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INFANT BOTULISM IN CANADA, 1979–2019

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INFANT BOTULISM IN CANADA, 1979–2019

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COMMENTARY

A warning about measurement and methodological issues associated with coronavirus tracking and evaluation across jurisdictions

Robert Ladouceur[1], Howard Shaffer[2], Paige Shaffer[3]*, Lucie Baillargeon[4]

Abstract

As people around the world experience a devastating pandemic, it is critical that policy-makers consider the methodological and measurement issues that might be associated with coronavirus disease 2019 (COVID-19) public health indicators. This commentary uses four primary variables to illustrate measurement and methodological issues that can complicate comparisons between jurisdictions. Jurisdiction refers to a variety of geographic areas, such as a country, a state, or a province/territory. These variables play a critical role in determining how we understand the trajectory of disease spread. These variables also contribute to our understanding of prevention strategies and their associated efficacy, reflecting the impact of COVID-19 on hospitals. It is critical for public health stakeholders and the public to recognize that these four simple variables can vary substantially across jurisdictions.

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Introduction

The world is going through a devastating pandemic. People from around the globe have observed the coronavirus and how its associated coronavirus disease 2019 (COVID-19) has affected various jurisdictions. No areas have been spared. As we submit this comment for publication, there are 100,746,915 total confirmed cases, and 2,170,467 deaths worldwide (1). Pathologists and medical experts have been working at an unprecedented pace to develop vaccines and treatments that can prevent and counteract COVID-19 and its adverse sequelae. Working in collaborative teams around the world, though promising interventions have been identified, most stakeholders do not expect to find a definitive solution within the upcoming months or perhaps years. Despite these energetic and enthusiastic efforts, public health government sectors have the responsibility to make urgent public health policy decisions to reduce and prevent the negative impacts of the COVID-19. To illustrate, statistical surveillance metrics have been used to guide screening and testing efforts as well as to limit personal movement between jurisdictions. These metrics have been used to advance public policy, protect health workers and citizens alike. How best to protect citizens by preventing the incidence of COVID-19 has become one of the most burning public health issues during these difficult times, and it will still remain even during vaccination dispensing phase and after it, for ongoing COVID-19 related surveillance.

During their decision-making process, public policy leaders rely on sparse and evolving scientific findings to guide their decision-making. These leaders recruit public health experts, epidemiologists, infectious disease experts, microbiologists and others to help interpret the scientific findings and provide insight into a rapidly changing landscape of evidence. However, because our understanding about the nature of this virus and its consequences is nascent in the scientific community, these decisions are difficult and complex. For example, setting policies around the length of time needed for confinement in a community is imprecise at best; in part, because infectious disease experts and epidemiologist do not fully understand the nature of the virus, even if the incubation period is understood.

To assist policy-making, decision-makers often look to other jurisdictions or countries to evaluate their practices and protocols. This tendency is closely linked with a variety of methodological and measurement issues. "Natural experiments" that compare different policies and approaches to the problem across areas are surely desirable. During a pandemic, every informed-based sources is welcome. However, analyses of what is being done in other countries or jurisdictions implies that the process of "making comparisons" rests on comparable data. Although commendable and necessary at this critical moment, these evaluations must be established on a shared foundation of evidence that is reliable and valid. Evidence must be established. For example, we must identify relevant and representative variables to make comparisons between areas. Further, we must use derive these comparisons from variables that are described clearly and operationalized precisely. Anything less leaves important comparisons as questionable and ultimately flawed. The bottom line is that we must compare "apples to apples" or we risk being misled.

The purpose of this brief comment is to identify some of the key variables that provide policy-makers with the information they might use to protect the public and track the spread of COVID-19. We primarily focus on this body of data and describe how readily observers can misinterpret it. We aim to discuss these fundamental variables to illustrate some of the problems associated with COVID-19 related evidence. However, we do not intend to discuss extensively the methodological issues raised in this paper. There are many fine texts to provide guidance about these investigative methods (2,3). Our main goal is to offer a clarion call that will raise cautiousness and clarify nuances about the comparisons often made between jurisdictions and countries.

Analyses of the impacts of COVID-19 in the media and among scientists tend to yield to a great deal of information. Although there are numerous variables worthy of consideration, a discussion of all measures is beyond the scope of this commentary. Here we will limit our discussion to the following four main variables selected in part because these surveillance metrics are commonly reported by the media across a wide variety of jurisdictions:

1. Number of positive COVID-19 cases
2. Hospitalized cases
3. Cases in the intensive care units in hospitals
4. COVID-19 related deaths

These variables are sensible and principal indicators of the various impacts of the coronavirus. The central question is "to what extent can stakeholders use these variables and the evidence they generate to make sound, pertinent and reliable comparisons across jurisdictions"? It is worth repeating: the opportunity to compare evidence across jurisdictions associated with different public policies provides an important opportunity to conduct natural research. During the following examination, we will raise key questions about these four variables and consider how stakeholders use them when comparing the impact of COVID-19 among different countries or other jurisdictions. In addition, we will raise similar questions about the initial preventive measures that investigators implement to mitigate the impacts of COVID-19.

Number of positive COVID-19 cases

- What is the definition of a case? Is it confirmed by a standardized test or by clinical symptoms associated with COVID-19 with or without high-risk contacts?
- Is the reporting procedure associated with identified cases the same across jurisdictions?
- How many tests were conducted per X thousands of people?
- Is the availability and accessibility of tests similar across jurisdictions?
- Do physicians handle cases similarly across jurisdictions if symptoms are mild?
- Is the validity of screening tests (sensitivity and specificity) identical across jurisdictions?
- Is the number of cases reported based on the same ratio (i.e. X number cases per X thousands of inhabitants)?
- Which individuals were tested? Volunteers, at-risk, randomly selected?
- Are the screening criteria the same across jurisdictions?

Hospitalized cases

- Are the hospitalisation criteria for COVID-19 applied identically across jurisdictions?
- Is the access to hospitals comparable across jurisdictions?
- Is the availability of hospitals identical across jurisdictions?
- Is the cost of hospitalisation identical across jurisdictions?

Cases in intensive care units

- Do doctors working in hospitals use the same criteria to transfer a patient to the intensive care unit?
- Is the availability of hospital intensive care units identical across jurisdictions?
- Is the cost of an intensive care unit stay identical across jurisdictions?

Deaths caused by COVID-19

- Are the same procedures used across jurisdictions to identify the cause of a death?
- How the authorities identify COVID-19 as the cause of death among patients suffering from other medical conditions (co-morbidity)?
- Are all deaths occurring in different human service locations included (e.g. hospitals, long-term care facilities, personal residence, etc.)?
- Is the number of deaths reported in a given time period complete, final and consistent across jurisdictions?

Implementation of preventive measures

At this moment, there are three main preventive measures that policy-makers use to compare COVID-19 influences across jurisdictions: physical distancing, quarantine and the use of personal protective equipment. These measures have been the source of considerable and heated debates across and within jurisdictions. Before making comparisons across geographic areas, we need to raise the following questions:

- Are the procedures of confinement and physical distancing operationalized and applied identically way across jurisdictions?
- Are social networks complying, confining and physical distancing the same across jurisdictions?
- Is the enforcement of confinement and physical distancing identical across jurisdictions?
- Are protective personal equipment recommendations similar across different jurisdictions?
- Is protective personal equipment availability similar across different jurisdictions?

We can address the same questions to the quarantine/de-quarantine procedure. In addition, we can raise the following questions:

- On which basis did the governmental authorities allow confinement/de-confinement to take place?
- Was it allowed in a vast or progressive way?
- Was it monitored the same way across jurisdictions?

Discussion

In this commentary, we describe some of the primary variables that influence the generation of COVID-19-related evidence across jurisdictions. Certain variables and associated measures are straightforward, but stakeholders apply others inconsistently. These differences encourage faulty comparisons and make public health policy difficult to evaluate. When comparing different products or procedures, we emphasize that a basic methodological research requirement is that measurement of these products and procedures be identical, or at least very similar.

In the case of the coronavirus crisis, stating that one jurisdiction is "doing better" or "worse" than another is questionable and potentially dangerous when politically employed. Policy-makers need to keep in mind that comparing jurisdictions about the efficacy of the methods to control the impacts of the COVID-19, without knowing whether investigators applied and enforced the measures in identical or similar ways might not be as informative as intended or, worse, misleading.

Additionally, to improve surveillance measurement for COVID-19 national and international experts such as the World Health Organization could propose standardized measures to enable cross-nation comparisons. Finally, we encourage public health stakeholders and the public to evaluate this data and its nuances more carefully when they interpret and report on the impacts of COVID-19.

Authors' statement

All authors have approved the final version sent for publication and are accountable for all aspects of the work.

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COVID-19: A case for the collection of race data in Canada and abroad

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Abstract

Racialized populations have consistently been shown to have poorer health outcomes worldwide. This pattern has become even more prominent in the wake of the coronavirus disease 2019 (COVID-19) pandemic. In countries where race disaggregated data are routinely collected, such as the United States and the United Kingdom, preliminary reports have identified that racialized populations are at a heightened risk of COVID-19 infection and mortality. Similar patterns are emerging in Canada but rely on proxy measures such as neighbourhood diversity to account for race, in the absence of person-level data. It follows that the collection of race disaggregated data in Canada is a crucial element in identifying individuals at risk of poorer COVID-19 outcomes and developing targeted public health interventions to mitigate risk among Canada's racialized populations. Given this continuing gap, advocating for timely access to this data is of great importance owing to the challenges that the COVID-19 pandemic has highlighted amongst racialized populations in Canada and worldwide.

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Keywords: COVID-19, coronavirus, race, racialized population, visible minority, infectious disease

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in December 2019. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic. As of March 23, 2021, there have been more than 124 million cases and 2.7 million deaths worldwide, with 947,024 cases and 22,712 deaths in Canada alone (1).

Studies have identified several factors associated with higher infection rates and more severe outcomes of COVID-19, including a history of chronic disease, being immunocompromised and older age (2,3). However, few studies have explored the impact of race on COVID-19 health outcomes. A variety of terms are used to describe racialized populations and individuals in the literature and disentangling these terms and definitions will require further dedicated research. For this article, we operationalize the term "race" as the social construct by which individuals are categorized based on perceived physical differences (4,5). Other terms, such as "visible minority", "Black, Asian and minority ethnic" and "ethnically diverse", are used when the author of the study in question used such terms. We also note that the term "race" does not encompass Indigenous persons, as these communities face distinct health inequities rooted in long-standing colonialism, and the self-identification of Indigenous identity should be distinct from how these individuals are racialized by society (4).

It is impossible to discuss racial health disparities without first addressing the social determinants of health and systemic inequities that directly impact racialized populations. Studies have shown that factors such as income, employment, education and housing differ vastly between racialized and non-racialized groups (6). In particular, racialized individuals are more likely to work in low paying jobs with limited access to paid sick leave, and live in poorly maintained, unstable or crowded housing (7), all of which have been associated with poorer COVID-19 outcomes. While these issues have been pushed to the forefront because of the pandemic, it is important to recognize that they are inherently rooted in systemic racism. Systemic racism is the system by which existing policies and structures reinforce and perpetuate racial inequities (8), and has been consistently linked with poorer general and physical health outcomes (9–11). An early commentary by Yancy noted how many of the proposed COVID-19 interventions, such as physical distancing, teleworking and accepting a furlough, are issues of privilege, and may not be accessible to those in the most marginalized communities (12). These inequities are not a result of the COVID pandemic itself,

but rather a symptom of a much more pervasive issue of racism embedded within societal policies, practices and institutions. While we are unable to provide a more thorough overview of systemic racism in this article, it is important to recognize that its impact on health care is far-reaching.

It follows that in the wake of COVID-19, disaggregated data are crucial to understanding the impact of the pandemic on diverse populations across Canada. There is increasing evidence that racialized individuals are disproportionately affected by the pandemic; emerging studies in the United States (US) and United Kingdom (UK) demonstrated an alarming trend in the burden of COVID-19 disease in these groups, including higher infection and mortality rates and more severe disease outcomes (13–15). Studies exploring the association between racialized populations and COVID-19 in Canada are limited and currently rely on proxy measures such as neighbourhood diversity rather than person-level data (16). Thus, the purpose of this article is two-fold. First, it explores the effect of the COVID-19 pandemic in exacerbating already existing health inequities among racialized compared with non-racialized populations by examining downstream metrics such as COVID-19 infection and mortality rates. Second, it advocates for the refinement of the collection of race data and timely access to these datasets to better support decision-making involving racialized populations in Canada.

Racialized populations and COVID-19 incidence

Increased risk of COVID-19 infection has frequently been linked with socioeconomic factors such as poor housing and precarious employment (10,17). The intersection of race, socioeconomic status and health is of particular importance to racialized persons, who consistently report higher rates of working poverty, below-standard housing and lower income (18). Preliminary reports from Public Health Ontario during the first months of the COVID-19 pandemic indicated that individuals living in ethnically diverse neighbourhoods experienced higher rates of COVID-19 disease, hospitalizations and deaths compared with less diverse neighbourhoods (19). Likewise, the Institute for Clinical Evaluative Sciences released a report detailing COVID-19 laboratory testing patterns in Ontario during the first three months of the pandemic. These early data suggest that Ontarians living in communities with the highest proportions of visible minorities or recent immigrants were three times more likely to test positive for COVID-19 than individuals living in the least diverse neighbourhoods: the most diverse communities had 10 COVID-19 cases per 100 tested individuals compared with 3.2 positive cases per 100 tested individuals in the least diverse neighbourhoods (20). Similar patterns have emerged in the US, where predominantly Black neighbourhoods are associated with an increase in positive COVID tests as compared to White neighbourhoods (21).

Racialized populations have also been cited as more likely to be essential service workers, putting them at higher risk of contracting COVID-19 due to increased exposure to infected individuals (22). In Canada, visible minorities make up approximately one third of nurse aides, orderlies and patient service associates, with higher proportions of Black, Filipino and South Asian workers in these occupations (23). This burden of labour has also become apparent in the US and UK, where racialized populations are more likely to work in low-paying service jobs with inadequate access to paid sick leave (14,24,25). Finally, these factors may also have significant biological consequences on individuals' susceptibility to infection. Persistent exposure to chronic stressors, such as poor living and working conditions, has been observed to activate the hypothalamic-pituitary axis, in turn leading to greater secretion of stress hormones. Long-term exposure and the inability to regulate these hormones has been hypothesized as a contributing factor to chronic diseases (26,27). For racialized populations, who already face significant differences in key health determinants as well as higher rates of comorbidity, the increased burden brought on by the COVID-19 pandemic may be driving these groups to a greater number of exposures and increased COVID-19 susceptibility.

Racialized populations and COVID-19 mortality

While person-level data on race are not readily accessible to researchers in Canada, proxies such as neighbourhood diversity have been used to study the disparities in COVID-19 deaths between racialized and non-racialized populations. A recent study from Statistics Canada linking provisional 2020 mortality data and data from the 2016 Census showed that COVID-19 mortality rates were approximately two times higher in Canadian neighbourhoods with the highest proportion of visible minorities compared with those with the lowest proportion. This contrast was especially stark in Ontario, Québec and British Columbia, where mortality rates were between three and 10 times higher in more diverse versus less diverse neighbourhoods (28). Similarly, an early report from Public Health Ontario indicated that death rates were three times higher in the most diverse neighbourhoods compared with the least diverse neighbourhoods (19). However, without access to person-level data, it is difficult to determine which groups have the highest death rates and why.

In the UK, race has been established as a strong predictor of COVID-19 mortality (29). OpenSAFELY, one of the largest running cohort studies on COVID-19-related deaths, identified that the risk of COVID-19 related deaths in Black, Asian and minority ethnic groups was nearly 1.5 times higher than White individuals, and this even after adjusting for age, sex, deprivation, and relevant comorbidities (13). In the US, despite making up less than a third of the population, Black individuals account for

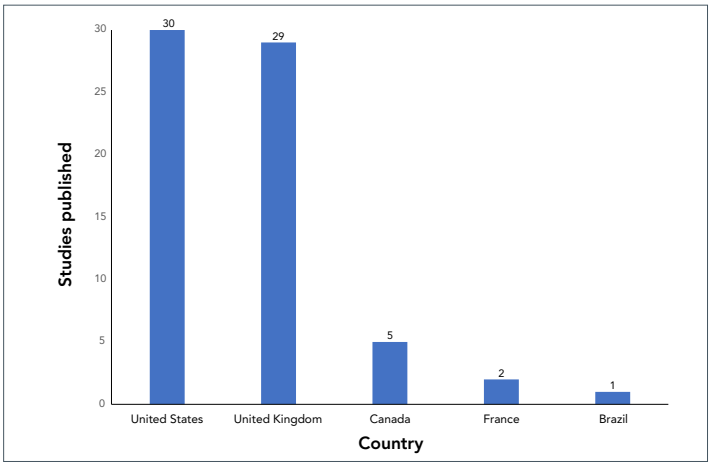
40% to 70% COVID-19-related deaths across several cities, with mortality rates almost six times higher in predominantly Black counties than predominantly White counties (12).

It should be noted that while several studies have reported increased mortality among racialized populations, the relationship between COVID-19 mortality and race remains unclear. A review from the Emerging Sciences Group of the Public Health Agency of Canada found considerable heterogeneity among studies looking at COVID-19 mortality and race, with no significant increase in mortality risk among Black or Asian individuals (30). Moreover, further investigation is required to understand the relationship between COVID-19 morbidity and race, as long-term impacts of illness are still under investigation.

Recommendations

Understanding the relationship between COVID-19 outcomes and racialized populations has been identified as a research priority in Canada. The pandemic has brought to the forefront longstanding inequities among Canada's racialized populations, highlighting the need for race-disaggregated health data. The limited availability of Canadian data has led to few published studies on racial differences in COVID-19 outcomes and mortality (**Figure 1**). Proxy measures, such as neighbourhood diversity, have provided insight into COVID-19 trends between visible minorities and non-minorities (28), but further investigation is required to tease apart variations in COVID-19 outcomes among different racialized populations.

Figure 1: Number of observational studies on associations of race with risk of COVID-19 infection, severity, or mortality, by country[a], published between June 1st and September 7th, 2020



[a] Canadian studies also include grey literature and ecological studies (30)

We acknowledge the strain and burden of COVID-19 on local, provincial and national resources and personnel, as well as the challenge in defining key variables consistent at all levels of government. However, it is strongly recommended that continued efforts be made to refine the data collection procedure for person-level race data to provide timely access of this information to researchers to assist with policy development and public health response. As the pandemic progresses in Canada, provinces such as Manitoba and Ontario, as well as their respective regional health authorities, have indicated their intention to perform race-disaggregated data collection. Other agencies, such as the Canadian Institute for Health Information, have released proposed standards for the collection of race-based and Indigenous identity data, though further input is needed for the implementation of this project (4). We also recognize the existence of significant barriers to the collection of race data in these instances, such as increased burden on healthcare workers (31), privacy concerns (32) and data quality and utility (32,33). Collaboration between provincial and federal health bodies is crucial to supporting initiatives that aim to collect person-level race data in Canada, which is a fundamental barrier in identifying care strategies to improve COVID-19 health outcomes for racialized populations and informing public policy to better support the most marginalized communities. Federal, provincial and territorial work is currently underway to standardize case reporting of commonly used terms such as race and ethnicity, to avoid misrepresentation of communities and adequate assessment of COVID-19 risk factors among different populations. To further improve upon these methods, we recommend that health institutions and researchers actively engage community members and stakeholders among the target demographics to assist in determining priorities for data collection, analysis, and reporting, as well as policy development and implementation. The collection of race-disaggregated must be undertaken with the express intent to dismantle patterns of systemic racism in health care, which can only be achieved by building racial equity within the data life cycle (34).

There are some limitations to our analysis. At this time, we were unable to undertake formal sub-analyses by gender or age, given the lack of data as well as the various ways in which race is operationalized across Canada and internationally. We note that these factors, as well as others such as socioeconomic status, housing, employment and education, are likely to impact racialized populations differently, and require further study. Finally, we did not discuss the repercussions of the COVID-19 pandemic within Canada's Indigenous populations, in recognition of the need to distinguish between racial and Indigenous identities. Indigenous peoples represent 4.9% of the population (35) and have historically had poorer health outcomes than non-indigenous Canadians (18,36). Currently, data on Indigenous status and COVID-19 outcomes are collected by Indigenous Services Canada.

Conclusion

Race disaggregated data are crucial to our understanding of how illness is experienced by the most marginalized Canadians, in terms of the COVID-19 pandemic and beyond. Mounting evidence of racial differences in COVID-19 incidence and mortality rates have emphasized the need for improved policies relating to the health of racialized populations and targeted interventions to improve COVID-19 outcomes. Efforts to collect this data in Canada are ongoing and should extend beyond the scope of the pandemic to identify disparities in healthcare and find solutions to minimize this gap.

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ET — Methodology, investigation, writing–original draft, review and editing
RE — Conceptualization, methodology, investigation, writing–original draft, review and editing, supervision
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RAPID COMMUNICATION

Epidemiologic and clinical characteristics of multisystem inflammatory syndrome in adults: a rapid review

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Abstract

Multisystem inflammatory disease in children (MIS-C) is one of the severe presentations of the coronavirus disease 2019 (COVID-19) that has been described in the literature since the beginning of the pandemic. Although MIS-C refers to children, cases with similar clinical characteristics have been recently described in adults. A description of the epidemiologic and clinical characteristics of multisystem inflammatory disease in adults (MIS-A) is a starting point for better knowledge and understanding of this emerging disease.

We identified nine case reports of MIS-A in the literature, five from the United States, two from France and two from the United Kingdom. The case descriptions revealed similarities in clinical features, including occurrence during post-acute disease phase, fever, digestive symptoms, cardiac involvement and elevated inflammatory markers. All the patients were hospitalized, three required admission to the intensive care unit and one died. The most common treatments were intravenous immunoglobulin, prednisolone and aspirin.

These findings suggest that MIS-A is a severe complication of COVID-19 disease that can lead to death. Further studies to improve our understanding of the pathogenesis of MIS-A, which will help improve treatment decisions and prevent sequelae or death.

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Keywords: COVID-19, SARS-CoV-2, MIS-A, MIS-C, multisystem inflammatory syndrome in adult

Introduction

The coronavirus disease 2019 (COVID-19) is a novel disease resulting from infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). As of May 29, 2021, the virus has infected more than 170 million people and caused more than 3.5 million deaths worldwide (2).

The clinical characteristics of COVID-19 disease vary from asymptomatic to severe. The most common symptoms are fever, cough, diarrhea and dyspnea (3). There are three clinical stages (4). The first stage is characterized by infection with SARS-CoV-2, with flu-like symptoms in certain cases. The second stage, characterized by viral pneumonia, possibly combined with pulmonary inflammation and coagulopathy, can require hospitalization and even mechanical ventilation. The third stage of the disease is characterized by fibrosis.

Multisystem inflammatory syndrome has been widely reported in children (5) and, more recently, in adults (6). In children, multisystem inflammatory syndrome (MIS-C) is a severe presentation that has been described in the literature since the beginning of the pandemic. Although MIS-C is defined as restricted to children, similar clinical characteristics have been described in adults. Knowing the epidemiologic and clinical characteristics of multisystem inflammatory syndrome cases in adults (MIS-A) provides a starting point to a better understanding of this emerging disease.

Methods

A database at the Public Health Agency of Canada is populated daily with new COVID-19 literature using standardized algorithms [e.g. "COVID-19" OR "SARS-CoV-2" OR "SARS-Coronoavirus-2"

OR "nCov" OR "novel CoV" OR ("novel AND coronavirus")] tailored to each searched database, that is, PubMed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN and Research Square. The literature is cross-referenced with the COVID-19 information centres run by the Lancet, the BMJ, Elsevier and Wiley.

Our search through the Public Health Agency of Canada database included studies published in English since the start of the pandemic until November 13, 2020. We gathered details about COVID-19–related studies in a RefWorks database and an Excel spreadsheet that are searchable by topic. Search terms used to retrieve the MIS-A literature from titles and abstracts in the Excel spreadsheet included "MIS-A," "Kawasaki," "multisystem inflam*," "multi-system inflam*," "inflammatory multisystem," "inflammatory multi-system," "inflammatory disease," "Kawasaki-like" and "COVID-19 linked disease." We screened articles (n=314) for relevance and included those that described MIS-A with a COVID-19 link (see **Appendix A** and **Appendix B**). We excluded paediatric cases and studies with cases similar to a MIS-A, but not formally diagnosed as MIS-A as per the authors. Since MIS-A is an emerging disease, a case definition does not yet exist. Authors of studies included in this review based case selection on the definition of MIS-C, while excluding the age criteria (see **Appendix C**).

Results

We identified nine case reports of MIS-A in the literature, five in the United States, two in France and two in the United Kingdom.

All nine cases of MIS-A occurred in relatively young adults, with a median age of 31 years (interquartile range [IQR]=25–45 years). Six patients were male (6–11). Six studies reported ethnicity: three patients were of African origin or African American (6,8,12), two were of Hispanic origin (11,13) and one was White (10). Seven out of nine studies reported on comorbidity. Two patients had both hypertension and obesity (6,12); one of these patients also had diabetes (12). Four patients had no known comorbidities (7,8,10,13); in three cases the comorbidity status was not reported (7,9,14).

All nine patients underwent a reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19. Five had negative RT-PCR results but positive serology tests (6–8,10,13). One had a negative RT-PCR result despite having had a positive RT-PCR result a few days earlier (12). The results of RT-PCR swab test and serology were both positive in one case (14). The two remaining patients had a positive RT-PCR test but did not have serology tests (9,11). These findings suggested that MIS-A probably occurred during the post-acute phase of the disease.

All the patients presented with fever. Seven had a fever for 5 to 7 days prior to hospital admission, while two did not report fever duration. Most (n=7) had digestive symptoms upon admission (7,9–14), with the most common diarrhea (n=6), followed by vomiting (n=4) and bilateral enlarged parotid glands (n=1). Rash (n=4) (8–10,14) and neck pain (n=3) (11–13) with or without lymphadenopathy were also common.

There was multi-organ effect in all cases. Involvement of the cardiovascular system was the most common (n=7) (6,7,10,12–15) and was documented via echocardiography in four cases. The four cases had an acute myocardial dysfunction with left ventricular systolic dysfunction and pericardial effusion. Two had ventricular fibrillation (11,12) and two other a dilated inferior vena cava (10,14). One of these patients also had overloaded right ventricular pressure and mild enlargement of the main pulmonary artery and hyperkinetic left ventricle (14).

The other manifestations were digestive (n=7) (7,9–14), ophthalmic (n=6) (8–11,13,14), renal (n=4) (6,11,12,14), dermatologic (n=5) (6,8–10,13), pulmonary (n=2) (7,12) and neurologic (n=1) (6).

C-reactive protein (CRP) test results and lymphocyte counts were reported in eight cases, and D-dimers and troponin in six cases. All cases had elevated inflammatory markers. The inflammatory markers that were most commonly elevated were CRP (n=8) (6,7,9–14), followed by D-dimers (n=6) (7,9,11–14) and troponin (n=6) (6–11). Lymphopenia was also common (n=6) (7–9,11,12,14). Three authors excluded rheumatic disease, HIV and hepatitis infection (9,11,13).

Intravenous immunoglobulin (IVIG; n=4) (8,9,11,14), prednisolone (n=3) (8,9,13) and aspirin (n=3) (7,13,14) were the most common treatments. Immunoglobulin was not given in one case because the patient responded well to aspirin (7). In another case, prednisolone was not provided because the patient had a concomitant tracheal aspiration positive for *Klebsiella aerogenes* (syn: *Enterobacter aerogenes*) that was then treated with trimethoprim sulfamethoxazole (6). One patient did not receive any specific treatment; she died while being evaluated for admission (12).

Of the nine patients, one died (12) and the outcome of another was not reported (9). Three patients had severe symptoms, requiring admission to the intensive care unit (ICU), but recovered (6,7,14). Two patients presented with hypotension and tachycardia upon admission but did not require admission to ICU and recovered (11,13). One patient presented with vasoplegic shock upon admission, had a length of stay in hospital of eight days and recovered under treatment (8). One case did not demonstrate shock-like signs and recovered under treatment (9). The case that died had been previously hospitalized for COVID-19 and discharged 12 days earlier; upon readmission she presented with rapid onset of fever and developed hemodynamic instability and ventricular fibrillation and could not be resuscitated.

Discussion

MIS-A appears to be a rare complication of COVID-19 disease. The RT-PCR and serology results and the absence of pulmonary involvement in most cases are consistent with MIS-A occurring during the post-acute phase of COVID-19 disease.

The clinical characteristics of MIS-A share similarities with MIS-C. The pathogenesis of MIS-C involves immune dysregulation similar to Kawasaki disease, macrophage activation syndrome (MAS) and cytokine release syndrome (16,17). Kawasaki disease is theorized to be from an aberrant immune response to a possible infectious trigger; it is described in children and less often in adults (15,18). In the case of MIS-A, the pathogenesis is not fully understood (19). Endothelial damage seems to have led to serious complications with multi-organ involvement in the reported cases (12). This process probably occurs post-infection based on the timing of the rise of MIS-C cases and peak of COVID-19 in the communities in which these cases were found (16,17).

While we identified some common features, the clinical presentations in the case reports of the MIS-A patients varied. For example, ophthalmologic signs (9) were predominant in one case and cardiac signs in another (6). Further studies are required on MIS-C pathophysiology and how it contributes to MIS-A pathogenesis.

The approach to management of children with MIS-C is evolving; management does require multidisciplinary care and a case-by-case approach. Since MIS-C is most likely a post-infectious complication rather than an active infection, the role of antivirals is not clear (20). Those that meet the criteria for Kawasaki disease may benefit from IVIG, as might those with moderate to severe MIS-C (20). Patients who may benefit from this treatment may include those with cardiac involvement or in shock states. Steroids might be considered for those who have severe or refractory shock (20). Other adjunctive therapies (IL-1 inhibitors or convalescent plasma) and their place in the treatment of MIS-C is uncertain (20). How these treatment options can be applied to MIS-A patients is also currently unknown. We need further studies outside of controlled clinical trials to ascertain the role of IVIG, steroids and other immunomodulatory agents in treating suspected cases of MIS-A (21).

Limitations

We based this current review on nine case reports from three countries. Although case reports can help in identifying new trends or diseases, there are limitations. Information from the case reports is difficult to generalize because patients have different backgrounds and are not representative of the population.

Currently, there is no case definition for MIS-A. Using the MIS-C case definition (minus age) has its challenges, as there are at least four definitions (see Appendix C). In addition, how each case met the definition was not always clear. For example, authors of the case reports did not always specify how they excluded all other potential causes of the multisystem inflammatory syndrome or report the duration of fever or presence of comorbidities. There was also a lack of information about ethnicity and severity of the disease. For example, when hypotension was identified, the presence or absence of shock-like syndrome was not always specified.

These are preliminary findings; additional studies will lead to a better understanding of common epidemiologic and clinical characteristics of this condition.

Conclusion

The case descriptions revealed similarities in clinical features such as fever, digestive symptoms, cardiac involvement and elevated inflammatory markers. The RT-PCR and serology results and the absence of pulmonary involvement suggest that MIS-A occurred during the post-acute phase of COVID-19 disease. All patients were hospitalized, three required admission to the ICU and one died. The most common treatments were IVIG, prednisolone and aspirin.

The findings suggest that MIS-A is a severe complication of COVID-19 disease that can lead to death. Early recognition of MIS-A may improve outcomes. A case definition for MIS-A is needed to help standardize reporting and facilitate disease recognition. Further studies to improve our understanding of pathogenesis of MIS-A will help improve treatment decisions and prevent sequelae and death.

Authors' statement

NA — Methodology, investigation, writing–original draft
RE — Conceptualization, writing–review and editing, supervision
MS — Writing–review and editing
LW — Writing–review and editing
NB — Writing–review and editing
TD — Writing–review and editing

Competing interests

None.

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Appendices

Appendix A: Comparison of nine MIS-A cases in the COVID-19 literature published up to November 2020

Patient/studies characteristics		Boudhabhay *et al.*, 2020 (6)	Chowdhary *et al.*, 2021 (7)	Fox *et al.*, 2020 (12)	Jones *et al.*, 2020 (8)	Kofman 2020 (14)	Lidder *et al.*, 2020 (9)	Moghadam *et al.*, 2020 (10)	Sokolovsky *et al.*, 2020 (13)	Shaigany *et al.*, 2020 (11)
Background	Ethnicity	African	NR	African American	African	NR	NR	White	Hispanic	Hispanic
	Age, years	46	26	31	21	25	45	21	36	45
	Sex	Male	Male	Female	Male	Female	Male	Male	Female	Male
	Presence of comorbidity	X	NR	X	NR	–	–	NR	–	–
Symptoms and system/organ involved	Fever	X	X	X	X	–	X	X	X	X
	Cardiovascular	X	X	X	–	X	X	X	X	X
	Digestive	–	X	X	–	X	X	X	X	X
	Ophthalmic	–	–	–	X	X	X	X	X	X
	Renal	X	–	X	–	X	–	–	–	X
	Dermatologic	X	–	–	X	–	X	X	X	–
	Pulmonary	–	X	X	–	–	–	–	–	–
	Neurologic	X	–	–	–	–	–	–	–	–
RT-PCR and serology test results	RT-PCR	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Positive
	Serology	Positive	Positive	NR	Positive	Positive	NR	Positive	Positive	NR
Elevated inflammatory markers and lymphopenia	CRP	X	X	X	NR	X	X	X	X	X
	Troponin	X	X	NR	X	–	X	X	NR	X
	D-dimers	NR	X	X	NR	X	X	NR	X	X
	Lymphopenia	NR	X	X	X	X	X	–	–	X
Exclusion of other infective and inflammatory conditions		NR	NR	NR	X	NR	X	X	X	X
Treatment	Immunoglobulin	–	–	–	X	X	X	–	–	X
	Prednisolone	–	–	–	X	–	X	–	X	–
	Aspirin	–	X	–	–	X	–	–	X	–
Outcome		Recovery	Recovery	Death	Recovery	Recovery	NR	Recovery	Recovery	Recovery

Abbreviations: CRP, C-reactive protein; NR, not reported; RT-PCR, reverse transcription polymerase chain reaction; –, not present characteristic; X, reported as present

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Boudhabhay *et al.*, 2020 (6) France 16 September 2020 The patient was a 46-year-old male of African descent with a history of hypertension and obesity	Fever and other signs and symptoms: • Admitted for hypertensive emergency (189/123 mmHg) and fever (duration not reported) Evidence of coagulopathy and renal involvement: • Acute kidney injury: Serum creatinine (sCr) level was 169 µmol/L associated with 1 g/day proteinuria, aseptic pyuria, no hematuria and low natriuresis (<20 mmol/L) • Renal biopsy light microscopy revealed typical lesions of thrombotic microangiopathy (TMA) including fibrin thrombi within glomeruli and myxoid intimal alterations of arterioles and small to medium-sized renal arteries • On Day 4, the patient presented evanescent facial erythema and developed acute myocardial dysfunction with reduced left ventricular ejection fraction to 40%, pericardial effusion • On Day 5, the patient presented with neurologic impairment. Abnormal supratentorial periventricular magnetic resonance imaging (MRI) signals responsible for a restriction of the diffusion due to an acute vasculitis PCR and serology for SARS-CoV-2: • RT-PCR negative, IgM negative and IgG positive (no previous COVID-19 symptoms were reported) Inflammatory markers: • CRP level was 312 mg/L • Thrombocytopenia: neutrophil count was 18.7 × 10^9/L • High sensitive troponin (hsTroponin) elevation	• No immunosuppressive treatment was introduced because of concomitant tracheal aspiration positive for *Klebsiella aerogenes* treated with trimethoprim sulfamethoxazole • Dobutamine and renal replacement therapy (RRT) • Specific complement inhibition with eculizumab therapy (900 mg) • On Day 5 of hospitalization, neurologic impairment presented with coma leading to intubation and mechanical ventilation The patient was discharged after 30 days in hospital
Chowdhary *et al.*, 2021 (7) United Kingdom September 2020 The patient was a 26-year-old male Ethnicity was not reported The presence or absence of comorbidity was not reported Exposure to SARS-CoV-2 was reported	Fever and other signs and symptoms: • Patient was admitted after five days of fever • Dry cough, myalgia, diarrhea, vomiting and abdominal pain • Patient was hypotensive and hypoxic upon admission One or more organs involved (pulmonary, cardiac, digestive): • CT showed bilateral pulmonary basal ground-glass changes and bowel edema • Initial transthoracic echocardiography demonstrated severe left ventricular systolic dysfunction with pericardial effusion • CT of the abdomen demonstrating mesenteric lymphadenopathy and small bowel edema PCR and serology for SARS-CoV-2: • RT-PCR negative, IgG and IgM positive serology Inflammatory markers: • CRP: 419 mg/L • Ferritin: 3,275 lg/L (normal <322 µg/L) • Procalcitonin: 164 lg/L (normal <50 µg/L) • Troponin I: 2,030 ng/L (normal <57 ng/L) • D-dimer: 2,722 ng/mL (normal <220 ng/mL)	• Vasopressor therapy, high-dose aspirin and broad-spectrum antibiotics in intensive care • Immunomodulatory therapy was not given due to the good response to aspirin The patient was admitted to the ICU and recovered over 10 days.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Fox *et al.*, 2020 (12) United States July 2020 The patient was a 31-year-old African American female Her comorbidities included hypertension treated with lisinopril, diabetes with poor adherence to metformin and glizide, and obesity (body mass index [BMI]= 36.1 kg/m^2) She had been discharged 12 days earlier after a hospitalization for COVID-19 disease with a positive RT-PCR	The patient was admitted for sudden fever 39.8°C (duration not specified), tachycardia (120 beats/min), left-sided neck pain, nausea and vomiting Inflammatory markers: • D-dimer level of 2.48 nmol/L (normal <1.37 nmol/L) • CRP levels 165 mg/L, then 580 mg/L (normal <9 mg/L) • Ferritin level, 411.2 µg/L (normal 10–150 µg/L) • Lactic acid level, 3.1 mmol/L (normal 0.3–2.0 mmol/L) • Lymphopenia One or more organs involved (pulmonary, cardiac, parotids, renal): • CT scan of her neck showed bilaterally enlarged parotid glands and swelling in the posterior nasopharynx to oropharynx • CT scan of her chest showed interval improvement of bibasilar ground-glass opacities, with cervical and anterior mediastinal lymphadenopathy • Creatinine level 202.44 µmol/L (44.20–97.24 µmol/L); glomerular filtration rate 32 mL/min/1.73 m^2 (>89 mL/min/1.73 m^2) PCR and serology for SARS-CoV-2: • RT-PCR was positive 12 days prior to readmission • MISC-A, RT-PCR was negative at readmission and serology was not performed	Patient developed hemodynamic instability and ventricular fibrillation during evaluation for hospital admission and died.
Jones *et al.*, 2020 (8) United Kingdom The date the study was conducted was not reported September 2020 The patient was a 21-year-old male of African descent The presence or absence of comorbidity was not reported	Fever and other signs or symptoms: • Six days of fever • Admitted for abdominal pain associated with constipation, anorexia • Transient maculopapular palmar rash four days into illness • Non-exudative conjunctivitis • Cervical lymphadenopathy • Cracked lips and prominent lingual papillae PCR and serology for SARS-CoV-2: • RT-PCR negative and serology was strongly positive, suggesting recent exposure to SARS-CoV-2 One or more organs involved: • Rash • Conjunctivitis • Cervical lymphadenopathy • Cracked lips and prominent lingual papillae Inflammatory markers: • Lymphopenia • Elevated inflammatory and elevated troponin T • Other infective and inflammatory conditions were excluded	• IVIG • Methylprednisolone The patient was discharged after a length of hospital stay of eight days.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Kofman *et al.*, 2020 (14) United States The date the study was conducted was not reported September 2020 The patient was a 25-year-old female; her ethnicity was not reported She was a non-smoker, did not use drugs, was not taking any prescription medications and had no known allergies She had taken ibuprofen and acetaminophen over the previous week for symptom relief	Fever and other signs and symptoms: • One week of low grade fever, weakness, dyspnea, fatigue • Also developed mild cough, sore throat, vomiting, diarrhea and lymph node swelling Upon admission: • She was afebrile, with mild hypotension (blood pressure 98/56 mmHg) • Oxygen saturation was normal on room air • She appeared ill, with tender cervical lymphadenopathy • Significant conjunctival injection without perilimbal sparing; injected, erythematous and cracked lips • Tenderness to palpation in the left lower abdominal quadrant One or more organs involved (renal, cardiac, digestive, ocular): • Acute kidney injury: Creatinine 7.74 mg/dL (normal: 0.5–1.2 mg/dL) and leukocytosis • Point-of-care echocardiogram revealed a dilated inferior vena cava and overloaded right ventricular pressure • CT angiogram of the chest showed mild enlargement of the main pulmonary artery • CT abdomen/pelvis demonstrated mild peripancreatic fat stranding, felt to possibly represent acute uncomplicated pancreatitis, as well as nonspecific bilateral perinephric fat stranding • Conjunctivitis PCR and serology for SARS-CoV-2: • Positive RT-PCR and IgG serology Inflammatory markers: • CRP: 90 mg/L (normal: 0–10 mg/L) • D-dimer: 960 mg/L (normal: 0–574 mg/L) • Ferritin: 798 ng/ml (normal: 11–307 ng/mL) • Lymphocytes: 3% (normal: 19–53)	• Aggressive fluid resuscitation and vasopressor • IVIG, 2 g/kg split equally between hospital days 2 and 3 • Aspirin 325 mg daily for seven days • Patient was offered remdesivir under an Emergency Use Authorization (EUA) basis, but declined • At discharge she was prescribed a seven-day course of apixaban for COVID-19–associated coagulopathy per Emory University Hospital COVID-19 treatment guidelines The patient was admitted to the ICU twice during her hospital stay. She was discharged on Day 5.
Lidder *et al.*, 2020 (9) United States May 2020 The case was a 45-year-old male with no comorbidities Ethnicity was not reported	Fever and other signs and symptoms: • Fever for five days, sore throat, diarrhea, eye redness, eyelid swelling and a diffuse rash including bilateral upper and lower eyelids One or more organs involved (renal, cardiac, digestive, ophthalmologic): • A transthoracic echocardiogram demonstrated global hypokinesis and a reduced ejection fraction of 40% • CT imaging showed unilateral cervical lymphadenopathy with a lymph node measuring 1.8 cm • Photophobia and swollen eyelids; no vision changes including blurry vision and eye pain • Uncorrected near visual acuity was 20/20 bilaterally • Bilateral superficial punctate keratitis, symmetric anterior chamber inflammation with 10–15 cells per high power field, and normal intraocular pressure. Dilated fundus exam was notable only for one small peripheral cotton wool spot in each eye • Punch biopsy of his erythema multiforme-like rash • Showed sparse superficial perivascular infiltrate of lymphocytes with neutrophils and scattered eosinophils, suggestive of toxic shock syndrome Excluding other cause: • Testing for myositis and HIV was negative • An exhaustive rheumatologic workup, including ANA, RF, anti-CCP, anti-Smith, anti-dsDNA, p-ANCA/MPO, c-ANCA/PR3, was negative • Blood cultures were negative PCR and serology for SARS-CoV-2: • Positive RT-PCR Inflammatory markers: • Lymphopenia • Ferritin, CRP, ESR, D-dimer and troponin were elevated	• Ophthalmic lubricating therapy in addition to prednisolone acetate 1% eye drops four times daily for his photophobia in the setting of anterior chamber inflammation • IVIG and an interleukin-6 (IL-6) inhibitor (tocilizumab) in addition to using a topical triamcinolone ointment for his diffuse rash The length of hospital stay was not reported, but the patient did not demonstrate shock-like signs.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Moghadam *et al.*, 2020 (10) France The date the study was conducted was not reported July 2020 21-year-old White male who did not smoke or use drugs The presence or absence of comorbidity was not reported	Fever and other signs and symptoms: • Fever and non-bloody watery diarrhea lasting for seven days • Asymptomatic rash over his trunk and palms, consisting of erythematous round-shaped macules with a darker and raised rim, 1–3 cm in diameter • Bilateral conjunctivitis • Blood pressure 80/40 mmHg • Respiratory rate was 38 breaths/min, and oxygen saturation was 97% on ambient air One or more organs involved (cardiac, digestive, pleural): • Electrocardiogram showed diffuse negative T-waves, and echocardiography displayed hyperkinetic left ventricle with normal ejection fraction, normal right cavities and dilated non-compressible inferior vena cava • Thoraco-abdominal CT scan showed: ° Signs of congestive heart failure ° Bilateral pleural effusion ° Wall thickening of the right colon ° Respiratory function deterioration PCR and serology for SARS-CoV-2: • Negative RT-PCR and IgG-positive serology Inflammatory markers: • Lymphocytes: 900/mm^3 • CRP: 365 mg/L • Procalcitonin: 3.4 ng/mL • Ferritin: 1,282 mg/L (normal <30) • Lactate: 2.4 mmol/L (normal <1.6) • Troponin level: 550 ng/L (normal <34) • Cutaneous biopsy showed a slightly inflammatory infiltrate in upper dermis. Direct cutaneous immunofluorescence was negative Exclusion of other causes: • Extensive infectious inquiry and search for antinuclear antibodies were negative • The rash was particular and diagnosis of erythema multiforma and subacute lupus erythematosus were ruled out	• Volume resuscitation • Noradrenaline • Antibiotics (i.e. ceftriaxone and amikacin) • High-flow nasal oxygenation The patient stayed in the ICU for eight days and recovered.
Sokolovsky *et al.*, 2020 (13) United States The date the study was conducted was not reported June 2020 The case was a 36-year-old Hispanic female with no known comorbidity	Fever and other signs and symptoms: • One week of fever, abdominal pain, vomiting and diarrhea • Two days of a diffuse rash and arthralgias • Tachycardia, tachypnea, hypotensive • Classic phenotype of complete Kawasaki disease: bilateral nonexudative conjunctivitis mucositis with cracked lips, edema of the bilateral hands and feet, diffuse maculopapular rash and cervical lymphadenopathy One or more organs involved (cardiac, digestive): • CT angiogram of the chest: normal lung parenchyma and a trace right pleural effusion • CT abdomen/pelvis illustrated mild circumferential gallbladder wall thickening and a small area of colitis • Echocardiogram after treatment with IVIG revealed an ejection fraction of 65% with moderate tricuspid valve regurgitation. Subsequent coronary computed tomography angiography (CCTA) was normal except for a trace pericardial effusion PCR and serology for SARS-CoV-2: • Negative RT-PCR and IgG-positive serology Inflammatory markers: • CRP: 30 mg/dL (normal 0.0–0.9) • D-dimer: 652 ng/mL (normal <318) Exclusion of other cause: • Anti-dsDNA, anti-Smith, anti-RNP, SSB, RF, CCP, ANCA, ASO and anti-Jo-1 antibodies were negative • HIV and hepatitis panels were negative	• Fluid resuscitation for shock • A single dose of aspirin 650 mg • IVIG 2 g/kg • Methylprednisolone 2 mg/kg for five days followed by a prednisone taper The patient stayed at least six days in hospital and recovered.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Shaigany *et al.*, 2020 (11) United States The date the study was conducted was not reported July 2020 The case was a 45-year-old Hispanic male He had no known comorbidity	Fever and other signs and symptoms: • Six days of fever, sore throat, diarrhea, bilateral lower extremity pain, conjunctivitis and diffuse exanthema • Exposure to SARS-CoV-2 infection two weeks earlier • Respiratory rate was 25–33 breaths per min • Hypotension (systolic blood pressure 80–90 mmHg) • Tachycardia with episodes of atrial fibrillation with rapid ventricular response • Bilateral, nonexudative conjunctival injection • Tender left neck swelling with palpable lymphadenopathy, periorbital edema with overlying erythema, lip cheilitis and targetoid erythematous papules and plaques with central duskiness involving the back, palms, neck, scalp, anterior trunk and upper thighs One or more organs involved (renal, cardiac, digestive, ophthalmologic): • CT of the neck revealed inflammation and edema involving the bilateral lower eyelid and pre-septal space, as well as sub-occipital reactive lymphadenopathy • Electrocardiogram demonstrated: ° ST elevations in the anterolateral leads ° Global hypokinesis of the left ventricular wall with a mild to moderately reduced ejection fraction of 40% • Diffuse conjunctivitis with chemosis as well as the presence of inflammatory cells within the anterior chamber, indicative of uveitis ° A 4-mm punch biopsy of the skin was performed on a papule on the back, with histology revealing rare intraepithelial collections of neutrophils with necrotic keratinocytes and a sparse interstitial, mixed-cell dermal infiltrate with vacuolar interface changes PCR and serology for SARS-CoV-2: • Positive RT-PCR Inflammatory markers: • Lymphopenia (0–700 lymphocytes per µL) • ESR of 120 mm/hour • Ferritin of 21,196 ng/mL • CRP of 546.7 mg/L • D-dimer of 2,977 ng/mL • Procalcitonin of 31.79 ng/mL • Interleukin-6 (IL-6) 117 pg/mL • Troponin 8.05 g/mL Exclusion of other causes: • HIV-1 and HIV-2 antibodies were negative • Bacterial blood cultures were negative	• Therapeutic dose low molecular weight heparin • IVIG of 2 g/kg over two days • A single intravenous dose of the interleukin-6 (IL-6) inhibitor tocilizumab (400 mg) The patient was in hospital for eight days and did not require vasopressor support or ICU level of care, and recovered.

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; c-ANCA; cytoplasmic antineutrophil cytoplasmic antibodies; anti-RNP, antinuclear ribonucleoprotein; ASO, anti-streptolysin O, CCP, cyclic citrullinated peptide; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; HIV, human immunodeficiency virus; IG, immunoglobulin; IgG; immunoglobulin G; IgM, immunoglobulin M; IVIG, Intravenous immunoglobulin; MIS-A, multisystem inflammatory disease in adults; MPO, myeloperoxidase; p-ANCA, perinuclear antinuclear antibody; PR3, proteinase 3; RF, rheumatoid factor; RT-PCR, reverse transcription polymerase chain reaction [test]; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SSB, Sjögren's syndrome type B

Appendix C: Definitions of multisystem inflammatory syndrome in children

Authors	Definitions of MIS-C
World Health Organization (WHO) (22)	Diagnosis of MIS-C in children and adolescents aged less than 19 years includes a positive COVID-19 test or likely contact with COVID-19-positive individuals and several signs and symptoms. These include fever lasting for more than three days and two of the following: • Rash • Bilateral non-purulent conjunctivitis • Signs of muco-cutaneous inflammation (in the mouth or on the hands or feet) • Hypotension or shock • Myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiogram findings or elevated troponin/NT-proBNP) • Coagulopathy (increased prothrombin time, activated partial thromboplastin time, elevated D-dimers) • Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain) There must be laboratory evidence of inflammation, such as an elevated erythrocyte sedimentation rate (ESR), CRP or procalcitonin. Other obvious microbial causes of inflammation such as bacterial sepsis and staphylococcal or streptococcal shock syndromes must be excluded as a plausible diagnosis.
Centers for Disease Control (CDC) (23)	An individual below the age of 21 years presenting with fever lasting for more than 24 hours and laboratory evidence of inflammation, such as an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH) or interleukin-6, elevated neutrophils, reduced lymphocytes and low albumin. The patient must also have an evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement and no alternative plausible diagnoses. The patient must be positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or must have been exposed to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms.
Royal College of Paediatrics and Child Health (RCPCH) (24)	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurologic disorder) with persistent fever over 38.5°C most of the time, oxygen requirement, hypotension and other features. The laboratory tests must show abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypoalbuminemia and/or lymphopenia. This may include children fulfilling full or partial criteria for Kawasaki disease. Any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus must be excluded. The SARS-CoV-2 PCR testing may be positive or negative.
Canadian Pediatric Society (CPS) (25)	The presence of high and persistent fever (≥3 days) unexplained by other causes. Fever together with laboratory evidence of marked systemic inflammation and temporal association with COVID-19 having been present in the community should raise the index of suspicion for MIS-C. The clinical presentations described to date have included fever with hyperinflammation; a Kawasaki-like syndrome; and shock or toxic shock-like states, with signs of hypotension and poor perfusion related to severe myocardial dysfunction. Gastrointestinal distress, that may or may not occur with neurologic signs such as neck stiffness, altered mental status or lethargy.

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Ivermectin treatment for *Strongyloides* infection in patients with COVID-19

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Abstract

Ivermectin, an antiparasitic agent, is not recommended for prophylaxis or treatment of coronavirus disease 2019 (COVID-19). Inappropriate use of ivermectin for treatment of COVID-19 may make it less available for patients with serious parasitic infections who could benefit from its use and worsen the current shortage of ivermectin in Canada. However, patients with COVID-19 who are candidates to receive immunomodulatory therapies (e.g. corticosteroids and interleukin-6 inhibitors) may be at risk of hyperinfection syndrome and disseminated disease from *Strongyloides stercoralis*. These complications can be severe and even fatal. It is important to recognize and screen patients who may be at risk of strongyloidiasis, as these patients may require treatment with ivermectin to avoid the potential for a hyperinfection syndrome and disseminated disease, which is frequently deadly. Clinicians should follow evidence-based recommendations to screen and treat for *Strongyloides* infection in patients with COVID-19 who are under consideration to receive specific COVID-19 therapies that alter immune response and may lead to hyperinfection syndrome or disseminated disease.

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Introduction

Ivermectin is an oral drug approved in Canada for the treatment of certain parasitic infections (e.g. strongyloidiasis and onchocerciasis) (1). *In vitro* data have demonstrated that ivermectin has antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and can prevent viral proteins from binding to and entering cells (2). This has contributed to the view that ivermectin may have antiviral effects *in vivo*. However, the plasma concentrations that are required to achieve antiviral effect are significantly higher than the maximum achievable plasma concentrations with tolerable doses in humans (3). Ivermectin is currently not recommended for prophylaxis or treatment of coronavirus disease 2019 (COVID-19) (4), as current evidence does not show clinical benefit (5). In the absence of evidence showing a clinical benefit for ivermectin in the treatment of COVID-19, there are compelling reasons to conserve limited national and provincial supplies of ivermectin by only using it for evidence-based indications.

It is important to note that the primary and approved use of ivermectin is as an antiparasitic agent. One parasite of interest is *Strongyloides stercoralis*. *Strongyloides* infection ranges in presentation from asymptomatic intestinal infection to hyperinfection and severe disseminated disease. Patients with chronic asymptomatic *S. stercoralis* infection and impaired immunity may develop "accelerated

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auto-infection", known as hyperinfection. These patients may also experience disseminated disease secondary to larval migration outside their usual anatomic reservoir, with varying presentations (e.g. pneumonia, central nervous system infection, recurrent gram-negative or polymicrobial bacteremia and sepsis). Immunosuppression, in particular corticosteroid use, has been associated with increased risk of hyperinfection syndrome in patients with chronic *Strongyloides* infection.

Clinicians can refer to the Ontario Science Advisory Table Science Brief "Ivermectin as Empiric Treatment for Strongyloides in Patients with COVID-19 Disease" for full details to further support the recommendations submitted in this article. The Science Table full brief is available online.

Current situation

In patients with strongyloidiasis (including asymptomatic *Strongyloides* infection), immunosuppression can lead to a worsening of the parasitic infection including hyperinfection and disseminated disease, which is a devastating illness with mortality rates approaching 90% if left untreated (6,7). Although most reports of hyperinfection syndrome implicate corticosteroids as the main risk factor, there are also reports with other immunosuppressive or immunomodulatory agents including tumour necrosis factor (TNF), interleukin-1 (IL-1) and other non-steroid lymphocyte depleting agents (6,7). A recent European Society of Clinical Microbiology and Infectious Diseases review on the safety of biological therapies did not identify *Strongyloides* as a major infectious risk with IL-6 inhibitors (including tocilizumab) (8). However, there have been case reports of *Strongyloides* hyperinfection developing in patients who received concomitant corticosteroid therapy with tocilizumab (9–11).

Dexamethasone and tocilizumab, two evidence-based therapies for the treatment of moderately and critically-ill patients with COVID-19, are both anti-inflammatory agents with immunosuppressive effects. There is no clear relationship between a threshold dose and duration of immunosuppression at which the risk of disseminated *Strongyloides* infection may occur. It is also currently not well described how concomitant immunosuppressive medications may interact to affect hyperinfection risk, or whether those who receive multiple immunosuppressive therapies are at additional risk for disseminated disease.

Current limited supply of ivermectin

Ivermectin is an essential medication for treatment of strongyloidiasis (and is an important component of combination therapy for hyperinfection syndrome and fulminant, disseminated disease). As of January 21, 2021, ivermectin has been listed on shortage by Drug Shortages Canada, with only limited quantities available due to increased demand for the drug; the estimated shortage end date is December 31, 2021, which is subject to change based on supply and demand (12). Therefore, clinicians are currently encouraged to use ivermectin only when necessary for evidence-based clinical indications, and may need to be prepared to consider using substitute agents if ivermectin becomes locally unavailable. In this brief review, we discuss the application of existing *Strongyloides* screening recommendations to patients with COVID-19, and suggested *Strongyloides* treatment strategies to preserve ivermectin supply while ensuring appropriate treatment for patients with COVID-19 at risk for hyperinfection (see **Appendix Table A1**).

Assessment of *Strongyloides* risk in patients with COVID-19

The rate of *Strongyloides* infection in Canada is not well described, but the Committee to Advise on Tropical Medicine and Travel (CATMAT) estimates that as many as 2.5 million individuals in Canada have simple intestinal strongyloidiasis (assuming a prevalence rate of 40% in the patient country of origin, although seroprevalence has been noted to be above 60% among immigrants from endemic regions). In 2016, CATMAT noted that almost seven million Canadians were foreign-born, and 85% of this population were from a country where *S. stercoralis* is endemic; therefore, the risk of strongyloidiasis in Canada is not negligible (6).

For patients with COVID-19 who are under consideration to receive immunosuppressive therapy, the first step is to assess their risk for progressing to severe strongyloidiasis based on both epidemiologic and clinical factors. We recommend following the CATMAT guidelines Step 1—epidemiologic assessment (based on country of prior residence or extended exposure) (6,13). Of note, the CATMAT guidelines outline risk related to a corticosteroid dose "equivalent to 20 mg/day of prednisone for ≥2 weeks", and we assume that the dose of corticosteroid recommended for COVID-19 treatment is similar to this relatively arbitrary cutoff. Hyperinfection syndrome has been reported with a range of corticosteroid doses and durations, and it is still unknown whether concomitant immunosuppressive therapies contribute to a higher relative risk of hyperinfection.

We also recognize that geographic epidemiologic risk alone may place many patients in the moderate risk category (if not the high risk category), and this may also overlap with patient demographics in neighbourhoods and communities which have been highly and disproportionately impacted by the COVID-19 pandemic (14).

We also recommend following CATMAT guidelines Step 2—assessment of clinical risk and suspected clinical syndrome. This Step will identify what diagnostic tests should be done to screen for strongyloidiasis. Ideally, *S. stercoralis* testing is performed

prior to administration of immunosuppressive therapy, but often this is not possible in patients with COVID-19. Patients at moderate or high epidemiologic risk of *Strongyloides* infection should proceed to serologic testing as soon as possible (even if immunosuppression has already been initiated), while patients at low epidemiologic risk of *Strongyloides* infection do not require diagnostic screening unless there is clinical suspicion of *Strongyloides* hyperinfection or dissemination. Clinicians should note that any patients who have clinical signs/symptoms of active strongyloidiasis, hyperinfection or dissemination will require additional diagnostic testing, empiric treatment, and expert consultation (6).

Treatment of strongyloidiasis in patients with COVID-19

Ivermectin dosing for treatment of strongyloidiasis differs depending on the clinical syndrome. Less severe forms of strongyloidiasis (e.g. mild intestinal or asymptomatic strongyloidiasis) are now mostly treated with a single weight-based dose of ivermectin (200 µg per kilogram), based on emerging evidence that a single dose is as effective as multiple doses (15). Clinicians may consider repeating serology after a single dose regimen if treatment failure is suspected. When a two-dose regimen of ivermectin is used, the doses are typically administered on consecutive days or separated by 14 days. When a two-dose regimen is administered, the separated-dose regimen is preferred to consecutive doses due to the risk of prepatent infection arising from auto-infection although consecutive doses may be used if medication adherence is a concern (e.g. healthcare system challenges related to increased frequency of intra and inter-hospital patient transfers during the COVID-19 pandemic). Severe forms of strongyloidiasis (e.g. hyperinfection and disseminated *Strongyloides* infection) often require daily weight-based dosing of ivermectin, sometimes given in combination with other antihelminthic agents such as albendazole (6).

We recommend following CATMAT guidelines Step 3 to decide whether a patient should be screened and/or treated with ivermectin for strongyloidiasis. This approach takes into account both the epidemiologic (Step 1) and clinical risks (Step 2) assessments. Most patients with an epidemiologic risk for *Strongyloides* infection, and for whom immunomodulatory therapies (either dexamethasone, tocilizumab, or both) are being considered during their hospitalization for COVID-19, are at risk for asymptomatic strongyloidiasis. As outlined earlier, many of these patients may also meet the "high" or "moderate" category of geographic epidemiologic risk. In these cases, it is important that clinicians send the appropriate specimens for diagnostic testing and also monitor the patient after receipt of immunomodulatory therapy for any signs/symptoms of *Strongyloides* infection which could potentially progress to hyperinfection syndrome and disseminated disease if not treated promptly.

The CATMAT guidelines (prior to COVID-19) indicate that empiric treatment with two doses of ivermectin may be given "in the rare circumstance where the patient is deemed high risk for strongyloidiasis and immunosuppression cannot await definitive diagnostic testing" (6). However, given the current limited national supply of ivermectin, we recommend waiting for *Strongyloides* serology results (if results can be obtained reasonably quickly—e.g. within 24 hours) before initiating ivermectin for treatment of asymptomatic strongyloidiasis. Patients with a reactive or indeterminate *Strongyloides* serology result should be treated for asymptomatic strongyloidiasis as described earlier. If laboratory results cannot be expedited, it is reasonable to wait for serology results if the patient is clinically stable and only administer empiric ivermectin therapy if the patient is clinically unstable. If there is suspicion for hyperinfection at the time of COVID-19 presentation, infectious disease specialist consultation is recommended.

Finally, an important consideration before any ivermectin therapy is initiated, is screening for the presence of concurrent loiasis (infection with the filarial nematode *Loa loa*), due to the risk of severe reactions, including fatal encephalopathy, if ivermectin is administered to a patient with untreated loiasis. Clinicians should consult with an infectious diseases/tropical medicine expert for recommendations on *Strongyloides* treatment in patients who are from *Loa loa* endemic areas; namely West and Central Africa (6,16). Recommended testing includes a daytime blood film examination for *Loa loa* microfilaria.

Serologic testing expected turn-around-time

In the absence of immunosuppression, screening for *Strongyloides* by microscopic examination of stool or sputum for ova and parasites (OAP) may only produce a positive result if the patient has a high burden of infection (e.g. if the patient is symptomatic or already experiencing hyperinfection syndrome). Therefore, although CATMAT guidelines recommend screening with both serology and stool OAP, we do not recommend sending stool OAP to screen for asymptomatic strongyloidiasis—especially given increased healthcare resource demands during the COVID-19 pandemic. Therefore, the ideal test to screen for *Strongyloides* (including asymptomatic infection) is a serologic test (17). *S. stercoralis* IgG serology testing is available through provincial laboratories and the turnaround time for results can be up to 10 days from receipt of blood sample by the laboratory (18). In situations where serology results will impact urgent treatment decisions, laboratories may be able to expedite serology test results. For example, in the most recent third wave of Ontario infections, the Public Health Ontario Laboratory has provided expedited *Strongyloides* serology testing results within 24 hours from receipt by the laboratory, for specimens marked as coming from a patient with COVID-19. A coordinated laboratory strategy can help to preserve limited ivermectin supplies while ensuring that patients at high risk of progression to hyperinfection are identified rapidly.

Conclusion

COVID-19 mild illness: In patients who have mild COVID-19 there is currently insufficient evidence to support the use of immunomodulatory therapies (dexamethasone and tocilizumab). If patients who are mildly ill are to receive immunomodulatory therapy for COVID-19 or for other established non-COVID-19 indications, clinicians may use the CATMAT guidance recommendations to guide screening and/or treatment decisions.

COVID-19 moderate illness and critical illness: Patients who have moderate or critical COVID-19 are likely to be candidates to receive immunomodulatory therapies for treatment of COVID-19, and should therefore be screened for *Strongyloides* exposure/infection and may require treatment with ivermectin based on geographic epidemiologic risk and suspected *Strongyloides* clinical syndrome (Appendix Table A1).

Authors' statement

EL — Wrote the first draft of the Science Brief
EL, SR, BJL, CG, NA, AMM, and MP — Contributed to the conception of the Science Brief

All authors revised it critically for important intellectual content and approved the final version.

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Competing interests

None.

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The Ontario COVID-19 Science Advisory Table is a group of scientific experts and health system leaders who evaluate and report on emerging evidence relevant to the COVID-19 pandemic, to inform Ontario's response. The mandate of the Science Advisory Table is to provide weekly summaries of relevant scientific evidence for the COVID-19 Health Coordination Table of the Province of Ontario, integrating information from existing scientific tables, Ontario's universities and agencies, and the best global evidence. The Science Table summarizes its findings for the Health Coordination Table and the public in Science Briefs.

The Drugs & Biologics Clinical Practice Guidelines Working Group is a group of clinicians and scientists with recognized expertise in drugs, biologics and clinical care. The Working Group evaluates existing scientific data, disease epidemiology, drug availability and implementation issues in order to develop Clinical Practice Guidelines for the treatment of COVID-19 using drugs and biologics. The Working Group reports its findings to the public and the Science Table. Its findings are also summarized in Science Briefs.

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Appendix: Therapeutic recommendations

For therapeutic recommendations, we used the following definitions for COVID-19 severity:

Critically ill: Patients requiring ventilatory and/or circulatory support, including high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation. These patients are usually managed in an intensive care setting.

Moderately ill: Patients newly requiring low-flow supplemental oxygen. These patients are usually managed in hospital wards.

Mildly ill: Patients who do not require new or additional supplemental oxygen from their baseline status, intravenous fluids, or other physiological support. These patients are usually managed in an ambulatory/outpatient setting.

Table A1: Recommendations for *Strongyloides* screening and treatment in patients who are candidates to receive immunomodulatory therapies for treatment of COVID-19 (moderately ill or critically ill)

Geographic epidemiologic risk category for *Strongyloides* exposure/infection	Suspected clinical syndrome upon COVID-19 presentation[a,b]		
	Asymptomatic strongyloidiasis +/- eosinophilia[c]	Simple intestinal strongyloidiasis	Hyperinfection syndrome OR disseminated strongyloidiasis
		Consult infectious diseases/tropical medicine specialist	
High risk[d] (birth or residence or long-term travel[e] in Sub-Saharan Africa, South America, Caribbean, Southeast Asia, Oceania excluding Australia/New Zealand)	Send serology **If an expedited serology result is expected:** No empiric ivermectin therapy is required (only treat if testing returns positive or indeterminate)[h] **If an expedited serology result is not available:** If clinically stable, await results of serology (only treat if testing returns positive or indeterminate) If clinically unstable, consider empiric treatment while awaiting serology results (ivermectin 200 µg/kg PO x1) If serology is positive or indeterminate and a 2nd dose is given, space next dose at interval of 14 days unless concern for adherence	Send serology and stool OAP Empiric treatment while awaiting diagnostic testing (ivermectin 200 µg/kg PO x1) If serology is positive or indeterminate and a 2nd dose is given, space next dose at interval of 14 days unless concern for adherence	Send serology[h], stool OAP, and sputum OAP (+/- other bodily fluid or tissues for examination for larvae) Empiric treatment while awaiting results (ivermectin 200 µg/kg PO q 24h until negative test results) Consider addition of empiric albendazole therapy
Moderate risk[d] (birth or residence or long-term travel[e] in Mediterranean countries, Middle East, North Africa, Indian sub-continent, Asia, Central America[f])	Send serology No empiric ivermectin therapy is required (only treat if testing returns positive or indeterminate)[h]		
Low risk[d] (birth or residence or long-term travel[e] in Australia, North America[g] or Western Europe)	Screening not generally required, no investigations required unless there is clinical suspicion of hyperinfection		Send serology[h], stool OAP, and sputum OAP (+/- other bodily fluid or tissues for examination for larvae) Unlikely to require empiric ivermectin therapy

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; OAP, ova and parasites
[a] Consult an infectious diseases / tropical medicine expert before administering ivermectin if patient is from a *Loa loa* endemic area
[b] Ivermectin weight-based doses should be rounded to the nearest whole tablet (3mg) size
[c] Most patients with acute COVID-19 will likely be in this category of suspected *Strongyloides* disease. Chronic strongyloidiasis is often associated with eosinophilia, but eosinophilia may not be present once the patient progresses to symptomatic or disseminated disease
[d] Low epidemiologic risk (<3% risk of infection based on exposure); Moderate epidemiologic risk (3%–10% risk of infection based on exposure); High epidemiologic risk (>10% risk of infection based on exposure)
[e] "Long-term travel" or "extended exposure" is defined as cumulative 6-month exposure in rural or beach areas or contact of skin with sand or soil in a risk area even during shorter-term travel. If significant re-exposure accumulates, consider re-screening if initially negative
[f] Areas of Central America outside of Mexico may be higher than moderate risk
[g] Areas of North America that may be higher than low risk include Florida, Kentucky and Virginia. Aboriginal Australians are also at elevated risk of strongyloidiasis
[h] Clinicians may consider a direct request to expedite *Strongyloides* serology testing (especially if a negative result will potentially avoid administration of an ivermectin dose)

A summary of surveillance, morbidity and microbiology of laboratory-confirmed cases of infant botulism in Canada, 1979–2019

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Abstract

Background: Infant botulism is a rare toxicoinfectious disease caused by colonization of the infant's intestine with botulinum neurotoxin-producing clostridia (i.e. *Clostridium botulinum* or neurotoxigenic strains of *C. butyricum or C. baratii*). Our goal was to examine data from laboratory-confirmed cases of infant botulism reported in Canada to summarize incidence over time, over geographic distribution by province or territory, and by sex, and to compare these parameters with data from the Canadian Notifiable Disease Surveillance System (CNDSS). The average age of onset, serotype of botulinum neurotoxin (BoNT), case outcomes, length of hospitalization and suitability of clinical specimens for laboratory confirmation were also determined.

Methods: We examined laboratory records from the Health Canada Botulism Reference Service and the British Columbia Centre for Disease Control (BCCDC) Public Health Laboratory. The Discharge Abstract Database (DAD) and the Hospital Morbidity Database (HMDB) of the Canadian Institute of Health Information (CIHI) were queried for data on hospitalization of infant botulism cases. The CNDSS was queried for data on reported cases of infant botulism.

Results: From 1979 to 2019, 63 laboratory-confirmed cases of infant botulism were confirmed by the Health Canada Botulism Reference Service and the BCCDC Public Health Laboratory for an annual rate of 4.30 cases per million live births. From 1983 to 2018, 57 cases of infant botulism were reported to the CNDSS. Of the 63 cases confirmed by the reference laboratories, the median age of onset was 16 weeks with a range of 2 to 52 weeks. The majority of cases were type A (76%) and B (21%), with single cases of type F and type AB. Of the 23 laboratory-confirmed cases with matched hospital records, 13 were transferred to special care and eight needed ventilator support; no deaths were reported.

Conclusion: Spores of *C. botulinum* are present naturally in the environment, thus diagnosis of infant botulism does not require a history of exposure to high-risk foods such as honey. Stool samples are the most useful diagnostic specimen.

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Keywords: *Clostridium botulinum*, *Clostridium butyricum*, *Clostridium baratii*, incidence rate, geographic distribution, Canada, serotype, environmental source, botulinum neurotoxin

Introduction

Botulism is a neuroparalytic disease caused by exposure to botulinum neurotoxin (BoNT). Manifestations of botulism are classified according to the route of exposure to BoNTs. Foodborne botulism is an intoxication resulting from the ingestion of BoNT in food or beverages that supported the growth of *Clostridium botulinum* (1). Wound botulism and intestinal toxemia botulism occur when *C. botulinum* spores colonize an infected wound or the adult intestinal tract, respectively, and release BoNTs *in situ* (2,3).

Infant botulism, first described in 1976 (4,5), is a form of intestinal toxemia botulism that occurs in children younger than one year. Infants are particularly susceptible to *C. botulinum* intestinal colonization because of the immaturity of their gut microbiota, whereas children over one year old can ingest *C. botulinum* spores without colonization (6,7). In rare instances, infant botulism has been caused by BoNT-producing species *C. butyricum* type E (8–10) and *C. baratii* type F (11–14).

The clinical spectrum of infant botulism includes a wide range of severities from subclinical to fulminant. Symptoms may include, but are not limited to, hypotonia, weak suck, dysphagia, constipation, weak cry and diaphragm weakness that may require that the infant receives mechanical ventilation. Almost all cases of infant botulism are caused by Group I *C. botulinum* that produce BoNT type A or type B. Type A generally has a more severe clinical presentation (6,7).

Infant botulism is treated with Botulism Immune Globulin Intravenous (BIG-IV or BabyBIG) antitoxin that binds to and neutralizes circulating BoNT in the bloodstream (15). It is generally recommended that infants are treated with BabyBIG as soon as possible based on a physician's differential diagnosis. Laboratory confirmation of infant botulism is based on detection of viable *C. botulinum* in stool or detection of BoNT in stool or serum.

There have been few published reports of infant botulism cases in Canada (16–20). Here we present a summary of infant botulism in Canada from 1979 to 2019, including incidence over reporting period, geographic distribution by province and territory, patient age and sex, serotype and group of *C. botulinum* involved, food or environmental source identification (where possible), as well as preferred clinical specimens for detection of BoNT and viable *C. botulinum*. Hospital records that match laboratory-confirmed cases demonstrate clinical outcomes of the disease.

Methods

Microbiology laboratory and national surveillance data

We examined two independent laboratory databases for laboratory-confirmed cases of infant botulism from 1979 to 2019. These databases are maintained by the Botulism Reference Service (BRS) for Canada at Health Canada, Ottawa, Ontario, and the British Columbia Centre for Disease Control (BCCDC) Public Health Laboratory, in Vancouver, British Columbia. The Health Canada BRS receives and tests clinical and food specimens associated with suspect cases of botulism from all provinces and territories when requested. The BCCDC laboratory maintains its capacity to test specimens from British Columbia, and has also tested specimens from the Yukon. Thus, these two databases do not overlap and, when combined, represent all the laboratory-confirmed cases of botulism in Canada.

We extracted information on patient age and sex, date and location of diagnosis, implicated source of *C. botulinum*, group of *C. botulinum* and BoNT serotype. The rates of disease per million live births were calculated using data from the United Nations Statistics Division and Statistics Canada (21,22).

We used the national case definition for confirmed cases of infant botulism to ensure consistency in data recording: "laboratory confirmation with symptoms compatible with botulism in a person less than one year of age [with] detection of botulinum toxin in stool or serum or isolation of *C. botulinum* from the patient's stool or at autopsy" (23). Cases meeting this definition were extracted from the Canadian Notifiable Disease Surveillance System (CNDSS) and included the reporting year, province/territory, age group and sex. The CNDSS maintains basic surveillance on nationally notifiable diseases by collecting voluntarily submitted data from provinces and territories. CNDSS data was compared to laboratory data for completeness.

Laboratory confirmation of clinical cases

Detection of BoNT and isolation of viable C. botulinum from environmental and clinical specimens were performed according to Health Canada method MFHPB-16 (24). BoNT serotype was determined by neutralizing toxicity with serotype-specific antibodies provided by the United States (US) Centers for Disease Control. The group of *C. botulinum* (Group I or II) was determined based on proteolysis of cooked-meat media (CMM) pellets in pure culture (24). The California Department of Public Health (CDPH) identified the lone isolate of *C. baratii* type F based on this isolate's ability to produce lecithinase, as demonstrated on egg yolk agar; its inability to produce lipase; and its ability to produce type F toxin in broth culture, detected using the mouse bioassay. API20 A was used to confirm the identification of *C. baratii* type F. All animal use followed protocols approved by institutional (Health Canada or CDPH) animal care and use committees.

Morbidity data

Records on patient clinical information were retrieved from the 2005–2018 Discharge Abstract Database (DAD) and the 2005–2010 Hospital Morbidity Database (HMDB) of the Canadian Institute for Health Information (CIHI) by querying all records currently available that listed botulism in the first 10 suspected diagnostic codes (25). These records were then matched to records by age, sex, date of admission, date of sample and province/territory of residence. Only laboratory-confirmed cases were included in the analyses of the DAD and HMDB data.

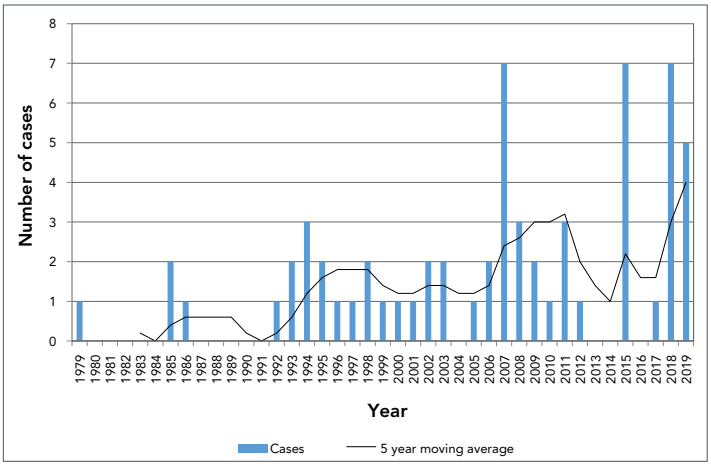
Ethics approval

Formal ethics approval was not required because this study used de-identified healthcare data that were obtained under an agreement with CIHI, and we report the results in aggregate form.

Results

While botulism has been nationally notifiable in Canada since 1933, the first case of infant botulism was reported in Canada in 1979 (16), three years after the first cases were described in the US (4,5). From 1979 to 2019, there were 63 laboratory-confirmed cases of infant botulism in Canada (**Figure 1**), that is, an average of 1.6 cases per year. The Health Canada BRS confirmed 44 cases, while the BCCDC confirmed 19 cases. These cases of infant botulism are further described as one complete dataset and will be referred to as "laboratory-confirmed".

Figure 1: Number of laboratory-confirmed infant botulism cases in Canada, 1979–2019



Infant botulism is a rare disease; the average annual incidence was calculated at 4.3 cases per million live births in Canada during this time period (**Table 1**). Confirmed cases occurred in Ontario (n=21), British Columbia (n=19), Québec (n=12), Alberta (n=8), Newfoundland and Labrador (n=2) and Nova Scotia (n=1) (Table 1). Of the 58 records that indicated sex, 34 were female (59%) and 24 were male (41%).

Table 1: Laboratory-confirmed infant botulism cases by serotype and province/territory, 1979–2019

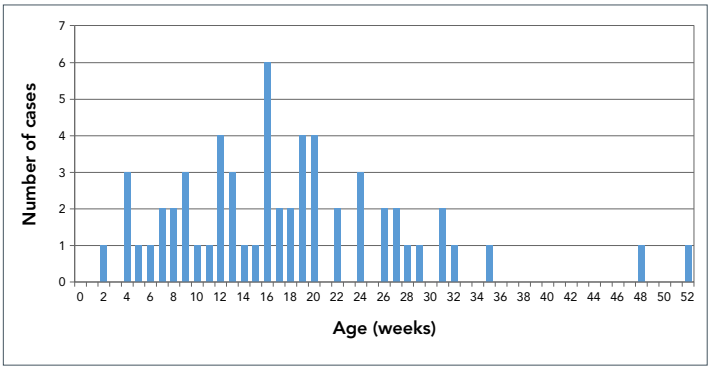
Province/ territory	Cases by BoNT serotype				Total	Annual rate/ million live births[a]
	A	B	AB	F		
Ontario	11	9	1	0	21	3.75
British Columbia	19	0	0	0	19	10.86
Québec	9	2	0	1	12	3.63
Alberta	8	0	0	0	8	4.41
Newfoundland and Labrador	1	1	0	0	2	9.93
Nova Scotia	0	1	0	0	1	2.66
Canada[b]	48	13	1	1	63	4.30

Abbreviation: BoNT, botulinum neurotoxin
[a] Annual rate per million live births was calculated as the total case count divided by the average number of annual live births from 1991–2018 multiplied by 40 (years), divided by a million (21,22)
[b] No laboratory-confirmed cases of infant botulism in Manitoba, New Brunswick, Northwest Territories, Nunavut, Prince Edward Island, Saskatchewan or Yukon

In comparison to the laboratory-confirmed cases, the CNDSS reported 57 cases of infant botulism from 1983 to 2018, giving an average of 1.6 cases per year. Considering the single laboratory-confirmed case in 1979 and the five laboratory-confirmed cases in 2019, the total number of cases reported to the CNDSS matches the total number of 57 laboratory-confirmed cases from 1983 to 2018. However, the number of cases reported by the provinces and territories differed. Cases were reported to the CNDSS from Ontario (n=22), British Columbia (n=14), Québec (n=10), Alberta (n=9), Newfoundland and Labrador (n=1) and Nova Scotia (n=1). Of the 57 cases, 36 were female and 21 male. From 1983 to 2018, the laboratory-confirmed cases were from Ontario (n=19), British Columbia (n=17), Québec (n=11), Alberta (n=8), Newfoundland and Labrador (n=2), and Nova Scotia (n=1).

The age of onset follows a unimodal distribution with mean 17.8 weeks and median 16 weeks (**Figure 2**). The youngest infant was two weeks of age, and the oldest infant was 52 weeks old. BoNT type A constituted the majority of cases (n=48; 76%), followed by type B (n=13; 21%), type AB (n=1; 2%) and type F (n=1; 2%) (Table 1). The single type F case was identified as caused by *C. baratii*; this was the youngest infant, with an age of onset of two weeks. All type A strains of *C. botulinum* are Group I (proteolytic), while type B strains may be either Group I or II (non-proteolytic). Of the type B strains isolated and tested for proteolytic activity, all (n=10) were classified as Group I *C. botulinum*.

Figure 2: Age of onset for laboratory-confirmed infant botulism cases, Canada, 1979–2019



Of the 63 cases identified from 1979 to 2019, 29 (46%) had environmental or food samples submitted for testing and only six were matched with environmental samples, including honey (n=4) and crib dust (n=1), as well as a change mat swab and a washing tub swab (n=1) (**Table 2**). Of the 58 records that were available, stool was by far the best clinical specimen for detection of BoNT (n=55; 95%) and viable *C. botulinum* (n=58; 100%) (**Table 3**). BoNT was detected in only 3 of 33 (9%) serum specimens tested, while neither BoNT nor *C. botulinum* were detected in three specimens of gastric contents tested.

Table 2: Laboratory-confirmed source attribution of infant botulism

Year	Province/territory	Source
1985	Québec	Honey
1993	Alberta	Honey
1995	Québec	Honey
2000	British Columbia	Honey
2005	Ontario	Crib dust
2009	Québec	Change mat swab and washing tub swab

Table 3: Laboratory detection of BoNT and viable *Clostridium botulinum* in clinical specimens

Specimen	Tested (n)	BoNT detected		*C. botulinum* detected	
		n	%	n	%
Gastric contents	3	0	0	0	0
Serum	33	3	9	0	0
Stool	58	55	95	58	100

Abbreviation: BoNT, botulinum neurotoxin

Of the 63 laboratory-confirmed infant botulism cases, 23 were cross-referenced to the 2005–2018 DAD and 2005–2010 HMDB. The mean (standard deviation [SD]) length of hospital stay of these patients was 20.3 (7.0) days (**Table 4**). Over a half (n=13) were transferred to special care units. These special care units are specifically designed, staffed and equipped for the continuous observation and treatment of patients who cannot be cared for in a general acute care unit. These include intensive care units and step-down units (25). The patients spent a mean (SD) of 12.2 (6.3) days in a special care unit; eight needed a ventilator (Table 4). Most were discharged to the patient's home with either no support (n=9) or with the support of home care workers (n=10). Three were transferred to acute care during hospitalization; the discharge disposition of one patient was unknown (**Table 5**). No deaths were reported for the 23 cross-referenced cases.

Table 4: Hospital metrics for laboratory-confirmed hospitalization cases (n=23)

Hospital metric	Mean	Standard deviation	Number of cases
Length of stay (days)	20.3	7.0	23
Time in special care (days)	12.2	6.3	13
Use of ventilator	N/A	N/A	8

Abbreviation: N/A, not applicable

Table 5: Clinical outcome of laboratory-confirmed hospitalization cases (n=23)

Discharge disposition	Number of cases
Home, no support	9
Home with support	10
Transferred to acute care	3
Unknown	1
Death	0

Discussion

From 1979 to 2019 there were 63 laboratory-confirmed cases of infant botulism in Canada. From 1983 to 2018, 57 cases were reported to the CNDSS, which matched the total number of laboratory-confirmed cases during this time period, however the provinces and territories reporting the cases differed. The reasons for the discrepancies is unknown; however, this discrepancy is not unexpected, as the reference laboratories are directly involved in case diagnosis while public health authorities may not be involved in every sporadic case. In recent years, the BRS for Canada and the Public Health Agency of Canada have collaborated to ensure more complete reporting to the appropriate public health authorities.

The annual incidence rate of 4.3 cases per million live births in Canada is similar to incidence rates reported in Australia (4.4 cases per million live births), Italy (2.1 cases per million live births) and Denmark (6.7 cases per million live births) and less than the rates reported in the US (20.3 cases per million live births) and Argentina (24.1 cases per million live births) (26).

The average age at onset was 17.8 weeks in Canada. This is higher than the reported mean ages of onset of 13.8 weeks in the US and 14.3 weeks globally outside the US (26). The age of onset may correspond to changes in gut microbiota after weaning (27) that leaves the gut more susceptible to colonization. A recent study found that breast-fed infant botulism patients were older at onset than formula-fed patients (28), although the role of breast feeding in infant botulism is controversial (29,30).

The finding that 98% of the cases were types A, B or AB is consistent with a report that *C. botulinum* types A and B accounted for 98.7% of all recorded infant botulism cases worldwide from 1978 to 2006 (26). The single case of type F identified as being caused by *C. baratii* is rare but not unprecedented. Cases of infant botulism caused by toxigenic strains of *C. butyricum* type E (8–10) and *C. baratii* type F (11–14), as well as a single case caused by *C. botulinum* type E (31), have been described elsewhere. The predominance of *C. botulinum* type A in the western US correlates with the occurrence of only type A cases in the two western provinces, Alberta and British Columbia (Table 1) (32).

The sporadic nature of infant botulism and the ubiquity of *C. botulinum* spores in the environment, combined with what is likely a low infectious dose, makes identifying the source of *C. botulinum* a significant challenge. In contrast, foodborne botulism outbreaks tend to involve multiple cases, allowing epidemiological investigation and determination of possible food sources. For the 29 cases with environmental or food samples submitted for testing, the isolation of *C. botulinum* was a rare occurrence. Honey accounted for four cases, based on isolation of the same serotype from honey fed to the infant. In one instance, *C. botulinum* was isolated from a sample of dust from the crib. In another instance, a change mat and bath tub were found to be positive for *C. botulinum*. In these cases, it is unknown whether the environmental samples were the source of illness for the infant or whether they were contaminated by shedding from the infant's stool. A case of infant botulism in Finland was linked to *C. botulinum* spores isolated from dust found in a vacuum cleaner (33). Absence of a history of honey consumption should not be considered reason to rule out infant botulism (18).

For laboratory detection of BoNT or isolation of viable *C. botulinum*, the proper collection and handling of clinical specimens is essential. Of the 58 records that were available, stool was by far the best clinical specimen for detection of BoNT (95%) and viable *C. botulinum* (100%). This is consistent with a previous report that stool or enema effluent are preferred diagnostic specimens for infant botulism (34).

Of the 23 infant botulism cases that were cross-referenced to the DAD and HMDB databases, 13 (57%) were transferred to special care and eight (35%) needed ventilator support. No deaths were reported. This is consistent with previous data indicating that infant botulism is a severe disease requiring intervention in the majority of cases. Outside the US, the percentage of reported cases who required ventilator or intubation support was 67% and deaths accounted for 1.1% of cases (26). In the US, 56% of hospitalized infant botulism cases required ventilator support or intubation during a trial of BabyBIG (15), while the mortality rate in the US is less than 1% (35).

Limitations

The narrow range of hospital records available from CIHI databases (2005–2018 for DAD and 2005–2010 for HMDB) reduced the number of cases that could be linked to the laboratory records and lowered the statistical power of data obtained from the hospital records, such as severity of illness and efficacy of treatment. Of note, treatment with BabyBIG antitoxin is not routinely recorded in the CIHI database; we recommend that this be included to properly evaluate the effect of this treatment.

Likewise, 28 instances from the CIHI database were coded as "botulism" based on differential diagnosis, yet samples were not sent to a laboratory for confirmation. Finally, there were several instances of laboratory-confirmed infant botulism cases that could not be identified in the CIHI databases, even within the reported years. Considering a recent summary of 1,345 infant botulism cases in California from 1976–2016 found that 99.3% of cases were hospitalized (36), it is likely that the missing hospital records for laboratory-confirmed cases in Canada were the result of a missing diagnostic code in the CIHI database. Improved communication between hospitals, public health officials and diagnostic laboratories would help to capture all cases of infant botulism in Canada and help in the diagnosis and evaluation of treatments. Physicians and hospital staff can refer to the Canadian botulism guide for healthcare professionals for instructions on differential diagnosis, proper sampling of clinical specimens and treatment with BabyBIG antitoxin (37).

Conclusion

Infant botulism is a rare disease in Canada. The unimodal distribution for age of onset suggests a temporal susceptibility to colonization by *C. botulinum* which peaks at 16 weeks. Although no deaths were reported in this time period, the average length of stay in the hospital and the number of cases transferred to special care demonstrate severe clinical outcomes for patients suffering from this disease. The effectiveness of the BabyBIG antitoxin could not be evaluated due to limitations in reporting and should be addressed in the future.

Authors' statement

RH — Examined the laboratory records of the Health Canada Botulism Reference Service; queried records of the Discharge Abstract Database and the Hospital Morbidity Database of the Canadian Institute of Health Information for data on hospitalization of infant botulism cases; performed all statistical analyses; performed additional literature searches; wrote the first draft
CT — Examined the laboratory records of the British Columbia Public Health Reference Microbiology Laboratory; commented on–approved the manuscript
NP — Examined the laboratory records of the British Columbia Public Health Reference Microbiology Laboratory; commented on–approved the manuscript
JC — Queried the Canadian Notifiable Disease Surveillance System for data on reported cases of infant botulism, wrote the section on the Canadian Disease Surveillance System and commented on–approved the manuscript
JA — Conceived the summary, examined laboratory records of the Health Canada Botulism Reference Service, performed additional literature searches, drafted certain sections and revised the article

Competing interests

None.

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A window of opportunity for intensifying testing and tracing efforts to prevent new COVID-19 outbreaks due to more transmissible variants

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Abstract

Background: When public health interventions are being loosened after several days of decline in the number of coronavirus disease 2019 (COVID-19) cases, it is of critical importance to identify potential strategies to ease restrictions while mitigating a new wave of more transmissible variants of concern (VOCs). We estimated the necessary enhancements to public health interventions for a partial reopening of the economy while avoiding the worst consequences of a new outbreak, associated with more transmissible VOCs.

Methods: We used a transmission dynamics model to quantify conditions that combined public health interventions must meet to reopen the economy without a large outbreak. These conditions are those that maintain the control reproduction number below unity, while accounting for an increase in transmissibility due to VOC.

Results: We identified combinations of the proportion of individuals exposed to the virus who are traced and quarantined before becoming infectious, the proportion of symptomatic individuals confirmed and isolated, and individual daily contact rates needed to ensure the control reproduction number remains below unity.

Conclusion: Our analysis indicates that the success of restrictive measures including lockdown and stay-at-home orders, as reflected by a reduction in number of cases, provides a narrow window of opportunity to intensify case detection and contact tracing efforts to prevent a new wave associated with circulation of more transmissible VOCs.

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Keywords: SARS-CoV-2, variants of concern, non-pharmaceutical interventions, relaxations

Introduction

The coronavirus disease 2019 (COVID-19) pandemic extended to Canada early in 2020, and a spring wave of epidemic transmission was controlled by restrictive closures that reduced the daily rate of people contacting one another, which drove the control reproduction number below unity (1). As restrictive closures were lifted in early summer 2020 several modelling studies have identified the need for enhancement to detection and isolation of cases, and tracing and quarantine of contacts ("testing and tracing"), to maintain control of the epidemic (i.e. to either prevent the increase in case numbers, or to prevent exceeding healthcare capacity in the short and long term) (2–5). These enhancements to detection and isolation and tracing and quarantining may compensate for the increase in daily contact rates in the general population and resultant transmission associated with lifting restrictions (2–5). As we know, the epidemic did resurge at the end of 2020, suggesting that capacity for testing and tracing was insufficient to control the epidemic, and further restrictive closures were required to bring the "second wave" under control. As provinces and territories contemplate lifting restrictive closures, a new threat emerged: new, more highly transmissible variants, also known as "variants of concern" (VOCs). Several of these variants, which were first identified elsewhere in the world, are now spreading in Canada, particularly the B.1.1.7 variant. The B.1.1.7 variant expanded rapidly in the United Kingdom during the fall 2020, likely assisted by the lifting of restrictive closures as well as the

intrinsically higher transmission rate of the new variant compared with the previously circulating virus strains (6). Here we explore what testing and tracing capacity would be needed to maintain control of the COVID-19 epidemic using data in Ontario, given that more transmissible variants are becoming or have become dominant, while vaccinations are being rolled out to the Canadian population.

Intervention

We used a transmission dynamics model (4) fitted to cumulative reported cases during the first and second wave of the COVID-19 epidemic in Ontario, Canada, to quantify conditions of combined public health interventions that could have allowed to partially reopen the economy without a large outbreak. These conditions are those that maintain the control reproduction number to remain below unity while accounting for the increased transmissibility of the VOC. These conditions must be checked before the province considers reopening again after mitigating the third wave. The approximate dates for each of the waves of COVID-19 experienced thus far in Ontario, Canada thus far are listed in **Table 1**.

Table 1: The three waves of COVID-19 in Ontario

Description	Approximate dates
Wave one (the first wave)	February 2020–August 2020
Wave two (the second wave)	September 2020–Mid-February 2021
Wave three (the third wave)	Mid-February 2021–June 2021[a]

[a] As of June 2021, the time of writing, Ontario is in its third wave of COVID-19

In the model, the population is divided into susceptible (S), exposed (E), asymptomatic infectious (A), infectious with symptoms (I), and recovered (R) compartments according to the epidemiological status of individuals. The model also includes diagnosed cases that are isolated (D), quarantined susceptible (S_q) and quarantined exposed (E_q) compartments to model the impact of contact tracing (i.e. identifying and contacting people who have had physical contact with infected individuals) and quarantine of these traced contacts. Within the model framework, a proportion, q, of individuals exposed to the virus are traced and quarantined (the "quarantine proportion"). The resulting transmission dynamics model is a system of ordinary differential equations.

The control reproduction number was calculated as

$$R_c = \frac{\beta\rho c(1-q)}{\delta_I + \alpha + \gamma_I} + \frac{\beta c\theta(1-\rho)\,(1-q)}{\gamma_A}$$

In this formula, c is the average number of daily contacts of one individual in the population, β is the probability of transmission upon contact, ϱ is the probability of having symptoms among infected individuals, θ is the relative infectiousness of asymptomatic cases, δ_I is transition rate of symptomatic infected individuals to the diagnosed and isolated class, α is the mortality rate, and γ_I and γ_A are the recovery rates of symptomatic and asymptomatic infected individuals, respectively. Therefore, the measures of effectiveness of testing and tracing are δ_I (the rate at which symptomatic people are detected and isolated) and q (the proportion of contacts of cases that are traced and quarantined before they become infectious). The proportion of infectious individuals who have been missed from the contact tracing and quarantine before entering the infectious period and are tested, confirmed and then isolated during the infectious period is given by $\delta_I/(\delta_I+\alpha+\gamma_I)$. We here focus on finding conditions on q and $\delta_I/(\delta_I+\alpha+\gamma_I)$, which, under different daily contacts and increased transmissibility due to the VOC, ensure $R_c < 1$.

We obtained values for model parameters that allow $R_c < 1$ using model fitting and data integration from multiple sources. We fit the transmission dynamics model to the cumulative reported cases in Ontario until December 23, 2020 using an established technique (4) (see **Appendix**) and accounted for the different phases of physical distancing in the province. Through model fitting, key values for the model were estimated. These included the proportion of cases detected and isolated, the proportion of contacts traced and quarantined, the probability of transmission on contact, infectiousness of asymptomatic cases and rates of recovery from infection. To incorporate the effect of the VOC, we modelled an increase by 40% in the probability of transmission β compared with the values estimated before December 2020. This value of 40% is taken from the lower estimates of the increased transmissibility of the B.1.1.7 strain obtained in the United Kingdom (6,7). We then investigated the case detection and contact tracing levels needed to prevent a new wave of COVID-19, assuming different increasing contact rates from three to 12 per day.

Outcomes

Quantification of the evolution of physical distancing measures

Since the beginning of the COVID-19 pandemic, like most Canadian provinces and territories, Ontario has gone through different phases of physical distancing escalation and enhanced testing for mitigating the first wave, followed by relaxation of closures to reopen the economy that led to the second wave and triggered a new second round of closures. It should be remarked that the second round of closures was also relaxed when the total cases declined but the more transmissible B.1.1.7 variant became dominant, leading to a third wave. While the quantification of the physical distancing measures in this research is based on data and analyses of the first two waves, the derived necessary conditions for reopening without a new large-scale outbreak that the Province of Ontario is experiencing clearly

supports the call for urgent attention to enhancing the capacity for testing-to-tracing and tracing-to-quarantine/isolation in preparation for the new reopening.

The escalation of closures implemented in Ontario in 2020 for mitigating the first wave involved stages from March 2020 (**Table 2**). The reopening process was more region-specific, but in general had three main stages: Phase 1, 2 and 3 reopening. Subsequently, enhanced measures began to be re-implemented in the province following Stage 3 reopening in fall 2020. The specific timeline which captures the essence of key events and is considered in this modelling study is shown in Table 2. In this study, December 23 marked the end date of data fitting, taken as the last day of data preceding the province-wide lockdown and not heavily affected by the Christmas festivities. The data fitting procedure (detailed in Appendix) also captured the effects of additional key events in the timeline related to the probability of transmission, case detection and contact tracing. In several regions, a requirement for the usage of face masks or coverings in enclosed public spaces was effective on July 7, 2020. Also, the variations in testing volumes, contact tracing and case detection during October 8–22, 2020 were quantified.

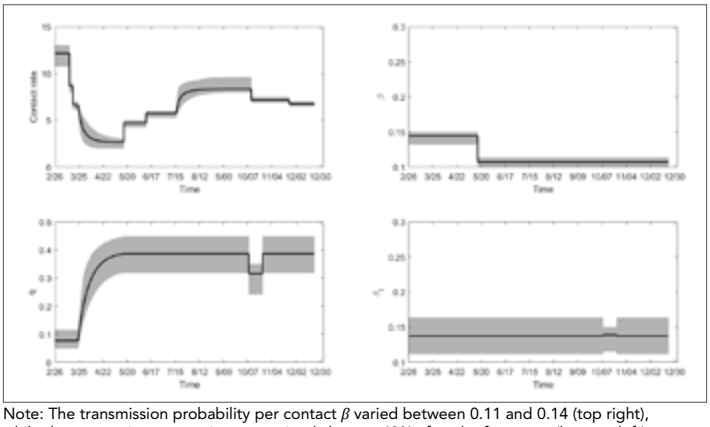
Table 2: Phases of physical distancing escalation and relaxations in Ontario, Canada

Description	Date
School closure until emergency declaration	March 14–18, 2020
Emergency declaration until the closure of non-essential workplaces	March 18–24, 2020
Closure of non-essential workplaces until the first easing of restrictions	March 24–May 16, 2020
Selected businesses and recreation services to resume activity, followed by Stage 1 reopening	May 16–June 12, 2020
Stage 2 reopening	June 12–July 17, 2020
Stage 3 reopening including school resumption	July 17–October 10, 2020
Modified Stage 2 effective in selected regions	October 10–November 23, 2020
Lockdown of the Toronto and Peel health regions and further enhanced measures across Ontario	November 23–December 23[a], 2020

[a] December 23, 2020 marked the end date of data fitting in this study. The phases listed are those that most regions in the province followed; some phases were regionally-specific based on local epidemiology

We estimated the effectiveness of interventions implemented in terms of the contact rate, the probability of transmission per contact, the symptomatic case detection rate and the proportion of contacts traced, quarantined or isolated. The transmission dynamics model was fitted to cumulative reported cases (4) using data until December 23, 2020 and accounted for different public health interventions (detailed below). We estimated daily individual contact rates between 2.66 and 12.17 contacts per day from March to December 2020. The estimated transmission probability per contact β varied between 0.11 and 0.14. The estimated quarantine proportion q remained close to 40% as of December 23. The rate of detection and isolation of symptomatic cases δ_I was estimated to be approximately 0.14/day. Further details on the parameter estimates and their time evolution are presented in **Figure 1**.

Figure 1: Parameters estimated by model fitting to cumulative reported cases in Ontario in 2020



Note: The transmission probability per contact β varied between 0.11 and 0.14 (top right), while the quarantine proportion q remained close to 40% after the first wave (bottom left). The daily average contact rates, which identify the different phases of implementation/lifting of restrictive closures (top left) were: prior to March 14: c = 12.17; March 14–18: c = 8.65; March 18–24: c = 6.64; May 16 (end of phase 3): c = 2.66; May 16–June 12 (Stage 1 reopening): c = 4.72; June 12–July 17 (Stage 2 reopening): c = 5.77; October 10 (end of Stage 3 reopening): c = 8.36; October 10–November 23 (modified Stage 2, enhanced measures): c = 7.14; November 23–December 23 (lockdown in Toronto and Peel regions, further enhanced measures): c = 6.78. The rate of detection and isolation of symptomatic cases δ_I remained at approximately 0.14/day for most of the period (bottom right), corresponding to approximately 45% of symptomatic cases being detected and isolated

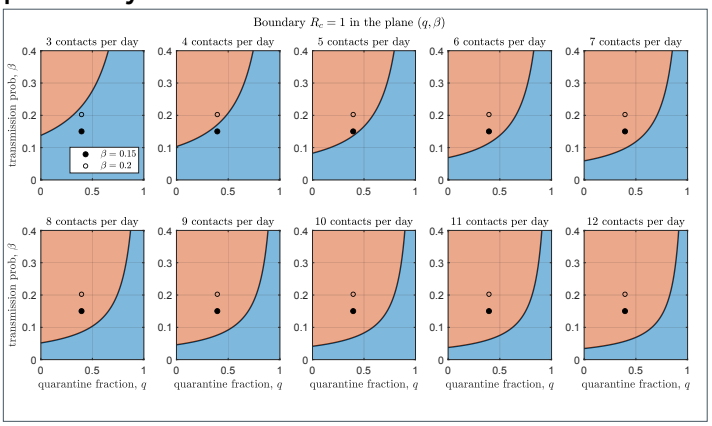
Feasibility of preventing a new outbreak with variants of concern

We then investigated the influence of different parameter values on the control reproduction number R_c, and assessed the necessary contact tracing and quarantine levels required for epidemic control when the VOC (B.1.1.7 strain) is the dominating strain. We considered, in particular, variations in the quarantine proportion, the proportion of symptomatic cases detected and isolated, and the different daily contact rates covering the values observed during the first and second waves.

A graph of the values for q (quarantine proportion) and β (transmission probability per contact) at which $R_c = 1$ is shown in **Figure 2**. These graphs separate the regions of parameters that do or do not allow to control the epidemic for daily contact rates between three and 12 people. We included the parameter estimates obtained during the first and second waves, with transmission probability per contact (β) increased by 40% compared with the previously estimated values, to account for the increased transmissibility of the VOC. The full circle corresponds to $\beta = 0.15$ (the lower estimate for the originally circulating virus, 0.11, increased by 40%), and the empty circle corresponds to $\beta = 0.2$ (the highest estimate for the originally circulating virus, 0.14, increased by 40%). For the quarantine fraction, we considered the estimated value before December 23. Notably, in the case of a contact rate equal to eight (corresponding to the contact rate estimated in Stage 3 of

reopening), increasing the quarantine proportion from 40% to 75% will allow the control reproduction number to remain below one even when VOC becomes dominant.

Figure 2: Boundary of values for the proportion of contacts traced and quarantined and the transmission probability



Note: The boundary of values for the proportion of contacts traced and quarantined q and the transmission probability β that determine whether the epidemic is controlled. The circles represent the parameters estimated by model fitting (quarantine proportion as of December 23, 2020, and the two estimated values of transmission probability increased by 40% due to the variants of concern, resulting in $\beta = 0.15$ and $\beta = 0.2$). The blue shaded area represents the parameter region that allows control, whereas the red shaded represents the region of epidemic spread

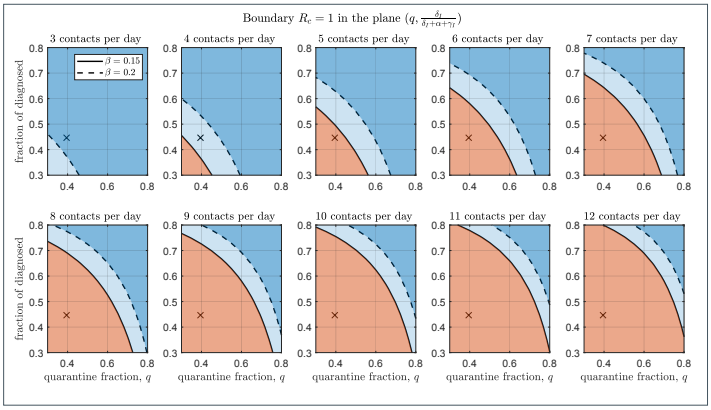
Similarly, we assessed the necessary contact tracing and quarantine, and case detection and isolation needed for epidemic control. A graph of the proportion of cases detected and isolated, and contacts traced and quarantined, at which $R_c = 1$ is shown in **Figure 3**. These graphs separate combinations of values for case detection and contact tracing that do and do not allow control of the epidemic. We estimated that a combination of 60% quarantine fraction and detection and isolation of 65% of symptomatic individuals is sufficient to prevent an outbreak using the contact rate estimated in Stage 2 of reopening ($c = 6$ contacts per day), even considering the highest estimate for the transmission probability (dashed lines in Figure 3).

Discussion

Using a transmission dynamics model fitted to cumulative reported COVID-19 cases in Ontario, we derived conditions under which a new wave could have been avoided despite the circulation of more transmissible VOCs. The fact that the province has experienced the third wave in the spring of 2021 shows that much could have been done in terms of testing-to-tracing and tracing-to-quarantine/isolation, along with physical distancing measures, to meet these conditions for reopening.

Our study shows that, if public health interventions can be sustained to ensure a declining trend in cases leading to a reduction of cases to a level such that testing capacity allows

Figure 3: Boundary of values for the proportion of contacts traced and quarantined and the proportion of symptomatic cases detected and isolated



Note: The boundary of values for the proportion of contacts traced and quarantined q and the proportion of symptomatic cases detected and isolated $\delta_I/(\delta_I + \alpha + Y_I)$ that determine whether the epidemic is controlled. The crosses represent the parameters estimated by model fitting until December 23, 2020. The solid and dashed curves represent the controllability threshold when the transmission probability β is at the lower and higher estimated values, respectively. The blue shaded area represents the parameter region that allows control (light blue: control is possible only if transmissibility is at the lower value $\beta = 0.15$; dark blue: control possible also for high transmissibility $\beta = 0.2$), whereas the red shaded represents the region of epidemic spread

more complete detection of cases, and contact tracing is conducted effectively with a high proportion of exposed individuals quarantined (and both occur rapidly enough), prevention of a new outbreak is feasible even under the worst case scenario that VOC becomes dominant. However, based on our analysis, this requires substantial increase in the proportion of cases that are detected, and in the proportion of contacts that are traced and quarantined. Specifically, if the daily individual contact rate in Ontario returns to its estimated value in the Stage 2 reopening (approximately six contacts per day), then a new outbreak (the third wave) could have been prevented if, for each new 100 infections generated, 60 of the 100 individuals were traced and isolated before becoming infectious; and further, of those who are not traced and go on to develop symptoms, 65 out of 100 were tested, diagnosed and isolated. Alternatively, if the detection rates among symptomatic individuals remain at their current estimated levels (i.e. about 45 out of 100 symptomatic individuals who missed tracing are diagnosed), a contact rate estimated during Stage 3 reopening (between eight and nine contacts per day) would be sustainable if, out of 100 new infections generated, approximately 75 were traced and isolated before entering their infectious period.

These high quarantine and isolation proportions can be achieved only if case numbers are reduced to low levels, creating a narrow window of opportunity to prevent a new wave. This cascading effect was discussed previously (8). When focused and coherent mitigation interventions lead to an accelerated rate of case decline to a level that reopening can start with a very small number of new infections, effective public health mitigation interventions can and should be further mobilized for swift focused reaction to any new localized hotspot, avoiding a full-scale subsequent wave in the presence of VOC. These

studies show that decision for reopening must take consideration of not only the decline rate of cases and case numbers, but the public health capacity for testing, tracing, quarantine and isolation. This is particularly relevant for any province that is implementing lockdown measures to mitigate an ongoing wave: creating the conditions for reopening must involve the enhancement of testing-to tracing and the follow-up quarantine and isolation logistics.

Strengths and limitations

Our study demonstrates that increased efforts in public health policies of symptomatic case detection and contact tracing could have allowed control of the epidemic even if a VOC with 40% increased transmissibility becomes dominant. One important advantage of our methodology is that it uses retrospective assessment and quantification of public health efforts (in terms of symptomatic diagnosis and quarantine of contacts) in the previous (first and second) COVID-19 epidemic waves, to estimate the necessary increase in effort to have prevented a third outbreak. However, our study is based on several assumptions, some of which could be easily relaxed, while others are specific to the chosen modelling framework. First, our estimates do not account for the decrease in the number of susceptible individuals due to infection-induced immunity or to the distribution of vaccines in the population; thus, they provide a somewhat conservative scenario. Moreover, we have here assumed a fixed increase (by 40%) in the VOC transmissibility, representing the lower values estimated for the B.1.1.7 variant. The methodology could be easily adapted to study different levels of increased transmissibility, which may be more descriptive of other existing and emerging VOCs. Another important aspect is that the transmission model is based on the assumption of homogeneous mixing of individuals, thus ignoring heterogeneity due to different age or risk groups, behaviors or settings. Some level of heterogeneity, for example between different age groups and social settings, could be incorporated in the model by using stratified compartments, although this comes at the cost of increased complexity in parameter estimation (9). Other levels of heterogeneity, for instance spatial heterogeneity or clusters of transmission, would require more complex modelling approaches. Another limitation is that we fitted the model to laboratory confirmed cases. While having the advantage of being widely accessible and timely, these data sets could be biased by several factors including temporal variations in daily tests or in testing protocols.

Conclusion

We have identified conditions under which a new wave (the third wave) could have been prevented in Ontario, considering the worst case that the more transmissible B.1.1.7 strain became dominant. Our analysis indicates that high levels of case isolation and quarantine would have been needed to maintain control to ensure a safe partial reopening. While this study focused on the prevention of the third wave in Ontario, the approach presented herein is amenable to be adapted to other geographic regions and circumstances. Several assumptions made in the mathematical model can be relaxed for a potentially more accurate assessment. The analysis of the control reproduction number R_c, informed by model fitting and emerging evidence, may be used to identify estimates of conditions in terms of measures from the public health system and activity levels in the population needed for controllability. In this light, results obtained by utilizing this approach may be helpful for decision-makers posed with questions of reopening given the emergence of additional variants of the SARS-CoV-2 virus with increased transmissibility.

Authors' statement

JW and NHO — Conceived the original idea
ZMC and YX — Performed the model fit
ZMC and FS — Curated the mathematical analysis and visualization

All authors discussed the results and contributed to the final manuscript.

Competing interests

None.

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Appendix: Details of the transmission dynamics model

Background

A central component of the intervention used to quantify conditions that combined public health interventions must meet to reopen the economy without a large outbreak is a transmission dynamics model. Here we provide details of the application of the transmission dynamics model established in prior study (10) to the present study, which enabled the calculations of the control reproduction number R_c under the scenarios presented in the main text (Figure 2 and Figure 3 in the main text). The key step for the established model's usage in the analysis of R_c is the model parametrization (i.e. estimating the model parameters using Ontario-specific incidence data until December 23, 2020). In this Appendix, we present the complete methods used for the model parametrization and detailed results from the model fitting. This model parameterization allowed for the estimation of the needed enhancements to public health interventions in terms of tracing and quarantine, and detection and isolation for a reopening amid the circulation of variants of concern (VOCs).

Transmission model

We utilized the transmission dynamics model established in a prior study (10), which captures essential epidemic features and key public health interventions including contact tracing, quarantining, testing and isolation. The model variables, key model parameters and their descriptions are presented in the main text of the article. In addition, we note that the quarantined individuals can either move to the compartment E_q or S_q, depending on whether transmission occurred (with transmission probability per contact β), while the other proportion, $1 - q$, comprises individuals exposed to the virus who are missed by contact tracing and, therefore, move to the compartment for those exposed and infected but not quarantined (E) if transmission occurred, or stay in the compartment S otherwise.

Here, we present the mathematical model equations and details of its parameterization. The transmission dynamics model was formulated in terms of ordinary different equations:

$$
\begin{aligned}
S' &= -\left(\beta c + cq(1-\beta)\right) S(I+\theta A)/N + \lambda S_q,\\
E' &= \beta c(1-q) S(I+\theta A)/N - \sigma E,\\
I' &= \sigma \varrho E - (\delta_I + \alpha + \gamma_I) I,\\
A' &= \sigma(1-\varrho) E - \gamma_A A,\\
S_q' &= (1-\beta) cq S(I+\theta A)/N - \lambda S_q,\\
E_q' &= \beta cq S(I+\theta A)/N - \delta_q E_q,\\
D' &= \delta_I I + \delta_q E_q - (\alpha + \gamma_D) D,\\
R' &= \gamma_I I + \gamma_A A + \gamma_D D,
\end{aligned}
$$

where the prime symbol (′) denotes the derivative with respect to time. The full list of model parameters and their descriptions is included in **Table A1**.

Table A1: Estimated parameter values for the COVID-19 transmission dynamics model in Ontario, Canada

Parameter		Definitions	Mean	Std	Source
$c(t)$	c_0	Contact rate before March 14, 2020	12.17	0.6172	Estimated
	c_1	Contact rate between March 14 to March 18 2020	8.65	0.2696	Estimated
	c_2	Constant contact rate on March 24, 2020	6.64	0.1922	Estimated
	r_1	Exponential decrease of contact rate between March 24 and May 16, 2020	0.1936	0.1086	Estimated
	c_b	Minimum contact rate after March 24, 2020	2.66	0.3314	Estimated
	c_3	Contact rate between May 16 to June 12, 2020	4.72	0.2224	Estimated
	c_4	Contact rate between June 12 to July 17, 2020	5.77	0.4068	Estimated
	c_m	Maximum contact rate between July 17 and October 10, 2020	8.36	0.2605	Estimated
	r_3	Exponential increase of contact rate between July 17 and October 10, 2020	0.3117	0.0032	Estimated
	c_5	Contact rate between October 10 to November 23, 2020	7.14	0.1299	Estimated
	c_6	Contact rate between November 23 to December 23, 2020	6.78	0.1746	Estimated
β_1		Probability of transmission per contact before May 16, 2020	0.1446	0.0051	Estimated
β_2		Probability of transmission per contact after May 16, 2020	0.1073	0.0076	Estimated
q_0		Fraction of quarantined exposed individuals before March 24, 2020	0.0775	0.0177	Estimated
$q(t)$	r_2	Exponential increase of quarantine fraction	0.0835	0.0314	Estimated
	q_b	The maximum quarantine fraction before October 8, 2020	0.3949	0.0334	Estimated
	q_1	The quarantine fraction between October 8 and October 22, 2020	0.3156	0.0368	Estimated
σ		Transition rate of exposed individuals to the infected class	1/5	0	(11)
λ		Rate at which the quarantined uninfected contacts were released into the wider community	1/14	0	(12)
ϱ		Probability of developing symptoms among infected individuals	0.7240	0.0278	Estimated
δ_1		Transition rate of symptomatic infected individuals to the quarantined infected class	0.1378	0.0133	Estimated
δ_{I1}		Transition rate of symptomatic infected individuals to the quarantined infected class between October 8 and October 22, 2020	0.1392	0.0100	Estimated
δ_q		Transition rate of quarantined exposed individuals to the quarantined infected class	0.1217	0.0301	Estimated

Table A1: Estimated parameter values for the COVID-19 transmission dynamics model in Ontario, Canada (*continued*)

Parameter	Definitions	Mean	Std	Source
γ_I	Recovery rate of symptomatic infectious individuals	0.1627	0.0164	Estimated
γ_A	Recovery rate of asymptomatic infectious individuals	0.139	0	(12)
γ_D	Recovery rate of quarantined diagnosed individuals	0.2	0	(13)
α	Disease-induced death rate	0.008	0	(13)
θ	Modification factor of asymptomatic infectiousness	0.0342	0.0068	Estimated

Abbreviations: COVID-19, coronavirus disease 2019, Std, standard deviation

We obtained the control reproduction number R_c of the above transmission model using the next generation method (14). In the analysis of the control reproduction number R_c in this study, we did not account for the decrease in the susceptible population due to infection-induced immunity or vaccination and assumed that $S(t)/N(t) = 1$. The resultant control reproduction number is:

$$R_c = \frac{\beta\rho c(1-q)}{\delta_I + \alpha + \gamma_I} + \frac{\beta c\theta(1-\rho)\,(1-q)}{\gamma_A}$$

To then estimate the model parameters from February 26, 2020 until December 23, 2020, we used the following process. We first considered the parameters θ, λ, σ, ρ, γ_A, γ_I, δ_q, γ_D, α as constant in time. On the other hand, we considered several model parameters as time-dependent based on the Ontario timeline of key events, intervention implementations and relaxations (detailed in the main text of the article): the contact rate c, the quarantine proportion q, the probability of transmission per contact β, and the symptomatic detection rate δ_I.

We allowed the contact rate c to change according to the timeline of public health interventions implemented in the Province. Specifically, we assumed the following piecewise form for the contact rate:

$$c(t) = \begin{cases} c_0,\ T_{initial} < t < T_0, \text{ (February 26 – March 14)}, \\ c_1, T_0 < t < T_1, \text{ (March 14 – March 18)}, \\ c_2,\ T_1 < t < T_s, \text{ (March 18 – March 24)}, \\ (c_2 - c_b)e^{-r_2(t-T_s)} + c_b, \quad T_s < t < T_2, \quad \text{(March 24 – May 16)}, \\ c_3, T_2 < t < T_3, \text{ (May 16 – June 12)}, \\ c_4, T_3 < t < T_4, \text{ (June 12 – July 17)}, \\ (c_4 - c_m)e^{-r_3(t-T_4)} + c_m,\ T_4 < t < T_5, \text{ (July 17 – October 10)}, \\ c_5,\ T_5 < t < T_6, \text{ (October 10 – November 23)}, \\ c_6, T_6 < t < T_f, \text{ (November 23 – December 23)}. \end{cases}$$

where $T_{initial}$, T_0, T_1, T_s, T_2, T_3, T_4, T_5, T_6, T_f, correspond to times matching the dates February 26, 2020, March 14, 2020, March 18, 2020, March 24, 2020, May 16, 2020, June 12, 2020, July 17, 2020, October 10, 2020, November 23, 2020 and December 23, 2020, respectively. These dates correspond to key dates detailed in the main text of the article. An exponential function was used to capture society's gradual adaptation to stricter or looser control measures during the non-essential workplace closure and Stage 3 reopening.

To estimate the resultant potential change in transmission risk per contact over time, we modelled the transmission probability per contact β using the following piecewise constant function:

$$\beta(t) = \begin{cases} \beta_1,\ T_{initial} < t < T_{May16}, \text{ (February 26 – May 16)}, \\ \beta_2,\ T_{May16} < t < T_f, \quad \text{(May 16 – December 23)}, \end{cases}$$

where T_{May16} corresponds to the date May 16, 2020 which marked the first easing of restrictions in Ontario.

We also allowed for alteration in the symptomatic detection rate during the dates October 8, 2020–October 22, 2020 to capture variations in testing, contact tracing and case detection during this period. The symptomatic detection rate δ_I we modelled as piecewise constant, with the form:

$$\delta_I(t) = \begin{cases} \delta_I,\ T_{initial} < t < T_{Oct8}, \text{ (February 26 – October 8)}, \\ \delta_{I1},\ T_{Oct8} < t < T_{Oct22}, \text{ (October 8 – October 22)}, \\ \delta_I,\ T_{Oct22} < t < T_f, \text{ (October 22 – December23)}, \end{cases}$$

where the dates $T_{initial}$, T_f, are defined above and T_{Oct8}, T_{Oct22} correspond to the dates October 8, 2020 and October 22, 2020, respectively.

Finally, the quarantine proportion was also modelled as time-dependent. We captured here the escalation of tracing efforts from the public health system after the non-essential workplace closure on March 24, 2020 with a modelled exponential increase in q. Similar to the detection rate, we also allowed for variation in quarantine proportion q between the dates October 8, 2020–October 22, 2020. The quarantine proportion was modelled as:

$$q(t) = \begin{cases} q_0,\ T_{initial} < t < T_S, \text{ (February 26 – March 24)} \\ (q_0 - q_b)e^{-r_2(t-T_S)} + q_b,\ T_s < t < T_{Oct8}, \text{ (March 24 – October 8)} \\ q_1,\ T_{Oct8} < t < T_{Oct22}, \text{ (October 8 – October 22)} \\ q_b,\ T_{Oct22} < t < T_f, \quad \text{(October 22 – December 23)} \end{cases}$$

With the model and its parameters now associated with a suitable form permitting us to capture key elements in the Ontario timeline, we next incorporated the coronavirus disease 2019 (COVID-19) data coupled with a model fitting procedure to quantify the model parameter values.

Data

To parameterize the transmission model, we utilized the confirmed positive cases of COVID-19 in Ontario and population demographic data for Ontario. The time series of the cumulative cases of COVID-19 in Ontario was generated using individual line listed data from the Ontario Ministry of Health, which was

made available to us through the Ontario COVID-19 Modeling Consensus Table. Second, the demographic data specific to Ontario in terms of the population size is available publicly by Statistics Canada (15). These were the main sources of data which enabled the fitting of mathematical model and the subsequent analyses.

Model fitting

To estimate the model parameters, we fit the transmission model the cumulative incidence of confirmed COVID-19 cases in Ontario. The fitting technique utilized has been outlined in prior study (10) and is summarized as follows: we informed the model with estimated parameters α, Υ_A from existing studies (Table A1), the necessary population size data from Statistics Canada (15) and the initial conditions (**Table A2**). We then run the model forward from $t = T_{initial}$ to T_f (February 26, 2020 to December 23, 2020), and determined the parameters which minimized the least square error against the cumulative incidence. Confidence intervals for parameters were estimated by employing a bootstrap method to generate 1,000 cumulative incidence time series (10). It was assumed that the newly reported cases followed a Poisson distribution, and the model was fitted to each of the 1,000 realizations of the observed time series. The process yielded 1,000 sets of parameters values for q, Υ_I, δ_I, θ, c, β, ρ, and the estimated mean and standard deviation for each are reported in Table A1. For non-fitted parameters α, Υ_A, the source is reported.

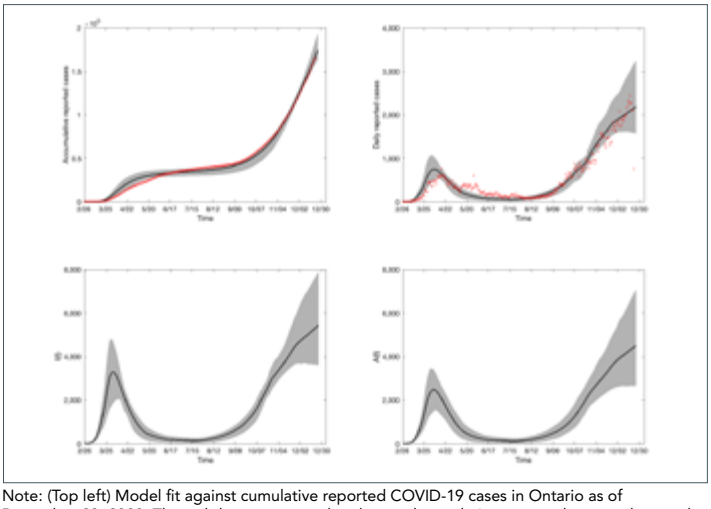
Table A2: Estimated initial values for the COVID-19 transmission dynamics model in Ontario, Canada

Initial values	Definitions	Mean	Std	Source
$S(0)$	Initial susceptible population	1.471 X 10^7	0	Data (15)
$E(0)$	Initial exposed population	16.0081	4.9432	Estimated
$I(0)$	Initial symptomatic infectious population	12.2829	3.7544	Estimated
$A(0)$	Initial asymptomatic infectious population	14.2352	6.1958	Estimated
$S_q(0)$	Initial quarantined susceptible population	0	0	Assumed
$E_q(0)$	Initial quarantined exposed population	0	0	Assumed
$D(0)$	Initial quarantined diagnosed population	5	0	Incidence data
$R(0)$	Initial recovered population	0	0	Assumed

Abbreviation: COVID-19, coronavirus disease 2019; Std, standard deviation

The model fit and quantified uncertainty against the true case data in Ontario is shown in **Figure A1** in terms of the daily reported cases (top right) and cumulative reported cases (top left); the estimated number of active symptomatic infectious individuals $I(t)$ (bottom left) and estimated number of active asymptomatic infectious individuals $A(t)$ (bottom right) and their time evolution are also depicted. The values (including 95% CIs) and time evolution of the key parameters β, δ_I, q, c are shown in Figure 1 in the main text.

Figure A1: Model fit results



Note: (Top left) Model fit against cumulative reported COVID-19 cases in Ontario as of December 23, 2020. The red dots represent the observed cumulative reported cases, whereas the black line denotes the mean of the 1,000 model runs and the grey shaded region representing the 95% confidence interval (CI). (Top right) Model fit against the daily reported cases in Ontario as of December 23, 2020. The red dots represent the daily number of reported cases in the province. (Bottom left) The estimated number of symptomatic infectious individuals as produced by the fitted model and the 95% CI. (Bottom right) The estimated number of active asymptomatic infectious individuals in Ontario as produced by the fitted model, as well as the corresponding 95% CI

Application

We have estimated the transmission model parameters as of December 23, 2020, which completely informed the control reproduction number R_c. To incorporate the effects of VOCs in the analysis of R_c, we integrated existing estimates of the increased transmissibility of the B.1.1.7 strain first identified in the United Kingdom (16,17) and increased the estimated values for β by 40%, as detailed in the main text. We then assessed R_c under different scenarios corresponding to the proportion of symptomatic individuals who are tested, confirmed and isolated during their infectious period $\delta_I/(\delta_I + \alpha + \Upsilon_I)$, the proportion of contacts traced and quarantined (q), the transmission probability per contact (β), and contact rate (c) by altering the parameters δ_I, q, β, c, accordingly. The main study outcomes in terms of conditions on the enhanced public health measures (Figure 2 and Figure 3 in the main text) needed to maintain $R_c < 1$ were generated by effectively viewing R_c as a function of β, δ_I, c, q. Thus, we identified the needed levels of (enhanced) controls to prevent a VOC wave while achieving contact rates that were estimated during different phases of public health interventions in Ontario.

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OUTBREAK

The development of a community-based public health response to an outbreak of post-streptococcal glomerulonephritis in a First Nations community

Jeffrey Jacob[1], Natalie Bocking[1], Ruben Hummelen[2], Jenna Poirier[2], Len Kelly[3]*, Sharen Madden[2], Yoko Schreiber[2,3,4]

Abstract

Background: Post-streptococcal glomerulonephritis (PSGN) is a rare immune-mediated condition that typically occurs in children as a result of group A streptococcus (GAS) infection. PSGN is not considered a disease of public health significance, or reportable, in Canada. Higher incidence of PSGN has been described among Indigenous people in Canada. No national or provincial guidance exists to define or manage PSGN outbreaks.

Objective: To describe an outbreak of seven paediatric cases of PSGN in a remote First Nations community in northwestern Ontario and the development of a community-wide public health response.

Methods: Following a literature review, an intervention was developed involving screening of all children in the community for facial or peripheral edema or skin sores, and treatment with antibiotics if noted. Case, contact and outbreak definitions were also developed. The purpose of the response was to break the chain of transmission of a possible nephritogenic strain of streptococcus circulating in the community. Relevant demographic, clinical and laboratory data were collected on all cases.

Outcome: Seven paediatric cases of PSGN presented to the community nursing station between September 25 and November 29, 2017. Community-wide screening for skin sores was completed for 95% of the community's children, including 17 household contacts, and as a result, the last of the cases was identified. Nineteen adult household contacts were also screened. Ten paediatric contacts and two adult contacts with skin sores were treated with one dose of intramuscular penicillin, and six paediatric contacts received oral cephalexin. No further cases were identified following the screening.

Conclusion: PSGN continues to occur in Indigenous populations worldwide at rates higher than in the overall population. In the absence of mandatory reporting in Canada, the burden of PSGN remains underappreciated and could undermine upstream and downstream public health interventions. Evidence-based public health guidance is required to manage outbreaks in the Canadian context. The community-based response protocol developed to contain the PSGN outbreak in this First Nations community can serve as a model for the management of future PSGN outbreaks.

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Keywords: post-streptococcal glomerulonephritis, outbreak, First Nations, community-based intervention

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Background

Post-streptococcal glomerulonephritis (PSGN) is considered a rare non-suppurative sequela of group A streptococcus (GAS) infection, affecting children more commonly than adults. Symptoms of nephritis, which include edema, hypertension and hematuria, typically manifest 2 to 6 weeks after GAS skin infection or streptococcal pharyngotonsillitis (1–3). Short-term prognosis is generally favourable, although renal function can be affected in later years (4).

Under current public health legislation, PSGN is not a reportable disease in Ontario or any other Canadian province, and as a result, provincial and national level incidence rates are unknown (5). Globally, PSGN remains a disease of social inequity, affecting children in low-income settings; young Indigenous people carry a higher burden in high-income countries such as Australia (4).

A case series has documented similarly high disease burden among First Nations communities in northwestern Ontario (6). Canadian efforts against GAS disease are targeted mainly towards invasive GAS (iGAS), such as toxic-shock syndrome and soft-tissue necrosis (7). No Canadian guidance for the public health management of PSGN is available.

Setting

An outbreak of PSGN occurred in a remote, fly-in First Nations community in northwestern Ontario with a population of approximately 900 people. Federal nurses provide primary care and public health services at the community nursing station. Physicians visit for a week each month and also provide 24/7 telephone support.

This outbreak report was requested by the community leadership and approved by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

This article documents the outbreak of PSGN in the First Nations community and the development of a public health response intervention to prevent the spread of nephritogenic strains of GAS to other children.

Presentation and response

On October 26, 2017, a front-line nurse reported to her manager a cluster of children presenting with possible PSGN to the community nursing station. In total, six cases presented between September 25 and November 17, 2017. The concern was brought forward to the federal agency, First Nations and Inuit Health, Ontario Region, Indigenous Services Canada (ISC) and the local Indigenous health services organization, Sioux Lookout First Nations Health Authority (SLFNHA). Representatives from First Nations and Inuit Health, ISC and SLFNHA met with local clinicians to determine if the cases constituted an outbreak and to develop an evidence-based response. The ISC medical officer also met with the community leadership to request their support in raising awareness and to engage the community in a collaborative response. The nursing station personnel also played a key role in engaging the community. The purpose of the response was to break the chain of transmission of a possible nephritogenic strain of streptococcus circulating in the community. An outbreak was declared on November 21, 2017.

Phase 1: Detection and declaration of outbreak

Case definition

A chart review was conducted to collect demographic, clinical and laboratory information and to ensure patients met the case definition for PSGN (see **Table 1**). Clinical data were collected by community nurses and physicians retrospectively for cases identified before the declaration of the outbreak and prospectively during community screening and contact tracing.

Table 1: Case definitions of PSGN developed for use in outbreak containment in a First Nations community in northwestern Ontario, 2017

Case definitions	
Confirmed case	Definitive evidence; or clinical and laboratory evidence
Probable case	Clinical evidence only
Possible case	Laboratory evidence only or expert opinion
Evidence description	
Definitive evidence	Renal biopsy suggestive of PSGN
Clinical evidence (at least two of the four required)	Facial edema
	Peripheral edema
	Moderate hematuria on dipstick
	Hypertension
Laboratory evidence (all three required)	Hematuria on microscopy
	Evidence of recent streptococcal infection (throat or skin culture or elevated ASOT)
	Reduced complement C3 level

Abbreviations: ASOT, antistreptolysin-O titre; PSGN, post-streptococcal glomerulonephritis
Source: Department of Health and Families, 2010 (8)

Patients were clinically assessed for hypertension, facial and peripheral edema, skin sores and scabies, and hematuria on urinalysis. Skin and throat swabs for culture were obtained if indicated. Laboratory investigation included blood urea nitrogen (BUN), creatinine (Cr), complete blood count (CBC), antistreptolysin-O titre (ASOT) and complement C3. Clinical management was provided by the community family physicians who consulted with a paediatrician.

Outbreak definition

We searched the literature for national and international evidence-based guidance on the definition and public health management of PSGN outbreaks, particularly in Indigenous communities. No Canadian resources were found, but grey

literature from Australia provided guidelines that were largely based on expert opinion and local experience (8,9). Based on their community screening criteria, an outbreak of PSGN was defined as:

- Two or more probable or confirmed cases in the same community with onset within one week of each other and with at least one case with a reduced complement C3

  OR

- One confirmed case and two probable cases in the same community, with onset within one month of each other

The Australian guidelines included in their criteria that "the cases are not contacts of each other" (8,9). We were unable to determine in a timely fashion whether the cases in the First Nations community were contacts of each other and removed this criterion from our definition of a PSGN outbreak.

An outbreak of PSGN was declared by the ISC medical officer on November 21, 2017. A multi-jurisdictional outbreak management team was formed. This team included ISC personnel, the public health physician from the SLFNHA, an infectious disease specialist from Sioux Lookout, the community family physicians and the nursing station manager. The community health director played a crucial role in the response.

An outbreak management protocol was developed based on approaches used in Western Australia and Northern Territory, Australia (8,9). These are described in the following sections.

Contact definition

Close contacts were defined as individuals who had stayed overnight in the house of a confirmed case in the two weeks preceding the onset of their illness. Both adult and child contacts of confirmed cases were identified and assessed by community health nurses. Contacts were examined for the presence of skin sores, scabies, facial and peripheral edema, and hematuria; their blood pressure was measured and recorded.

Phase 2: Immediate control measures

Educational materials were developed according to community needs and distributed widely through a variety of communication channels.

The community health nurses received education in early case detection.

The cases, analyses and treatment are described in the section "Descriptive epidemiology."

Phase 3: Community-wide screening

Screening of the community took place from November 27 to December 3, 2017. All children and youth between 12 months and 17 years old were eligible for screening. The list of eligible children was developed from the community member evacuation list for regional forest fire management. Screening was implemented over a one-week period and took place first at the Band Office and then at the community nursing station to minimize disruption to regular primary care services. Screening was led by nurses who have an ongoing relationship with the community.

The children were screened for skin sores, scabies, and facial or peripheral edema (**Table 2**). Contact tracing and treatment occurred concurrently. Informed consent was obtained prior to assessment so that skin sores or scabies could be treated during the same visit.

Table 2: Diagnostic criteria for confirmed or suspected PSGN cases in a First Nations community in northwestern Ontario, September 25 to December 10, 2017

Diagnostic criteria	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Definite evidence							
Renal biopsy	No biopsy	No biopsy	No biopsy	No biopsy	+	No biopsy	No biopsy
Clinical evidence (2 of 4 required)							
Facial edema	+	+	+	+	+	+	-
Peripheral edema	–	–	–	–	–	–	–
Moderate hematuria on dipstick	+	+	+	+	+	+	+
Hypertension	+	+[a]	+	+	+	+	+[a]
Laboratory evidence (3 of 3 required)							
Hematuria on microscopy	+	+	+	+	+	+	–
Evidence of recent streptococcal infection (throat or skin culture or elevated ASOT)	+	+	+	+	+	+	+
Reduced complement C3 level	+	+	+	+	+	+	+

Abbreviations: ASOT, antistreptolysin-O titre; PSGN, post-streptococcal glomerulonephritis; –, absent; +, present

[a] Cases 2 and 7 were normotensive at initial presentation and developed hypertension subsequently

Contact tracing, community screening and management

A total of 36 household contacts were identified, with 17 contacts between 1 and 17 years old and 19 contacts over 17 years old. Of the contacts, all the adults and all but one child were screened (see **Table 3**). In our protocol, paediatric contacts received one dose of intramuscular benzathine penicillin or an alternative, whether skin sores were present or not; 10 of the 17 paediatric contacts were treated with intramuscular penicillin and seven with oral cephalexin. Of the 19 adult contacts, two had skin sores and were treated with intramuscular penicillin; only the adult contacts who had skin sores were treated.

Table 3: Community screening for PSGN cases in a First Nations community in northwestern Ontario, November 27 to December 3, 2017

Characteristics	Screened population				Total
	Children			Adults	
	Total of participants	Contacts	Non-contacts	Contacts	
Eligible for screening	224	17	207	19	243
Screened	212	16	196	19	231
Refused screening	12	1	11	0	12
New cases	1	1	0	0	0
Treated	20	16[a]	4[b]	2[b]	22
Penicillin G	11	10	1	2	13
Cephalexin	10	7	3	0	10

Abbreviation: PSGN, post-streptococcal glomerulonephritis
[a] Three with skin sores
[b] With skin sore

No cases of scabies were identified.

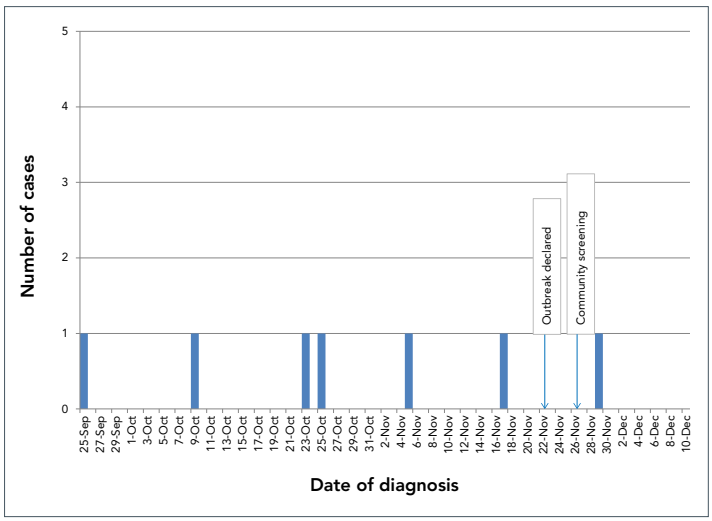
As shown in Table 3, 95% (212/224) of eligible children/youth, including the contacts noted above, were screened. Prevalence of skin sores was low (2.0%). Community screening identified the seventh case of PSGN.

Descriptive epidemiology

Five cases presented to the community nursing station between September 25 and October 28, 2017. A sixth case presented on November 17, 2017, when concerns about a possible outbreak were being raised. A seventh possible case was identified during contact tracing/community screening on November 29 and confirmed on December 10, 2017.

The epidemiologic curve for the outbreak is shown in **Figure 1**. No additional cases were identified in the three years following the outbreak.

Figure 1: Epidemiologic curve of cases of suspected or confirmed[a] PSGN in a First Nations community in northwestern Ontario, September 25 to December 10, 2017



Abbreviation: PSGN, post-streptococcal glomerulonephritis
[a] Case #7 presented in November 29, but was confirmed on December 10; the presentation was ill-defined. In this case, the confirmatory date is used in the epidemiologic curve

The seven patients were between 3 and 13 years old; five were male. Clinical and laboratory information for case confirmation is shown in Table 3 and **Table 4**. Almost all the patients presented with facial edema (6/7) and hypertension was common (5/7). Six of the seven children had concurrent or antecedent skin infection, four of which were GAS positive, and three children had throat swabs confirming GAS. One case with a negative throat swab and no skin findings was found to have a high ASOT

Of the seven PSGN cases, six patients required antihypertensive therapy and five required diuretics; all seven patients—the six confirmed and one initially probable case—were prescribed antibiotics. Six were hospitalized (Table 4); five were transferred to tertiary care paediatric hospitals for up to 16 days, including one who was admitted to the intensive care unit. Recovery was complete in four children; three had ongoing hematuria at their two-year follow-up.

Table 4: Clinical presentation and laboratory evidence, treatment and outcomes for PSGN cases in a First Nations community in northwestern Ontario, 2017

Clinical data	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age range, years	3–6	10–13	3–6	3–6	3–6	10–13	3–6
Sex	M	M	M	F	F	M	M
Day of presentation of confirmed or suspected PSGN[a]	0	14	28	30	41	64	76
Clinical presentation							
Initial blood pressure	170/115	128/77	168/123	147/117	150/112	150/88	112/64
Edema	Facial, pedal	Facial	Facial	Facial	Facial	Facial	–
Pharyngitis	–	–	–	–	–	–	–
Skin sores	+	+	+	+	+	–	+
Proteinuria[b]							
Macroscopic hematuria	+	–	+	+	+	+	–
Decreased urine output	–	–	+	–	+	–	–
Lethargy, anorexia	+	+	+	+	+	+	–
Laboratory assessments[c]							
Hemoglobin (105–140 g/L)	102	67	102	117	102	117	98
BUN (2.5–6.1 mmol/L)	4.8	16.1	6.6	9.4	15.1	6.2	4.5
Creatinine (46–92 µmol/L)	79.4	173	47.5	43.5	195	60	38
Complement C3 (0.88–1.65 g/L)	<0.4	<0.4	<0.4	<0.4	<0.4	<0.4	<0.4
ASOT (<200 IU/mL)	N/A	N/A	>1,600	800–1,600	1,600	397	N/A
Microscopic hematuria (≤3/HPF)	30 and more	20–51	30 and more	30 and more	100 and more	20–51	≤3
Throat culture	+GAS	−GAS	+GAS	−GAS	−GAS	+GAS	N/A
Skin lesion culture	Not done[d]	+GAS	+GAS	Not done[d]	+GAS	Not done[d]	+GAS
Treatment							
Antihypertensive							
Beta blocker	N/A	N/A	N/A	+	N/A	N/A	N/A
Ca^{++} channel blocker	+	N/A	+	+	N/A	+	N/A
ACE inhibitor	N/A	+	N/A	N/A	N/A	N/A	N/A
Vasodilator/alpha-agonist	N/A	N/A	+	+	+	+	N/A
Diuretic – furosemide	+	N/A	+	+	+	+	N/A
Antibiotic							
Penicillin	N/A	N/A	N/A	N/A	N/A	+	+
Amoxicillin	+	N/A	+	N/A	N/A	N/A	N/A
Ceftriaxone	N/A	N/A	+	+	N/A	N/A	N/A
Cephalexin	N/A	+	N/A	N/A	+	N/A	N/A
Azithromycin	N/A	N/A	N/A	+	N/A	N/A	N/A
Fluid restriction	+	–	–	+	+	–	–
Disposition	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Length of hospital stay, days	5	7	9	1	16	12	0
Outcome	Ongoing	Resolved	Ongoing	Resolved	Ongoing	Resolved	Resolved

Abbreviations: ACE, angiotensin-converting enzyme; ASOT, antistreptolysin-O titre; BUN, blood urea nitrogen; F, female; GAS, group A streptococcus; HPF, high-power field; IU, international units; M, male; N/A, not available; PSGN, post-streptococcal glomerulonephritis; –, absent; +, present

[a] Counted from date of first case

[b] Although proteinuria is determined via a laboratory test, it is listed as a clinical presentation because it was measured at the community nursing station

[c] Values in parentheses are the normal ranges

[d] The swab was not performed

Discussion

PSGN outbreaks have been reported in several Indigenous communities in Australia, but this is the first outbreak reported in Canada (4,10–12). A 2016 six-year review of sporadic PSGN cases in northwest Ontario documented 10 paediatric and five adult cases, an incidence triple that of developed countries, but the review found no clustering of cases in any one community (6). This identification of an outbreak of PSGN in a remote First Nations community adds to the growing body of evidence of the disparate burden of post-streptococcal sequelae carried by Indigenous peoples in Canada and worldwide.

Because there is no national or provincial public health guidance to define or manage outbreaks of PSGN in Canada, we developed a community-based response protocol modelled on interventions used in Indigenous communities in Australia. The protocol and process can serve as a model for the management of future PSGN outbreaks.

Other GAS-related disease is also prevalent regionally: iGAS infections and an acute rheumatic fever, another immune-mediated GAS complication, occur at rates 10 and 75 times higher, respectively, than overall provincial rates (13–15). A spike in invasive GAS cases was observed in the two health units spanning northwestern Ontario in 2017, with *emm*74 and *emm*81 being the most prevalent strains circulating that year (16). Of note, *emm*74 had not been identified in the region before and was associated with outbreaks in an under-housed population in Southern Ontario (17), thus raising the possibility that no protective immunity existed in the population. Unfortunately, we were unable to obtain *emm*-typing to determine whether the outbreak was triggered by a new, nephritogenic strain of GAS. Furthermore, regional hospitals and clinics noted an increase in the number of patients presenting with skin and soft-tissue infections during that period (16).

The interconnectedness between GAS-related disease presentations remains poorly understood in this population. While the rarity of PSGN in high-income settings in Ontario may not warrant active surveillance, we argue that adding PSGN to the reportable disease list would enhance knowledge and awareness surrounding transmission dynamics of GAS, which in turn could inform intervention.

Unlike acute rheumatic fever, treatment of initial GAS infection does not prevent PSGN, so public health efforts to address PSGN need to focus on primary prevention. Indigenous communities in Australia have high rates of GAS infections that are associated with inadequate water and housing capacity; improved housing decreased skin infections and positively impacted child health (18,19). The First Nations community described in this report, like 60 other First Nations communities in Canada, was under a boil-water advisory at the time of the outbreak (20). Overcrowding in housing is well recognized in many First Nations communities and is the subject of the newly developed Nishnawbe Aski Nation Housing Strategy (21). Improving housing and other environmental determinants of health is grounded in human rights, and ongoing inequities trace back to the effects of colonization and poverty.

Preventing infectious diseases and their sequelae requires a broad, multifaceted approach. A recent Canadian Medical Association Journal editorial identified a two-fold greater likelihood of dying from a preventable cause in Canada's poorer communities, including First Nations, than in the most affluent neighbourhoods (22). The authors referenced New Zealand's "well-being budget," which includes social determinants of health in the healthcare equation with substantial investment in Indigenous peoples, mental healthcare and poverty reduction (23). There is much Canada can learn from this approach. PSGN is a prime example of a syndemic disease, where particular environmental, economic, social, legal, colonial and political contexts mutually potentiate each other with harmful consequences (24).

Public health response to cases and outbreaks of reportable communicable diseases in remote northern First Nations communities in Ontario is typically led by ISC and implemented at the front line by federal community health nurses. Outbreak management involved collaboration with the local Indigenous health services organization, SLFNHA, and an infectious disease specialist and family physicians from Sioux Lookout, who are funded by the province. A pre-existing working relationship between all partner organizations and individual members, as well as knowledge of the realities of healthcare delivery in a remote and isolated setting, facilitated the rapid formation of an outbreak management team. The team brought together expertise and experience at all levels and enabled rigorous protocol development that "fit" the setting, and the development of appropriate educational material. Strong community support, by community leadership in particular, ensured community engagement and the successful screening of the paediatric population (95%) and contact tracing.

Strengths and limitations

Geography presents challenges for medical care in remote communities; access to paediatricians and nephrologists requires emergency medical evacuation for seriously ill patients or elective travel to Sioux Lookout and subsequent specialty referral to either Thunder Bay, Ontario, or Winnipeg, Manitoba. The absence of an existing protocol slowed the implementation of screening, which occurred eight weeks after the initial case presentation, and recovered or subclinical cases may have been missed. The absence of accurate prospective surveillance impedes early identification of outbreaks and underestimates the true burden of PSGN particularly in low-resource settings in Canada. Furthermore, limited capacity at the regional laboratory to store and process the potential number of swabs collected during screening prevented microbiologic confirmation of GAS-related skin sores among children and adults, as well as *emm*-typing of GAS strains.

Although no additional cases of PSGN were identified in the weeks following the intervention, the length of time between the declaration of the outbreak and the response, as well as the lack of accurate pre and post-outbreak surveillance data precludes any conclusions on the effectiveness of the intervention in curbing the outbreak. The strength of the initiative was the degree of community involvement and mobilization, engendering disease awareness and acknowledging the concerted interagency efforts to improve community health.

Conclusion

This first reported outbreak of PSGN in Canada occurred in a remote First Nations community in Ontario. We developed a community-based response protocol where collaboration between all partners was critical; this can serve as a model for the management of future PSGN outbreaks.

In the absence of mandatory reporting, the burden of PSGN remains underappreciated and could undermine upstream and downstream public health interventions. The public health management of PSGN requires the decolonization of legal, political, social and economic structures to allow rapid identification and management of outbreaks and primary prevention.

Authors' statement

JJ — Project administration, resources
NB — Conceptualization, data curation, investigation, project administration, writing–review & editing
RH — Conceptualization, data curation, investigation, project administration, writing–review & editing
JP — Data curation
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SM — Writing–original draft, writing–review & editing
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The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None.

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A public health response to a newly diagnosed case of hepatitis C associated with lapse in Infection Prevention and Control practices in a dental setting in Ontario, Canada

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Abstract

Background: Haliburton, Kawartha, Pine Ridge District Health Unit (HKPRDHU) investigated an exposure in an Ontario operatory dental facility related to a newly diagnosed hepatitis C virus (HCV) infection caused by a virus with an uncommon hepatitis C genotype. Lapses in Infection Prevention and Control (IPAC) and a second epidemiologically-linked case (with the same uncommon hepatitis C genotype) were identified, prompting a broader public health response and outbreak investigation.

Objectives: a) To describe the investigation of a newly diagnosed case of hepatitis C; b) to describe the broader public health response, and c) to address a paucity in the literature related to the risk of disease transmission in dental settings due to IPAC lapses.

Methods: A collaborative approach with two dental practices, public health partners and regulatory bodies was used. An IPAC inspection was completed to determine and mitigate the risk of blood borne infection transmission within the facilities. Appropriate protocols were followed for the IPAC investigation and public health response.

Results: The investigation identified a risk of potential HCV transmission between two cases linked to the same dental facility. There were no other epi-linked cases of HCV identified. Challenges included a lack of adherence to IPAC standards in one of the dental settings and awareness in the dental community regarding HCV transmission, coordination with regulatory bodies and public health experts and low uptake of laboratory testing by patients.

Conclusion: Despite the unique challenges associated with the investigation, HKPRDHU conducted a successful IPAC lapse investigation and public health response. Public health units need to maintain collaborative approaches with regulated health professionals, their regulatory bodies and public health experts.

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Keywords: IPAC, hepatitis C, dental, lapse, transmission

Introduction

The Haliburton, Kawartha, Pine Ridge District Health Unit (HKPRDHU) was notified through routine reporting of infectious diseases of a newly diagnosed case of hepatitis C virus (HCV) infection, genotype 2, in a client who had attended two different dental clinics (Facility A and Facility B) during the viral incubation period. The index case had no other reported current or past risk

factors related to HCV infection. The index case was defined as the newly confirmed case for this suspect outbreak investigation. An Infection Prevention and Control (IPAC) investigation was launched to determine the risk of HCV transmission in both dental settings. An HCV outbreak was not declared but this investigation was conducted as a potential outbreak. The objectives of this article are to 1) describe the investigation of a newly diagnosed case of HCV in a client who had potential exposures at two different community dental clinics; 2) describe the broader public health response; and 3) address a paucity in the literature related to the risk of disease transmission in dental clinics due to IPAC lapses.

Background

Hepatitis C virus infection is a reportable disease of public health significance (1). Dental standards of practice and IPAC best practices support the prevention of blood borne infection (BBI) transmission (2). Hepatitis C virus infection-related IPAC investigations in dental facilities associated with improper IPAC practices have occasionally been reported (3,4). Public health units in Ontario are required to investigate IPAC complaints and suspect IPAC lapses associated with an infectious disease transmission risk, adhering to infectious disease investigation principles and protocols (5).

Hepatitis C virus is a ribonucleic acid (RNA) virus belonging to the *Flaviviridae* family and has at least six major genotypes and approximately 100 subtypes. Genotype 1 is the predominant genotype in Canada (6), whereas genotype 2 accounts for approximately 10%–15% of Canadian HCV infections (7–9).

Reported case counts and rates of HCV in Ontario have increased in recent years. The newly reported rate of HCV in Ontario was 36.5 cases per 100,000 population in 2018, of which 22.5% were newly acquired infections (10). Hepatitis C virus is primarily transmitted by blood-to-blood contact and acute infection is often asymptomatic.

Methods

Review of the manuscript by privacy experts at HKPRDHU and Public Health Ontario (PHO) was performed.

The index case was diagnosed with HCV in December of year 0 and was reported to HKPRDHU in January of year 1. The HKPRDHU began an IPAC investigation in January of year 1 to determine if either of the two clinics attended by the HCV-positive client (Facility A or Facility B) could have been the source of HCV transmission. The index case received procedures at both facilities within the incubation period for HCV. Dental procedures included teeth cleaning at Facility A and, subsequently, a tooth extraction with intravenous medication at Facility B.

An IPAC inspection was completed at each facility to determine and mitigate the risk of BBI transmission within the facilities. Appropriate protocols (5,6,11) were followed for the IPAC investigation and public health response.

Infection Practices and Control inspections

Onsite inspections were conducted for both facilities to determine if there was evidence of BBI transmission risk through IPAC lapses. The inspection team included a public health inspector, a nurse certified in infection control and a dental hygienist. Other public health professionals assisted in inspections and visits with the facilities as needed. The inspection team utilized standardized PHO checklists (12,13) to guide the inspections. Applicable regulatory bodies were contacted by the investigation team prior to conducting inspections for any support required and were invited to participate.

Case definitions

An HCV outbreak is defined as the occurrence of two or more cases of HCV infection linked by time or a common exposure source or setting (6). The preliminary case definition in this investigation included both settings; however, the final case definition for the investigation was as follows: a laboratory-confirmed case of HCV genotype 2 who had dental procedures on or between November 10, year 0 to November 20, year 0 (three business days before, on the day of, or three business days after the day of the procedure of the index case at Facility B).

Case-finding

The index case (female, 50–60 years of age) had her dental procedure completed on November 15, year 0 and became symptomatic with acute HCV infection on December 9, year 0. Blood work detected elevated liver enzymes and HCV antibodies, with further blood work indicating detection of HCV RNA and genotype 2 HCV.

As a preliminary case-finding step in the investigation, an HCV case look-back exercise was conducted using the Integrated Public Health Information System (iPHIS) database to identify any confirmed cases of HCV reported January to December year 0 in the HKPRDHU's jurisdiction who had dental procedures at one of the clinics reported in the investigation, or any case who had identified a dental procedure as a risk factor. None were reported as being associated with Facility A or Facility B.

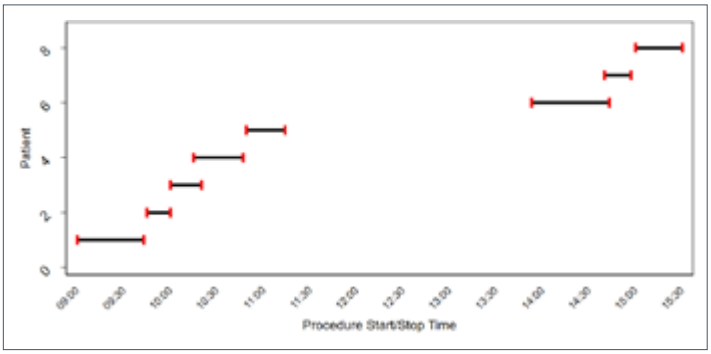
Patient rosters were collected from both dental facilities. The first roster was received from Facility B in April year 1. Case look-back regarding the patients listed was conducted by PHO using laboratory information system-based data. The identification of a second case (female, 70–80 years of age), previously positive (defined as any case reported historically to public health) in year 0 minus 10, with chronic HCV (genotype 2), prompted the continuation of case look-back at Facility B. This case was seen at Facility B on the same day and prior to the index case. In May year 1, a patient notification was initiated, to identify any new

HCV cases associated with this investigation. The notification was sent to patients seen at Facility B between three business days prior to the index case's procedure (November 10, year 0) and up until IPAC practices met standards (February 21, year 1).

Chart review

Following the second IPAC inspection of Facility B, a chart review was conducted for all patient procedures that took place on the day the index case and potential source case were seen. On the day of suspected transmission, chart documentation confirmed a single operatory room was used for all procedures completed on that day and overlapping appointments were scheduled and occurred (**Figure 1**).

Figure 1: Dental procedure start and end time[a] of the procedure at the dental Facility B[b]



[a] One appointment is missing from Figure 1 due to incomplete documentation related to an appointment that began at 13:00 hours but no end time had been documented
[b] This figure shows the procedure start and end time for each patient seen on the day both potential source case and index case underwent their dental procedure at Facility B in year 0, the day potential transmission may have happened

Public health response

Patients who had dental procedures conducted at Facility B between November 10, year 0 and February 21, year 1 were notified in writing of the potential risk of exposure to HCV, and were advised to get tested for HCV, hepatitis B and human immunodeficiency virus (HIV). A total of 264 initial notification letters signed by the Medical Officer of Health and the Dental Surgeon along with a blood test requisition were mailed out on May 25, year 1. For those patients who required a follow-up test, 167 additional notification letters were sent recommending repeat testing six months after the date of the patient's dental appointment. Phone calls were made to follow-up with each patient to complete an assessment and to provide health education using the Health Canada HCV fact sheet (14). A media release was also issued in consultation with the owner of Facility B, and an information page was created on the HKPRDHU's website.

Epidemiologic and statistical analyses

Laboratory results received were entered into an Excel database and were exported into Stata 15 (15) for further analysis to generate an epidemiological curve and summary.

An Excel spreadsheet was used for tracking patient follow-up as well as to log any community calls.

Laboratory investigation

Patient blood samples were requested to be sent to the PHO laboratory for testing. All serum specimens for HCV antibody were initially tested using the Abbott ARCHITECT anti-HCV antibody test. Negative results were reported with no further testing performed. Positive or indeterminate results underwent supplemental testing using a second validated assay (Siemens AD VIA Centaur HCV Assay or the Ortho Clinical Diagnostics VITROS HCV assay), and final HCV antibody results were based on the results of both tests. The HCV genotyping/subtyping were performed on all first-time HCV RNA-positive specimens with a viral load of 500 IU/mL or greater.

Results

Investigation findings ruled out Facility A as a possible source of the HCV infection. Investigation findings in Facility B supported proceeding with a case-finding exercise, including patient notification, to identify any possible epidemiologically linked cases related to the facility.

Considering the person, place and time perspectives, the same uncommon genotype identified; the second case identified had a high likelihood of being the source case. Unfortunately, further confirmatory subtype testing of the probable source case could not be conducted due to the demise of the case. The demise was unrelated to Facility B.

Infection Prevention and Control investigation of the facilities

Inspections were conducted focusing on reprocessing of dental and medical equipment. No evidence of a lapse in reprocessing practices supporting BBI transmission risk was observed during the inspection at Facility A. The inspection at Facility B identified issues with reprocessing practices that may have led to an IPAC lapse. A risk assessment was conducted in collaboration with PHO, which prompted a second inspection of Facility B to observe IPAC practices in relation to patient procedures, including medication administration practices.

During the initial inspection of Facility B, key issues identified included the following:

- Lack of physical separation between the dirty and clean areas for reprocessing
- Reassembly and over packaging of instruments prior to sterilization
- Inconsistent use of chemical indicators with every wrapped pack/pouch
- Routine non-availability of biological indicator results

- Release of instruments prior to completion of sterilization process
- No evidence of monitoring the physical parameters of the sterilizer for each cycle
- Incomplete record keeping
- Use of damaged instruments

During the second inspection of Facility B, key issues identified included the following:

- Medications were pre-drawn and not labelled for specific patients
- Inadequate use of personal protective equipment by staff during patient procedures
- Inconsistent pre-cleaning of dirty dental handpieces prior to sterilization
- Improper use of contaminated unpunctured carpules: unpunctured carpules were taken from a contaminated instrument tray and were used for a different patient (the carpules were "reprocessed" with a disinfectant wipe prior to use with a different patient)
- Retention of unused medication syringes from one procedure were subsequently used for additional procedures on other patients
- No staff dedicated to overseeing IPAC in the facility

The Health Unit issued the owner of Facility B orders to correct the IPAC deficiencies identified during the inspections, resulting in a temporary closure of Facility B. Follow-up inspections were completed by the Health Unit in collaboration with the dental regulatory body and all deficiencies were found to have been corrected.

Descriptive data analyses

Descriptive analyses of the initial and 6-month follow-up lab results were completed.

Figure 2 shows the number of laboratory results for HCV received for individuals who received dental procedures (by treatment date) at Facility B between November 10, year 0 and February 21, year 1. Out of the 264 patients notified, 259 required testing. The five patients from the patient roster who received only a dental consult did not require testing. Of the 259 who required testing, 231 completed the initial test (89.2%). Among the initial test results there were two previously positive HCV cases, in addition to the probable source case and index case. With the exception of the index case, three of these four cases had other risk factors for HCV infection. Twenty-eight patients did not have an initial lab test as recommended by the Health Unit.

Figure 3 shows the test results for patients (among the same patient cohort) for whom a 6-month follow-up HCV laboratory testing was required. The 6-month testing was not required for all patients: among the 145 notified patients, 99 completed their 6-month HCV laboratory test (68.2%). There were no positive test results.

Figure 2: Number of positive and negative hepatitis C laboratory testing results, by date of dental procedure, at dental Facility B at the time of the initial investigation

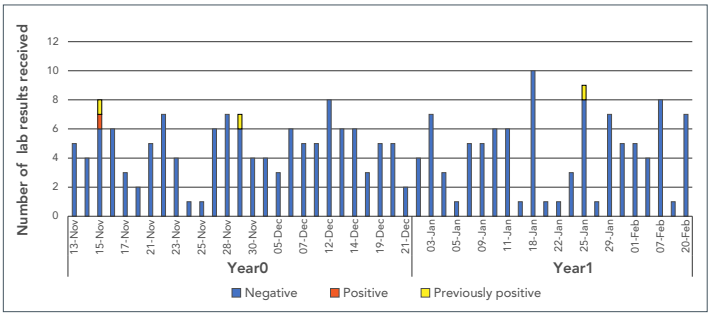
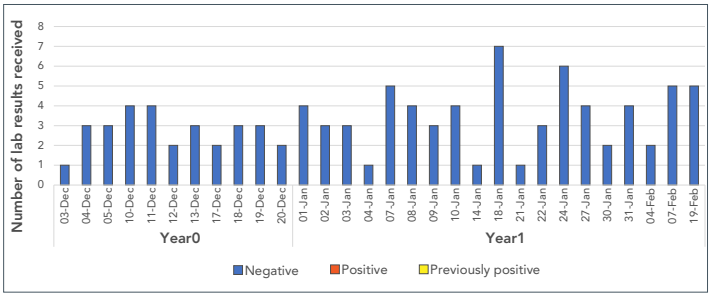


Figure 3: Number of positive and negative hepatitis C laboratory results at the 6-month follow-up, by date of dental procedure, at dental Facility B



Case management and public health resource allocation

Approximately 805 interventions (phone calls, faxes and email interactions) were conducted by public health nurses in the process of patient notification and related follow-up. An average of three interventions per patient was conducted (ranging from one to seven). The total staffing hours spent on HKPRDHU's response to this suspected outbreak was 1,187.5 hours.

Discussion

Our IPAC investigation led to a broader public health response. To our knowledge, this is the first time in Ontario that an IPAC investigation in a dental office was initiated based on a reported confirmed case of HCV with an uncommon genotype.

No evidence was found to suggest that Facility A was the source of the HCV infection. Through a collaborative consultation process, it was determined that a case look-back exercise would be completed for three days before, the day of, and three days after the index case was seen at Facility B. Based on the viability

of HCV on surfaces (16), and literature on HCV transmission through medication administration (17), a narrow search window of a few days around the index case's likely exposure was deemed appropriate.

Through our patient notification process, other than the probable source case and the epidemiologically-linked index case, no further related cases were identified. Although we were not able to confirm further transmission of HCV beyond the index case, the epidemiological and IPAC investigation findings provided us with enough evidence to support our hypothesis that HCV transmission may have occurred at Facility B between the source case and the index case.

At the time of this investigation, there was a perceived lack of awareness among the dental community regarding the potential for HCV transmission related to dental procedures. However, concern about the possible spread of BBIs and other diseases is growing (2), and our findings suggest that lapses in IPAC practices could result in the transmission of HCV. Further studies and publications of relevant investigations are needed to clearly understand the implications of HCV transmission during dental procedures, both due to direct transmission and through virus survival on surfaces.

Results from this IPAC investigation suggest that the lack of designated IPAC staff within Facility B led to inadequate IPAC procedures. One staff person assisting with dental procedures was also responsible for equipment reprocessing throughout the day, and Figure 1 shows how limited time there was between appointments. Guidelines recommend having a staff person designated to manage IPAC in each office (18), and reprocessing requires specific training and skills along with adequate time and staffing.

Issues discovered during the subsequent inspection of Facility B related to improper medication practices significantly increased the likelihood of BBI transmission (2,3). More emphasis on IPAC requirements for dental facilities is recommended to ensure community dental facilities are meeting IPAC standards. It is recommended that health units and regulatory bodies seek out opportunities to conduct proactive inspections and provide ongoing education and support to dental health professionals regarding IPAC practices (19,20), with emphasis on reprocessing and safe medication practices.

The development of best practice guidelines for IPAC inspections and investigations should help to support Ontario health units to streamline their approaches to IPAC investigations.

Limitations

Despite extensive patient follow-up, obtaining complete lab test results for all exposed patients through public notification was an identified challenge. While our initial test response rate was 89.2%, our 6-month follow-up test response rate dropped to 68.2%.

Previous studies have shown that HVC infection related to dental settings is rarely reported in the scientific literature (21). There is minimal scientific evidence of transmission of HCV in dental settings, which posed challenges to this investigation. This could be complicated by the fact that many newly infected individuals are asymptomatic, and if diagnosed subsequently, they cannot link their infection to the procedure.

Conclusion

The HKPRDHU supported the IPAC investigation and broader public health response related to a dental facility, with an epidemiologically-linked pair of HCV cases with an uncommon genotype. The public health measures included case follow-up, patient notification, communication of test results, provision of counseling and resources for patients and the public, recommendation of IPAC measures and collaboration with healthcare professionals. This investigation presented the Health Unit with unique challenges as it was complex, with multiple regulatory bodies involved. Community dental facilities need to be informed of the most current IPAC requirements to prevent risk of transmission of BBIs. Public health efforts will continue to focus on collaborating with and supporting our dental health professionals to mitigate any such risks to the public.

Authors' statement

CJ, VS, and DS — Conceived the analysis, analyzed the data, and drafted the manuscript
AMH and ALN — Contributed to the content of the manuscript and interpreted the data
GG, LM and DR — Reviewed the manuscript
EK, TM and RO — Contributed to laboratory content of the manuscript

All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None.

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COVID-19, protective measures and air travel

Source: Emerging Science Group of the Public Health Agency of Canada. Evidence Brief of the Evidence on the Risk of COVID-19 Transmission in Flight, Update 2; May 2021. Full report available from: phac.ocsoevidence-bcscdonneesprobantes.aspc@canada.ca

Background: Many changes have been implemented by airlines during the pandemic to reduce the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission during air travel. This evidence brief is an update on in-flight transmission of SARS-CoV-2 and the strategies developed to mitigate transmission during boarding, flight and disembarkation.

Methods: Twenty databases and key websites were searched for relevant reviews, peer-reviewed publications and pre-prints up to April 26, 2021. These articles were screened, potentially relevant citations were examined, and relevant data were extracted into evidence tables.

Results: Sixty-four studies were identified in total including 29 studies published between October 2020 and April 26, 2021.

- Most in-flight transmission events occurred on flights early in the pandemic when mandatory use of face masks in flights was not yet in place. Those seated within two rows of an index case were at higher risk of contracting coronavirus disease 2019 (COVID-19). Increasing the duration of a trip increased infection transmission risk. This increased transmission may be partially due to travellers removing their masks during meal service on longer flights.
- Combining multiple interventions was the most effective strategy for reducing transmission risk. Enhanced protective measures included the following: enhanced cleaning; universal use of face masks; hand hygiene; reduced flight capacity; physical distancing on embarkation and disembarkation; designated crew only areas; and quarantine areas for unwell passengers and crew.
- The risk of transmission in simulation models was higher on flights near capacity compared with those with empty middle seats that allowed for more physical distancing.
- Symptom checks were not always effective due to lack of compliance.
- Airplane ventilation systems quickly refresh cabin air, reducing opportunities for transmission. Environmental studies estimated that in-flight airborne particle numbers and mass were lower than those of other forms of transportation and of retail/grocery stores, restaurants, office spaces and homes.

Conclusion: Effective ventilation and layered interventions, in combination with enhanced protective measures, were shown to reduce the risk of COVID-19 transmission during air travel across the 64 studies included in this review. Future research needs to assess both the effects of the new variants on transmissibility risk and the vaccine status of both travellers and airline staff in mitigating risk.

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