspected highly pathogenic bacteria and RG3 practices, including preparation in a biosafety cabinet. Written procedures for the recognition of the agents of bioterrorism and training should also be considered, in alignment with American Society for Microbiology and APHL sentinel guidelines, and bench cards illustrating features of high consequence bacteria can be incorporated into practice. Of note, all laboratories in Canada that reported exposure to an SSBA from MALDI-TOF MS use from 2015–2017 developed enhanced standard operating procedures, with triggers such as slow growth and observation of small gram-negative coccobacilli (8). Further incorporation of near neighbour warnings as detailed herein should further limit potential exposure incidents.

## Authors' statement

DT — Performed laboratory technical work, data analysis and interpretation, drafted and revised the paper
AD — Performed laboratory technical work, data analysis and interpretation, and revised the paper
KA and CC — Provided study conceptualization, data analysis and revised the paper

## Competing interests

None.

## Acknowledgements

Thank you to the staff of the National Microbiology Laboratory, including Dr. AD Tyler and the Bioforensics Assay Development and Diagnostics (BADD) section, the Special Bacteriology group, the National Microbiology Laboratory (NML) Media core service and NML's Mass Spectrometry & Proteomics core service.

## Funding

This work was supported by the Public Health Agency of Canada, Government of Canada.

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OVERVIEW

# Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of the current landscape of invasive meningococcal disease in children

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## Abstract

**Background:** Immunizations have led to a decrease in the incidence of invasive meningococcal disease (IMD) in Canada, but this infection still leads to significant morbidity and mortality.

**Objectives:** The purpose of this study was to determine the burden of illness and management of IMD in paediatric hospitals.

**Methods:** Data were collected on all cases of IMD in eight paediatric hospitals from 2013 to 2017.

**Results:** There were 17 cases of IMD. Three of eight hospitals had no cases. Just over half of the cases were serogroup B (n=9); a quarter (n=4) were serogroup W; less than a quarter (n=3) were serogroup Y; and one was unknown. Two infected children were not started on antibiotics until day one and day five after the initial blood culture was collected, but had uneventful recoveries. Six cases required admission to intensive care units; two died. Six cases had probable or proven meningitis. Thrombocytopenia was documented in seven cases. All cases had elevated C-reactive protein levels. Seven children received more than seven days of antibiotics; of these seven, only two had complications that justified prolonged therapy (subdural empyema and septic knee). Six cases had a central line placed.

**Conclusion:** IMD is now rare in Canadian children, but about one-third of the cases in our study required treatment in the intensive care unit and two died. Clinicians appear to not always be aware that a five to seven-day course is adequate for uncomplicated cases of bacteremia or meningitis.

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***Suggested citation:*** Robinson JL, Fanella S, Lopez A, Frankel C, McDonald J, Alghounaim M, Slinger R, Bowes J, Khan S, Comeau JL, Leifso K, Gunawan J, Barton M. Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of the current landscape of invasive meningococcal disease in children. Can Commun Dis Rep 2020;46(10):339–43. https://doi.org/10.14745/ccdr.v46i10a05

***Keywords:*** immunization, meningococcal disease, IMD, serotype W

## Introduction

Invasive meningococcal disease (IMD) manifests as bacteremia with or without seeding to other sites including the meninges. Despite marked advances in intensive care, IMD still leads to significant morbidity and mortality worldwide, with rates of over 200 cases per 100,000 population in some countries in select years (1).

An increasing number of cases due to a virulent serogroup C strain from the sequence type 11 (ST-11) clonal complex (CC) was first noted in 1986 in Canada, with outbreaks occurring in 1999–2001 (2). In response to these outbreaks, monovalent serogroup C meningococcal vaccines were added to routine infant immunization programs across Canada in 2002 through 2007 (2). All jurisdictions provide one dose at 12 months of

age and some also provide doses at younger ages (3). One dose of quadrivalent vaccine is now provided to adolescents in Canada with the exception of Québec, where a booster dose of monovalent C vaccine is given (4).

The incidence of IMD in Canada has decreased from approximately 1.5 cases per 100,000 population in 1990–1992 to 0.5 cases per 100,000 in 2006–2011 (5), primarily due to the virtual disappearance of disease due to serogroup C (6).

Up-to-date national data on uptake of infant or adolescent meningococcal vaccines in Canada are not available, but extrapolating from other vaccines, it seems likely that the uptake is approximately 85% for the infant vaccine and somewhat lower for the adolescent vaccine (7). Vaccine efficacy is difficult to study given the rarity of IMD, but waning of titres (8) and vaccine failures (9) have been described with monovalent C vaccine in other countries. To date, there is no evidence that serotype replacement has occurred with meningococcal vaccines in Canada (3,6) or elsewhere (10).

National data on IMD have appeared in peer review publications since 2011 (5). The objective of this study was to describe the characteristics, management and outcomes of children with IMD in paediatric tertiary care hospitals in Canada in recent years.

## Methods

This retrospective chart review study was conducted by the Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) at eight participating tertiary care paediatric hospitals in Halifax, Montréal, Ottawa, Kingston, Hamilton, London, Winnipeg and Edmonton. IMD was defined as a positive blood culture for *Neisseria meningitidis*. At each of the sites, the local laboratory identified inpatients and outpatients, aged up to and including 17 years, with positive blood cultures for *N. meningitidis*, from January 1, 2013, through December 31, 2017. Cases of bacteremia with positive blood cultures for species other than *N. meningitidis* were excluded. There were no other exclusions.

Chart reviews were then conducted for cases identified by the laboratories. Data on demographics, clinical course, treatment and outcome for eligible cases were entered into REDCap (Research Electronic Data Capture), a secure web application for building and managing online surveys and databases hosted by the University of Alberta. Given the small sample size, data analysis was limited to descriptive statistics.

Approval to conduct the study was obtained from the ethics review board at each site.

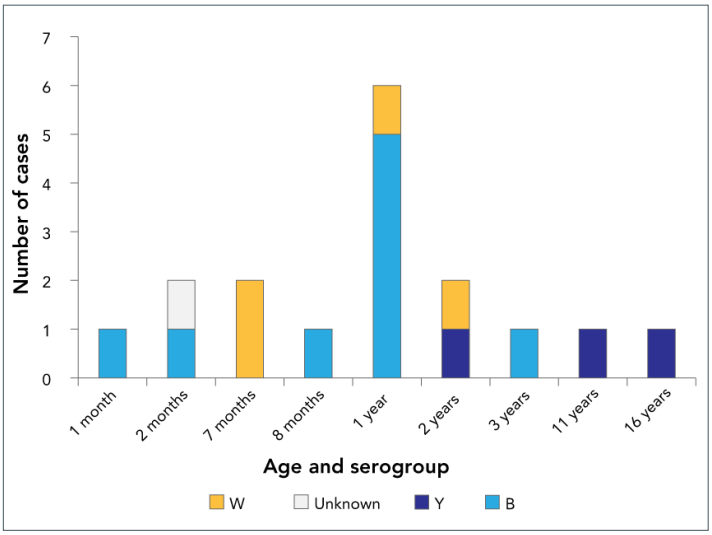
## Results

### Characteristics of cases of invasive meningococcal disease

From 2013 through 2017, five of the eight participating sites reported 17 cases of *N. meningitidis* bacteremia, with four cases reported annually in 2013 and 2014, and three cases annually in 2015, 2016 and 2017. The remaining three sites had no cases of bacteremia due to *N. meningitidis*.

Five cases of bacteremia due to other *Neisseria* species were excluded: two cases of *N. sicca*, one each of *N. mucosa* and *N. gonorrhea* and one of an unidentified species. Just over half of the cases (n=9) were serogroup B; a quarter (n=4) were serogroup W; less than a quarter (n=3) were serogroup Y; and one was an unknown serogroup (**Figure 1**).

**Figure 1: Age and serogroup of cases of invasive meningococcal disease (n=17) at eight tertiary care paediatric hospitals in urban centres, Canada, 2013–2017**




Of the 17 children, 13 were boys and six were younger than 12 months (Figure 1). Two cases had major underlying conditions: a two-month-old had repaired gastroschisis and a one-year-old had intestinal failure, neither of which has been linked to IMD. However, a two-year-old case was subsequently diagnosed with complement component 8 deficiency, which does increase the risk of IMD.

### Clinical course of cases

Three patients were transferred to the participating sites from smaller hospitals for unknown reasons. All but two were admitted on the day the blood culture was collected and were started on empiric antibiotic therapy that covered *N. meningitidis*. A febrile two-month-old patient with repaired gastroschisis was sent home and admitted for antibiotics the following day when the blood culture was found to be growing gram-negative

bacilli. A three-year-old patient with no history of fever was admitted five days after blood was sampled for culture when growth of *N. meningitidis* was found; the reason for obtaining the blood culture was unknown and the child remained bacteremic at admission. Both cases with delayed treatment had uncomplicated courses.

Data on fever were available for 15 cases. With the exception of the three-year-old mentioned above who was never febrile, all had fever prior to or within 24 hours of admission to hospital. Three children remained febrile for longer than 72 hours after appropriate antibiotics were started; all had probable meningitis.

Six of the 17 cases required admission to intensive care unit (ICU), with four requiring mechanical ventilation. Two of the patients, a 16-year-old with serogroup Y and a one-year-old with serogroup B, died on day 5 and day 18 of their ICU stay, respectively; both had extensive necrotic tissue. The four other patients stayed in the ICU for 1, 2, 6 and 22 days. The child with the longest stay required bilateral below-knee amputations.

### Laboratory findings

It is not known how many of the 17 children had lumbar punctures for a definitive diagnosis of meningitis, but two cases were proven meningitis and four were probable meningitis. The two proven cases, with *N. meningitidis* identified in cerebrospinal fluid (CSF), were a two-month-old and a two-year-old.

The first two probable cases were a two-month-old and seven-month-old with sterile CSF with pleocytosis (obtained after antibiotics); the seven-month-old developed a subdural empyema. The other two probable cases were the 16-year-old who died and a one-year-old who presented with a febrile seizure and was sent home on amoxicillin three days prior to the positive blood culture being drawn; neither had a lumbar puncture performed. Other sites of infection included septic arthritis of the knee in a two-year-old and circumferential cellulitis of the arm that was initially thought to be compartment syndrome in a one-month-old.

Initial peripheral white blood cell count ranged from 2.0 to 36.9 $\times 10^9$/L (mean 17.1 $\times 10^9$/L), with peak white blood cell count ranging from 13.7 to 40.9 $\times 10^9$/L (mean 24.3 $\times 10^9$/L). Seven children had thrombocytopenia (<150 $\times 10^9$/L). Mean peak C-reactive protein levels were 121 mg/L in the nine cases where it was measured (range: 50.7–189.9 mg/L).

### Antimicrobial therapy

The median duration of antibiotic therapy for IMD was seven days (minimum five days and maximum 17 days). Seven children received courses of antibiotic therapy that exceeded seven days; only two, the cases of subdural empyema and septic arthritis, clearly required a course of antibiotics longer than seven days.

Treatment was with ceftriaxone in all but one case; this patient was treated with cefotaxime. Patients were admitted for the entire course of intravenous antibiotics except for one who was treated on their sixth (and final) day as an outpatient. Oral antibiotics were used only for the child with septic arthritis who received seven days of amoxicillin-clavulanate treatment following eight days of ceftriaxone.

Ten patients were managed with peripheral intravenous (IV) cannulation only; of the remaining seven cases, one child already had a peripherally inserted central line (PICC) for intestinal failure, three children had traditional central lines placed, two children had PICCs inserted and one patient who was admitted to ICU had more than one central line inserted.

## Discussion

There were 17 cases of IMD in eight Canadian paediatric hospitals over a five-year period. Although there are no data for previous years, from 2013 to 2017 there was less than one case per centre every two years, which is low considering that these are primarily regional referral centres. This success may be attributed to infant and adolescent immunization programs. Still, about one-third of the children required ICU admission and two died.

Although this is a small number of cases, a hypervirulent clone that is not well covered by the current vaccines could lead to a much larger outbreak. For example, there are concerns that the hypervirulent serogroup W ST-11 CC is emerging in Canada (11). Serogroup W accounted for 19% (15/80 cases) of all cases of IMD in 2016 (11) versus 24% of cases in the current study. The ST-11 CC was first detected in Canada in 2014, but accounted for 85 of 93 serogroup W cases (91%) in 2016–2018 (11). This clone appears to primarily infect adults; it is possible that adolescent immunization has prevented disease in immunized children and indirectly prevented disease in younger siblings by preventing carriage.

The most common serogroup in IMD in children in Canada (6) and the United States (10) is B. An infant and an adolescent monovalent B vaccine are now licensed in Canada but are not used routinely due to the large number needed to vaccinate (NNV) to prevent one case of IMD (3). The relatively small absolute number of cases due to serogroup B infection in the current study (nine cases in eight centres over five years) supports that decision. The first dose of vaccine can be given at two months of age (depending on the province), but one dose is probably not sufficient to prevent IMD. Unlike serogroup C vaccines, the serogroup B vaccine licensed for infants does not prevent carriage so widespread use in the population may not prevent disease in young infants (12).

Management of IMD in Canada could be improved. Seven of the 17 cases received more than seven days of antibiotics (a five to seven-day course is recommended for bacteremia or meningitis) (13); only two of the seven cases had an indication for

longer therapy (subdural empyema and septic arthritis). Clinicians assume that an infection with an approximately 10% mortality rate (14) warrants a longer course of antibiotics, but this prolongs hospital stay and often necessitates placement of a central line.

### Strengths and limitations

The strength of this study is that it provides data on management and outcomes for IMD in Canada in recent years. The major limitation is that the study is not population based; some of the eight participating sites have no defined catchment area.

In addition, not all Canadian paediatric tertiary care hospitals participated in the study. What's more, children with an uncomplicated course or with rapid demise may never be admitted to a tertiary care hospital. Another limitation is that follow-up data were not collected; long term sequelae are typically not apparent at discharge.

Some of the longer courses of antibiotics may have been prescribed for legitimate indications that were not documented in patients' charts. Other limitations are that only eight centres were involved and immunization status was not available.

### Conclusion

IMD is now a rare condition in Canadian paediatric hospitals, although over one-third of cases identified in eight paediatric hospitals from 2013 to 2017 required ICU admission and two died. Many residents in training may never see a case. In this era of antimicrobial stewardship, clinicians should be reminded that a long course of antibiotics is rarely indicated for IMD. Ongoing surveillance should continue so that outbreaks are rapidly identified. Future studies should verify immunization status.

## Authors' statement

MB and JR had the idea for the study, wrote the protocol and designed the REDCap (Research Electronic Data Capture) form. JR wrote the first draft of the manuscript. All other authors collected data and reviewed the manuscript.

### Competing interests

None.

## Funding

No funding was received for this study.

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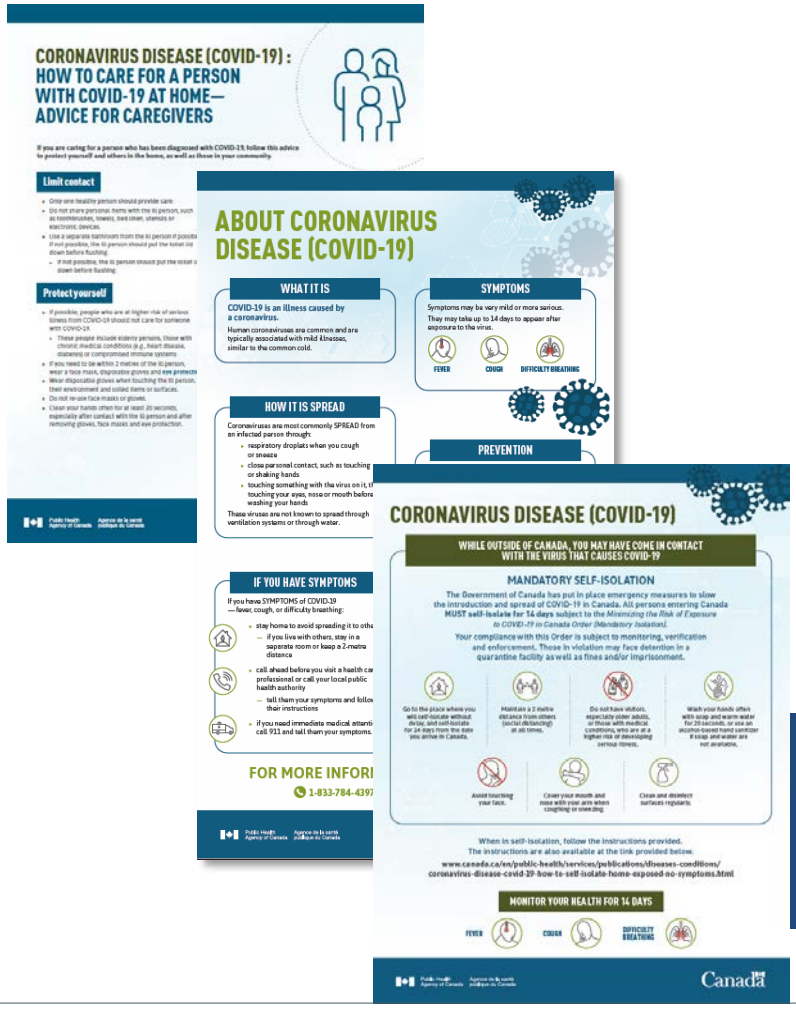
PREVENT THE SPREAD OF COVID-19

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# Descriptive epidemiology of deceased cases of COVID-19 reported during the initial wave of the epidemic in Canada, January 15 to July 9, 2020

Public Health Agency of Canada COVID-19 Surveillance and Epidemiology Team[1]

## Abstract

This rapid communication describes deaths among cases of coronavirus disease 2019 (COVID-19) in Canada by province and territory and by case characteristics. Of the 106,804 cases of COVID-19 reported in Canada as of July 9, 2020, 8,749 resulted in death, which represents a mortality rate of 23.3 per 100,000 population, and a case fatality rate (CFR) of 8.2%. Within Canada, the CFR ranged from 0% to 10.0% by province and territory, with the differences likely reflecting differences in the extent of the epidemic within each jurisdiction, and where and among whom localized outbreaks occurred (e.g. outbreaks in long term care homes, affecting older individuals with multi-morbidities). The CFRs increased with age and with the number of pre-existing medical conditions, and among residents of long term care and seniors' homes. Plans are underway to collect more detailed information on cases, including race and ethnicity, which will add to our understanding of the communities most impacted by COVID-19. Studies of excess mortality, a measure of the number of people who died from any cause as compared with the historical average, will help to clarify the full impact of COVID-19 within Canadian jurisdictions.

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***Suggested citation:*** Public Health Agency of Canada COVID-19 Surveillance and Epidemiology Team. Descriptive epidemiology of deceased cases of COVID-19 reported during the initial wave of the epidemic in Canada, January 15 to July 9, 2020. Can Commun Dis Rep 2020;46(10):344–8.
https://doi.org/10.14745/ccdr.v46i10a06
***Keywords:*** COVID-19, Canada, mortality, epidemiology, case fatality rate

## Introduction

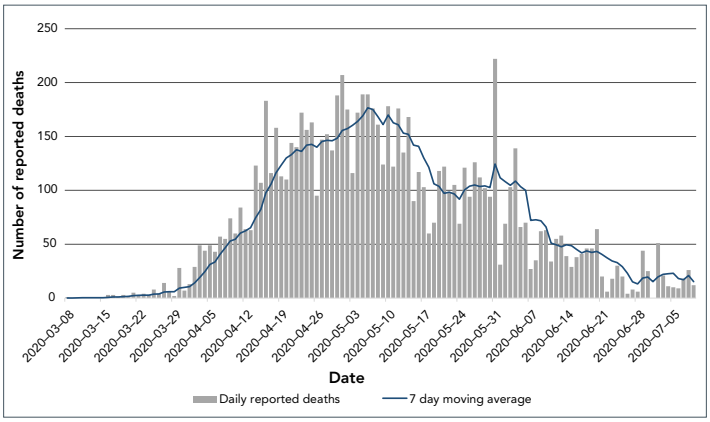
By early July 2020, Canada had successfully flattened the initial wave of the coronavirus disease 2019 (COVID-19) pandemic, bringing the average number of reported daily cases down from a peak of 1,600 in the last week of April to 290 cases in the week leading up to July 9, 2020. Tragically, during this initial wave, Canada reported the 20th highest crude mortality rate in the world as of July 9, 2020 (1). This rapid communication describes deaths among COVID-19 cases, using available data reported during this initial wave from January 1, 2020 to July 9, 2020, to inform action to minimise deaths due to COVID-19 moving forward.

## Current situation

As of July 9, 2020, 106,804 cases of COVID-19 have been reported in Canada, and the number of reported deaths among these cases was 8,749. The number of deaths reported daily increased steadily from the end of March to a peak in early May; an average of 177 deaths was reported daily between April 30 and May 6. The daily number of reported deaths steadily declined thereafter and in the week leading up to July 9, 2020, an average of 15 deaths was reported daily (**Figure 1**). This parallels the trend in the number of cases reported daily that was observed two to three weeks earlier. This was expected, since COVID-19-related deaths represent infections that occurred several weeks prior (2–4).

Canada's crude mortality rate as of July 9, 2020 was 23.3 COVID-19-related deaths per 100,000 population. Due to the time between the date of infection and the date of death, the final clinical outcome for more recently reported cases is not yet known and, therefore, this mortality rate likely underestimated the true rate. Canada's COVID-19 mortality rate was the 20th highest worldwide, based on available data, though it was comparable or lower than several European and North American countries (1). It is important to note, however, that the number of COVID-19-related deaths within a country is based on several interrelated factors, including the capacity of the healthcare system, how deaths are defined and captured, the stage of the

**Figure 1: Daily reported deaths among cases of COVID-19 in Canada and seven day moving-average, March 8 to July 9, 2020 (N=8,749)[a]**




Abbreviation: COVID-19, coronavirus disease 2019
[a] The large increase on May 31, 2020 is a reporting artifact, and was due to Québec reporting deaths that were previously identified but unreported

epidemic and the health and age distribution of a country's population. For these reasons, comparisons across countries should be interpreted with caution.

As of July 9, 2020, Canada's case fatality rate (CFR), calculated by dividing the number of total deaths by the number of reported cases, was 8.2%. As with the crude mortality rate, this is likely a biased measure of the true CFR, since the outcome (i.e. recovered or deceased) is not yet known for recently reported cases.

Across Canada, CFR ranged from 0% to 10.0% by province/territory (**Table 1**), and the mortality rate per 100,000 Canadian population ranged from 0.3 to 66.1 (among provinces and territories where there were deaths). After age standardizing, which adjusted for differences in the age distribution across provinces, the mortality rate per 100,000 population ranged from 0.2 to 60.4. After age-standardization, differences in mortality rates by province were likely due to a number of factors, including, most prominently, the spread of COVID-19 within long term care and seniors' homes. Ontario and Québec had the highest age-standardized mortality rates at 18.4 and 60.4, respectively, with over 70% of these deaths occurring in long term care homes and seniors' residences (Table 1).

Indeed, the impact of the COVID-19 pandemic on residents of long term care and seniors' homes has been severe. Approximately 81% of Canada's COVID-19 deaths have occurred among residents, as of July 9, 2020 (Table 1), with Ontario and Québec particularly affected, with 2,011 and 4,765 deaths, respectively, among residents of long term care and seniors'

**Table 1: Deaths among COVID-19 cases in Canada as of July 9, 2020, by province and territory**

| Province/territory | Total cases | Deaths[a] | Deaths among residents of long term care and seniors' homes[b] | Case fatality rate | Deaths per 100,000 population[c,d] | Age standardized death rate per 100,000[c,e,f] |
|---|---|---|---|---|---|---|
| Québec | 56,216 | 5,609 | 4,765 | 10.0% | 66.1 | 60.4 |
| Ontario | 36,348 | 2,703 | 2,011 | 7.4% | 18.6 | 18.4 |
| Alberta | 8,519 | 161 | 117 | 1.9% | 3.7 | 4.8 |
| British Columbia | 3,028 | 186 | 131 | 6.1% | 3.7 | 3.5 |
| Nova Scotia | 1,066 | 63 | 57 | 5.9% | 6.5 | 5.8 |
| Saskatchewan | 813 | 15 | 2 | 1.8% | 1.3 | 1.3 |
| Manitoba | 325 | 7 | 1 | 2.2% | 0.5 | 0.6 |
| Newfoundland and Labrador | 261 | 3 | 0 | 1.2% | 0.6 | 0.5 |
| New Brunswick | 166 | 2 | 2 | 1.2% | 0.3 | 0.2 |
| Prince Edward Island | 33 | 0 | 0 | 0% | NDC[g] | NDC[g] |
| Yukon | 11 | 0 | 0 | 0% | NDC[g] | NDC[g] |
| Northwest Territories | 5 | 0 | 0 | 0% | NDC[g] | NDC[g] |
| Nunavut | 0 | 0 | 0 | 0% | NDC[g] | NDC[g] |
| Canada[h] | 106,804 | 8,749 | 7,086 | 8.2% | 23.3 | 23.3[i] |

Abbreviations: COVID-19, coronavirus disease 2019; NDC, no deaths calculated
[a] Deaths were defined as per the World Health Organization guideline, which defines COVID-19 deaths as those in probable or laboratory-confirmed COVID-19 cases where there was no period of recovery between illness and death, unless there was a clear alternative cause of death that cannot be related to COVID-19 (e.g. trauma) (5). Exceptions included: British Columbia and Ontario excluded deaths in epidemiologically-linked probable cases; and British Columbia, Saskatchewan, Ontario, New Brunswick and Nova Scotia included deaths that occurred in COVID-19 cases regardless of whether or not the death was attributed to COVID-19, in instances where there was no period of complete recovery between illness and death
[b] Based on provincial and territorial websites, press briefings, web scanning, as of July 9, 2020
[c] Deaths per 100,000 population were not calculated for provinces and territories where there were no deaths
[d] Statistics Canada July 1, 2019 population estimates
[e] Direct age standardization using July 1, 2019 population estimates
[f] Age standardized death rate per 100,000 was determined using the detailed case information received by the Public Health Agency of Canada for 106,198 cases and 8,711 deaths
[g] Deaths per 100,000 and age standardized death rate per 100,000 were not calculated in jurisdictions where there were no deaths
[h] The total for Canada includes 13 cases identified in repatriated travellers who were under quarantine in March 2020. Update on their status was unavailable
[i] The age standardized death rate per 100,000 were standardized to the national Canadian population

homes. This may have been due to the population size, density and the extent of community transmission within these particular provinces (6).

Of the 106,804 cases and 8,749 deaths reported in Canada on July 9, 2020, more detailed information was reported to the Public Health Agency of Canada for 106,321 (99.5%) cases and 8,711 (99.6%) deaths by that same date. An analysis of COVID-19 related deaths by age, gender, pre-existing medical conditions and long term care and seniors' home resident status was conducted using this more detailed dataset provided by provinces and territories.

CFR was less than 1% in all age groups up until the age of 50 years, and then increased rapidly with age, with a CFR of 1.2% for those aged 50 to 59 years, increasing up to 34.4% for those aged 80 years and over (**Table 2**). Canadian females overall were more impacted, with a higher rate of deaths per 100,000 (24.9 among females compared with 21.3 among males). However, among cases, males had a higher CFR than females (8.5% compared with 7.9%). These latter findings echo a gender difference observed among cases of severe illness due to COVID-19 in other countries (7,8), which may reflect gender differences in the prevalence of pre-existing medical conditions and in risk behaviours such as smoking (8).

Based on the limited information available on pre-existing medical conditions (n=6,350), CFR generally increased as the number of pre-existing medical conditions increased, overall and across all age groups (**Table 3**). This increase was marked among those aged 60 to 79 years, where the CFR was 3.1% among those without a pre-existing medical condition and 25.5% among those with three or more pre-existing medical conditions. Pre-existing medical conditions assessed in case reports provided to the Public Health Agency of Canada included cardiac disease, chronic neurological or neuromuscular disorder, diabetes, immunodeficiency disease/condition, liver disease, malignancy, renal disease and respiratory disease. Being a resident of a long term care or seniors' home also resulted in a higher CFR overall (26.8%) and within each of the age groups. While the information on whether or not the case was a resident of a long term care or seniors' home was limited (n=10,150), these findings were similar to those of other Canadian studies, in which the overall CFR among residents was estimated to be 36% (6), and was greater than that of older Canadians who were not living in such a setting (*Personal communication, D. Fisman et al.*). The higher CFR among this population likely reflects a degree of frailty and multi-morbidity among residents that increases the risk of severe outcomes, including death (9).

**Table 2: Case fatality rates and deaths per 100,000 population by age and gender, as of July 9, 2020 (N=106,321)**

| Case characteristics | Cases | Deaths | Case fatality rate | Deaths per 100,000 population[a] |
|---|---|---|---|---|
| Age group[b] | | | | |
| 0–19 years | 7,791 | 1 | 0.01% | 0.01 |
| 20–29 years | 14,813 | 8 | 0.05% | 0.2 |
| 30–39 years | 14,854 | 15 | 0.1% | 0.3 |
| 40–49 years | 16,175 | 45 | 0.3% | 0.9 |
| 50–59 years | 16,140 | 200 | 1.2% | 3.8 |
| 60–69 years | 10,427 | 615 | 5.9% | 13.3 |
| 70–79 years | 7,832 | 1,570 | 20.1% | 54.7 |
| 80 and older | 18,166 | 6,257 | 34.4% | 385.1 |
| Total | 106,198 | 8,711 | 8.2% | 23.0 |
| Age group by gender[b,c] | | | | |
| Female | | | | |
| 0–39 years | 19,814 | 8 | 0.04% | 0.1 |
| 40–59 years | 17,827 | 94 | 0.5% | 1.9 |
| 60–79 years | 9,095 | 885 | 9.7% | 22.9 |
| 80 and older | 12,457 | 3,713 | 29.8% | 381.8 |
| Total | 59,193 | 4,700 | 7.9% | 24.9 |
| Male | | | | |
| 0–39 years | 17,519 | 16 | 0.1% | 0.2 |
| 40–59 years | 14,412 | 151 | 1.1% | 3.0 |
| 60–79 years | 9,117 | 1,294 | 14.2% | 35.8 |
| 80 and older | 5,596 | 2,509 | 44.8% | 384.6 |
| Total | 46,644 | 3,970 | 8.5% | 21.3 |

[a] Statistics Canada July 1, 2019 population estimates
[b] Information was not available for 0.12% (n=123) of cases on age and 0.35% (n=371) of cases on gender
[c] Provinces and territories may define gender differently and some may be referring to biological sex

**Table 3: Age-specific case fatality rates among COVID-19 cases by pre-existing medical conditions and by long term care or seniors' home resident status, July 9 2020[a]**

| Case characteristics | Deaths/cases (case fatality rate) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Age (years) | | | | | | | |
| | 0–59 | | 60–79 | | 80 and older | | Total cases | |
| | n/N | % | n/N | % | n/N | % | n/N | % |
| Number of pre-existing medical conditions[a,b] | | | | | | | | |
| 0 | 4/4,150 | 0.1% | 32/1,028 | 3.1% | 67/224 | 29.9% | 103/5,402 | 1.9% |
| 1 | 2/135 | 1.5% | 6/157 | 3.8% | 12/55 | 21.8% | 20/347 | 5.8% |
| 2 | 0/66 | 0.0% | 18/141 | 12.8% | 39/129 | 30.2% | 57/336 | 17.0% |
| 3 and more | 1/39 | 2.6% | 26/102 | 25.5% | 47/124 | 37.9% | 74/265 | 27.9% |
| Long term care or seniors' home resident[c] | | | | | | | | |
| No | 6/8,122 | 0.1% | 34/1,098 | 3.1% | 35/171 | 20.5% | 75/9,391 | 0.8% |
| Yes | 3/33 | 9.1% | 45/213 | 21.1% | 155/512 | 30.3% | 203/758 | 26.8% |

Abbreviation: COVID-19, coronavirus disease 2019
[a] Information on pre-existing medical conditions was not available for 94.03% (n=99,971) of cases
[b] Pre-existing medical conditions were defined as: cardiac disease, chronic neurological or neuromuscular disorder, diabetes, immunodeficiency disease/condition, liver disease, malignancy, renal disease, and respiratory disease
[c] Information on whether or not the case was a resident of a long term care or seniors' home was not available for 90.45% (n=96,171) of cases

There is increasing evidence that, similar to findings from the United States and the United Kingdom (10), individuals from racial and ethnic minorities within Canada are at increased risk for acquiring COVID-19 and for severe outcomes, including death (11,12). Nationally, plans are underway to begin the collection of more detailed case information in the fall 2020, including race, ethnicity and socio-economic status.

## Conclusion

Public health authorities across the country will continue to monitor closely the number of deaths among COVID-19 cases to inform additional measures to prevent fatal outcomes. Although deaths provide a late indication of COVID-19 transmission, they provide a clear indication of the severity and impact of the disease and highlight the need to protect vulnerable populations, including those who are older and living with multiple pre-existing medical conditions. Most especially, Canadians living in long term care and seniors' homes have been severely impacted, with higher case fatality rates compared with older Canadians who are not living in such settings. Accordingly, federal, provincial and territorial jurisdictions have implemented multiple measures to prevent transmission within such settings. These measures include updated guidelines on infection prevention and control, and specifically regarding care of residents in long term care homes (13), policy measures to ensure adequate staffing and to limit the movement of healthcare workers between facilities.

The infection fatality rate and excess mortality are other measures of mortality than can be used to describe the impact of COVID-19 in Canada. The infection fatality rate is defined as the number of deaths divided by the number of individuals infected. Unlike CFR, the infection fatality rate is not influenced by factors such as changes in laboratory testing strategies. Plans are currently underway to conduct rapid pan-Canadian and regional serologic surveys to determine the extent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the population and these results will permit the estimation of Canada's infection fatality rate (14).

Estimating excess mortality will increase our understanding of the impact of the COVID-19 pandemic beyond the disease itself. For example, an increase in deaths due to other causes may be expected as a result of individuals whose fear of infection prevents them from seeking timely health care. Excess mortality is the difference between the total number of people who died from any cause during a specified period, and the historical average for the same time of year in previous years. In June 2020, Statistics Canada released a provisional dataset on excess deaths for January to the week of May 2, 2020, as compared with the previous five years (15). These data were preliminary and, as more information becomes available for all Canadian jurisdictions, we will gain a better understanding of the true impact of the pandemic on Canadians.

## Authors' statement

DP — Conceptualization, original draft, review and editing
CB — Conceptualization, data curation, formal analysis, review and editing
JM — Data curation, formal analysis, review and editing
LW — Review and editing
AC — Conceptualization, review and editing
CA — Review and editing
LS — Review and editing
DT — Review and editing
DM — Review and editing
JP — Review and editing

### Competing interests

None.

## Acknowledgements

Authors wish to thank provincial and territorial surveillance partners, the National Microbiology Laboratory, provincial public health laboratory partners, and the Health Portfolio Operations Centre's Surveillance Team, Public Health Agency of Canada.

Public Health Agency of Canada COVID-19 Surveillance and Epidemiology Team included D Paquette, C Bell, J Macri, L Whitmore, A Currie, C Archibald, L Shah, D Taylor, D MacDonald and J Pennock.

## Funding

This work was supported by Public Health Agency of Canada.

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RAPID COMMUNICATION

# Acute flaccid myelitis in Canada, 2018 to 2019

Catherine Dickson[1]*, Brigitte Ho Mi Fane[1], Susan G Squires[1]

## Abstract

Starting in 2014, biennial clusters of acute flaccid myelitis (AFM), frequently described as "polio-like" illness, have been reported across the United States and elsewhere, often linked to enteroviruses. To assess AFM trends in Canada, we reviewed the Canadian Acute Flaccid Paralysis Surveillance System (CAFPSS) for cases reported during the 2018 and 2019 calendar years that meet the Centers for Disease Control and Prevention case definitions for AFM. A total of 10 cases (8 in 2018 and 2 in 2019) met the confirmed AFM case definition and 30 (26 in 2018 and 4 in 2019) met the probable AFM case definition. Sixty percent of confirmed and probable cases were younger than five years old, and all cases had symptom onset between the months of July and October. Enteroviruses were detected in 50% of confirmed cases. At the time of writing this report, 2020 AFM data were not yet available; it is unknown if a spike in AFM cases will be seen in 2020.

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***Suggested citation:*** Dickson C, Ho Mi Fane B, Squires SG. Acute flaccid myelitis in Canada, 2018 to 2019. Can Commun Dis Rep 2020;46(10):349–53. https://doi.org/10.14745/ccdr.v46i10a07

***Keywords:*** acute flaccid myelitis, acute flaccid paralysis, enterovirus, infectious disease, surveillance

## Introduction

Spikes in acute flaccid myelitis (AFM), an emerging form of acute flaccid paralysis (AFP) related to viral infections and frequently described as "polio-like" illness, have been reported in the United States and elsewhere, in a seemingly biennial pattern in the summer and fall, in 2014, 2016 and 2018 (1–5).

AFP is defined as a sudden onset of paralysis with reduced muscle tone in one or more limbs. This syndrome is caused by a range of etiologies, such as Guillain–Barré syndrome, transverse myelitis or neuropathies. These conditions are associated with neurotropic viruses, such as enteroviruses, including polio, *Herpesviridae* and parainfluenzavirus (6). AFM is a subtype of AFP associated with lesions in the grey matter of the spinal cord. It has been linked to viral infections, particularly enteroviruses EV-D68 and EV-A71, which can be spread via oral–fecal and respiratory routes (3,7,8).

AFM has been associated with disability and large healthcare requirements, mostly in children (9,10). The Centers for Disease Control and Prevention (CDC) has reported extensively on recent trends of AFM, in the United States (3,11). This emerging trend has led to concerns about the potential effect of AFM on Canadians. The seriousness of the condition as well as the lack of clear knowledge about the etiology of the disease underscore the need to better understand the epidemiology of AFM to further identify prevention and patient management measures (3).

This study describes the preliminary analysis of AFM in Canada for the years 2018 and 2019, using data from the Canadian Acute Flaccid Paralysis Surveillance System (CAFPSS). Understanding seasonality trends of AFM can be helpful for public health and healthcare systems in their resource planning and messaging in preparation for a potential seasonal spike in 2020.

## Methods

CAFPSS collects information on cases of AFP in children younger than 15 years old through reports from the Canadian Immunization Program Monitoring Active (IMPACT) and from the Canadian Paediatric Surveillance Program (CPSP). IMPACT is a network of 12 paediatric centres across Canada, representing 90% of paediatric tertiary care beds. CPSP collects information on rare paediatric conditions from a network of over 2,500 paediatricians across the country (12,13). By monitoring for potential cases of polio presenting with AFP, CAFPSS is part of Canada's ongoing efforts to maintain our polio elimination status. CAFPSS collects information on clinical presentation and investigations including laboratory results and magnetic resonance imaging (MRI) reports. All cases in the CAFPSS are adjudicated against the AFP case definition by a specially trained physician.

AFM is not a notifiable disease in Canada; as such, following the increase in AFM cases reported in the United States in 2018, CAFPSS has been leveraged to monitor for AFM as it would

be captured within the broader case definition of AFP. Each confirmed AFP case is reviewed by the adjudicating physician against the CDC case definition to determine the AFM status of AFP cases reported in Canada. For this paper, we used the 2018 CDC case definition for AFM (6):

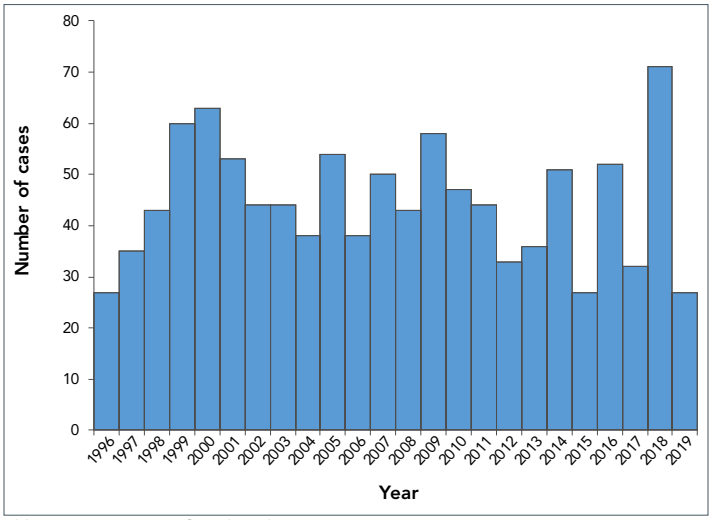
- A case was classified as confirmed AFM if the MRI results show a spinal cord lesion with predominant grey matter involvement spanning one or more vertebral segments
- A case was classified as probable AFM if the cerebrospinal fluid had a white blood cell count greater than 5 cells/mm$^3$

We extracted 2018 and 2019 AFP data from CAFPSS and aggregated these by year of paralysis/weakness onset. We then conducted descriptive analyses by year, age group, sex, AFM status (using the 2018 CDC case definition), outcome and virology results.

## Results

Since the implementation of CAFPSS in 1996, an average of 45 confirmed cases of AFP have been reported to the Public Health Agency of Canada (PHAC) annually, from 27 cases in 1996 and 2019 to 71 cases in 2018 (**Figure 1**). Between 2018 and 2019, PHAC received 120 reports of sudden onset muscle weakness in children younger than 15 years old. Of these reports, 98 were confirmed as AFP cases, eight did not meet the AFP case definition and were discarded, nine were duplicates and five remain under investigation, meaning that additional information has been requested to determine if they meet the AFP case definition.

**Figure 1: Number of confirmed AFP cases in Canada, by year, 1996–2019 (n=1,070)[a]**




Abbreviation: AFP, acute flaccid paralysis
[a] As of July 24, 2020

Following the review of the 2018 and 2019 AFP confirmed cases using the 2018 CDC case definition, 10 cases were classified as confirmed AFM and 30 as probable AFM (**Table 1**). Of both confirmed and probable cases, 60% were younger than five years old. Boys accounted for slightly more than half of all AFM cases (**Table 2**).

**Table 1: Number of confirmed AFP cases reported to the CAFPSS by AFM status, 2018–2019[a]**

| Classification | 2018 | | 2019 | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Confirmed AFP cases | 71 | 100 | 27 | 100 | 98 | 100 |
| AFM status[b] | | | | | | |
| Confirmed | 8 | 11 | 2 | 7 | 10 | 10 |
| Probable | 26 | 37 | 4 | 15 | 30 | 31 |
| Not AFM | 23 | 32 | 17 | 63 | 40 | 41 |
| Unable to determine[c] | 14 | 20 | 4 | 15 | 18 | 18 |

Abbreviations: AFM, acute flaccid myelitis; AFP, acute flaccid paralysis; CAFPSS, Canadian Acute Flaccid Paralysis Surveillance System
[a] As of July 24, 2020
[b] Cases reviewed against Centers for Disease Control and Prevention 2018 case definition of acute flaccid myelitis (6)
[c] Insufficient information available in the case report to determine if the case definition was met

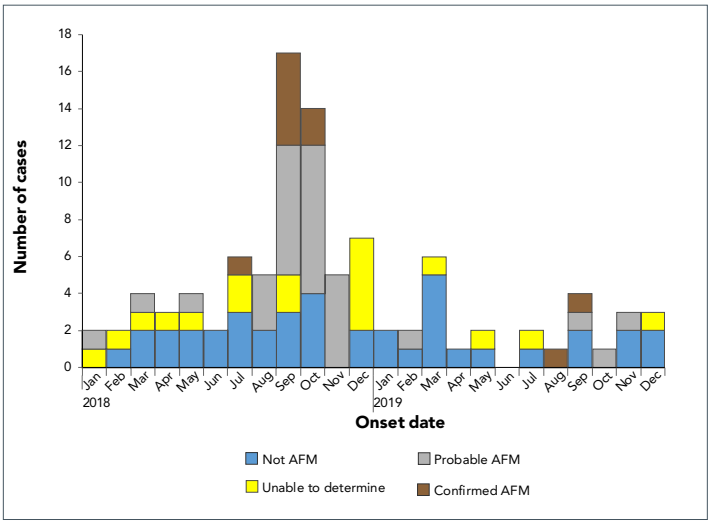
**Table 2: Age, and number and distribution by age group, sex and outcome of confirmed AFP cases reported to the CAFPSS by AFM status, 2018–2019[a]**

| Parameter | AFM cases | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Confirmed (n=10) | | Probable (n=30) | | Not AFM (n=40) | | AFM status not determined (n=18) | |
| Median age (years) | 4.9 | | 4.8 | | 2.9 | | 5.8 | |
| Age range | (11 months to 13.6 years) | | (7 months to 14.5 years) | | (3 months to 14.5 years) | | (1.5 to 14.8 years) | |
| Age group (years) | | | | | | | | |
| Younger than 1 | 1 | 10% | 1 | 3% | 5 | 13% | 0 | 0 |
| 1–4 | 5 | 50% | 17 | 57% | 24 | 60% | 8 | 44% |
| 5–9 | 3 | 30% | 6 | 20% | 6 | 15% | 3 | 17% |
| 10–14 | 1 | 10% | 6 | 20% | 5 | 13% | 7 | 39% |
| Sex | | | | | | | | |
| Female | 4 | 40% | 14 | 47% | 16 | 40% | 6 | 33% |
| Male | 6 | 60% | 16 | 53% | 23 | 58% | 12 | 67% |
| Missing | 0 | 0 | 0 | 0 | 1 | 3% | 0 | 0 |
| Outcome at the time of most recent case report update | | | | | | | | |
| Fully recovered | 0 | 0 | 7 | 23% | 7 | 18% | 2 | 11% |
| Partial recovery with residual paralysis/ weakness | 3 | 30% | 7 | 23% | 14 | 35% | 6 | 33% |
| Deceased | 0 | 0 | 0 | 0 | 1 | 3% | 0 | 0 |
| Unknown[b] | 7 | 70% | 16 | 53% | 18 | 45% | 10 | 56% |

Abbreviations: AFM, acute flaccid myelitis; AFP, acute flaccid paralysis; CAFPSS, Canadian Acute Flaccid Paralysis Surveillance System
[a] As of July 24, 2020
[b] Includes outcome pending, 60 days follow-up not applicable, unknown outcome and missing data

Of the 10 confirmed AFM cases, all had a symptom onset date between July and October. Probable AFM cases had a symptom onset between January and November, although 87% (n=26) of these had a symptom onset between August and November (**Figure 2**).

**Figure 2: Confirmed AFP cases reported to PHAC by paralysis or weakness onset date and by AFM status, 2018–2019[a]**




Abbreviations: AFM, acute flaccid myelitis; AFP, acute flaccid paralysis; PHAC, Public Health Agency of Canada
[a] As of July 24, 2020

All confirmed and probable cases were hospitalized. The median duration of hospitalization for confirmed AFM cases was 17.5 days (range: 2–70 days) and for probable AFM cases was 12 days (range: 3–46 days). Of the 10 confirmed AFM cases, none had fully recovered at the time of most recent case report update and three (30%) had partially recovered with residual paralysis/weakness. As for the 30 probable AFM cases, seven (23%) had recovered and seven (23%) had partially recovered with residual paralysis/weakness at the time of most recent case report update.

Enteroviruses were detected in five of the confirmed AFM cases: two were positive for EV-D68, one case was positive for EV-A71, one case was positive for enterovirus type unspecified and the remaining case was positive for rhinovirus/enterovirus single target. These viruses were detected through stool samples (n=3), throat swabs (n=1) and nasopharyngeal swabs (n=1). No other viral agents were detected in confirmed AFM cases, although viral testing was performed for all cases.

Of the 30 probable AFM cases, 26 (87%) had viral testing results available. Of these, enteroviruses were detected in 10 (38%) cases: five (50%) had EV-D68, three (30%) had enterovirus type unspecified, one (10%) had EV-A71 concurrent with rhinovirus and one (10%) was positive for rhinovirus/enterovirus single target. These probable AFM cases had enterovirus or rhinovirus/enterovirus single target detected through throat swabs (n=4), nasopharyngeal swabs (n=4), stool samples (n=1) and cerebrospinal fluid (n=1). In addition, six (23%) probable AFM cases had other viral agents detected.

Of the 40 cases classified as not AFM cases, 17 (43%) had viral testing results available. Of these, three (18%) cases tested positive for enteroviruses: one case was positive for enterovirus type unspecified, one for rhinovirus/enterovirus single target and one for rhinovirus/enterovirus single target along with another viral infection. These infections were detected from nasopharyngeal swabs (n=2) and stool samples (n=1). One additional case classified as not AFM was positive for another viral agent.

Of the 18 cases for which AFM status could not be determined, 13 (72%) had viral testing results available. Of these, one case was positive for enterovirus type unspecified detected via a throat swab. The remaining cases were either positive for other viral agents (n=2) or had negative virology results (n=10).

Other viral agents detected in the cases that were not confirmed AFM included bocavirus, adenovirus, rhinovirus, coxsackievirus, Epstein–Barr virus, West Nile virus and norovirus.

## Strengths and limitations

The increase in AFP case reports in 2018 may be due, in part, to increased awareness of AFM among Canadian clinicians following the increase in number of AFM cases in the United States during that year.

Because the purpose of CAFPSS is to monitor for poliovirus in children, it is not an ideal surveillance tool for AFM. CAFPSS is limited to cases in children younger than 15 years old. As such, the trends described here are limited by data collection availability only for people younger than 15 years. Although cases of AFM have been reported in adults, the majority have been in young children (3). This suggests that CAFPSS can be expected to capture the majority of AFM cases. We anticipate that, although this limitation would reduce overall AFM case counts, it would not affect overall AFM trends.

MRI is essential for the confirmation of AFM. However, in this report, assessments were limited to the information provided to CAFPSS, which were often brief summaries of the MRI report. In other words, it was not possible to ascertain whether some cases met the case definition for AFM. CAFPSS did, however, allow for the use of an existing surveillance tool to monitor trends during periods when spikes in AFM activity have been reported elsewhere and to identify AFM activity related in part to non-polio enterovirus with a similar pattern in seasonality to reports coming out of the United States.

At the time of writing this report, 2020 AFM data were not yet available. The data will need to be analyzed in relation to recent historical trends. It is yet to be seen whether physical distancing

and infection control practices in the community will reduce the burden of AFM by reducing community transmission of viruses other than coronavirus disease (COVID-19). The authors will continue to monitor reports of AFP and AFM in Canada and work with surveillance partners to ensure ongoing reporting.

## Conclusion

In 2018, a record number of AFP cases was reported to CAFPSS, substantially higher than in 2019. A small proportion (10%) of the cases reported from 2018 and 2019 met the 2018 CDC case definition for confirmed AFM, with the majority having onset of paralysis in the late summer and early fall of 2018. This coincides temporally with the cyclical increase in AFM cases observed in the United States (3), suggesting that a similar trend might be occurring in Canada.

A larger proportion of AFP cases (31%) met the 2018 CDC case definition for probable AFM. It is anticipated that a larger proportion of AFP cases would meet the case definition for probable AFM cases given the broad requirement criteria. The CDC has revised the 2020 probable AFM case definition to be more specific (14). We anticipate this greater specificity will lead to fewer diagnosed cases of probable AFM in future years when the new case definition is applied to our surveillance data.

Enterovirus or rhinovirus/enterovirus was detected in non-cerebrospinal fluid specimens of half of the confirmed AFM cases, a greater proportion than seen in any of the other AFM categories. This is consistent with other reports of AFM being linked to enterovirus infections (3,7). No other viral infections were reported in confirmed AFM cases, whereas a variety of other viral infections were reported in each of the other AFM categories, suggesting that these cases might be linked to multiple viral etiologies.

## Authors' statement

CD — Conceptualization, investigation, writing–original draft, writing–review and editing
BHMF — Methodology, investigation, formal analysis, writing–original draft, writing–review and editing
SGS — Conceptualization, writing–review and editing

### Competing interests

None.

## Acknowledgements

The authors would like to thank F Reyes Domingo, M Roy and D MacDonald for their work on acute flaccid paralysis surveillance as well as Dr. J Ahmadian-Yazdi for his assistance with the preparation of this manuscript. The authors would also like to thank the Canadian Paediatric Surveillance Program and the Canadian Immunization Program Monitoring Active (IMPACT) surveillance program, particularly the IMPACT nurse monitors.

## Funding

This work was supported by the Public Health Agency of Canada.

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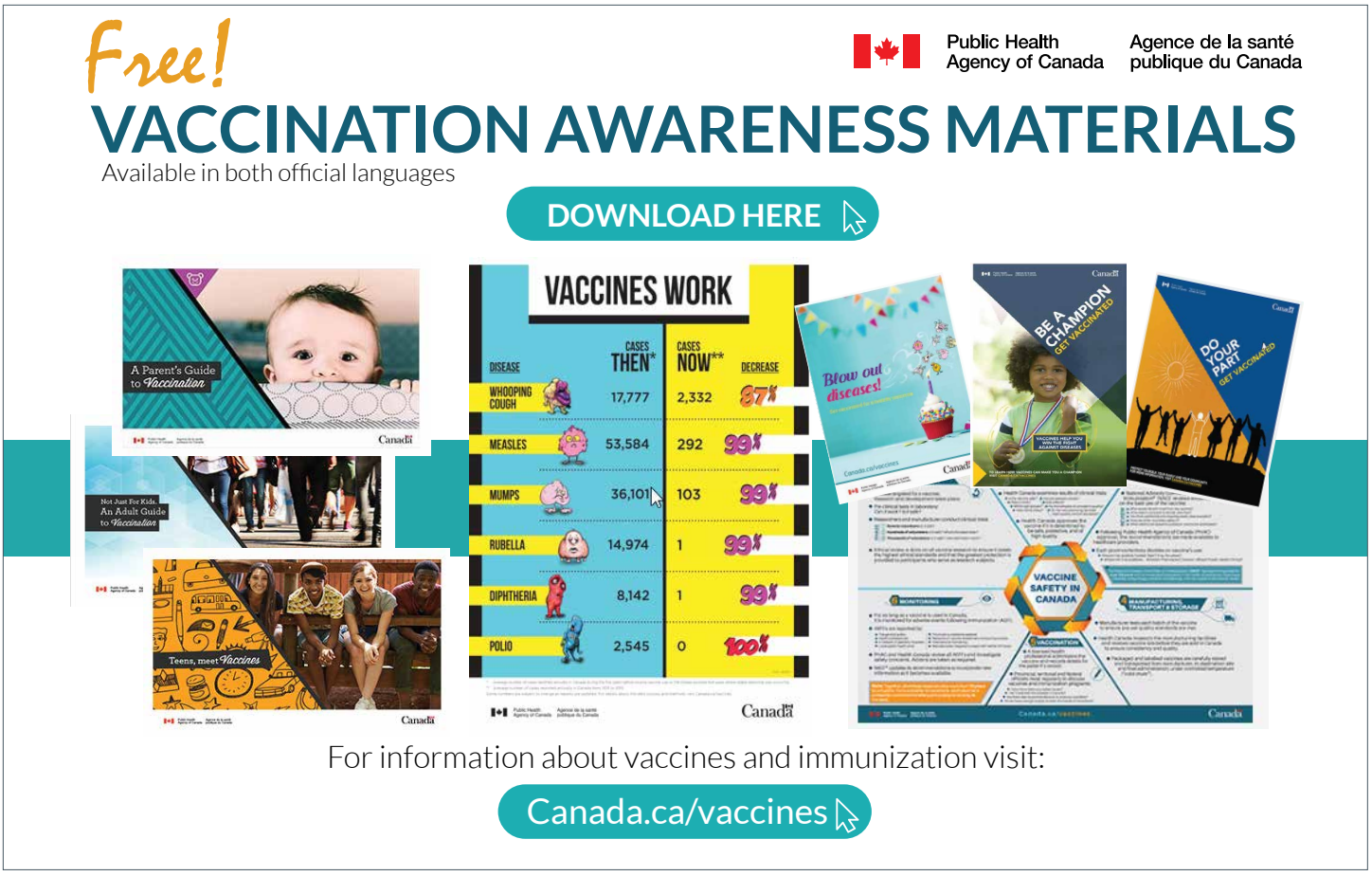

# Sentinel surveillance of Lyme disease risk in Canada, 2019: Results from the first year of the Canadian Lyme Sentinel Network (CaLSeN)

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## Abstract

**Background:** Lyme disease is an emerging vector-borne zoonotic disease of increasing public health importance in Canada. As part of its mandate, the Canadian Lyme Disease Research Network (CLyDRN) launched a pan-Canadian sentinel surveillance initiative, the Canadian Lyme Sentinel Network (CaLSeN), in 2019.

**Objectives:** To create a standardized, national sentinel surveillance network providing a real-time portrait of the evolving environmental risk of Lyme disease in each province.

**Methods:** A multicriteria decision analysis (MCDA) approach was used in the selection of sentinel regions. Within each sentinel region, a systematic drag sampling protocol was performed in selected sampling sites. Ticks collected during these active surveillance visits were identified to species, and *Ixodes* spp. ticks were tested for infection with *Borrelia burgdorferi*, *Borrelia miyamotoi*, *Anaplasma phagocytophilum*, *Babesia microti* and Powassan virus

**Results:** In 2019, a total of 567 *Ixodes* spp. ticks (*I. scapularis* [n=550]; *I. pacificus* [n=10]; and *I. angustus* [n=7]) were collected in seven provinces: British Columbia, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia and Prince Edward Island. The highest mean tick densities (nymphs/100 $m^2$) were found in sentinel regions of Lunenburg (0.45), Montréal (0.43) and Granby (0.38). Overall, the *Borrelia burgdorferi* prevalence in ticks was 25.2% (0%–45.0%). One *I. angustus* nymph from British Columbia was positive for *Babesia microti*, a first for the province. The deer tick lineage of Powassan virus was detected in one adult *I. scapularis* in Nova Scotia.

**Conclusion:** CaLSeN provides the first coordinated national active surveillance initiative for tick-borne disease in Canada. Through multidisciplinary collaborations between experts in each province, the pilot year was successful in establishing a baseline for Lyme disease risk across the country, allowing future trends to be detected and studied.

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***Suggested citation:*** Guillot C, Badcock J, Clow K, Cram J, Dergousoff S, Dibernardo A, Evason M, Fraser E, Galanis E, Gasmi S, German GJ, Howse DT, Jardine C, Jenkins E, Koffi J, Kulkarni M, Lindsay LR, Lumsden G, McKay R, Morshed M, Munn D, Nelder M, Nocera J, Ripoche M, Rochon K, Russell C, Slatculescu A, Talbot B, Thivierge K, Voordouw M, Bouchard C, Leighton P. Sentinel surveillance of Lyme disease risk in Canada, 2019: Results from the first year of the Canadian Lyme Sentinel Network (CaLSeN). Can Commun Dis Rep 2020;46(10):354–61. https://doi.org/10.14745/ccdr.v46i10a08

***Keywords:*** Lyme disease, sentinel surveillance, *Ixodes* tick, *Borrelia*, Canadian Lyme Disease Research Network (CLyDRN)

## Introduction

In Canada, Lyme disease is an emerging vector-borne zoonotic disease of increasing public health importance (1). Lyme disease is caused by the bacterium *Borrelia burgdorferi* and is primarily transmitted to humans by the blacklegged tick (*Ixodes scapularis*) in central and eastern Canada and the western blacklegged tick (*Ixodes pacificus*) in British Columbia. Since Lyme disease became a nationally notifiable disease in 2009, the number of cases confirmed annually has risen from 144 to over 2,000 in 2017 (2,3).

In response to the increasing risk of Lyme disease to the Canadian population and ongoing knowledge gaps, the Canadian Institutes of Health Research (CIHR) funded the creation of a national research network on Lyme disease (4). Launched in 2018, the Canadian Lyme Disease Research Network (CLyDRN) is a multidisciplinary initiative bringing together patients, physicians, social scientists, veterinarians and academic and government researchers with a patient-centred approach focused on improving the diagnosis, surveillance, prevention and treatment of Lyme disease in Canada. A key objective of the network is to better understand the risk of Lyme disease across the country and how this risk is evolving. Thus, one of the first actions of the network was to establish a pan-Canadian surveillance structure to collect comparable data about environmental risk across the country.

An important consideration in the planning of surveillance is that the risk of Lyme disease is not uniform across the country (5). This is largely due to regional differences in tick species and environments (6–9) and the uneven pattern of ongoing range expansion of *I. scapularis* populations in Canada (10). Regional differences in socioeconomic status of Canadians are also likely to influence how environmental risk affects regional incidence of Lyme disease cases (11).

While considerable effort has been invested in the measurement of Lyme disease risk for Canadians, surveillance remains heterogeneous across the country. Passive surveillance, the submission of ticks collected on humans or animals, provides valuable information on risk (12,13), but cannot be maintained uniformly across the country due to resource limitations. Active surveillance, the collection of ticks from the environment by drag sampling or rodent capture, is resource-intensive and is carried out in each province according to region-specific objectives, sampling protocols and funding availability.

Here we report the first results from the Canadian Lyme Sentinel Network (CaLSeN), a new pan-Canadian LD surveillance network launched by CLyDRN in 2019. In this pilot year, we carried out standardized active surveillance of ticks in the environment across Canada using a sentinel surveillance approach. Sentinel surveillance has the advantage of concentrating surveillance effort in selected sentinel regions, providing a comparable measure of environmental risk for Lyme disease and other tick-borne diseases across the country and in-depth risk information that is complementary to ongoing federal and provincial surveillance activities.

### Objectives

With surveillance carried out annually in sentinel regions in each Canadian province, the objectives of CaLSeN aim to: 1) provide the first standardized, national, real-time portrait of evolving environmental Lyme disease risk in Canada and 2) support research on regional variation in risk and its determinants.

## Methods

### Sentinel region selection

Sentinel regions were selected by CLyDRN's Surveillance Working Group, a group of tick-borne disease surveillance experts from both academic and public health settings. Sentinel regions were defined geographically as the area within a 25 km radius around the geographic centre of a selected focal municipality. The Surveillance Working Group used a multicriteria decision analysis (MCDA) approach to prioritize one to four initial sentinel regions in each province, with the objective of including additional regions over time (14).

Selection criteria included evidence of the emergence of Lyme disease based on existing passive surveillance data (number of *Ixodes* tick submissions/100,000 people) (10); human population covered by the network; and logistical criteria associated with field sampling and suitability of the environment for *Ixodes* ticks, such as presence of deciduous or mixed forests. Sentinel regions were not established in Yukon, the Northwest Territories, Nunavut or the mainland portion of Newfoundland and Labrador because current environmental conditions at these latitudes are not suitable for *Ixodes* spp. ticks to establish (15).

### Tick collection

Ticks were collected in each sentinel region using a standardized drag sampling protocol (16,17). This involved dragging a 1 m × 1 m piece of white flannel cloth over 2,000 $m^2$ of ground vegetation in linear transects, stopping every 25 m to collect questing ticks that had clung to the passing cloth. Multiple sampling sites were selected in each sentinel region. Locations were chosen because they had suitable tick habitats. Surveillance efforts were increased in known Lyme disease–endemic areas to obtain fine-scale information on the distribution of risk within these areas (**Table 1**). Each site was sampled once during the summer (May–August 2019), targeting the regional peak in activity of nymphal *Ixodes* spp. ticks, the stage of greatest public health significance (18–20). In addition to collecting ticks, we collected data on leaf litter depth, canopy cover and soil humidity at each sampling location and noted ambient temperature and weather conditions during collection to account for the possible effects of these variables on tick collection.

**Table 1: Density of *Ixodes* spp. nymphs collected across all sampling sites within each sentinel region of the Canadian Lyme Sentinel Network, 2019**

| Sentinel region | No. of sites visited (n) | Density (no. of nymphs / 100 m²) | | | Standard deviation |
|---|---|---|---|---|---|
| | | Minimum | Maximum | Mean | |
| Vancouver, BC | 5 | 0 | 0.10 | 0.04 | 0.04 |
| Lethbridge, AB | 3 | 0 | 0 | 0 | 0 |
| Saskatoon, SK | 3 | 0 | 0 | 0 | 0 |
| Winnipeg, MB | 5 | 0 | 0 | 0 | 0 |
| Hamilton, ON | 5 | 0 | 0.1 | 0.02 | 0.04 |
| Kingston, ON | 15 | 0.05 | 1.15 | 0.27 | 0.38 |
| Ottawa–Gatineau, ON/QC | 10 | 0 | 0.4 | 0.06[a] | 0.12 |
| Montréal, QC | 10 | 0 | 2.90 | 0.43 | 0.91 |
| Granby, QC | 5 | 0 | 1.15 | 0.38 | 0.48 |
| Sherbrooke, QC | 5 | 0 | 0 | 0 | 0 |
| Saint John, NB | 5 | 0 | 0.30 | 0.09 | 0.13 |
| Charlottetown, PEI | 5 | 0 | 0.05 | 0.01 | 0.02 |
| Lunenburg, NS | 10 | 0 | 2.45 | 0.45 | 0.74 |
| St. John's, NL | 5 | 0 | 0 | 0 | 0 |

Abbreviations: AB, Alberta; BC, British Columbia; MB, Manitoba; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; ON, Ontario; PEI, Prince Edward Island; QC, Québec; SK, Saskatchewan; spp., species
[a] Site visits in the Ottawa–Gatineau region were conducted in early June, prior to the peak in nymphal tick abundance. Thus, reported densities may not be representative of densities later in the summer

## Laboratory analyses

The species of all ticks collected by drag sampling were identified, but only *I. scapularis* (n=550), *I. pacificus* (n=10) and *I. angustus* (n=7) were tested for the presence of pathogens as they are known vectors for *B. burgdorferi* and other pathogens. Individual ticks were tested for the presence of *Anaplasma phagocytophilum*, *Babesia microti*, *B. burgdorferi*, *Borrelia miyamotoi* and Powassan virus by real-time polymerase chain reaction (PCR) or reverse transcriptase-PCR with slight modifications to previously described methods (21). Briefly, nucleic acids were extracted from ticks using QIAGEN RNeasy 96 kits (QIAGEN Inc., Mississauga, Ontario, Canada). The extracts contained both RNA and DNA, and were screened for all the pathogens listed above. Modifications to testing algorithms included the use of an in-house triplex screening assay targeting the 18S rRNA gene of *Babesia* species, followed by the *B. microti*-specific CCT-eta real-time assay for confirmation, as well as a duplex assay (22) to confirm the presence of *B. burgdorferi* and/or *B. miyamotoi*.

## Statistical analyses

Results are presented as descriptive statistics. We used a paired Wilcoxon test to compare mean *Borrelia* prevalence in adult and nymphal ticks. Analyses were conducted using R version 3.6.2 (23).

# Results

## Sentinel regions and sampling sites

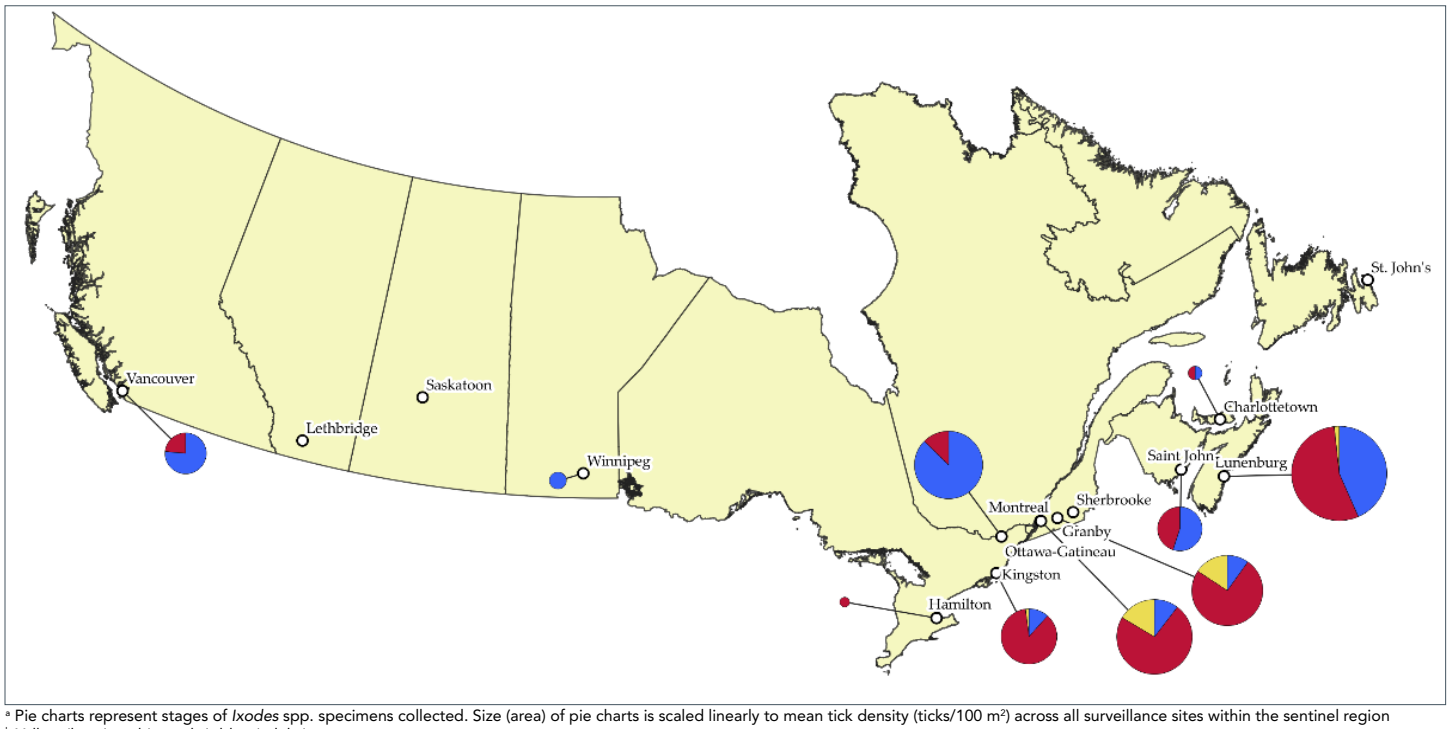
In total, 96 sites in 14 sentinel regions (**Figure 1**) were sampled from 22 May 2019 to 20 August 2019, with three to 15 sampling sites per region (Table 1).

## *Ixodes* spp. ticks

A total of 567 *Ixodes* spp. ticks were collected in 10 sentinel regions in seven provinces: British Columbia, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia and Prince Edward Island. *I. pacificus* (n=10) and *I. angustus* (n=7) ticks were collected exclusively in Vancouver, British Columbia. *I. scapularis* ticks (n=550) were collected in Manitoba, Ontario, Québec, New Brunswick, Nova Scotia and Prince Edward Island.

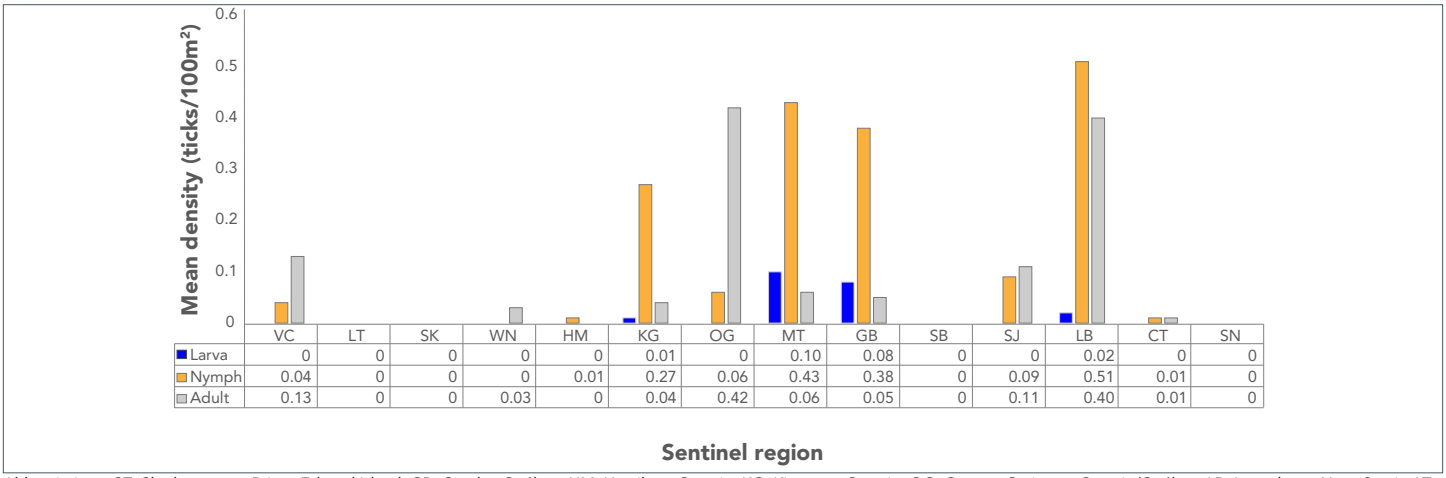
Nymphs were collected in each of these provinces, except for Manitoba (Winnipeg) where only adults were collected (**Figure 2**). Mean density of nymphs (nymphs/100 m² [SD]), which pose the greatest risk of infection to humans, was highest in the sentinel regions of Lunenburg (0.45 [0.74]), Montréal (0.43 [0.91]), Granby (0.38 [0.48]) and Kingston (0.27 [0.38]) (Table 1). The Ottawa–Gatineau region was sampled early in the season, yielding a lower density of nymphs (0.06 [0.12]) but a high density of adults (0.42 [0.72]), which also pose a significant health risk.

**Figure 1: Location of sentinel regions in the Canadian Lyme Sentinel Network in 2019[a,b]**




[a] Pie charts represent stages of *Ixodes* spp. specimens collected. Size (area) of pie charts is scaled linearly to mean tick density (ticks/100 m²) across all surveillance sites within the sentinel region
[b] Yellow (larva); red (nymphs); blue (adults)

**Figure 2: *Ixodes* spp. tick densities by stage (larva, nymph and adult) for each sentinel region in the Canadian Lyme Sentinel Network in 2019**




| | VC | LT | SK | WN | HM | KG | OG | MT | GB | SB | SJ | LB | CT | SN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Larva | 0 | 0 | 0 | 0 | 0 | 0.01 | 0 | 0.10 | 0.08 | 0 | 0 | 0.02 | 0 | 0 |
| Nymph | 0.04 | 0 | 0 | 0 | 0.01 | 0.27 | 0.06 | 0.43 | 0.38 | 0 | 0.09 | 0.51 | 0.01 | 0 |
| Adult | 0.13 | 0 | 0 | 0.03 | 0 | 0.04 | 0.42 | 0.06 | 0.05 | 0 | 0.11 | 0.40 | 0.01 | 0 |

Abbreviations: CT, Charlottetown, Prince Edward Island; GB, Granby, Québec; HM, Hamilton, Ontario; KG, Kingston, Ontario; OG, Ottawa–Gatineau, Ontario/Québec; LB, Lunenburg, Nova Scotia; LT, Lethbridge, Alberta; MT, Montréal, Québec; SB, Sherbrooke, Québec; SJ, Saint John, New Brunswick; SK, Saskatoon, Saskatchewan; SN, St. John's, Newfoundland and Labrador; spp., species; VC, Vancouver, British Columbia; WN, Winnipeg, Manitoba

## Laboratory analyses

*B. burgdorferi* infection prevalence in all *Ixodes* ticks (nymphs and adults) ranged from 0% to 45% (**Table 2**). Mean infection prevalence was higher in adult ticks (36.3%) than nymphal ticks (22.0%), but this difference was not statistically significant (paired Wilcoxon test; *P*=0.142; V=3). *B. miyamotoi* was found in two specimens, one from Ottawa–Gatineau and the other from Montréal. *A. phagocytophilum* infection prevalence varied from 0% to 4.1% in sentinel regions where *I. scapularis* ticks were found. *B. microti* was found in one *I. angustus* tick in the Vancouver sentinel region. One adult *I. scapularis* was positive for Powassan virus in the Lunenburg sentinel region.

**Table 2: *Ixodes* spp. tick abundance in sentinel regions of the Canadian Lyme Sentinel Network in 2019 and infection prevalence of tick-borne pathogens**

| Sentinel region | *Ixodes* spp. abundance (n) | | | | Infection prevalence (%)[a,b] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Larva | Nymph | Adult | Total | BbN | BbA | BbT | Bm | Ap | Bmi | POWV |
| Vancouver, BC | 0 | 4 | 13 | 17 | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] | 5.9[e] | 0[c] |
| Lethbridge, AB | 0 | 0 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA |
| Saskatoon, SK | 0 | 0 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA |
| Winnipeg, MB | 0 | 0 | 3 | 3 | NA | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] |
| Hamilton, ON | 0 | 2 | 0 | 2 | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] |
| Kingston, ON | 2 | 82 | 11 | 95 | 28.0[f] | 54.5[f] | 31.2[f] | 0[c] | 1.1[d] | 0[c] | 0[c] |
| Ottawa–Gatineau, ON/QC | 0 | 12 | 83 | 95 | 33.3[f] | 39.8[f] | 38.9[f] | 1.1[d] | 0[c] | 0[c] | 0[c] |
| Montréal, QC | 19 | 85 | 12 | 116 | 14.1[e] | 66.7[f] | 20.6[f] | 1.0[d] | 1.0[d] | 0[c] | 0[c] |
| Granby, QC | 3 | 37 | 5 | 45 | 13.5[e] | 60[f] | 19.0[e] | 0[c] | 2.4[d] | 0[c] | 0[c] |
| Sherbrooke, QC | 0 | 0 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA |
| Saint John, NB | 0 | 9 | 11 | 20 | 55.6[f] | 36.4[f] | 45[f] | 0[c] | 5[e] | 0[c] | 0[c] |
| Charlottetown, PEI | 0 | 1 | 1 | 2 | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] | 0[c] |
| Lunenburg, NS | 3 | 96 | 73 | 172 | 24.0[f] | 31.5[f] | 26.6[f] | 0[c] | 4.1[d] | 0[c] | 0.6[d] |
| St. John's, NL | 0 | 0 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA |
| Total number | 27 | 328 | 212 | 567 | NA | NA | NA | NA | NA | NA | NA |
| Overall prevalence | NA | NA | NA | NA | 22.0 | 36.3 | 26.6 | <0.01 | 0.02 | <0.01 | <0.01 |

Abbreviations: AB, Alberta; Ap, *Anaplasma phagocytophilum*; BbA, *Borrelia burgdorferi* infection prevalence in adult ticks; BbN *Borrelia burgdorferi* infection prevalence in nymphal ticks; BbT, *Borrelia burgdorferi* infection prevalence in adult and nymphal ticks; BC, British Columbia; Bm, *Borrelia miyamotoi*; Bmi, *Babesia microti*; MB, Manitoba; NA, not applicable; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; ON, Ontario; PEI, Prince Edward Island; POWV, Powassan virus; QC, Québec; SK, Saskatchewan; spp., species
[a] Only adult and nymphal *Ixodes* spp. ticks were tested
[b] Infection prevalence presented as tick numbers in some sentinel regions are too small to infer a prevalence rate
[c] Zero (green) no infected ticks
[d] Infection prevalence <5% (blue)
[e] Infection prevalence 5%–20% (yellow)
[f] Infection prevalence >20% (red)

## Discussion

In its pilot year, the Canadian Lyme Sentinel Network documented the presence of *Ixodes* tick species that are vectors of *B. burgdorferi* and four other human pathogens in seven out of 10 Canadian provinces, with an overall infection prevalence of 25.2% (0%–45.0%) for *B. burgdorferi*. However, we noted a great variability between regions: while no *Borrelia* were found in British Columbia, Prince Edward Island or Manitoba, infection prevalence in sentinel regions in Ontario, Québec, New Brunswick and Nova Scotia ranged between 19.0% and 45.0%. These results align with the results of recent studies of the distribution of *I. scapularis* ticks in Canada (24–27), suggesting that the sentinel approach adopted by CaLSeN is successfully capturing regional variations in Lyme disease risk.

Surveillance results highlighted notable regional variation in density of *I. scapularis* within Ontario and Québec. Mean density of nymphs in the Granby and Montréal regions of Québec were 0.38 and 0.43 ticks per 100 $m^2$, respectively, whereas no blacklegged ticks were found in Sherbrooke. In Ontario, nymph densities were high in Kingston (0.27 nymphs/100 $m^2$), but much lower in southern Ontario, with only 0.02 nymphs/100 $m^2$ in Hamilton. Nymph densities from Ottawa should be interpreted with caution, as sampling was undertaken earlier in the summer, prior to the summer peak in nymph activity.

The 2019 surveillance by CaLSeN represents the first effort to detect locally reproducing populations of *I. scapularis* ticks through active surveillance in both Prince Edward Island and the island of Newfoundland. Thus, the presence of *I. scapularis* confirmed by drag sampling in Prince Edward Island was a novel finding. The detection of two different stages (nymph and adult) in the environment at two separate sampling sites is early evidence that local reproduction of ticks may be occurring. However, it is possible that the two specimens were adventitious ticks carried to the island by migrating birds. Further active surveillance will be necessary to confirm whether ticks are established in the province.

Laboratory analyses of collected ticks yielded two noteworthy pathogen detections. Firstly, *B. microti* was detected in an *I. angustus* nymph, the first report of a tick infected with this pathogen in British Columbia. Secondly, the deer tick lineage of Powassan virus was detected in the Lunenburg sentinel region and this is only the second detection of this pathogen in questing ticks in the region (28).

## Strengths and limitations

A major strength of our surveillance network is the collaboration established between provinces and between public health authorities and academics. These links have allowed knowledge translation between the involved parties and have been crucial during the planning phases of the network. Partnership was essential during the selection of sentinel regions and in carrying out the fieldwork. To strengthen these collaborations, CaLSeN will continue to work closely with provincial health authorities to ensure that the activities of the network are complementary to and coordinated with provincial surveillance objectives.

An important limitation to the interpretation of results is the variable timing of the sampling in each region. This may have contributed to differences in the abundance of the tick stages collected, as adults are generally active earlier in the spring whereas nymphal abundance peaks slightly later in the summer (29). The absolute values of reported tick densities therefore need to be interpreted with caution.

The inclusion of variables such as temperature and weather during the sampling event in further statistical analyses carried out on gathered data will also be important to control for variability in timing of tick sampling. Finally, pursuing yearly sampling within a time-frame more closely aligned with the peak in nymphal activity will provide better data for documenting change in regional risk over time.

## Conclusion

The Canadian Lyme Sentinel Network provides the first coordinated national active surveillance initiative for tick-borne disease in Canada. To our knowledge, the sentinel surveillance approach has not been applied to Lyme disease on the national scale elsewhere in North America or Europe, making CaLSeN a useful model for other countries affected by Lyme disease and other tick-borne illnesses. Following the establishment of baseline data on Lyme disease vectors and prevalence of *Borrelia*, an important next step will be to establish the link between the environmental risk and the regional incidence of human cases. Further collection of environmental, social and human case data across sentinel regions will allow for the exploration of the broader representativity of sentinel-based risk measures for tick-borne disease surveillance.

## Authors' statement

CG — Conceptualization, methodology, analysis, interpretation, writing original draft, review and editing
PAL — Conceptualization, methodology, interpretation, review and editing
CB, KC, SG, CJ, JK, MK, LRL, RM, MN, MR, CR, AS, BT — Methodology, interpretation, review and editing
JB, AD, SD, ME, EF, EG, GG, DH, EJ, GL, DM, MM, JN, KR, KT, MV — Methodology

## Competing interests

None.

## Acknowledgements

We thank the many field and laboratory technicians who were involved in tick collection and testing. We gratefully acknowledge the support of regional and provincial health authorities in facilitating site selection, and regional and national parks for providing access to field sites.

## Funding

This work was supported by the Canadian Lyme Disease Research Network (CLyDRN), a network funded by the Canadian Institutes of Health Research (CIHR). The Institut national de santé publique du Québec (INSPQ) and Ministère de la santé et des services sociaux (MSSS) funded data collection in 12 sampling sites within Québec sentinel regions as part of annual surveillance activities. The National Microbiology Laboratory confirmed the species determinations and undertook the testing of ticks for tick-associated pathogens for specimens collected in all jurisdictions outside of Ontario.

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# A case of tick-borne relapsing fever in pregnancy

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## Abstract

Tick-borne relapsing fever (TBRF) is an infection caused by *Borrelia* spirochetes. In North America, *Borrelia hermsii* is the most common cause for TBRF. This vector-borne disease is transmitted by *Ornithodoros hermsi*, a soft-bodied tick found in high altitudes in northwestern United States and southwestern Canada. Once bitten by the tick and infected by *B. hermsii*, episodes of fever alternating with afebrile periods can occur.

A case of TBRF in a pregnant host was complicated by Jarisch-Herxheimer reaction requiring critical care. This case emphasizes the importance of maintaining a high index of suspicion in TBRF. Clinician recognition, diagnosis and treatment of TBRF as well as public awareness of strategies to prevent tick bites should be strengthened.

***Suggested citation:*** Lam JC, Larios OE, Parkins MD, Vaughan SD. A case of tick-borne relapsing fever in pregnancy. Can Commun Dis Rep 2020;46(10):362–4. https://doi.org/10.14745/ccdr.v46i10a09
***Keywords:*** tick-borne relapsing fever, *Borrelia hermsii*, *Ornithodoros*, Jarisch-Herxheimer reaction, disease surveillance

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## Introduction

Tick-borne relapsing fever (TBRF) can be challenging to diagnose because of difficulties in isolating the causative bacterium, *Borrelia hermsii*, in the laboratory. Furthermore, clinicians may not consider TBRF in the differential diagnosis of febrile illnesses as the vector is often unrecognized. In addition, TBRF is a non-reportable illness.

Here, we report a life-threatening case of TBRF in a pregnant individual, discuss some treatment aspects and advocate for active case surveillance by public health officials in areas of high risk.

Written informed consent was obtained from the patient to publish this case report and the accompanying images.

## Case

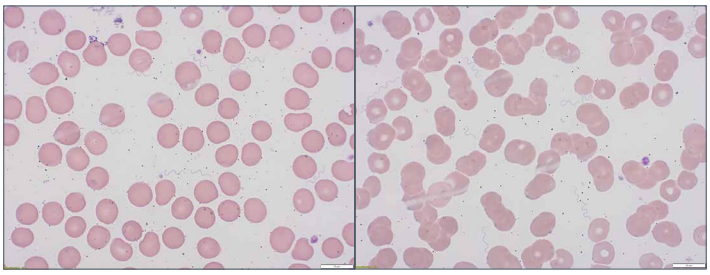
A 30-year-old previously healthy primagravida woman, at 17 weeks' gestation, presented to hospital in Calgary, Alberta, with a four-day history of fevers, chills and multiple episodes of emesis. Prior to symptom onset, she had spent five days in the Okanagan region of British Columbia on a summer family hiking trip. The entire family stayed in a well-kept air-conditioned house in Vernon, British Columbia, that her extended family regularly inhabited. There was no history of rodent inhabitation or pest control concerns in or around the house.

The patient had had an unremarkable prenatal course, with negative screening serology for syphilis and HIV. There was no exposure history consistent with rat bite fever, leptospirosis or louse-borne relapsing fever. She reported multiple unknown insect bites across her torso, but no rash, during her holiday. On presentation, she was febrile (temperature 38.9°C), hypotensive (blood pressure 85/52) and tachycardic (heart rate 128 beats/minute). The remainder of her examination was otherwise non-contributory.

Initial investigations identified pancytopenia with hemoglobin of 78 g/L, platelets of 27 × $10^9$/L and white blood cells of 3.4 × $10^9$/L and with lymphopenia at 0.1 × $10^9$/L. Metabolic acidosis with pH of 7.21 and lactate of 4.3 mmol/L were also identified. A peripheral blood smear found the presence of spirochetes and a presumptive diagnosis of TBRF was made (**Figure 1**).

Treatment with penicillin G at four million units intravenously every four hours was commenced. Two hours after penicillin initiation, the patient developed chills and worsened hypotension (blood pressure 70/50) despite administration of 6 L of crystalloid resuscitation. This is characteristic of a Jarisch-Herxheimer reaction. The patient was subsequently transferred to the intensive care unit for closer monitoring. Her hypotension resolved within one day, and pancytopenia improved within the week. She was discharged to complete a 14-day course

**Figure 1: Wright-Giemsa stained peripheral blood smear showing spirochetes**



of intravenous penicillin G. Molecular testing of blood by 16S ribosomal polymerase chain reaction confirmed *B. hermsii* as the causative pathogen.

At 40 weeks, the patient delivered a healthy infant.

## Discussion

*B. hermsii* is a spirochete implicated in TBRF. *B. hermsii* commonly occurs in mountainous regions of North, Central and South America. In Canada, approximately 50 cases have been reported over the last two decades (1). TBRF is transmitted via the night-biting soft tick *Ornithodoros hermsi* (2). *O. hermsi* are found in southern British Columbia and northwestern United States, preferring coniferous forests at 450–2,450 m occupied by rodents such as tree squirrels and chipmunks (3). *O. hermsi* live in the nests of rodent reservoirs and feed nocturnally. In the absence of rodents, *O. hermsi* will feed on humans.

Infected individuals present with characteristic recurrent three-day fevers punctuated by week-long periods of being afebrile. Episodes of fevers and tachycardia, known as the "chill phase," are followed by the "flush phase," during which transient hypotension and drenching sweats occur. The acuity of the patient's presentation is likely linked to the relative immunosuppression of pregnancy, based on reports of increased severity in pregnant patients (4). The potential for poor neonatal outcomes is well documented (5).

Microscopy may be useful in diagnosing TBRF because the spirochetes associated with *B. hermsii* are clearly visible, particularly during febrile episodes. Peripheral blood smears stained with Wright-Giemsa stain are positive for the presence of extracellular spirochetes in about 70% of patients, particularly during the flush phase (6). Although molecular testing can be used to confirm spirochete species, testing turnaround time is lengthy, and it is not appropriate to wait for results prior to initiating therapy. Similarly, serological testing performed weeks after infection confirms presence of appropriate antibody response but is of little use in the acute management of the illness.

TBRF during pregnancy is rare, and considerations of drug therapy and neonatal consequences are important. Oral doxycycline or intravenous beta-lactams are suitable therapies, but intravenous beta-lactams are preferable in pregnancy because of the teratogenicity of tetracyclines (7). Jarisch-Herxheimer reaction, characterized by chills, fevers and hypotension, can develop within 24 hours in patients treated for spirochetal infections. Jarisch-Herxheimer reaction has been documented in upwards of 50% of patients treated for TBRF (8,9). Thrombocytopenia associated with acute TBRF poses risks of preterm labour and spontaneous abortion. Cases of placental transmission to the neonate have also been reported (4).

Because TBRF is not a reportable disease in Canada, it is not known whether distribution of *B. hermsii* and incidence of TBRF is similar to a decade ago. Over 80% of patients will not develop a rash from a nighttime painless bite or exhibit the characteristic fever syndrome. As such, the burden of TBRF in southwestern Canada is likely underestimated (10). Case surveillance and reporting may improve systemized approach to diagnosis and greater clinician awareness of this disease.

Although rare, TBRF can have severe sequelae and be fatal (11). Enhanced public awareness for TBRF may lead to a more concerted effort to prevent TBRF by reducing rodent habitats, contacting pest control for chemical treatment of rodent-infested areas and educating people to apply topical repellants (e.g. permethrin) when sleeping (12). Active case surveillance could be considered by public health officials in areas of high risk.

Geographic distribution of *O. hermsi* may expand in Canada with predicted changes in climate (13).

### Conclusion

This case illustrates TBRF as a life-threatening complication of pregnancy in the absence of the typical exposure in a rustic dwelling.

Surveillance data would be useful for characterizing the epidemiology of this probable underdiagnosed infection in Canada.

## Authors' statement

All authors were involved in the management of the patient. JCL wrote the initial draft of the manuscript and all authors contributed to its revision. SDV oversaw manuscript preparation and revisions. All authors read and approved the final manuscript.

A copy of the written consent is available for review by the Editor-in-Chief of *Canada Communicable Disease Report*.

## Competing interests

None.

The case was presented in part at the Clinical Grand Rounds, European Congress of Clinical Microbiology & Infectious Diseases 2019, Amsterdam Noord, the Netherlands.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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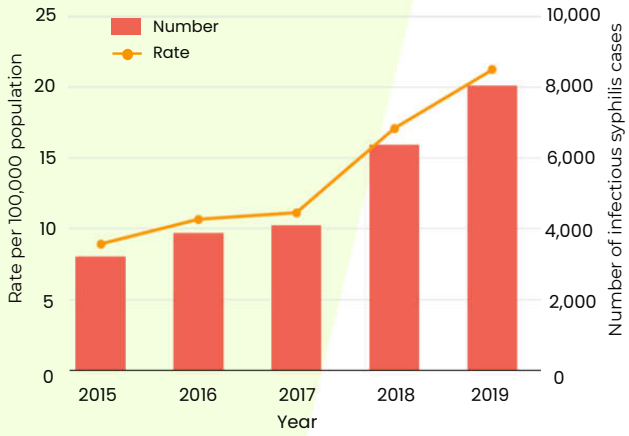
# Infectious Syphilis in Canada, 2019

## Number and Rates of Infectious Syphilis in Canada, 2015-2019




Between 2018 and 2019, the **highest relative increase** in rates has been observed among **15-24 year olds**

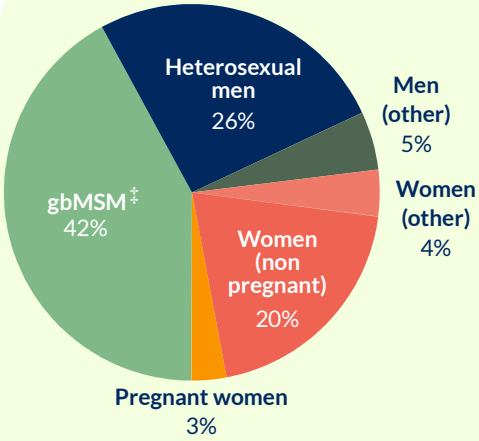
**8,066*** **cases of infectious syphilis were reported in 2019**

Since 2015, **rates among females** have increased by more than

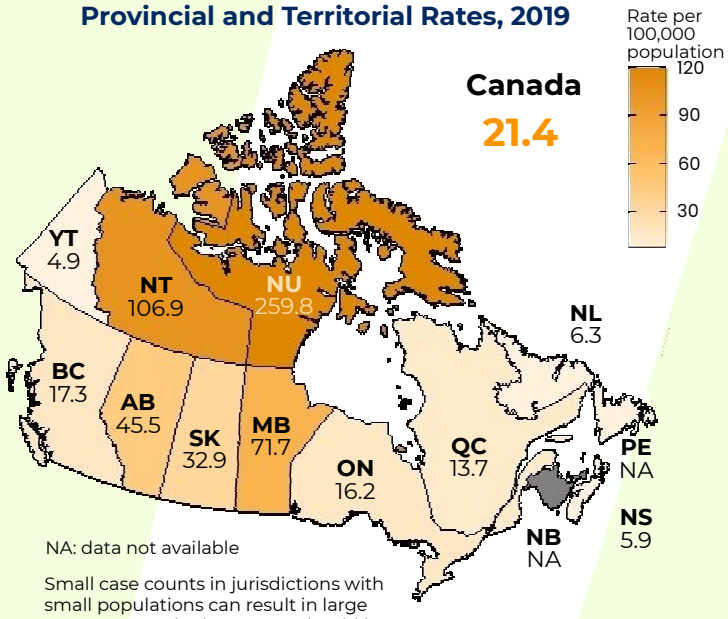
**▲890%**

while **rates among males** increased by 91%

## Proportion of Cases per Subpopulation, 2019†




## Provincial and Territorial Rates, 2019




NA: data not available

Small case counts in jurisdictions with small populations can result in large rates; as a result, these rates should be interpreted with caution

There were **45 confirmed cases** of **congenital syphilis** in 2019

An increasing number of reports suggest that **substance use** is associated with syphilis

*Preliminary 2018 and 2019 data were cordially shared by all provinces and territories and are expected to differ slightly from final counts
†Subpopulation data include data from all provinces and territories with the exception of Quebec, Prince-Edward Island and Nunavut
‡gbMSM: Gay, bisexual and other men that have sex with men

Public Health Agency of Canada / Agence de la santé publique du Canada

Canada

# Syphilis in Women and Congenital Syphilis in Canada, 2019

In 2019, almost **2,000** cases of infectious syphilis were reported among females in Canada

### Nearly 1 in every 4 syphilis cases is female

The proportion of female cases increased from 6% in 2015, to **24%** in 2019

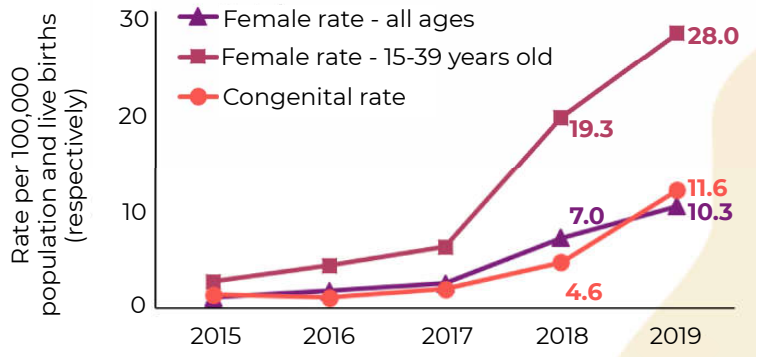
### Females of reproductive age are most affected

Between 2015 and 2019, the rates were highest in females aged **15-39 years**

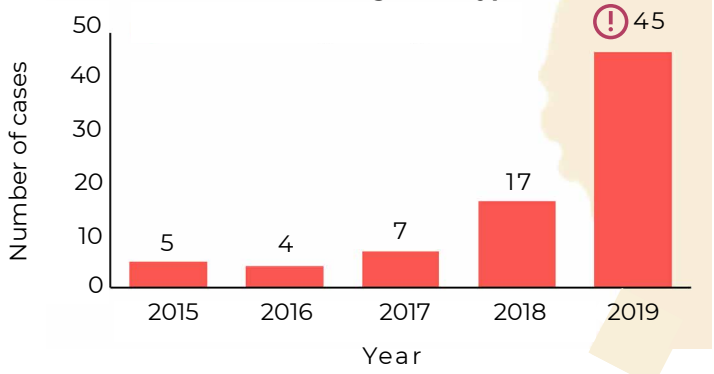
### Congenital syphilis cases are the highest ever reported

In 2019, there were **45 confirmed cases** and **25 probable cases*** of congenital syphilis

**Infectious syphilis rates in females and congenital syphilis rates**




**Number of confirmed cases of congenital syphilis**




### Risk factors for maternal and congenital syphilis in Canada†

**Access to and use of prenatal care**
Inadequate or none

**Substance use**
Alcohol, tobacco and methamphetamines

**Socioeconomic status**
Lower income

**Geography**
Rural and remote residence

**Stigma**
Historical trauma
Discrimination in healthcare

Preliminary 2018 and 2019 data were cordially shared by provinces and territories and are expected to differ slightly from final counts

*Alberta, Saskatchewan, Manitoba and Quebec have a probable congenital syphilis case definition

†For more information, please refer to the *Syphilis in Canada - Technical Report on Epidemiological Trends, Determinants and Interventions, 2020*

Public Health Agency of Canada / Agence de la santé publique du Canada

Canada

# Benchmarking public health pain management practices during school immunizations

Lucie M Bucci[1]*, Noni E MacDonald[2,3], Tamlyn Freedman[4,5], Anna Taddio[4,5]

## Abstract

**Background:** Pain and fear during immunizations can affect children and their future behaviour toward immunization. These negative experiences can be amplified when children receive vaccines as part of school-based immunization programs, where parental or tutor supports are missing. In 2015, HELPinKIDS&ADULTS, a Canadian network of experts, published a clinical practice guideline (CPG) on the management of pain and fear during immunization. This guideline has been endorsed by international, national and provincial organizations. However, the level of integration and implementation of the CPG into local and community immunization programs such as school-based immunization clinics is unclear.

**Methods:** An investigation whether public health units in Ontario integrated and implemented the pain and fear interventions recommended by the CPG into school-based immunization policies and practices was concluded.

**Results:** The study shows that the majority of public health units do have pain and fear policies and procedures in place, but interventions are not integrated in a consistent and formal manner, leading to suboptimal uptake of interventions during immunizations at school.

**Conclusion:** For pain interventions to be applied with sufficient fidelity and in enough individuals to have a meaningful effect, organizational leaders need to create directives and procedures that support implementation in a systematic and accountable manner.

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***Suggested citation:*** Bucci LM, MacDonald NE, Freedman T, Taddio A. Benchmarking public health pain management practices during school immunizations. Can Commun Dis Rep 2020;46(10):367–72. https://doi.org/10.14745/ccdr.v46i10a10

***Keywords:*** immunization, school programs, public health, pain, fear, clinical practice guideline, vaccine hesitancy

## Introduction

Immunizing students at school is an effective way to increase immunization coverage. All public health jurisdictions in Canada have mass school-based programs that roll out vaccines against invasive meningococcal disease (IMD), hepatitis B and human papillomavirus (HPV), among others. The positive outcomes of these programs are numerous. For example, vaccines given at school improve completion of multiple-dose regimens and provide well-timed immunizations relative to when protection is needed (1). In addition, vaccines delivered on time reduce the risk of infection and negative health outcomes.

A substantial number of students who receive vaccines at school have negative experiences; such reactions may lead to future vaccine refusal (2). These negative experiences are often related to pain and a fear of needles. As many as two out of three individuals are afraid of needle pain (3). Students who experience fear may have episodes of fainting, headaches, nausea and other symptoms. Such immunization stress–related responses may occur in clusters and, if not managed well, may undermine trust in immunization programs (4).

Evidence-based interventions exist to mitigate negative experiences due to pain and fear during immunizations. In 2015, HELPinKIDS&ADULTS, a Canadian network of experts, published a clinical practice guideline (CPG) on the management of pain and fear during immunization (5). The World Health Organization (WHO) has recognized the guideline and referenced it in its first global policy paper on reducing pain at the time of immunization (6). More recently, the Public Health Agency of Canada integrated the guideline into the *Canadian Immunization Guide* (7). In addition, both the Ontario Ministry of Health and Long-Term Care (MOHLTC) and the BC Centre for Disease Control (BCCDC) adopted the guideline into their immunization policies and procedures (8,9).

While the guideline has been endorsed at the international, national and provincial levels, it is unclear how many public health units have integrated and implemented the CPG recommendations into their school-based immunization programs.

Since school immunization programs are carried out at the local level, it is important to explore what local public health units are doing to fully integrate and implement the guideline. There is little doubt that making broad practice changes in public health takes time. Readiness to change may also not be present at the local and/or community levels.

In 2015, MOHLTC published a roadmap for improving immunization in the province. This plan identified the 2015 CPG as an evidence-based approach for improving the immunization experience, strengthening vaccine delivery and reducing barriers to immunization (10).

To understand the status of CPG implementation, we undertook a benchmarking survey to document pain management practices and barriers and facilitators to CPG uptake by public health units across Ontario.

## Methods

During the timeframe of our survey (September 2017 to March 2019), the school-based immunization program in Ontario delivered three vaccines to Grade 7 students: a one-dose regimen of the meningococcal vaccine and two doses of the hepatitis B and HPV vaccines. A research team member from Immunize Canada emailed an invitation to a contact at each public health unit to identify a staff member familiar with school immunization policies and practices and qualified to answer the survey. The contact was identified from a list maintained by Immunize Canada and verified by MOHLTC. Using a structured telephone interview, a trained interviewer conducted the survey and questioned the identified staff member from each unit (i.e. a public health nurse, vaccine-preventable disease manager, supervisor, or director of immunization clinics).

The interview guide was designed according to standard survey construction guidelines. The guide included 53 questions in binary, multiple-choice and open-ended formats. Questions probed the following domains: presence of policies regarding school immunizations; consenting processes; staff and student training about how to cope with pain and fear during injection; coping interventions used during immunization clinics; assessment of student symptoms (pain, fear) and satisfaction; perceived barriers to pain mitigation; and characteristics of the unit (i.e. size of population served). The survey took approximately 45 to 60 minutes.

The survey was pretested with members of the Canadian Nurses Coalitions on Immunization (CNCI). This national coalition of nurses from the public health sector and provincial health ministries is familiar with policy and procedures in school immunization programs.

Ethical approval was obtained from the IWK Health Centre Research Ethics Board.

## Results

Of the 36 eligible public health units, individuals from 24 units participated in the survey. Six respondents (25%) were from public health units that served a population of 500,000 or more.

The responses from the different survey domains are summarized in **Table 1**. All respondents stated that their public health unit had a local policy to oversee planning, implementation and reporting of immunization practices in schools. In addition, 14 of 24 (58%) individuals reported that their unit had pain and fear management policies in place. The majority of respondents (n=19; 79%) indicated that they formally educate students ahead of school clinics. This education typically includes the rationale for immunization, how vaccines work and their potential side effects. None of the respondents reported providing information to students about how to cope with needle pain or fear.

Coping interventions were inconsistently applied during immunization clinics (**Table 2**). While the majority of respondents reported using various coping interventions, less than half reported "always" or "almost always" using coping interventions

**Table 1: Characteristics of school immunization programs in Ontario public health units (n=24)**

| Survey topic | Number that responded "yes" |
|---|---|
| Have school immunization policies on: | |
| Vaccine delivery process | 24 |
| Anaphylaxis management | 24 |
| Clinic procedures | 24 |
| Fainting management | 22 |
| Education and communication with students | 19 |
| Education and communication with school staff[a] | 18 |
| Pain and fear management | 14 |
| Program evaluation/quality | 12 |
| Have consenting procedures | |
| Sent home with students | 20 |
| Mailed to parents | 1 |
| Accept student consent from high school students | 1 |
| Other: not explained | 2 |

**Table 1: Characteristics of school immunization programs in Ontario public health units (n=24)** (*continued*)

| Survey topic | Number that responded "yes" |
|---|---|
| Have student education prior to immunization clinic[b] | |
| Reason for vaccine, how it works and side effects | 15 |
| Reason for vaccine, how it works, side effects and exemptions | 1 |
| Reason for vaccine, how it works, side effects, logistics of vaccine day and website for Q&A | 1 |
| Reason for vaccine, how it works, side effects, risks and benefits | 1 |
| Reason for vaccine and side effects | 1 |
| Have formal training for public health staff on: | |
| Anaphylaxis treatment[a] | 22 |
| Fainting mitigation | 19 |
| Program delivery[a] | 17 |
| Communication with school staff[a] | 14 |
| Communication with students[a] | 14 |
| Pain mitigation[a] | 12 |
| Fear/anxiety mitigation | 12 |
| Monitor students during immunization clinics for: | |
| Student preferences for coping strategies[a] | 7 |
| Documented in computer database | 4 |
| Documented manually | 3 |
| Student experience with immunization[a] | 6 |
| No written record of how specified | 6 |
| Fear | 6 |
| Informal description (not documented) of how specified | 6 |
| Pain[a] | 5 |
| Informal description (not documented) of how specified | 2 |
| Computer database | 1 |
| No answer | 2 |

Abbreviation: Q&A, questions and answers
[a] n=1 missing
[b] n=2 missing

except for verbal distraction, comfortable seating, short wait times and vaccinating most fearful students first. Few respondents solicited student coping preferences, overall immunization experience or injection-related symptoms (pain, fear).

Respondents identified several challenges that affected the implementation of pain and fear mitigation interventions. These included budget constraints and physical space constraints

**Table 2: Pain and fear interventions applied by public health units in Ontario (n=24)**

| Intervention | Number that use intervention | Frequency of use of the intervention | |
|---|---|---|---|
| Distraction with personal items[a]<br>Personal items used include personal mobile phone (n=21) and/or other object (n=1) | 22 | Always | 6 |
| | | Almost always | 4 |
| | | Sometimes | 9 |
| | | Almost never | 1 |
| | | Never | 0 |
| | | No answer | 2 |
| Verbal distraction[a] | 23 | Always | 8 |
| | | Almost always | 5 |
| | | Sometimes | 3 |
| | | Almost never | 0 |
| | | Never | 0 |
| | | No answer | 5 |
| Sitting in a comfortable position[a] | 20 | Always | 11 |
| | | Almost always | 2 |
| | | Sometimes | 0 |
| | | Almost never | 1 |
| | | Never | 0 |
| | | No answer | 6 |
| Short wait times[a] | 18 | Always | 10 |
| | | Almost always | 5 |
| | | Sometimes | 3 |
| | | Almost never | 0 |
| | | Never | 0 |
| | | No answer | 0 |
| Presence of peer support[b] | 18 | Always | 0 |
| | | Almost always | 6 |
| | | Sometimes | 8 |
| | | Almost never | 1 |
| | | Never | 0 |
| | | No answer | 3 |
| Privacy[c]<br>Approaches used for providing privacy depends on the school (n=6) and include using a private room (n=5), immunizing students at the beginning or end of clinic (n=3) and using a privacy screen (n=1) | 17 | Always | 6 |
| | | Almost always | 1 |
| | | Sometimes | 6 |
| | | Almost never | 3 |
| | | Never | 0 |
| | | No answer | 1 |

**Table 2: Pain and fear interventions applied by public health units in Ontario (n=24)** (*continued*)

| Intervention | Number that use intervention | Frequency of use of the intervention | |
|---|---|---|---|
| Use of topical anesthetics[a] | 16 | Always | 0 |
| | | Almost always | 0 |
| | | Sometimes | 3 |
| | | Almost never | 10 |
| | | Never | 0 |
| | | No answer | 3 |
| Vaccinate most fearful first[a] | 15 | Always | 8 |
| | | Almost always | 3 |
| | | Sometimes | 2 |
| | | Almost never | 1 |
| | | Never | 0 |
| | | No answer | 1 |
| Distraction provided by public health[c]<br>Examples of items used include juice box, stress ball, toys (e.g. bubbles, pinwheels, stuffed animals), books | 12 | Always | 2 |
| | | Almost always | 1 |
| | | Sometimes | 4 |
| | | Almost never | 1 |
| | | Never | 0 |
| | | No answer | 4 |

[a] n=1 missing
[b] n=3 missing
[c] n=2 missing

in schools. In addition, respondents reported being unable to negotiate optimal clinic spaces in schools because of poor relationships with school administrators.

## Discussion

Implementing interventions proven to alleviate pain and fear during school immunization clinics requires integration across immunization policies and practices and collaboration among all stakeholders (public health, school staff, students, parents). At present, the CPG recommendations appear to be insufficiently integrated into clinic planning and delivery activities. This limits frontline staff in their ability to implement different types of pain interventions at the required frequency.

To achieve broader and more consistent use of interventions, we recommend that public health leaders and policy and program managers develop policies and procedures that explicitly incorporate pain mitigation interventions into immunization clinic planning and delivery activities and track student symptoms as a quality indicator for their programs.

A vaccine delivery framework, the CARD™ system, was developed to help facilitate the integration of the CPG in the school immunization program (11). Each letter of the word "card" encompasses a category of evidence-based interventions (C – Comfort, A – Ask, R – Relax, D – Distract) to reduce pain, fear and fainting. All these interventions can be used ahead of time to prepare students for the procedure.

The CARD™ system provides a systematic approach to planning, delivering and monitoring school-based immunizations. The system incorporates student needs and preferences, promoting student-centred care and health equity (12). The program includes, for example, meeting with school principals ahead of time to identify suitable clinic spaces, setting up clinic spaces to minimize cues that elicit fear, and asking students to report on their symptoms.

To be successful, CARD™ requires the backing of organizational leaders who create policies and procedures to support implementation. Education and training of all the relevant stakeholders is also required so that they are versed in and committed to the program and can deliver it with fidelity (13).

To date, CARD™ has been evaluated in one public health unit in Ontario, Niagara Region Public Health, where it was demonstrated to reduce student fear and dizziness (a precursor of fainting) during school-based immunizations (14). After the evaluation, CARD™ was implemented across the unit's entire school immunization program.

There are several potential benefits to addressing pain and fear during school immunizations. First, students will have more positive immunization experiences because they will have less pain and fear. Second, utilizing pain and fear mitigation strategies equips students with coping skills that may be applied to other stressful situations. Third, by reducing pain and fear, nurses demonstrate both competence and caring, qualities needed to develop trusting relationships. Long term, students may develop more positive attitudes about immunization and healthcare providers, which may lead to higher acceptance of vaccines and other healthcare interventions, in turn leading to improved health outcomes (15).

### Limitations

There are a few shortcomings that should be acknowledged, including changes in practices over time, potential errors in measurement and potential errors in data interpretation. The study took place between 2017 and 2019, and it is possible that some public health unit practices changed after participation in this study. For instance, as previously stated, a public health unit that participated in the development of CARD™ subsequently implemented it across the entire school program in 2019.

In addition, participants self-reported practices and may have introduced random error and bias (e.g. social desirability bias) into their responses. However, given that the results

demonstrated low uptake of CPG recommendations in general, it is unlikely that bias contributed to a significant source of error.

Finally, the design of the study does not allow for estimating the actual utilization rates of specific pain interventions, and responses may inadvertently be interpreted as actual use. For instance, while most respondents indicated they use personal distraction items almost always or always, this intervention requires students to come to school with these items in hand. Given that students and their families are not informed ahead of time about being able to use personal distraction devices during immunization clinics, it is likely that many do not actually bring anything to distract themselves.

### Conclusion

This survey of Ontario public health units demonstrated limited integration and implementation of the immunization pain mitigation CPG into school clinic practice at the local level. While the majority of public health units have policies and procedures on pain and fear management, they do not appear to be put into action in a formal way by the public health staff. This leads to inconsistent and suboptimal integration of pain interventions in the school immunization program. For pain interventions to be applied with sufficient fidelity and in enough individuals to have a meaningful effect, organizational leaders need to create directives and procedures that support implementation in a systematic and accountable manner.

## Authors' statement

LMB — Project administration, supervision, investigation, data curation, formal analysis, writing original draft
NEM — Conceptualization, writing–review and editing
TF — Data curation, writing–review and editing
AT — Conceptualization, methodology, supervision, writing–review and editing

### Competing interests

This study originated at the Canadian Public Health Association/Immunize Canada with collaborators from the University of Toronto and Dalhousie University. There are no other disclosures.

## Acknowledgements

The authors would like to thank the individuals who participated in this study, the HELPinKIDS&ADULTS team, and L Lee and R Segall for their contribution.

## Funding

AT reports Section 9 Trademark No. 924835 for CARD.

LMB reports that Immunize Canada received grants from Pfizer Canada, Merck Canada, GSK Canada, Seqirus Canada and Sanofi Pasteur outside the submitted work.

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# What increases and decreases the risk of COVID-19 outbreaks in the workplace

**Source:** Emerging Sciences Group of the Public Health Agency of Canada. Evidence Brief on what increases and decreases the risk of COVID-19 Outbreaks in the Workplace. Full report available from: phac.emergingsciencesecretariat-secretariatdessciencesemergentes.aspc@canada.ca

**Background:** As countries come out of lockdown, an urgent question is how to keep people safe in the workplace. To inform this inquiry, studies on COVID-19 in the workplace that identified: 1) what increased the risk of SARS-CoV-2 transmission, or 2) what decreased the risk of transmission were summarized. The definition of workplace for this review was all-encompassing with the exception of healthcare workplaces, which were excluded.

**Methods:** Twenty databases and key websites were searched for relevant reviews and primary research that were either peer-reviewed publications or pre-prints (published before peer review). Search terms included: workplace, work*, occupation, colleague, manufacturing, factory, employee, superspread and gathering. Data from relevant studies were extracted into evidence tables and the evidence summarized. This review contains research published until August 21, 2020.

**Results:** A total of 58 publications on what may increase risk of COVID-19 in the workplace were included in this review. A major risk factor for work-related outbreaks is occupation, specifically: drivers and transport workers, service and sales workers, personal care occupations (daycares, preschools, religious professionals, personal care workers, dental and salon staff), and those who work in dental offices, community and social services, construction and related trades, public safety (e.g. correctional officers, police, firefighters) and the food industry. In all cases, these occupations require presence of employees onsite and/or frequent contact with clients. Extensive outbreaks have occurred with migrant workers and in meat packing plants, often associated with high density of workers, prolonged contact, a lack of hygiene stations, physical barriers or masks and potentially magnified by employer-provided shared accommodation and transportation. Outbreaks most commonly occur in indoor environments with an OR 18.7 (95% CI, 6.0–57.9) compared with outdoor environments and, in some cases, were epidemiologically linked to specific environmental characteristics (e.g. airflow) or use of common areas (e.g. bathrooms).

There were 20 publications on strategies to reduce the risk of SARS-CoV-2 infection in the workplace; most were mathematical models. These identified decreasing the number of people at work at any one time, cohorting employees, decreasing time in the workplace, limiting social contact as well as increasing the use of masks, teleworking, and enhancing income support programs to help ensure all symptomatic people stay home. Two studies identified the importance of contact tracing when someone in the workplace is identified with COVID-19. One noted the importance of a clear delegated authority to address this. Modelling suggested this would only be useful if there was good compliance with quarantine of all contacts. Public information campaigns were found to be effective, supported by clear guidelines in the workplace. Several studies looked at testing employees or environmental monitoring for SARS-CoV-2. These studies explored the frequency and volume required to be effective. One study identified that environmental monitoring of workplace meeting areas and washrooms could lead to the detection of asymptomatic disease, and another study found environmental monitoring and regular disinfection resulted in decreased transmission.

**Conclusion:** The prevention of COVID-19 transmission in the workplace depends on basic public health interventions, such as physical distancing, good hygiene practices, the use of masks and physical barriers as well as early detection of cases for self-isolation and contact tracing to identify contacts for quarantine. Environmental decontamination of surfaces may be protective. Work indoors appears to be at higher risk than work outdoors. This Evidence Brief should be read in conjunction with the Evidence Brief on Public Gatherings for additional information on associated risk factors, such as length and type of exposure and the protective effect of good ventilation when indoors. This is a rapidly evolving area of study; this Evidence Brief will be updated as new evidence is published.

# CCDR

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Published by authority of the Minister of Health.

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This publication is also available online at

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