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HEALTHCARE-ASSOCIATED INFECTIONS AND ANTIMICROBIAL RESISTANCE

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The cover photo represents a colony of *Staphylococcus aureus* bacteria—the most common cause of biofilm associated infections. Bacterial biofilms and nosocomial infections concept. This image was taken from Adobe Stock #514753655.

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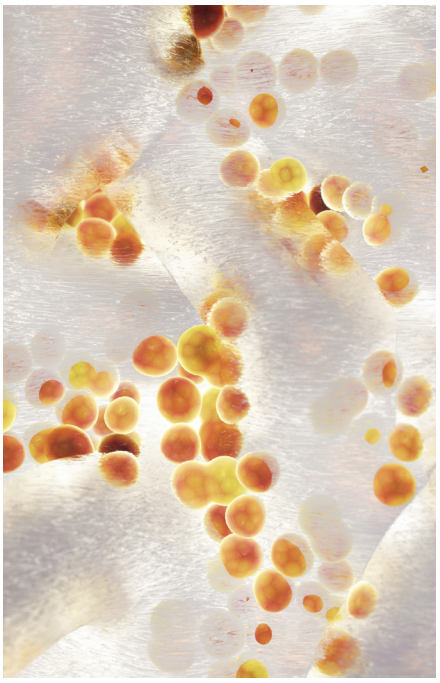

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Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: What could have happened?

Nicholas H Ogden[1]*, Patricia Turgeon[1], Aamir Fazil[1], Julia Clark[2], Vanessa Gabriele-Rivet[1], Theresa Tam[2], Victoria Ng[1]

Abstract

This study illustrates what may have happened, in terms of coronavirus disease 2019 (COVID-19) infections, hospitalizations and deaths in Canada, had public health measures not been used to control the COVID-19 epidemic, and had restrictions been lifted with low levels of vaccination, or no vaccination, of the Canadian population. The timeline of the epidemic in Canada, and the public health interventions used to control the epidemic, are reviewed. Comparisons against outcomes in other countries and counterfactual modelling illustrate the relative success of control of the epidemic in Canada. Together, these observations show that without the use of restrictive measures and without high levels of vaccination, Canada could have experienced substantially higher numbers of infections and hospitalizations and almost a million deaths.

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Keywords: COVID-19, Canada, vaccination, public health measures, counterfactual, modelling

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic because 1) it is highly transmissible from human to human and 2) at the time of the spillover to humans, there was no known immunity to the virus in the global human population. Pandemics end only when there is a sufficient proportion of the population immune (following infection and/or vaccination) to drive the causal pathogen to extinction or to some form of global endemic state that arises due to waning immunity in the human population and/or emergence of immune escape variants. The "wild type" (WT) variant that emerged in late 2019 had a basic reproduction number (R_0) of approximately two in high-income countries (i.e. on average, every infected person will infect two people in a population with no immunity and with no public health [PH] measures in place). With an R_0 of approximately two, and without vaccines, more than 50% of the population needs to acquire infection and become immune before the pandemic begins to come under control, and approximately 75% of the population has acquired the infection by the time the pandemic ends (1). Due to the relatively high virulence of SARS-CoV-2—an infection fatality rate approaching 1% and an infection-hospitalization rate approaching 10% (see public health measures section) and a lack of effective therapies and vaccines—the consequences for Canadians, and the Canadian health system, of unrestrained SARS-CoV-2 spread in 2020 were dire (**Table 1**) (1). Such a situation and resultant consequences were seen in Italy in early 2020 (2). In this article, the coronavirus disease 2019 (COVID-19) epidemic that occurred in Canada, impacted by public health measures and vaccination, is described and compared with outcomes in similar countries (the first section of the study), and then compared with possible alternative outcomes in Canada using modelling of counterfactual scenarios for different levels of vaccination and PH measures than those actually implemented (the second section of the study).

Table 1: Counterfactual total numbers of expected cases, hospitalizations and deaths from coronavirus disease 2019 from modelling compared to observed numbers

Outcome	Counterfactual without public health measures or vaccines	Observed as of April 24, 2022, with public health measures and vaccines
Cases	Up to 34 million[a]	3.3 million[a]
Hospitalizations	Up to 2 million	150,602
Deaths	Up to 800,000	38,783

[a] Reported cases mostly do not include approximately one-third infections that would be asymptomatic, which would mostly go undetected by surveillance. Many mild immunity-breakthrough cases during the Omicron waves are also not captured in surveillance data but are included in counterfactuals

Description of the evolving epidemic, public health measures and evidence

Evolving knowledge of the epidemiology of severe acute respiratory syndrome coronavirus 2

Key epidemiological variables for planning and modelling include estimates of the speed of transmission (particularly R_0) and of the severity of infections such as case or infection-hospitalization and fatality rates. Since early March 2020, the Public Health Agency of Canada has conducted daily literature searches to obtain the most up-to-date estimates of these values. Initially, estimates of R_0 (approximately 2–3) and case-hospitalization and fatality rates (10% and 1.2%, respectively) were obtained from studies in China (3). Given that transmission varies depending on the rate of contact between people (4), R_0 values vary depending on the country or region in which they are measured (5). Overall fatality rates are also dependent on the demography of the country studied, due to age-varying fatality rates (6). The estimated values of the key epidemiological variables varied over time. For example, it became evident that up to 30% of infections are asymptomatic and unlikely to be efficiently detected in surveillance systems (7). Furthermore, variants emerged that were increasingly transmissible (WT < Alpha < Delta < Omicron: R_0 increased from 2–3, to 3.5, to 5–7, and then to approximately 10) (8). Except for Omicron (9), these variants were also more virulent than the original WT strains (10,11).

Public health measures to control coronavirus disease 2019

Canadian pandemic planning that focused on a pandemic influenza virus as the most likely cause–response to its emergence would involve treatment of severely affected people with antivirals until the vaccine industry develops a modified influenza vaccine to control infection, as occurred during the H1N1 pandemic (12). In March 2020, Canada was faced with a highly transmissible and virulent pathogen (infection fatality rate [IFR] of approximately 1% compared to 0.04% for seasonal influenza) for which there was no natural immunity, no vaccine (or immediate prospect of a vaccine) and no effective antivirals. Therefore, in March 2020 and until vaccines were developed, the only available interventions were non-pharmaceutical interventions (NPIs or PH measures) that prevent transmission in the population, either by 1) reducing the frequency of contacts between infected and uninfected people, or 2) reducing the probability that transmission occurs when infected people come into contact (directly or indirectly) with uninfected people. The "frequency of contact-reducing" measures are those that target people known to be, or most likely to be, infected (testing to detect and then isolate cases, and contact tracing and quarantine of contacts) (13), and restrictive closures that aim to reduce contacts more widely in the population, which included closures of schools, "non-essential" businesses and leisure/recreation venues, teleworking, limitations on religious and private gatherings and curfews, etc. (14). The "transmission probability-reducing" measures are those personal measures such as distancing, hand-washing, screens and masks that limit spread of droplets (14,15) and enhancements to ventilation that reduce the density of aerosol-borne virions (16). In addition, international and domestic travel restrictions were used to limit introduction of infection into locations (e.g. the Canadian Territories and Atlantic provinces) to where it had not yet spread or was at low prevalence and slow the rate of introduction of infection to the population more generally. In this article, the use of these NPIs is tracked over time using a stringency index, which is a semi-quantitative combination of information from nine different PH interventions (school closure, workplace closure, cancelling public events, restrictions on gathering sizes, closure of public transport, stay at home requirements, restrictions on internal movement, restrictions on international travel and public information campaigns) obtained from the Government Response Tracker (17).

Medical counter measures—therapeutics and vaccines

According to the Pan-American Health Organization review on COVID-19 therapeutic options, hundreds of therapeutic options are being assessed through more than 10,000 studies (18). Among them, six have been approved to date in Canada (19). These include monoclonal antibodies that aim to prevent SARS-CoV-2 virus from infecting healthy cells. In Canada, four anti-SARS-CoV-2 spike protein monoclonal antibody therapies have been approved. Three monoclonal antibody therapies have been approved for treatment in people with a higher risk of being hospitalized or dying due to COVID-19, because of their age or medical conditions: casirivimab/imdevimab; bamlanivimab; and sotrovimab. In addition, cilgavima/tixagevimab (Evusheld™) is approved for the prevention of COVID-19 for people with weak immune systems, or for those whom vaccination is not recommended. Some of these drugs might lose efficacy against the Omicron variant (or particular sub-lineages) due to multiple mutations in the spike protein (20,21). Two antiviral drugs, nirmatrelvir/ritonavir (Paxlovid™) and remdesivir (Veklury®), which prevent virus replication, have been approved in Canada. Utilization of these antivirals is limited due to a combination of issues regarding efficacy, interactions with other pharmaceuticals and limitations on which and when COVID-19 patients should receive them. The development of vaccines has been a far greater success story; the mRNA vaccines have been highly effective against both infection and severe outcomes for WT, Alpha and Delta variants (22–24). Waning of immunity against infection became evident over a period of a few months following vaccination (although less so in Canada where most received an initial two doses at an extended three-month interval) (25,26). Some waning of immunity against severe outcomes is also thought to be occurring, but this appears to be very slow and to occur to a lesser extent, and a third vaccine

dose provides higher and more sustained protection (9,24,26,27). The emergence of the Omicron variant changed the landscape of the role of vaccines as a means of controlling the epidemic because of its capacity to significantly escape vaccine-induced immunity to infection, with vaccine effectiveness of two doses against infections falling from approximately 90% for the Delta variant of concern (VOC) to 30% or less for Omicron (24,26). Vaccines continue to protect against severe outcomes from infections with all variants, including Omicron, particularly after a third dose (24,26).

Chronology of the epidemic and public health measures in Canada

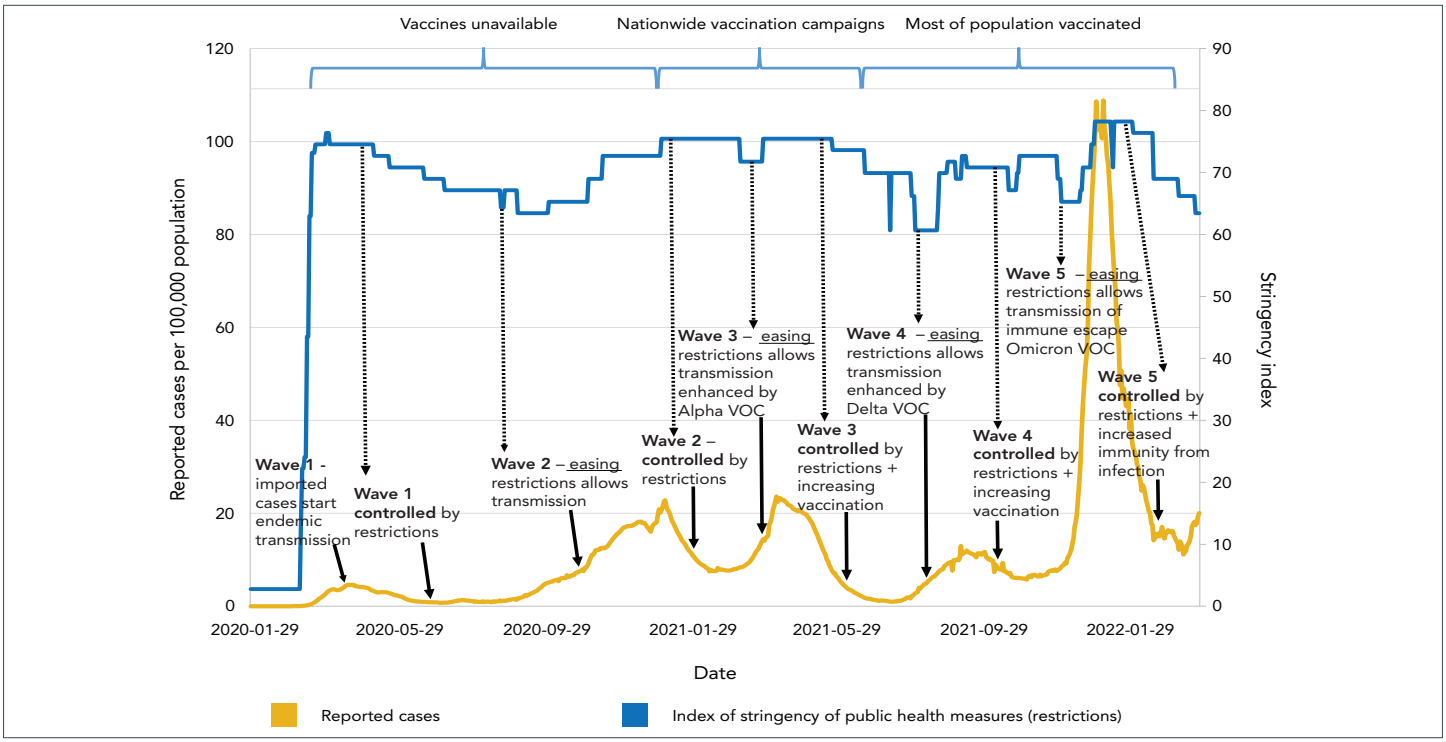
In the absence of vaccines, two possible control strategies were considered: 1) eradication and prevention of importation, often called the Zero-COVID strategy (see Alternative management of the epidemic section), largely achieved by the Atlantic provinces and Territories for most of the pandemic; or 2) suppression of transmission so that healthcare capacity was not exceeded (the strategy applied in the larger provinces for most of the pandemic). Having observed the severe impact of initially unrestrained SARS-CoV-2 transmission in Italy, when transmission within Canada was recognized and the first wave became evident an initial period of restrictive closures was instigated to pause the epidemic, enhance surveillance and allow alternative NPIs to be resourced and implemented (**Figure 1**). As cases in surveillance began to decline, modelling studies were conducted to estimate the proportions of cases detected and isolated and contacts traced and quarantined that were needed to control transmission if restrictions were to be lifted (13,28,29). After the lifting of restrictions in early summer 2020, transmission in the larger provinces began to resurge, indicating that test-and-trace capacity was not sufficient to control the epidemic, and eventually restrictions were reintroduced to safeguard healthcare capacity (30) (Figure 1). Throughout the pandemic, this cycle of lifting of restrictions followed by a resurgence of the epidemic followed by reintroduction of restrictions has been a feature of control in the larger provinces (Figure 1). The effect of lifting of restrictions on transmission was exacerbated by the invasion and spread of more transmissible VOCs; Alpha VOC emerging with wave three in spring 2021, and Delta VOC emerging with wave four in late summer/fall 2021. As the vaccines rolled out in 2021, it was hoped that restrictions could be lifted permanently, and many provinces made plans to do this when target percentages of the population were vaccinated. However, the emergence of the more transmissible Alpha and Delta variants meant that higher percentages of the population needed to be vaccinated to allow restrictions to be lifted. Consequently, reintroduction of restrictions was needed to control the waves caused by the Alpha and Delta variants. Most recently, the Omicron variant invaded and spread within Canada in late 2021/early 2022. This variant had characteristics of lower virulence but immune escape. These characteristics were expected from an evolutionary standpoint (31); the latter limiting the capacity of the vaccines to control transmission. The combination of high transmissibility and relatively low efficacy of two vaccine doses in preventing the transmission of this variant meant that, despite reduced virulence, healthcare capacity was again challenged and restrictions had to be reintroduced. It is likely that this variant has infected a high proportion of the Canadian population. In a questionnaire study, one-in-five Canadians reported COVID-19 infection in their household since December 1, 2021 (32), while in blood donors, seropositivity due to infection rose from 6.4% in December 2021 to 23.7% in mid-February 2022 (33). This unprecedented rate of infection during the Omicron wave, combined with the high percentage of the population with two or more vaccine doses (**Table 2**), has brought the immunity of the Canadian population to levels that, at the time of writing, are likely to mean that restrictions can be lifted long-term in Canada (and in many countries across the world), providing that another VOC, that escapes immunity and is virulent, does not emerge. The introduction of vaccines has meant that post-vaccination immunity, rather than simply post-infection immunity, will permit lifting of PH measures, while prior to sufficient levels of immunity being reached, restrictive PH measures have kept the epidemic under control and together this approach has limited severe outcomes and deaths (Table 1). Overall, comparisons of deaths in Canada to those in other high-income countries (**Figure 2**), selected because their levels of public health measures stringency and of vaccine uptake were somewhat different to those in Canada (Table 2), illustrate the relative effectiveness of the Canadian response.

Table 2: Cumulative numbers, as of April 20, 2022, of reported deaths due to coronavirus disease 2019 per 100,000 population in countries that did and did not adopt a Zero-COVID approach to managing the pandemic[a]

Country	Cumulative deaths per 100,000 population	Percent of the population vaccinated with two doses
Did not adopt a Zero-COVID approach[b]		
Canada	101.3	82%
Denmark	103.7	82%
Germany	159.3	77%
Sweden	183.1	75%
France	214.6	78%
United Kingdom	259.8	73%
Belgium	268.7	79%
United States	291.9	66%
Did adopt a Zero-COVID approach		
New Zealand	11.7	80%
Singapore	24.2	90%
Australia	26.7	83%
South Korea	42.2	87%

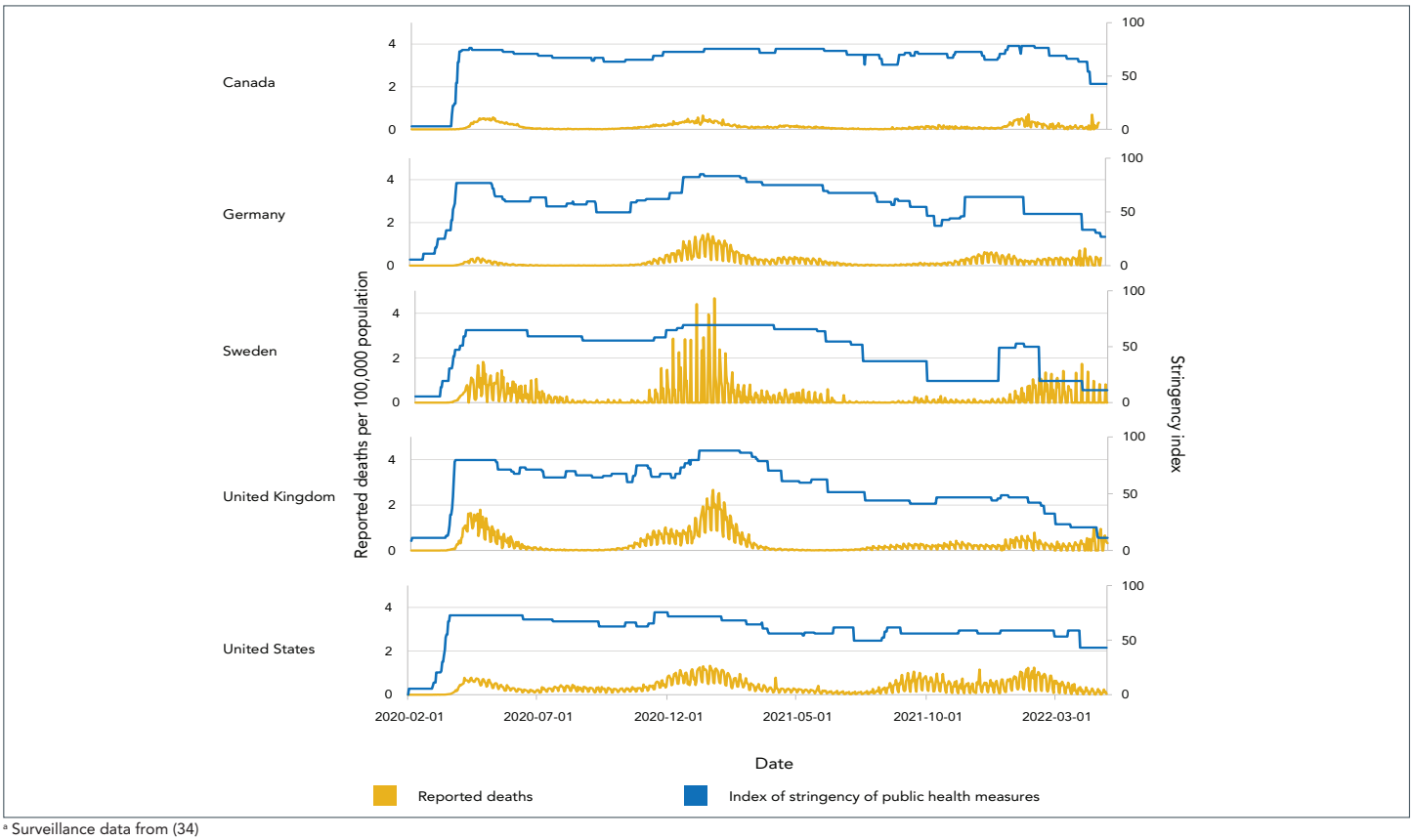
Abbreviation: COVID, coronavirus disease
[a] Percentage coverage with two vaccine doses is also shown. Data from (34)
[b] As a country as a whole

Figure 1: Chronology of the coronavirus disease 2019 epidemic, and public health responses, in Canada up to April 1, 2022[a]



Abbreviation: VOC, variant of concern
[a] The timeline is curtailed due to reductions in national surveillance

Figure 2: Comparison of the daily reported deaths per 100,000 population and stringency of public health measures in Canada and other high-income countries[a]



[a] Surveillance data from (34)

Alternative management of the epidemic

Early in the pandemic, it was suggested by some that COVID-19 might be no more serious than seasonal influenza; however, in high-income countries such as Canada, with often relatively older populations, the IFR for COVID-19 in non-immune people has been approximately 1% (10,11,35), while for seasonal influenza in the United States, the case-fatality rate is approximately 0.1% (36) with an IFR of approximately 0.04% accounting for an estimated 70% of influenza cases that are asymptomatic (37). Despite this, some advocates have proposed that management of the pandemic as occurred in Sweden, where management initially relied on voluntary efforts by the public rather than mandatory restrictions, would have been preferable. In fact, Canada has had a low death rate compared with other high-income countries, and a rate approximately a half of that reported in Sweden (Figure 2; Table 2). Counterfactual studies suggest that application of the approach taken in Sweden to countries such as the United Kingdom and Denmark would have resulted in approximately double the number of deaths seen in these countries (38). Early in the pandemic, some early, low estimates of COVID-19-specific death rates in North America, particularly for younger age groups, combined with concerns of unintended mental and physical health consequences of restrictive closures, led to the idea of applying restrictions ("shielding") only to the most vulnerable elderly age groups, allowing younger age groups to live a more normal life (39). It became clear, however, that this approach would require shielding to be extended to include much younger age groups (45 years of age and older), which would be impractical and still result in severe outcomes with high mortality rates in all age groups (40).

A Zero-COVID strategy was implemented by some countries (e.g. Australia, New Zealand, Singapore) and in the Atlantic Provinces and Territories of Canada, earlier in the pandemic. The objective of the strategy is to completely stop transmission by aggressively using PH measures such as mass testing, contact tracing, border measures and, when necessary, lockdowns, to eliminate new infections and allow a return to normal economic and social activities. Those jurisdictions and countries that adopted this approach were, for the most part, those with limited spread of SARS-CoV-2 when responses began, and with opportunities (e.g. for the island states of Australia and New Zealand) for ease of control of imported cases. As the Omicron variant emerged, most of these countries experienced major outbreaks and have now abandoned this approach; however, this approach allowed vaccination levels in their populations to rise to high levels before significant transmission occurred, therefore limiting the burden on the health system and the numbers of deaths that occurred (Table 2).

Counterfactual modelling

Methods

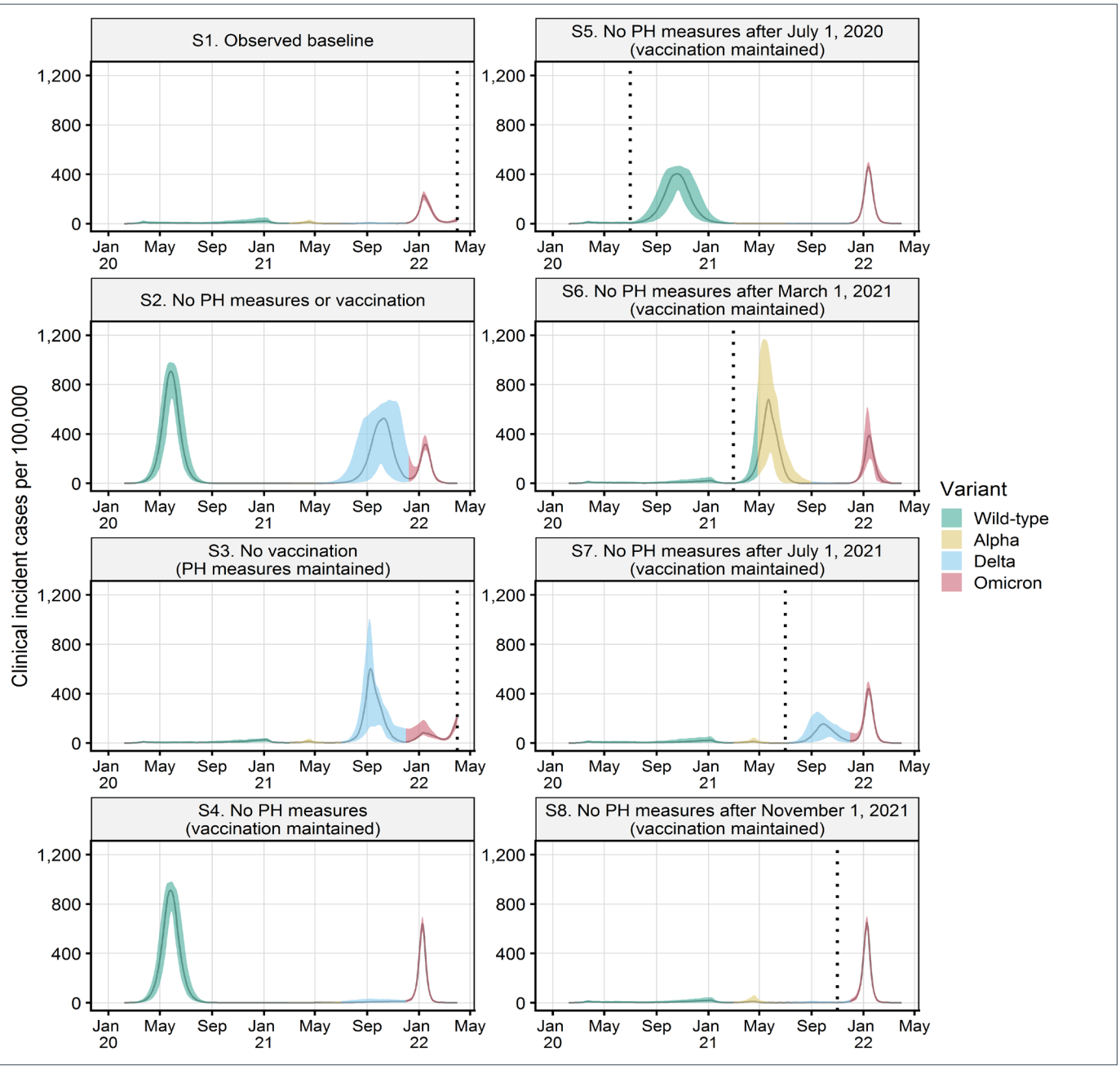
A modelling study is presented to illustrate the importance of both PH measures and vaccination in limiting severe COVID-19 outcomes and deaths in Canada. The study used an agent-based model of a representative 100,000 individuals of the Canadian population (28,41). The model was modified to simulate the epidemic in Canada up to the time of writing (April 2022). The model incorporated simulation of the implementation and lifting of the PH measures used (Figure 1), vaccination rollout (first, second and third doses by age groups and priority groups), invasion of the Alpha, Delta and then Omicron BA.1 variants, vaccine effectiveness against infections and severe outcomes specific to each variant, protection against reinfections of the same or a different variant and waning of immunity following vaccination and natural infection. Many parameter values were obtained from the literature, but some were obtained by fitting the model to surveillance and hospitalization data (full details are provided in **Supplemental material**). There were eight scenarios including the baseline (S1), in which an approximation of the actual implementation/lifting of PH measures (including a final complete lifting in March 2022) and vaccination of the population were modelled; and then seven counterfactual scenarios: 1) S2: a worst-case scenario in which no PH measures or vaccinations were implemented; 2) S3: a scenario in which the PH measures were implemented but there were no vaccinations; 3) S4: a scenario in which there were no PH measures but vaccines were administered as observed; and four scenarios in which vaccines were administered as observed and PH measures were also implemented as observed but were lifted early on 4) S5: July 1, 2020 (after the first wave); 5) S6: March 1, 2021 (after the second wave); 6) S7: July 1, 2021 (after the third, combined WT and Alpha variant wave); and 7) S8: November 1, 2021 (after the fourth, Delta variant wave).

Results

The simulations show that the combination of PH measures and vaccinations that occurred in Canada resulted in far fewer infections, hospitalizations and deaths than in the counterfactual scenarios in which other decisions were made on rollout of vaccines and/or implementation of PH measures (**Figure 3** and **Figure 4**; **Table 3**). In the absence of PH measures and vaccinations (S2), a very large initial wave far exceeded hospital capacity as did a subsequent large Delta-driven wave as immunity waned, and this resulted in a very high number of hospitalizations and deaths (Table 1). In the absence of vaccination, but with PH measures maintained (S3), a very large Delta-driven wave occurred. In the absence of PH measures but with vaccination in place (S4), similar to S2, a very large initial wave in hospitalization would have been observed but the vaccination rollout would have prevented a subsequent Delta-driven wave from occurring. Early lifting of PH measures (S5 to S8) resulted in the resurgence of the epidemic at various points in time corresponding to the timing of lifting, with healthcare

capacity being exceeded. The earlier measures were lifted, the worse were the outcomes in terms of hospitalizations and deaths. Lifting after the second wave (S6) coincided with the introduction of a more transmissible and virulent Alpha strain, causing higher hospitalizations and deaths than lifting earlier after the first wave when the WT strain was dominant (S5), whereas lifting after the third wave (S7) caused fewer hospitalizations and deaths despite a more virulent Delta strain in circulation due to higher vaccination coverage. As Omicron is less virulent than all the other strains that have emerged in Canada, a lifting after the fourth wave (S8) would have caused a high number of infections but considerably lower number of hospitalizations compared with the other counterfactual scenarios (Figure 3 and Figure 4). The baseline scenario (S1), modelled on an approximation of actual vaccination and PH measures in Canada, was the only scenario in which hospitalizations were consistently below the hospital bed threshold.

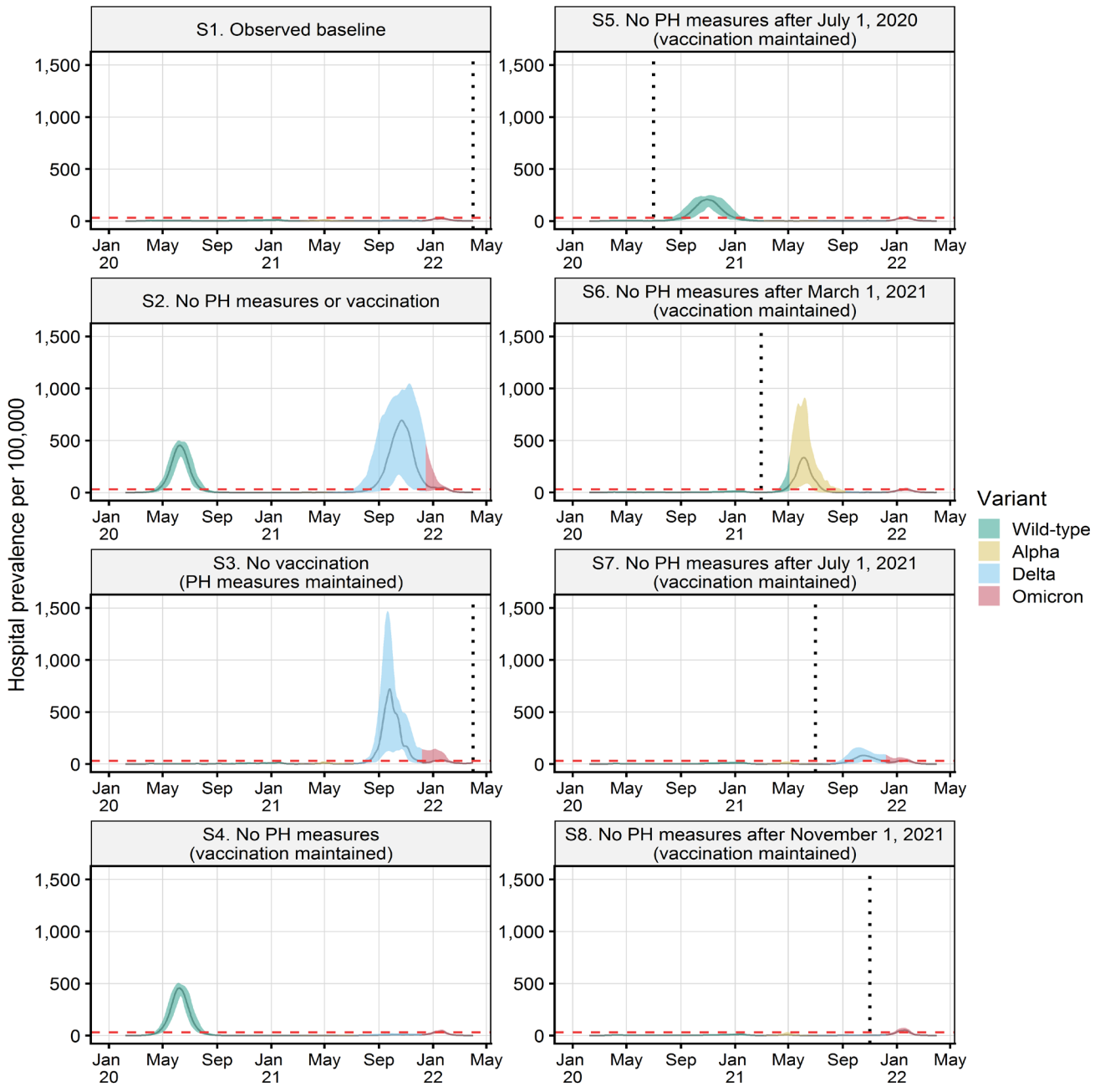
Figure 3: Number of symptomatic infections estimated for seven counterfactual scenarios with different combinations of public health measures and vaccinations to those in the observed baseline scenario[a]



Abbreviation: PH, public health

[a] Vertical dotted lines indicate the timing of lifting of all public health measures in the baseline, the no-vaccination scenario and four counterfactual scenarios with progressive PH measures lifting. Graphs show the median and 95 percentile values for 100 model runs. The dominant SARS-CoV-2 variant (i.e. more than 50% of cases) for each time period is shown

Figure 4: Number of hospitalized cases estimated for seven counterfactual scenarios with different combinations of public health measures and vaccinations to those in the observed baseline scenario[a]



Abbreviation: PH, public health

[a] Vertical dotted lines indicate the timing of lifting of all public health measures in the baseline, the no-vaccination scenario and four counterfactual scenarios with progressive PH measures lifting. Graphs show the median and 95 percentile values for 100 model runs. The dominant SARS-CoV-2 variant (i.e. more than 50% of cases) for each time period is shown. The red horizontal dashed line shows estimated hospital capacity in Canada

Table 3: Key metrics (median and 95 percentiles for 100 model runs) of cases[a], hospitalizations and deaths estimated by the agent-based model simulations for the observed baseline and seven counterfactual scenarios for the period February 7, 2020 to March 31, 2022

Transmission control methods in the scenarios and outputs of modelling	Counterfactual scenarios							
	S1 Observed baseline	S2 No PH measures or vaccination	S3 No vaccination (PH measures maintained)	S4 No PH measures (vaccination maintained)	S5 No PH measures after July 1, 2020 (vaccination maintained)	S6 No PH measures after March 1, 2021 (vaccination maintained)	S7 No PH measures after July 1, 2021 (vaccination maintained)	S8 No PH measures after November 1, 2021 (vaccination maintained)
Vaccination rollout	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Lifting of PH measures	March 31, 2022	No PH measures	March 31, 2022	No PH measures	July 1, 2020	March 1, 2021	July 1, 2021	November 1, 2021
Clinical cases per 100,000[b]	12,001 (10,028–15,306)	90,154 (89,299–91,277)	38,858 (29,438–43,633)	59,574 (58,509–61,940)	44,746 (43,783–45,556)	47,472 (39,046–52,298)	25,368 (22,115–27,848)	17,983 (16,139–20,842)
Asymptomatic cases per 100,000[b]	47,638 (44,775–51,455)	113,752 (110,854–117,951)	58,754 (52,099–60,876)	108,293 (107,001–111,504)	90,302 (89,493–91,334)	92,660 (74,662–103,826)	84,869 (81,558–87,347)	81,098 (79,752–83,044)
Hospitalizations per 100,000	256 (182–387)	4,715 (4,572–4,918)	2,529 (1,541–3,225)	2,246 (2,136–2,348)	1,619 (1,541–1,722)	1,469 (871–2,150)	601 (500–710)	324 (240–438)
ICU admissions per 100,000	74 (48–111)	1,428 (1,360–1,489)	779 (455–988)	681 (626–724)	498 (452–557)	446 (249–681)	174 (140–212)	93 (66–134)
Deaths per 100,000	48 (32–76)	2,034 (1,938–2,115)	947 (563–1,301)	849 (803–899)	583 (538–634)	350 (182–603)	131 (101–163)	70 (47–92)

Abbreviations: ICU, intensive care unit; PH, public health
[a] Cases include reinfections and vaccine breakthrough cases, which occurred particularly during the Omicron-driven waves
[b] Cases are higher than the model population (100,000) in some scenarios due to reinfections in the population

Discussion

The review and analyses here underline the possibly catastrophic outcomes of the epidemic in Canada, had a combination of non-pharmaceutical PH measures and vaccinations not been implemented to control it. Public health measures, particularly measures that restricted contact between people, maintained control of SARS-CoV-2 transmission until levels of immunity in the population from a combination of high levels of vaccination and infections were sufficient to allow restrictions to be lifted. The relative effectiveness of the response to COVID-19 in Canada is illustrated by the substantially fewer deaths that have occurred in Canada compared with other similar countries. The success of the response is also illustrated by the modelled counterfactual scenarios. While non-pharmaceutical PH measures and the vaccination rollout individually contributed to minimizing severe outcomes, counterfactual modelling suggests that it was the combination of the two that limited morbidity and mortality in the Canadian population. Failure to have implemented restrictions early in the pandemic, and lifting of these PH measures too early (before a sufficient proportion of the population became immune due to vaccinations), may have resulted in catastrophic outcomes in terms of deaths and an overwhelmed health system.

Limitations

Limitations of this study include the likely under-ascertainment of cases, hospitalizations and deaths in surveillance data, and the use of a model that simulated the epidemic in an "average Canadian community" without accounting for regional variations in demography, contact rates and sensitivity to infection. However, the model outcomes appear conservative projecting circa 4.5 million cases for Canada as a whole in the "observed baseline" scenario (suggesting, with 3.3 million reported cases, an optimistic 73% ascertainment rate) but 18,000 deaths compared to the 38,000 observed. The model did not consider outbreaks with high transmission and high case fatality rates in health care and long-term care settings (28); therefore, infections, hospitalizations and deaths were underestimated in the counterfactual scenarios.

Conclusion

Re-analysis of the COVID-19 pandemic and public health responses will be common in the coming months and years.

While the response to COVID-19 in Canada may have been relatively effective, it was not perfect, and further studies, including more regional analyses for Canada, will be needed to learn from this pandemic. This will require examination of the broader impacts of COVID-19 (particularly Long COVID), the range of public health measures and unintended consequences of public health measures on health.

Authors' statement

NHO — Manuscript conception and writing
PT — Manuscript writing
AF — Manuscript writing
JC — Manuscript writing
VG-R — Manuscript writing, modelling
TT — Manuscript writing
VN — Modelling, manuscript writing

Competing interest

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

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Laboratory-acquired infections in Canada from 2016 to 2021

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Abstract

Laboratory incidents that result in an exposure to human pathogens and toxins can lead to laboratory-acquired infections or intoxications (LAIs). These infections can pose a risk to the public as well, should person-to-person transmission occur outside the laboratory after an LAI. Understanding factors that contribute to exposure incidents involving LAIs may contribute to ways to mitigate future occurrences to ensure the safety of laboratory workers and the communities in which they work. This paper describes nine exposure incidents resulting in LAIs that occurred in Canada from 2016 to 2021. Of the nine cases, most affected people had both high level of education and years of experience working with pathogens. There were varying laboratory types and activities where *Salmonella* spp. and *Escherichia coli* accounted for six out of the nine cases. Procedural issues, personal protective equipment issues and sharp-related incidents were the most cited root causes. From this information, it is clear that regular training (even of experienced staff), clear and accurate standard operating procedures, proper hygiene (especially with *Salmonella* spp. and *E. coli*) and recognition of exposure incidents at the time of occurrence are important in preventing future LAIs. Only regulated laboratories working with risk group 2 or higher organisms are required to report exposures and LAIs to the Laboratory Incident Notification Canada surveillance system. Because of the small sample size, results and inferences are based on descriptive analyses only.

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Introduction

Working with human pathogens and toxins (HPTs) in a laboratory setting is an inherently risky activity, particularly when working with higher-risk group pathogens and toxins. While safety protocols, practices and equipment are all utilized to keep laboratory workers safe, accidents, failures or other incidents can still occur. Incidents that result in an exposure to HPTs can lead to laboratory-acquired infections or intoxications (LAIs). These infections can pose a risk to the public as well, should person-to-person transmission occur outside the laboratory after a LAI.

The Public Health Agency of Canada's Centre for Biosecurity contributes to the Agency's efforts to protect the health, safety and security of the Canadian public against the risks posed by human pathogens and toxins. The Centre for Biosecurity launched the Laboratory Incident Notification Canada (LINC) surveillance system in late 2015. Beginning in 2016, licensed facilities are required to submit reports to LINC detailing any laboratory incidents involving HPTs of risk group (RG) 2 or higher, in accordance with the *Human Pathogens and Toxins Act*. Reports submitted to LINC may describe exposure or non-exposure incidents, where exposures are defined as an incident that could have resulted in intoxication/infection or has resulted in a suspected or confirmed LAI (1,2). A more general overview of LINC, including detailed descriptions of the incidents reported to LINC, is available in the annual reports (2016 to present) (3–7).

A search of the literature found nine LAI case reports that highlight key risk factors (none were from Canada). Results from one study indicated that the lack of adherence to standard biosafety procedures was a major factor in LAIs (8). Several studies found that improper use of personal protective equipment (PPE) was associated with the occurrence of LAIs (8–12). Additionally, the lack of respiratory PPE was the most common risk factor among 16 cases (11). Other risk factors identified in the literature include improper use of laboratory equipment (13), working with needles (14–16), lack of hygienic practices (7,12) and insufficiently trained staff (13,14). Among the studies reviewed, the most common pathogens involved in LAIs were *Salmonella* spp., *Brucella* spp., *Staphylococcus aureus*, *Escherichia coli*, *Neisseria meningitidis* and *Vaccinia virus*. Additionally, recent analysis of LINC (*forthcoming*) exposure reports found that standard operating procedure (SOP)-related issues were a significant risk factor to the overall increase in exposure events in Canadian laboratories (15).

This study describes nine cases of LAIs that occurred in Canada between 2016 and 2021. Data were extracted from the LINC surveillance system for all confirmed LAI reports. The objective of this study is to describe the LAIs and to identify potential risk factors associated with LAIs in Canada.

Results

Between 2016 and 2021, nine LAIs were reported to LINC. During the same period, 322 exposure incidents that could have resulted, or did result, in LAIs were reported to LINC. Multiple individuals can be exposed during a single incident, and in total, 668 people were exposed in the 322 incidents. Therefore, 1.3% of people exposed ended up developing an LAI (and less than 3% of incidents).

All nine LAIs occurred in technicians, students and laboratory aids (**Table 1**). Most of the LAIs occurred in people who had either a high level of education or many years of laboratory experience; and sometimes both. The median number of years of experience was six years for the eight people for whom the information is known. None of these LAIs led to secondary infections.

Additionally, there were a range of laboratory types involved (Table 1), indicating that LAIs can occur in different settings. The most common laboratory activities associated with these LAIs were microbiology (n=5), followed by animal work (n=2), microscopy (n=1) and maintenance (n=1).

Consistent with previously published articles, the agents associated with the nine LAIs were *Salmonella* spp. (n=4), *E. coli* (n=2), *S. aureus* (n=1), *Brucella* spp. (n=1) and *Vaccinia virus* (n=1).

Of the two animal-related incidents, both LAIs resulted from inoculation via sharps-related exposure. The other seven incidents were a mix of ingestion (n=5), absorption (n=1) and inhalation (n=1). In addition to the two sharps-related incidents, the other commonly cited root causes were procedural, PPE, equipment or spill-related.

Of the nine confirmed LAIs, only four exposure incidents were recognized as such at the time of the event. The other five exposure incidents were retrospectively identified, after the workers became ill.

Of the four LAIs where the exposure incident was recognized at the time, two people received immediate first aid attention and three of the four received prophylaxis. In addition, three of four people consulted a medical professional within seven days of the exposure. Unfortunately, even with these preventative interventions, three of the four people became acutely ill, while the fourth tested positive for seroconversion (indicating an asymptomatic infection).

Of the five LAIs that stemmed from unrecognized exposure events, all five became acutely ill and sought medical and/or occupational health consultations, after which an LAI was identified and reported to LINC. These illnesses led to investigations into whether the illnesses were related to exposure to HPTs. Exposure incidents that led to the LAIs were then retroactively identified where possible, working backwards from the date of illness using the incubation period of the HPT.

Three of nine people received drug treatment for their illness. While the recovery period varied, it often took more than a week (n=5).

Discussion

The primary objectives for this study were to describe the nine LAIs that have occurred in Canada between 2016 and 2021 and to identify potential risk factors associated with these incidents. Because of the small sample size, results and inferences are based on descriptive analyses only. In addition, only regulated laboratories working with RG2 or higher organisms are required to report exposures and LAIs to LINC. Exposures and LAIs stemming from work with primary specimens (such as blood or other samples from patients) are not required to be reported to LINC, although it is strongly recommended. All nine LAIs described here are from mandatory reporting situations.

Most of the people with LAIs in this study had either a high level of education, many years of laboratory experience, or both. This suggests that inexperience or lower levels of education may not be a risk factor for LAIs. Regular training and reviewing of standard operating procedures with staff, both new and experienced, is key to preventing exposure incidents and LAIs.

Additionally, the range of laboratory types (academic, hospital and government) and activity types (microbiology, animal care, etc.) reported suggest that work in any laboratory type and any laboratory activity could lead to a LAI.

As seen in the literature, *Salmonella* spp. and *E. coli* were the most common HPTs involved in LAIs. Further investigation into the reasons and mechanisms behind the association of these two pathogens and LAIs is recommended.

Many underlying causes are mentioned amongst the nine reports, but procedural issues are cited in most of them. Having detailed, accurate and up-to-date SOPs in place is critical, as is the ongoing training and refreshing of staff on the proper SOPs for their activities. In addition, the use of appropriate PPE is always critical to protect laboratory personnel from infections. Procedural issues may include a lack of an appropriate SOP, following a SOP inappropriate for the activity or failing to follow the SOP as written. The PPE-related incidents may include lack of PPE, misuse of PPE or a failure or malfunction of the PPE.

Table 1: Descriptions of each of the nine confirmed laboratory-acquired infections in the Laboratory Incident Notification Canada surveillance system, Canada, 2016–2021

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Role	Student	Technician	Technician	Technician	Technician	Technician	Technician	Aide	Student
Highest degree	Master's Degree	Technical diploma	Bachelor's degree	Bachelor's degree	Bachelor's degree	Technical diploma	Bachelor's degree	High School diploma	Bachelor's degree
Years of experience	Fewer than 5	Fewer than 5	Unknown	Fewer than 5	10–20	5–10	5–10	20 or more	Fewer than 5
Laboratory type	Academic	Hospital	Government Public Health	Hospital	Government Public Health	Hospital	Academic	Hospital	Government (other)
Main work activity	*In vivo* animal work	Micro-biology	Micro-scopy	Micro-biology	Micro-biology	Micro-biology	Animal care	Maintenance	Micro-biology
Biological agent	*Staphylococcus aureus*	*Salmonella* spp.	*Salmonella* spp.	*Brucella* spp.	*Salmonella* spp.	*E. coli*	*Vaccinia virus*	*Salmonella* spp.	*E. coli*
Risk group	RG2	RG2	RG2	RG2 or RG3	RG2	RG2	RG2	RG2	RG2
Exposure route	Inoculation	Ingestion (presumed)	Ingestion	Inhalation	Ingestion	Ingestion	Inoculation	Ingestion	Absorption
Exposure cause	Sharps	Unknown	Equipment, PPE, procedural	PPE, procedural	Unknown	Procedural	Sharps, procedural	PPE, Procedural	Spill, equipment, procedural
Exposure recognized at time?	Yes	No	No	Yes	No	No	Yes	No	Yes
Immediate first aid?	Yes	N/A	N/A	No	N/A	N/A	Yes	N/A	No
Acute illness	Yes	Yes	Yes	No (sero-conversion)	Yes	Yes	Yes	Yes	Yes
Medical consult (fewer than 8 days)	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Medical consult (8 or more days)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Occupational health consult (fewer than 8 days)	No	Yes	No	Yes	No	Yes	Yes	No	No
Occupational health consult (8 or more days)	Yes	Yes	No	No	No	Yes	No	Yes	No
Prophylaxis	Yes	N/A	N/A	Yes	N/A	N/A	Yes	N/A	No
Drug treatment	Yes	No	Yes	No	No	No	No	Yes	No
Recovery time	Unknown	8–14 days	14 or more days	N/A	8–14 days	Fewer than 8 days	Unknown	14 or more days	8–14 days

Similarly, equipment issues can include misuse of equipment or a failure or malfunction of the equipment.

It is important to recognize and respond to exposure events when they occur in order to prevent LAIs and community transmission. Of the nice LAIs identified, fewer than half of the exposure incidents were recognized as such at the time of the event. This is problematic, as failure to identify exposures at the time of the incident does not enable implementation of recommended procedures. Laboratories have specific procedures in place to respond to accidental exposures, including first aid, immediate medical consultation, prophylaxis and measures to prevent spread should a LAI occur (such as quarantine). When an exposure is overlooked, none of these preventative actions can take place, increasing the likelihood that an LAI will occur. Furthermore, these events are then more likely to lead to community transmission as a person may be contagious without knowing until they develop signs and symptoms of an LAI.

Conclusion

There have been nine reported LAIs in Canada in the last five and a half years, none of which led to community spread. *Salmonella* spp. and *E. coli* are two HPTs of concern when it comes to LAIs. It is important for laboratories to train all staff on the proper procedures for their duties, with regular retraining, including updates as soon as possible when procedures change. In addition, exposure incidents should always be reported immediately, with guidelines for actions after exposure followed thoroughly to prevent LAIs and community spread.

Authors' statement

MEJ — Methodology, investigation, writing–original draft, review and editing
MS — Writing–original draft, review and editing
RE — Conceptualization, methodology, writing–original draft, review and editing, supervision
SBA — Review and editing

Competing interests

None.

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Healthcare-associated infections and antimicrobial resistance in Canadian acute care hospitals, 2016–2020

Canadian Nosocomial Infection Surveillance Program[1]*

Abstract

Background: Canadians experience increased morbidity, mortality and healthcare costs due to healthcare-associated infections (HAIs) and antimicrobial resistance (AMR). The Canadian Nosocomial Infection Surveillance Program (CNISP) collects and utilizes epidemiologic and laboratory surveillance data to inform infection prevention and control and antimicrobial stewardship programs and policies. The objective of this report is to describe the epidemiologic and laboratory characteristics and trends of HAIs and AMR from 2016 to 2020 using surveillance data provided by Canadian hospitals participating in the CNISP.

Methods: Data were collected from 87 Canadian sentinel acute care hospitals between January 1, 2016, and December 31, 2020, for *Clostridioides difficile* infection (CDI), methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections, vancomycin-resistant *Enterococci* (VRE) bloodstream infections and carbapenemase-producing *Enterobacterales* (CPE). Case counts, rates, outcome data, molecular characterization and antimicrobial resistance profiles are presented.

Results: From 2016 to 2020, increases in rates per 10,000 patient days were observed for MRSA bloodstream infections (33%; 0.84–1.12, p=0.037), VRE bloodstream infections (72%; 0.18–0.31, p=0.327), and CPE infections (67%, 0.03–0.05, p=0.117) and colonizations (86%, 0.14–0.26, p=0.050); however, CDI rates decreased by 8.5% between 2016 and 2020 (from 5.77–5.28, p=0.050).

Conclusion: Surveillance findings from a national network of Canadian acute care hospitals indicate that rates of MRSA and VRE bloodstream infections, CPE infections and colonizations have increased substantially between 2016 and 2020 while rates of CDI have decreased. The collection of detailed, standardized surveillance data and the consistent application of infection prevention and control practices in acute care hospitals are critical in reducing the burden of HAIs and AMR infections in Canada. Further investigations into the impact of coronavirus disease 2019 and associated public health measures are underway.

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Introduction

Healthcare-associated infections (HAIs), including those caused by antimicrobial resistant organisms (AROs), are an ongoing threat to the health and safety of patients. The morbidity and mortality caused by HAIs place significant burden on patients and healthcare resources (1–5). A 2017 Canadian point-prevalence survey estimated that 7.9% of patients had at least one HAI; results comparable to those reported by the European Centre for Disease Prevention and Control where HAI prevalence among tertiary hospitals was estimated to be 7.1% (6,7). A similar 2015 point-prevalence study in the United States estimated that there were 687,000 HAIs in acute care hospitals (8). During the coronavirus disease 2019 (COVID-19) pandemic that was declared on March 11, 2020 (9), changes in hospital infection prevention and control and antimicrobial stewardship efforts may have had impacts on rates of HAIs and AMR (10).

Antimicrobial resistance (AMR) has been recognized as a growing danger to global health (11). Worldwide, an estimated 700,000 people die of resistant infections each year (12). In Canada, it is estimated that 1 in 19 deaths are attributable to resistant bacterial infections. The cost of AMR to the healthcare sector is $1.4 billion per year and is projected to increase to $7.6 billion per year by 2050 (13). Global surveillance, improved antibiotic stewardship, enhanced infection prevention and control and public awareness are vital to curbing existing and emerging infections and identifying patterns of antimicrobial resistance.

In Canada, the Public Health Agency of Canada collects national data on various HAIs and AMR through the Canadian Nosocomial Infection Surveillance Program (CNISP). Established in 1994, CNISP is a collaboration between the Public Health Agency of Canada, the Association of Medical Microbiology and Infectious Disease Canada and sentinel hospitals from across Canada. The goal of CNISP is to facilitate and inform the prevention, control and reduction of HAIs and AROs in Canadian acute care hospitals through active surveillance and reporting.

Consistent with the World Health Organization's core components of infection prevention and control (10), CNISP performs consistent, standardized surveillance to reliably estimate HAI burden, establish benchmark rates for national and international comparison, identify potential risk factors and assess and inform specific interventions to improve patient health outcomes. Data provided by CNISP directly supports the collaborative goals outlined in the 2017 Pan-Canadian Framework for Action for tackling antimicrobial resistance and antimicrobial use (11).

In this report, we describe the most recent HAI and AMR surveillance data collected from CNISP participating hospitals between 2016 and 2020.

Methods

Design

The Canadian Nosocomial Infection Surveillance Program conducts prospective, sentinel surveillance for HAIs (including AROs).

Case definitions

Standardized case definitions for healthcare-associated (HA) and community-associated (CA) infections were used. Refer to **Annex A** for full case definitions.

Data sources

Between January 1, 2016, and December 31, 2020, participating hospitals submitted epidemiologic data on cases meeting the respective case definitions for *Clostridioides difficile* infection (CDI), methicillin-resistant *Staphylococcus aureus* bloodstream infections (MRSA BSI), vancomycin-resistant *Enterococci* bloodstream infections (VRE BSI) and carbapenemase-producing *Enterobacterales* (CPE) infections and colonizations. In 2020, 87 hospitals across Canada participated in HAI surveillance and are further described in **Table 1**. In 2020, nearly half of patient admissions captured in CNISP HAI surveillance were from medium-sized adult (sites=21, 27%) and mixed hospitals (sites=14, 22%) (**Supplemental file Figure S1**).

Epidemiologic (demographic, clinical and outcome data) and denominator data (patient days and patient admissions) were collected and submitted by participating hospitals through the Canadian Network for Public Health Intelligence platform, a secure online data platform.

Reviews of standardized protocols and case definitions were conducted annually by established infectious disease expert working groups and training for data submission was provided as required. Data quality for each surveillance project was periodically evaluated (14,15).

Laboratory data

Patient-linked laboratory isolates (stool samples for CDI cases) were sent to the Public Health Agency of Canada's National Microbiology Laboratory for molecular characterization and susceptibility testing. The MRSA BSI, VRE BSI, CPE and paediatric CDI isolates were submitted year-round. Adult CDI isolates were submitted annually during a targeted two-month period (March 1 to April 30).

Statistical analysis

Rates of HAI were calculated and represent infections and/or colonizations identified in patients admitted to CNISP participating hospitals. The HAI rates were calculated by dividing the total number of cases by the total number of patient admissions (multiplied by 1,000) or patient days (multiplied by 10,000). The HAI rates are reported nationally and by region (Western: British Columbia, Alberta, Saskatchewan and

Table 1: Summary of hospitals participating in the Canadian Nosocomial Infection Surveillance Program, by region, 2020

Details of participating hospitals	Western[a]	Central[b]	Eastern[c]	Northern[d]	Total
Total number of hospitals	28	32	26	1	87
Hospital type					
Adult[e]	12	21	16	0	49
Mixed	12	7	9	1	29
Paediatric	4	4	1	0	9
Hospital size					
Small (1–200 beds)	10	8	18	1	37
Medium (201–499 beds)	11	17	8	0	36
Large (500+ beds)	7	7	0	0	14
Admissions and discharge					
Total number of beds	9,617	12,130	3,302	22	25,071
Total number of admissions	424,296	494,428	133,894	2,271	1,054,889
Total number of patient days	3,137,774	3,721,010	933,042	6,085	7,797,911

[a] Western refers to British Columbia, Alberta, Saskatchewan and Manitoba
[b] Central refers to Ontario and Québec
[c] Eastern refers to Nova Scotia, New Brunswick, Prince Edward Island and Newfoundland and Labrador
[d] Northern refers to Nunavut
[e] Seven hospitals classified as "adult" had a neonatal intensive care unit

Manitoba; Central: Ontario and Québec; Eastern: Nova Scotia, New Brunswick, Prince Edward Island and Newfoundland and Labrador; Northern: Nunavut). Sites that were unable to provide case data were excluded from rate calculations and missing denominator data were estimated, where applicable. Missing epidemiological and molecular data were excluded from analysis. The Mann-Kendall test was used to test trends over time. Significance testing was two-tailed and differences were considered significant at $p \leq 0.05$.

Where available, attributable and all-cause mortality were reported for HAIs. Attributable mortality rate was defined as the number of deaths per 100 HAI cases where the HAI was the direct cause of death or contributed to death within 30 days after the date of the first positive laboratory or histopathology specimen, as determined by physician review. All-cause mortality rate was defined as the number of deaths per 100 HAI cases 30 days following positive culture.

Results

Clostridioides difficile infection

Between 2016 and 2020, overall CDI rates significantly decreased by 8.5% (5.77–5.28 infections per 10,000 patient days, $p=0.050$); however, a similar increase of 8.0% in CDI rates (4.89–5.28 per 10,000 patient days) was observed in 2020 compared to 2019 (**Table 2**). Stratified by source of infection, the incidence of HA-CDI significantly decreased by 13.4% from 4.39–3.80 infections per 10,000 patient days ($p=0.050$) (**Table S1.1**). Community-associated-CDI (Annex A) rates have decreased 3.0% when comparing 2016 to 2020 rates per 1,000 patient admission; however, the decreasing trend was not considered significant ($p=0.327$). Both HA and CA-CDI rates increased in 2020 compared to 2019 (5.0% and 11.1%, respectively). Regionally, HA-CDI rates have steadily decreased across all regions except in the East where rates have remained relatively consistent. For CA-CDI, Eastern and Central region rates have decreased between 2016 and 2020 while Western rates have remained the same. Overall CDI attributable mortality remained low and fluctuated (range: 1.3–2.7 deaths per 100 cases) from 2016 to 2020 ($p=0.801$) (Table 2).

The proportion of *C. difficile* isolates resistant to moxifloxacin decreased by 9.1% between 2016 (15.7%, n=103/657) and 2020 (6.6%, n=28/426). Since 2016, moxifloxacin resistance decreased significantly among HA-CDI isolates (11.0%, $p=0.050$) while a smaller non-significant decrease was observed among CA-CDI (3.4%, $p=0.624$) (**Table S1.2**). All tested *C. difficile* isolates were susceptible to vancomycin and tigecycline. There was a single case of metronidazole resistance in 2018. From 2016 to 2020, the prevalence of ribotype 027 associated with NAP1 decreased for both HA and CA-CDI (5.3% vs. 5.9%, respectively) (**Table S1.3**).

Methicillin-resistant *Staphylococcus aureus* bloodstream infections

Between 2016 and 2019, overall MRSA BSI rates significantly increased by 33.3% (0.84–1.12 infections per 10,000 patient days, $p=0.037$), and remained stable in 2020 during the COVID-19 pandemic (**Table 3**). Stratified by case type, a continued steady increase (75%, $p=0.023$) was observed from 2016 to 2020 in CA-MRSA BSI (Annex A) compared to HA-MRSA BSI, which fluctuated over time (**Table S2.1**). In 2020, HA-MRSA BSI and CA-MRSA BSI rates were highest in Western

Table 2: *Clostridioides difficile* infection data, Canada, 2016–2020[a]

C. difficile infection data	Year									
	2016		2017		2018		2019		2020	
Number of infections and incidence rates										
Number of *C. difficile* infection cases	4,008		4,012		3,842		3,595		3,645	
Rate per 1,000 patient admissions	4.34		4.28		4.13		3.71		3.92	
Rate per 10,000 patient days	5.77		5.67		5.39		4.89		5.28	
Number of reporting hospitals	67		68		68		73		82	
Attributable mortality rate per 100 cases (%)[b]	2.4		2.3		1.3		2.3		2.7	
Antimicrobial resistance[c]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Clindamycin	145	22.1	149	22.0	307	48.6	219	40.0	66	15.5
Moxifloxacin	103	15.7	114	16.9	70	11.1	64	11.7	28	6.6
Rifampin	9	1.4	14	2.1	10	1.6	5	0.9	4	0.9
Metronidazole	0	0.0	0	0.0	1	0.2	0	0.0	0	0
Total number of isolates tested[d]	657	N/A	676	N/A	632	N/A	547	N/A	426	N/A

Abbreviations: *C. difficile*, *Clostridioides difficile*; N/A, not applicable
[a] All *C. difficile* isolates from 2016 to 2020 submitted to National Microbiology Laboratory were susceptible to tigecycline and vancomycin
[b] Deaths where *C. difficile* infection was the direct cause of death or contributed to death 30 days after the date of the first positive lab specimen or positive histopathology specimen. Mortality data are collected during the two-month period (March and April of each year) for adults (age 18 years and older) and year-round for children (age 1 year to younger than 18 years old). Among paediatric patients, there was no death attributable to healthcare-associated *C. difficile* infection
[c] *C. difficile* infection isolates are collected for resistance testing during the two-month period (March and April of each year) for adults (age 18 years and older) and year-round for children (age 1 year to younger than 18 years old) from admitted patients only
[d] Total number reflects the number of isolates tested for each of the antibiotics listed above

Table 3: Methicillin-resistant *Staphylococcus aureus* bloodstream infections data, Canada, 2016–2020

MRSA BSI data	Year									
	2016		2017		2018		2019		2020	
Number of infections and incidence rates										
Number of MRSA bloodstream infections	604		606		767		881		845	
Rate per 1,000 patient admissions	0.61		0.61		0.78		0.84		0.83	
Rate per 10,000 patient days	0.84		0.84		1.05		1.12		1.12	
Number of reporting hospitals	64		65		62		69		80	
All-cause mortality rate[a]										
Number of deaths	111		99		144		144		146	
All-cause mortality rate per 100 cases	19.1		16.4		18.8		16.4		17.4	
Antimicrobial resistance[b]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Erythromycin	418	78.7	455	81.0	531	75.6	511	75.6	447	72.3
Ciprofloxacin	411	77.4	432	76.9	504	71.8	473	70.0	404	65.4
Clindamycin	230	43.3	239	42.5	290	41.3	144	21.3	202	32.7
Tetracycline	31	5.8	35	6.2	50	7.1	48	7.1	39	6.3
Trimethoprim/sulfamethoxazole	11	2.1	8	1.4	14	2.0	10	1.5	14	2.3
Rifampin	10	1.9	9	1.6	6	0.9	7	1.0	6	1.0
Tigecycline	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Daptomycin	5	0.9	5	0.9	0	0.0	0	0.0	4	0.6
Total number of isolates tested[c,d]	531	N/A	562	N/A	702	N/A	676	N/A	618	N/A

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MRSA BSI, methicillin-resistant *S. aureus* bloodstream infection; N/A, not applicable
[a] Based on the number of cases with associated 30-day outcome data
[b] All MRSA isolates from 2016 to 2020 submitted to National Microbiology Laboratory were susceptible to linezolid and vancomycin
[c] In some years, the number of isolates tested for resistance varied by antibiotic
[d] Total number reflects the number of isolates tested for each of the antibiotics listed above

Canada (0.46 and 0.79 infections per 10,000 patient days, respectively). Among hospital types, HA and CA-MRSA BSI rates have generally remained highest among adult and mixed hospitals. Stratified by hospital size, HA-MRSA BSI rates were highest among large hospitals (500+ beds) since 2018 while CA-MRSA BSI rates have remained highest among medium size hospitals (201–499 beds) since 2019. All-cause mortality decreased 1.7% from 2016 to 2020 (19.1%–17.4%, p=0.449) (Table 3). In 2020, all-cause mortality was higher among those with HA-MRSA (19.9%) compared to those with CA-MRSA (15.9%) (data not shown).

Clindamycin resistance among MRSA isolates decreased by 10.6% between 2016 (43.3%, n=230/531) and 2020 (32.7%, n=202/618) (Table 3). Since 2016, the proportion of MRSA isolates with erythromycin and ciprofloxacin resistance has decreased, yet remains high (72.3% and 65.4% in 2020, respectively). Between 2016 and 2020, daptomycin resistance was detected in 14 isolates. All tested MRSA isolates from 2016 to 2020 were susceptible to linezolid and vancomycin.

Stratified by case type, clindamycin resistance among HA-MRSA isolates (45.8%) was, on average, consistently higher from 2016 to 2020 compared to CA-MRSA isolates (34.1%) during the same period (**Table S2.2**). There were no other notable differences in antibiotic resistance patterns by MRSA BSI case type.

Between 2016 and 2020, the proportion of epidemic types identified as CMRSA2 (USA100/800) and most commonly associated with MRSA infections acquired in a hospital or healthcare setting continued to decrease; from 33.6% of all isolates in 2016 to 21.2% in 2020. The proportion of epidemic types identified as CMRSA7 (USA400) and CMRSA10 (USA300) and most commonly associated with MRSA infections acquired in the community continued to increase and account for the largest proportion of all isolates from 2016 (52.8%) to 2020 (63.8%). The CMRSA10 (USA300) was the most common epidemic type identified from 2016 to 2020, with 50.2% identified in 2020 (n=311/620) (**Table S2.3**).

Vancomycin-resistant *Enterococci* bloodstream infections

From 2016 to 2020, VRE BSI rates increased 72.2%, from 0.18 to 0.31 infections per 10,000 patient days, with the highest rate of 0.35 infections per 10,000 patient days observed in 2018 (**Table 4**). During the COVID-19 pandemic in 2020, VRE BSI rates in the CNISP network remained stable compared to 2019. Regionally, VRE BSI rates were highest in Western and Central Canada (0.36 and 0.33 infections per 10,000 patient days in 2019, respectively) with few VRE BSIs reported in Eastern Canada (range: 0–0.03 infections per 10,000 patient days) (**Table S3.1**). In 2020 compared to 2019, VRE BSI rates decreased among large (500+ beds) and small (1–200 beds) hospitals while increasing by 28.6% (0.28–0.36 infections per 10,000 patient days) among medium (201–499 beds) hospitals.

Vancomycin-resistant *Enterococci* bloodstream infections were predominantly healthcare-associated, as 93.2% (n=887/952) reported from 2016 to 2020 were acquired in a healthcare facility (**Table S3.2**). All-cause mortality remained high (32.7%) from 2016 to 2020.

Between 2016 and 2020, high-level gentamycin resistance among VRE BSI isolates (*Enterococcus faecium*) increased from 13.2% to 26.1%; however, a 7.0% decrease was observed more recently between 2019 and 2020. Daptomycin non-susceptibility was first identified in 2016 (n=7/91, 7.7%) and decreased to 3.5% (n=4/115) in 2020 (Table 4). Since 2016, the majority (98.4%–100%) of VRE BSI isolates were identified as *Enterococcus faecium*; however, in 2018, three *E. faecalis* VRE BSI isolates were identified (**Table S3.3**). Among *E. faecium* isolates, the proportion identified as sequence type 1478 was highest in 2018 (38.7%, n=70/181) and decreased in 2020 (17.6%, n=21/119; p<0.001) (**Table S3.4**).

Carbapenemase-producing *Enterobacterales*

From 2016 to 2020, CPE infection rates have remained low but increased from 0.03 to 0.05 infections per 10,000 patient days (p=0.117), while a significant increase (85.7%) was observed in CPE colonization rates (from 0.14 to 0.26 colonizations per 10,000 patient days, p=0.050) (**Table 5**). Both CPE infections and colonizations rates decreased in 2020 compared to 2019 (16.7% and 10.3%, respectively).

From 2016 to 2020, the majority of CPE infections (97.5%) were identified in Central (50.0%, n=80/160) and Western Canada (47.5%, n=76/160) while few infections were identified in the East (2.5%; n=4/160) (**Table S4.1**). During this same period, most CPE colonizations were identified in Central Canada (80.4%; n=600/746), followed by Western Canada (19.1%, n=143/746), while only three colonizations were reported in Eastern Canada (**Table S4.2**). From 2016 to 2020, large hospitals (500+ beds) reported the highest rates of CPE infections (0.04–0.09 infections per 10,000 patient days); however, small hospitals (1–200 beds) reported the highest CPE infection rates in 2019 (0.10 infections per 10,000 patient days). The CPE colonization rates remained highest among large hospitals from 2016 to 2020 (range: 0.25–0.35 infections per 10,000 patient days).

Thirty day all-cause mortality was 15.2% (n=22/145) among CPE-infected patients. Among all CPE cases reported from 2016 to 2020, 39.2% (n=312/795) reported travel outside of Canada and of those, 83.3% (n=240/288) received medical care while abroad.

From 2016 to 2020, the prevalence of amikacin and gentamicin resistance among CPE isolates decreased by 18.5% and 9.4%, respectively, while trimethoprim-sulfamethoxazole resistance increased by 12.8% (Table 5). The predominant carbapenemases identified in Canada were *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-ß-lactamase (NDM), and Oxacillinase-48 (OXA-48), accounting for 91.9% of identified carbapenemases in 2020.

Table 4: Vancomycin-resistant *Enterococci* bloodstream infections data, Canada, 2016–2020

VRE BSI data	Year									
	2016		2017		2018		2019		2020	
Vancomycin-resistant *Enterococci* bloodstream infections data										
Number of VRE BSI infections	121		154		246		247		207	
Rate per 1,000 patient admissions	0.13		0.16		0.26		0.23		0.24	
Rate per 10,000 patient days	0.18		0.23		0.35		0.32		0.31	
Number of reporting hospitals	59		59		59		68		62	
Antimicrobial resistance of *Enterococcus faecium* isolates	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Ampicillin	91	100	116	100	181	100	169	100	112	97.4
Chloramphenicol	2	2.2	11	9.5	4	2.2	28	16.6	22	19.1
Ciprofloxacin	91	100	116	100	181	100	169	100	113	98.3
Daptomycin[a]	7	7.7	10	8.6	12	6.6	7	4.1	4	3.5
Erythromycin	83	91.2	108	93.1	173	95.6	162	95.9	108	93.9
High-level gentamicin	12	13.2	45	38.8	77	42.5	56	33.1	30	26.1
Levofloxacin	91	100	116	100	179	98.9	169	100	112	97.4
Linezolid	1	1.1	0	0	2	1.1	3	1.8	0	0
Nitrofurantoin	35	38.5	52	44.8	55	30.4	68	40.2	40	34.8
Penicillin	91	100	116	100	181	100.0	169	100	113	98.3
Quinupristin/Dalfopristin	9	9.9	8	6.9	18	9.9	18	10.7	8	7.0
Rifampicin	85	93.4	110	94.8	163	90.1	155	91.7	98	85.2
High-level streptomycin	32	35.2	39	33.6	60	33.1	43	25.4	23	20.0
Tetracycline	46	50.5	66	56.9	108	59.7	119	70.4	72	62.6
Tigecycline	0	0	0	0	1	0.6	0	0	0	0
Vancomycin	88	96.7	111	95.7	176	97.2	166	98.2	110	95.7
Total number of isolates tested[b]	91	N/A	116	N/A	181	N/A	169	N/A	115	N/A

Abbreviations: VRE BSI, vancomycin-resistant *Enterococci* bloodstream infection; N/A, not applicable
[a] Daptomycin does not have intermediate or resistant breakpoints in 2016, 2017 & 2018. Clinical and Laboratory Standards Institute (CLSI) resistance breakpoints came into effect in 2019
[b] Total number reflects the number of isolates tested for each of the antibiotics listed above
Note: Aggregate mortality data reported in-text due to fluctuations in the small numbers of VRE BSI deaths reported each year

Among submitted isolates from 2016 to 2020, the proportion of carbapenemase-producing pathogens identified as *Escherichia coli* increased 11.9% while those identified as *K. pneumoniae* and *Acinetobacter baumannii* decreased by 10.9% each (**Table S5**).

Discussion

Surveillance data collected via CNISP have shown that between 2016 and 2020 infection rates (including both HA and CA-cases) in Canada have decreased 8.5% for CDI, but increased for MRSA BSI and VRE BSI (33.3% and 72.2%, respectively). The CPE infection rates increased, but remained low; however, colonizations increased 85.7%. The COVID-19 pandemic has potentially had mixed impacts on the rates of HAIs in Canada and in the United States (16). Further investigation is required to assess the influence of pandemic-related factors that may be attributed to the changes in observed rates of HAIs, such as public health measures implemented in both the hospital and the community, population travel and mobility, changes in infection control practices, screening, laboratory testing and antimicrobial stewardship (10).

The CDI rates in Canada declined and followed similar trends observed globally; however, rates remained higher in North America relative to other regions (17). In Canada, rates of CDI during the 2020 COVID-19 pandemic were higher than those observed in 2019 and contrast with results seen in the United States where CDI rates have continued to decline (16).

The CDI moxifloxacin resistance decreased in Canada to 6.6% in 2020 and remained lower than previously published weighted pooled resistance data for North America (44.0%) and Asia (33.0%) and corresponds to the declining prevalence of ribotype 027 (18,19). The overall reduction in CDI rates across Canada suggests improvements in infection prevention and

Table 5: Carbapenemase-producing *Enterobacterales* data, Canada, 2016–2020[a]

CPE data	Year									
	2016		2017		2018		2019		2020	
Number of infections and incidence rates										
Number of CPE infections	21		20		36		48		35	
Infection rate per 1,000 patient admissions	0.02		0.02		0.04		0.05		0.04	
Infection rate per 10,000 patient days	0.03		0.03		0.05		0.06		0.05	
Number of CPE colonizations	88		112		142		214		190	
Colonization rate per 1,000 patient admissions	0.10		0.12		0.16		0.21		0.20	
Colonization rate per 10,000 patient days	0.14		0.18		0.22		0.29		0.26	
Number of reporting hospitals	55		56		57		64		72	
Drugs tested for antimicrobial resistance										
Antibiotics[b,c]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Piperacillin-Tazobactam	116	72.0	159	85.0	210	92.1	237	90.8	184	87.6
Ceftriaxone	149	92.5	173	92.5	212	93.0	250	95.8	186	88.6
Ceftazidime	139	86.3	160	85.6	192	84.2	233	89.3	173	82.4
Meropenem	140	87.0	159	85.0	198	86.8	190	72.8	130	61.9
Ciprofloxacin	133	82.6	138	73.8	158	69.3	183	70.1	150	71.4
Amikacin	42	26.1	32	17.1	44	19.3	23	8.8	16	7.6
Gentamicin	62	38.5	64	34.2	80	35.1	86	33.0	61	29.1
Tobramycin	75	46.6	71	38.0	101	44.3	121	46.4	78	37.1
Trimethoprim-sulfamethoxazole	102	63.4	113	60.4	143	62.7	193	73.9	160	76.2
Tigecycline	32	19.9	18	9.6	30	13.2	36	13.8	0	0
Total number of isolates tested[d]	161	N/A	187	N/A	228	N/A	261	N/A	210	N/A
Carbapenemases identified										
KPC	84	52.2	86	46.0	122	53.5	127	48.7	82	39.1
NDM	45	28.0	53	28.3	59	25.9	74	28.4	66	31.4
OXA-48	20	12.4	33	17.6	30	13.2	40	15.3	45	21.4
SME[e]	4	2.5	2	1.1	4	1.8	1	0.4	2	1
NDM/OXA-48	4	2.5	5	2.7	6	2.6	10	3.8	7	3.3
GES	1	0.6	1	0.5	1	0.4	2	0.8	0	0
IMP	0	0.0	0	0.0	3	1.3	1	0.4	1	0.5
NMC	2	1.2	4	2.1	2	0.9	4	1.5	6	2.9
VIM	2	1.2	3	1.6	3	1.3	3	1.1	0	0
Other	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Total number of isolates tested[f]	161	N/A	187	N/A	228	N/A	261	N/A	210	N/A

Abbreviations: CPE, carbapenemase-producing *Enterobacterales*; GES, Guiana extended-spectrum β-lactamase; IMP, active-on-imipenem; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; NMC, not metalloenzyme carbapenemase; OXA-48, Oxacillinase-48; N/A, not applicable; SME, *Serratia marcescens* enzymes; VIM, Verona integron-encoded metallo-β-lactamase

[a] Includes data for all CPE isolates submitted

[b] All isolates were resistant to ampicillin, and all but one to cefazolin. All carbapenemase-producing organism isolates were screened for the *mcr*-type gene which is an acquired gene associated with colistin resistance

[c] The denominator for some drugs were adjusted as minimum inhibitory concentration values were not given in all cases due to VITEK® algorithms

[d] Total number reflects the number of isolates tested for each of the antibiotics listed above

[e] Only found in *Serratia marcescens*

[f] Some isolates contain multiple carbapenemases therefore the total number of isolates tested and the number of carbapenemases indicated may not match

Note: Aggregate mortality data reported in-text due to fluctuations in the small numbers of CPE deaths reported each year

control practices and quality-improvement initiatives such as hand hygiene compliance, environmental cleaning, improved diagnostic techniques and antibiotic stewardship (20,21). The decline of RT027 from 2016 to 2020 may also have influenced the decline in CDI rates among CNISP hospitals as this ribotype has been associated with increased virulence and fluoroquinoline resistance (22).

The rise in MRSA BSI rates in Canada, attributed to the increase in CA-MRSA BSI rates, is concerning due to the severe clinical outcomes, increased length of hospital stays and increased healthcare costs associated with BSI's among admitted patients (23–26). A reduction in clindamycin resistance from 2016 to 2019 is most likely associated with the decrease in the proportion of CMRSA2 epidemic type identified among tested isolates (27). Compared to the increase observed in MRSA BSI rates in Canada, MRSA BSI rates in select large Australian tertiary care hospitals were lower and fluctuated between 2016 and 2019 (28). Similarly, in England, a plateau in MRSA BSI rates has been observed since 2015 (1.4–1.5 per 100,000 population and 0.8–0.9 hospital-onset cases per 100,000 bed days) (29). Both globally and in Canada, the prevalence of CA-MRSA is increasing and may provide a reservoir that could contribute to the increasing number of patients identified with CA-MRSA admitted to hospitals (30,31). The increasing rate of patients hospitalized with MRSA BSI acquired in the community observed in CNISP data suggests that further strategies to reduce or prevent MRSA infections in the community may be needed. Although beyond the scope of CNISP, studies at the broader population level to identify the prevalence of MRSA in the community, especially among populations at increased risk of contracting CA-MRSA, such as children, athletes, incarcerated populations, people who live in crowded conditions or people who inject drugs, may be worthwhile and could help to inform prevention strategies in the community (32).

The increasing rates of VRE BSI in Canadian acute care hospitals are of concern as this infection is associated with a high mortality and increased hospital burden (33–35). The increase in VRE BSI rates observed among CNISP hospitals may be linked to changes in infection control policies, specifically the discontinuation of VRE screening and isolation programs in some Canadian acute care hospitals (36). Additionally, the rise in VRE BSI rates from 2013 to 2018 and subsequent decrease in 2019 and 2020 coincides with the emergence and decline of the *pstS*-null sequence type 1478 (ST1478) (37). The ST1478 sequence type is associated with daptomycin non-susceptibility and high-level gentamicin resistance, and the resistance patterns among VRE BSI isolates for these two antibiotics correspond to the trend in ST1478. It is important to note that the observed VRE BSI trends are, for the most part, being driven by a limited number of hospitals that have experienced outbreaks while caring for high risk patients (e.g. bone marrow transplants, solid organ transplants, cancer patients, etc.) (38). Similarly, increasing trends in prevalence of VRE BSI have also been observed in Europe (39–42), which may be associated, in part, with the introduction and spread of a new clone and gaps in infection prevention practices (37,41).

The CPE infections are of clinical significance and public health concern as they are associated with significant morbidity and mortality, limited treatment options and an ability to spread rapidly in healthcare settings (43–47). The incidence of CPE infection in Canada remains low; however, an 85.7% increase in CPE colonization rates was observed over the same period of time. Recent decreases in CPE infection and colonization rates in 2020 require further research to investigate the impact of changes in previously identified risk factors such as travel and receipt of healthcare in high-risk areas, as well as changes to infection control practices such as patient screening (44,48–50).

Data on the incidence of CPE in other countries remains limited (51); however, a few countries have also reported a low but increasing incidence of CPE (52,53). Increased awareness and changes in screening and testing practices may reflect the increase in CPE colonization. Coordinated public health action, including strict implementation of infection control measures such as enquiry regarding travel, and enhanced surveillance are essential in reducing the transmission of CPE in Canadian acute care hospitals.

Strengths and limitations

The CNISP collects standardized and detailed epidemiological and laboratory-linked data from 87 sentinel hospitals across Canada to provide national HAI and AMR trends that can be used for benchmarking hospital infection prevention and control practices in serving to reduce HAIs and AROs in Canadian acute care hospitals. It is important to note that data included in this report include the COVID-19 pandemic, and 2020 rates of HAI's and AMR may be impacted by changes in hospital admissions, mobility and national, regional, local and hospital-based infection prevention and control measures.

The epidemiologic data collected by CNISP were limited to the information available in patient charts. Turnover of hospital staff reviewing medical charts may affect the consistent application of CNISP definitions and data quality over time; however, these data are collected by experienced and training infection prevention and control staff who receive periodic training with respect to CNISP methods and definitions. Data quality assessments are also conducted to maintain and improve data quality. The CNISP network may not fully represent the general inpatient population in Canada; however, efforts in recruitment have increased representation and coverage of Canadian acute care beds from 27% to 30% from 2016 to 2020, particularly among Northern, rural communities and Indigenous populations.

Next steps

Continued recruitment of Canadian acute care hospitals to increase acute care bed coverage from all ten provinces and three territories is ongoing in order to improve the quality and representativeness of Canadian HAI estimates. Furthermore,

an enhanced hospital screening practice survey is conducted annually to better understand changes in HAI rates across Canada. In recent years, CNISP has initiated surveillance for new and emerging pathogens, such as *Candida auris*, and epidemiologic and laboratory-led working groups were formed to further investigate new pathogens such as VRE BSI ST1478 and extensively drug-resistant CPE. In 2019, CNISP re-established viral respiratory infection surveillance to collect and report detailed epidemiologic information on patients hospitalized with viral respiratory infections. This surveillance was expanded in 2020 to include patients hospitalized with COVID-19. The CNISP continues to support the national public health response to the COVID-19 pandemic. Future studies aim to analyze the impact of the COVID-19 pandemic on HAI rates and AMR.

Conclusion

Findings from surveillance conducted by a national network of Canadian acute care hospitals indicate that rates of MRSA BSI, VRE BSI and CPE infections and colonizations substantially increased between 2016 and 2020 while rates of CDI decreased. Ongoing surveillance and reporting of epidemiologic and laboratory data are essential to inform infection prevention and control and antimicrobial stewardship policies to help reduce the burden of HAI and impact of AMR in Canadian acute care hospitals.

Authors' statement

Canadian Nosocomial Infection Surveillance Program hospitals provided expertise in the development of protocols in addition to the collection and submission of epidemiological data and lab isolates. The National Microbiology Laboratory completed the laboratory analyses and contributed to the interpretation and revision of the paper. Epidemiologists from Public Health Agency of Canada were responsible for the conception, analysis, interpretation, drafting and revision of the article.

Competing interests

None.

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Annex A: Surveillance case definitions and eligibility criteria, 2020

Clostridioides difficile infection

A "primary" episode of *Clostridioides difficile* infection (CDI) is defined either as the first episode of CDI ever experienced by the patient or a new episode of CDI that occurs greater than eight weeks after the diagnosis of a previous episode in the same patient.

A patient is identified as having CDI if:

- The patient has diarrhea or fever, abdominal pain and/or ileus AND a laboratory confirmation of a positive toxin assay or positive polymerase chain reaction (PCR) for *C. difficile* (without reasonable evidence of another cause of diarrhea)

  OR

- The patient has a diagnosis of pseudomembranes on sigmoidoscopy or colonoscopy (or after colectomy) or histological/pathological diagnosis of CDI

  OR

- The patient is diagnosed with toxic megacolon (in adult patients only)

Diarrhea is defined as one of the following:

- More watery/unformed stools in a 36-hour period

  OR

- More watery/unformed stools in a 24-hour period and this is new or unusual for the patient (in adult patients only)

Exclusion:

- Any patients younger than one year
- Any paediatric patients (aged one year to younger than 18 years) with alternate cause of diarrhea found (i.e. rotavirus, norovirus, enema or medication, etc.) are excluded even if *C. difficile* diagnostic test result is positive

CDI case classification

Once a patient has been identified with CDI, the infection will be classified further based on the following criteria and the best clinical judgment of the healthcare and/or infection prevention and control practitioner.

Healthcare-associated (acquired in your facility) CDI case definition

- Related to the current hospitalization:
  - The patient's CDI symptoms occur in your healthcare facility three or more days (or 72 hours or longer) after admission
- Related to a previous hospitalization:
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient had been previously hospitalized at your healthcare facility and discharged within the previous four weeks
  - Outpatient: the patient presents with CDI symptoms at your emergency room (ER) or outpatient location AND the patient had been previously hospitalized at your healthcare facility and discharged within the previous four weeks
- Related to a previous healthcare exposure at your facility:
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient had a previous healthcare exposure at your facility within the previous four weeks
  - Outpatient: the patient presents with CDI symptoms at your ER or outpatient location AND the patient had a previous healthcare exposure at your facility within the previous four weeks

Healthcare-associated (acquired in any other healthcare facility) CDI case definition

- Related to a previous hospitalization at any other healthcare facility:
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient is known to have been previously hospitalized at any other healthcare facility and discharged/transferred within the previous four weeks
  - Outpatient: the patient presents with of CDI symptoms at your ER or outpatient location AND the patient is known to have been previously hospitalized at any other healthcare facility and discharged/transferred within the previous four weeks
- Related to a previous healthcare exposure at any other healthcare facility
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient is known to have a previous healthcare exposure at any other healthcare facility within the previous four weeks
  - Outpatient: the patient presents with CDI symptoms at your ER or outpatient location AND the patient is known to have a previous healthcare exposure at any other healthcare facility within the previous four weeks

Healthcare-associated CDI but unable to determine which facility

The patient with CDI DOES meet both definitions of healthcare-associated (acquired in your facility) and healthcare-associated (acquired in any other healthcare facility), but unable to determine to which facility the case is primarily attributable to.

Community-associated CDI case definition

- Inpatient: the patient's CDI symptoms occur less than three days (or fewer than 72 hours) after admission, with no history of hospitalization or any other healthcare exposure within the previous 12 weeks
- Outpatient: the patient presents with CDI symptoms at your ER or outpatient location with no history of hospitalization or any other healthcare exposure within the previous 12 weeks

Indeterminate CDI case definition

The patient with CDI does NOT meet any of the definitions listed above for healthcare-associated or community-associated CDI. The symptom onset was more than four weeks but fewer than 12 weeks after the patient was discharged from any healthcare facility or after the patient had any other healthcare exposure.

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection

MRSA bloodstream infection (BSI) case definition:

- Isolation of *Staphylococcus aureus* from blood

  AND

- Patient must be admitted to the hospital

  AND

- Is a "newly identified *S. aureus* infection" at a Canadian Nosocomial Infection Surveillance Program (CNISP) hospital at the time of hospital admission or identified during hospitalization.

Infection inclusion criteria

- Methicillin-susceptible *Staphylococcus aureus* (MSSA) or MRSA BSIs identified for the first time during this current hospital admission
- MSSA or MRSA BSIs that have already been identified at your site or another CNISP site but are new infections

Criteria to determine NEW MSSA or MRSA BSI

- Once the patient has been identified with a MSSA or MRSA BSI, they will be classified as a new MSSA or MRSA if they meet the following criteria: more than 14 days since previously treated MSSA or MRSA BSI and in the judgment of infection control physicians and practitioners represents a **new** infection

Infection exclusion criteria

- Emergency, clinic, or other outpatient cases who are **NOT admitted** to the hospital

Healthcare-associated (HA) case definition:

Healthcare-associated is defined as an inpatient who meets the following criteria and in accordance with the best clinical judgment of the healthcare and/or infection prevention and control practitioner:

- Patient is on or beyond calendar day 3 of their hospitalization (calendar day 1 is the day of hospital admission)

  OR

- Has been hospitalized in your facility in the last 7 days or up to 90 days depending on the source of the infection

  OR

- Has had a healthcare exposure at your facility that would have resulted in this bacteremia (using best clinical judgment)

  OR

- Any patient who has a bacteremia not acquired at your facility that is thought to be associated with any other healthcare exposure (e.g. another acute-care facility, long-term care, rehabilitation facility, clinic or exposure to a medical device)

Healthcare-associated (HA) case definition (newborn):

- The newborn is on or beyond calendar day 3 of their hospitalization (calendar day 1 is the day of hospital admission)
- The mother was **NOT** known to have MRSA on admission and there is no epidemiological reason to suspect that the mother was colonized prior to admission, even if the newborn is fewer than 48 hours of age
- In the case of a newborn transferred from another institution, MSSA or MRSA BSI may be classified as HA your acute-care facility if the organism was **NOT** known to be present and there is no epidemiological reason to suspect that acquisition occurred prior to transfer

Community-associated case definition:

- No exposure to healthcare that would have resulted in this bacteremia (using best clinical judgment) and does not meet the criteria for a healthcare-associated BSI

Vancomycin-resistant *Enterococci* (VRE) infection

VRE BSI case definition:

- Isolation of *Enterococcus faecalis* or *faecium* from blood

  AND

- Vancomycin MIC **at least** 8 µg/ml

  AND

- Patient must be admitted to the hospital

  AND

- Is a "newly" identified VRE BSI at a CNISP facility at the time of hospital admission or identified during hospitalization

A newly identified VRE BSI is defined as a positive VRE blood isolate more than 14 days after completion of therapy for a previous infection and felt to be unrelated to previous infection in accordance with best clinical judgment by Infection Control physicians and practitioners.

Exclusion criteria:

- Emergency, clinic, or other outpatient cases who are **not admitted** to the hospital

Healthcare-associated (HA) case definition:
Healthcare-associated is defined as an inpatient who meets the following criteria and in accordance with the best clinical judgment of the healthcare and/or infection prevention and control practitioner:

- Patient is on or beyond calendar day 3 of their hospitalization (calendar day 1 is the day of hospital admission)

  OR

- Has been hospitalized in your facility in the last 7 days or up to 90 days depending on the source of the infection

  OR

- Has had a healthcare exposure at your facility that would have resulted in this bacteremia (using best clinical judgment)

  OR

- Any patient who has a bacteremia not acquired at your facility that is thought to be associated with any other healthcare exposure (e.g. another acute-care facility, long-term care, rehabilitation facility, clinic or exposure to a medical device)

Carbapenemase-producing *Enterobacterales* (CPE) infection

Case eligibility:

- Patient is admitted to a CNISP hospital or presents to a CNISP hospital emergency department or a CNISP hospital-based outpatient clinic
- Laboratory confirmation of carbapenem resistance or carbapenemase production in *Enterobacterales* spp.

Following molecular testing, only isolates determined to be harbouring a carbapenemase are included in surveillance. If multiple isolates are submitted for the same patient in the same surveillance year, only the isolate from the most invasive site is included in epidemiological results (e.g. rates and outcome data). However, antimicrobial susceptibility testing results represent all CPE isolates (including clinical and screening isolates from inpatients and outpatients) submitted between 2016 and 2020; duplicates (i.e. isolates from the same patient where the organism and the carbapenemase were the same) were excluded.

Annex B: List of supplementary figure and tables

These documents can be accessed on the Supplemental material file.

Figure S1: Number and proportion of patient admissions included in the Canadian Nosocomial Infection Surveillance Program by hospital type and size, 2020

Table S1.1: Cases and incidence rates of healthcare-associated and community-associated *Clostridioides difficile* infection by region, hospital type and hospital size, Canada, 2016–2020

Table S1.2: Antimicrobial resistance of healthcare-associated and community-associated *Clostridioides difficile* infection isolates, Canada, 2016–2020

Table S1.3: Number and proportion of common ribotypes of healthcare-associated and community-associated *Clostridioides difficile* infection cases, Canada, 2016–2020

Table S2.1: Cases and incidence rates of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* bloodstream infections by region, hospital type and hospital size, 2016–2020

Table S2.2: Antimicrobial resistance of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* bloodstream infection isolates, Canada, 2016–2020

Table S2.3: Number and proportion of select methicillin-resistant *Staphylococcus aureus* epidemic types identified

Table S3.1: Number of vancomycin-resistant *Enterococci* bloodstream infections incidence rates by region, hospital type and hospital size, 2016–2020

Table S3.2: Number of healthcare-associated vancomycin-resistant *Enterococci* bloodstream infections and incidence rates by region, hospital type and hospital size, 2016–2020

Table S3.3: Number and proportion of vancomycin-resistant *Enterococci* bloodstream infections isolate types identified, 2016–2020

Table S3.4: Distribution of vancomycin-resistant *Enterococci* bloodstream (*Enterococcus faecium*) sequence type, 2016–2020

Table S4.1: Number of carbapenemase-producing *Enterobacterales* infections and incidence rates by region, hospital type and hospital size, 2016–2020

Table S4.2: Number of carbapenemase-producing *Enterobacterales* colonizations and incidence rates by region, hospital type and hospital size, 2016–2020

Table S5: Number and proportion of main carbapenemase-producing pathogens identified

Device and surgical procedure-related infections in Canadian acute care hospitals from 2011 to 2020

Canadian Nosocomial Infection Surveillance Program[1]*

Abstract

Background: Healthcare-associated infections (HAIs) continue to place a burden on patient health and safety as well as on the healthcare system. In Canada, national surveillance of HAIs at sentinel acute care hospitals is conducted by the Canadian Nosocomial Infection Surveillance Program. This article describes ten years of device and surgical procedure-related HAI epidemiology in Canada from 2011 to 2020.

Methods: Data were collected from over 40 Canadian sentinel acute care hospitals between January 1, 2011, and December 31, 2020, for central line-associated bloodstream infections (CLABSIs), hip and knee surgical site infections (SSIs), cerebrospinal fluid shunt SSIs and paediatric cardiac SSIs. Case counts, rates, patient and hospital characteristics, pathogen distributions, and antimicrobial resistance are presented.

Results: Between 2011 and 2020, 4,751 device and surgical procedure-related infections were reported, with CLABSIs in intensive care units (ICUs) representing 67% (n=3,185) of all reported infections. Over the surveillance period, significant rate increases were observed in adult mixed ICU CLABSIs (0.8 to 1.6 per 1,000 line days, p=0.004) while decreases were observed in neonatal ICU CLABSIs (4.0 to 1.6 per 1,000 line days, p=0.002) and SSIs following knee arthroplasty (0.69 to 0.29 infections per 100 surgeries, p=0.002). No trends were observed in the other reported HAIs.

Of the 5,071 pathogens identified, the majority were gram-positive (68%), followed by gram-negative (23%) and fungi (9%). Coagulase-negative staphylococci (27%) and *Staphylococcus aureus* (16%) were the most frequently isolated pathogens.

Conclusion: This report describes epidemiological and microbiological trends among select device and surgical procedure-related HAIs, essential for benchmarking infection rates nationally and internationally, to identify any changes in infection rates or antimicrobial resistance patterns and to help inform hospital infection prevention and control and antimicrobial stewardship policies and programs.

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Keywords: hospital-associated infection, acute care, surveillance, antimicrobial resistance, device-associated infection, surgical procedure-related infection, surgical site infections, Canada

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Introduction

Healthcare-associated infections (HAIs) threaten patient safety and quality of care, contributing to prolonged hospital stays, increased antimicrobial resistance, costs to the health system and unnecessary deaths (1). Healthcare-associated infections may arise through the use of invasive devices, surgical procedures and inappropriate antibiotic use (2). A 2017 point prevalence study at Canadian sentinel acute care hospitals found that device and surgical procedure-related infections accounted for 35.6% of all reported HAIs (3). Among these device and surgical procedure-related infections, 19.4% of surgical site infections (SSIs) were associated with a prosthetic implant while 21.2% were associated with central line-associated bloodstream infections (CLABSIs) (3). The risk of device and surgical procedure-related HAIs varies among patient populations and within hospital types, with patients admitted to the intensive care unit (ICU) being at higher risk of developing a HAI (4). During the coronavirus disease 2019 (COVID-19) pandemic declared by the World Health Organization on March 11, 2020 (5), rates of HAIs and antimicrobial resistance (AMR) may have been impacted by necessary changes to hospital infection prevention and control practices and antimicrobial stewardship (6).

Antimicrobial resistance is known to impact length of stay and healthcare costs (7). It is expected that by 2050 an estimated 10 million annual deaths will be attributable to AMR (8); thus, antimicrobial susceptibility information is key to ensuring appropriate treatment and use of antimicrobials to help reduce AMR (9).

Understanding the trends in device and surgical procedure-related HAIs is essential to provide benchmark rates over time which helps to inform effective antimicrobial stewardship and infection prevention and control measures. This report provides an epidemiological overview of select device and surgical procedure-related HAIs from 2011 to 2020 in over 40 Canadian Nosocomial Infection Surveillance Program (CNISP) hospitals.

Methods

Design

Since its establishment in 1994, CNISP has conducted national HAI surveillance at sentinel acute care hospitals across Canada, in collaboration with the Public Health Agency of Canada and the Association of Medical Microbiology and Infectious Disease Canada. Data are presented for the following device and surgical procedure-related HAIs: central line-associated bloodstream infections (CLABSIs); hip and knee arthroplasty SSIs; cerebrospinal fluid (CSF) shunt SSIs; and paediatric cardiac SSIs.

Case definitions

Device and surgical procedure-related HAIs were defined according to standardized protocols and expert-reviewed case definitions (see **Appendix**). Only complex infections, defined as deep incisional and organ/space, were included in hip and knee SSI surveillance, while only CLABSIs identified in ICU settings. Adult mixed ICU, adult cardiovascular surgery intensive care unit (CVICU), paediatric intensive care unit (PICU) and neonatal intensive care unit (NICU) were included in CLABSI surveillance.

Data source

Epidemiological data on device and surgical procedure-related infections occurring between January 1, 2011 and December 31, 2020 were submitted by participating hospitals. Data submission and case identification were supported by training sessions and periodic evaluations of data quality.

Statistical analysis

To calculate hip and knee SSI, CSF shunt SSI and paediatric cardiac SSI rates, the number of cases were divided by the number of surgical procedures performed (multiplied by 100). To calculate CLABSI rates, the number of cases were divided by line day denominators (multiplied by 1,000). To calculate proportions of pathogens, the number of pathogens were divided by the total number of identified pathogens. Denominators may vary, as missing and incomplete data were excluded from analyses. Interquartile ranges (IQR) were calculated. Trends over time were tested using the Mann-Kendall test. Significance testing was two-tailed and differences were considered significant at a *p*-value of ≤0.05. Analyses were conducted using R version 4.1.2 and SAS 9.4.

Results

Over 40 hospitals contributed device and surgical procedure-related infection data to CNISP between 2011 and 2020, most of which were medium (201–499 beds) adult hospitals (**Table 1**). Overall, 4,751 device and surgical procedure-related infections were reported. Among all reported HAIs, CLABSIs were the most common representing 67% (n=3,185) of all device and surgical procedure-related HAIs. Among all SSIs reported (N=1,566), hip and knee infections represented 70% (n=1,093).

A total of 5,071 pathogens were identified from device and surgical procedure-related HAI cases between 2011 and 2020. Coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* were the most frequently reported pathogens (**Table 2**). Of the identified pathogens, 67.7% were gram-positive, 23.0% were gram-negative and 9.3% were fungal.

Table 1: Characteristics of acute care hospitals participating in device and surgical procedure-related healthcare-associated infection surveillance, 2011–2020

Characteristic of hospitals	CLABSI- adult mixed ICU	CLABSI- adult CVICU	CLABSI-PICU	CLABSI-NICU	CSF shunt SSI	Paediatric cardiac SSI	Hip and knee SSI
Number of HAIs reported	1,544	200	396	1,045	239	234	1,093
Total number of participating hospitals	31–40	6–9	9–12	15–19	11–15	4–5	12–28
Hospital type							
Adult	21–29	5–8	N/A	3–4[a]	3–4	N/A	8–16
Mixed	9–13	1–2	4	4–6	2–3	N/A	4–13
Paediatric	N/A	N/A	5–8	6–9	6–8	4–5	N/A
Hospital size							
Small (1–200 beds)	2–5	0–1	4–8	5–10	5–6	4	0–2
Medium (201–499 beds)	19–27	3–4	3–5	5–8	4–6	0–1	7–18
Large (500+ beds)	9–12	3–4	0–1	1–4	2–3	N/A	5–8

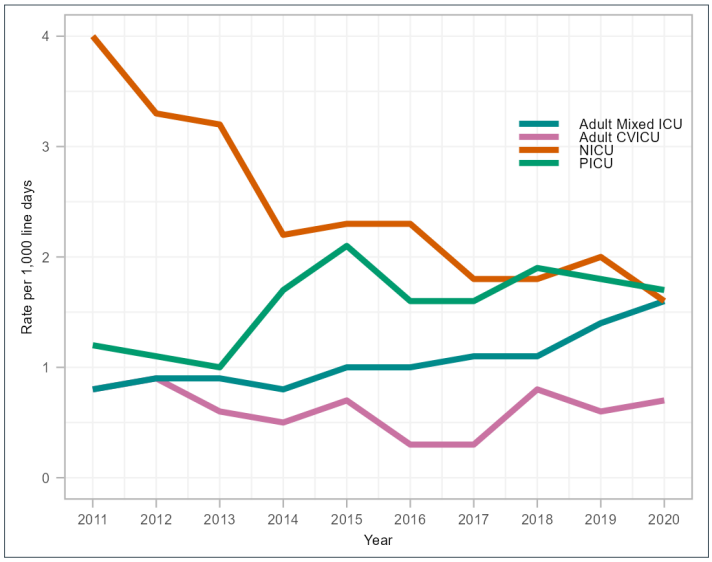
Abbreviations: CLABSI, central line-associated bloodstream infection; CSF shunt SSI, cerebrospinal fluid shunt surgical site infection; CVICU, cardiovascular surgery intensive care unit; HAIs, healthcare-associated infections; ICU, intensive care unit; N/A, not applicable; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; SSI, surgical site infection
[a] Four hospitals classified as "adult" also had a NICU

Central line-associated bloodstream infections

A total of 3,185 CLABSIs were reported between 2011 and 2020, with the majority occurring in adult mixed ICUs (n=1,544, 48.5%) and NICUs (n=1,045, 32.8%). Overall, NICUs had the highest rates of CLABSIs between 2011 and 2020 (2.3 infections per 1,000 line days), followed by PICUs (1.6 per 1,000 line days), adult mixed ICUs (1.1 per 1,000 line days) and adult CVICUs (0.6 per 1,000 line days) (**Table A1**).

While CLABSI rates fluctuated in PICUs and adult CVICUs, adult mixed ICU CLABSI rates doubled between 2011 and 2020 (0.8 to 1.6 infections per 1,000 line days, p=0.004) (**Figure 1**), driven by the Central region (Ontario and Québec) since 2015 and the Western region (British Columbia, Alberta, Saskatchewan and Manitoba) since 2017 (data not shown). Concomitantly, a 60% rate decrease was observed in NICU CLABSIs (4.0 to 1.6 infections per 1,000 line days, p=0.002). Compared to 2019, CLABSI rates in 2020, during the COVID-19 pandemic, followed similar trends to those observed since 2011; adult mixed ICU CLABSIs continued to increase (14%, 1.4 to 1.6 infections per 1,000 line days) and NICU CLABSIs decreased (20%, 2.0 to 1.6 infections per 1,000 line days), while adult CVICU and PICU CLABSIs remained stable.

Figure 1: Rate of central line-associated bloodstream infection per 1,000 line days by intensive care unit type, 2011–2020



Abbreviations: CLABSI, central line-associated bloodstream infection; CVICU, cardiovascular intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit

Among CLABSIs identified in adult mixed ICUs, the median age was 61 years (IQR=48–71 years), with males representing 61.6% of cases. All-cause mortality within 30 days following the first positive culture, for adult mixed ICU CLABSI patients was 32.2% (n=491/1,524). Among CLABSIs identified in adult CVICUs, the median age was 66 years (IQR=56–73 years), with males representing 69.0% of cases. Within 30 days following the first positive culture, all-cause mortality for adult CVICU CLABSI patients was 31.5% (n=62/197). Among CLABSIs identified in PICUs, the median age was six months (IQR=2–28 months), with males representing 55.6% of cases. Within 30 days following the first positive culture, all-cause mortality for PICU CLABSI patients was 9.6% (n=38/396). Among CLABSIs identified in NICUs, the

Table 2: Distribution and rank of the five most frequently reported gram-negative, gram-positive and fungal pathogens, 2011–2020[a]

Pathogen category	Rank	Pathogen	CLABSI N=3,185		Hip and knee N=1,093		CSF shunt N=239		Paediatric cardiac N=234		Total pathogens	
			n	%	n	%	n	%	n	%	n	%
Gram-positive	1	Coagulase-negative staphylococci[b]	991	28.6	218	18.2	99	40.1	36	22.2	1,344	26.5
	2	*Staphylococcus aureus*[c]	268	7.7	381	31.8	59	23.9	77	47.5	785	15.5
	3	*Enterococcus* spp.	523	15.1	84	7.0	14	5.7	1	0.6	622	12.3
	4	*Streptococcus* spp.	63	1.8	106	8.9	6	2.4	11	6.8	186	3.7
	5	Methicillin-resistant *S. aureus*	67	1.9	79	6.6	9	3.6	9	5.6	164	3.2
	Other gram-positive[d]		206	5.9	104	8.7	21	8.5	1	0.6	332	6.5
	Total gram-positive		2,118	61.1	972	81.2	208	84.2	135	83.3	3,659	67.7
Gram-negative	1	*Klebsiella* spp.	235	6.8	22	1.8	3	1.2	0	0.0	260	5.1
	2	*Escherichia coli*	183	5.3	32	2.7	10	4.0	2	1.2	227	4.5
	3	*Enterobacter* spp.	154	4.4	43	3.6	4	1.6	3	1.9	204	4.0
	4	*Pseudomonas* spp.	93	2.7	51	4.3	10	4.0	4	2.5	158	3.1
	5	*Serratia* spp.	83	2.4	15	1.3	2	0.8	3	1.9	103	2.0
	Other gram-negative[e]		150	4.3	57	4.8	5	2.0	3	1.9	215	4.2
	Total gram-negative		898	25.9	220	18.4	34	13.8	15	9.3	1,167	23.0
Fungi	1	*Candida albicans*	212	6.1	0	0.0	1	0.4	1	0.6	214	4.2
	2	Other *Candida* spp.[f]	221	6.4	4	0.3	2	0.8	8	4.9	235	4.6
	Other fungi[g]		16	0.5	1	0.1	2	0.8	3	1.9	22	0.4
	Total fungal		449	13.0	5	0.4	5	2.0	12	7.4	471	9.3
Total			3,465	3,465	1,197	1,197	247	247	162	162	5,071[h]	5,071[h]

Abbreviation: CLABSI, central line-associated bloodstream infections
[a] Frequency distribution percentage rounded to the nearest tenth decimal
[b] Coagulase-negative staphylococci included *S. lugdunensis, S. haemolyticus, S. epidermidis, S. capitis, S. hominis* and *S. warneri*
[c] *Staphylococcus aureus* includes methicillin-susceptible *S. aureus* and unspecified *S. aureus*
[d] Other gram-positive pathogens included anaerobic gram-positive cocci, *Finegoldia magna*, *Clostridioides* spp., *Lactobacillus* spp. and others
[e] Other gram-negative pathogens included *Stenotrophomonas* spp., *Morganella morganii*, *Proteus mirabilis*, *Prevotella* spp., *Bacteroides fragilis* and others
[f] Other *Candida* spp. included *C. dubliniensis, C. glabrata, C. krusei, C. lusitaniae, C. parapsilosis* and *C. tropicalis*
[g] Other fungi included *Aspergillus* spp., *Trichophyton tonsurans* and yeast
[h] Up to three pathogens per device and surgical procedure-related infection were included in the analysis and exceeded the number of total reported infections overall

median age at first positive culture was 17 days (IQR=9–47 days). Males represented 58.6% of NICU cases and all-cause mortality within 30 days of positive culture was 9.2% (n=96/1,043).

The most commonly identified pathogens among CLABSIs overall were CoNS and *Enterococcus* spp. (28.5% and 15.0%, respectively), which aligned with the most commonly identified pathogens among PICUs and adult CVICUs. Among adult mixed ICUs and NICU CLABSIs, CoNS and *S. aureus* were the most commonly identified pathogens.

Hip and knee surgical site infections

A total of 1,093 complex hip and knee SSIs were reported between 2011 and 2020, the majority (n=672, 61.5%) among hip arthroplasties. Among hip and knee SSIs, 51.7% (n=565) were organ/space infections and 48.3% (n=528) were deep incisional infections (**Table 3**). From 2011 to 2020, knee SSI rates decreased significantly (58.0%, 0.69 to 0.29 infections per 100 surgeries, p=0.002) while hip SSI rates fluctuated between 0.48 and 0.88 infections per 100 surgeries (p=0.33). Hip SSI rates decreased 31% in 2020 compared to rates observed in 2019 (0.70 to 0.48 infections per 100 surgeries) while knee SSI rates remained stable (**Figure 2** and **Table A2**).

The median patient age was 68 years (IQR=59–77 years) for hip SSIs and 66 years (IQR=60–74 years) for knee SSIs. The median time from procedure to hip and knee infections was 21 days (IQR=14–32 days) and 23 days (IQR=14–35 days), respectively. For complex SSIs following hip and knee arthroplasties, the median length of stay was 3 days (IQR=2–6 days). Data collected between 2018 and 2020 indicate that 90.6% of patients with an SSI following hip or knee arthroplasty were readmitted (hip: n=211/233, 90.6%; knee: n=108/119, 90.8%) and 67.2% (n=231/344) required revision surgery. Within 30 days after first

Table 3: Frequency of hip and knee surgical site infections by year and infection type, 2011–2020

Year	Deep incisional SSI		Organ/space SSI		All cases
	n	%	n	%	n
Hip arthroplasty					
2011	18	43.9	23	56.1	41
2012	32	66.7	16	33.3	48
2013	36	57.1	27	42.9	63
2014	36	50.7	35	49.3	71
2015	34	52.3	31	47.7	65
2016	28	41.2	40	58.8	68
2017	34	42.0	47	58.0	81
2018	34	34.7	64	65.3	98
2019	46	51.1	44	48.9	90
2020	22	46.8	25	53.2	47
Overall	320	47.6	352	52.4	672
Knee arthroplasty					
2011	20	51.3	19	48.7	39
2012	26	52.0	24	48.0	50
2013	21	55.3	17	44.7	38
2014	26	48.1	28	51.9	54
2015	21	47.7	23	52.3	44
2016	15	41.7	21	58.3	36
2017	18	43.9	23	56.1	41
2018	22	55.0	18	45.0	40
2019	25	53.2	22	46.8	47
2020	14	43.8	18	56.3	32
Overall	208	49.4	213	50.6	421

Abbreviation: SSI, surgical site infection

positive culture, four all-cause deaths (1.8%, n=4/225) were reported among patients with a complex SSI following a hip arthroplasty while zero were reported following a knee arthroplasty SSI. Among hip and knee SSI cases, *S. aureus* and CoNS were the most commonly identified pathogens at 32% and 18%, respectively, and did not differ by deep or organ/space infection type (data not shown).

Cerebrospinal fluid shunt surgical site infections

Between 2011 and 2020, 239 CSF shunt SSIs were reported, with an overall rate of 2.9 infections per 100 surgeries (range: 1.4 to 5.2 infections per 100 surgeries, **Table A3**). Paediatric and adult/mixed hospitals had similar infection rates at 3.0 and 2.8 infections per 100 surgeries, respectively. In 2020, CSF shunt SSI rates decreased compared to 2019 (28%, 4.0 to 2.9 infections per 100 surgeries); however, this decrease was in keeping with the fluctuating rate trend since 2011 (Figure 3).

Figure 2: Rate of hip and knee surgical site infections per 100 surgeries, 2011–2020

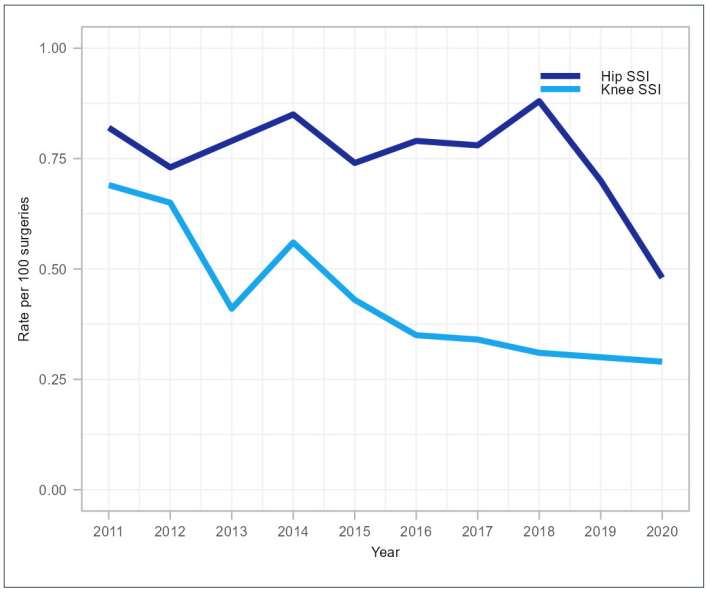
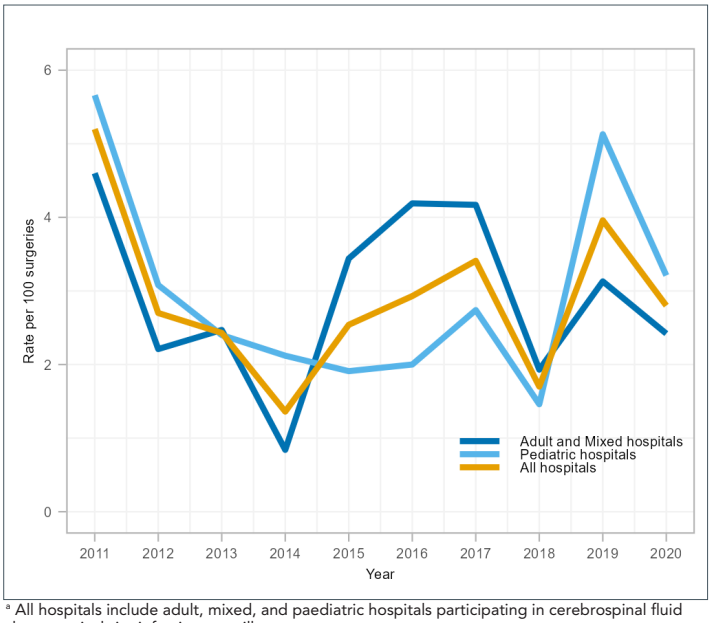


Figure 3: Cerebrospinal fluid shunt surgical site infection rates per 100 surgeries by hospital type[a], 2011–2020



[a] All hospitals include adult, mixed, and paediatric hospitals participating in cerebrospinal fluid shunt surgical site infection surveillance

More than half of CSF shunt SSIs (55.6%, n=130/234) were identified from new surgeries while 44.4% (n=104/234) were identified from revision surgeries. The median age was 47 years (IQR=34–60 years) for adult patients and 0.9 years (IQR=0.2–6.6 years) for paediatric patients. Females represented 52.3% (n=123/235) of cases and median time from surgery to infection was 21 days (IQR=12–43 days). The most commonly identified pathogens from CSF shunt SSIs were CoNS and *S. aureus* (40% and 24% of identified pathogens, respectively). Outcome data are not collected for CSF shunt SSI surveillance.

Paediatric cardiac surgical site infections

A total of 234 paediatric cardiac SSIs were reported between 2011 and 2020 (**Table 4**), most of which were superficial infections (63.1%). Organ/space infections accounted for 29.2% of these SSIs. Overall, the average paediatric cardiac SSI rate was 4.1 infections per 100 surgeries (**Table A4**). While rates remained generally consistent over the surveillance period (p=0.089), there was a significant increase in 2018 (7.5 infections per 100 surgeries, p<0.001) compared to the overall rate from 2011 to 2017 (3.5 infections per 100 surgeries) (**Figure 4**), which was an outlier attributable to two hospitals where investigations are ongoing. Since 2018, the rate decreased by 48% from 7.5 to 3.9 infections per 100 surgeries in 2020, returning to rates observed prior to 2018.

Table 4: Paediatric cardiac surgical site infection rates by year and infection type, 2011–2020

Year	Superficial incisional SSI cases		Organ/space SSI cases		Deep incisional SSI cases		All cases[a]
	n	%	n	%	n	%	
2011	8	53.3	5	33.3	2	13.3	15
2012	15	83.3	2	11.1	1	5.6	18
2013[b]	12	66.7	6	33.3	0	0.0	18
2014	11	57.9	8	42.1	0	0.0	19
2015	12	66.7	5	27.8	1	5.6	18
2016	9	64.3	3	21.4	2	14.3	14
2017	17	70.8	5	20.8	2	8.3	24
2018	18	46.2	15	38.5	6	15.4	40
2019	16	51.6	13	41.9	2	6.5	31
2020	29	78.4	6	16.2	2	5.4	37
Overall	147	63.1	68	29.2	18	7.7	234

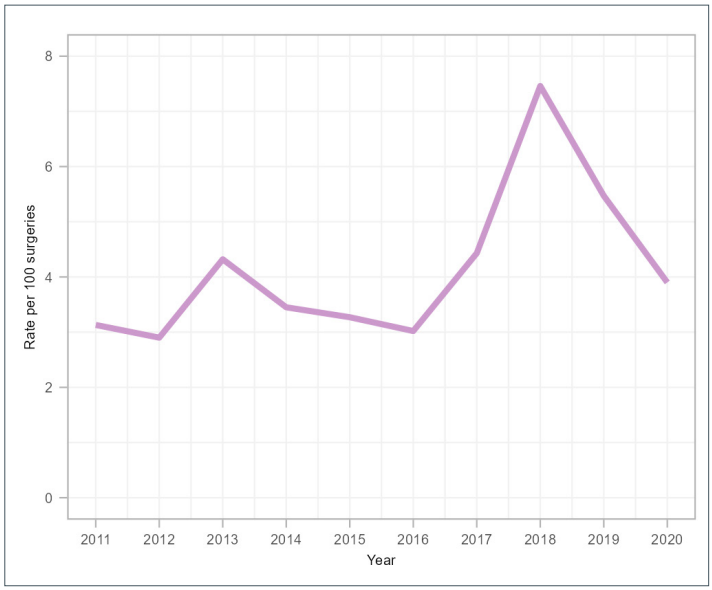
Abbreviation: SSI, surgical site infection
[a] Excludes cases with missing infection type information
[b] Excludes one site with missing denominator data (number of cases=0 in that year)

The median age of patients with a paediatric cardiac SSI was 19 days (IQR=7–193 days), and the median time from surgery to onset date of infection was 10 days (IQR=5–19 days). Among the four deaths reported within 30 days of infection onset (1.7% of cases), two deaths were unrelated to the paediatric cardiac SSI, while two were attributable to the paediatric cardiac SSI. *Staphylococcus aureus* and CoNS were the most commonly identified pathogens from paediatric cardiac SSIs (48% and 22% of identified pathogens, respectively) and did not differ by superficial, organ/space or deep infection type (data not shown).

Antibiogram

Results of antimicrobial susceptibility testing for the most frequently identified gram-positive, gram-negative and fungal pathogens from device and surgical procedure-related HAIs are listed in **Table 5** and **Table 6**. The *S. aureus* isolates were resistant to cloxacillin/oxacillin (methicillin-resistant *S. aureus*

Figure 4: Paediatric cardiac surgical site infection rates per 100 surgeries, 2011–2020



[MRSA]) in 15% (n=32/218) of CLABSIs and 14% (n=40/284) of other reported SSIs. Meropenem resistance ranged from 2%–7% in gram-negative pathogens identified from CLABSIs. No meropenem resistance was observed among pathogens isolated from SSIs. Fifty-one vancomycin-resistant *Enterococci* were identified among CLABSIs (16%).

Discussion

This report summarizes 4,751 device and surgical procedure-related HAIs identified over 10 years of surveillance from 2011 to 2020. Rates of device and surgical procedure-related HAIs have doubled for adult mixed ICU CLABSIs while NICU CLABSI and knee SSI rates have significantly decreased 60% and 58%, respectively. The most frequently reported pathogens in this report were generally aligned with those reported in a 2020 United States (US) National Healthcare Surveillance Network (NHSN) report of adult HAIs, indicating *S. aureus*, *E. coli* and *Klebsiella* among the most frequently reported pathogens for device and surgical procedure-related HAIs in both Canada and the US, while CoNS was identified more commonly in Canada (9). The COVID-19 pandemic may have had differing impacts on the rates of device and surgical procedure-related HAIs in Canada and the US (10). Investigation is underway to assess the influence of pandemic-related factors such as changes in infection control practices, hospital resource capacity, screening, laboratory testing and antimicrobial stewardship on the observed rates of HAIs.

Central line-associated bloodstream infections

The overall rates of CLABSI in adult ICUs (0.6 and 1.1 per 1,000 line days for CVICUs and mixed ICUs, respectively) were similar

Table 5: Antibiogram results[a] from pathogens identified from central line-associated bloodstream infections, 2015–2020

Antibiotic	Number of resistant/number tested and %															
	Gram-positive						Gram-negative						Fungi			
	Coagulase-negative staphylococci[b]		*S. aureus*[c]		*Enterococcus* spp.		*Klebsiella* spp.		*E. coli*		*Enterobacter* spp.		*C. albicans*		*Candida* spp. other[d]	
	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%
Ampicillin	13/15	87	N/A	N/A	126/368	34	119/122	98	71/112	63	60/64	94	N/A	N/A	N/A	N/A
Cefazolin	167/193	87	16/120	13	N/A	N/A	35/95	37	29/92	32	55/56	98	N/A	N/A	N/A	N/A
Ceftriaxone	15/19	79	4/12	33	N/A	N/A	16/100	16	13/84	15	37/65	57	N/A	N/A	N/A	N/A
Clindamycin	159/305	52	31/126	25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ciprofloxacin	N/A	N/A	N/A	N/A	N/A	N/A	11/105	10	22/76	29	1/86	1	N/A	N/A	N/A	N/A
Cloxacillin/ Oxacillin	306/351	87	32/218	15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Erythromycin	77/91	85	17/64	27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gentamicin	20/39	51	1/25	4	13/109	12	9/128	7	13/109	12	7/92	8	N/A	N/A	N/A	N/A
Meropenem	17/18	94	N/A	N/A	N/A	N/A	4/59	7	1/42	2	1/64	2	N/A	N/A	N/A	N/A
Piperacillin-tazobactam	N/A	N/A	N/A	N/A	3/13	23	11/99	11	14/88	16	25/66	38	N/A	N/A	N/A	N/A
Penicillin	105/106	99	58/65	89	6/22	27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rifampin	2/64	3	0/20	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trimethoprim-sulfamethoxazole	91/183	50	4/102	4	0/1	0	13/102	13	37/84	44	12/69	17	N/A	N/A	N/A	N/A
Tobramycin	N/A	N/A	N/A	N/A	N/A	N/A	7/106	7	4/99	4	4/77	5	N/A	N/A	N/A	N/A
Vancomycin	0/28	0	1/114	1	51/313	16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amphotericin B	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/24	0	0/18	0
Caspofungin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/35	0	1/56	2
Fluconazole	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1/107	1	24/93	26

Abbreviations: *C. albicans*, *Candida albicans*; *E. coli*, *Escherichia coli*; N/A, not available; *S. aureus*, *Staphylococcus aureus*
[a] Antibiotic/organism combinations with fewer than six tests were excluded
[b] Coagulase-negative staphylococci included *S. lugdunensis*, *S. haemolyticus*, *S. epidermidis*, *S. capitis*, *S. hominis* and *S. warneri*
[c] Included methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus*
[d] Other *Candida* spp. included *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, *C. parapsilosis*, and *C. tropicalis*

to those reported in the US and Australia. The 2013 CLABSI rate in US medical/surgical ICUs was estimated to be 0.8 per 1,000 line days (11). In Australia, annual rates of CLABSIs in adult ICUs ranged between 0.9 and 1.4 CLABSIs per 1,000 line days from 2011–2013 (12). While CLABSI rates in adult mixed ICUs, CVICUs and PICUs have increased or remained stable in Canada since 2011, rates in NICUs have decreased by 60%. Data available from the US since 2016 indicate similar trends for CLABSIs in neonatal critical care locations, where the standardized incidence ratios (defined as the ratio of observed number of infections compared to the 2015 baseline) decreased by 27% (13–17). These decreased CLABSI rates in the US may be attributed to the updated NHSN guidelines for the prevention of CLABSI, implemented in 2011 (18,19).

Higher rates of CLABSIs are seen in other regions; a large surveillance study of intensive care units in 45 countries from Latin America, Europe, Eastern Mediterranean, Southeast Asia and Western Pacific World Health Organization regions reported pooled mean CLABSI rates of 7.2 per 1,000 line days in PICUs, 5.1 in medical/surgical adult ICUs and 12.0 in NICUs (between January 2012 and December 2017) (11).

Surgical site infections

Among SSIs included in this surveillance report, hip and knee SSIs were the most common. Hip SSI rates remained stable across the reported years, while a decreasing trend in knee SSI rates was observed. Surveillance from the European Centre for Disease Prevention and Control reported similar trends, indicating stable hip SSI rates and decreasing knee SSI rates for study years 2014 to 2017 (20). In a US point prevalence study, a reduction in the prevalence of complex SSIs was observed between 2011 and 2015 (21). In accordance with pathogen results from other regions, the most common pathogens among hip and knee-SSIs were *S. aureus* and CoNS (20,22). Frequent identification of these two pathogens may be attributable to the use of implant devices and contamination from the patient's endogenous skin flora (9). Joint replacements typically occur in older adults, which explains the high median age for hip and knee SSI (23). Joint replacements among older populations are

Table 6: Antibiogram results[a] from pathogens identified from paediatric cardiac, cerebrospinal shunt fluid and hip and knee surgical site infections[b], 2015–2020

Antibiotic	Number of resistant/number tested and %															
	Gram-positive						Gram-negative						Fungi			
	Coagulase-negative staphylococci[c]		*S. aureus*[d]		*Enterococcus* spp.		*Klebsiella* spp.		*E. coli*		*Enterobacter* spp.		*C. albicans*		*Candida* spp. other[e]	
	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%	# of resistant	%
Ampicillin	N/A	N/A	N/A	N/A	1/42	2	6/6	100	11/19	58	16/20	80	N/A	N/A	N/A	N/A
Cefazolin	41/61	67	21/159	13	N/A	N/A	N/A	N/A	4/17	24	18/18	100	N/A	N/A	N/A	N/A
Ceftriaxone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3/10	30	8/17	47	N/A	N/A	N/A	N/A
Clindamycin	18/77	23	43/212	20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ciprofloxacin	1/7	14	3/24	13	N/A	N/A	0/8	0	6/17	35	0/19	0	N/A	N/A	N/A	N/A
Cloxacillin/ Oxacillin	80/133	60	40/284	14	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Erythromycin	20/48	42	35/105	33	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gentamicin	N/A	N/A	0/15	0	5/14	36	2/9	22	4/20	20	1/23	4	N/A	N/A	N/A	N/A
Meropenem	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/9	0	0/7	0	N/A	N/A	N/A	N/A
Piperacillin-tazobactam	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1/7	14	6/11	55	N/A	N/A	N/A	N/A
Penicillin	13/16	81	52/56	93	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rifampin	0/27	0	2/53	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trimethoprim-sulfamethoxazole	19/69	28	2/198	1	N/A	N/A	0/6	0	3/15	20	1/17	6	N/A	N/A	N/A	N/A
Tobramycin	N/A	N/A	N/A	N/A	N/A	N/A	1/8	13	1/16	6	0/19	0	N/A	N/A	N/A	N/A
Vancomycin	0/96	0	1/114	1	0/24	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Amphotericin B	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Caspofungin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fluconazole	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: *C. albicans*, *Candida albicans*; *E. coli*, *Escherichia coli*; N/A, not available; *S. aureus*, *Staphylococcus aureus*
[a] Antibiotic/organism combinations with fewer than six tests were excluded
[b] Antibiogram data collection for HK SSI began in 2016
[c] Coagulase-negative staphylococci included *S. lugdunensis, S. haemolyticus, S. epidermidis, S. capitis, S. hominis* and *S. warneri*
[d] Included methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus*
[e] Other *Candida* spp. included *C. dubliniensis, C. glabrata, C. krusei, C. lusitaniae, C. parapsilosis,* and *C. tropicalis*

also prone to surgical complications, such as prosthetic joint infections (23). Data indicate that surgical site infections frequently lead to readmission and revision surgery, both of which result in high financial and resource burdens on the healthcare system (24).

The overall rate of surgical site infections from CSF shunts was 2.9 per 100 surgeries. This aligns with rates reported from a 2012 multi-country review, which range from 3% to 12% (25). Stratification of CSF shunt SSI data by paediatric and adult/mixed hospitals showed that adult rates (2.8/100 surgeries) and paediatric rates (3.0/100 surgeries) were similar from 2011–2020. Data from a previous CNISP study conducted between 2000 and 2002 indicated a higher paediatric rate than the adult rate of CSF shunt SSI (26). Given that the rate of CSF shunt SSI among paediatric patients from 2011–2020 (3.0%) is lower than that from 2000–2002 (4.9%), there is evidence of a decrease in SSI rates among paediatric populations (26). Meanwhile, the rate of CSF shunt SSI among adult patients from 2011–2020 (2.8%) remains relatively unchanged compared to that of 2000–2002 (3.2%) (26).

The overall rate of paediatric cardiac SSI between 2011 and 2020 was 4.1 per 100 surgeries. The 2018 paediatric cardiac SSI rate should be interpreted with caution; given that the number of cases used to calculate this rate was limited, the rates may be sensitive to fluctuation attributed to individual hospital sites. Nevertheless, the overall rate was found to be comparable with infection rates reported elsewhere, despite limited literature about paediatric cardiac SSIs. A 2009–2012 intervention study of neonates undergoing cardiac surgery at a New York tertiary-care centre found pre and post-intervention paediatric cardiac SSI rates of 6.2 and 5.8/100 surgeries, respectively (27). In France, 19% of patients younger than one year of age and undergoing cardiac surgery presented with a SSI during the study period, between 2012 and 2013 (28). The hospital-acquired cardiac-SSI rate at two New York hospitals was 1.4 infections per 100

procedures within 90 days for patients younger than 18 years of age, based on a retrospective study from 2010–2012 (29).

Antibiogram

The percentage of *S. aureus* isolates that were MRSA in this study (14%–15%) (Table 5 and Table 6) was slightly higher to what was reported from a Swiss surveillance network where 8% of *S. aureus* SSI cases were MRSA in 2010–2015 (30). Higher rates of MRSA have been reported elsewhere, such as in several centres in Latin America where resistance averaged 44.7% in 2017 (31). In the US, 42%–48% of *S. aureus* isolates from HAIs (including SSI, CLABSI and others) in NHSN surveillance were MRSA (9).

Of the identified *Enterococcus* spp. in CLABSIs, 16% were vancomycin-resistant *Enterococci,* which is less than 30.9% identified as resistant in ICUs in Poland (32). From NHSN surveillance in the US, 84.5% of *Enterococcus faecium* and 8.5% of *Enterococcus faecalis* pathogens identified from CLABSIs in ICUs were vancomycin-resistant *Enterococci* in 2015–2017 (9).

Meropenem resistance was low among the gram-negative pathogens identified among CLABSIs and SSIs (0%–7%). Similarly in the US, the percent of carbapenem resistance among *Klebsiella* spp. ranged from 3.1% (among SSIs) to 6.9% (among expanded list of device-associated infections); the percent of carbapenem resistance among *E. coli* ranged from 0.6% (among SSIs) to 0.7% (expanded list) (9).

Strengths and limitations

The main strength of this study is the standardized collection of detailed data from a large network of sentinel hospitals for over ten years. The CNISP network extends across Canada, although it may not be representative of all Canadian acute care hospitals since the number of hospitals participating in each HAI surveillance project differed. However, recruitment is ongoing and CNISP coverage of Canadian acute care beds increased from 25% in 2011 to 30% in 2020. The CNISP is continuing to increase representativeness, especially among northern, community, rural and Indigenous populations.

The epidemiologic data collected were limited to the information available in the patient charts. For CLABSI surveillance, data were limited to infections occurring in the ICU settings, and as such may only represent a portion of CLABSIs occurring in the hospital. Further, differences in surveillance protocols and case definitions, as well as the lack of recent comparable data, limit comparison with data from other countries. The CNISP continues to support the national public health response to the COVID-19 pandemic. Future studies are ongoing to assess the impact of the COVID-19 pandemic on device and surgical procedure-related HAIs and AMR.

Conclusion

This report provides an updated summary of rates, pathogen distributions and antimicrobial resistance among select device and surgical procedure-related HAIs and relevant pathogens. The collection and analysis of national surveillance data are key to understanding and reducing the national burden of device and surgical procedure-related HAIs by providing benchmark rates for comparison nationally and internationally and informing antimicrobial stewardship and infection prevention and control programs and policies.

Authors' statement

Canadian Nosocomial Infection Surveillance Program hospitals provided expertise in the development of protocols in addition to the collection and submission of epidemiological and microbiological data. Epidemiologists from Public Health Agency of Canada were responsible for the conception, analysis, interpretation, drafting and revision of the article.

Competing interests

None.

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Appendix: Case definitions

Central line-associated bloodstream infection

Only central line-associated bloodstream infections (BSIs) related to an intensive care unit (ICU) admission were included in surveillance.

Bloodstream infections case definition:

Bloodstream infection is **NOT** related to an infection at another site and it meets one of the following criteria:

Criterion 1: Recognized pathogen cultured from at least one blood culture, unrelated to infection at another site.

OR

Criterion 2: At least one of: fever (higher than 38°C core), chills, hypotension; if aged younger than 1 year, fever (higher than 38°C core), hypothermia (lower than 36°C core), apnea or bradycardia **AND** common skin contaminant (see list below) cultured from at least two blood cultures drawn on separate occasions or at different sites, unrelated to infection at another site. Different sites may include peripheral veins, central venous catheters or separate lumens of a multilumen catheter. Different times include two blood cultures collected on the same or consecutive calendar days via separate venipunctures or catheter entries. The collection date of the first positive blood culture is the date used to identify the date of positive culture. Two positive blood culture bottles filled at the same venipuncture or catheter entry constitute only one positive blood culture.

Central line-associated bloodstream infection case definition:

A central line-associated bloodstream infections (CLABSI) must meet one of the following criteria:

Criterion 1: A laboratory-confirmed bloodstream infection (LCBSI) where a central line catheter (CL) or umbilical catheter (UC) was in place for more than two calendar days on the date of the positive blood culture, with day of device placement being Day 1.

OR

Criterion 2: A LCBSI where a CL or UC was in place more than two calendar days and then removed on the day or one day before positive blood culture was drawn.

Intensive care unit-related central line-associated bloodstream infection case definition:

A CLABSI related to an ICU if it meets one of the following criteria:

Criterion 1: CLABSI onset after two days of ICU stay.

OR

Criterion 2: If the patient is discharged or transferred out of the ICU, the CLABSI would be attributable to the ICU if it occurred on the day of transfer or the next calendar day after transfer out of the ICU.

Note: If the patient is transferred into the ICU with the CL and the blood culture was positive on the day of transfer or the next calendar day, then the CLABSI would be attributed to the unit where the line was inserted.

Common skin contaminants:

Diphtheroids, *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp. and *Rhodococcus* spp.

Hip and knee surgical site infection

Only complex surgical site infections (SSIs) (deep incisional or organ/space) following hip and knee arthroplasty were included in surveillance.

A deep incisional surgical site infection must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g. facial and muscle layers) of the incision and the patient has at least **ONE** of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- Deep incision that spontaneously dehisces or is deliberately opened by the surgeon and is culture-positive or not cultured when the patient has at least one of the following signs or symptoms: fever (higher than 38°C) or localized pain or tenderness (a culture-negative finding does not meet this criterion)
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation or by histopathologic or radiologic examination
- Diagnosis of a deep incisional SSI by a surgeon or attending physician

An organ/space surgical site infection must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia or muscle layers, that is opened or manipulated during the operative procedure and patient has at least **ONE** of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space

- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathologic or radiologic examination
- Diagnosis of an organ/space SSI by a surgeon or attending physician

Cerebrospinal fluid shunt surgical site infection

Only patients who underwent a placement or revision of a cerebrospinal fluid (CSF) shunting device and the infection occurred within one year of surgery were included in surveillance.

Cerebrospinal fluid shunt-associated surgical site infection case definition:

An internalized CSF shunting device is in place **AND** a bacterial or fungal pathogen(s) is identified from the cerebrospinal fluid **AND** is associated with at least **ONE** of the following:

- Fever (temperature 38°C or higher)
- Neurological signs or symptoms
- Abdominal signs or symptoms
- Signs or symptoms of shunt malfunction or obstruction

Paediatric cardiac surgery surgical site infection

Only surgical site infections following open-heart surgery with cardiopulmonary bypass among paediatric patients (younger than 18 years of age) were included in surveillance.

A **superficial incisional SSI** must meet the following criterion: Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and meets at least **ONE** of the following criteria:

- Purulent drainage from the superficial incision
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least **ONE** of the following signs or symptoms of infection:
  - Pain or tenderness, localized swelling, redness or heat, and the superficial incision is deliberately opened by a surgeon, and is culture-positive or not cultured (a culture-negative finding does not meet this criterion)
  - Diagnosis of superficial incisional SSI by the surgeon or attending physician

A **deep incisional SSI** must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure **AND** involves deep soft tissues (e.g. facial and muscle layers) of the incision **AND** the patient has at least **ONE** of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- Deep incision spontaneously dehisces or is deliberately opened by the surgeon and is culture-positive or not cultured when the patient has at least one of the following signs or symptoms: fever (higher than 38°C) or localized pain or tenderness (a culture-negative finding does not meet this criterion)
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation or by histopathologic or radiologic examination
- Diagnosis of a deep incisional SSI by a surgeon or attending physician

An **organ/space SSI** must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure **AND** infection involves any part of the body, excluding the skin incision, fascia or muscle layers, that is opened or manipulated during the operative procedure **AND** the patient has at least **ONE** of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathologic or radiologic examination

Table A1: Rate of central line-associated bloodstream infection per 1,000 line days by intensive care unit type, 2011–2020

Year	Adult Mixed ICU	Adult CVICU	NICU	PICU
2011	0.8	0.8	4.0	1.2
2012	0.9	0.9	3.3	1.1
2013	0.9	0.6	3.2	1.0
2014	0.8	0.5	2.2	1.7
2015	1.0	0.7	2.3	2.1
2016	1.0	0.3	2.3	1.6
2017	1.1	0.3	1.8	1.6
2018	1.1	0.8	1.8	1.9
2019	1.4	0.6	2.0	1.8
2020	1.6	0.7	1.6	1.7
Overall	1.1	0.6	2.3	1.6

Abbreviations: CLABSI, central line-associated bloodstream infection; CVICU, cardiovascular intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit

Table A2: Rate of hip and knee surgical site infections per 100 surgeries, 2011–2020

Year	Hip	Knee
2011	0.82	0.69
2012	0.73	0.65
2013	0.79	0.41
2014	0.85	0.56
2015	0.74	0.43
2016	0.79	0.35
2017	0.78	0.34
2018	0.88	0.31
2019	0.70	0.30
2020	0.48	0.29
Overall	0.79	0.45

Table A3: Cerebrospinal fluid shunt surgical site infection rates per 100 surgeries by hospital type, 2011–2020

Year	Adult and Mixed hospitals	Paediatric hospitals	All hospitals[a]
2011	4.60	5.66	5.20
2012	2.21	3.08	2.70
2013	2.47	2.40	2.43
2014	0.84	2.12	1.36
2015	3.44	1.91	2.54
2016	4.19	2.00	2.93
2017	4.17	2.74	3.41
2018	1.93	1.46	1.70
2019	3.13	5.13	3.96
2020	2.42	3.21	2.80
Overall	2.84	2.96	2.90

[a] All hospitals include adult, mixed, and paediatric hospitals participating in cerebrospinal fluid shunt surgical site infection surveillance

Table A4: Paediatric cardiac surgical site infection rates per 100 surgeries, 2011–2020

Year	Rate
2011	3.13
2012	2.90
2013	4.32
2014	3.45
2015	3.27
2016	3.02
2017	4.43
2018	7.46
2019	5.47
2020	3.90
Overall	4.14

National healthcare-associated infections surveillance programs: A scoping review

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Abstract

Background: National surveillance of healthcare-associated infections (HAIs) is necessary to identify areas of concern, monitor trends, and provide benchmark rates enabling comparison between hospitals. Benchmark rates require representative and large sample sizes often based on pooling of surveillance data. We performed a scoping review to understand the organization of national HAI surveillance programs globally.

Methods: The search strategy included a literature review, Google search and personal communications with HAI surveillance program managers. Thirty-five countries were targeted from four regions (North America, Europe, United Kingdom and Oceania). The following information was retrieved: name of surveillance program, survey types (prevalence or incidence), frequency of reports, mode of participation (mandatory or voluntary), and infections under surveillance.

Results: Two hundred and twenty articles of 6,688 identified were selected. The four countries with most publications were the US (48.2%), Germany (14.1%), Spain (6.8%) and Italy (5.9%). These articles identified HAI surveillance programs in 28 of 35 countries (80.0%), operating on a voluntary basis and monitoring HAI incidence rates. Most HAIs monitored surgical site infections in hip (n=20, 71.4%) and knee (n=19, 67.9%) and *Clostridoides difficile* infections (n=17, 60.7%).

Conclusion: Most countries analyzed have HAI surveillance programs, with characteristics varying by country. Patient-level data reporting with numerators and denominators is available for almost every surveillance program, allowing for reporting of incidence rates and more refined benchmarks, specific to a given healthcare category thus offering data that can be used to measure, monitor, and improve the incidence of HAIs.

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Keywords: healthcare-associated infections, surveillance, surgical site infections, *Clostridoides difficile*, Methicillin-resistant *Staphylococcus aureus*

Introduction

Healthcare-associated infections (HAI) are acquired by patients during the process of care for other health conditions (1). They are the most frequently reported adverse event in healthcare delivery (2), affecting millions of patients each year worldwide and leading to significant morbidity, mortality and financial costs to healthcare programs. In the beginning of 2000, HAI prevalence in high-income countries ranged between 3.5% and 12%; in Europe, for example, the average prevalence is 7.1%, representing over four million people infected each year (3).

The emergence of antimicrobial-resistant organisms (AROs) complicates the situation, making HAIs more difficult to treat. The Public Health Agency of Canada estimated that approximately 2% of patients admitted to large academic Canadian hospitals will have acquired an infection during their hospital stay (4) and that at any time, 3%–10% of hospitalized patients are either infected with or a carrier of an ARO (5).

Surveillance of HAIs is considered a necessary component of infection prevention and control, public health and patient safety. National surveillance requires representative and large enough sample sizes to produce meaningful infection rates for benchmarking, detection of trends and prioritization of interventions at a regional or local level, and for specific populations.

Many countries have national HAI surveillance programs, but a comprehensive review of these countries' program characteristics is not currently available. We conducted a scoping review to identify national HAI surveillance programs globally and summarized their characteristics to inform decisions on possible national programs for Canada.

Methods

Research question

The main research question was: What are the characteristics of HAI surveillance programs in a selected sample of high-income countries, defined by the World Bank as countries with a gross national income per capita of at least US$12,696 (6) We added the following sub-questions to have a more complete picture: Is the program mandatory or voluntary? Is it based on incidence or prevalence analysis? What are the infections or procedures under surveillance? What is the frequency of public reporting?

Scoping review

The first step was a scoping review using Medline. We performed a search strategy developed with a medical research librarian. Keywords and MeSH were created in Medline with the following four concepts: nosocomial, epidemiology, surveillance and administration (**Table S1**). The inclusion criteria consisted of articles identifying surveillance of HAIs in four selected high-income regions in the world: North America, Europe through the European Centre for Disease Prevention and Control (ECDC), United Kingdom (UK) and Oceania. The ECDC encompassed 27 countries (26 countries and ECDC itself), for a total of 35 countries in these four regions. Surveillance needed to be reported at the national level. We included articles published between January 1, 1996, and December 31, 2020, written in English or French. Government publications or reports and grey literature that contained any surveillance data on HAI were kept. Opinion, editorial, news reports, abstracts from conferences or meetings were excluded. Only human health articles were considered. We searched Medline, grey literature and communicated with key people.

Grey literature

Grey literature was used to compile unidentified HAI surveillance programs from Medline. National organizations' websites of the four regions cited in the inclusion criteria were considered. Once the program name was retrieved, usually from published articles, a Google search was performed to get publicly available information on the HAI surveillance program, aiming to obtain protocols or surveillance reports. For this search, no language limitation was applied.

We used Google to identify surveillance programs in countries that were not found through our Medline search and to validate identified programs to obtain publicly available protocols and surveillance reports. We compiled each surveillance program's characteristics, as not all programs publish their results as peer-reviewed articles.

Personal communication

When information was not available in official surveillance protocols or on organizations' websites, an email was sent to authors or program managers to get publicly available documents, such as annual reports of the surveillance performed. A reminder was sent if no answer was received after two weeks from the first communication. Only one reminder was sent.

Data management

Studies meeting the inclusion criteria were uploaded to DistillerSR (Evidence Partners, Ottawa, Canada), which was used to remove duplicates. Independent screening for title/abstract and full text was performed by the first two authors. If the HAI surveillance program name was available in this section, the information was extracted and validated with a Google search. If the program name was correct, full text review was not performed. If the program name was not found in the title or the abstract for the country, these articles' full texts were read. Conflicts were resolved through discussion until a consensus was reached.

Data extraction and quality assessment

An electronic data form was developed on DistillerSR. The following information was extracted from articles, websites and government reports: general information, name of national HAI surveillance programs, HAIs included in the program, jurisdiction, modes of participation (mandatory or voluntary), survey type (incidence or prevalence), reporting periodicity, percentage of facilities involved in the surveillance, microorganisms, medical devices, type of data (individual or aggregated) and official website.

Results

We identified 6,688 articles with the selected keywords and MeSH. From these, 261 duplicate articles were removed. An additional 6,206 articles were removed because no HAI surveillance program was identified in full-text review. A total of 220 articles (**Data S1**) were used in this review (**Figure S1**). Some articles identified programs for more than one country and were counted more than once, which is why the number of articles in **Table S2** is 245. The four countries most represented were the US (n=106, 48.2%), Germany (n=31, 14.1%), Spain (n=15, 6.8%) and Italy (n=13, 5.9%).

We identified surveillance programs for 20 of 35 countries. A Google search identified eight additional programs, for a total of 28 of 35 countries (80.0%) having a national program. For the remaining nations (Cyprus, Estonia, Greece, Iceland, Latvia, Malta, and Slovenia), a HAI surveillance program could not be found, but four participated in at least one annual ECDC project. Only 5 of 19 (26.3%) contacted program managers replied (**Table 1** summarizes the information).

Table 1: Characteristics of national hospital-acquired infection surveillance programs identified

Program	Country	Type	Frequency of public report	VRE	MRSA	MSSA	CDI	CPE[a]	Gram negative	CLABSI	BSI	SSI	UTI	Venti[b]	ARO	Other
Oceania																
ACSQHC	Australia	I	Annual/ quarterly	-	-	-	V	-	-	M,V	M[c]	M,V	-	-	-	-
ANZICS		-	-	-	-	-	-	-	-	M,V	-	-	-	-	-	-
AIHW		-	Annual	-	-	-	-	-	-	-	M[c]	-	-	-	-	-
AGAR		P	Annual	-	-	-	-	-	-	-	-	-	-	-	V[d]	-
North America																
CNISP	Canada	I, P	Annual	V	V	V	V	V	-	V	-	V	-	-	V	V: PPS, *Candida auris*, CSF
NHSN	US	I	Annual	V	V	V	V	V	-	V	-	V	V	V	V	-
United Kingdom																
PHE	England	I	Monthly/ annual	-	M[d]	M[d]	M	-	M[d]	-	-	M,V	-	-	-	-
-	North-Ireland	I	Quarterly	-	M	-	M	-	-	-	-	M	-	-	-	V: PPS
WHAIP	Wales	I	Annual/ monthly	-	M	-	M	-	-	-	-	M	-	M	-	-
SSHAIP	Scotland	I, P	Quarterly/ annual	-	M[d]	-	M	U	M[d]	M[e]	M[e]	M,V	U	M[e]	-	M: norovirus (outbreak), PPS, ICU
Europe																
ANISS	Austria	I	Annual	-	-	-	-	-	-	-	-	V	-	-	-	V: ICU, PPS
NSIH	Belgium	I	Annual	V	M	-	V	-	M	V[e]	M	V	V[e]	M[e]	-	-
-	Croatia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NRC-HAI	Czech Republic	I ,P	-	-	-	-	U	-	-	-	-	U	-	-	-	U: PPS, ICU
HAIBA	Denmark	I	Annual	-	-	-	U	-	-	-	U	U	U	-	-	-
DANMAP		P	-	M	M	-	-	M	-	-	-	-	-	-	-	-
HAI-NET	ECDC	I, P	I: Annual P: every five years	-	-	-	V	-	-	-	V[e]	V	V[e]	-	-	V: PPS, V[e]: pneumonia
SIRO	Finland	I	Annual	-	-	-	V	-	-	-	V	V	-	-	-	V: PPS
RAISIN-I	France	I	Annual	-	-	-	-	-	-	-	-	V	-	-	-	-
RAISIN-P		P	Every five years	-	-	-	-	-	-	-	-	-	-	-	-	V: PPS
KISS	Germany	I	Annual	V[f]	V	-	V	-	V[f]	-	V[e]	V	V[e]	V[e]	-	V: neo, LRI[e]
NNSR	Hungary	I	Annual	-	-	-	M	-	-	-	M	V	-	-	M	V: ICU, neonatal M: outbreak
HPSC	Ireland	I	Quarterly/ annual	V[d]	V[d]	V[d]	V	M	V[d]	-	-	-	-	V[e]	-	M: PPS
SPIN-UTI	Italy	I	Every two years	-	-	-	-	-	-	V[e]	V[e]	-	V[e]	V[e]	-	-
GiViTi		I	Annual	-	-	-	-	-	-	V[e]	V[e]	-	-	V[e]	-	V[e]: pneumonia

Table 1: Characteristics of national hospital-acquired infection surveillance programs identified (*continued*)

Program	Country	Type	Frequency of public report	VRE	MRSA	MSSA	CDI	CPE[a]	Gram negative	CLABSI	BSI	SSI	UTI	Venti[b]	ARO	Other
Europe (*continued*)																
-	Lithuania	I	Annual	-	-	-	-	-	-	-	-	V	-	-	-	V: ICU
-		P	Annual	-	-	-	-	-	-	-	-	-	-	-	-	PPS
NOSIX	Luxembourg	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PREZIES	Netherlands	I, P	Annual	-	-	-	-	-	-	M	-	M	-	-	-	V: PPS
SWAB		P	Annual	-	-	-	-	-	-	-	-	-	-	-	V	-
NOIS	Norway	I ,P,	Annual	-	-	-	-	-	-	-	M	M	M	-	U	V: PPS, U: LRI, neonatal
-	Poland	I, P	PPS: annual	-	-	-	-	-	-	-	V[e]	-	V[e]	V[e]	-	V: PPS
PPCIRA	Portugal	I	-	-	-	-	-	-	-	V[e], M[g]	-	V	-	V[e],M[g]	-	-
EPIS	Slovakia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ENVIN	Spain	I	Annual	-	-	-	-	-	-	V[e]	V[e]	-	V[e]	V[e]	-	-
NEO-KISS		I	-	-	-	-	-	-	-	-	V[g]	-	-	-	-	V[g]: CFS
EPINE		P	Annual	V	V	V	V	V	V	V	V	V	V	V	V	V: PPS
INCLIMECC		I, P	-	-	M	-	M	M	-	M[e]	M[e]	M	M[e]	M[e]	-	M: PPS
SALAR	Sweden	P	Twice a year	-	-	-	-	-	-	-	-	-	-	-	-	M: PPS

Abbreviations: ACSQHC, Australian Commission on Safety and Quality in Health Care; AGAR, Australian Group on Antimicrobial Resistance; AIHW, Australian Institute of Health and Welfare; ANISS, Austrian Nosocomial Infection Surveillance System; ANZICS, Australian And New Zealand Intensive Care Society; ARO, antimicrobial-resistant organisms; BSI, bloodstream infections; CDI, *Clostridoides difficile*; CLABSI, central line-associated bloodstream infection; CNISP, Canadian Nosocomial Infection Surveillance Program; CPE, carbapenemase-producing Enterobacteriaeceae; CPO, carbapenemase-producing organisms; CRE, carbapenem-resistant Enterobacteriaceae; CSF, cerebrospinal fluid shunt; DANMAP, Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; ECDC, European Centre for Disease Prevention and Control; ENVIN, Estudio Nacional de Vigilancia de Infección Nosocomial en Servicios de Medicina Intensiva; EPINE, study on the prevalence of nosocomial infections in Spain; EPIS, national epidemiologic surveillance systems; GiViTi, Gruppo italiano per la Valuatazion degli interventi In Terapia intensiva; HAIBA, Healthcare-Associated Infections Database; HAI-NET, Healthcare-Associated Infections Surveillance Network; HPSC, Health Protection Surveillance Center; I, incidence; ICU, intensive care unit; INCLIMECC, Indicadores Clínicos de Mejora Continua de la Calidad; KISS, German Nosocomial Infection Surveillance System; LRI, lower respiratory infection; M, mandatory; MRSA, methicillin-resistant *Staphylococcus aureus* bloodstream infections; MSSA, methicillin-susceptible *Staphylococcus aureus* bloodstream infection; NEO-KISS, Neonatology-KISS; NHSN, National Healthcare Safety Network; NNSR, National Nosocomial Surveillance System; NOIS, surveillance system for hospital acquired infections; NOSIX, Luxembourg Nosocomial Infection Surveillance System; NRC-HAI, National Reference Center for Healthcare Associated Infections; NSIH, National Surveillance of Healthcare associated and antimicrobial resistance; P, prevalence; PHE, Public Health England; PPCIRA, Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos; PPS, point prevalence survey; PREZIES, Prevention of Nosocomial Infection through Surveillance; RAISIN, Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales; SALAR, Swedish Association of Local Authorities and Regions; SIRO, Finnish Hospital Infection Programme; SPIN-UTI, Italian Nosocomial Infections Surveillance in Intensive Care Units; SSHAIP, Scottish Surveillance of Healthcare Associated Infection Programme; SSI, surgical site infection; SWAB, Dutch Working Party on Antibiotic Policy; U, unknown; US, United States; UTI, urinary tract infection; V, voluntary; VAE, ventilator-acquired event; VAP, ventilator-acquired pneumonia; VRE, vancomycin-resistant enterococci; WHAIP, Welsh Healthcare Associated Infection Programme; -, not applicable

[a] CPE and/or CPO and/or CRE
[b] VAP and/or VAE
[c] *Staphylococcus aureus*
[d] Sepsis
[e] ICU
[f] ARO
[g] Neonatal

We kept information from national HAI surveillance programs as we aimed to understand how alliance of regions pooled data; thus, programs that were not at least national in scope and those for which we could not differentiate between community-acquired or hospital-acquired infections were excluded.

Surveillance programs

We identified 38 national HAI surveillance programs for 28 countries with a national surveillance program (Table 1). Some countries have two or more surveillance programs. Most national surveillance programs reported yearly incidence on a voluntary basis. Surgical site infection (SSI) surveillance was done in 21 of 35 countries (**Table 2**). Infections and procedures under surveillance are detailed in Table 1. Twenty-six programs for which data was available used active surveillance. None reported use of administrative surveillance as the only source of data.

The HAI surveillance network (HAI-NET) from the ECDC performs two types of surveillance: 1) a point prevalence survey (PPS) of HAIs in European acute care hospitals (7), every five years; and 2) three annual incidence surveillance for *Clostridoides difficile* infections (CDI) (8), infections acquired in intensive care unit (ICU) (9) and SSI (10) (**Table S3**). In total, 33 countries/regions (29 ECDC countries and four UK regions) participated in the PPS (7,11,12). Four periods were selected for data collection (April–June and September–November of each year), avoiding the summer holidays (lower staffing) and the winter period (higher antimicrobial use). Denominator data could be either: patient-based (optional) or unit-based (mandatory). Patient present on the ward at 8 a.m. and not discharged during the survey were counted in the denominator.

Table 2: National surveillance programs for surgical site infections, 21 countries

Program	Country	CABG	Laparoscopic CHOL	Open CHOL	Laparoscopic COLO	Open COLO	CSEC	HPRO	KPRO	LAM	Other
ACSQHC	Australia	X	-	-	-	-	X	X	X	X	Appendectomy, cholecystectomy, colectomy, craniotomy, hernia repair and spinal fusion
CNISP	Canada	-	-	-	-	-	-	X	X	-	Paediatric cardiac surgery
NHSN	US	X	X	X	X	X	X	X	X	X	30 more
NINSS	England	X	-	-	-	-	-	X	X	-	Abdominal hysterectomy, bile duct, liver or pancreatic, breast, cardiac surgery (non-CABG), cholecystectomy, cranial, gastric, large bowel, limb amputation, reduction of long bone fracture, repair of neck of femur, small bowel, spinal, vascular
-	North Ireland	-	-	-	-	-	X	X	X	X	-
WHAIP	Wales	-	-	-	-	-	X	X	X	-	-
SSHAIP	Scotland	X	-	-	-	-	X	X	X	-	Abdominal hysterectomy, breast, cardiac, cranial, large bowel, reduction of long bone fracture, repair of neck of femur, vascular
ANISS	Austria	X	X	X	X	X	X	X	X	-	Abdominal hysterectomy, appendectomy, ear nose throat, genitourinary, herniorrhaphy, kidney, mastectomy, prostate, skin (correctional and scar), small bowel and vaginal hysterectomy
NSIH	Belgium	X	X	X	X	X	X	X	X	X	-
NRC-HAI	Czech Republic	-	-	-	-	-	-	-	-	-	Site under construction
HAIBA	Denmark	-	-	-	-	-	-	X	X	-	-
HAI-NET	ECDC	X	X	X	X	X	X	X	X	X	-
SIRO	Finland	-	-	-	-	-	-	X	X	-	Paediatric open heart
RAISIN	France	X	X	X	X	X	X	X	X	X	Bariatric, coronary, orthopedic, digestive, neurosurgery, obstetric gynecology, reconstructive, thoracic, traumatological, urological and vascular
KISS	Germany	X	X	X	X	X	X	X	X	X	-
NNSR	Hungary	X	X	X	X	X	X	X	X	X	Abdominal hysterectomy, appendectomy, cardiac, limb amputation, reduction of long bone fracture
-	Lithuania	X	X	X	X	X	X	X	X	-	Appendix, inguinal hernia, orthopedic, traumatological, vascular (venous)
PREZIES	Netherlands	X	X	X	X	X	X	X	X	X	Breast, femoral head replacement, isolated open aortic valve, pacemaker implantation
NOIS	Norway	X	X	X	X	X	X	X	-	-	-
PPICRA	Portugal	X	X	X	X	X	X	X	X	X	-
EPINE	Spain	X	X	X	X	X	X	X	X	X	30 more
INCLIMECC		X	-	-	X	X	-	X	X	-	Appendectomy, fusion vertebral, gastric, herniorrhaphy, rectum
Total: N (%)	-	15 (71.4%)	12 (57.1%)	12 (57.1%)	12 (57.1%)	12 (57.1%)	16 (76.1%)	20 (95.2%)	19 (90.5%)	11 (52.4%)	-

Abbreviations: ACSQHC, Australian Commission on Safety and Quality in Health Care; ANISS, Austrian Nosocomial Infection Surveillance System; CABG, coronary artery bypass graft; CHOL, cholecystectomy; CNISP, Canadian Nosocomial Infection Surveillance Program; COLO, colon surgery; CSEC, caesarean section; ECDC, European Centre for Disease Prevention and Control; EPINE, study on the prevalence of nosocomial infections in Spain; HAIBA, Healthcare-Associated Infections Database; HAI-NET, Healthcare-Associated Infections Surveillance Network; HPRO, hip prosthesis surgery; INCLIMECC, Indicadores Clínicos de Mejora Continua de la Calidad; KISS, German Nosocomial Infection Surveillance System; KPRO, knee prosthesis surgery; LAM, laminectomy; NHSN, National Healthcare Safety Network; NINSS, Nosocomial Infection National Surveillance Scheme; NNSR, National Nosocomial Surveillance System; NOIS, surveillance system for hospital acquired infections; NRC-HAI, National Reference Center for Healthcare Associated Infections; NSIH, National Surveillance of Healthcare associated and antimicrobial resistance; PPCIRA, Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos; PREZIES, Prevention of Nosocomial Infection through Surveillance; RAISIN, Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales; SIRO, Finnish Hospital Infection Programme; SSHAIP, Scottish Surveillance of Healthcare Associated Infection Programme; US, United States; WHAIP, Welsh Healthcare Associated Infection Programme;X, surveillance done by the country; -, not applicable

The SSI surveillance included nine surgical procedures: coronary artery bypass graft; open and laparoscopic cholecystectomy; open and laparoscopic colon surgery; caesarean section; hip prosthesis; knee prosthesis; and laminectomy, according to three case definitions: superficial incisional; deep incisional; and organ/space (13). Two indicators are produced: 1) proportion of SSIs by surgical procedure category (HAI/specific surgical procedure) in the 30 days after surgery, if no implant, and in the 90 days, if implant; and 2) proportion of SSIs diagnosed before hospital discharge. Fifteen countries/regions participated to the last annual surveillance (10).

The CDI surveillance was recommended as a continuous surveillance over 12 months, with a minimal duration of three consecutive months (14). The denominator includes all hospitalized patients regardless of age. Every case meeting the case definition is included in the numerator. According to the last available published report, 20 countries/regions participated in the surveillance (8).

In the last ECDC ICU-based surveillance, 11 countries/regions participated (9). Five infections were included: pneumonia, bloodstream infection (BSI), urinary tract infection (UTI), device-related infections (e.g. ventilator-associated pneumonia [VAP], central line-associated bloodstream infection [CLABSI], catheter-associated CA-UTI), catheter-related infection (CRI), and other HAI (including neonatal infections). Two surveillance options were available: unit-based and patient-based (15). To be considered in the denominator, a patient must stay for at least three days in the ICU. HAI surveillance is recommended for three to six months each year.

The National Healthcare Safety Network (NHSN, US) is separated in six components with HAI surveillance included in Patient Safety (16). Participating hospitals must produce a monthly reporting plan of what will be under surveillance and an annual facility survey. In acute care, six infections/procedures are monitored: CLABSI, CA-UTI, ventilator associated event (VAE) and paediatric VAE, SSI, multidrug-resistant organisms (MDRO) and CDI (16).

Many rates are produced for CDI and MDRO (16). For MDRO, prevalence rates are calculated for inpatients, community onset, healthcare facility onset, and outpatients, MDRO infection/colonization incidence or incidence density rates are also calculated (**Table 3**). In the last NHSN report (17), all states/territories reported at least one acute care facility for one month of data for every infection. The state's mandate for NHSN varies by infection (**Table 4**).

Table 3: Numerator and denominator information collected per hospital-acquired infections for rate calculations, National Healthcare Safety Network, U.S., 2021

HAI	Numerator	Denominator	Outcomes		
			Incidences rates		Device utilization ratio
CLABSI	# infections	Device-days Patient-days	# infections/# central-line days	X 1,000	# central-line days/# patient days
Pneumoniae	# infections	Device-days Patient-days	# VAP/# ventilation-days	X 1,000	# ventilation-days/# patient days
CA-UTI	# infections	Device-days Patient-days	# infections/# catheter-days	X 1,000	# catheter-days/# patient days
SSI	# infections: superficial, deep, organ/space	All patients for each procedure	# SSI/# specific procedure	X 100	-
VAE or PedVAE	# infections	Device-days Patient-days	# VAE/# ventilation-days	X 1,000	# ventilation-days/# patient days
MDRO	Laboratory confirmed MDRO Healthcare facility onset	Admission Patient-days	# MDRO BSI/# admission # MDRO BSI/# patient-days	X 100 X 1,000	-
CDI	Laboratory confirmed CDI Community-onset healthcare facility associated Healthcare facility onset	Patient-days	# CDI/# patient-days # CDI HO/# patient-days # CDI (HO + CO-HCFA)/# patient-days	X 10,000	-

Abbreviations: BSI, bloodstream infection; CA-UTI, catheter-associated urinary tract infection; CDI, *Clostridoides difficile* infection; CLABSI, central line-associated bloodstream infection; CO-HCFA, community-onset healthcare facility associated; HAI, healthcare-associated infections; HO, healthcare facility onset; MDRO, multidrug-resistant organisms; PedVAE, paediatric ventilator-associated event; SSI, surgical site infection; VAE, ventilator-associated event; VAP, ventilator-associated pneumonia; -, not applicable

Table 4: States with mandatory participation in US National Healthcare Safety Network, surveillance program, per infection, 2018

Mandated	CLABSI	CA-UTI	VAE	COLO	HYST	MRSA	CDI
Yes	29	23	6	25	24	23	25
No	15	21	38	19	20	21	19
Unknown	10	10	10	10	10	10	10

Abbreviations: CA-UTI, catheter-associated urinary tract infections; CDI, *Clostridoides difficile* infection; CLABSI, central line-associated bloodstream infection; COLO, colon surgery; HYST, hysterectomy; MRSA, methicillin-resistant *Staphylococcus aureus* bloodstream infections, VAE, ventilator-associated event

To compare each state's performance, NHSN calculated the specific standardized infection ratio (SIR) each year (17), which is "the ratio of the observed number of infections to the number of predicted infections per year" (18). Three benchmarks are compared with each state's annual SIR: the current national SIR (removing specific state from national SIR), the state's SIR from 2019, and the 2015 national baseline (17).

The Canadian Nosocomial Infection Surveillance Program (CNISP) included 87 of 620 Canadian hospitals (14.0%) in 2021 (19) and performs two types of surveillance: 1) PPS of HAIs with an estimation of the proportion of infections caused by AROs (4), which is done approximately every seven years; and 2) annual incidence surveillance for HAIs.

CNISP conducted three PPS (2002, 2009 and 2017). In the last report, 47 of 66 (71.2%) invited hospitals participated (4). Data collection included hospital profile, patients' demographic data and information on HAI. In 2017, data were collected for VAP, SSI (hip and knee), UTI, methicilin-resistance *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase producing organisms, carbapenemase-producing organisms (CPO) and CDI. Surveillance includes patients of any age admitted to the hospital for at least 48 hours, or for less than 48 hours if they were admitted in the month prior to the survey.

Several infections were part of the annual incident surveillance: *Candida auris*; CDI; CLABSI; CPO; SSI (knee, hip, cardiac [paediatric], and cerebrospinal fluid shunt); and methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA and VRE BSI. Patient-level data were collected for all infections, except for CDI for which aggregated data could be submitted (minimum dataset). Hospitals chose which surveillance program they participated in. For example, in 2018, 62 hospitals participated in the MRSA and VRE BSI surveillance, 59 to carbapenemase-producing Enterobacteriaceae (CPE) and 68 to CDI (20).

In Australia, the Australian Commission on Safety and Quality in Health Care (ACSQHC) was established in 2011. It develops protocols used by other groups, such as the Australian Institute of Health and Welfare and the Australian and New Zealand Intensive Care Society, to perform surveillance. Established in 1985, the Australian Group on Antimicrobial Resistance performs the surveillance for antimicrobial resistance (MSSA, MRSA, VRE, gram-negative bacteria and CPE) in blood. This voluntary surveillance is based on laboratories' participation.

Public Health England does surveillance for CDI, bacteremia (gram-negative, MRSA and MSSA) and SSI. The SSI surveillance is mandatory for orthopedic surgery for a minimum of three consecutive months per fiscal year (21). The other surveyed procedures are voluntary (Table 2). Patients are followed for 30 days (non-implant procedures) and one year (prosthetic implant procedures). In the last available report, 156 hospitals reported for hip and knee replacements. In comparison, only 20 and 16 hospitals reported for large bowel surgery and spinal and breast surgeries (voluntary program), respectively. Public Health England analyzes submitted data quarterly to identify high (hospitals whose SSI risk is greater than the 90th percentile) and low outliers (less than the 10th percentile). Low outliers are supported to ensure all cases are being reported. High outliers are asked to explore their clinical practices to identify possible reasons to explain high rates. CDI and BSI are mandatory programs (22). Public Health England receives data from all hospitals and publicly shares monthly or annual rates on their website.

Discussion

The objective of this scoping review was to synthesize characteristics of national HAI surveillance programs from 35 selected countries to inform decisions on possible national programs for Canada. Most surveillance was done on a voluntary basis. CDI, hip and knee prosthesis surgery and caesarean sections were the four main infections and procedures under surveillance.

Characteristics of surveillance programs appear to vary, including for frequency of reporting to ministries. Some countries use prevalence point surveys as their main method of surveillance. The percentages of participating hospitals vary (from 1.4% to 100%). With 9.5% to 11.0% participation, CNISP is in the lower range (**Table S4**). Double data entry (at the hospital and at the national program level) can be a barrier to participation, given the additional workload. From the 18 programs with available information, 16 (88.9%) required double data entry through forms to collect data. Finally, all surveillance program with available information used active surveillance and 77.8% reported data at the hospital level (n=21/27, data not shown).

The published reports reviewed for this scan did not describe how benchmarks were set; for example, in Lithuania, a national average of infection rates was used as a threshold for comparison. In Australia since 2016–2017, the National Healthcare Agreement sets a national benchmark of less than or equal to 1.0 HAI of *S. aureus* BSI per 10,000 bed days (23,24). The NHSN goes further by stratifying benchmarks according to patient population; for example, an NSHN surveillance report in

2006–2007 separated average rates by different characteristics (25). Data collected in ICUs, specialty care area or wards were stratified by patient population: adult or paediatric. Data collected on infections from neonatal ICU are stratified by birthweight categories. The VAP and CLABSI rates are stratified by department or ICU type (e.g. trauma, surgical). Greater precision in benchmarks allows for a better understanding of where interventions are needed, by allowing for more refined comparisons.

In view of other national surveillance programs, some elements must be considered for HAI surveillance in Canada. Although provinces have their own surveillance programs, there is a need for large enough sample sizes to stratify infection rates for specific units (e.g. cardiac, neonatal or paediatric ICUs): this will require data to be pooled at the national level. Data transmitted from provinces to the federal surveillance program could be aggregated, but numerators and denominators and harmonized surveillance definitions are required. The CNISP is currently using harmonized definitions across the country with patient or unit-level data, but it currently lacks representativeness, as it represents only a fraction of Canadian healthcare, with a bias towards teaching urban hospitals. Recruitment of new hospitals into CNISP requires funding. Voluntary participation of all Canadian hospitals in CNISP is being considered but the risk of selection bias remains.

Limitations

This study has several limitations. First, for us to be able to identify a program, the country must publicly report it. Non-English websites or grey literature reports were translated using two tools. The first was the internet navigator itself, using Google Chrome tools for website translation. The second tool was the software DeepL Translator (DeepL, Cologne, Germany). Although these tools may have inherent limitations, data extracted were objective and straightforward and did not require any subtle interpretation. The risk of selection bias from published literature was mitigated by a web search for each identified country. Although we may have missed some smaller national programs, we think that most elements of a HAI surveillance program have been captured via larger national or multinational programs, such as ECDC. Other information (process and not results) was extracted from official available protocols and reports from the program website or by speaking to the program's manager.

Conclusion

In the four regions studied, 80% of high-income countries had national HAI surveillance programs. Although some differences exist, the overarching theme was that national surveillance programs had individual-level data, or at least aggregated data at a hospital level, with a numerator and a denominator and not just an overall incidence rate by region. Infections and procedures under surveillance are quite uniform. This literature scan is the first step towards identifying the best approach for a national HAI surveillance program for Canada.

Authors' statement

EP — Conceptualization, methodology, investigation, validation, formal analysis, writing–original draft
VB — Investigation, validation, writing–review
AM — Conceptualization, resources, writing–review and editing, funding acquisition
CQ — Conceptualization, writing–review & editing, supervision, funding acquisition

Competing interest

A MacLaurin is an employee of Healthcare Excellence Canada. The other authors have no conflict of interest to disclose.

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Supplemental material

These documents can be accessed on the Supplemental material file.

Table S1: Keywords and MeSH classification of the four concepts identified for the scoping review

Data S1: List of 220 articles identified by systematic review through Medline

Figure S1: Flow chart of the scoping review

Table S2: Number of articles found by countries

Table S3: Number of participating hospitals for four HAI-NET's surveillance programs, European Centre for Disease Prevention and Control

Table S4: Infections surveyed in national surveillance programs, 37 countries, 2021

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Multivariate analyses of risk factors associated with laboratory exposure incidents

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Abstract

Background: Laboratories involved in the study of pathogenic biological agents pose an inherent risk of exposure to the laboratory workforce and the community. Laboratory biosafety and biosecurity activities are fundamental in minimizing the likelihood of unintentional exposure incidents. The objective of this study is to describe the factors that are associated with the occurrence of exposure incidents in a laboratory setting through a predictive model.

Methods: The Laboratory Incident Notification Canada is a nationally mandated surveillance system that gathers real-time data from submitted reports of laboratory incidents involving human pathogens and toxins. Data on laboratory exposure incidents were extracted from the system between 2016 and 2020. The occurrence of exposure incidents per month was modelled using a Poisson regression with several potential risk factors, including seasonality, sector, occurrence type, root causes, role and education of people exposed and years of laboratory experience. A stepwise selection method was used to develop a parsimonious model with consideration of the significant risk factors identified in the literature.

Results: After controlling for other variables in the model, it was found that 1) for each human interaction related root cause, the monthly number of exposure incidents was expected to be 1.11 times higher compared to the number of incidents without human interaction (p=0.0017) as a root cause and 2) for each standard operating procedure-related root cause, the monthly number of exposure incidents was expected to be 1.13 times higher compared to the number of incidents without a standard operating procedure related root cause (p=0.0010).

Conclusion: Laboratory biosafety and biosecurity activities should target these risk factors to reduce the occurrence of exposure incidents. Qualitative studies are needed to provide better reasoning for the association of these risk factors with the occurrence of exposure incidents.

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Keywords: laboratory exposures, laboratory-acquired infections, risk factor, human pathogens and toxins

Introduction

Laboratory work involving the study of biological agents poses an inherent risk of exposure to the laboratory personnel and the community. Although laboratory biosafety and biosecurity guidelines have advanced considerably, there is still a need to guide risk mitigation decisions to target the most important risks that are associated with exposure incidents (1).

There were several risk factors identified in the literature that are associated with exposure incidents in a laboratory, with the most significant factors being human errors (2,3). Evidence from case report studies has shown that the common risk factors associated with exposure incidents occurrence are improper use of personal protective equipment (4–6), insufficiently trained staff (7,8) and fewer years of work experience (9). Other case report studies found that high-risk work tasks (9) and working with needles (4,10,11) were also associated with the occurrence of exposure incidents. In addition, risk factors identified in a case-control study and a cross-sectional study included a lack of standard operating procedures (SOP) (12) and inadequate biosafety risk assessments (13), respectively.

Although these studies are important for identifying trends in the occurrence of exposure incidents, case report studies may not be generalizable to all laboratory settings. Additionally, many of

these studies use descriptive statistics to identify the risk factors which have the potential to produce biases (2,3,6,9,13). These studies were mostly cross-sectional or case reports and may not capture the most important risk factors contributing to exposure incidents. To adequately mitigate risks, it is critical to prioritize risk factors involved in exposure incidents that have been identified through surveillance over a longer period of time. To identify the significant risk factors that are associated with an increase or decrease in exposure incidents, inferential analyses using existing surveillance data over a long period of time are warranted.

In this report, surveillance data were analyzed and a mathematical model that predicts the risk factors that are associated with exposure incidents was developed. This model could inform licensed facilities to prioritize laboratory biosafety and biosecurity activities on important risk factors to reduce the occurrence of exposure incidents in the future.

Methods

Data sources

The Laboratory Incident Notification Canada (LINC) surveillance system collects real-time data from licensed laboratory incidents involving human pathogens and toxins. It is the only mandated surveillance system that is required to collect exposure incidents from licensed laboratories across Canada. Notification and follow-up reports of laboratory incidents are received through the Biosecurity Portal and then captured by the internal Customer Relationship Management system.

Exposure incidents were defined as those with the potential to cause infection/intoxication or had resulted in a suspected or confirmed laboratory-acquired infection involving human pathogens and toxins that are within the scope of the *Human Pathogens and Toxins Act* (14) and the *Human Pathogens and Toxins Regulations* (15).

Data were extracted from this system on the exposure incidents that took place from January 1, 2016, to December 31, 2020. Incidents that did not have a known occurrence date were also included if they were reported during this period. Data of the most recent follow-up reports were used for analysis, while the data of initial reports were used where corresponding follow-up reports and/or data were not present as of the data extraction date, February 8, 2021. The extracted data were cleaned and inspected for any missing values, duplicate entries and/or outliers.

Data analysis

TThe data from the LINC surveillance system was imported into SAS EG 7.1 to perform data manipulation and multivariate analyses. The original database contained 284 rows collected over five years, where each row contained one incident. One incident can involve multiple occurrence types and more than one root cause can be identified for one incident. Data were transformed to obtain a monthly count of exposure incidents and to examine their seasonality occurrence over five years. In this transformation, 284 individual exposure incidents were grouped by month to give 60 monthly observations. The sample size was smaller due to the transformation from reported incidents per row to reported incidents per month per row. Three months were excluded from our sample because there were no incidents reported. The final dataset had 57 observations.

A Poisson regression was used to model the occurrence of exposure incidents per month because count data is not normally distributed. Using a stepwise selection method, the following independent variables were analyzed: seasonality (year, month); monthly count of sector (hospital, academic, government, environmental, private, public health, veterinary); occurrence type (animal related, equipment, insect, loss containment, personal protective equipment, procedure, sharp, spill, unknown, other); root causes (training, communication, equipment, human interaction, management, SOP, other); role (technician, student, researcher, manager, animal handler, other); education of person exposed (high school, technical, university degree); and route of exposure (inhalation, inoculation, absorption, other). The monthly number of affected persons as well as their median years of laboratory experience using the monthly data points were also included in the analysis.

Both univariate and bivariate analyses were first conducted to explore the associations between the predictive independent variables and the outcome variable of interest. Independent significant parameters identified in the bivariate analyses were included in the multivariate Poisson regression analysis. A *p*-value of 0.05 was chosen as the cut-off point for entry and exit into the stepwise procedure. Stepwise selection of variables was conducted by groups of variables to identify factors associated with the occurrence of exposure incidents because of the high number of variables and small sample size.

Results

From 2016 to 2020, there were 614 individuals exposed in the 284 confirmed exposure incidents reported to LINC. The average monthly occurrence of incidents was 4.98. Laboratory characteristics of the exposure incidents can be found in **Table 1**. In this dataset, the median years of laboratory experience was 7.25. Most exposed individuals had a technical/trade diploma (66.3%) or a bachelor's degree (25.5%) and belonged in the hospital sector (57.5%), academic (17.7%) or private (11.2%) sectors. Most individuals exposed were technicians/technologists (74.9%). Among exposed individuals, the most common route of exposure to human pathogens and toxins was through inhalation (62.2%) or inoculation (14.2%). The most commonly reported occurrence types were procedural (23%) and sharps-related (22.0%). Standard operating procedures (25.6%) and human interactions (19.4%) were the most commonly cited root causes. Additional descriptive data on exposure incidents may be found in our annual reports between 2016 and 2020 (2,16–19).

Table 1: Descriptive and bivariate analyses of all predictive variables of exposure incidents

Variables	Exposure incidents		Coefficient	*p*-value
	n	%		
Root cause (N=679)				
Training	72	10.6	1.28	<0.0001
Communication	73	10.8	1.35	<0.0001
Equipment	84	12.4	1.32	<0.0001
Human interaction	132	19.4	1.22	<0.0001
Management	75	11.0	1.37	<0.0001
SOP	174	25.6	1.22	<0.0001
Other	69	10.2	1.24	0.0001
Occurrence type (N=378)[a]				
Animal related	17	4.5	1.29	0.0077
Equipment	23	6.1	1.25	0.0002
Loss containment	18	4.8	1.55	<0.0001
PPE	45	11.9	1.27	<0.0001
Sharp	83	22.0	1.30	<0.0001
Procedure	87	23.0	1.28	<0.0001
Spill	45	11.9	1.40	<0.0001
Unknown	11	2.9	1.11	0.4005
Other	49	12.9	1.27	<0.0001
Role (N=614)				
Technician	460	74.9	1.03	<0.0001
Student	58	9.4	1.25	0.0001
Researcher	18	2.9	1.21	0.0185
Animal handler	7	1.1	1.25	0.1714
Manager	15	2.4	1.22	0.0058
Other	56	9.1	1.15	<0.0001
Sector (N=273)				
Hospital	95	34.8	1.27	<0.0001
Academic	101	37.0	1.26	<0.0001
Environmental	2	0.7	1.43	0.1955
Private	29	10.6	1.15	0.0671
Public health	29	10.6	1.38	<0.0001
Veterinary	10	3.7	1.10	0.5149
Other government	7	2.6	1.42	0.0292
Education (N=510)				
High school	42	8.2	1.09	<0.0001
Technical	338	66.3	1.03	<0.0001
University (Bachelor's degree)	130	25.5	1.05	0.0001
Route of exposure (N=614)				
Inoculation	87	14.2	1.32	<0.0001
Inhalation	382	62.2	1.02	<0.0001
Absorption	48	7.8	1.29	<0.0001

Table 1: Descriptive and bivariate analyses of all predictive variables of exposure incidents (*continued*)

Variables	Exposure incidents		Coefficient	*p*-value
	n	%		
Route of exposure (N=614) (*continued*)				
Other	97	15.8	1.02	0.0226
Years of experience (Median)	7.25	N/A	1.01	0.6020

Abbreviations: N/A, not applicable; PPE, personal protective equipment; SOP, standard operating procedure
[a] No exposure incidents were insect-related

Bivariate regression analysis results can also be found in Table 1. The relationship between the outcome of interest (number of exposure incidents per month) and each independent variable was determined through Poisson regression. The exponents of the estimated regression coefficients and the *p*-values are listed in Table 1.

Multivariate Poisson regression analyses for the association between the number of exposure incidents and predictive independent variables are shown in **Table 2**. The exponents of the estimated regression coefficients and the *p*-values are listed in Table 2. With consideration of the significant risk factors identified in the literature, a parsimonious model was developed, which included the following predictive variables: human interaction and SOP issues as root causes; and roles (including students and technicians). The analyses revealed that having a role as a student or as a technician/technologist in the laboratory was not significantly associated with the number of exposure incidents per month. It was found that for each human interaction and SOP related root cause, the monthly number of exposure incidents is expected to be 1.11 times higher (p=0.0017) compared with the occurrence of incidents without human interaction as a root cause, after controlling for other variables in the model. It was also found that for each SOP related root cause, the monthly number of exposure incidents is expected to be 1.13 times higher (p=0.0010) compared with the occurrence of incidents without an SOP related root cause, after controlling for other variables.

Table 2: Multivariate analysis of exposure incidents by risk factors using Poisson regression (Model 1)

Parameter	Coefficient[a]	SE	Coefficient (95% CI)	*p*-value
Student	1.04	0.0584	0.92, 1.16	0.5488
Technician	1.00	0.0055	0.99, 1.01	0.6444
Human interaction	1.11	0.0347	1.04, 1.19	0.0017
SOP	1.13	0.0362	1.05, 1.21	0.0010

Abbreviations: CI, confidence interval; SE, standard error; SOP, standard operating procedure
[a] The exponents of the estimated regression coefficients after controlling for other variables

Bivariate Poisson regression analyses for the association between the number of exposure incidents and seasonality in Table 3. The exponents of the estimated regression coefficients and the *p*-values are listed in **Table 3**. The analyses revealed that the month of June was significantly associated with less occurrence of exposure incidents when compared with December (p=0.0286).

Table 3: Bivariate analysis of exposure incidents by seasonality using Poisson regression (Model 2)

Parameter (month)[a]	Exponent (estimate)	SE	Exponent (95% CI)	*p*-value
January	0.89	0.2928	0.50, 1.58	0.6987
February	0.98	0.2849	0.56, 1.72	0.9496
March	0.86	0.2782	0.50, 1.48	0.5795
April	0.75	0.2887	0.43, 1.32	0.3190
May	1	0.2673	0.59, 1.69	1.000
June	0.45	0.3684	0.22, 0.91	0.0286
July	1	0.2673	0.59, 1.69	1.000
August	0.82	0.2814	0.47, 1.43	0.4845
September	1.07	0.2628	0.64, 1.79	0.7929
October	0.86	0.2782	0.51, 1.48	0.5795
November	0.93	0.2724	0.55, 1.58	0.7855

Abbreviations: CI, confidence interval; SE, standard error
[a] Reference category=December

Discussion

Our primary objective for this study was to identify the risk factors that were associated with exposure incidents occurrence in laboratory settings through a predictive model. Multivariate Poisson regression analyses revealed that human interaction and SOP related root causes were significantly associated with the occurrence of exposure incidents. The monthly number of exposure incidents was also found to be significantly lower in June through bivariate analyses.

Through descriptive analysis, previous studies identified 1) lack of awareness of or compliance with SOP and 2) human interactions as leading root causes (2,3,12); however, our study provided adjusted estimates that quantify and confirm the contribution of these causes to the increase in exposure incidents. Human interaction was commonly described as, but not limited to, a violation (cutting a corner, not following correct procedure, deviating from SOP) or an error (a mistake, lapse of concentration, or slip of some sort) (18). Standard operating procedure-related issues were described as documents not being followed correctly for the task, or as SOP not being in place (18).

Technicians and technologists were commonly identified as those more often involved in exposure incidents when compared with other individuals in the laboratories (2,3,20). These previous findings were based on descriptive statistics and might be explained by the high number of technicians and technologists working in laboratory settings (2,3,20); however, the multivariate model of our study highlighted that the contribution of the role of technicians to the increase in exposure incidents was not significant, when the other variables remain constant. Risk mitigation decisions in licensed facilities should mainly target human interaction and lack of compliance to SOP, to prevent the occurrence of exposure incidents.

Contrary to the widespread evidence that work experience is correlated with risk of errors (21), our study did not find an association between the median years of experience and the increase in exposure incidents. This result could be due to the lack of granularity of the work experience variable that summarizes the years of experience of all affected people during a given month.

When considering seasonality as a factor involved in the occurrence of exposure incidents, our results revealed that the month of June had significantly lower occurrence of exposure incidents. It is unclear why there are fewer exposure incidents during this month; however, a potential explanation could be a smaller laboratory workforce during the summer due to summer vacations, and thus a reduced number of human interactions and consequently a reduced number of exposure incidents.

The results from this study could be used to inform licensed facilities about the factors that are associated with exposure incidents so that adequate measures are implemented to minimize the likelihood of exposure incidents. Human interactions, non-compliance with SOP and seasonality are important factors to consider for reducing the occurrence of exposure incidents; however qualitative research is required to better understand these findings. A qualitative study would provide insights into why these factors contribute to exposure incidents and how they can be properly addressed in laboratory settings to avoid or reduce exposure incidents.

Strengths and limitations

The main strength of this study is the use of inferential statistics and multivariate models to identify the risk factors associated with the occurrence of exposure incidents. The majority of previous studies use descriptive statistics to identify the risk factors that have the potential to introduce biases because of potential confounding variables. The use of descriptive statistics is also limited since they do not take into account the relationships between variables, and can therefore only be used to describe and report observations. With the use of inferential analyses, we were able to determine which factors contributed significantly to the occurrence of exposure incidents and also the magnitude of their effects through a predictive model. This study also benefited from the use of existing national surveillance data over a longer period compared with previously published articles, allowing for more accurate identification of the most significant risk factors that predict the occurrence of exposure incidents. Our predictive model could inform licensed facilities to prioritize laboratory biosafety and biosecurity activities on the risk factors identified to reduce the occurrence of exposure incidents in the future.

The most significant limitation of this study was the low sample size due to the transformation of the data into monthly data, which was required to conduct the multivariate analyses and to examine the seasonality. In addition, the LINC surveillance system only captures the information on the affected people and not for the entire laboratory workforce. The information on the entire laboratory workforce could be valuable to compare the characteristics of those who are exposed and those who are not. Furthermore, the surveillance system does not collect sufficient data on all potential predictive variables. For example, the system collects data on management oversight; however, additional information on the role of management oversight in controlling biosafety and biosecurity risks in the laboratories could be valuable.

Conclusion

This study found that human interactions and SOP-related issues were significantly associated with the occurrence of exposure incidents. These findings are also consistent with the literature, which emphasizes the need for licensed facilities to examine current safety protocols regarding compliance to SOP and human interactions. Additional research, such as qualitative studies, is needed to provide better reasoning for the association of these risk factors with the occurrence of exposure incidents.

Authors' statement

MEJ — Methodology, investigation, writing original draft, review and editing
NA — Methodology, investigation, writing original draft, review and editing, supervision
RE — Conceptualization, methodology, investigation, review and editing, supervision
MS — Writing–review and editing
SBA — Writing–review and editing

Competing interests

None.

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Compliance with COVID-19 preventive measures is high among university-level students in Québec, Canada

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Abstract

Background: Canada's nationwide lockdown to curb coronavirus disease 2019 (COVID-19) infections affected many sectors of activity, including universities. During the 2020–2021 academic year, all students were forced to follow their lectures from home and the only in-person activity permitted to Québec university level students was to study in designated spaces of campus libraries where COVID-19 preventive measures were in place and mandatory at all times for all staff and students. The objective of this study is to evaluate university-level students' compliance with COVID-19 preventive measures in a Québec campus library.

Methods: A direct in-person evaluation by a trained observer was put in place to assess students' compliance with COVID-19 preventive measures defined as proper mask wearing and 2 meter distancing. Measurements were made each Wednesday, Saturday, and Sunday at 10 a.m., 2 p.m., and 6 p.m. from March 28 to April 25, 2021, in a university library in Québec, Canada.

Results: Students' compliance with COVID-19 preventive measures was high overall (78.4%) and increased over the weeks, with differences between weeks, weekdays, and time of day. Non-compliance was lower on weeks three and four of the assessment compared with week one, and higher on Sunday compared with Wednesday. Differences seen throughout the day were not statistically significant. Non-compliance with physical distancing was rarely seen.

Conclusion: Most university-level students are compliant with COVID-19 preventive measures in a Québec university library: an encouraging behaviour from a public health perspective. These findings may support public health authorities or university administrators in decisions regarding different COVID-19 preventive measures directed to different universities settings, as this method can be applied to focused, rapid observational studies and can lead to data of sufficient statistical power.

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Keywords: coronavirus disease, COVID-19 surveillance, COVID-19 preventive measures, compliance

Introduction

On March 11, 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic (1). COVID-19 is transmitted predominantly by inhalation of fine aerosols, particles and droplets, direct exposition of mucous membranes of the mouth or eye to respiratory droplets and to a lesser extent through contact with contaminated surfaces (2). It has been established that the risk of transmission can be reduced using well-fitting masks and by physical distancing, surface disinfection, adequate ventilation, and avoidance of crowded spaces (2–6).

Studying in designated spaces, such as libraries, remained one of the very few in-person activity accessible to students in Québec, Canada who were enrolled in university during the 2020–2021 academic year (7,8). During the 2021 winter semester, designated study spaces in universities in this province were adapted for student safety by mandating both proper surgical mask use and physical distancing at all times (9–17). In-person activities for university-level students have been proven to be important for education, professional networking and

socialization, and for good physical and mental health (18). Thus, knowledge of students' compliance rate with COVID-19 preventive measures (COPM) in universities will help university administrators better apply public health policies for a rapid and safe return to in-person activities.

One way of evaluating the efficacy of a measure put in place is to assess compliance with it. Direct observation by trained observers has been used when evaluating the hand hygiene compliance of healthcare workers and remains the gold standard method for monitoring compliance towards similar measures (19). Many research teams have demonstrated the ability to evaluate compliance with COPM by using a direct in-person observation method (20–23); however, studies evaluating compliance with all COPM in university establishments are currently lacking.

In this study, we evaluated the compliance rate of students with COPM implemented in designated study spaces of a university. The hypothesis was that compliance by the students would be high. Indeed, previous studies of Canadians over 18 years of age have shown high compliance rate with COPM and high level of knowledge about mask use among university level students in Canada (24,25).

Methods

Library setting

The study was conducted in a university library that extends over seven stories, with a total capacity of 852 (pre-pandemic) and 313 (during pandemic) individual study workstations. These numbers exclude team study rooms and classrooms within the library. This library offers various services for students and holds collections in literature and human sciences. Library employees were assigned to remind each student of the COPM at the entrance of the library while also providing a procedural mask and alcohol hand disinfectant. An online reservation system was put in place to monitor arrival of the students and allocate them to a study space. Moreover, security agents regularly patrolled the entire library to ensure compliance with the COPM. Students were asked to properly wear the procedural masks (covering both mouth and nose) at their designated space at all times, even when studying alone.

Observations

Observations were conducted using the in-person trained observer method. This method was favoured over a self-reported survey method because the risk of information bias is lower. We used a sampling methodology based on published studies and on a report released by Resolve to Save Lives (20,23,26,27). The two observers were themselves students. They self-trained to 1) evaluate proper mask wearing and 2) estimate a 2 meter distance to reduce the risk of variability between observers. Observers were compliant with the COPM put in place by the library (properly wearing a mask at all times and physically distancing). Observations were restricted to students who were sitting or were near the area of their designated study space (i.e. at desks in open spaces of the library). Gender and age were not considered, as the goal of the study was to evaluate university level students' compliance with the COPM, which applied to students from any gender and all ages. Each observer was assigned a floor in the library and circulated on that floor directly observing each student. All observers participated in every time point to eliminate any interobserver confounding of week, weekday or time of day effects. Proper mask wearing and physical distancing were evaluated for each student observed and were assessed as being met or not. Students meeting both criteria were counted as complying with the COPM while students meeting one or no criterion were counted as non-complying with the COPM. Students circulating in the library were not included among the observations because 1) they did not represent a significant number of observations and 2) it would increase the complexity of the task, therefore increasing the risk of counting error for the observers. Students in individual study rooms (enclosed rooms with a door) were also excluded since the use of face masks was not required there. Moreover, since it is known that the Hawthorne effect can falsely increase compliance (28,29), observers counted students' behaviour change, such as properly placing the mask or physical distancing, in the presence of the observer as non-compliance with the COPM. Data collection was done by filling out standardized paper forms that were then entered electronically into an Excel (version 2104; Microsoft Office Professional Plus 2019) spreadsheet after each period of observation. Observations were carried out at three time points (10 a.m., 2 p.m. and 6 p.m.) every Wednesday, Saturday, and Sunday over a period of four weeks from March 28 to April 25, 2021. Frequency of observations was spread evenly during the day and weekday to control for possible behaviour and occupancy variability. We chose to favour full coverage of weekends over weekdays for observations as it was assumed that lectures were given during the week, which would result in fewer students studying in the library. This 1-month time frame was chosen for observations as it covered most undergraduates' end of semester exams and study period; a period when students tend to study more.

Statistical analysis

Binary univariate and multivariate logistic regression analyses were performed. Multivariate regression included all three independent variables. Odds ratios and their confidence interval (CI) were calculated as un-adjusted (OR) and adjusted (AOR) for univariate and multivariate analysis respectively. SPSS version 27.0 software (SPSS, Inc., Chicago, Illinois, United States) was used for all statistical analyses.

Ethics

Exemption from ethical review was granted by the Institutional Review Board of the university where observations were made. Disclosure of the university where the study took place was not permitted by the Institutional Review Board.

Results

A total of 2,109 students were observed over 39 observation time points (13 days of observation, 3 observation time points per day), 27 during the weekends (on Saturdays and Sundays) and 12 during the week (on Wednesdays). All observations are summarized in **Table 1** and **Annex** (**Table S1** and **Table S2**).

Non-compliance by week, weekday and time of day

Observations were first grouped as compliant or not with the COPM: 1,653 (78.4%) students were compliant whereas 456 (21.6%) students were non-compliant (Table 1).

Binary logistic regressions showed that student's non-compliance with the COPM was dependent on the week, weekday, and time of the day. Non-compliance with COPM was lower on weeks three and four when compared with week one (AOR=0.51 and AOR=0.56, respectively) and non-compliance with COPM was higher on Sunday compared with Wednesday (AOR=1.53). As for time of day, non-compliance with COPM was lower at 2 p.m. (AOR=0.81) and higher at 6 p.m. (AOR=1.22) when compared with 10 a.m., but these differences were not statistically significant.

Similar results were seen for non-compliance with proper mask use alone (Table S1). Physical distancing was rarely inadequate; n=50 (2.4 %) and n=14 (0.6 %) were observed not physically distanced whether properly or improperly wearing the mask, respectively (Table S2).

Discussion

The observed 78.4% level of compliance with COPM is close to the 80% threshold suggested as necessary to reduce the spread of COVID-19 (30). Compliance with COPM increased over the weeks, probably because higher numbers of students in the library lead to increased enforcement of COPM. Observers noted that enforcement of COPM was variable and might not have been consistent over time. Indeed, our study has been conducted at the end of the 2021 winter semester: a time when students tend to study more because end-term exams are approaching. Students were less likely to be compliant with the COPM on Sunday.

Our study was carried out one month prior to the widespread vaccination availability in Québec, Canada (which began April 30, 2021). This timing could have positively affected students' attitude towards COPM (31,32). A direct observation method has proven to be valuable in an acute period of the pandemic as it allowed for rapid evaluation of compliance in a large sample. This is especially valuable when public health measures are changing rapidly, as this method can be quickly implemented as well. It also eliminates reporting bias, a limitation that is often encountered in survey-based studies (33). This method proved to be challenging as it does not allow much flexibility in the observers' work schedule. Indeed, the distribution of observation time points across the day (10 a.m., 2 p.m., and 6 p.m.) required the observers to be disciplined in their work schedules and for them to determine the circulating library floors before each observation time point, as observations must take place at each established time point to prevent compromising

Table 1: Non-compliance with COVID-19 preventive measures[a] by week, weekday and time of day, Canada, Québec, March–April 2021

Characteristics	Number (%) of students							
	Non-compliance (N=456, 21.6%)		Compliance (N=1,653, 78.4%)		Non-compliance OR		Non-compliance AOR	
	n	%	n	%	OR	95% CI	AOR	95% CI
Week								
1	113	28.2	288	71.8	1	N/A	1	N/A
2	110	27.4	292	72.6	0.96	0.71–1.31	0.99	0.72–1.35
3	89	16.2	461	83.8	0.49	0.36–0.67	0.51	0.37–0.70
4	144	19.0	612	81.0	0.60	0.45–0.80	0.56	0.42–0.75
Weekday								
Wednesday	118	18.8	509	81.2	1	N/A	1	N/A
Saturday	133	20.9	533	79.1	1.08	0.82–1.42	1.09	0.82–1.43
Sunday	205	24.4	611	75.6	1.45	1.12–1.87	1.53	1.18–1.99
Time of day								
10 a.m.	84	21.8	302	78.2	1	N/A	1	N/A
2 p.m.	203	18.7	883	81.3	0.83	0.62–1.10	0.81	0.61–1.08
6 p.m.	169	26.5	468	73.5	1.30	0.96–1.75	1.22	0.90–1.65

Abbreviations: AOR, adjusted odds ratio; COVID-19, coronavirus disease 2019; N/A, not applicable; OR, un-adjusted odds ratio
[a] COVID-19 preventive measures refers to both proper masking and adequate physical distancing

the robustness of the study. Future studies could evaluate masking behaviour across multiple universities using the same method. Indeed, now that vaccination coverage is higher, and that the current pandemic situation has changed significantly (34), compliance with masking and physical distancing mandates could differ from those we observed, suggesting that COPM are context-dependent. These methods could also be used to investigate university-level students' rationale towards their change of behaviour, and the influence of socio-demographic characteristics such as age, gender, level of education and socio-economic status on compliance with the COPM. University administrators could then better adapt their public health policies to increase compliance.

Limitations

One limitation of our study was that because the two observers were randomly assigned different library floors at each time point, only one observer circulated per library floor. Therefore, we could not ensure inter-observer agreement per library floor for any observation time point. Moreover, observers circulated only once per library floor at each time point for the whole observation period. A second limitation of our study concerns students' gender and age assessment. Because our study was not designed to assess the effect of gender and age, it could not determine if these variables influenced compliance with COPM. A third limitation of our study is that enforcement of COPM was not a parameter measured and analyzed. Consequently, we couldn't explain with certainty why students were less likely to be compliant with the COPM on Sundays. Perhaps this could be explained by a lower enforcement of COPM that day. A fourth limitation of our study concerns its generalizability to other university libraries and other universities. Nevertheless, our findings provide an encouraging insight into university level students' compliance with the COPM put in place due to COVID-19, and we believe that they could be complemented with similar observations during other prevention activities implemented in universities.

Conclusion

University students were highly compliant with COPM in a university library, although there were differences in compliance over time and between weekdays and times of day. These data suggest that in the event of a subsequent SARS-CoV-2 wave, university libraries can remain open, although the latter will need to strengthen COPM at specific time points on specific days, for example, by increasing security surveillance. However, these findings cannot be generalized to other mass-gathering university settings, such as sports facilities and classrooms, as students' behaviour with COPM might be different. Nevertheless, these findings may support public health authorities in decisions regarding COPMs directed to different universities settings as this method can be applied to focused, rapid observational studies and can lead to data of sufficient statistical power. These findings may also support university administrators in implementing health policies that would lead to the safe resumption of as many in-person activities as possible: a welcome reprieve for university students.

Authors' statement

YP and RT — Conceptualization, methodology, analysis, writing, reviewing, and editing
RA — Analysis, review and editing
YP and RT shared co-first authorship. These authors have contributed equally to this work.

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Competing interest

None.

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Annex: Tables

Table S1: Non-compliance with proper mask use by week, weekday and time of day, Québec, Canada, March–April 2021

Characteristics	Number (%) of students							
	Non-compliance (N=406, 19.3%)		Compliance (N=1,703, 80.7%)		Non-compliance OR		Non-compliance AOR	
	n	%	n	%	OR	95% CI	AOR	95% CI
Week								
1	104	25.9	297	74.1	1	N/A	1	N/A
2	97	24.1	305	75.9	0.91	0.66–1.25	0.93	0.68–1.29
3	75	13.6	475	86.4	0.45	0.32–0.63	0.47	0.34–0.66
4	130	17.2	626	82.8	0.60	0.44–0.80	0.56	0.42–0.76
Weekday								
Wednesday	106	16.9	521	83.1	1	N/A	1	N/A
Saturday	119	17.9	547	82.1	1.07	0.80–1.43	1.08	0.81–1.45
Sunday	181	22.2	635	77.8	1.40	1.07–1.83	1.47	1.12–1.93
Time of day								
10 a.m.	77	19.9	309	80.1	1	N/A	1	N/A
2 p.m.	173	15.9	913	84.1	0.76	0.57–1.02	0.74	0.55–1.00
6 p.m.	156	24.5	481	75.5	1.30	0.96–1.70	1.22	0.89–1.66

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval, N/A, not applicable; OR, un-adjusted odds ratio

Table S2: Total numbers of COVID-19 preventive measures observations by category, Québec, Canada, March–April 2021

Categories	Number of students	% of students
Mask worn correctly and physically distanced	1,653	78.4
Mask worn correctly and not physically distanced	50	2.4
Mask worn incorrectly and physically distanced	392	18.6
Mask worn incorrectly and not physically distanced	14	0.6
Total	2,109	100

Abbreviation: COVID-19, coronavirus disease 2019

RAPID COMMUNICATION

Summary of the National Advisory Committee on Immunization (NACI) statement update on the recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants

Dorothy Moore[1], Angela Sinilaite[2], April Killikelly[2]; on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in young children worldwide. Underlying health conditions, especially premature birth, chronic lung disease and congenital heart disease, predispose to severe RSV illness. The only means of prophylaxis against RSV disease is passive prophylaxis with the monoclonal antibody, palivizumab (PVZ) (Synagis™). The National Advisory Committee on Immunization (NACI) published a statement for PVZ use in 2003. The purpose of this article is to update previous NACI recommendations for the use of PVZ, taking into consideration recent data on RSV burden of illness, effectiveness of PVZ in infants at risk of more severe RSV disease and economic implications of PVZ use.

Methods: The NACI Working Group and external experts performed systematic literature reviews on three topics to support updated NACI guidance: 1) RSV burden of disease; 2) PVZ effectiveness; and 3) cost effectiveness of PVZ prophylaxis. Full details and results are presented in the statement and supporting documents.

Results: Respiratory syncytial virus hospitalization (RSVH) rates are highest in children younger than one year of age and especially in the first two months of life. In various populations of infants at risk of severe RSV infection, PVZ prophylaxis is associated with reductions of 38%–86% in the risk of RSVH. Only rare cases of anaphylaxis have been reported after decades of use. Palivizumab is expensive and only cost-saving in rare scenarios.

Conclusion: Updated NACI recommendations on use of PVZ for the prevention of complications of RSV in infants are now available.

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Keywords: NACI, National Advisory Committee on Immunization, guidance palivizumab, PVZ, respiratory syncytial virus, RSV

Introduction

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in young children worldwide. It causes yearly outbreaks of respiratory tract disease; in Canada from late fall to early spring. While many infections are simple colds, children younger than two years of age are at risk of severe disease such as bronchiolitis or pneumonia and may be hospitalized. Underlying health conditions, especially premature birth, chronic lung disease and congenital heart disease

predispose to more severe RSV illness. Reinfections occur throughout life as infection produces only partial and temporary immunity, although reinfections are usually milder than the initial one. At present, there is no vaccine available to prevent RSV; the only means of prophylaxis against RSV disease is temporary passive protection with the monoclonal antibody preparation, palivizumab (PVZ) (Synagis™).

In 2003, the National Advisory Committee on Immunization (NACI) published recommendations on the use of PVZ for the prevention of RSV disease (1). At that time, NACI recommended PVZ be used during the RSV season for premature infants (younger than or equal to 32 weeks gestational age [wGA] who would be younger than six months of chronological age at the start of RSV season), children younger than 24 months of age with chronic lung disease of prematurity requiring oxygen and/or medical therapy in the previous six months or other pulmonary disorders requiring oxygen therapy, and children younger than 24 months of age with hemodynamically significant congenital heart disease. Palivizumab prophylaxis could also be considered for children born at younger than 35 wGA who are younger than six months of age at the start of RSV season and who live in remote northern communities (1).

The purpose of this article is to update previous NACI recommendations for the use of PVZ, taking into consideration recent data on burden of illness due to RSV disease, the efficacy and effectiveness of PVZ in infants at risk of more severe RSV disease and the economic implications of PVZ use.

Details can be found in the updated NACI Advisory Committee statement: *"Recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants"* (2).

To support this work, the Working Group and other expert bodies performed three systematic literature reviews using standard NACI methodology: the burden of RSV disease in young children in high-income countries comparable to Canada (published in September 2021) (3); the effectiveness of PVZ prophylaxis on reducing the complications associated with RSV in infants (results summarized in the statement and full details to be published as a separate document) (4); and the cost-effectiveness of PVZ prophylaxis for RSV (results summarized in the statement and full details to be published as a separate document) (5).

The respiratory syncytial virus hospitalization (RSVH) rates are highest in children younger than one year of age and especially in the first two months of life. Prematurity is associated with greater risk for RSVH, longer hospital length of stay and a higher rate of admission to an intensive care unit. Children younger than two years of age with chronic lung disease of prematurity or younger than one year of age with hemodynamically significant congenital heart disease are also at greater risk for RSVH. Those with cystic fibrosis, Down syndrome and immunodeficiency may also be at increased risk. High rates of hospitalization for RSV have been reported in term infants living in some remote indigenous communities. Respiratory syncytial virus hospitalization in infancy may be associated with greater wheeze and asthma medication use in early childhood, but RSV causation has not been established.

Palivizumab has only been studied in children younger than two years of age with underlying health conditions, with the exception of one recent study of healthy term Inuit infants residing in remote northern communities. In various populations of infants at risk of severe RSV infection, PVZ prophylaxis is associated with reductions of 38%–86% in the risk of RSVH, with number of treatments needed to treat to prevent one hospitalization of 2 to 54. Reductions in RSVH of 38%–80% for premature infants, 39%–86% for those with chronic lung disease of prematurity, and 45%–51% for those with hemodynamically significant congenital heart disease have been reported. Recommendations for other groups considered to be at equivalent risk of severe RSV disease are based on extrapolations from these data.

A previous Canadian Immunization Guide recommendation that PVZ prophylaxis should be considered for all Inuit children in northern remote communities who are younger than six months of age at the start of RSV season, regardless of gestational age, was reassessed. NACI now recommends that PVZ should not be offered routinely to healthy term infants living in remote northern Inuit communities but may be considered for such communities if the documented RSVH rate for term infants is very high. This change was based on the limited evidence available, including one study showing no effect of PVZ prophylaxis on RSVH in healthy full-term infants living in a northern Inuit population in one region of Canada with a RSVH rate for all infants younger than one year of age of 5%, and a qualitative study in that same population that identified significant acceptability and feasibility issues with PVZ prophylaxis.

Palivizumab has been used for over two decades in many countries and has a good safety record, with very rare cases of anaphylaxis being the major serious adverse event. Palivizumab is expensive, with incremental effectiveness ratios per quality-adjusted life year estimated from less than $1,000 to over $2M in various scenarios. In various high-risk groups, 64%–100% of estimates were less than $50,000 per quality-adjusted life year. In rare scenarios it may be cost saving.

The key recommendations are summarized below.

2022 NACI recommendations for use of palivizumab to reduce complications of respiratory syncytial virus infection in infants

- Palivizumab **should be offered** to premature infants of younger than 30 wGA and younger than 6 months of age at onset of or during the RSV season; children aged younger than 24 months with chronic lung disease of prematurity who require ongoing oxygen therapy within the six months preceding or during the RSV season; infants aged younger than 12 months with hemodynamically significant congenital heart disease; and infants born at younger than 36 wGA and age younger than six months old living in remote northern Inuit communities who would require air transport for hospitalization. For children with both hemodynamically significant congenital heart disease and chronic lung disease, recommendations for chronic lung disease should be followed.
- Palivizumab **may be considered** for premature infants of 30–32 wGA and age younger than three months who are at high risk for exposure to RSV; selected children younger than 24 months of age with severe chronic lung disease due to cystic fibrosis or other etiology who require ongoing oxygen therapy or assisted ventilation in the six months preceding or during the RSV season; infants younger than 12 months of age with hemodynamically significant chronic cardiopathy other than congenital; children aged 12–24 months awaiting heart transplant or having received a heart transplant within six months of onset of the RSV season; and children aged younger than 24 months with severe immunodeficiency. It may also be considered for term infants aged younger than six months living in remote Inuit communities with very high rates of hospitalization for RSV among term infants and for infants of younger than 36 wGA and age younger than six months living in other remote communities with high rates of hospitalization for RSV and where air transport would be required for hospitalization.
- Palivizumab **should not be offered** to otherwise healthy infants born at or after 33 wGA; or to siblings in multiple births who do not otherwise qualify for prophylaxis. It should not be offered **routinely** for children younger than 24 months of age with cystic fibrosis; for children younger than 24 months of age with Down syndrome without other criteria for PVZ; or for healthy term infants living in remote northern Inuit communities unless hospitalization rates for RSV are very high. It should not be used for the prevention of recurrent wheezing or asthma in the absence of other indications.
- Palivizumab **should not be given** to prevent hospital-associated RSV infection in eligible children who remain in hospital. It **may be considered** when all other measures have failed to control an RSV outbreak in a neonatal intensive care unit.

Authors' statement

DM — Writing, original draft, review, editing
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The *NACI Statement on the Recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants* was prepared by D Moore, A Sinilaite, R Stirling, MW Yeung, on behalf of the NACI RSV Working Group, and was approved by NACI.

Competing interests

None.

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RAPID COMMUNICATION

Summary of the National Advisory Committee on Immunization (NACI) Rapid Response—Interim guidance on the use of Imvamune in the context of monkeypox outbreaks in Canada

April Killikelly[1], Nicholas Brousseau[2] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Monkeypox is endemic in Central and West Africa. Cases in non-endemic countries, including Canada, have been increasing since May 2022. Imvamune®, a live, non-replicating smallpox vaccine, was approved by Health Canada for active immunization against smallpox and monkeypox infections and disease in adults determined to be at high risk for exposure. The aim of this interim guidance is to consider the use of Imvamune for post-exposure prophylaxis (PEP) and to summarize the available evidence in support of Imvamune use in this specific current context.

Methods: The National Advisory Committee on Immunization (NACI) High Consequence Infectious Disease Working Group (HCID WG) reviewed data on the current status of the monkeypox outbreak, along with additional evidence included in published scientific literature and from manufacturers, regarding the safety, immunogenicity and protection offered by Imvamune. NACI approved these HCID WG recommendations on June 8, 2022.

Results: In brief, NACI recommends that PEP, using a single dose of the Imvamune vaccine, may be offered to individuals with high-risk exposures to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. After 28 days, if an individual is assessed as having a predictable ongoing risk of exposure, a second dose may be offered. Imvamune may be offered to special populations; including individuals who are immunosuppressed, pregnant, breastfeeding, younger than 18 years of age and/or with atopic dermatitis.

Conclusion: NACI has rapidly developed guidance on the use of Imvamune in Canada in the context of many uncertainties. Recommendations may be revisited as new evidence emerges.

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Keywords: National Advisory Committee on Immunization, monkeypox, Canada, Imvamune interim guidance

Introduction

Monkeypox virus is a member of the *Orthopoxvirus* genus, which also includes variola virus (smallpox virus), vaccinia virus, cowpox and other poxviruses. The disease is usually self-limiting and resolves within 14–28 days. Symptoms differ from smallpox and may include fever, headache, back pain, myalgia, asthenia, lymphadenopathy and skin lesions/rash. The duration of communicability for monkeypox virus may be up to 2–4 weeks, based on limited evidence of polymerase chain reaction detection of monkeypox in the upper respiratory tract (1). Potential complications of monkeypox include

secondary bacterial infections, pneumonia, sepsis, encephalitis and vision loss from corneal inflammation. Monkeypox virus may cause severe disease in young children, individuals who are immunocompromised (2), and those who are pregnant. Information about monkeypox in people who are pregnant is sparse, but cases of first trimester miscarriage and stillbirths have been reported (3). In the current 2022 multi-country outbreak, monkeypox cases may have an atypical presentation including oral, genital, and/or anal lesions with or without fever, or systemic symptoms.

The 2022 multi-country monkeypox outbreak represents the first incidence of broader community transmission in a number of countries outside of certain regions of Africa. According to open-source information, the Québec cases are mainly men 30–55 years of age who presented to sexually transmitted and blood-borne infection clinics in the Montréal area.

Imvamune® (also called Modified Vaccinia Ankara-Bavarian Nordic [MVA-BN], Jynneos®, Imvanex®) is a non-replicating, third-generation smallpox vaccine manufactured by Bavarian Nordic. Imvamune was approved on November 5, 2020 by Health Canada for active immunization against smallpox, monkeypox and related *Orthopoxvirus* infections and disease in adults 18 years of age and older determined to be at high risk for exposure (3). Imvamune differs from previous generations of smallpox vaccines as it is a non-replicating vaccine virus in humans, meaning that based on preclinical studies, it is not able to produce more copies of itself (4). Imvamune is stockpiled within Canada's National Emergency Strategic Stockpile for the purposes of national security due to its potential efficacy against variola, the virus that causes smallpox.

In the context of the rapidly evolving multi-country monkeypox outbreak, the planned task for this Rapid Response was to consider the use of Imvamune for post-exposure prophylaxis and to summarize the available evidence in support of Imvamune use in this specific current context. Unrelated to the current monkeypox outbreak, the National Advisory Committee on Immunization (NACI) was also asked to consider use of Imvamune in laboratory research settings where replicating orthopoxviruses are studied.

Details can be found in the updated NACI advisory committee statement: *NACI Rapid Response—Interim guidance on the use of Imvamune in the context of monkeypox outbreaks in Canada* (5).

Methods

On May 26 and May 27, 2022, monkeypox data were discussed and reviewed by the NACI High Consequence Infectious Disease working group (HCID WG), along with input from the Public Health Ethics Consultative Group, Canadian Immunization Committee, NACI's Vaccine Safety Working Group and two lesbian, gay, bisexual, transgender, queer or questioning and two-spirit (LGBTQ2S+) stakeholder groups. The HCID WG reviewed data on the current status of the monkeypox outbreak, along with additional evidence included in published scientific literature and from manufacturers, regarding the safety, immunogenicity and protection offered by Imvamune. NACI approved these HCID WG recommendations on June 8, 2022.

Results

Table 1 summarizes the very limited evidence upon which the NACI recommendations were based as well as the unknowns for each recommendation area.

Recommendations

1. NACI recommends that post-exposure prophylaxis (PEP) using a single dose of the Imvamune vaccine may be offered to individuals with high-risk exposures (6) to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. The PEP should be offered as soon as possible and within four days of last exposure and can be considered up to 14 days since last exposure. The PEP should not be offered to individuals who are symptomatic and who meet the definition of suspect, probable or confirmed case. After 28 days, if an individual is assessed as having a predictable ongoing risk of exposure, a second dose may be offered. A second dose should not be offered to individuals who are symptomatic and therefore after medical evaluation meet suspect, probable or confirmed monkeypox case definitions. For individuals who had received a live replicating first or second generation smallpox vaccine in the past and who sustain a high-risk exposure to a probable or confirmed case of monkeypox, a single dose of Imvamune PEP may be offered (i.e. as a booster dose). The benefit of protection against infection should be discussed with a healthcare provider and weighed against the potential risk of recurrent myocarditis for individuals with a history of myocarditis/pericarditis linked to a previous dose of live replicating first and second generation smallpox vaccine and/or Imvamune; a precautionary approach is warranted at this time until more information is available.

2. NACI recommends that Imvamune pre-exposure prophylaxis (PrEP) may be offered to personnel working with replicating orthopoxviruses that pose a risk to human health (vaccinia or monkeypox) in laboratory settings and who are at high risk of occupational exposure. If Imvamune is used, two doses should be given at least 28 days apart. A booster dose may be offered after two years if the risk of exposure extends beyond that time. This recommendation does not apply to clinical diagnostic laboratory settings at this time, due to very low risk of transmission. For immunocompetent

Table 1: Knowns and unknowns[a]

Knowns		Unknowns
Pre-exposure prophylaxis		
From early-stage clinical trials, most of the reported AEFIs were mild to moderate and resolved within seven days following vaccination. Some cardiac AEFIs were reported in Imvamune® recipients and none were considered serious. Indirect clinical immunological evidence showed that Imvamune was able to generate immune responses by week two after a first dose, and comparable immune responses to previous generation smallpox vaccines after two doses by week six. Indirect clinical evidence showed that two doses of Imvamune was able to generate protection from symptomatic vaccinia (*Orthopoxvirus* related to monkeypox). Imvamune immune responses may decrease after two years. Immune responses to booster doses of Imvamune were fast and to the level of primary series responses.		The efficacy or effectiveness of Imvamune PrEP against monkeypox infection or disease is unknown. There were no direct efficacy or effectiveness data for Imvamune against monkeypox. There was limited safety data for Imvamune PrEP. The degree to which preclinical, immunological or *Othopoxvirus* data was predictive of Imvamune protection or durability against monkeypox is unknown. The number of doses, or dose interval, for optimal protection by Imvamune PrEP in immunocompetent adults without underlying medical conditions is unknown. The protection offered by previous smallpox vaccination (potentially from decades ago) and the best use of Imvamune PrEP in those previously vaccinated is unknown. Due to the limited context of Imvamune use (i.e. clinical trials), low frequency AEFIs (frequency fewer than one in 10,000) are unknown. The degree to which previous infection or vaccination impacts the efficacy/effectiveness and safety Imvamune PrEP is unknown.
Post-exposure prophylaxis		
Indirect preclinical immunological evidence showed that Imvamune PEP was able to generate comparable immune responses to previous generation smallpox vaccines. Based on historical data for first generation vaccination against variola, the earlier the PEP was given, the better the protection from disease. Indirect clinical immunological evidence from PrEP studies showed that Imvamune was able to generate immune responses by week two after a first dose, and comparable immune responses to previous generation smallpox vaccines after two doses by week six.		The safety, efficacy or effectiveness of Imvamune PEP against monkeypox infection or disease is unknown. There were no direct safety, efficacy or effectiveness data for Imvamune PEP against monkeypox. The number of doses, dose interval or timing from exposure, for optimal protection by Imvamune PEP in immunocompetent adults without underlying medical conditions is unknown. The degree to which previous infection or vaccination impacts the efficacy/effectiveness and safety Imvamune PEP is unknown.
Special populations		
Immunosuppressed individuals	Based on limited clinical study, safety among people living with HIV (CD4 at least 100 cells/μL) and HSCT seemed comparable with non-immunosuppressed controls. Compared to people without HIV, individuals living with HIV may have had lower immune responses to one dose of Imvamune and may have had decreased durability of immune responses. Imvamune was well tolerated in 20 individuals who received hematopoietic stem cell transplant.	The efficacy or effectiveness of Imvamune PEP or PrEP against monkeypox infection or disease is unknown. There were no direct efficacy or effectiveness data for Imvamune in this population against monkeypox. There were limited safety data for Imvamune PrEP. It is not yet clear if some immunocompromised groups will be less protected by the vaccine and may require specific vaccine doses, intervals or antigen levels.
Pregnant and breastfeeding individuals	No safety concerns were identified during limited clinical and preclinical testing of Imvamune.	The safety, efficacy or effectiveness of Imvamune PEP or PrEP against monkeypox infection or disease is unknown. Imvamune has never been tested in this population. There were no direct safety, efficacy or effectiveness data for Imvamune in this population against monkeypox.
Children younger than 18 years	No safety concerns were identified in limited clinical testing of Imvamune-like vaccines in approximately 2,000 children under 18 years of age.	The safety, efficacy or effectiveness of Imvamune PEP or PrEP against monkeypox infection or disease is unknown. Imvamune has never been tested in this population. There are no direct safety, efficacy or effectiveness data for Imvamune in this population against monkeypox. It is not yet clear if some age groups may require specific vaccine doses, intervals or antigen levels or if there is a minimum age for vaccination.
Individuals with AD	In limited clinical testing, Imvamune was well tolerated in individuals with AD, though individuals with AD may experience a higher frequency of local and systemic reactogenicity compared to those without AD.	The safety, efficacy or effectiveness of Imvamune PEP or PrEP against monkeypox infection or disease is unknown. There are no direct efficacy or effectiveness data for Imvamune in this population against monkeypox. There are limited safety data for Imvamune.

Abbreviations: AEFIs, adverse events following immunization; AD, atopic dermatitis; HSCT, hematopoietic stem cell transplantation; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis
a Summarized from the *Interim guidance on the use of Imvamune in the context of monkeypox outbreaks in Canada* (5)

individuals who have received a live replicating first or second generation smallpox vaccine in the past and who are at high risk for occupational exposure, a single dose of Imvamune may be offered (i.e. as a booster dose), rather than the two dose primary vaccine series. This single Imvamune dose should be given at least two years after the latest live replicating smallpox vaccine dose. In consultation with a physician, the benefit of protection against infection should be weighed against the risk of recurrent myocarditis for individuals with a history of myocarditis/pericarditis linked to a previous dose of live replicating first and second generation smallpox vaccine and/or Imvamune; a precautionary approach is warranted at this time until more information is available.

3. NACI recommends that Imvamune vaccine may be offered to the following populations, if recommended to receive vaccine based on exposure risk: individuals who are immunocompromised due to disease or treatment; individuals who are pregnant; individuals who are lactating; children/youth; and individuals with atopic dermatitis.

4. NACI recommends that Imvamune given as PEP or PrEP should not be delayed due to recent receipt of a messenger ribonucleic acid (mRNA) coronavirus disease 2019 (COVID-19) vaccine. If vaccine timing can be planned (i.e. prior to employment within a research laboratory), NACI recommends that Imvamune be given at least four weeks after or before an mRNA vaccine for COVID-19.

Conclusion

Based on limited available evidence, NACI and other stakeholders were able to develop and deliver guidance on the use of Imvamune in the context of the monkeypox outbreak in Canada 22 calendar days from the first case reported in Canada. These recommendations were made in the context of many unknowns and uncertainties and may be revisited as new evidence emerges.

Authors' statement

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Competing interests

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What do people think about COVID-19 booster doses?

Source: Emerging Sciences Group of the Public Health Agency of Canada. Evidence Brief on attitudes and acceptance of COVID-19 booster doses. April 2022. Full report available from: ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca

Background: Attitudes towards the coronavirus disease 2019 (COVID-19) vaccines in the "Five Eye" countries—Canada, United States (US), United Kingdom (UK), New Zealand and Australia—have been followed throughout the pandemic. After tracking relatively high rates of acceptance for the first two doses of COVID-19 vaccine (89% in Canada), the focus has now turned to boosters. In late 2021, booster doses were authorized for those aged 18 years and older in all five countries. In March 2022, second boosters were initially recommended only for individuals who were immunocompromised or living in long-term care and congregate settings, but this varied by age from older than 50 years in the US, to older than 70 years in Canada and older than 75 years in the UK. In Canada, the National Advisory Committee on Immunization also strongly recommended the second booster for all people older than 80 years of age. Some jurisdictions have expanded these recommendations to include eligibility of all adolescents for the first booster and all adults older than 60 years of age for the second booster. The National Advisory Committee on Immunization noted the primary vaccine series and booster recommendations also apply to those who were previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has indicated that a second booster may be needed for the broader population in the future, depending on COVID-19 activity. A review was conducted to examine the evidence on the facilitators, barriers and hesitancy to accept or refuse COVID-19 booster doses among both vaccinated and unvaccinated populations.

Methods: Seven databases and targeted websites were searched for relevant articles up to April 1, 2022. Data from these articles were extracted into evidence tables and the key findings summarized.

Results: Twenty articles were identified including those from Canada (n=6), US (n=6), UK (n=5), New Zealand (n=1) and Australia (n=1) and globally (13 countries including Canada, US, UK and Australia, n=1). Fourteen of the articles were conducted since the approval of the COVID-19 booster dose in their respective countries, and the remaining six were conducted prior to the approvals in early to mid-2021.

Intention to receive COVID-19 booster doses

- The most recent Canadian articles from February to March 2022 report that among those with two doses, 69% of those in British Columbia and 23% of those in Québec intended to receive a COVID-19 vaccine booster dose. In Québec, this decreased from 43% in January. Intention to accept a booster was highest in Atlantic Canada and lowest in the Prairies.
- A longitudinal study in the UK showed that intention to receive a COVID-19 vaccine booster was steady from 88% to 95% between August and December 2021, but decreased to 72% in January 2022 and 53% in March 2022.

Factors associated with the intention to accept or reject booster doses

Overall, factors associated with intention to accept or reject a COVID-19 booster were similar to accepting/rejecting the first and second doses of the vaccine.

- Intention to accept a booster dose was most commonly associated with older age, higher education, having long-term health conditions, being a past voter for the Liberal/Democrat parties, living in a larger more populated area and having trust in science and COVID-19 information. Asian or Caucasian people reported a higher intention to receive a booster than Black people.
- Hesitancy about initial COVID-19 vaccination may be a strong predictor for hesitancy about booster doses of the vaccine. The main reasons reported for rejecting a booster were concerns about short and long-term side-effects and beliefs that a booster dose would not offer extra protection and/or that they were protected if they had already had COVID-19.
- Overall support for vaccine donations to low-income countries before rolling out booster doses was high in both Canada and the UK.

Conclusion: Intentions to receive COVID-19 booster doses decreased between late 2021 and early 2022 in Canada and other countries. None of the previously published articles explored why this occurred. This review is based on self-reported results from surveys, so findings may be limited by response and social desirability bias. Additional public opinion studies are warranted as the course of COVID-19 and the booster recommendations evolve.

CCDR

CANADA COMMUNICABLE DISEASE REPORT

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