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ANTIMICROBIAL USE AND STEWARDSHIP

GUEST EDITOR: DON SHEPPARD

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The cover photo represents a sample of green, yellow and blue pills or capsules on a white background illustrating the importance of slowing the spread of antimicrobial resistance by measuring and promoting the proper use of antimicrobials. This image was taken from Adobe Stock #212212617

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Guest Editor:

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Short-course antibiotic therapy: The next frontier in antimicrobial stewardship

Donald Sheppard[1,2,3,4]*

Abstract

Ensuring appropriate use of antibiotics is critical to preserving their effectiveness through limiting the development and spread of antimicrobial resistance. Evidence is accumulating that shorter courses of antibiotics are as effective as traditional longer regimens for many common infections and can reduce the risk of adverse events. Despite the availability of evidence and guidelines supporting short-course antibiotic therapy for these conditions, prolonged use of antibiotics remains common. This article will review the origins and evolution of our approach regarding antimicrobial prescription duration, the evidence for the use of short-course therapy for selected infections, barriers to the uptake of this practice and potential approaches that can be taken to reduce inappropriately long antibiotic use.

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Introduction

Antibiotics have transformed modern medicine, but their continued viability is threatened by rising rates of antimicrobial resistance (AMR). Limiting inappropriate use of antibiotics is an important approach to reducing the antibiotic pressure that can accelerate the evolution and spread of AMR. Evidence is emerging that for many common infections, short-course antibiotic therapy (1–7 days) can be equally as effective as traditional, longer courses of treatment (1,2). Expanded use of short-course antibiotic therapy has the potential to reduce healthcare costs, reduce risks of adverse drug events and help curb AMR. This editorial will review the history of the development of antibiotic treatment duration, highlight key evidence for appropriate reductions in antibiotic therapy duration, and outline future directions in antimicrobial stewardship and knowledge generation that could support the reduction of unnecessary prolonged antibiotic therapy.

Origins of the current approach to antibiotic therapy duration

The modern antibiotic era began with the introduction of penicillin in 1940, and with it, the dilemma of determining the appropriate duration of therapy for infectious diseases. Albert Alexander, a British constable, was the first human to receive penicillin therapy for extensive streptococcal and staphylococcal facial abscesses following an injury sustained in a bombing raid (3). Constable Alexander received five days of penicillin therapy with an excellent short-term response; however, despite attempt to re-purify penicillin from his urine, the supply of purified penicillin was exhausted and therapy was discontinued as a result. Sadly, within several weeks, his infection returned and he eventually succumbed to his disease. While this first use of penicillin demonstrated the power of antibiotics to treat bacterial infections, it also presaged the current challenge of determining antibiotic therapy duration, highlighting both the question of "how much is enough", and the legitimate fear that inadequate therapy may result in relapse or poorer outcomes.

Despite this somewhat disheartening first experience with short-course antibiotic therapy, early prescribers of penicillin reported that 1.5–4 days of treatment was sufficient to cure the majority of patients with diseases like pneumococcal pneumonia (1). Indeed, one of the earliest trials of penicillin therapy for pneumococcal pneumonia demonstrated that when therapy was discontinued 2–3 days after clinical improvement and resolution of fever, only 3 of 54 patients relapsed after initial therapy (4). One of these cases occurred in a patient receiving only 24 hours of therapy, and in the other two cases the strain at relapse was found to be a different serotype than the original infecting isolate, suggesting a reinfection rather than a relapse (4). Collectively these observations suggest that longer courses of 1–2 weeks of penicillin for pneumonia are unnecessary for the majority of patients.

Many factors have likely influenced the shift from this original approach of using antibiotics for short courses, tailored to patient responses, to the modern, longer, 1–2 weeks fixed duration of therapy (1). The rise in outpatient care and the shift away from intensive patient follow-up makes daily assessment of response to therapy less practical and favours the use of fixed duration prescriptions. Experience with infections that require longer term antibiotic therapy like tuberculosis and endocarditis may have influenced attitudes towards the duration of therapy required for all infectious diseases. Public perceptions of risk and the current medico-legal climate have also combined to create a culture of caution in modern medicine. As antibiotics are largely well tolerated and safe, there is always the temptation to extend prescription duration to reduce perceived risks of relapse. Finally, and perhaps most importantly, a perceived lack of rigorous evidence supporting shorter course antibiotic therapy limits prescriber confidence in breaking with traditional longer, fixed duration therapies (5).

The case for shortening antimicrobial duration of therapy in selected infections

Although antibiotics are commonly viewed as "safe" medications, the potential advantages of prolonging antibiotic therapy duration must be weighed against the costs and potential for harm. From an economic perspective, it has been estimated that the cost of antimicrobial prescribing in Canada exceeds $750 million per year (6). It is evident that reducing the duration of antibiotic therapy has significant potential to reduce these costs. Prolonged antibiotic therapy can also increase the chance of medication for adverse events or drug-drug interactions and has been linked to increased risk of *Clostridioides difficile* infection (7). One study reported that in patients with pneumonia receiving continued antibiotic therapy after discharge, each excess day of treatment was associated with a 5% increase in the odds of self-reported antibiotic-associated adverse events (8). Beyond these direct costs and risks, longer courses of antibiotic therapy have been linked to an increased burden of resistance (9). In a study of antibiotic therapy for ventilator-associated pneumonia, recurrent infections with multidrug-resistant organisms were more commonly observed in patients receiving antibiotic prescriptions of 18 days as compared with those receiving only eight days (10). These data may suggest a need to revisit the broad use of public health messaging that encourages patients to complete their course of antibiotic therapy even after they feel better. For many conditions, this practice may be unnecessary and actually favour the emergence of resistance (1).

Clinical trials comparing short- and long-course therapy are accumulating, and a common theme is emerging supporting equivalent or better outcomes with short-course therapy. Multiple trials have demonstrated that short-course therapy (1–3 days) is highly effective for the treatment of uncomplicated urinary tract infection (11,12), and that pyelonephritis and urosepsis in adults can be treated with seven days of an appropriate agent (13–15). Similarly, studies in both community and hospital-acquired pneumonia comparing the efficacy of short-course (5–7 days) therapy have found equivalent efficacy, and reduced rates of adverse events when compared with longer courses of treatment (8,16,17). The efficacy of short-course therapy extends to severe infections as well. Three randomized controlled clinical trials have demonstrated the safety and efficacy of seven days of antibiotic therapy for bacteremia with gram-negative bacilli (18–21). A single large study has even challenged the dogma that antibiotic therapy for the treatment of febrile neutropenia must be continued until neutrophil recovery (22). This trial reported that antibiotic therapy for febrile neutropenia could be safely discontinued in patients with resolution of fever and clinical recovery, irrespective of their neutrophil counts (22). In recognition of the mounting evidence for short-course therapy, the Association of Medical Microbiology and Infection Disease Canada has recently published a practice point summary of duration of antibiotic therapy for common infections highlighting recent evidence for reduced duration of antibiotic treatment in select infectious diseases syndromes (23).

While the majority of trials on the duration of antibiotic therapy have supported the use of short-course therapy, there are some notable exceptions. A single trial reported that a six-week course of antibiotic therapy had inferior outcomes than a 12 weeks for prosthetic joint infection (24), although a second trial found that eight weeks was equally effective as longer course therapy for early prosthetic joint infection (25). Several meta-analyses of treatment trials of streptococcal pharyngitis found that bacterial eradication rates were higher with 10-day courses of penicillin; these differences were less marked with non-penicillin antibiotic treatments (26–28). Finally, although trials of treatment for otitis media in children found that 5–7 days of antibiotic therapy was effective (29), a single trial in children under the age of two years

reported that five days of therapy was less effective than 10 days (30). A detailed list of these and other studies of antibiotic treatment duration has been curated by Dr. Brad Spellberg, University of Southern California.

Awareness of evidence in support of short-course antibiotic therapy: a knowledge mobilization opportunity

Despite the availability of new recommendations and position pieces from professional associations, adherence to best practices in reducing inappropriately long antibiotic prescriptions remains suboptimal. International studies have reported high levels of unnecessarily prolonged antibiotic therapy in both primary care and hospital settings. A review of primary care data in England from 2013 to 2015 recorded an estimated 1.3 million days of excess antibiotic prescriptions (31). Similarly, a study of pneumonia treatment in the United States revealed that as many as two out of three patients received excess antibiotic therapy (8). Canadian data on the appropriateness of the duration of antibiotic prescriptions are relatively sparse. A recent report on a stewardship intervention in primary care reported that 29.3% of prescriptions for community-acquired infections were inappropriately long (defined as more than seven days) (32). This report likely underestimates the degree of inappropriately prolonged prescription as it included cystitis, for which three days of antibiotic therapy is the standard of care. Similar findings have been reported in long-term care centres; a province-wide review of antimicrobial use in long-term care found that 44.9% of prescriptions exceeded seven days' duration (33). A limited number of studies have also identified high levels of prolonged antibiotic therapy in the Canadian hospital setting. An early study of treatment for hospital-acquired pneumonia found that only 30% of patients were treated with an appropriate duration of antibiotics (34). A second retrospective survey of the treatment of ventilator-associated pneumonia in a large Canadian urban health region found that more than 50% of patients received inappropriately prolonged antibiotic therapy (35). Collectively, these data suggest there is significant room for improvement in ensuring appropriate duration of antibiotic therapy in both the Canadian community and hospital sectors.

Behavioural science studies are beginning to shed light on the drivers underlying the continued use of prolonged antibiotic treatments by prescribers. International trials have suggested that prescriber preference and habit, rather than patient characteristics are the primary determinant of duration of antibiotic prescription trials (36), an observation that was replicated in the Canadian long-term care setting (33). Building on these findings, a recent behaviour change analysis in Canadian long-term care institutions highlighted a number of barriers to improving uptake of short-term antibiotic therapy, including a perceived lack of evidence, the often incorrect belief that short-course therapy could increase rates of antimicrobial resistance, as well as the previously documented strong effects of prior habits and belief in guiding prescription behaviours (5).

There are multiple approaches that could be taken to improve the uptake of short-course antibiotics in Canada. Increasing the awareness of new guidelines for short-course antibiotic therapies should be a goal of stewardship programs and targeted awareness campaigns and should be incorporated into professional education and maintenance of competence. There is evidence that these types of stewardship interventions can improve appropriate antibiotic prescription duration. Use of a multifaceted program of clinician education, clinical decision aids, patient information and audit and feedback in the Canadian outpatient setting resulted in significantly lower rates of inappropriately long-prescription duration as compared with clinics that did not receive the intervention (32). In parallel, the inclusion of measures of appropriateness of the duration of antibiotic use in antimicrobial use surveillance and epidemiologic studies will be critical in identifying populations and settings where prolonged antibiotic use is high, as well as monitoring the effectiveness of interventions and awareness campaigns designed to reduce this overuse. Traditionally, most surveillance programs and epidemiologic studies of antimicrobial use have focused on quantitative measures of total antibiotic use and quality measures that are driven by matching diagnoses to prescriptions, but often do not capture the duration of therapy by indication. Looking forward, although evidence is slowly emerging that the mantra of "short is better" is often correct, it is by no means a universal truth. Further studies are required to validate some of the seminal studies referenced here, and to explore the appropriate duration of therapy for other infectious diseases where prolonged antibiotic therapy has been linked to the emergence of resistance, such as sternal surgical infections following cardiac surgery (37). As evidence emerges, it may be possible to develop a better scientific framework to guide our understanding of what factors determine the need for prolonged antibiotic therapy to allow better identification of clinical predictors that can guide prescription duration in specific patient populations. Finally, expanding behavioural science research to better understand the barriers and enablers to implementing short-course antibiotic therapy has the potential to guide the development of novel approaches to improve rates of appropriate antibiotic therapy duration. The potential of behavioural science to guide effective stewardship initiatives has been clearly demonstrated in the United Kingdom at the national scale. In 2014, social norm feedback was provided to high prescribers of antibiotics in the form of a letter from England's Chief Medical Officer, accompanied by a leaflet on appropriate antibiotic use (38). This single intervention resulted in a sustained 3.3% reduction in antibiotic prescriptions, approaching the level of the five-year United Kingdom target of a 4% reduction of antibiotic use in primary care (38).

Conclusion

Ensuring antibiotics are used for an appropriate duration has the potential to reduce cost, improve patient outcomes and reduce antimicrobial resistance. There are multiple opportunities to advance the use of short-course therapy in clinical infectious diseases in Canada, including 1) improving awareness and education of existing duration of therapy guidelines, 2) implementing effective surveillance for appropriateness of antimicrobial prescription duration and 3) conducting studies to identify both the optimal length of therapy across a wide range of infectious diseases syndromes and the behavioural factors underlying prescriber practises in order to guide interventions aimed at reducing inappropriately long antibiotic prescriptions.

Author's statement

DCS conceived and wrote the manuscript.

Competing interests

The author reports no competing interests.

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Moving the needle on dental antibiotic overuse in Canada post COVID-19

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Abstract

Antimicrobial resistance due to over-prescribing in health care, including in dentistry, has been acknowledged as one of the top ten threats to global health by the World Health Organization. Dentistry is responsible for approximately 10% of antibiotics prescribed worldwide and research has shown up to 80% of antibiotics prescribed by dentists may be unnecessary. During the early months of the coronavirus disease 2019 pandemic, when dental offices handled only dental emergencies, it is probable that antibiotics were prescribed more readily and for longer duration to defer treatment for non-urgent cases. These unprecedented times strengthened the realization that strong dental antimicrobial stewardship practises are required in Canada to keep antimicrobial overuse under control. In countries, such as the United Kingdom and Australia, significant work is ongoing in this regard. Canada has made progress in developing tools for antimicrobial stewardship specifically for physicians in community settings, where the vast majority of antibiotics are prescribed, and it is now time to pay attention to antimicrobial stewardship in the field of dental care. Investments in developing a national level dental prescription database, along with monitoring, education and feedback mechanisms, can strongly support moving the needle on dentist-driven antibiotic overuse in Canada.

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Introduction

At the G7 Health Ministers meeting in Berlin in May 2022, antimicrobial resistance was listed as one of four priority areas of focus, along with coronavirus disease 2019 (COVID-19), future pandemic preparedness and health risks from climate change (1). Antibiotics are essential to the practice of dentistry for the prevention of distant site infections such as infectious endocarditis, as adjuncts for the prevention of some surgical site infections, and for the treatment of serious odontogenic infections.

Globally, dentistry is responsible for approximately 10% of antibiotics prescribed across health care, and research has shown up to 80% of dental antibiotics may be unnecessary, with wide variation between countries (2). Reliable information on prescribing by dentists is not available in most Canadian provinces, but data from the BC PharmaNet database indicates that during a ten-year period, antibiotic prescriptions by physicians decreased by 18.2%, while prescriptions by dentists increased by 62.2% (3). The reasons for this are unclear, but self-reported data from a 2016 survey of Canadian dentists (4) indicated that there is misunderstanding by dentists of both the medical indications as well as the dental procedures requiring antibiotic prophylaxis for the prevention of infective endocarditis. A lack of awareness of changes to antibiotic guidelines for patients with total joint replacement, variation in prescribing practices among dentists for antibiotic prophylaxis for the prevention of surgical site infections, use of antibiotics for conditions where antibiotics are not necessary and general overuse of clindamycin and underuse of penicillin V. Furthermore, where the most appropriate management of dental infections (surgical intervention) is most likely unavailable, visits to family physicians and emergency departments for non-traumatic dental conditions (5), may result in inappropriate antibiotic prescribing.

The COVID-19 pandemic has had a profound impact on oral health and dental practices worldwide. Deferred care during the early months of the pandemic created a huge backlog of needed dental treatment. During the months of virtual triage or office closures, with only the most urgent care provided in person, it is not difficult to imagine that when patients presented with dental issues, antibiotics were prescribed more readily and for longer duration. Data from the United Kingdom and Alberta support

this (6,7). The contribution of dentist-driven prescription adds to global increase in antibiotic prescribing across health care as a result of the pandemic (8).

Dental antimicrobial stewardship

The World Dental Federation encourages all national dental associations across all low, middle and high-income economies to commit to antimicrobial stewardship (AMS) by advocating for the inclusion of dentistry in national action plans and supporting their members to prescribe antibiotics wisely (9,10). To date, 58 national dental associations, including the Canadian Dental Association, have taken the World Dental Federation Pledge to tackle antibiotic resistance and enhance patient safety in their countries through three pillars: raising awareness and understanding about the concerns associated through effective communication, education and training; reducing the incidence of dental infection through effective sanitation, hygiene and infection prevention and control measures; and optimizing the use of antibiotics in human health.

Dental AMS programs focus primarily on reducing inappropriate antibiotic prescribing. Whilst reducing the use of antibiotics in dentistry is important, the significance of changes in prescribing rates to patient outcomes is poorly understood (11). It is important to ascertain that harm to patients is also reduced through the study of patient-related clinical outcomes (11). From a behavioural sciences perspective, it can be challenging to convince patients and clinicians to avoid an unnecessary antibiotic prescription due to its contribution to antimicrobial resistance. Describing the individual risks and benefits of an unnecessary antibiotic prescription can help support shared decision-making to avoid unnecessary antibiotic prescribing (12). To this end, research is underway to develop an international consensus on a core outcome set for dental AMS (13). At the present time, however, efforts comprise a combination of dissemination of guidelines, educational components for both clinicians and patients, and audit and feedback to improve dental antibiotic prescribing.

Guidelines for appropriate dental antibiotic use have largely focused on prophylaxis of distant site infections such as infective endocarditis and late prosthetic joint infections. These vary significantly by region and there continues to be some controversy (14). In Canada, the American Heart Association guidelines are followed for prevention of infective endocarditis (15) and the tripartite consensus statement from the Canadian Dental Association, the Canadian Orthopaedic Association and the Association of Medical Microbiology and Infectious Disease Canada provides solid advice against the use of antibiotics for patients with total joint replacement (16). Useful guidelines have recently been published by the American Dental Association on the use of antibiotics in the management of dental pain and/or intra-oral swelling (17).

Educational interventions for dentists are increasingly focused on toolkits, designed using concepts from the behavioural change literature and co-designed with patients. Significant work is ongoing in the United Kingdom and Australia in this regard (18–21). Although specific to care delivery in those countries, many of the concepts and tools can be adapted for Canadian dental practice. Similarly, through its Using Antibiotics Wisely campaign, Choosing Wisely Canada has developed excellent tools for physicians and resources for patients, which include a "viral prescription pad" and delayed prescription, alongside educational posters and pamphlets (22). Opportunities exist to leverage this work in the development of dental AMS strategies.

"Audit and feedback" is used to measure an individual's professional practice, compare it to targets, professional standards or peer performance, and provide feedback to the individual to improve quality of care. It can lead to small but potentially important improvements in professional practice, especially when baseline performance is low, and the feedback is carefully designed and delivered (23). This method has been shown to improve antibiotic prescribing in Canadian medical practice (24) and dental antibiotic prescribing in Scotland (25). Future studies to assess the most impactful design approach to audit and feedback are being planned in medicine (26) and dentistry (27). That said, because dental care is privately funded and delivered in Canada, accessibility to dental prescribing data is a challenge.

How can we move the needle forward in Canadian dentistry?

Canadian efforts in dental AMS are nascent, but there is strong interest and support for moving forward (28). The Canadian dental profession is well positioned to evaluate international dental AMS programs, as well as programs developed in medicine such as Choosing Wisely campaigns, to develop a strategy for a Canadian dental AMS program. Learning from international experiences in the field of dentistry can provide opportunities to implement such strategies in the Canadian context. To help move the needle forward, the authors have received a research grant from the tri-university Manchester-Melbourne-Toronto (MMT) Research Fund June 2022 competition. The funding is for the specific purpose of holding a workshop in Toronto in the fall of 2023, the goal of which will be to develop a strategic framework and action plan for AMS in Canadian dentistry, with international contributions from experienced researchers in the field from Manchester and Melbourne. Engagement with key dental and inter-professional stakeholders and organizations, as well as patients and members of the public, will help to shape this initiative and, we hope, provide momentum for change.

Conclusion

Addressing the significant data gap in dental antibiotic prescribing will be challenging. The likely implementation of the National Dental Care Program, targeting more than six million Canadians, presents an opportunity for establishing a dental prescription database at the national level, which can be routinely monitored to support reviewing the prescription practises of participating dentists across provinces and territories (29). Lessons learned emerging from the workshop may suggest other processes to explore in this regard. This will also support developing audit processes and feedback strategies to ultimately move the needle forward to optimize antibiotic prescribing practices among Canadian dentists.

Authors' statement

SS — Conception, reviewing literature, analysis of findings, writing manuscript and finalizing
KB — Reviewing the manuscript, providing constructive feedback, and finalizing
SS — Conception, reviewing literature, analysis of findings, writing manuscript and finalizing

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

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The Canadian Nosocomial Infection Surveillance Program: Keeping an eye on antimicrobial resistance in Canadian hospitals since 1995

Canadian Nosocomial Infection Surveillance Program[1]*

Abstract

Surveillance is essential to inform evidence-based policy and control measures that combat antimicrobial resistance (AMR). The Canadian Nosocomial Infection Surveillance Program (CNISP) collaborates with 88 sentinel hospitals across Canada to conduct prospective surveillance of infections and antimicrobial resistant organisms important to hospital infection prevention and control. This article aims to increase awareness of CNISP hospital-based surveillance activities. Since its inception in 1995, the scope of CNISP has expanded to include community-associated infections, outpatient *Clostridioides difficile* infections, viral respiratory infections such as coronavirus disease 2019, and emerging pathogens such as *Candida auris*. This change in scope, along with expansion to include rural, northern and community hospitals, has improved the generalizability of CNISP surveillance data. To generate actionable surveillance data, CNISP integrates demographic and clinical data abstracted from patient charts with molecular and microbiological data abstracted from laboratory testing. These data serve as a benchmark for participating hospitals and stakeholders to assess the burden of AMR in hospital and intervene as needed. Further, CNISP surveillance data are now available on a public-facing data blog that provides interactive visualizations and data syntheses sooner than peer-reviewed publications. Future directions of CNISP include the Simplified Dataset, which will capture aggregate AMR data from hospitals outside of the CNISP network, surveillance in long-term care facilities and a fourth point prevalence survey. Given its strengths and future directions, CNISP is well positioned to serve as the reference point for hospital-based AMR data in Canada.

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Keywords: antimicrobial resistance, Canada, hospitals, surveillance, healthcare-associated infections, community-associated infections, antimicrobial resistant organisms, Canadian Nosocomial Infection Surveillance Program

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Introduction

Antimicrobial resistance (AMR) is a threat to global public health. Surveillance is an essential pillar of the World Health Organization global action plan to combat AMR and a key component of the Pan-Canadian Framework for Action, which provides the context and foundation to guide a pan-Canadian response to combat AMR (1,2). Both community and hospital-based surveillance are needed to inform evidence-based action, such as antimicrobial stewardship (3). We provide an overview of the Canadian Nosocomial Infection Surveillance Program (CNISP)—a hospital-based surveillance system. In describing its scope, functions and future directions, we aim to increase awareness of the CNISP hospital-based surveillance activities that contribute to combatting AMR in Canada.

Structure

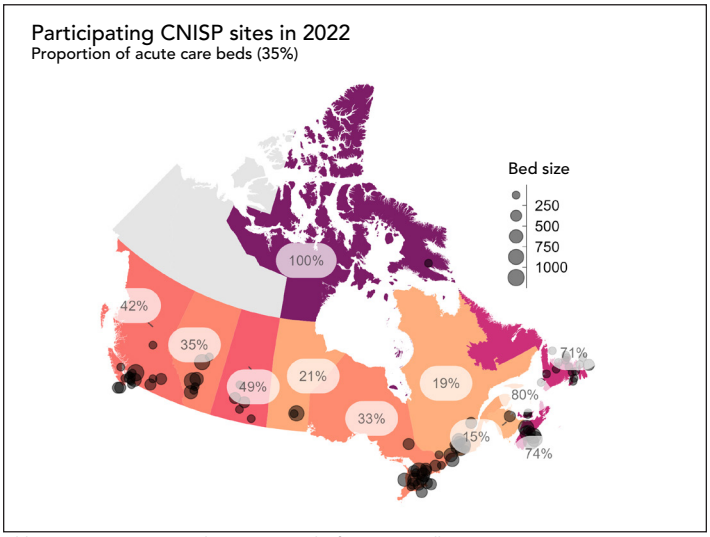
Prompted by a World Health Organization recommendation focused on combatting AMR, Health Canada established and fully funded CNISP as a hospital-based surveillance system in 1995. CNISP is a collaboration between the Public Health Agency of Canada, including the National Microbiology Laboratory, the Association of Medical Microbiology and Infectious Disease Canada and sentinel hospitals across Canada.

Scope

In 1995, CNISP conducted active surveillance in 18 hospitals across seven provinces and reported on only one antibiotic-resistant organism (ARO): methicillin-resistant *Staphylococcus aureus* (MRSA). By 2022, CNISP has expanded to conduct surveillance on 12 different pathogens in 88 hospitals across 10 provinces and 1 territory. **Figure 1** presents the complete list of pathogens CNISP conducts surveillance on, which includes healthcare-associated infections and AROs, along with the year surveillance of each started. CNISP also annually collects and analyzes data from Canadian hospitals on antimicrobial use (AMU), antibiogram, infection prevention and control (IPC) practises, laboratory practises and viral respiratory illness including coronavirus disease 2019 (COVID-19). **Figure 2** presents the geographical distribution and characteristics of hospitals across Canada participating in CNISP surveillance in 2022.

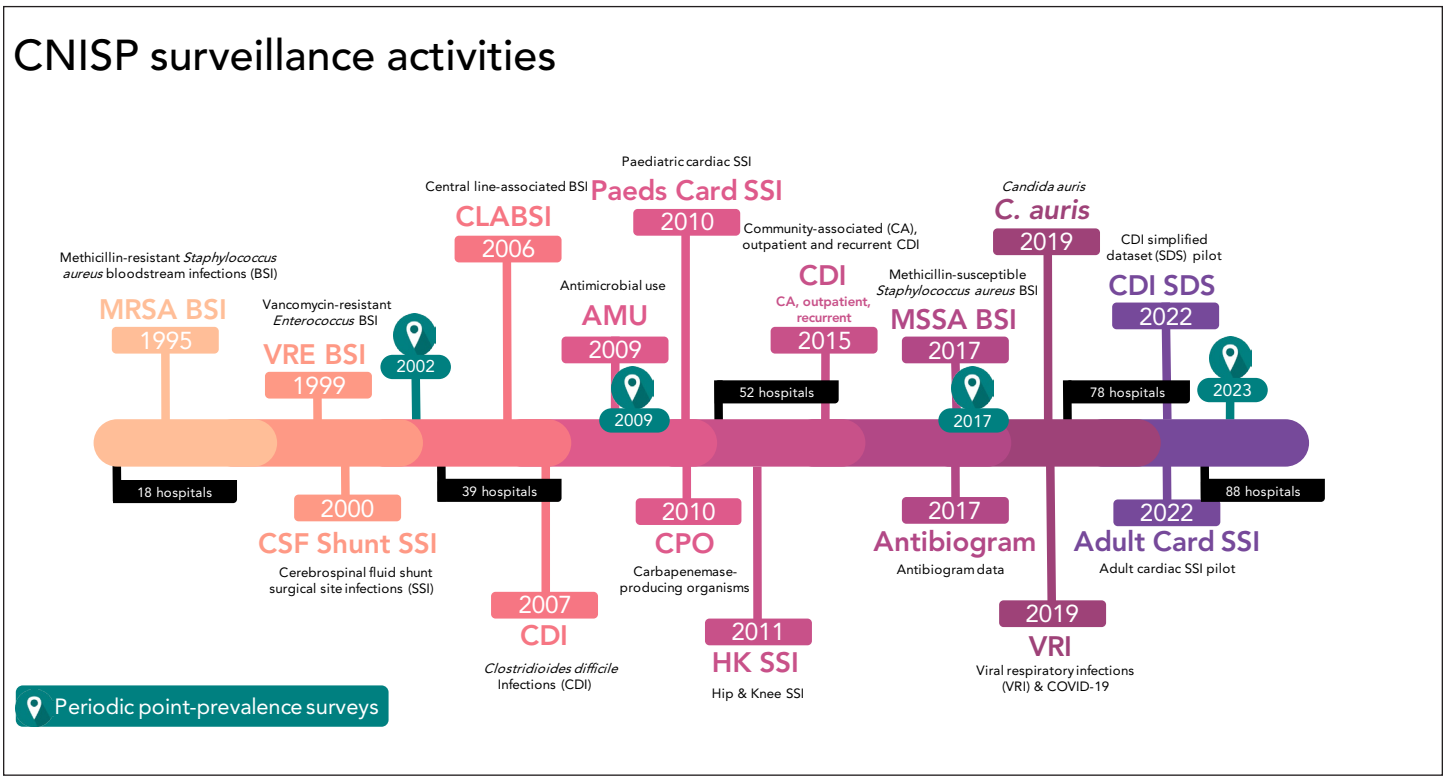
The expansion of CNISP to include rural, northern and community hospitals has improved the generalizability of its hospital-based surveillance data. As of 2022, one-third of CNISP participating hospitals (n=28/88, 32%) are non-teaching hospitals in the community, as defined by the Canadian Institute for Health Information (4). Further, the number of beds across the 88 hospitals participating in CNISP surveillance in 2022 ranged from 3 to 1,087 and 1 of 3 territories are represented. In addition to improvements in CNISP representativeness, the scope of CNISP has expanded. CNISP began collecting data on community-associated (CA) MRSA in 2010 and has since expanded to collect data on CA infections (e.g.

Figure 2: Geographical distribution and characteristics of the Canadian Nosocomial Infection Surveillance Program participating hospitals across Canada[a,b]



Abbreviation: CNISP, Canadian Nosocomial Infection Surveillance Program
[a] Percentage labels represent the percentage of acute care beds within each province/territory captured by CNISP
[b] Circles represent CNISP participating hospitals. The size of the circle is proportional to the hospital's bed capacity

Figure 1: Summary of the Canadian Nosocomial Infection Surveillance Program surveillance activities, 1995 to 2022



Abbreviations: Adult Card, Adult cardiac; AMU, antimicrobial use; BSI; bloodstream infection; CA, community-associated; *C. auris*, *Candida auris*; CDI, *Clostridioides difficile* infection; CLABSI, central line-associated bloodstream infection; CPO, carbapenemase-producing organism; CSF, cerebrospinal fluid shunt; HK, hip and knee; MRSA, methicillin-resistant *Staphylococcus aureus*; MMSA, methicillin-susceptible *Staphylococcus aureus*; Paeds Card, paediatric cardiac; SDS, simplified dataset; SSI, surgical site infection; VRE, vancomycin-resistant *Enterococci*; VRI, viral respiratory infection

CA *Clostridioides difficile* infections; CDI) and AROs (e.g. CA carbapenemase-producing *Enterobacterales*; CPE). Other areas in which CNISP has expanded its scope is with surveillance of outpatient CDI and emerging pathogens such as *Candida auris*.

Functions

Collect and analyze data

CNISP is the only national hospital sentinel system in Canada that actively collects AMR data via standardized methods. Definitions and protocols, which are publicly available online, facilitate this standardized data collection. CNISP analyzes demographic and clinical data abstracted from patient charts by trained IPC professionals, with linked molecular and microbiological data abstracted from centralized laboratory testing conducted by the National Microbiology Laboratory. A major strength of CNISP, relative to other surveillance systems, is its integration of these data. This comprehensive dataset has been essential in the monitoring of emerging AMR pathogens, including, for example, the hyper virulent *C. difficile* NAP1 (rt027) strain type, the emergence of CA-MRSA strain types (CMRSA10/USA300 and CMRSA7/USA400), vancomycin-resistant *Enterococci* (VRE) sequence type 1478 and CPE (5–9).

Provide benchmarks

A key function of CNISP is to provide participating hospitals and knowledge users, such as IPC and antimicrobial stewardship professionals, with benchmarks for hospital-acquired infection, ARO and AMU rates. By comparing their own site-specific rates to regional and national rates, participating hospitals can assess their progress in AMR prevention and intervene as needed. To facilitate this for selected surveillance projects, such as AMU, CNISP has developed and automated a site-specific report that presents site-specific rates relative to the rates of comparable hospitals in the CNISP network (de-identified in the site-specific report). In addition, participating hospitals have access to visual analytics for CDI on the Canadian Network for Public Health Intelligence platform, the secure on-line platform where hospitals submit their data. The Canadian Network for Public Health Intelligence visual analytics offers CNISP hospitals the ability to compare their rates of CDI to hospitals similar in size, type (community vs. teaching) or services offered, and to regional, provincial and national rates. Hospitals can also view resistance profiles and molecular characteristics (e.g. ribotypes). Antimicrobial stewardship groups, administrators and IPC staff may further benefit by utilizing these hospital-based surveillance data to guide quality improvement initiatives that tackle AMR, such as reducing AMU or implementing bundled interventions to reduce the risk of infection.

Disseminate scientific evidence

Since 1995, in collaboration with the National Microbiology Laboratory and stakeholders from participating hospitals, CNISP has produced over 260 publications, including peer-reviewed articles, reports and conference abstracts. These provide scientific evidence to inform public health action to reduce AMR. CNISP annually publishes reports summarizing trends in healthcare-associated infections and AMR in the *Canada Communicable Disease Report* and on the Government of Canada website. To improve accessibility and uptake of CNISP surveillance data among the public and healthcare professionals outside of the CNISP network, in 2022, CNISP launched an interactive data blog on the Government of Canada website. These data are consistent with those reported in the *Canada Communicable Disease Report* and additionally include data pertaining to AMU in hospitals, demonstrating CNISP's progress towards achieving integrated AMR/AMU surveillance across Canadian hospitals. This publicly available interface provides timely data syntheses and interactive visualizations to inform strategies to combat AMR sooner than peer-reviewed publications.

Guide policy and practice

CNISP surveillance data informs evidence-based policy and guidelines within Canada and internationally. For example, the Manitoba provincial government applies CNISP standardized definitions in their CDI clinical management protocol (10). Further, CNISP hospital-based surveillance informed provincial guidelines for the prevention and control of AROs (11). The CNISP supports the collaborative work plan of the Public Health Agency of Canada as demonstrated by its international partnerships with the Transatlantic Taskforce on Antimicrobial Resistance and the World Health Organization Global Antimicrobial Resistance and Use Surveillance System. CNISP provides antibiogram data to the Global Antimicrobial Resistance and Use Surveillance System for incorporation into their international database and report, which provide insights into the global burden of AMR (12). In addition, CNISP contributes hospital-based AMR data to the Canadian Antimicrobial Resistance Surveillance System annual report, which presents human data from CNISP with data from the animal, environmental and food safety sectors (13).

Adapt to public health needs

At the start of the COVID-19 pandemic, CNISP leveraged its existing network of sentinel hospitals across Canada to expand the scope of its viral respiratory illness surveillance to include CA and healthcare-associated COVID-19. CNISP participating hospitals collect COVID-19 patient level data, including demographic, clinical, outcome, AMU and ARO co-infection data. Using these patient level data, CNISP published a peer-reviewed article describing the epidemiology of patients with COVID-19 admitted to CNISP participating hospitals (14). Currently, CNISP is analyzing the impact of COVID-19 on ARO rates calculated from CNISP hospital-based surveillance data to better understand how the burden of AMR in hospitals has changed in Canada. CNISP also demonstrated its adaptability to respond to new and emerging pathogens by way of its initiation of *C. auris* surveillance in 2019. Since then, CNISP has contributed to understanding the prevalence of *C. auris* in

Canadian acute-care hospitals and preparedness for *C. auris* in CNISP participating hospitals (15,16).

Discussion

For more than 20 years, CNISP has been a successful collaboration between the federal government, national organizations and sentinel hospitals across Canada. In the future, CNISP will seek to recruit hospitals from the Northwest Territories and provinces with currently low representation. To further increase participation and improve the representativeness of its hospital-based surveillance data, CNISP has launched a Simplified Dataset (SDS). The SDS uses CNISP standardized definitions and aims to capture data on healthcare-associated infections and AROs from acute-care hospitals outside of the CNISP network. While hospitals participating in CNISP active surveillance submit patient-level data, hospitals participating in the SDS submit aggregate data (annual number of cases, patient days and patient admissions). In combining both data sources, CNISP will be able to report national and regional rates of AMR from a greater number and more representative sample of Canadian hospitals. After successful pilot testing of the SDS for CDI surveillance, CNISP is seeking to recruit additional hospitals outside of the network to participate in the SDS for CDI surveillance.

To further describe the burden of AMR in Canadian hospitals, CNISP will be conducting a point prevalence survey in 2023, which aims to include acute-care hospitals within and outside of the CNISP network. This survey will build upon three-point prevalence surveys conducted in 2002, 2009 and 2017 by CNISP. For Canadian hospitals, these repeated surveys are widely utilized to benchmark hospital-acquired infection, ARO and AMU rates, measure changes in prevalence over time, provide information on AMR control programs and identify new targets for surveillance (17–19). CNISP also seeks to expand its use of whole-genome sequencing to enable a deeper analysis of the evolving molecular epidemiology and transmission of AMR pathogens in Canada. Data from whole-genome sequencing can support IPC and stewardship practises in hospitals, and ultimately enhance public health interventions for AMR and infectious diseases (20).

Because CNISP is a hospital-based surveillance system, its AMR and AMU data are not generalizable to settings such as primary and long-term care. To improve our understanding of AMR in Canada, future surveillance efforts should focus on ascertaining AMR and AMU data from these under-represented settings (3,21). While CNISP captures data on CDI in outpatient settings and CA AROs, such as CA MRSA, CA CPE, CA VRE and CA CDI, there remains an important gap in our understanding of AMR and AMU in community settings (3,21). To help address this, future expansion of CNISP also includes the initiation of AMR surveillance in long-term care. The scope and methodology for long-term care surveillance are currently under development.

Conclusion

Supported by the federal government, CNISP is a core national program that has monitored AMR in Canadian acute-care hospitals since 1995. Surveillance data from this network of urban and community hospitals across Western, Central, Eastern and Northern Canada is used to provide benchmarks and inform evidence-based action, such as antimicrobial stewardship. Given its achievements in recent years and future directions, CNISP is well positioned to serve as the reference point for hospital-based AMR data in Canada.

Authors' statement

Epidemiologists from Public Health Agency of Canada were responsible for the conception, interpretation, drafting and revision of the article. The National Microbiology Laboratory and CNISP co-chairs contributed to the interpretation and revision of the paper.

Competing interests

None.

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Antibiotic prescribing and antimicrobial stewardship in long-term care facilities: Past interventions and implementation challenges

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Abstract

Background: The threat of antimicrobial resistance (AMR) is rising, leading to increased illness, death and healthcare costs. In long-term care facilities (LTCFs), high rates of infection coupled with high antibiotic use create a selective pressure for antimicrobial-resistant organisms that pose a risk to residents and staff as well as surrounding hospitals and communities. Antimicrobial stewardship (AMS) is paramount in the fight against AMR, but its adoption in LTCFs has been limited.

Methods: This article summarizes factors influencing antibiotic prescribing decisions in LTCFs and the effectiveness of past AMS interventions that have been put in place in an attempt to support those decisions. The emphasis of this literature review is the Canadian LTCF landscape; however, due to the limited literature in this area, the scope was broadened to include international studies.

Results: Prescribing decisions are influenced by the context of the individual patient, their caregivers, the clinical environment, the healthcare system and surrounding culture. Antimicrobial stewardship interventions were found to be successful in LTCFs, though there was considerable heterogeneity in the literature.

Conclusion: This article highlights the need for more well-designed studies that explore innovative and multifaceted solutions to AMS in LTCFs.

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Keywords: antimicrobial stewardship, antibiotic stewardship, antibiotic prescribing, long-term care, long-term care facilities, nursing homes, antimicrobial resistance

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Introduction

Antimicrobial resistance (AMR) is a global health emergency with rising human and financial costs (1). The threat is especially pertinent in long-term care facilities (LTCFs), which provide a range of healthcare options to older adults unable to live independently in the community, ranging from resident and long-term care to post-acute rehabilitation care (2). Older adults living in LTCFs are often clinically frail and at high risk of infection and subsequent antibiotic use (3,4). The leading indications for antibiotic use in LTCFs were urinary tract infections (UTIs), lower respiratory tract infections (LRTIs) and skin and soft tissue infections (SSTIs) (5). Of these, suspected UTIs provided the greatest challenge to antimicrobial stewardship (AMS), with up 70.5% of antibiotic prescriptions being considered clinically unnecessary, compared with 55.7% of prescriptions for LRTI and 22.0% for SSTI (5). While antibiotics are indispensable tools for combatting serious infections, inappropriate use, in terms of initiation, duration or dose, increases the possibility of selecting antimicrobial-resistant organisms (AROs) (3,6). Long-term care facilities can become reservoirs for AROs, threatening the well-being of LTCF residents and staff as well as the surrounding hospital and community (7–9).

Methods

Antimicrobial stewardship programs have been implemented in some LTCFs, often leading to reduced prevalence of AROs and improved resident outcomes (10). However, there was a paucity

of reviews from a Canadian perspective examining these AMS programs. This article describes factors influencing antibiotic prescribing decisions and the effectiveness of AMS interventions that have attempted to support those decisions. The emphasis of this literature review is on the Canadian LTCF landscape; however, due to the limited number of studies performed in Canada, we included international studies as well. The Embase, Medline and Global Health databases were searched to identify relevant articles published prior to April 2022 (see **Appendix** for a complete list of search terms). This search resulted in 26 primary research articles examining factors affecting antibiotic prescribing (seven Canadian) (6,11–16) and 22 articles assessing the success of AMS interventions in LTCFs (four Canadian) (17–20). The overwhelming majority of these studies occurred in LTCFs or nursing homes, though one of the studies examining factors affecting antibiotic prescribing queried staff in assisted living facilities (21) and another included a sample of five nursing homes and two residential care facilities (22). Of the AMS intervention studies we assessed, two were implemented in skilled nursing facilities (23,24), while another studied assisted living facilities (25).

Factors influencing antibiotic prescribing in long-term care facilities

Prescribing decisions are influenced by the context of the individual patient, their caregivers, the clinical environment, the healthcare system and the society that surrounds the prescriber. **Figure 1** summarizes the evidence for barriers to AMS in LTCFs that operate at each level.

Prescriber factors

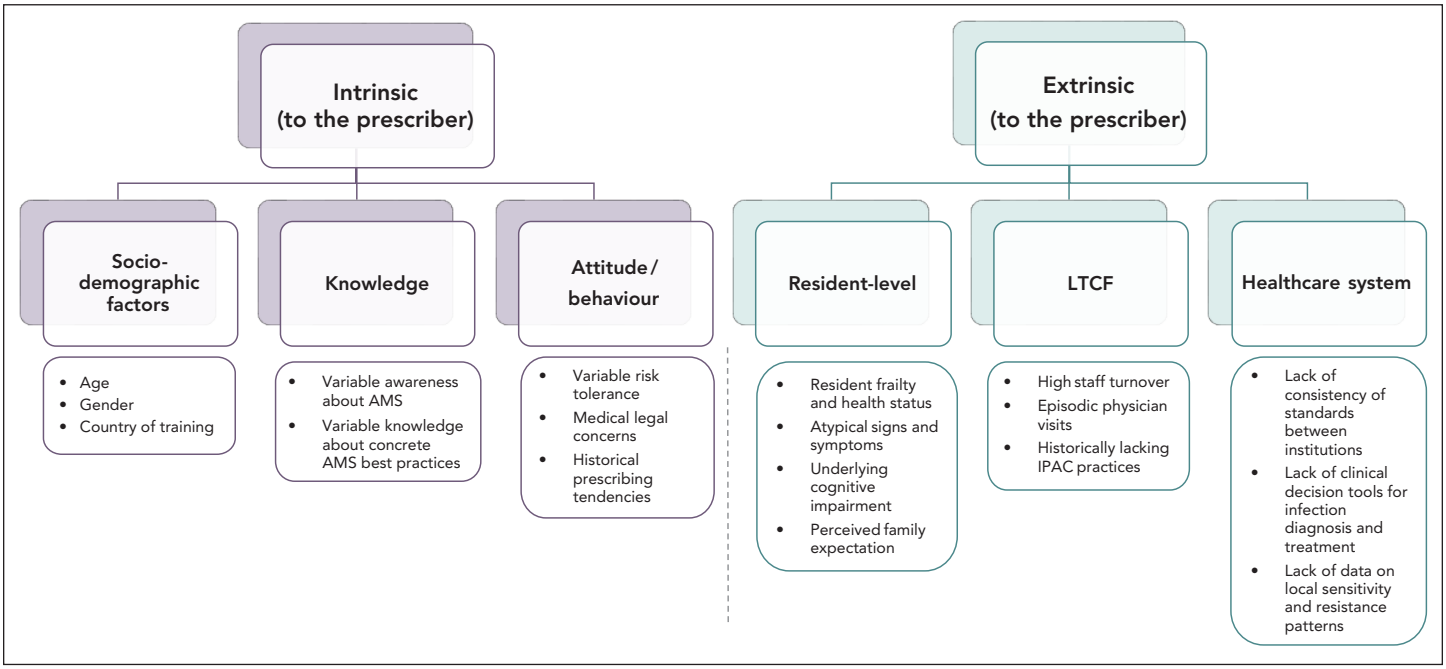
Antibiotic prescribing habits are highly variable among prescribers in LTCFs, and this variability is not accounted for by differences in resident characteristics (6) suggesting that individual prescribers have a role in driving antibiotic use and overuse. Past prescribing behaviour is a strong predictor of future prescribing (6), and being older, male and having completed medical school outside of Canada are associated with higher levels of antibiotic prescribing (6). Furthermore, tendency towards risk aversion (i.e. risk of delayed treatment and associated consequences) also influence antibiotic prescribing decisions (9,14,22,26).

Research also suggests that knowledge about AMR is variable in physicians and nurses and that knowledge gaps are associated with inappropriate prescribing (16,27,28). The search did not identify articles examining AMR knowledge in non-regulated caregivers, who provide much of the primary care in LTCFs.

Resident population factors

Residents of LTCFs are an increasingly frail population with complex care needs (29,30). Medical complaints from LTCF residents often present with non-specific or atypical symptoms that create diagnostic uncertainty, posing a challenge to confident antibiotic prescribing (13,21,22,28,31). Furthermore, a high proportion of residents have underlying cognitive impairment that limits their ability to communicate the specific symptoms and disease course that would inform diagnosis (13,21,22,28,31). Caregivers, who are important advocates for residents, may be perceived as having expectations that can influence antibiotic prescribing decisions (16,32–34).

Figure 1: Antibiotic prescribing decisions are affected by factors intrinsic and extrinsic to the prescriber



Abbreviations: AMS, antimicrobial stewardship; IPAC, infection prevention and control; LTCF, long-term care facility

Long-term care facilities environmental factors

Staffing patterns also contribute to antibiotic prescribing practices in LTCFs. Physicians visit LTCFs episodically, causing reliance on asynchronous communication strategies (i.e. fax, email, calls), which may lead to care team members not having the information they need to prescribe judiciously (9,27,28,31,32,35,36). High nursing and personal support worker turnover are also a major barrier to AMS in the LTCFs (16), perpetuating knowledge gaps among staff from lack of stability. Moreover, effective infection prevention and control practices, which are recognized to limit the spread of AMR, have historically been lacking in LTCFs due to limited resources and training opportunities (8,16,37–39). Prescribers may also perceive pressure due to medical legal concerns associated with adverse patient outcomes following the decision not to initiate an antibiotic prescription (38).

Healthcare systems factors and surveillance

At the healthcare system level, lack of access to resident-relevant information and consistency of standards between different healthcare institutions are key factors impeding informed decision-making in antibiotic prescribing (16,36,38). While many hospitals have robust antibiogram programs, LTCFs lack data on local sensitivity or resistance patterns. In fact, most specimens collected from LTCFs are processed in private laboratories in Canada and antimicrobial susceptibility data from those sites are not always made available to prescribers, leaving them without local resistance determinants to inform prescribing (*personal communication, RP Rennie*). There is also a lack of specific guidelines or clinical decision tools regarding infection diagnosis and treatment for LTCF residents (14,22,28,35,38); these gaps impede informed antibiotic decision-making and ultimately increase the risk of selecting for AROs (22,28). Lastly, there are limited antibiotic surveillance data from Canadian LTCFs and an absence of data on appropriate use, which represent a missing foundation for AMS programs in the sector.

Effectiveness of antimicrobial stewardship interventions in long-term care facilities

A variety of AMS intervention approaches in LTCF have been reported, with most articles testing multiple methods. Of the 22 articles reviewed, twelve used educational strategies and clinical practice guidelines (17,18,20,22,23,35,40–45). Others used a range of strategies, including audit and feedback (18,19,44,46–48), clinical care pathways (25,41,44), modified urine culture reporting (49), use of an infectious disease team (43,47,50,51) and interventions tailored to local needs (18,23,42,43). There was no single AMS intervention best practice; instead, articles have shown generally positive, but heterogeneous, results for many approaches. The AMS interventions most commonly targeted physicians (18,19,23,42,46,47,50,51) or both physicians and nurses (17,22,24,25,35,44,48,52). It was less common for AMS trials to focus solely on nurses (40,41,45,53), pharmacists (22,52), caregivers (25,43,44) or residents (44). Antimicrobial stewardship intervention approaches were reported only rarely in Canada; four of the 22 articles were implemented in Canadian LTCFs (17–20).

In the following sections, the results from these 22 articles are summarized and organized by outcome measure.

Antibiotic prescribing

Available evidence suggests that AMS interventions have generally been effective in reducing antibiotic prescribing, with a recent meta-analysis finding interventions associated with a 14% overall reduction in antimicrobial use (AMU) (10). Primary research points to the positive effects of AMS interventions in reducing antibiotic prescriptions, especially for the treatment of UTIs (20,45,53). It should be noted that outcomes assessing the appropriateness of antibiotic prescriptions are a more precise measure of stewardship than AMU; however, collecting these data is more labour-intensive and fewer articles examined this outcome measure (18,22–24,41,46,52). Among the studies that did measure the appropriateness of antibiotic prescriptions, the evidence was mixed; with some showing statistically significant improvements (18,41,46) and others not (22–24,52). Another important study outcome was the duration of therapy, where deprescribing interventions (i.e. the planned process of reducing or stopping medications that are no longer needed or may be causing harm) showed promise (54). Two articles showed reductions in the duration of antibiotic therapy following an AMS intervention (19,48), but more research is needed in this area.

Balancing measures

A recent systematic review found AMS interventions did not increase hospital admissions or deaths, indicating that these programs did not lead to under-treatment of infections (55). There was still limited evidence in this area and a need for further study. Future AMS articles should continue to monitor the safety of interventions by tracking mortality and morbidity outcomes as well as appropriateness measures.

Special focus on urinary tract infection

Antibiotic prescribing for suspected UTIs is a primary focus of AMS in LTCF. At the core of this challenge is the diagnosis of asymptomatic bacteriuria, which has a remarkably high incidence among LTCF residents (3,56). The judicious use of diagnostic tools for UTIs plays an important role in supporting UTI treatment decisions. The practice of routine dipstick analysis regardless of UTI symptoms increased the frequency of antibiotic use despite the known lack of utility of these tests among LTCF residents (22,38). Dipstick analysis is generally not recommended for LTCF residents (57); however, the rate of de-adoption is

unknown. Only one article examined this outcome and it did not show a decrease in the use of dipstick analysis following an AMS intervention that included the education of staff about new clinical practice guidelines through AMS program champions (40).

An upstream focus on the judicious use of urine cultures may be helpful in reducing unnecessary antibiotic prescriptions for UTIs given the high rates of asymptomatic bacteriuria in the LTCF population. Three articles have taken this approach, all showing a successful reduction in urine cultures, as well as, importantly, AMU (13,20,48). The timing of microbiology test results was also relevant, as delayed results increased the use of antibiotics, especially when coupled with increased risk aversion in the prescriber (16,22,31,32,38). Lastly, providing prescribers with local annual antibiograms may also be effective in reducing the rate of urine cultures and urinary antibiotics (58).

Discussion

Antimicrobial resistance is a public health threat with considerable health and economic burden (3) and a serious health-related issue for LTCF residents (7,59). Available evidence points to multiple factors influencing antibiotic overprescribing in LTCFs operating at various levels. These range from 1) individual differences in health care workers' knowledge of AMS to 2) variability in risk tolerances in nurses and doctors to 3) lack of consistent clinical guidelines and to 4) established practices (e.g. dipstick analysis). A significant issue in the Canadian context is the lack of institutional surveillance on AMU and local resistance patterns, which is foundational to successful AMS programs. Published articles showed that the adoption of AMS interventions in LTCFs can be effective, albeit with significant variability in effect sizes. Meaningful, sustainable implementation of AMS programs in LTCFs will require multifaceted solutions that address barriers faced by different decision-makers in the system.

The most frequently used interventions in AMS programs were educational components and clinical practice guidelines; however, there was no consensus on one specific strategy for an effective stewardship program, as no single intervention generated sufficient, sustainable improvement in antibiotic prescribing (60,61). Multifaceted AMS interventions at different levels could help reduce unnecessary or inappropriate AMU, ensure the optimal selection of antimicrobial therapies (i.e. dosage and duration) and help impede selective pressure for AROs (9,10). Implementation of a multifaceted AMS intervention would require dedicated resources in LTCFs (9). The practice of behavioural science has at its core a focus on changing behaviour—a foundational pillar of AMS. In other sectors, including acute care hospitals and community, behavioural science trials have been successful in delivering impactful, low-cost components to AMS programs (62,63). Heavier-handed solutions, like antibiotic restriction policies, may also play a role in enforcing stewardship, though their implementation must be carefully considered (64).

In the Canadian context, barriers to AMS partly reflect a historical and ongoing under-emphasis of vulnerable older adults, which manifests as poorly funded institutions with substandard working conditions, and a struggle to attract and retain a stable and qualified workforce—a situation only made more precarious during the coronavirus disease 2019 pandemic. A more thorough examination of social and cultural drivers of AMS in Canada has been conducted by other researchers (65).

The literature documents many barriers to AMS in LTCFs, with a particularly strong focus on factors that affect prescribers. This is crucial given the integral role these clinicians play in AMS; however, there is room for further study of the perspectives of non-prescribing healthcare providers on AMS, who provide most of the primary care in LTCFs (e.g. registered nurses, registered practical nurses, and personal support workers) and who are often the first to identify infections within the residents of LTCFs. A study of the diverse stakeholders in LTCFs may reveal novel opportunities for a broader set of individuals to participate in stewardship. Additionally, the relative importance and interconnectedness of barriers are unclear and further study is needed to parse the potential benefits of AMS interventions focused on each part of the system. A multifaceted problem warrants a multifaceted approach. Learning from the hospital sector (66), systems dynamics modelling may provide an important role on this front, as outcomes in non-linear systems like LTCFs are difficult to predict with conventional methods. Most of the articles assessing AMS effectiveness also rely on small sample sizes, limiting generalizability, which is particularly relevant given a heterogeneous LTCF landscape. Finally, we note that there is limited national-level surveillance data on AMU and AMR in Canadian LTCFs, which is necessary to inform future AMS efforts.

Conclusion

This article identified a wide range of barriers to judicious antibiotic prescribing in LTCFs and summarized evidence that indicates that AMS programs can be effective in this environment. While this article focused on LTCFs, its findings may also be relevant to assisted living facilities as the resident populations in these settings are similar. Future work should consider perspectives from a diverse group of stakeholders to help uncover how a larger group of actors can be supported as allies in AMS in LTCFs. The development of further high-quality trials is also needed, especially in Canada, to help understand which interventions retain effectiveness over time and across the heterogeneous LTCF landscape. Finally, strengthening the national surveillance system for AMU and AMR in LTCFs in Canada will be foundational to measure the impact of AMS strategies in this challenging setting.

Authors' statement

NV — Literature search, wrote the first draft
TG — Conceptualization, oversaw data collection, revisions
JC — Revisions
MM — Conceptualization, oversaw data collection, revisions
DGT — Conceptualization, oversaw data collection, revisions

Competing interests

The authors report no competing interests.

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Appendix

Table A1: Embase, 1974 to April 1, 2022

Table A2: Ovid MEDLINE(R) ALL, 1946 to April 1, 2022

Table A3: Global Health, 1973 to April 1, 2022

Table A1: Embase, 1974 to April 1, 2022

#	Search terms
1	*Antimicrobial Stewardship/
2	(antimicrobial stewardship or amr).ti,kw.
3	((stewardship* or "use" or misus* or abus* or overus* or therap* or prescrib*) and (antimicrobial* or antibiotic* or antibacterial* or antiviral* or antifungal* or anti microbial* or anti biotic* or anti bacterial* or anti viral* or anti fungal*)).ti,kw.
4	or/1-3 [AMR]
5	residential home/ or nursing home/ or assisted living facility/
6	(long term care facilit* or convalescence home or convalescence facilit* or nursing home? or group home? or assisted living or seniors home? or seniors residence? or old age home? or old age residence? or aged care home? or aged care residence? or residential facilit* or residential institution?).tw,kw.
7	(elder* or older adult? or old age? or seniors or geriatric).tw,kw.
8	or/5-7 [long term care facilities]
9	exp Clinical Audit/
10	(program* or intervention* or audit or feedback or prescriber education or pharmacist education).ti,kw. or (stewardship adj2 program*).ab. or (intervention* or audit or feedback or prescriber education).ab. /freq=2
11	or/9-10 [interventions]
12	exp health personnel attitude/
13	exp health care personnel/ or (doctor? or physician? or family practitioner? or clinician? or nurse? or nursing staff or personal support worker? or caregiver? or care giver? or health care professional? or Health Personnel or health care personnel or pharmacist?).tw,kw.
14	(perspective? or perception? or perceive? or believe? or belief? or view? or attitude? or opinion?).tw,kw.
15	and/13-14
16	or/12,15 [attitude of health personell]
17	4 and 8 and (11 or 16)
18	limit 17 to (english or french)

Table A2: Ovid MEDLINE(R) ALL, 1946 to April 1, 2022

#	Search terms
1	*Antimicrobial Stewardship/
2	(antimicrobial stewardship or amr).ti,kw,kf.
3	((stewardship* or "use" or misus* or abus* or overus* or therap* or prescrib*) and (antimicrobial* or antibiotic* or antibacterial* or antiviral* or antifungal* or anti microbial* or anti biotic* or anti bacterial* or anti viral* or anti fungal*)).ti,kw,kf.
4	or/1-3 [AMR]
5	exp Residential Facilities/
6	(long term care facilit* or convalescence home or convalescence facilit* or nursing home? or group home? or assisted living or seniors home? or seniors residence? or old age home? or old age residence? or aged care home? or aged care residence? or residential facilit* or residential institution?).tw,kw,kf.
7	(elder* or older adult? or old age? or seniors or geriatric).tw,kw,kf.
8	or/5-7 [long term care facilities]
9	exp Clinical Audit/
10	(program* or intervention* or audit or feedback or prescriber education or pharmacist education).ti,kw,kf. or (stewardship adj2 program*).ab. or (intervention* or audit or feedback or prescriber education).ab. /freq=2
11	or/9-10 [interventions]
12	exp "attitude of health personnel"/
13	exp Health Personnel/ or (doctor? or physician? or family practitioner? or clinician? or nurse? or nursing staff or personal support worker? or caregiver? or care giver? or health care professional? or pharmacist?).tw,kw,kf.
14	(perspective? or perception? or perceive? or believe? or belief? or view? or attitude? or opinion?).tw,kw,kf.
15	and/13-14
16	or/12,15 [attitude of health personell]
17	4 and 8 and (11 or 16)
18	limit 17 to (english or french)

Table A3: Global Health, 1973 to April 1, 2022

#	Search terms
1	(antimicrobial stewardship or amr).ti,hw.
2	((stewardship* or "use" or misus* or abus* or overus* or therap* or prescrib*) and (antimicrobial* or antibiotic* or antibacterial* or antiviral* or antifungal* or anti microbial* or anti biotic* or anti bacterial* or anti viral* or anti fungal*)).ti,hw.
3	or/1-2 [AMR]
4	residential institutions/ or nursing home/ or long term care/
5	(long term care facilit* or convalescence home or convalescence facilit* or nursing home? or group home? or assisted living or seniors home? or seniors residence? or old age home? or old age residence? or aged care home? or aged care residence? or residential facilit* or residential institution?).tw,hw.
6	(elder* or older adult? or old age? or seniors or geriatric).tw,hw.
7	or/4-6 [long term care facilities]
8	(program* or intervention* or audit or feedback or prescriber education or pharmacist education).ti,hw. or (stewardship adj2 program*).ab. or (intervention* or audit or feedback or prescriber education).ab. /freq=2
9	exp health care workers/ or (doctor? or physician? or family practitioner? or clinician? or nurse? or nursing staff or personal support worker? or caregiver? or care giver? or health care professional? or Health Personnel or health care personnel or pharmacist?).tw,hw.
10	(perspective? or perception? or perceive? or believe? or belief? or view? or attitude? or opinion?).tw,hw.
11	and/9-10
12	3 and 7 and (8 or 11)
13	limit 12 to (english or french)

Overview of Canada's Antimicrobial Resistance Network (AMRNet): A data-driven One Health approach to antimicrobial resistance surveillance

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Abstract

The Antimicrobial Resistance Network (AMRNet) is a laboratory-based antimicrobial resistance (AMR) surveillance system under development at the Public Health Agency of Canada's (PHAC's) National Microbiology Laboratory. The AMRNet surveillance system captures information on antimicrobial susceptibility testing from clinical and veterinary laboratories including both public and private facilities. In the future, the AMRNet system will also capture relevant data from existing PHAC surveillance systems for AMR including the Canadian Integrated Program for Antimicrobial Resistance Surveillance, the Canadian Nosocomial Infection Surveillance Program and the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea program, and contribute to the Canadian Antimicrobial Resistance Surveillance System. AMRNet's integrated "One Health" approach will allow health professionals and researchers to take a multi-dimensional perspective of AMR in both human and animal health in Canada and will make Canada a leader in AMR surveillance.

AMRNet is a collaboration between PHAC, provincial and territorial public health organizations as well as clinical and veterinary laboratories across the country. As part of a phased rollout, AMRNet is now collecting human clinical data from three provinces, from both inpatients and outpatients. Ultimately, AMRNet aims to capture all antimicrobial susceptibility testing results from all bacterial and fungal pathogens across Canada.

This article describes the AMRNet surveillance system, including program objectives, system structure and the data collected. The integration of human and animal data in AMRNet will inform One Health responses to AMR issues. The capacity to collect and to disseminate data to stakeholders in real time is a critical step to addressing emerging AMR issues in Canada.

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Keywords: surveillance, antimicrobial resistance, antimicrobial susceptibility, one health, bacteria, fungi, Antimicrobial Resistance Network

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Introduction

Antimicrobial-resistant organisms are a major global public health concern; the World Health Organization identified antimicrobial resistance (AMR) as a "top-ten" threat to global health in 2019 (1). With the increase in antimicrobial-resistant organisms globally and the lack of new antimicrobials in the development pipeline, it is critical that Canada responds to this emerging threat and limits the spread of these organisms to prevent difficult-to-treat infections. Antimicrobial resistant

surveillance is critical to Canada's ability to respond to emerging antimicrobial-resistant organisms and to provide intelligence to limit their spread. The surveillance of AMR was identified as a key pillar in the 2015 *Federal Framework, Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*. This framework outlines the Government of Canada's commitment to address AMR challenges and the need to expand Canada's AMR surveillance (2).

While Canada has world-class AMR surveillance programs in a variety of settings, there are important gaps in surveillance, notably in the community, long-term care settings and smaller hospitals. Recognizing these gaps, a 2022 evaluation of the One Health AMR surveillance landscape in Canada recommended the "development of a complete, integrated AMR/AMU [antimicrobial use] surveillance program" (3). The 2015 Federal Framework describes how the "expansion of community-based surveillance will address a gap in the understanding of antimicrobial resistance" (2). The Antimicrobial Resistance Network (AMRNet) surveillance system is designed to address these gaps and to provide a flexible platform that will adapt to emerging and future needs of AMR surveillance in Canada. AMRNet has the potential to expand to include not only new human and animal pathogens but also new domains such as wastewater, AMU and monitoring the susceptibility of newly available or newly commercialized antibiotics in humans and agriculture. Additionally, there is the potential to integrate whole genome sequencing into AMRNet to examine transmission patterns between and within species.

AMRNet will allow for international comparisons and will augment Canada's contribution to the World Health Organization Global Antimicrobial Resistance and Use Surveillance System. Large laboratory-based AMR surveillance systems have been developed internationally including the European Antimicrobial Resistance Surveillance Network (4), the United States Centers for Disease Control and Prevention's Antimicrobial Resistance Laboratory Network (AR Lab Network) and the Global Antimicrobial Resistance Laboratory and Response Network (5).

Over the years, many Canadian jurisdictions have made significant strides towards capturing and standardizing lab-based AMR data and AMU data in their jurisdictions (6–14). The scope and design of these programs vary, but all have increased the availability of AMR-related data in Canada. These achievements have laid the groundwork for the development of a Canada-wide system for AMR-related data.

The Public Health Agency of Canada (PHAC) has long-standing programs for capturing data on AMR in various settings, including the Canadian Nosocomial Infection Surveillance Program (CNISP), the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea (ESAG) and the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). AMRNet will work with federal partners to incorporate data from these programs to fill gaps in AMR data that would not be otherwise collected by front line laboratories and for in-depth investigations of AMR issues when identified.

Description of the AMRNet surveillance system

AMRNet is a collaboration between PHAC, provincial and territorial public health organizations as well as clinical and veterinary laboratories across the country. The AMRNet surveillance system captures information on antimicrobial susceptibility testing from laboratory information systems in clinical and veterinary laboratories, including both public and private facilities, and including reference laboratories. The AMRNet system will also capture data from long-standing PHAC surveillance programs that conduct in-depth AMR surveillance in specific settings (e.g. CNISP, ESAG and CIPARS). Ultimately, AMRNet aims to capture all antimicrobial susceptibility testing results from all bacterial and fungal pathogens across Canada.

Objectives of the AMRNet surveillance program include the following: 1) to integrate monitoring of trends in AMR rates across human and animal populations, nationally, regionally and locally; 2) to detect emergence and spread of AMR in Canada; 3) to disseminate timely information on AMR in Canada; 4) to fulfill Canada's commitment to the World Health Organization's Global Antimicrobial Resistance and Use Surveillance System initiative; 5) to support research and innovation on AMR; and 6) to build antimicrobial stewardship capacity at provincial/territorial/local public health levels.

To meet these objectives, the AMRNet team has worked closely with the Canadian Public Health Laboratory Network's (CPHLN) AMR Working Group to ensure provincial and territorial AMR needs are met. AMRNet collects antimicrobial susceptibility testing results of bacterial and fungal pathogens, along with select patient or animal characteristics (**Table 1** and **Table 2**). These "linelist" data are captured from laboratory information systems in clinical and veterinary laboratories (**Figure 1**). Ideally, AMRNet captures both the minimum inhibitory concentration (MIC) value and the interpretation (e.g. susceptible, intermediate, resistant) of each result. Currently, capturing MIC values is not feasible for all jurisdictions and thus MIC values are not a mandatory field for data submission.

The data captured by AMRNet will be used to understand trends in AMR at the national and regional level, to identify areas for in-depth investigations and to fulfill Canada's obligations for international reporting. These data will provide Canadians with tools to better understand AMR trends from a One Health perspective in Canada and around the world. Data from AMRNet will also enable subgroup analyses by sex and age group.

Table 1: Mandatory and optional data elements for AMRNet surveillance among humans

Category	Data elements
Mandatory	Unique patient identifier Age group[a] Sex Forward sortation area[a] or region[b] Inpatient versus outpatient Date of isolation or collection Specimen identifier Organism (genus and species) Interpretation (susceptible, intermediate, or resistant) results for each antimicrobial Source/anatomical site of culture Data source/submitting organization Province/region of data submitter
Optional	Minimum inhibitory concentration results Nosocomial acquisition/hospital origin Patient setting details (e.g. ward, clinic, etc.) Subtype/serotype of bacteria/fungi Laboratory comments Other data elements selected by the data provider

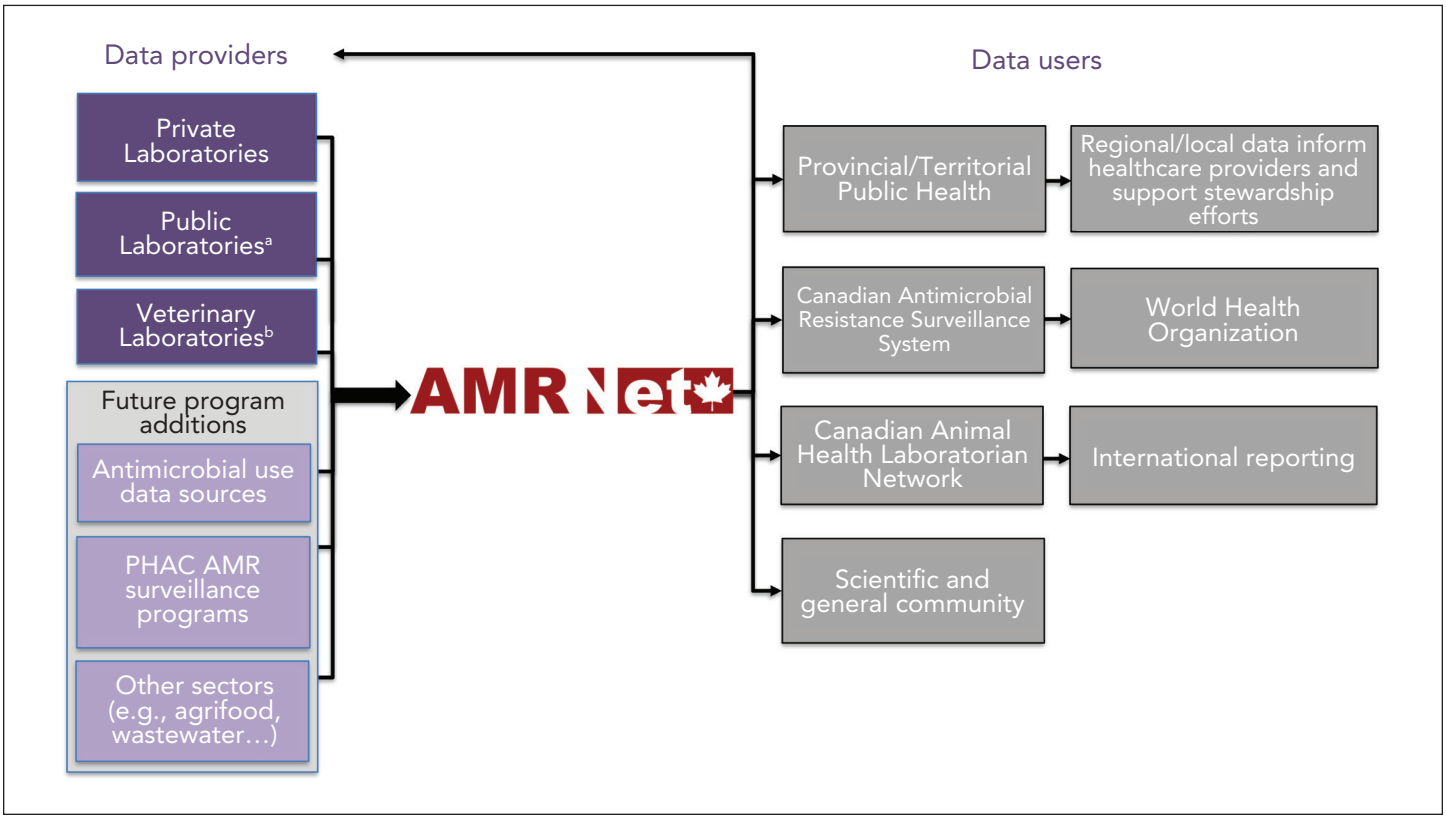
Abbreviation: AMRNet, Antimicrobial Resistance Network
[a] Forward sortation area: first three digits of postal code
[b] Granularity of data collection determined by population size and privacy considerations in the jurisdiction

Table 2: Mandatory and optional data elements for AMRNet pilot programs among animals

Category	Data elements
Mandatory	Unique submission identifier Animal species Province where animal lives or veterinary clinic operates Pooled vs individual animal Date of isolation or collection Specimen identifier Bacteria genus/species Interpretation (susceptible, intermediate, or resistant) results for each antimicrobial Source/anatomical site of culture Data source/submitting organization
Optional	Duplicate specimens identified Screening specimens identified Minimum inhibitory concentration results Additional animal characteristics (e.g. age, commodity, etc.) Subtype/serotype of bacteria/fungi Locality where animal lives[a] Specimen comments

Abbreviation: AMRNet, Antimicrobial Resistance Network
[a] Granularity of data collection determined by population size and privacy considerations in the jurisdiction

Figure 1: Data flow for AMRNet surveillance system



Abbreviations: AMR, antimicrobial resistance; AMRNet, Antimicrobial Resistance Network; PHAC, Public Health Agency of Canada
[a] Laboratories funded, managed or operated by governmental health organizations
[b] AMRNet is currently conducting surveillance among veterinary laboratories as a pilot program

Through standardization and automation, AMRNet aims to make AMR data and analyses more timely and accessible for the organizations submitting AMR data. Once data have been submitted and validated, data providers will be able to download their cleaned and standardized data. Data providers will also be able to explore their data through the creation of antibiograms and visualizations within the AMRNet module. In addition to viewing their own data, data providers can compare their data to other regions in their province, to other regions in Canada (i.e. West, Central, East), and to national data. It will also be possible to monitor trends in multidrug-resistant organisms or extensively drug-resistant organisms following Canadian recommendations on laboratory interpretation (15).

Inclusion and exclusion criteria

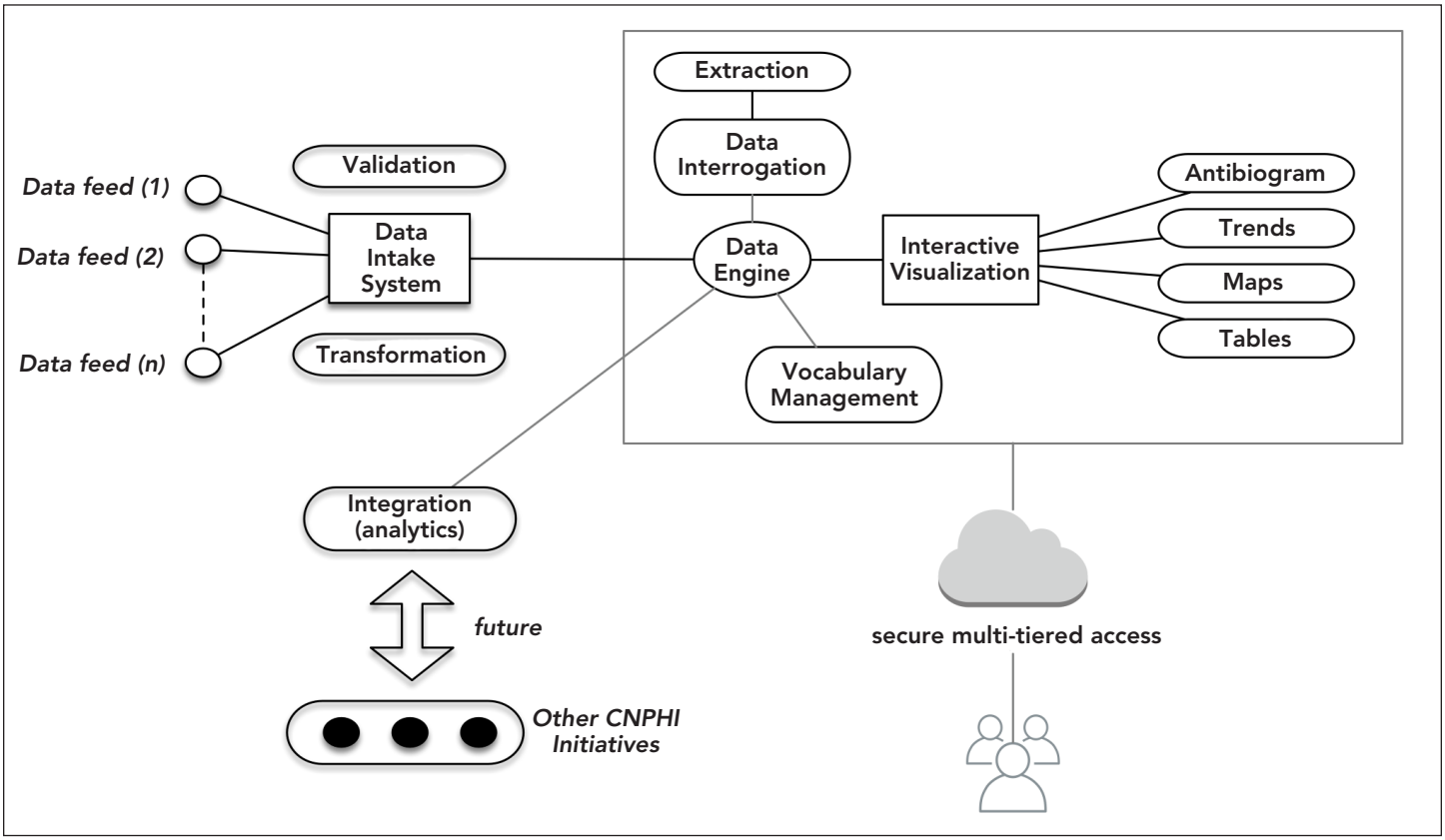
For specimens from humans, AMRNet collects data on all antimicrobial susceptibility results from bacterial/fungal pathogens regardless of whether the results were reported to physicians. Duplicate specimens from the same patient are identified or removed as per the recommendations of the Clinical and Laboratory Standards Institute (16). Screening specimens are also identified or removed prior to submission.

These data are extracted from laboratory information systems using existing or newly developed procedures and subsequently uploaded to a secure online AMRNet system (see **Figure 2** for description of the AMRNet system on the Canadian Network for Public Health Intelligence, CNPHI). Data may be transferred daily through an automated process or less frequently if automation is not feasible for the data provider. Once the data are uploaded and validated, the standardized data will be available for data providers to access and download. Data providers will be able to access their own data as well as aggregate data from other providers. Antibiograms and data visualizations are under development.

Annual collection of metadata

In addition to the line-list data, the AMRNet surveillance system will collect metadata from each data provider. These metadata will inform data interpretation and improve understanding of system limitations. These data will be collected via an annual questionnaire and will include the following: geography and time period covered by the data submission; specimen types, organisms and antimicrobials included in the data submission; breakpoint interpretations used; details of relevant testing cascades; and laboratory methods (e.g. type of panels, software versions, specialized testing).

Figure 2: High-level depiction of the technical vision behind the AMRNet initiative on the Canadian Network for Public Health Intelligence platform



Abbreviations: AMRNet, Antimicrobial Resistance Network; CNPHI, Canadian Network for Public Health Intelligence

Animal surveillance pilot program

Three pilot projects are underway to capture data from veterinary laboratories in three provinces. There are additional challenges implementing surveillance among veterinary laboratories as veterinary breakpoints to indicate susceptibility or resistance are not always available (17), and procedures for producing antibiogram data are less standardized between laboratories. In addition, there is variation in what data elements are captured electronically. The feasibility of collecting the proposed data elements, de-duplication strategies and the identification of screening specimens are under evaluation in these pilot projects. AMRNet has engaged with the Canadian Animal Health Laboratorians Network Antimicrobial Susceptibility Testing (CAHLN AST) Working Group to seek advice and recommendations on these challenges.

Role of the Canadian Network for Public Health Intelligence

The CNPHI, an initiative of the National Microbiology Laboratory, is a secure platform of purpose-built technology resources designed to support and enable Canada's national public health community.

The CNPHI works closely with multi-jurisdictional program partners to provide agile and innovative scientific public health informatics solutions and progressively enhance disease surveillance, preparedness and response capabilities, while fostering intelligence generation and the advancement of research.

Recognizing the importance of AMR as a public health issue, CNPHI played an early role in discussions with partners involved in AMR-related surveillance, fostering collaborative participation and a technical vision for bringing together various initiatives and data streams into a broader, unified picture.

With wide agreement that AMR surveillance is best optimized through an integrated (One Health) approach, CNPHI is proud to contribute as the technical lead, working in close partnership with the experts at the AMRNet Program to help enable the tools and capabilities that can bring a broad AMR surveillance picture into focus.

What is next?

Governance

The AMRNet is a collaborative effort between PHAC, provincial and territorial public health and clinical and veterinary laboratories. The AMRNet is engaged with the CPHLN AMR Working Group as well as the CAHLN AST Working Group to provide recommendations and guidance on the development of the human and veterinary programs, respectively.

An initial governance structure is being formalized. An AMRNet Working Group will be responsible for overseeing program development and direction. It will include representatives from PHAC programs as well as from AMRNet advisory groups. The AMRNet Working Group will create advisory groups to provide expertise, consultation and recommendations across various domains. The advisory groups will include representation from the following: provincial and territorial laboratories; CPHLN and CAHLN; federal partners; data users (including clinicians, veterinarians and pharmacists); and other stakeholders.

Advisory groups will include groups for human surveillance, animal surveillance, data privacy and ethics, as well as data access. Advisory groups can be permanent or time limited.

Cross country rollout

After starting as a series of pilot projects, AMRNet began collecting routine data from a subset of provinces in 2022. Currently AMRNet is collecting data from approximately 1.5 million bacterial and fungal isolates per year from Ontario, Saskatchewan and Prince Edward Island (duplicate isolates excluded as per recommendations of the Clinical and Laboratory Standards Institute) (16). The first publication of AMRNet data from these jurisdictions will be included in the *Canadian Antimicrobial Resistance Surveillance System Report* in November 2022 (18).

From discussions with provincial and territorial representatives, it is clear that ease of participation will vary by jurisdiction, but AMRNet is slated to rollout across the country in the coming years. PHAC will work with provinces and territories on developing agreements and building the technical capacity for data sharing.

Although AMRNet aims to collect line list data for all requested variables from all bacterial and fungal susceptibility results, this is currently challenging in some jurisdictions due to technical difficulties, resource limitations or other structural barriers. In these situations, AMRNet will work with jurisdictions to build capacity and work towards full program participation. In the short-term, submission of only priority organisms (19), exclusion of some variables or data aggregation may be feasible interim solutions. Differences in methods, reporting processes and data availability across jurisdictions will present challenges in interpreting these data.

PHAC will work with partners on data validation and interpretation to ensure integrity of presented data. AMRNet will form but one component of PHAC's AMR surveillance. As a lab-based surveillance program, AMRNet will conduct wide-scoping surveillance across all bacterial and fungal organisms but will collect limited epidemiological data and will not collect isolates. Other surveillance programs focus more narrowly on particular organisms or infection types but collect detailed epidemiological information and often include the collection of isolates. While

AMRNet will be well poised to identify emerging issues, surveillance programs such as CNISP, ESAG and CIPARS will be better suited for in-depth epidemiological investigations.

Conclusion

AMRNet is a unique collaboration that will provide valuable information on existing and emerging AMR in Canada and help fulfill Canada's international commitments. The capture of susceptibility testing results from all settings and patient types will close gaps in the Canadian AMR surveillance landscape. The integration of human and animal data will inform One Health responses to AMR issues. The capacity to collect and to disseminate data to stakeholders in real time is a critical step in helping Canadian health professionals detect and respond to emerging AMR issues.

Authors' statement

WR — Conception, writing–original draft, review & editing, visualization
SNM — Conception, writing–original draft & review, visualization
RJRS — Conception, writing–review & editing
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Competing interests

None.

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Hospital and related resource costs associated with antimicrobial-resistant infections in Canada, 2019

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Abstract

Background: Antimicrobial resistance (AMR) occurs when microorganisms become resistant to treatment by standard, or first-line, antibiotic drugs. These infections create an enormous burden on society due to longer hospital stays and increased morbidity and mortality, resulting in increased medical costs and foregone resources. The objective of this paper is to estimate the hospital costs associated with two of the most significant antibiotic-resistant organisms: methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile* (*C. difficile*), for Canada, for the year 2019, as well as the value of other resource use attributed to the lost production due to disability and premature mortality.

Methods: The Discharge Abstract Database was employed for the analysis using a two-step process: first, the number of cases for each diagnosis was estimated; and then an average cost per case was derived, which was used to multiply the number of cases to obtain the total costs. Costs were derived using a regression model, accounting for demographic and other important confounding variables.

Results: There were a total of 16,070 and 9,889 cases of *C. difficile* infections and MRSA infections, respectively, in Canada in 2019, resulting in an estimated 1,743 premature deaths. The majority of cases occurred in the older age groups. The hospital costs attributable to these infections were over $125 million, while the indirect resource costs were between $18.8 and $146.9 million.

Conclusion: Quantifying the outcomes associated with antimicrobial-resistant infections provides valuable information for policymakers and is an essential first step in understanding the total economic impacts of AMR.

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Keywords: antimicrobial resistance, methicillin-resistant *Staphylococcus aureus*, *Clostridioides difficile*, hospital costs, health resources

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Introduction

Antimicrobial resistance (AMR) is a serious and growing global public health threat in Canada and worldwide (1–3). Left unchecked, global economic costs could surpass $100 trillion by 2050, with Canada seeing a decrease in gross domestic product (GDP) upwards of $20 billion (2–5). Antimicrobial resistance occurs when microorganisms become resistant to treatment by standard, or first-line, antibiotic drugs. In recent years, more microbes have become resistant to current antibiotics, and few new antimicrobials have been brought to the market, resulting in increased illness due to previously treatable infections.

These infections create an enormous burden on society as patients face increased morbidity and mortality. In addition, AMR increases the burden on the healthcare system through increased lengths of stay in hospitals and the need for more expensive treatments and resources, which could be used to treat other

conditions. With no effective treatment, antimicrobial-resistant infections persist, with a risk of spreading the infection to others.

Two of the most significant antibiotic-resistant organisms are methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile* (*C. difficile*). Methicillin-resistant *Staphylococcus aureus (S. aureus)* can also be resistant to other first-line antibiotics such as oxacillin and cloxacillin. *Staphylococcus aureus* is present on the skin or mucosal surfaces of 20%–30% of the healthy population and is also known to cause systemic infection (6). Methicillin-resistant *S. aureus*, a specific type of staph bacteria, can be present on the skin or mucosal surfaces of both healthy populations and hospitalized patients, as well as on environmental surfaces, and can enter the body through broken areas in the skin, respiratory tract, surgical sites and/or open wounds and intravenous catheters, and can cause severe and sometimes fatal infections in the hospital setting. *Clostridioides difficile* is an important healthcare-associated infection that causes significant morbidity and mortality. It is the most common cause of infectious diarrhea in hospitals and can range from asymptomatic to life-threatening. Most cases occur in patients who are elderly and who have other underlying medical conditions. It spreads rapidly in healthcare settings by direct contact because it is naturally resistant to many antimicrobials used to treat other infections, and *C. difficile* spores in the environment tend to be resistant to commonly used disinfectants (7).

In addition to the direct medical costs, antimicrobial-resistant infections result in other foregone resources due to decreased production resulting from disability and premature mortality. If increases in AMR continue, the future burden associated with AMR may also increase significantly through its impact on the overall healthcare system. For example, as Smith and Coast (2012) noted, if antimicrobial resistance were to continue unchecked, we may face a world in which there is no longer any effective antibiotics available for situations in which they are currently routinely used (8).

Currently, there are few methodologically sound, comprehensive and comparable cost studies of AMR. Recent systematic reviews focusing on the costs of AMR found a wide variation in results due to the methodologies employed, type of resistance studied and the cost components included (8–10). For example, Naylor *et al.* found that excess healthcare system costs ranged from insignificance to $1 billion per year, while the economic burden ranged from $21,832 per case to $3 trillion in GDP loss (9). **Table 1** summarizes the results from these systematic reviews and recent Canadian studies that focused on the economic burden of AMR (11–14). Of note is the large variation in cost estimates due to the aforementioned reasons (all monetary costs were converted to 2019 Canadian dollars using Purchasing Power Parity values and inflated accordingly).

The Council of Canadian Academies (CCA) recently estimated the current and future health, social and economic impacts of AMR in Canada (2). Based on a review of several Canadian studies, the authors estimated an average cost of $16,280 per MRSA patient. Examining cost studies of other antimicrobial-resistant infections, the CCA estimated an average hospital case of AMR cost of $18,000. The studies included in the CCA analysis tended to be small-scale studies, many of which included data from only one or two hospital settings. Based on these cost estimates, total AMR hospital costs were estimated to be $1.4 billion in 2018. By 2050, AMR is projected to cost the Canadian healthcare system $6 billion at the current infection rate. Additionally, the report estimated that the cumulative loss in GDP due to AMR from 2018 to 2050 would be $268 billion if there were no changes to the current infection rate.

Table 1: Results of selected antimicrobial resistance economic burden studies

Reference (year of publication)	Region	Type of infection	Type of study	Estimated costs[a]
Smith and Coast (2013)	International	AMR in general	Systematic review	$5 to greater than $74,000 per patient episode
Levy *et al.* (2015)	Canada	*C. difficile*	Economic model using multiple data sources	$291 million in hospital costs $13 million in community medical costs $11 million in lost productivity
Thampi *et al.* (2015)	Ontario, Canada	MRSA	Multi-centre costing study	$14,100 direct costs per hospital patient
Zhang *et al.* (2016)	United States	*C. difficile*	Meta-analysis	$28,756 per patient
Naylor *et al.* (2018)	International	AMR in general	Systematic review	Healthcare system costs: up to $1 billion per year Economic burden: $29,595 per case to over $3 trillion in GDP losses
Canadian Council of Academies (2018)	Canada	AMR in general	Review of selected Canadian studies	$16,979 per MRSA patient $18,773 per AMR patient $1.5 billion in total AMR hospital costs
Zhen *et al.* (2019)	International	MRSA	Systematic review	$9,998 to $242,599 per patient

Abbreviations: AMR, antimicrobial resistance; *C. difficile*, *Clostridioides difficile*; GDP, gross domestic product; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] 2019 Canadian dollars

Notwithstanding the important concerns of researchers such as Smith and Coast, who warn that unless AMR is properly addressed, we are headed to a drastically different healthcare system than the one with which we are familiar, accurate estimates of the current overall burden of AMR are needed by policymakers. It is important to properly understand the current situation from which projections and modelling of future costs associated with AMR can be based. Valid data on the costs related to AMR in Canada would provide valuable information on the magnitude of its burden, address gaps in data, and provide evidence and inputs for policy analysis.

The objective of this paper was to estimate the hospital costs and vale of lost production associated with antimicrobial-resistant infections, specifically MRSA and *C. difficile* infections, in Canada for 2019. The incidence of antimicrobial-resistant infections was based on diagnosis only, using administrative data; no distinction was made between healthcare-acquired and community-acquired infections. Antimicrobial-resistant infections caused by other bacteria were excluded due to the lack of valid and reliable data.

Methods

Data sources

The main data source employed in the analysis was the Discharge Abstract Database (DAD) from the Canadian Institute for Health Information, from 2010 to 2019. The DAD contains administrative data on hospital discharges, diagnoses and patient characteristics, facilities in all provinces and territories except Québec are required to report to DAD. In addition to employing the standard DAD variables, data on the cost of a standard hospital stay and on the resource intensity weight associated with each hospital discharge were obtained. This allowed for the estimation of costs associated with each discharge. The cost of a standard hospital stay provides a cost for the standard hospital patient, while the resource intensity weight allows for the cost to be adjusted based on the patients' characteristics and diagnoses. All analyses were run for data from 2010 to 2019. The cross-sectional results were from the most recent year, 2019, while the remaining data provided a look at AMR in Canada over time. Analysis was limited to those 18 years of age and over due to the low incidence in younger age groups.

While administrative rather than surveillance data were employed in the analysis, a recent study found that the DAD performed exceptionally well in identifying MRSA cases compared to surveillance data in Ontario and Alberta (r=0.79 for Ontario, r=0.92 for Alberta for overall, MRSA infections and r=0.95 for bloodstream MRSA infections in Ontario) (15). Thus, we are confident that the incidence rates produced using the DAD were valid estimates.

For each separation recorded, the DAD contains up to twenty-five possible diagnoses according to the tenth revision of the International Classification of Diseases (ICD-10) codes. Each record notes the most responsible diagnosis (MRDX), defined as "the diagnosis or condition that can be described as being most responsible for the patient's stay in hospital. If there is more than one such condition, the one held most responsible for the greatest portion of the length of stay (LOS) or greatest use of resources is selected." (16). All other diagnoses (up to twenty-four) were considered secondary diagnoses. For this analysis, all cases of MRSA and *C. difficile* infections (CDI) were identified (see **Table 2** for the specific ICD-10 codes employed in the analysis).

Table 2: ICD-10 codes employed to identify *Clostridioides difficile* infections and methicillin-resistant *Staphylococcus aureus* infections

Diagnosis	ICD-10 code(s)
CDI	A04.7
MRSA, non-BSI	B95.6 (*S. aureus*) and U82.1 (methicillin resistance) and in the same cluster[a]
MRSA, BSI	B95.6 (Staph Aureus) and U82.1 (methicillin resistance) and A49 (bloodstream infection), and in the same cluster or A41.0 (Sepsis due to Staphylococcus) and U82.1 (methicillin resistance) and in the same cluster[a]

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infection; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] Starting in 2009, the Discharge Abstract Database included a variable noting which diagnoses are related by showing them in the same cluster. For an individual to have a methicillin-resistant infection, they must possess both the methicillin resistance and the infection diagnoses, and both diagnoses must be in the same cluster

As the DAD does not include data from the province of Québec, age-adjusted values for costs and mortality for Québec were estimated, based on the results obtained from the DAD, and included in the total values. Thus, all values of the total burden represent estimates for all of Canada. Results are presented in 2019 Canadian dollars.

Incidence rates

Incidence and costs for MRSA infections were divided into bloodstream (BSI) and non-bloodstream (non-BSI) infections due to the differences in patients and treatment protocols. Prior to 2009, to be classified as a case of MRSA, the observation had to include both 1) a diagnosis of methicillin resistance and 2) a diagnosis of a *Staphylococcus* infection. In 2009, a cluster variable was introduced in the DAD to note whether the two diagnoses were related; thus, to be considered an MSRA case, the observation had to include both diagnoses and both diagnoses had to be identified as being within the same cluster. Incidence and costs for *C. difficile* diagnoses were estimated separately for those cases where *C. difficile* appeared as either a most responsible diagnosis or a secondary diagnosis (CDI MRDX and CDI non-MRDX, respectively.

Hospital costs

Incremental costs—those costs associated with treating the conditions above and beyond the costs associated with the rest

of that hospital stay—were estimated in two ways. Firstly, the average cost of patient stays with and without the diagnosis in question were estimated. The difference between the two estimates was then assumed to be the incremental costs attributable to the specific infection. The challenge with this approach is that the likelihood of an AMR infection increases with age, LOS, number of comorbidities and the reason for admission. Thus, unadjusted incremental costs derived in this manner are likely to overestimate the actual incremental costs that can be validly attributed to the presence of the infection only.

To account for the aforementioned confounding effects, the following regression model was employed to estimate the incremental costs associated with treating antimicrobial-resistant infections:

$$Cost = \beta_0 + \beta_1 MRSA\_non\_BL + \beta_2 MRSA\_BL + \beta_3 CDI\_non\_mrdx + \beta_4 Comorbidites + \sum_{I=1}^{130} \gamma_i ISHMT_i + \sum_{I=1}^{11} \lambda_i PROV_i + \beta_5 Sex + \beta_6 LOS + e$$

Where:

- Cost=the log of cost per discharge
- MRSA_non_BL=1 if non-bloodstream MRSA diagnosis present
- MRSA_BL=1 if bloodstream MRSA diagnosis present
- CDI_non_mrdx=1 if *C. difficile* diagnosis present as a comorbid condition
- Comorbidities=number of diagnosed comorbidities (excluding antimicrobial-resistant infections)
- $ISHMT_i$=1 if the patient most responsible diagnosis is in International Short List of Hospital Morbidity Tabulation (ISHMT) code i (excluding the *C. difficile* code)
- PROV=a dummy for the province
- Sex=1, if female
- LOS=length of stay associated with the observation

The model employed included variables for most responsible diagnosis (to account for different reasons of admission), number of comorbidities (based on records in the DAD), sex, and province. The estimated beta coefficients were used to estimate the incremental costs associated with the infections. Specifically, the coefficients on the variables associated with infections (β_1, β_2, β_3) were transformed to show the percentage increase in average costs that could be attributable to the infection (MRSA or *C. difficile*).

For those individuals with *C. difficile* as a secondary diagnosis or with a diagnosis of MRSA (which was always a secondary diagnosis), the incremental costs associated with that diagnosis were estimated.

Cost data are usually right-skewed, as costs cannot be negative and most of the observations are close to zero, with several observations having relatively high costs. Thus, a log-linear model was employed, allowing for a much better fit. The resulting beta coefficients, once transformed, can be interpreted as the incremental costs attributable to the presence of either MRSA or *C. difficile* infections, respectively, accounting for the age, diagnosis, sex, comorbidities and other relevant factors. Separate regressions were run by age group to account for differences by age. Once the incremental cost has been estimated, the cost is multiplied by the number of cases for that diagnosis. For patients classified as having *C. difficile* as a most responsible diagnosis, all costs associated with that hospital stay were employed.

The most responsible diagnosis, for each observation, was coded according to ISHMT. The ISHMT is a classification system based on ICD-10 Chapters, and it further breaks down the ICD Chapters into a total of 130 diagnostic categories. The ISHMT codes were employed to define the diagnoses as they represent a manageable number of well-defined diagnoses, while still being granular enough to be meaningful.

Mortality estimates

To estimate the value of lost production due to premature mortality attributable to antimicrobial-resistant infections, it was necessary to estimate the increased mortality attributable to the infections employed in the analysis. While *C. difficile* is a possible listed cause of death, deaths attributable to MRSA infections are coded otherwise, making it difficult to obtain valid and reliable estimates on the number of deaths attributable to MRSA (17). Separate logistic regression with a binary variable of whether the patient died or was discharged from the hospital was used to estimate the mortality rate for each of the five age groups, namely 18–34, 35–54, 55–64, 65–74 and 75 years of age and older. The coefficients from such regression produce the log-odds, from which it was possible to estimate odd ratios for the mortality rates associated with each infection. Specifically, the following model was implemented:

$$Dead = \beta_0 + \beta_1 MRSA_{non_{BL}} + \beta_2 MRSA_{BL} + \beta_3 CDiff + \beta_4 comorbidites + \sum_{I=1}^{130} \gamma_i ISHMT_i + \sum_{I=1}^{11} \lambda_i PROV_i + \beta_5 sex + e$$

Where:

- Dead=1 if patient died, 0 otherwise
- All other variables were previously defined

To estimate the total number of deaths attributable to each type of AMR infection, the age-specific death rate for all discharged patients and the number of AMR-specific infected patients were obtained from the data. Then, the infection-specific death rate can be calculated by multiplying the odds ratio of the specific infection and the overall death rate. Lastly, the estimated number of deaths for the infection can be estimated by multiplying the infection-specific death rate and the number of infections in the age group.

Value of lost production

To obtain a more complete estimate of the economic burden, the value of the lost production, for both disability and premature mortality, attributable to antimicrobial-resistant infections was also estimated. Two approaches are generally employed to estimate production losses in cost of illness studies: the friction cost approach and the human capital approach (18). This friction cost approach assumes that a deceased worker will eventually be replaced by individuals currently in the pool of unemployed workers once those seeking employment are lined up with an employer currently offering employment (i.e. the friction period), with three months being a common time period employed (19). In contrast, the human capital approach measures the value of foregone gross lifetime earnings resulting in significantly larger estimates; that is, the human capital approach assumes that an individual's production is lost for their entire working life. Given the ongoing debate on the appropriate method, and general higher rates of unemployment (the friction cost approach was originally proposed during periods of high unemployment), both methods were employed to increase the comparability of the results.

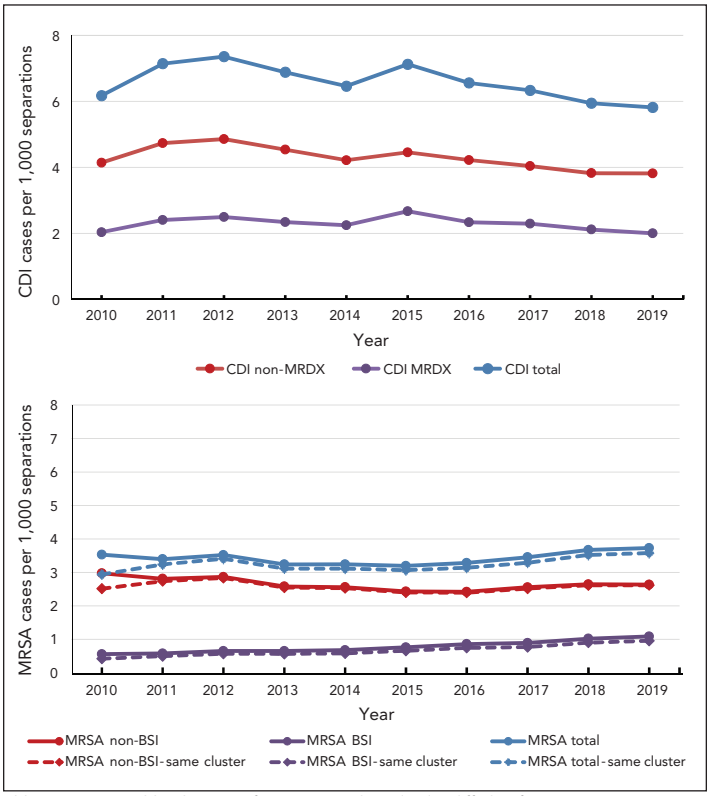
The length of time absent from work due to absenteeism or premature mortality was estimated using both approaches and was then multiplied by an average wage rate. The incremental LOS in hospitals attributable to these infections was estimated based on the previously estimated incremental costs to derive the amount of time missed due to absenteeism. Time missed from work was multiplied by age-specific average earnings (as a proxy for the marginal product). The average income and employment rate for persons aged 15 years of age and older were obtained from Statistics Canada (20,21).

Results

Incidence rates

Figure 1 shows the incidence of *C. difficile* and MRSA infections from 2010 to 2019. The incidence of *C. difficile* infections has fallen since 2015, from 7.1 cases per 1,000 hospital separations to 5.8 cases per 1,000 hospital separations in 2019 (2.0 as a most responsible diagnosis and 3.8 as a secondary diagnosis). When examining the methicillin-resistant and *Staphylococcus* infection diagnoses, it was observed that, in 2010 (the first year after the cluster variable was introduced), all cases had both a diagnosis of methicillin resistance and a *Staphylococcus* infection, and only 85% were in the same cluster. The majority (76%) of infections diagnosed as both methicillin-resistant and having a bloodstream *Staphylococcus* infection were also within the same cluster. In 2011, the percentage changed to 97% and 85%, and by 2019 the percentages stabilized at 99% and 88%, respectively. It likely took some time for the coding to be applied appropriately.
In 2019, the overall rate for MRSA infections was 3.6 per 1,000 separations—2.6 for non-BSI and 1.0 for MRSA-BSIs. Note that bloodstream MRSA infections have increased steadily since 2010 and more than doubled between 2010 and 2019; from 0.4 to 1.0 cases per 1,000 hospital separations. These findings are consistent with the results of Canadian surveillance studies; however, due to differences in methodologies, results are not directly comparable (1,7).

Figure 1: Incidence of *Clostridioides difficile* infections and methicillin-resistant *Staphylococcus aureus* infections, Canada[a], 2010–2019



Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infections; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] Excludes data from Québec

In 2019 there were over 2.1 million hospital separations included in the DAD. **Table 3** presents summary statistics for the overall sample and individuals with either MRSA infections or CDI. Patients with any type of infection had a much longer average LOS; however, it should be noted that the difference between the average LOS for the entire sample and those with antimicrobial-resistant infections is attributable to many factors. Those with *C. difficile* infections tended to be older, and those with MRSA tended to be younger than the entire sample. While the average age for the entire sample increased over the study period, the average age of those with these infections decreased slightly. Males were more likely than females to have been diagnosed with an MRSA infection. **Table 4** shows the incidence rates for the antimicrobial-resistant infections by age group. Not surprisingly, those 75 years of age and over had the highest overall rates, except MRSA infections peaked for those 35–54 years of age.

Table 3: Summary statistics and incidence rates of antimicrobial-resistant infections, Canada[a], 2019

Type of infection	Incidence (cases per 1,000 separations)	Percent female	Average LOS (days)	Average age (years)
Entire sample	N/A	57.0%	7.6	59.5
No infection	N/A	57.0%	7.5	59.5
CDI (MRDX) as most responsible diagnosis	2.00	58.9%	11.7	70.6
CDI, as non-MRDX	3.82	51.1%	31.7	68.8
CDI (total)	5.82	53.8%	24.8	69.4
MRSA non-BSI	2.62	40.5%	22.6	58.4
MRSA, BSI	0.96	38.6%	25.4	57.5
MRSA (total)	3.58	40.0%	23.3	58.2

Abbreviations: BSI, bloodstream infections; CDI, *Clostridioides difficile* infections; LOS, length of stay; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*, N/A, not applicable
[a] Excludes data from Québec

Table 4: Incidence rates of antimicrobial-resistant infections, by age group, Canada[a], 2019 (cases per 1,000 discharges)

Age group (years)	CDI, MRDX	CDI, non-MRDX	CDI, total	MRSA, non-BSI	MRSA, BSI	MRSA, total
18–34	0.537	0.994	1.531	1.970	0.758	2.728
35–54	1.119	2.492	3.611	3.805	1.455	5.261
55–64	1.929	4.315	6.244	3.055	1.141	4.195
65–74	2.415	5.028	7.443	2.509	0.909	3.418
75 and older	3.312	5.472	8.785	2.105	0.701	2.806
Total	2.002	3.816	5.818	2.621	0.960	3.580

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infections; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] Excludes data from Québec

Hospital costs

The unadjusted costs were relatively high as expected and ranged from over $19,000 per patient (MRSA, non-BSI) to over $30,000 per patient (CDI). As previously noted, this is likely due to those with AMR having longer, more resource intensive, lengths of stay due to other characteristics. To derive the adjusted incremental costs, separate regressions were run for each age group (the main regression results are presented in **Appendix**, **Table A1** and **Table A2**). **Table 5** presents incremental cost estimates by age group). The average incremental costs across all age groups were $2,301 and $3,654 for non-BSI MRSA cases and BSI MRSA cases, respectively, resulting in a total hospital cost of MRSA estimated to be $24.4 million. For *C. difficile*, the average cost of patients having a most responsible diagnosis was $11,056 per patient and the incremental costs associated with a secondary *C. difficile* diagnosis was $3,749. Total hospital costs associated with *C. difficile* were estimated at $100.7 million.

Table 5: Hospital costs for antimicrobial-resistant infection per patient, by age group, Canada, 2019

Age group (years)	All diagnoses (average cost)	CDI, MRDX (incremental cost)	CDI, non-MRDX (incremental cost)	MRSA, non-BSI (incremental cost)	MRSA, BSI (incremental cost)
18–34	$5,251	$7,297	$2,806	$1,411	$1,828
35–54	$8,001	$7,866	$3,883	$1,694	$2,589
55–64	$10,785	$10,153	$3,731	$2,271	$3,022
65–74	$11,414	$12,389	$4,057	$2,309	$5,006
75 and older	$12,098	$11,806	$3,641	$2,408	$5,802
Average	$9,721	$11,056	$3,479	$2,031	$3,654

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infections; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*

Mortality estimates

The hospital separations provide the discharge disposition information; however, it was not specified whether a patient died in or outside the hospital. According to the DAD, the observed number of deaths with *C. difficile,* MRSA non-BSI, and MRSA BSI infection were 1,455, 353, and 351, respectively. As there is no cause of death for these patients noted in the data, the mortality might be due to other competing risks such as comorbidities or aging, instead of AMR infection alone.

To prevent the overestimation of AMR-related mortality, logistic regressions were conducted for the patients in each age group to estimate the death rates attributable to the infections, adjusted for sex, number of comorbidities and ISHMT diagnostic group. The results clearly showed a positive relationship between the number of deaths and the age of the patients. Table A2 presents the odds ratios obtained from the regression results, and **Table 6** shows the number of estimated deaths attributable to *C. difficile* and MRSA infections, for all of Canada. According to the estimates, the number of deaths attributable to *C. difficile,* MRSA non-BSI, and MRSA BSI was 1,309, 257, and 177, respectively. The majority of the estimated deaths, near 70%, occurred among those aged 75 years and older.

Value of lost production

Table 7 shows the incremental LOS associated with antimicrobial-resistant infections. The average LOS was multiplied by the number of cases, the average wage rate, and the employment rate to obtain the value of lost production due to morbidity, which totalled $5.6 million. The value of lost production due to premature mortality was estimated at $13.2 million using the friction cost approach, and $141.4 million using the human capital approach. This is consistent with other findings. The value of lost production is greatest for those aged 35 to 64 years old, resulting from higher earnings and employment in those age groups.

Total costs

Table 8 summarizes the increased burden in terms of mortality and economic costs associated with antimicrobial-resistant infections in Canada in 2019. Antimicrobial-resistant infections resulted in 1,743 extra deaths and accounted for between $143.8 million and $272 million in total economic costs.

Table 6: Estimated mortality by age group attributable to antimicrobial-resistant infections, Canada[a], 2019

Type of infection	Age (years)					Total mortality
	18–34	35–54	55–64	65–74	75 and older	
CDI, any	2	28	98	206	975	1,309
MRSA, non-BSI	2	23	34	54	144	257
MRSA, BSI	2	17	25	49	84	177
Total	6	68	157	309	1,203	1,743

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infections; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] Excludes data from Québec

Table 7: Incremental length of stay associated with antimicrobial-resistant infections, Canada[a], 2019

Type of infection	Age (years)				
	18–34	35–54	55–64	65–74	75 and older
CDI, MRDX[b]	6.9	7.5	9.3	12.6	13.5
CDI, non-MRDX	1.9	2.6	2.5	3.0	3.5
MRSA, non-BSI	1.0	1.1	1.5	1.7	2.3
MRSA, BSI	1.3	1.7	2.0	3.6	5.5

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infections; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] Excludes data from Québec
[b] For CDI, MRDX the values refer to the average length of stay

Table 8: Burden associated with antimicrobial-resistant infections, Canada[a], 2019

Type of infection	Number of cases	Increased mortality	Hospital costs[b]	Lost production[b] (disability)	Lost production[b] (premature mortality)		Total costs[b]
					FCM	HCM	
CDI, any	16,070	1,309	$100.65	$3.99	$9.92	$66.90	$114.56–$171.54
MRSA, non-BSI	7,238	257	$14.70	$0.93	$1.95	$42.62	$17.5–$58.26
MRSA, BSI	2,651	177	$9.69	$0.64	$1.34	$31.82	$11.6–$42.15
Total	25,959	1,743	$125.04	$5.56	$13.22	$141.35	$143.8–$271.95

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile* infections; FCM, friction cost method; HCM, human capital method; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] Estimates include Québec
[b] 2019 Canadian dollars, in millions

Discussion

There were an estimated 16,070 and 9,989 cases of *C. difficile* and MRSA infections, respectively, in Canada in 2019, resulting in an estimated 1,743 premature deaths. The majority of cases occurred in the older age groups, and nearly 70% of the premature deaths occurred among those aged 75 years and older. The annual hospital-related costs were over $125 million, while the value of lost production was estimated to be between $18.8 million and $146.9 million; total economic costs were between $143.8 million $272 million. Given the assumptions employed and noting that only two types of antimicrobial-resistant infections were incorporated in the analysis, these results can be considered lower values of the economic burden of antimicrobial-resistant infections in Canada.

The estimates for LOS, attributable mortality and incremental costs were consistent with those found in the literature, although at the low end. This finding is not unexpected, given that the methodology employed in the estimation of hospital costs was likely to produce conservative estimates. In addition, the analysis attempted to account for factors that may influence the risk of antimicrobial-resistant infections and would affect total costs, including age, LOS, number of comorbidities and the most responsible diagnosis. Differences in per patient hospital costs were likely due to estimating incremental, rather than average costs.

Direct comparisons with the previous literature are challenging due to the wide range of outcomes included, perspective, and methodologies employed. Naylor *et al.* (9) noted that much of the previous evidence on the economic burden of AMR did not employ established health economic modelling techniques; they produced recommendations for AMR economic burden research, which we attempted to follow. This included using a representative population sample, taking into account confounding variables (including comorbidities and age), describing the data employed and how rates were derived, and clearly describing the model employed.

Limitations

While attempting to consider many of the covariates related to antimicrobial-resistant infections, the analysis had several limitations. As previously noted, the analysis did not distinguish between health care-acquired and community-acquired infections. The differences between these two patient groups may affect overall outcomes and ideally should be accounted for. In addition, the data employed focussed on hospital separations instead of actual individuals. Thus, it was not possible to account for possible readmissions. Having such data would allow a better estimate of overall AMR cases rather than episodes. Related to the latter point, antimicrobial-resistant infections may result in long-term health impacts and thus costs. For example, Nanwa *et al.* conducted a longitudinal, matched cohort, study in Ontario, Canada, that estimated the three-year costs associated with CDI finding that the costs were greater than $31,000 and $37,000 (2014 CDN$) for non-elective and elective admission patients (22).

Conclusion

Quantifying the outcomes associated with antimicrobial-resistant infections provides valuable information for policymakers and is an essential first step in understanding the total economic impacts of AMR. Quantifying these outcomes is also an important input that can be used in economic evaluations of policies to reduce the future impacts of AMR.

Authors' statement

AD — Conceptualization, methodology, writing–review and editing, formal analysis
HW — Writing–review and editing, formal analysis
MN — Writing–original draft, formal analysis

Competing interest

None.

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Appendix: List of tables

Table A1: Incremental cost regression results

Age group	Independent variable	Coefficient[a]	Standard error	T-statistic	Regression statistics
18–34	*C. difficile*, non-MRDX	0.4282	0.0221	19.37	Number of observations: 398,445
	MRSA, non-BSI	0.2380	0.0159	14.93	F–statistic: 3,964.2
	MRSA, BSI	0.2987	0.0256	11.68	Probability >F: <.0001
	Female	-0.0363	0.0023	-15.93	R-squared: 0.573
	Length of stay	0.0301	0.0001	323.55	Adj. R-squared: 0.573
	Comorbidities	0.0777	0.0003	223.69	
	Constant	7.8083	0.0162	482.12	
35–54	*C. difficile*, non-MRDX	0.3956	0.0167	23.70	Number of observations: 401,292
	MRSA, non-BSI	0.1921	0.0137	14.04	F–statistic: 3,965.0
	MRSA, BSI	0.2803	0.0220	12.75	Probability >F: <.0001
	Female	-0.0213	0.0020	-10.74	R-squared: 0.575
	Length of stay	0.0274	0.0001	340.48	Adj. R-squared: 0.575
	Comorbidities	0.0807	0.0004	230.28	
	Constant	7.7870	0.0186	417.89	
55–64	*C. difficile*, non-MRDX	0.2971	0.0153	19.47	Number of observations: 326,065
	MRSA, non-BSI	0.1911	0.0181	10.53	F–statistic: 3,192.3
	MRSA, BSI	0.2470	0.0296	8.35	Probability >F: <.0001
	Female	-0.0100	0.0021	-4.80	R-squared: 0.566
	Length of stay	0.0248	0.0001	326.28	Adj. R-squared: 0.566
	Comorbidities	0.0815	0.0004	223.42	
	Constant	7.8015	0.0248	315.15	
65–74	*C. difficile*, non-MRDX	0.3041	0.0126	24.08	Number of observations: 403,732
	MRSA, non-BSI	0.1842	0.0178	10.33	F–statistic: 4,221.8
	MRSA, BSI	0.3637	0.0296	12.30	Probability >F: <.0001
	Female	-0.0012	0.0018	-0.65	R-squared: 0.578
	Length of stay	0.0238	0.0001	388.35	Adj. R-squared: 0.578
	Comorbidities	0.0796	0.0003	262.67	
	Constant	7.9524	0.0240	331.05	
75 and older	*C. difficile*, non-MRDX	0.2631	0.0099	26.63	Number of observations: 606,518
	MRSA, non-BSI	0.1815	0.0159	11.44	F–statistic: 6,794.8
	MRSA, BSI	0.3917	0.0275	14.25	Probability >F: <.0001
	Female	0.0065	0.0015	4.34	R-squared: 0.595
	Length of stay	0.0215	0.0000	559.10	Adj. R-squared: 0.595
	Comorbidities	0.0760	0.0002	328.88	
	Constant	8.3914	0.0243	345.42	

Abbreviations: Adj., adjusted; BSI, bloodstream infection; CDI, *Clostridioides difficile*; MRDX, most responsible diagnosis; MRSA, methicillin-resistant *Staphylococcus aureus*
[a] All coefficients were statistically significant at the 1% confidence level except for sex in the 65–74 age group. Coefficients for the provincial/territorial and International Short List of Hospital Morbidity Tabulation dummies are not shown. Source: Health Canada, Policy Research, Economics and Analytics

Table A2: Mortality regression results

Age group	Independent variable	Odds ratio	Standard error	Wald Chi-square	Regression statistics
18–34	*C. difficile*, any	1.095	0.303	0.090	Number of observations: 398,445 Likelihood ratio: 6,205.05 Probability >F: <0.0001 R-squared: 0.016 Max-rescaled R-square: 0.4071
	MRSA, non-BSI	0.684	0.371	1.049	
	MRSA, BSI	2.123	0.285	6.956	
35–54	*C. difficile*, any	1.178	0.137	1.430	Number of observations: 401,292 Likelihood ratio: 19,382.09 Model significance: <0.0001 R-squared: 0.0472 Max-rescaled R-square: 0.3699
	MRSA, non-BSI	0.901	0.181	0.330	
	MRSA, BSI	1.815	0.157	14.367	
55–64	*C. difficile*, any	1.179	0.098	2.864	Number of observations: 326,065 Likelihood ratio: 27,465.87 Model significance: <0.0001 R-squared: 0.0808 Max-rescaled R-square: 0.3308
	MRSA, non-BSI	0.838	0.172	1.059	
	MRSA, BSI	1.595	0.167	7.805	
65–74	*C. difficile*, any	1.113	0.074	2.068	Number of observations: 403,732 Likelihood ratio: 44,814.01 Model significance: <0.0001 R-squared: 0.1051 Max-rescaled R-square: 0.3312
	MRSA, non-BSI	0.884	0.129	0.904	
	MRSA, BSI	2.172	0.143	29.419	
75 and older	*C. difficile*, any	1.584	0.047	95.419	Number of observations: 606,518 Likelihood ratio: 84,928.33 Model significance: <0.0001 R-squared: 0.1307 Max-rescaled R-square: 0.2888
	MRSA, non-BSI	0.973	0.095	0.082	
	MRSA, BSI	1.715	0.126	18.212	

Abbreviations: BSI, bloodstream infection; CDI, *Clostridioides difficile*; MRSA, methicillin-resistant *Staphylococcus aureus*

National Hepatitis C estimates: Incidence, prevalence, undiagnosed proportion and treatment, Canada, 2019

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Abstract

Background: Estimates of the number of hepatitis C virus (HCV) infections are important for monitoring efforts aimed at preventing disease transmission, especially following the introduction of a highly effective treatment. This report provides updated estimates of HCV incidence, prevalence, undiagnosed proportion and treatment in Canada.

Methods: A combination of back calculation modelling and a modified version of the workbook method were used to estimate the incidence and prevalence of anti-HCV positive persons, the prevalence of chronic HCV infection and the undiagnosed proportion. The number of people treated for chronic HCV was estimated using administrative pharmaceutical data.

Results: An estimated 9,470 new infections occurred in 2019, corresponding to an incidence rate of 25 per 100,000 population, a 7.7% decrease since 2015. The estimated prevalence of anti-HCV antibodies in the Canadian population was 1.03% (plausible range: 0.83%–1.38%), and the estimated prevalence of chronic HCV was 0.54% (plausible range: 0.40%–0.79%). The overall proportion of anti-HCV positive persons who were undiagnosed was estimated at 24% of all infections, with individuals born between 1945 and 1975 being the priority population the most likely to be undiagnosed. An estimated 74,500 people with chronic HCV have been treated since the introduction of direct-acting antivirals in 2014.

Conclusion: Estimates of HCV incidence and prevalence are key metrics to guide interventions and resource allocation. While our estimates show that HCV incidence has decreased in Canada in recent years and treatment of chronic HCV has continued to increase, ongoing efforts are required to reduce the burden of HCV in Canada.

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Keywords: Hepatitis C, prevalence, incidence, epidemiology, Canada

Introduction

Globally, an estimated 58 million people have chronic hepatitis C virus (HCV) infection, with about 1.5 million new infections occurring per year (1). The number of people living with HCV has continued to increase, even though an effective cure exists (2). Canada has developed a pan-Canadian framework for action (3) as well as an accompanying Government of Canada five-year action plan (4) to help guide Canada's efforts towards reducing the health impacts of sexually transmitted and blood-borne infections (STBBIs) in Canada by 2030.

The Global Health Sector Strategies on human immunodeficiency virus (HIV), viral hepatitis and sexually transmitted infections introduced targets for viral hepatitis control and elimination by 2030 (2). These include targets for the following: reduction of the annual number of new infections overall and among people who inject drugs; the reduction of the number of deaths from HCV; and an increase in the proportion of people living with HCV who have been diagnosed and cured. While the Government of Canada endorses these global targets, the first priority of

the pan-Canadian STBBI action plan (4) is to develop domestic indicators and targets that will allow for the monitoring of Canada's progress.

This report provides an update for 2019 on Canada's estimates of HCV incidence, prevalence, proportion of undiagnosed and treated cases, which supports the Government of Canada's commitment to monitor and report on progress towards hepatitis C elimination.

Methods

A combination of back-calculation statistical modelling (5) and a modified version of the workbook method (6) were used to estimate new anti-HCV seropositivity (incidence), prevalence of anti-HCV positive persons (i.e. persons who have ever been infected with HCV), the prevalence of ribonucleic acid (RNA)-positive persons (i.e., persons with active infection, as a proxy for chronic HCV infection) and the undiagnosed/unaware proportion of the population. This methodology was developed and refined through a series of consultations that took place between 2019 and 2022. Experts from a variety of backgrounds were consulted, including hepatologists, research epidemiologists, laboratory specialists and mathematical modellers.

Back calculation modelling

Back calculation is a widely used computational method to infer disease infections—which are not observable—from consequential results such as reported diagnostic cases. The method was initially designed to estimate the HIV/acquired immunodeficiency syndrome incidence (5) and was later adopted to estimate Canadian HCV incidence and prevalence for 2011 (7). Following the same approach, back calculation modelling was conducted using HCV routine surveillance data from the Canadian Notifiable Diseases Surveillance System, extracted on October 22, 2021. All reported cases (acute, chronic and unspecified) from 1991 to 2019 from five large Canadian provinces (British Columbia, Alberta, Saskatchewan, Ontario and Québec) were used. These provinces, which represented 90% of the Canadian population in 2019 (8), are the only ones who provide record-level HCV surveillance data. Modelled results were then extrapolated to the entire country. More information on the modelling can be found in **Appendix A**.

Modified workbook method

The workbook method is an established approach previously used to produce estimate of HIV prevalence in low level and concentrated HIV epidemics (6). A modified version of this method was used to estimate the number of anti-HCV positive persons as well as their diagnosis status, and the number of HCV RNA-positive persons in Canada. We divided the Canadian population into subgroups that are known to be at higher risk of infection, and synthesized published and unpublished data to estimate prevalence within each subgroup. Each anti-HCV seroprevalence measure was classified as an "underestimate", "overestimate" or "appropriate estimate" based on a review of the methodology of each study. The under and over-estimates were used as plausible ranges of the appropriate estimates.

Estimates of the population size of each subgroup in Canada were based on data from Statistics Canada (8–10), as well as unpublished data obtained through personal communications, as detailed in the systematic review section. Point estimates of HCV prevalence were produced along with their upper and lower bounds by multiplying the HCV prevalence by the corresponding population size estimate.

The workbook subgroup populations were based on the following priority populations, as outlined in the *Blueprint to inform hepatitis C elimination efforts in Canada* (11):

- People who inject drugs (PWID)
- Adults in the 1945–1975 birth cohort
- Immigrant populations
- Indigenous peoples (First Nations, Inuit and Métis)
- Gay, bisexual and other men who have sex with men (gbMSM)
- People who are incarcerated (PWAI) in federal and provincial prisons

Due to the extensive overlap between these priority populations, they were not considered to be mutually exclusive.

Systematic review

A health librarian at the Public Health Agency of Canada conducted a series of literature searches to obtain data on 1) HCV incidence and prevalence in Canada from January 1, 2019, to October 1, 2021, and 2) the unaware/undiagnosed proportion of HCV infection in Canada from January 1, 2016, to October 1, 2021. The literature searches yielded an initial 1,187 records, with an additional 31 records found outside of the librarian search. Using the systematic review protocol for prevalence and incidence studies developed by Joanna Briggs Institute (12), two independent reviewers screened all studies for inclusion. Discrepancies between reviewers were resolved through discussion. A total of 43 records were included after the final review and considered for use in the workbook method. Details about this process can be found in **Appendix B**.

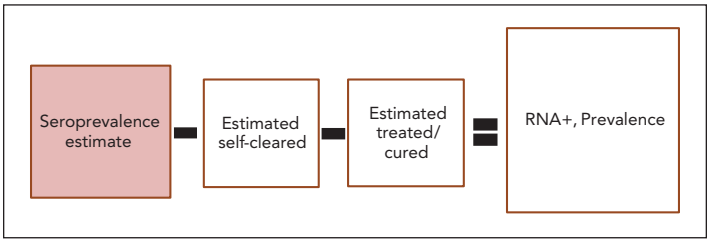
In addition to the sources identified through the systematic review, unpublished data were requested from organizations and researchers. These sources included Canadian Blood Services (*unpublished data from Hepatitis C Surveillance, Canadian Blood Services, 2015–2019*) and Héma-Québec (*unpublished data on first-time donors, Héma-Québec, 2015–2019*), Correctional Services Canada (*unpublished data from Correctional Services Canada, 2015–2021*), Tracks bio-behavioural survey data (*unpublished data from Tracks survey of people who inject drugs in Canada, Phase 4 Public Health Agency of Canada, 2017–*

2019), and the Engage cohort study (*unpublished data from Engage Cohort Study, 2017–2019*).

Chronic hepatitis C prevalence and undiagnosed proportion estimates

The overall seroprevalence estimate derived from the workbook method was used as the starting point to estimate the overall chronic hepatitis C prevalence in Canada (**Figure 1**). First, we subtracted the estimated number of individuals who had spontaneously cleared the virus, using a 30% clearance estimate based on a range of clearance proportions measured in Canadian studies (13–17). We then subtracted the estimated number of cured individuals, which was calculated using Canadian treatment estimates from the British Columbia Centre for Disease Control (2012–2016) (*unpublished data on HCV Treatment Initiation in Canada, British Columbia Centre For Disease Control, 2012–2016)* and IQVIA *(unpublished data from Provincial Patient Summary report, IQVIA, 2017–2019*), using a cure rate of 48% for 2012–2014, and of 90% for 2015–2019. This calculation yielded a remaining number of HCV RNA-positive individuals in Canada, which was used as a proxy for chronic HCV infection.

Figure 1: Equation used to estimate chronic hepatitis C prevalence, overall Canadian population



Lastly, the estimate of the undiagnosed/unaware proportion of anti-HCV infection in Canada was determined by taking the midpoint between the back calculation modelling estimate and the modified workbook estimate (**Figure 2**). This approach was chosen to minimize the uncertainty that is inherent to estimates, which are partly based on assumptions due to the incompleteness of available data. Although uncertainty can never be completely eliminated, the true number likely lies between those two estimates.

Results

Hepatitis C virus incidence

According to back calculation modelling, an estimated 9,470 new HCV antibody-positive infections occurred in 2019, corresponding to an annual incidence rate of 25 per 100,000 population. When modelled by birth cohort, the highest annual incidence was estimated among persons born after 1974 at 5,115 new infections, followed by persons born between 1945 and 1974 at 4,354 new infections. There were no new HCV infections estimated among persons born before 1945 (**Figure 3**).

Figure 2: Equation used to estimate the undiagnosed proportion

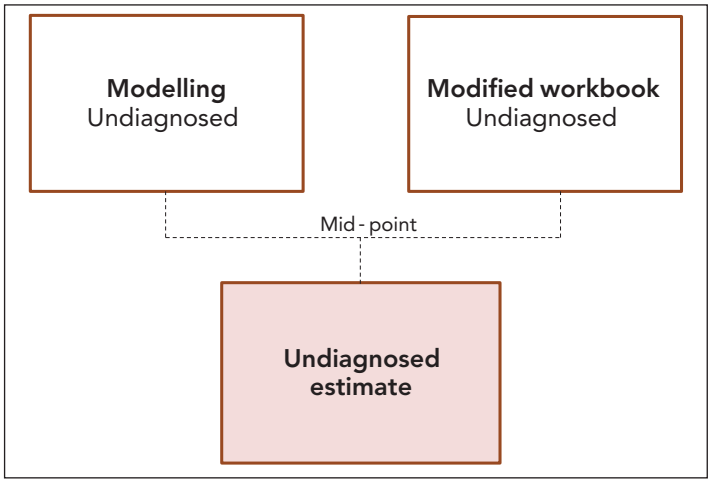
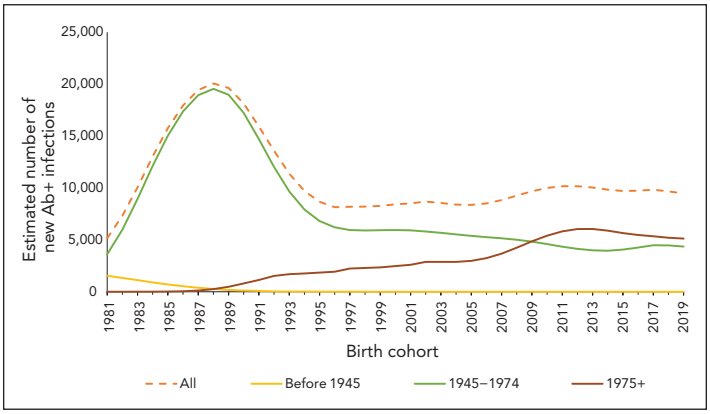


Figure 3: Estimated number of new hepatitis C infections by birth cohort, Canada, 1980–2019

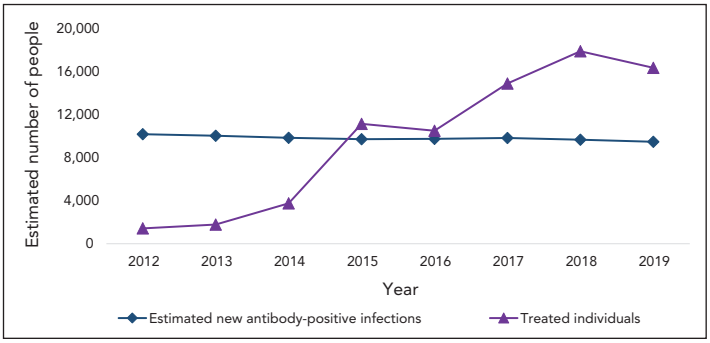


Abbreviation: Ab+, antibody-positive

Hepatitis C virus treatment

We estimate that since the introduction of direct-acting antivirals in Canada in 2014, approximately 74,500 people living with chronic HCV were treated, with 65.9% of those treatments having occurred between 2017 and 2019. **Figure 4** shows the yearly number of individuals treated, contrasted with the estimated number of new HCV infections.

Figure 4: Estimated number of new hepatitis C infections and estimated number of people treated, Canada, 2012–2019



Hepatitis C virus prevalence

Using the modified workbook method, the estimated prevalence of anti-HCV in Canada in 2019 was 1.03% (plausible range: 0.83%–1.38%) or 387,000 (plausible range: 312,000–519,000) persons. Among priority populations, the highest prevalence of anti-HCV was among PWID (past 6–12 months) at 46.1% (plausible range: 28.0%–64.2%), followed by those with a lifetime history of infection drug use at 44.9% (plausible range: 25.6%–64.2%). Anti-HCV prevalence was also significantly higher among PWAI and Indigenous peoples than among the general population, at 10.7% (plausible range: 8.19%–13.2%) and 7.4% (plausible range: 3.49%–11.2%), respectively (**Table 1**).

Of the estimated number of persons ever infected with HCV (anti-HCV positive), an adjustment of 30% or 116,188 persons was made to account for individuals who spontaneously cleared HCV infection. A second adjustment of 67,018 persons was made to account for individuals who were cured of HCV infection through treatment. After adjusting for HCV clearance and treatment, the estimate of chronic HCV prevalence was 0.54% (plausible range: 0.40%–0.79%) or 204,000 persons (plausible range: 151,000–296,000).

Among priority populations, the highest prevalence rate of chronic HCV infection was among current PWID at 36.9% (plausible range: 12.6%–55.1%). The lowest prevalence rate among priority populations was found among adults in the 1945–1975 birth cohort at 0.9% (plausible range: 0.4%–1.3%) (**Table 2**).

Undiagnosed proportion

The overall proportion of anti-HCV positive persons in Canada who were undiagnosed or unaware of their HCV status was estimated at 24% or 79,500 persons (data not shown). This was calculated by taking the midpoint between the modelling estimate (n=60,200, 19.2%) and the modified workbook estimate (n=98,800, 25.5%). Among priority populations, the highest proportion of undiagnosed/unaware HCV infection was estimated among adults in the 1945–1975 birth cohort at 34.4% (plausible range: 18.8%–50.0%), followed by 22% among current PWID (plausible range: 18.5%–25.4%) and 22% among PWAI (plausible range: 12.3%–31.6%). The lowest proportion of undiagnosed/unaware was among the gbMSM population at 8.8% (plausible range: 6.7%–22.2%) (**Table 3**). The proportion of undiagnosed individuals could not be measured for people with a lifetime history of injection drug use, Indigenous peoples, and immigrant populations due to insufficient data.

Table 1: Estimated anti-hepatitis C antibodies positive prevalence by priority population, Canada, 2019

Population	Population size	Anti-HCV positive prevalence (%)			Number of anti-HCV positive persons			References
		Point estimate	Lower bound	Upper bound	Point estimate	Lower bound	Upper bound	
General population	37,601,230	1.03%	0.83%	1.38%	387,000	312,000	519,000	(8,18–21) *Unpublished data from Hepatitis C Surveillance, Canadian Blood Services, 2015–2019* *Unpublished data on first-time donors, Héma-Québec, 2015–2019*
PWID—Current (PWID in the past 6–12 months)	133,651	46.1%	28.0%	64.2%	61,600	37,400	85,800	(18,22,23) *Personal communication, Williams A. Sorge J., 2022*
PWID—History (People who have a lifetime history of injection drug use)	389,574	44.9%	25.6%	64.2%	175,000	99,800	250,000	(18) *Personal communication, Williams A. Sorge J., 2022*
Adults in the 1945–1975 birth cohort	13,975,919	1.74%	1.27%	2.20%	242,000	177,000	307,000	(8,18–20,24–27)
Immigrant population	11,778,177	1.51%	0.70%	2.32%	178,000	82,500	273,000	(18,20,28)
Indigenous peoples (First Nations, Inuit, Métis)	1,826,356	7.35%	3.49%	11.2%	134,000	63,700	205,000	(18,29)
gbMSM	640,785	3.70%	1.70%	5.10%	23,400	10,900	32,700	(30–32) *Unpublished data from Engage Cohort Study, 2017–2019*
People who are incarcerated—Federal and provincial	37,932	10.7%	8.19%	13.2%	4,050	3,110	5,000	(9,33–35) *Unpublished data from Correctional Services Canada, 2015–2021*

Abbreviations: gbMSM, gay, bisexual and other men who have sex with men; HCV, hepatitis C virus; PWID, people who have used injection drugs

Table 2: Estimated chronic hepatitis C infection prevalence by priority population, Canada, 2019

Population	Population size	Chronic hepatitis C prevalence (%)			Number of persons living with chronic hepatitis C			References
		Point estimate	Lower bound	Upper bound	Point estimate	Lower bound	Upper bound	
PWID—Current (PWID in the past 6–12 months)	133,651	36.9%	12.6%	55.1%	49,300	16,800	73,600	(18,22) *Unpublished data from Tracks survey of people who inject drugs in Canada, Phase 4 – Public Health Agency of Canada, 2017–2019* *Personal communication, Williams A. Sorge J, 2022*
PWID—History (People who have a lifetime history of injection drug use)	389,574	29.6%	22.3%	36.9%	115,000	87,000	144,000	(18,22,24)
Adults in the 1945–1975 birth cohort	13,975,919	0.87%	0.44%	1.30%	122,000	61,500	182,000	(8,18,20)
Immigrant population	11,778,177	Insufficient data						N/A
Indigenous peoples (First Nations, Inuit, Métis)	1,826,356	3.5%	2.0%	5.0%	63,900	36,500	91,300	(18,29,36)
gbMSM	640,785	1.1%	0.4%	1.7%	7,050	2,560	10,900	(32) *Unpublished data from Engage Cohort Study, 2017–2019*
People who are incarcerated—Federal and provincial	37,932	3.7%	2.3%	5.1%	1,400	870	1,940	(35) *Unpublished data from Correctional Services Canada, 2015–2021*

Abbreviations: gbMSM, gay, bisexual and other men who have sex with men; N/A, not applicable; PWID, people who have used injection drugs

Table 3: Estimated number and proportion of people unaware of their hepatitis C virus antibody-positive status by priority population, Canada, 2019

Population	Anti-HCV positive estimate	Undiagnosed/unaware (%)			Number of anti-HCV positive persons who were unaware/undiagnosed			References
		Point estimate	Lower bound	Upper bound	Point estimate	Lower bound	Upper bound	
PWID—Current (PWID in the past 6–12 months)	61,600	22.0%	18.5%	25.4%	12,400	10,500	14,300	*Unpublished data from Tracks survey of people who inject drugs in Canada, Phase 4 – Public Health Agency of Canada, 2017–2019*
PWID—History (People who have a lifetime history of injection drug use)	175,000	Insufficient data						N/A
Adults in the 1945–1975 birth cohort	242,000	34.4%	18.8%	50.0%	83,400	45,600	121,000	(27,37–40)
Immigrant population	178,000	Insufficient data						N/A
Indigenous peoples (First Nations, Inuit, Métis)	134,000	Insufficient data						N/A
gbMSM	23,400	8.8%	6.7%	22.2%	2,060	1,570	5,200	*Unpublished data from Engage Cohort Study, 2017–2019*
People who are incarcerated—Federal and provincial	4,050	22.0%	12.3%	31.6%	890	499	1,280	(34) *Unpublished data from Correctional Services Canada, 2015–2021*

Abbreviations: gbMSM, gay, bisexual and other men who have sex with men; HCV, hepatitis C virus; N/A, not applicable; PWID, people who have used injection drugs

Discussion

The national hepatitis C estimates for 2019 provided updated insights into the hepatitis trends in Canada. These estimates will be used to support the pan-Canada five-year action plan on STBBI, with the goal of reducing the health impacts of STBBI in Canada by 2030. Based on our modelling, an estimated 9,470 new hepatitis C infections (25 per 100,000 population) occurred in 2019 in Canada, which corresponds to a reduction of 7.7% in incidence compared to 2015 (Figure 4). However, this reduction rate is insufficient to meet the 90% reduction in new chronic infections outlined in the World Health Organization 2030 elimination goals, thus confirming the need for continued efforts to curb HCV transmission and improve access to treatment for all HCV-infected individuals. We estimated that in 2019, approximately 1% of the Canadian population, or roughly 387,000 persons, were anti-HCV positive, meaning they were infected by the virus at some point in time (i.e., past or current infection). Of these individuals, an estimated 76% were diagnosed as anti-HCV-positive, leaving an estimated 24% who were unaware of their anti-HCV positive status. While this figure is encouraging, more progress needs to be made to reach the goal of 90% of people living with HCV being diagnosed by 2030. Of the different priority groups, baby boomers (e.g., adults born between 1945 and 1975) were the most likely to be undiagnosed.

Additionally, an estimated 204,000 persons, or approximately half of those who were estimated to be anti-HCV positive, were HCV RNA-positive in 2019, suggesting an active infection. Direct-acting antivirals are a cornerstone in treatment to reduce the risk of complications among those individuals and avert further transmission. Since this highly effective treatment was introduced in Canada in 2014, an estimated 74,500 people with chronic hepatitis C were treated. Encouragingly, our data also shows that between 2017 and 2019, the yearly number of treated individuals largely exceeded the number of new infections. As suggested elsewhere (41), maintaining high treatment uptake in the upcoming years will be essential to achieve HCV elimination in Canada by 2030.

Although our 2019 estimates confirmed that the burden of hepatitis C on the overall population is relatively low, certain populations and communities are disproportionately impacted. This is especially true for people who use injection drugs, who may face concomitant social, financial and health challenges and, therefore, require a more comprehensive approach to prevention, diagnosis and treatment. Other priority populations, including people who are incarcerated, Indigenous peoples and gbMSM, are also disproportionately affected. Targeted approaches, such as peer-supported and culturally competent outreach interventions, could be considered to reduce the burden of HCV among these groups.

Strengths and limitations

Key strengths of our approach include the use of Canadian Notifiable Diseases Surveillance System data, a comprehensive database that encompasses all laboratory-confirmed cases of HCV in Canada. The combination of back-calculation and workbook methods also provides an opportunity to improve the overall estimates and increase accuracy. Our modified workbook approach allowed us to produce the first national HCV estimates specific to the priority populations based on the *Blueprint to inform hepatitis C elimination efforts in Canada* (11), thus making these data more actionable for policy-makers and service providers working with these groups.

Our analysis also has several limitations. First, estimates of HCV incidence were based on data on all reported cases (acute and chronic); therefore, the estimated incidence represents all individuals who developed anti-HCV antibodies. Separate estimates for the undiagnosed proportion among persons with acute and chronic infections could not be produced. Second, data by priority population were not available through routine national surveillance; therefore, national incidence estimates by priority population were not produced. As a result of these limitations, reporting on a full set of indicators against global targets was not possible at this time. Third, since individuals may identify as being members of more than one priority population, these categories are not mutually exclusive. However, unlike the workbook method used in previous national estimates, the modified workbook method does not use addition or subtraction between priority groups to yield an overall estimate for the general population. Instead, representative data for the general Canadian population were collected and a prevalence estimate was calculated independently of the other priority populations. Fourth, it was not possible to distinguish reinfections from initial infections; therefore, it is possible that individuals infected twice within the same year were counted twice in the yearly incidence estimates. Finally, treatment estimates were based on administrative pharmaceutical records of HCV treatment initiation; therefore, individuals who received HCV treatment through clinical trials or compassionate access may not be captured.

Conclusion

Estimates of HCV incidence and prevalence can be used to guide health interventions and resource allocation to link chronically infected persons to screening, care, treatment and ultimately cure. While our estimates show that overall HCV incidence has been decreasing in Canada since 2010, continued efforts are required to eliminate chronic HCV as a public health threat by 2030. Significant progress towards HCV elimination will require targeted interventions to prevent new infections, especially among priority populations, innovative testing approaches to find undiagnosed persons and strategies to ensure linkage to care and prompt treatment. The Public Health Agency of Canada will continue to work closely with provinces and territories and

other partners to enhance methods and data sources to improve the ability to measure and assess progress against elimination targets.

Authors' statement

NP — Designed the study methodology, interpreted the results, drafted the manuscript
AW — Designed the study methodology, analyzed the data, interpreted the results, drafted the manuscript
SP — Designed the study methodology, analyzed the data, interpreted the results
LC — Interpreted the results, drafted the manuscript
QY — Designed the study methodology, interpreted the results
FZ — Designed the study methodology, analyzed the data
PY — Designed the study methodology
JJF — Designed the study methodology, reviewed the results
NZJ — Designed the study methodology, reviewed the results
MBK — Designed the study methodology, reviewed the results
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WWLW — Designed the study methodology, reviewed the results
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All authors approved the final version of the manuscript.

Competing interests

MBK reports grants for investigator-initiated studies from ViiV Healthcare, AbbVie, and Gilead, and consulting fees from ViiV Healthcare, AbbVie, and Gilead, all outside the submitted work. MBK is supported by a Tier I Canada Research Chair. NZJ has participated in advisory work for AbbVie and has received speaking fees from AbbVie and Gilead, not related to the submitted work. No other competing interests were declared.

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Appendix

Appendix A: Methodology for back calculation modelling

Appendix B: Literature search

Appendix A: Methodology for back calculation modelling

We use the same back calculation modelling approach as in the previous work for Canadian hepatitis C virus (HCV) estimation (7). In the back calculation modelling method, the time from HCV infection to diagnosis is considered a random variable that follows a certain probabilistic distribution. Once the transition probabilities *P* are known, the back calculation method calculates the expected number of infections *I* (as the estimated HCV incidence) through minimizing the gap between the reported HCV cases and the expected diagnosed HCV cases which is *P* x *I*. In the computation process, other modelling outcomes, such as expected HCV infections diagnosed in the same year, the expected HCV-related mortality and not-yet diagnosed HCV cases, are also produced.

The probabilities *P* are not known in advance, however, and it is assumed to follow a commonly used family of distribution called log-logistic distribution with a shape parameter and a scale parameter. As in the previous work (7), these parameters are determined from a wide range through iteratively searching the optimal fitting of the reported diagnosed cases, and HCV-related mortality data. In addition, the reported acute cases are also used to further calibrate the parameters by minimizing the gap between the acute cases and the expected HCV infections diagnosed in the same year. The calibration uses the standard BFGS-method available in R.

Using this method, HCV incidence was estimated by five-year birth cohort plus an extra open cohort (born after the year 2000). Five-year birth cohorts were then grouped into larger birth cohorts: before 1945, 1945–1974, and after 1975.

Appendix B: Literature search

A health librarian at the Public Health Agency of Canada conducted a series of literature reviews based on the specific objectives of obtaining data on (1) HCV incidence and prevalence in Canada from January 1, 2019, to October 1, 2021, and (2) the unaware/undiagnosed proportion of HCV infection in Canada from January 1, 2016, to October 1, 2021. The following databases were searched by the Health Librarian for relevant publications: Ovid MEDLINE(R) ALL, Embase and Scopus. Additional grey literature searches were conducted using the Google search engine. In total, both literature searches yielded an initial 1,187 records, with an additional 31 records found outside of the librarian search.

Using the systematic review protocol for prevalence and incidence studies developed by Joanna Briggs Institute (JBI), two independent reviewers screened all studies for inclusion. For the initial screening, reviewers independently read either the abstract or the full text and made assessments based on the following inclusion criteria:

- Condition: HCV infection (past [seroprevalence] or present [active or chronic])
- Outcome:
  - Literature search 1: Reporting data on proportion with HCV infection, prevalence or incidence
  - Literature search 2: Reporting data on awareness of HCV infection, and/or undiagnosed proportion of people with HCV
- Context: In Canada
- Population: All populations used for the workbook method

After the initial screening, 66 records were included for final assessment. In the final assessment, both reviewers independently read and evaluated each paper using the *JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data* to determine whether the paper should be included. Data from cross-sectional and cohort studies with a testing component were prioritized, but studies using administrative data and modelling studies were also included, when appropriate. Discrepancies between reviewers were resolved through discussion. After the final review, 43 records were included and considered for use in the workbook method (Tables 1, 2 and 3). Due to a limited number of records on the incidence and prevalence of HCV among gay, bisexual and other men who have sex with men (gbMSM) and baby boomers, a subsequent literature review with an extended date range of January 1, 2016, to December 31, 2018, was conducted for those two subgroups. This allowed us to find an additional seven records for inclusion in the workbook method.

Understanding Canadians' knowledge, attitudes and practices related to antimicrobial resistance and antibiotic use: Results from public opinion research

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Abstract

Background: Antimicrobial resistance is a current and pressing issue in Canada. Population-level antibiotic consumption is a key driver. The Public Health Agency of Canada undertook a comprehensive assessment of the Canadian public's knowledge, attitudes and practices in relation to antimicrobial resistance and antibiotic use, to help inform the implementation of public awareness and knowledge mobilization.

Methods: Data were collected in three phases: 1) six in-person focus groups (53 participants) to help frame the survey; 2) nationwide survey administration to 1,515 Canadians 18 years and older via cell phone and landline; and 3) 12 online focus groups to analyze survey responses. Survey data is descriptive.

Results: A third (33.9%) of survey respondents reported using antibiotics at least once in the previous 12 months, 15.8% more than twice and 4.6% more than five times. Antibiotic use was reported more among 1) those with a household income below $60,000, 2) those with a medical condition, 3) those without a university education and 4) among the youngest adults (18–24 years of age) and (25–34 years of age). Misinformation about antibiotics was common: 32.5% said antibiotics "can kill viruses"; 27.9% said they are "effective against colds and flu"; and 45.8% said they are "effective in treating fungal infections". Inaccurate information was reported more often by those 1) aged 18–24 years, 2) with a high school degree or less and 3) with a household income below $60,000. In focus groups, the time/money trade-offs involved in accessing medical care were reported to contribute to pushing for a prescription or using unprescribed antibiotics, particularly in more remote contexts, while the cost of a prescription contributed to sharing and using old antibiotics. A large majority, across all demographic groups, followed the advice of medical professionals in making health decisions.

Conclusion: High trust in medical professionals presents an important opportunity for knowledge mobilization. Delayed prescriptions may alleviate concerns about the time/money constraints of accessing future care. Consideration should be given to prioritizing access to appropriate diagnostic and other technology for northern and/or remote communities and/or medical settings serving many young children to alleviate concerns of needing a prescription or of needing to return later.

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Keywords: antimicrobial resistance, antibiotic resistance, antibiotic use, public opinion, survey, Canada

Introduction

Antimicrobial resistance (AMR) is a current and pressing issue in Canada, though information on more benign infections is limited, some calculations estimate that as many as 26% of infections may be resistant to first line antimicrobials (1). In Canada, AMR is estimated to cause 15 deaths a day and cost $1.4 billion dollars a year (1). Population-level antibiotic consumption is a key driver of AMR (2). Assessing the Canadian public's knowledge, attitudes and practices (KAP) related to antibiotics can help identify barriers to curbing antibiotic use, offer insight into consumption practises and provide a baseline for assessing different interventions.

In 2008, the Public Health Agency of Canada collected a small amount of data on KAP relating to antibiotics as part of a larger public opinion survey on pathogens and infection control (3). This was followed, in 2018, by a rapid response module from Statistics Canada's 2018 community health survey that gathered data specifically on oral antibiotic use (4). To have both a current and more comprehensive assessment of the Canadian public's KAP as they relate to AMR and antibiotics, the Public Health Agency of Canada undertook public opinion research between 2019 and 2022. The data from this research will be used to inform the *Pan-Canadian Action Plan on Antimicrobial Resistance* and to target stewardship and awareness activities.

Methods

Researchers from The Strategic Counsel collected data in three phases. In-person focus groups were held in July 16–18, 2019 to gather preliminary insights into KAP related to antibiotics and AMR, to frame the survey questionnaire. Participants were divided into six focus groups representing different gender and age categories; each group had a cross-section of different employment statuses, household incomes and ethnicities. This phase was followed by the development of a 19-minute-long telephone survey on AMR and antibiotic KAP adhering to the *Standards for the Conduct of Government of Canada Public Opinion Research—Telephone surveys* (5). The survey was pre-tested in both official languages (English and French) among 20 respondents on December 7, 2021, and the overwhelming majority of respondents (95%) reported the questionnaire was easily understood. The survey was administered nationwide to 1,515 Canadians 18 years of age and older, via cell phone and landline (60/40 split) between December 10, 2021, and January 7, 2022. Participants were informed that the survey data was for the Public Health Agency of Canada and that their participation was voluntary and confidential.

The survey broadly covered three areas: knowledge and perception of antibiotics; antibiotic use and health practises; and knowledge, awareness and perception of AMR. It included standard public opinion research questions on antibiotic use and familiarity with terms. It also included questions on health decision-making strategies more broadly to identify the most impactful circumstances for education on antibiotics and AMR.

A stratified sample design was utilized to ensure sufficient data from Saskatchewan, Manitoba and the Atlantic provinces for the possibility of regional comparisons for future analyses. Nationally, the results have an associated margin of error of (+/-) 2.5%, at a 95% confidence level. Results for population subgroups have a higher associated margin of error. All percentages reported are based on the weighted sample. Descriptive analyses of the survey data were done using SAS software 9.4 (SAS Institute; Cary, United States).

The telephone survey took place while the Omicron wave of coronavirus disease 2019 (COVID-19) was rampant in most parts of the country. Questions referring to the prior 12 months refer to a period when COVID-19 was prevalent and there were associated public health measures in many areas. The anomalous circumstances of this period appear to have impacted at least some facets of antibiotic use. Data on subscription of systemic antibiotics shows a decline in community antibiotic use in 2020 and 2021 beginning at the onset of COVID-19 (6). We do not have data specifically on unprescribed, non-systemic or over the counter use during this period.

The third phase consisted of 12 online focus groups (held between February 23 and March 1, 2022), whose participants were recruited from both urban centres and more rural and northern communities to probe more deeply into attitudes and behaviours linked to antibiotics and AMR. Focus groups used a moderated round-table discussion format following a set moderator guide and touched on three subject areas: knowledge and awareness of antibiotics; antibiotic use; and knowledge and awareness of antimicrobial resistance. A qualitative approach allowed for a more in-depth exploration of mindset, motivations, barriers, and personal or social considerations as they related to these issues. Participants were again divided into groups representing different gender and age categories, each with a cross-section of different employment statuses, household incomes and ethnicities. Additionally, some groups were restricted to parents of young children, Indigenous or Asian-Canadian participants to ensure representation of their views. A preliminary analysis of themes reported in the focus groups was performed by The Strategic Counsel and these were subsequently analyzed for cross-cutting themes related to antibiotic use.

Results

Participants, response rate and sample of telephone survey

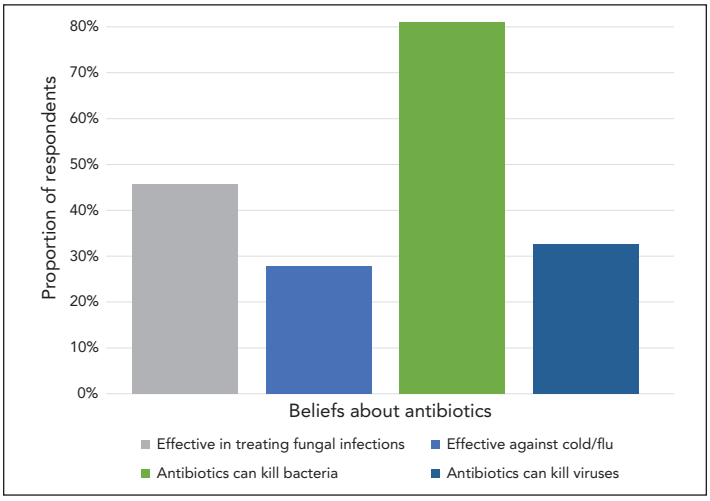
There were 53 participants in the in-person focus groups (phase 1) and 101 participants in the on-line focus groups (phase 3). In total, 1,515 respondents completed the telephone survey, with a completion rate of 99.62%. The overall response rate was 2.77% calculated using the empirical method formula of R/(U + IS + R). There were 1,583 responding (R) participants (completed, disqualified and over-quota respondents), 44,436 unresolved numbers (U) and 11,283 in scope non-responding participants (IS).

The demographics of all respondents (both weighted and unweighted) are summarized in **Table 1**.

Knowledge of antibiotics

More than three quarters (81.0%) of survey respondents correctly identified that antibiotics "can kill bacteria"; however, many respondents were misinformed about many other elements of antibiotic use and misuse. Nearly a third (32.5%) said that antibiotics "can kill viruses" or that they are "effective against colds and flu" (27.9%). Almost half (45.8%) said they "are effective in treating fungal infections" (**Figure 1**).

Figure 1: Knowledge of antibiotics among respondents



Inaccurate information on antibiotics' effectiveness against viruses, colds and flu and fungal infections was consistently reported more often by those aged 18–24 years (41.9%, 54.7%, 58.0%, respectively), those with a high school degree or less (45.0%, 41.4%, 54.2%, respectively) and those with a household income below $60,000 (41.3%, 36.7%, 51.9%, respectively). Those who spoke French at home were more likely to report effectiveness against viruses (42.9%) and fungal infections (53.7%), while those who spoke neither English or French at home were more likely to report that they were effective against colds and flu (41.2%).

Table 1: Demographics of respondents

Respondent demographics	Respondents, N=3,015		
	Weighted, n=1,500		Unweighted, n=1,515
	n	%	
Gender			
Male	723	48.2	697
Female	764	50.9	808
Other	13	0.9	10
Age group			
18–24 years	163	10.9	95
25–34 years	244	16.2	209
35–44 years	242	16.2	234
45–54 years	266	17.8	241
55–64 years	260	17.3	285
65 years and older	314	21.0	440
Prefer not to answer	11	0.7	11
Education			
High school or less	375	25.0	393
College/trades	389	25.9	398
University	720	48.0	708
Prefer not to answer	16	1.1	16
Income			
Less than $60,000	477	31.8	498
$60,000 to less than $100,000	364	24.3	361
$100,000 or more	446	29.8	432
Prefer not to answer	213	14.2	224
Language			
English	1,027	68.5	1,047
French	312	20.8	321
Other	155	10.3	141
Prefer not to answer	5	0.4	6
Medical condition			
Yes	383	25.6	362
No	1,109	74.0	1,145
Prefer not to answer	7	0.5	8

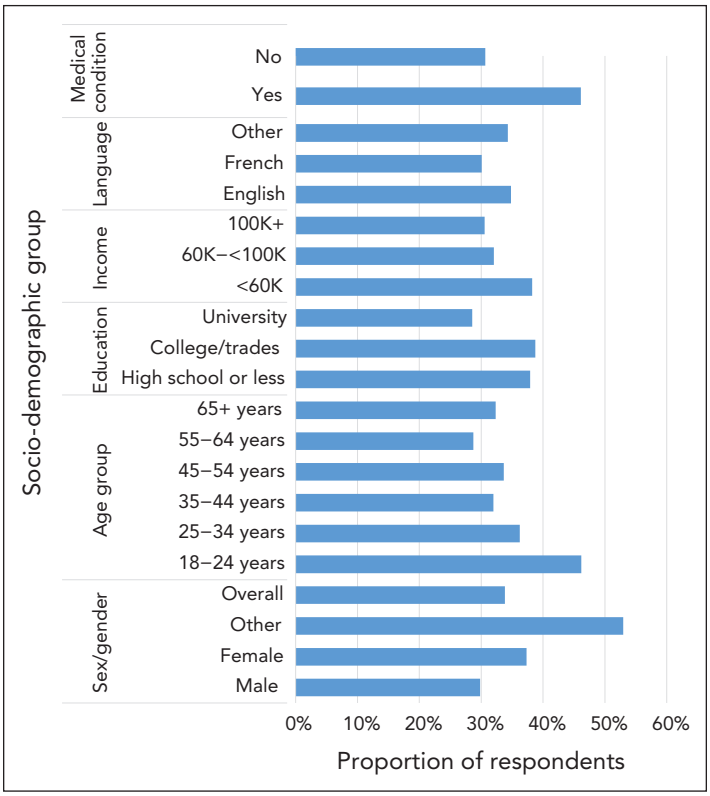
Antibiotic use

Slightly more than a third (33.9%) of survey respondents reported using antibiotics at least once in the past 12 months: 15.8% had used antibiotics more than twice in the past 12 months; and 4.6% had used antibiotics more than five times in the past 12 months. The questions in this survey cover all antibiotic use regardless of format (e.g. pill, injection, topical), mechanism of action (e.g. systemic or local) and means of access (prescribed, unprescribed over the counter).

Antibiotic use was reported more among those with a medical condition (46.1%), young adults (18–24 years of age, 46.2%; 25–

34 years of age, 36.3%), those with a household income below $60,000 (38.2%) and those without a university education (38.8% for those with college or trades and 37.9% for those with high school). Slightly more women (37.3%) than men (29.7%) reported using antibiotics (**Figure 2**). Similarly, frequent use (more than twice in the past 12 months) was reported more by those with a medical condition (26.9%), by the youngest adults (18–24 years of age, 25.2%), by those with a household income below $60,000 (21.7%) and by those with high school or less (21%) or college/trade diplomas (20.6%) (**Table 2**).

Figure 2: Reported antibiotic use in past 12 months by socio-demographic variable



Strategies for health decision-making

Respondents reported three main strategies for making health decisions in general (multiple answers were permitted). A large majority (85.6%) indicated that they follow the advice of a health professional, almost two thirds report searching for relevant information themselves (63.3%) or relying on their previous experience (59.3%) (**Figure 3**).

Women were more likely than men to report following the advice of a health professional (89.3% vs 81.9%). There were very high reported levels of following the advice of a health professional, irrespective of household income, education level, age, or language spoken. Younger respondents were more likely to report looking up health information themselves, to base their decision on their previous experience and/or to follow the advice of family or friends compared with older respondents (**Figure 4**).

Figure 3: Decision-making - strategies reported among different groups of respondents

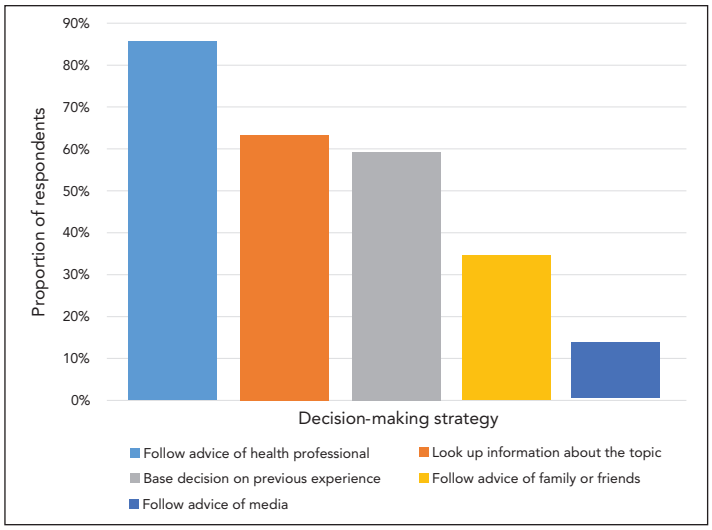
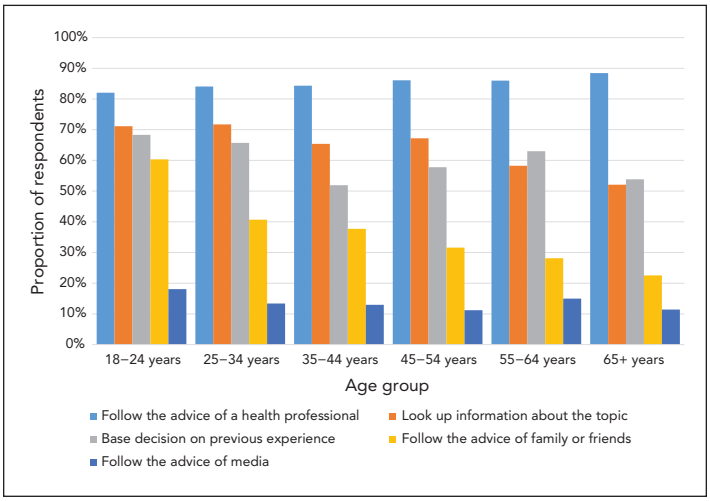


Figure 4: Decision-making strategies by age group



Factors shaping antibiotic use: cross-cutting themes from focus groups

Two cross-cutting themes emerged out of the focus groups related to factors shaping antibiotic practices. The first was the role of difficulties accessing primary care and the time/money trade-offs involved in going to the doctor. Many respondents disclosed that they shared antibiotics or wanted to get an antibiotic prescription when they saw a health professional because of the difficulties of accessing care or of being able to return to get a prescription later if eventually needed. Women in a focus group with high Indigenous representation noted it was common practice in their communities to keep some antibiotic from a prescription in case those were needed in the future, due to the lack of access to a doctor.

Another cross-cutting theme was the cost of prescriptions and resultant financial pressures on families. This was cited as a reason for sharing prescriptions or keeping old pills. It was also

Table 2: Reported antibiotic use by socio-demographic variables and by frequency in the previous 12 months

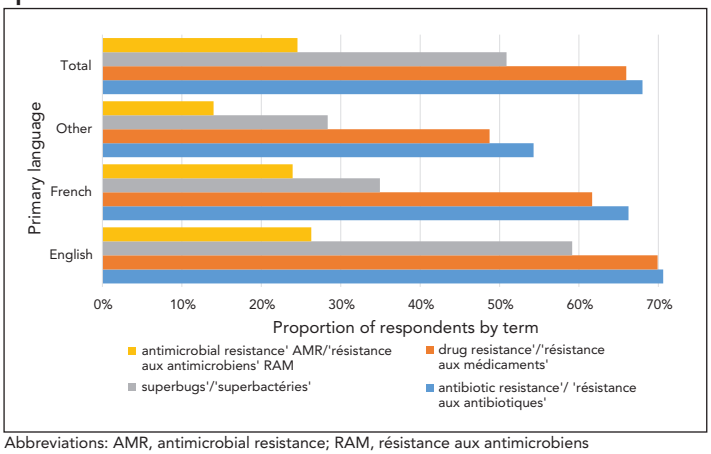
Socio-demographic variables	Once		2–5 times		5 or more times		Never/none		Don't know/ refused to answer	
	n	%	n	%	n	%	n	%	n	%
Medical condition										
Yes	61	19.2	50	15.9	35	10.9	165	52.3	5	1.6
No	209	17.8	116	9.9	35	3.0	803	68.5	10	0.8
Language										
English	193	18.8	122	11.9	42	4.1	656	63.8	14	1.4
French	47	15.0	26	8.4	21	6.7	218	69.9	N/A	N/A
Other	32	20.4	17	11.3	4	2.6	101	65.2	1	0.5
Income										
Less than $60,000	79	16.5	73	15.3	31	6.5	290	60.8	5	0.9
$60,000 to less than $100,000	66	18.2	32	8.8	19	5.1	242	66.5	5	1.4
$100,000 or more	88	19.8	39	8.8	9	1.9	309	69.3	1	0.1
Education										
High school or less	64	17.0	58	15.4	21	5.6	227	60.5	6	1.6
College/trades	71	18.3	51	13.2	28	7.2	234	60.2	4	1
University	134	18.6	55	7.6	17	2.4	509	70.8	5	0.7
Age group										
18–24 years	34	21.0	31	19.2	10	6.0	88	53.8	0	0.0
25–34 years	41	16.8	31	12.7	17	6.8	152	62.4	3	1.4
35–44 years	54	22.4	16	6.8	7	2.8	164	67.8	1	0.2
45–54 years	51	19.3	26	9.8	12	4.6	177	66.4	0	0.0
55–64 years	46	17.9	22	8.5	6	2.3	181	69.8	4	1.5
65 years and older	44	14.1	40	12.6	18	5.6	206	65.7	6	2.0
Gender										
Male	109	15.1	80	11.0	26	3.6	497	68.8	10	1.4
Female	158	20.7	86	11.2	41	5.4	475	62.1	4	0.5
Total	271	18.1	168	11.2	69	4.6	977	65.1	15	1.0

the main reason cited by a small number of respondents for purchasing large quantities of antibiotics abroad, where they were available over the counter, for their children's eventual use in Canada.

Knowledge and attitudes related to antibiotic/ antimicrobial resistance

Approximately, a quarter of Canadians polled (24.6%) reported knowing the term "antimicrobial resistance" / "résistance aux antimicrobiens", 68.0% knew "antibiotic resistance" / "résistance aux antibiotiques" and 66.0% knew "drug resistance" / "résistance aux médicaments". Half (50.9%) of respondents were familiar with "superbugs" / "superbactéries"—these terms were only known to a majority of people who spoke English at home (**Figure 5**).

Figure 5: Knowledge of terms by primary language spoken at home



Abbreviations: AMR, antimicrobial resistance; RAM, résistance aux antimicrobiens

Nearly a quarter (22.0%) reported that they or someone they knew had experienced antibiotic resistance, while 8.4% reported that they or someone they knew had experienced antimicrobial resistance. This discrepancy is most likely due to lower familiarity with the term "antimicrobial" as compared with "antibiotic". In focus groups, a theme that emerged was that many people did not feel AMR was an issue that affected them or their families directly.

Once provided with an explanation of AMR, a majority (57.5%) expressed concern: 41.5% were "somewhat worried" and 16.0% were "very worried". In focus groups, AMR was not necessarily seen as a "top 10" global public health threat nor viewed as a particularly urgent issue. Concern about AMR was slightly higher among those with a university education (62.2%), those who spoke French at home (62.4%) and those aged 55–64 years (62.1%).

Discussion

The results reported here are quite similar to those reported in 2008, which were based on a nationwide sample of 1,500 participants, a representative sample of the Canadian population at the time (3). The proportion of Canadians reporting antibiotic use in the prior 12 months has declined slightly, from 38% to 34%, in the past 14 years. A slightly higher proportion of respondents now incorrectly reports that antibiotics are effective against "colds and flu" (28%) than those that reported they were effective against "colds" in 2008 (24%). Concern about resistance to antibiotics has declined slightly since 2008—from 59% to 57% (3). These differences may fall within the combined margins of error for both surveys (2.4% in 2008 and 2.5% in 2022). A slightly lower proportion of Canadians now incorrectly reports that antibiotics kill viruses (39% in 2008 vs. 33% vs in 2022) (3).

Regarding knowledge of antibiotics and antimicrobial resistance, further research might help clarify whether misinformation is rooted in a conflation of antiviral or antifungal medication with antibiotics, a misunderstanding of the different kinds of pathogens that can cause infection or a lack of clarity on antibiotics' scope of action. A more refined understanding of the sources of misinformation could assist in targeting education efforts. The large gap between the proportion of respondents reporting familiarity with the terms "drug resistance" (66.0%) and "antibiotic resistance" (68.0%) versus "antimicrobial resistance" (24.6%) is important to keep in mind for public education efforts as public education efforts increasingly move towards the latter language. When the concept is explained, Canadians report much lower concern about antimicrobial resistance (57%) when compared to other high-income countries such as the United States (81%) (7) and the United Kingdom (88%) (8). Canadians report a similar level of incorrect information on antibiotics killing viruses as people in the United Kingdom (33% and 28%, respectively) and a similar level of antibiotic use (34% and 33%, respectively) (8).

In this study, people with lower income levels had much higher frequent use of antibiotics than their peers. Multiple factors may contribute to this observation. This may be driven by a high burden of medical conditions in lower-income communities in Canada (9), including infections (10). Antibiotic use may be linked to lower vaccination rates with various vaccines in low-income communities (11,12). Those with household incomes below $60,000 also had lower levels of knowledge about antibiotic use; however, individuals with low incomes and low education levels both expressed high trust in doctors as a source of health information and a large majority followed medical professionals' advice in making health decisions, presenting an important opportunity for stewardship interventions.

Young adults (18–34 years of age) reported use, and in particular frequent use, of antibiotics—far more than other age groups. Our findings likely underestimate use among the elderly due to the use of a broad older age category (65 years of age and older) and under-sampling of the very elderly who may be more dependent on caregivers or living in hospitals or long-term care. It is possible that higher levels of misinformation on antibiotics among young adults (18–24 years of age) led to overreporting of antibiotic use in the youngest age group, though depending on the mistaken underlying belief, it could also be consistent with high use. As well, due to higher margins of error among subgroups, these differences may not be significant or may fall within the margin of error. High levels of reported use among young adults are nonetheless consistent with findings from the 2018 Canadian Community Health Survey (CCHS) and those from public opinion research in Québec. Indeed, CCHS (25,787 participants over 18 years of age from all provinces, weighted to be representative) found a high frequency of specifically oral antibiotic use reported in this age group (4) while public opinion research in Québec (a representative sample of 7,254 participants) found that 25–34 year-olds had the highest reported levels of antibiotic use (13). Young adults were also more likely to have recent prescriptions in the 2008 nationwide survey (3). In contrast, national surveillance data on antibiotic dispensation according to tonnage (defined daily doses) and according to the overall number of prescriptions per 1,000 inhabitants show levels rising with age (14). This discrepancy may be due to the latter data excluding non-systemic antibiotics (such as creams, gels, vaginal tablets, eye drops and other formats), which can be used to treat some infections that are found disproportionately in young adults, to different metrics that are difficult to compare directly or to the inability of surveillance data to capture unprescribed use, which may be higher in young adults.

Young adults are also frequently the parents of young children and are an important group to consider for health promotion; however, initiatives need to be tailored to respond to specific

use patterns and challenges. The youngest adults (18–24 years of age) report more incorrect information on appropriate antibiotic use than older age groups. Adults younger than 35 years of age were more likely to make health decisions based on their previous experience, by following the advice of family or friends or by looking up health information themselves in comparison with older age groups. They are also more vulnerable to health misinformation (15). Finally, young adults, and in particular young men, are among the groups with the highest vaccine hesitancy or opposition in Canada (12), with the lowest rates of vaccination for the flu and for three or more doses of the COVID-19 vaccine (11,16). This is a concern given the effectiveness of vaccination as a strategy for reducing antibiotic use (17).

The focus group's findings echo previous research that identified the challenges of accessing care and the time/money trade-offs involved in doing so as factors in understanding antibiotic use, particularly in relation to gendered care burdens (18). Concerns about time/money trade-offs are also specifically associated with unprescribed use in other studies (19). This report illustrates that this issue may particularly affect remote and/or Indigenous communities. These findings provide insight into the 2008 public opinions research results that almost twice as many northern residents reported that their most recent antibiotic was from an old prescription as compared with other Canadians (14% vs 8%, respectively) (3). High rates of use in some Northern Indigenous communities are attributed to the high burden of infections, lack of access to physician care and lack of diagnostic capabilities (20).

Limitations and strengths

There are several limitations to this study. Data are self-reported and subject to recall bias and response bias. Respondents may not have understood certain terms in the questions. Any survey may contain potential errors such as coverage and measurement errors. The response rate was consistent with very low response rates for telephone surveys in recent years, following a two decade declining trend (21,22). In 2018, the Pew Center found the average response rate for telephone surveys was 6% (21). Low response rates can introduce greater nonresponse bias; however, a number of studies have found that response rates are not strongly associated with accuracy (21–23).

Telephone surveys exclude vulnerable populations, such as institutionalized and homeless populations, as well as populations that may not have a phone due to low incomes or precarity. Telephone surveys may also exclude people who are not well enough to respond or who are dependent on a caregiver for phone access; this may disproportionately exclude the elderly and/or disabled.

An important limitation is that this data set can only be used for descriptive purposes. Additionally, results are not disaggregated by racialized group, ethnic group and/or Indigenous status, and the sex/gender category of "other" has too few respondents to be able to meaningfully interpret results. Lastly, this survey did not collect disaggregated data specifically on prescribed, unprescribed, or over-the-counter use.

A strength of this research is the breadth of antibiotic use that it captures. It is one of the only current data streams in Canada to include unprescribed use and non-systemic use. This allows important insight into how common antibiotic use is, which is an important consideration for any awareness or education effort.

Conclusion

This public opinion research offers insight into the general population's knowledge, attitudes and practices with regards to antibiotics and AMR, helping to shape and inform efforts to address AMR reduction initiatives for the general population. Gaps remain in knowledge on how to support health promotion and stewardship in high-risk environments for AMR in the community, such as long-term care facilities and prisons, and with key populations at higher risk or with a higher burden of community-acquired resistant pathogens. Further studies using electronic medical records and studies on unprescribed use and over-the-counter use can shed light on some of the discrepancies between public opinion research findings and antibiotic dispensing data and help us better understand patterns of use in different demographics.

High trust in medical professionals and reported adherence to medical advice presents an important opportunity for reaching populations reporting high levels of antibiotic use and holding incorrect information frequently, such as young adults and those in low-income households. Findings from research on vaccine hesitancy have similarly identified medical providers as playing a key role as trusted and persuasive sources of medical advice (24–31) and, of relevance to medical provider interventions regarding antibiotic use and AMR. These studies have found that the most effective interventions include clear information on both individual and community risks and benefits (25) and direct medical recommendations (24–31).

As well, delayed prescriptions—prescriptions made available at a later date if symptoms persist in a way consistent with bacterial infection—may reduce unnecessary use while alleviating concerns about the time/money constraints of accessing future care. Access to appropriate diagnostic and other technology could be prioritized for Northern, Indigenous and/or remote communities and/or healthcare settings serving many young children to alleviate concerns of needing a prescription or of needing to return later for a prescription.

Authors' statement

A-LC — Original draft, analysis, review and editing
SA — Review and editing, analysis, supervision and project administration
KA — Analysis, review and editing
DGT — Conceptualization, analysis, review and editing, supervision and project administration
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Competing interests

None.

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SURVEY REPORT

Prevalence of antimicrobial-resistant organisms in smaller Canadian hospitals: Community, Rural, and Northern Acute Care Point Prevalence (CNAPP-19) Survey, 2019

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Abstract

Background: The availability of national data on the prevalence of antimicrobial resistant infections in smaller, community, northern and rural acute care hospitals is limited. The objective of this article is to determine the prevalence of infections caused by selected antimicrobial-resistant organisms (AROs) in these smaller hospitals.

Methods: A point prevalence survey was conducted by 55 hospitals between February and May 2019 and included representation from all 10 Canadian provinces. Eligible hospitals were those with 350 or fewer beds. Data were collected on hospital characteristics. De-identified patient data were collected on selected infections (pneumonia, urinary tract infections, bloodstream infections, skin/soft tissue infections, surgical site infections, and *Clostridioides difficile* infections) for selected AROs (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, extended-spectrum β-lactamase–producing organisms and carbapenemase-producing organisms). Data on antimicrobial prescribing and infection prevention and control precautions were also collected.

Results: A total of 3,640 patients were included in the survey. Median patient age was 73 years, and 52.8% (n=1,925) were female. Selected infections were reported in 14.4% (n=524) of patients, of which 6.9% (n=36) were associated with an ARO infection. Infection prevention and control additional precautions were in place for 13.7% (n=500) of patients, of which half (51.0%, n=255) were due to an ARO. Approximately one third (35.2%, n=1,281) of patients had at least one antimicrobial prescribed.

Conclusion: Antimicrobial-resistant organisms remain a serious threat to public health in Canada. The results of this survey warrant further investigation into AROs in smaller Canadian hospitals as a potential reservoir of antimicrobial resistance.

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Keywords: point prevalence study, antimicrobial resistance, antimicrobial resistant organisms, *Clostridioides difficile* infection, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, carbapenemase-producing Enterobacterales, *Escherichia coli*, nosocomial infections

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Introduction

Antimicrobial resistance (AMR) is a serious threat to public health, as it erodes the efficacy of commonly used therapies in treating and preventing a wide range of infectious diseases (1). Infections by antimicrobial-resistant organisms (ARO) are associated with increased hospitalization costs, greater disease severity, and poor patient outcomes (2).

Surveillance is a key component to support efforts to reduce the burden of illness associated with AROs. The Canadian Nosocomial Infection Surveillance Program (CNISP) has prospectively monitored healthcare-associated infections (HAI) in larger tertiary care hospitals in major urban areas (3,4), including a subset of infections caused by AROs that have been prioritized by the Public Health Agency of Canada (PHAC) (5). Data on AMR in smaller, non-academic hospitals (often located in community, rural and northern regions) remain limited (3). The Community, Rural, and Northern Acute Care Point Prevalence (CNAPP) survey, administered by PHAC, was designed to assess the burden of AMR and antimicrobial use (AMU) in this underrepresented area of the Canadian healthcare system.

The primary study objective was to describe the prevalence of selected infections in participating hospitals on the date of the point-prevalence survey. Secondary objectives were to describe the prevalence of AMU, screening practices related to AROs and the prevalence of patients under additional infection prevention and control (IPAC) precautions.

Methods

Survey design and sampling

This study was an observational point prevalence study conducted by PHAC. Information was collected on hospital characteristics and de-identified patient information through two respective standardized questionnaires (6), one at the hospital level and one at the patient level. The CNAPP survey was adapted from existing CNISP point prevalence surveys and materials (4). Eligible hospitals were those with fewer than 350 acute care beds. Hospitals that provided only day and overnight surgery, rehabilitation, psychiatric care, paediatric care, palliative care, outpatient clinics, maternity services or long-term care were ineligible to participate. Sites that provided these services in addition to other eligible services were included; however, patients from those ineligible areas were excluded from the hospital census for the purpose of CNAPP. Hospital sites were recruited by convenience sampling using pre-existing professional associations and relationships; efforts were made to recruit representation from all Canadian provinces. Data were collected by nurses, pharmacists, IPAC staff, or infectious disease physicians (based on facility specific availability). Training was provided to all participating sites. The survey was conducted during a 24-hour period between February 1, 2019, and March 30, 2019 (except hospitals in Québec, which conducted the survey between April 1, 2019, and May 31, 2019).

The hospital questionnaire consisted of twelve questions relating to the size and services of the facility, hospital screening practices and antimicrobial stewardship practises (**Supplemental material S1**). Data pertaining to the hospital (hospital questionnaire) and eligible patients (patient questionnaire) were obtained from patient hospital charts, nurses' logs, laboratory reports and administrative systems, or by any other means as seen appropriate by the participating hospital.

The patient questionnaire consisted of eight questions relating to patient demographics, additional IPAC precautions, presence of selected infections (pneumonia, urinary tract infections [UTI], bloodstream infections [BSI], skin/soft tissue infections [SSTI], surgical site infections [SSI] and *Clostridioides difficile* infections [CDI]), presence of selected AROs and antimicrobials prescribed (**Supplemental material S2**).

Setting and participants

All inpatients in acute care units were identified using the hospital census. Patient information was collected over one 24-hour period, starting at 8:00 a.m. on the date of the hospital census and ending at 8:00 a.m. the following day. Data were collected retrospectively to ensure that all patient charts were updated with eligible information (e.g. swabs taken on the date of the survey). The survey collected patient-level data on demographics, transmission-based precautions, presence of specific infections, presence of selected AROs and antimicrobial use. Selected infection types included: pneumonia, UTIs, BSIs, SSTIs, SSIs and CDIs. Definitions for selected infections can be found in **Appendix A1**. An infection was considered to be present if a patient was symptomatic or receiving antimicrobial therapy for the treatment of the infection at the time of the hospital census. As the census day elapses 24 hours (from 8:00 a.m. to 8:00 a.m.), isolates recovered prior to 8:00 a.m. on the day following the census were eligible to be included in the prevalence survey.

The AROs selected for inclusion in the survey were aligned to PHAC priority organisms (5), and included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), extended-spectrum β-lactamase (ESBL)–producing organisms and carbapenemase-producing organisms CPOs. Definitions used in this point-prevalence survey, including those for selected AROs, are the same as those used by CNISP. Detailed case definitions can be found in **Appendix A2**.

This prevalence survey was observational and did not involve any alteration to patient routine care. As such, this study was considered exempt from the requirement for ethics approval as a quality assurance study within the mandate of hospital infection

prevention and control programs or approved by the research and ethics boards at participating hospitals if required by institution-specific policies. A unique encrypted identifier linked to patient name was used to identify patients at the participating hospitals and was not disclosed to PHAC. All data were strictly confidential.

Data analysis

We described the characteristics of participating hospitals and patients that were surveyed, the prevalence of selected infections and selected AROs and AMU. We compared the characteristics of patients with selected infections to those who did not have selected infections, using chi square tests to calculate *p*-values. A bivariate analysis of selected infections and AROs was performed to assess the prevalence of AROs contributing to these infections. Prevalence was calculated as the proportion of patients with an infection/ARO divided by the total population, multiplied by 100. Mean hospital prevalence was calculated as the mean of each individual hospital's prevalence for each infection/ARO; 95% confidence intervals (CI) were calculated for all means and proportions. Data analysis was conducted in Microsoft Excel and SAS EG 7.1 (Cary, North Carolina).

Results

Hospitals

A total of 55 hospitals from 10 provinces with a combined total of 4,159 beds participated in the survey between February 6, 2019, and May 21, 2019. Hospitals in two territories expressed interest in participating but were unable to at the time of the study. Median hospital size was 53 beds (n=5 to 347 beds). While all Canadian provinces were represented in the study, participation varied by province. Facilities in Eastern Canada were, on average, smaller than hospitals in Western and Central Canada. All surveyed hospitals provided medical services, and none provided services for solid organ transplant, bone marrow transplant, paediatric intensive care or burn care. **Table 1** further describes the characteristics of the hospitals that participated in the survey.

Antimicrobial-resistant organism screening practices at admission varied by hospital (e.g. screening all patients as part of admission, screening patients based on risk criteria or only screening patients admitted to medical and surgical wards). All centres performed some screening for MRSA at admission, 78.2% (n=43) for VRE, 70.9% (n=39) for CPOs and only 9.1% (n=5) for ESBL-producing organisms. The ARO screening practices after admission also varied (e.g. screening close contacts of new cases, periodic ward surveys, screening of targeted units). More than two thirds of the participating hospitals screened some patients for MRSA (n=48), VRE (n=39) or CPO (n=38) after admission; however, fewer than one in five (n=9) hospitals screened for ESBL-producing organisms at any

Table 1: Characteristics of participating hospitals (n=55)

Variable	N	%
Provincial distribution		
BC	5	9.1
AB	8	14.6
SK	3	5.5
MB	6	10.9
ON	7	12.7
QC	9	16.4
NB	2	3.6
NS	9	16.4
PE	2	3.6
NL	4	7.3
Regional distribution		
Eastern	17	30.9
Central	16	29.1
Western	22	40.0
Hospital size distribution (number of beds)		
Median	53	N/A
Mean	76	N/A
Range	5–347	N/A
Distribution by availability of services in each facility[a]		
Medical	55	100
Surgical	42	76.4
Obstetrics & gynecology	37	67.3
Paediatric	30	54.6
Dialysis	25	45.5
Rehabilitation	19	34.6
Other[b]	19	34.6
Oncology	18	32.7
LTC	17	30.9
Trauma	12	21.8
ICU, neonatal	7	12.7
Solid organ transplant	0	0
Bone marrow transplant	0	0
Burn unit	0	0
Screening at admission		
MRSA	55	100
VRE	43	78.2
CPO	39	70.9
ESBL	5	9.1

Table 1: Characteristics of participating hospitals (n=55) (*continued*)

Variable	N	%
Screening after admission[c]		
MRSA	48	87.3
VRE	39	70.9
CPO	38	69.1
ESBL	9	16.4
Hospitals with at least one selected ARO infection	25	45.4
MRSA	14	25.5
VRE	2	3.6
ESBL	11	20.0
CPO	0	0

Abbreviations: AB, Alberta; ARO, antimicrobial-resistant organism; BC, British Columbia; CPO, carbapenemase-producing organisms; ESBL, extended-spectrum β-lactamase producing organisms; ICU, intensive care unit; LTC, long-term care; MB, Manitoba; MRSA, methicillin-resistant *Staphylococcus aureus*; N/A, not applicable; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; ON, Ontario; PE, Prince Edward Island; QC, Québec; SK, Saskatchewan; VRE, vancomycin-resistant *Enterococci*

[a] Services available at the facility. As described in the methods, not all services were included in the Community, Rural, and Northern Acute Care Point Prevalence survey

[b] Other includes special care units, psychiatric units, mental health and addictions care, etc.

[c] Includes screening of close contacts of new cases, periodic ward surveys and/or targeted units only

point after admission. The ESBL-producing organisms were the only selected ARO for which more hospitals screened patients during their stay rather than upon admission (Table 1).

At least one patient with an MRSA infection was reported from 14 hospitals (25.5%) and patients with ESBL-producing organisms were reported from 11 hospitals (20.0%). Only two hospitals (3.6%) reported VRE infections and no hospitals reported patients with CPO infection.

Patients

A total of 3,640 patients were identified from hospital census during a 24-hour period between February 6, 2019, and May 21, 2019 (inclusive). A slight majority (52.8%) of those included were female and one third of patients were 65 years of age or older (66.4%). The median patient age was 73 years old, ranging from newborns to 103 years of age. The geographic distribution was similar to that of hospitals, in that the largest proportion came from Western Canada (43.6%). Almost half of patients (47.7%) were located in a medical ward; 19.5% were in a surgical ward and 12.4% were in a mixed medical/surgical ward. **Table 2** further describes the characteristics of the patients that were included in the survey.

Table 2: Patient characteristics (n=3,640)

Characteristics		With selected infections (n=524)	%	Without selected infection (n=3,116)	%	*p*-value	Total population (N=3,640)	%
Region *p*=0.02	Eastern	109	20.80	686	22.02	N/A	795	21.84
	Central	209	39.89	1,048	33.63	N/A	1,257	34.53
	Western	206	39.31	1,382	44.35	N/A	1,588	43.63
Sex *p*=0.81	Male	250	47.71	1,465	47.02	N/A	1,715	47.12
	Female	274	52.29	1,649	52.92	N/A	1,923	52.83
	Other	0	0.0	2	0.06	N/A	2	0.05
Age *p*=0.03	Mean (SD)	67.43 (20.36)	N/A	67.76 (21.69)	N/A	0.75	67.7 years (21.50)	N/A
	Median	72	N/A	73	N/A	N/A	73 years	N/A
	Infants (<1 year)	4	0.76	82	2.63	N/A	86	2.36
	Children (1–17 years)	9	1.72	52	1.67	N/A	61	1.68
	Adults (18–64 years)	172	32.82	903	28.98	N/A	1,075	29.53
	Seniors (>65 years)	339	64.69	2,079	66.72	N/A	2,418	66.43
Location of patient on survey day *p*<0.01	Medical	247	47.14	1,488	47.75	N/A	1,735	47.66
	Surgical	105	20.04	607	19.48	N/A	712	19.56
	Mixed medical/surgical	58	11.07	393	12.61	N/A	451	12.39
	ICU	31	5.92	154	4.94	N/A	185	5.08
	Adult ICU	31	5.92	99	3.18	N/A	130	3.57
	Neonatal ICU	0	0.0	55	1.77	N/A	55	1.51
	Mixed ICU/CCU	0	0.0	34	1.09	N/A	41	1.13
	Hematology/oncology/ bone marrow transplant	15	2.86	40	1.28	N/A	55	1.51
	Paediatrics	13	2.48	71	2.28	N/A	84	2.31
	Coronary care	1	0.19	26	0.83	N/A	27	0.74
	Obstetrics	2	0.38	83	2.66	N/A	85	2.34

Table 2: Patient characteristics (n=3,640) (*continued*)

Characteristics		With selected infections (n=524)	%	Without selected infection (n=3,116)	%	*p*-value	Total population (N=3,640)	%
Location of patient on survey day *p*<0.01	ER	32	6.11	144	4.62	N/A	176	4.84
	Step down unit	4	0.76	12	0.39	N/A	16	0.44
	Other	9	1.72	64	2.05	N/A	73	2.01
Patients prescribed antimicrobials	At least one antimicrobial	505	96.37	776	24.90	<0.01	1,281	35.19
	Multiple antimicrobials	195	37.21	232	7.45	<0.01	427	11.73
Patients on additional IPAC precautions	For any reason	140	26.72	360	11.55	<0.01	500	13.7
	Due to selected ARO	65	12.40	190	6.10	<0.01	255	7.01

Abbreviations: ARO, antimicrobial-resistant organism; CCU, critical care unit; ER, emergency room; ICU, intensive care unit; IPAC, infection prevention and control; N/A, not applicable; SD, standard deviation

One in seven patients (14.4%) had at least one selected infection (n=524). Of these, 27.8% (n=146) were healthcare-associated (4.0% of all patients). Urinary tract infections and pneumonia were the most commonly reported infections (each of them accounting for almost 4.1 per 100 inpatients; 95% CI, 3.4–4.7), while SSI were the least commonly reported (0.8 per 100 inpatients; 95% CI, 0.5–1.1). Considering hospital size, the mean hospital prevalence of selected infections followed a similar distribution to the aforementioned distribution of overall prevalence, with pneumonia having the highest mean hospital prevalence (4.6; 95 % CI, 2.9–6.2), followed by UTIs (4.3; 95 % CI, 3.2–5.3) and SSTIs (3.1; 95 % CI, 2.3–3.9). The SSIs had the lowest mean hospital prevalence (0.7; 95 % CI, 0.4–0.9) (**Table 3**).

Table 3: Mean prevalence of selected antimicrobial resistant organisms and selected infections

Selected infections	N	Proportion of patients (per 100 inpatients)		Mean hospital prevalence	
		n	95 % CI	n	95 % CI
Patients with selected infections					
UTI	149	4.09	3.45, 4.74	4.26	3.20, 5.32
Pneumonia	148	4.07	3.42, 4.71	4.56	2.93, 6.19
SSTI	112	3.08	2.52, 3.64	3.09	2.27, 3.90
BSI	90	2.47	1.97, 2.98	1.67	1.12, 2.23
CDI	34	0.93	0.62, 1.25	1.44	0.0, 3.27
SSI	30	0.82	0.53, 1.12	0.65	0.37, 0.93
Patients with selected ARO infections					
MRSA	18	0.49	0.27, 0.72	0.44	0.19, 0.69
VRE	4	0.11	0.0, 0.22	0.04	0.0, 0.11
ESBL	14	0.38	0.18, 0.59	0.25	0.09, 0.41
CPO	0	0	0	0	0

Abbreviations: ARO, antimicrobial-resistant organism; BSI, bloodstream infection; CDI, *Clostridioides difficile* infection; CI, confidence interval; CPO, carbapenemase-producing organisms; ESBL, extended-spectrum β-lactamase producing organisms; MRSA, methicillin-resistant *Staphylococcus aureus*; SSI, surgical site infection; SSTI, skin/soft tissue infection; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococci*

The characteristics of patients with selected infections were like those who did not have selected infections, except that patients with selected infections were more likely to be prescribed antimicrobials than those who did not have selected infections (96.4% of patients with selected infections compared to 24.9% of patients without selected infections *p*<0.01) (Table 2).

In total, we identified 36 patients with 39 unique infections from which a selected ARO was recovered, for a prevalence of 1.0% of the total patient population (n=36/3,640) and 6.9% of patients with a selected infection (n=36/524). Almost twice as many females as males were affected by these ARO infections. Eighteen patients were infected with MRSA (0.5 per 100 inpatients; 95% CI, 0.3–0.7); of these 18 patients, three were infected at multiple sites, 14 were infected with an ESBL-producing organism (0.4 per 100 inpatients; 95% CI, 0.2–0.6) and four were infected with VRE (0.1 per 100 inpatients; 95% CI, 0.0–0.2). One of the patients infected with VRE had concurrent CDI. No patients were reported to have CPO infections (Table 3).

Five hundred patients were under additional infection prevention and control precautions (13.7% of total patients). Of these 500 patients, 255 (51.0%) were under additional precautions due to an ARO. Patients with a selected infection were more likely to be on additional precautions than those who did not have a selected infection (26.7% compared to 11.6%, respectively, *p*<0.01). This was also true of patients who were on additional precautions due to an ARO (12.4% compared to 6.1%, respectively, *p*<0.01) (Table 2). The most common additional precautions were contact (n=468, 93.6% of patients on additional precautions), followed by droplet (n=157, 31.4%), cohorting (n=9, 1.4%), airborne and other (both n=7, 1.4%). Other precautions encompassed those patients who were placed on additional precautions due to their length of stay or other facility specific policies.

Among all selected infections caused by an ARO, BSIs were most frequent (11.1%; 95% CI, 4.6–17.6), followed by SSTIs (8.9%; 95% CI, 3.6–14.2) and UTIs (8.7% of UTIs; 95% CI, 4.2–13.3) (**Table 4**).

Table 4: Selected antimicrobial resistant organisms by selected infection type[a]

Infection type	Total patients with selected infection	MRSA	VRE	ESBL-producing organisms	CPO	Selected infections caused by (one or more) selected AROs	Selected infections caused by (one or more) selected AROs	
	n	n	n	n	n	n	%	95% CI
UTI	149	1	1	11	0	13	8.7%	4.2–13.3
Pneumonia	148	3	0	1	0	4	2.7%	0.1–5.3
SSTI	112	10	0	0	0	10	8.9%	3.6–14.2
BSI	90	5	3	2	0	10	11.1%	4.6–17.6
SSI	30	2	0	0	0	2	6.7%	0–15.6
CDI	34	N/A	N/A	N/A	N/A	N/A	N/A	N/A

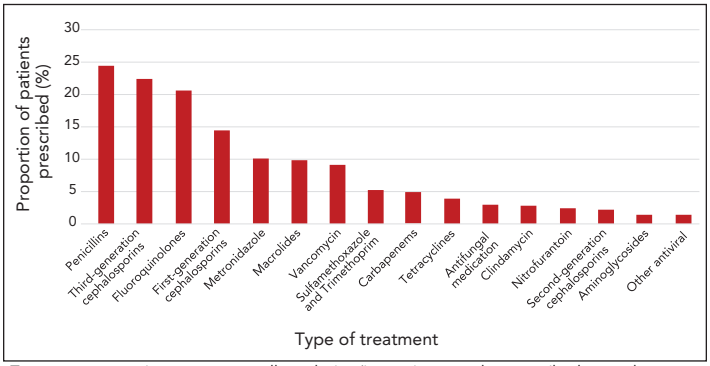
Abbreviations: ARO, antimicrobial-resistant organism; BSI, bloodstream infection; CDI, *Clostridioides difficile* infection; CI, confidence interval; CPO, carbapenemase-producing organisms; ESBL, extended-spectrum β-lactamase producing organisms; MRSA, methicillin-resistant *Staphylococcus aureus*; N/A, not applicable; SSI, surgical site infection; SSTI, skin/soft tissue infection; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococci*

[a] Infection sites were not mutually exclusive (i.e. patients could have multiple selected infections associated with multiple selected AROs): 36 patients had infections with selected AROs, with three patients having AROs in multiple sites (two patients with MRSA BSI and MRSA pneumonia one patient with MRSA BSI and MRSA SSTI)

Antimicrobial use

On the day of the census, 35.2% (95% CI, 33.6–36.7) of patients were being prescribed at least one antimicrobial and 11.7% of patients were being prescribed more than one antimicrobial. Antimicrobial use was most prevalent among the oldest patients. Among patients of all ages who received an antimicrobial, penicillin-class antibiotics were the most prevalent prescriptions (24.4%), followed by third-generation cephalosporins (22.4%), fluoroquinolones (20.6%), first-generation cephalosporins (14.4%), metronidazole (10.1%), macrolides (9.8%) and vancomycin (9.1%). **Figure 1** further describes the prevalence of antimicrobial use in the study population.

Figure 1: Prevalence of treatments[a,b] among patients surveyed (n=1,281)



[a] Treatment categories are not mutually exclusive (i.e. patients can be prescribed more than one antimicrobial)

[b] Other antibiotics, daptomycin, linezolid, other non-antimicrobials, anti-tb medication, aztreonam and colostin were all prescribed for <1% of patients

More than half (60.8%) of AMU was prescribed empirically (without microbiologic laboratory results), compared to 22.8% prescribed as targeted therapy (accompanied by microbiologic laboratory results) and 11.9% as prophylactic therapy. The reason for prescription was unknown for 4.8% of prescriptions.

Among patients with an ARO infection (n=36), penicillins were the most commonly prescribed antimicrobial class (27.8%), followed by carbapenems (19.4%), fluoroquinolones (16.7%), first generation cephalosporins (11.1%) and third-generation cephalosporins (8.3%).

Discussion

We measured the burden of specific infections and selected AROs among small, community hospitals in Canada based on findings from a point prevalence survey administered in 2019. The overall prevalence of infections in our survey was14.4%, while the prevalence of HAIs was 4.0%. This is similar to what has been reported from large tertiary care hospitals by the United States Centers for Disease Control and Prevention (4.0% in 2011 and 3.2% in 2015) (7), and lower than reported from the European Centre for Disease Control and Prevention (7.1% in 2016/2017) (8) and previous CNISP point prevalence surveys (11.3% in 2009 and 7.9% in 2017) (9). Our study showed a CDI prevalence of 0.9 per 100 inpatients. This is consistent with other studies from large Canadian hospitals as well as from hospitals in many other countries (5,10,11). Pneumonia and UTI were the most prominent selected infections in our study. This is similar to what has been reported by point prevalence surveys in larger Canadian tertiary care centres (9), but different from the United States Centers for Disease Control and Prevention, which reported pneumonia and CDI as predominant (7). While BSI were the most common infection caused by AROs in our study, they were the third least common selected infection overall. Bloodstream infections were also less common than other infections in the United States and in larger Canadian tertiary centres (7,9).

Methicillin-resistant *Staphylococcus aureus* was the most common ARO reported in our study, with an infection prevalence of 0.5 per 100 inpatients. This was similar to the MRSA point prevalence reported in 2010, 2012 and 2016 by IPAC Canada point prevalence studies in large hospitals (5). Our study revealed a low ESBL-producing organism infection prevalence of 0.4 per

100 inpatients, which is identical to the mean ESBL prevalence reported by IPAC Canada point prevalence studies in 2012 and 2016 (5). While the prevalence of ESBLs was low in our study, ESBLs remain an important multi-resistant pathogen in hospitals (12) as they are associated with poor patient outcomes, reduced rates of clinical response, longer hospital stays and greater expenses (13). This was followed by VRE, with a prevalence of 0.1 infections per 100 inpatients. No patient in our study was infected with CPO. This is consistent with surveillance data that demonstrated that CPO remained infrequently identified in Canadian hospitals (14). This may indicate that enhanced infection prevention and control methods can still be used to prevent CPOs from being a common healthcare-associated threat in Canada.

The prevalence of AMU in our study was 35.2%, which was slightly lower than what has been reported from larger Canadian hospitals (39.6% [95% CI, 38.7–40.6] in 2017) (15). These surveys reported that the overall prevalence of AMU increased between 2002 and 2009 and stabilized between 2009 and 2017. The prevalence of AMU observed in our study could be due to our patient population. It is possible that patients in smaller community hospitals may have been less acutely ill than those in larger tertiary care centres and therefore required less treatment. Penicillins were the most common drug class prescribed in our study, followed by third-generation cephalosporins, fluoroquinolones, first-generation cephalosporins and carbapenems. This distribution is similar to the distribution of AMU reported from Canadian point prevalence studies (15). There is the potential to improve antimicrobial stewardship programs in smaller facilities given that 60.8% of AMU in our study was prescribed empirically. Potential drivers of the decline/stabilization of AMU that has been observed in larger Canadian hospitals could include the development of antimicrobial stewardship programs, changes to antimicrobial prescribing guidelines and changes in patient populations not captured through current survey methods (15). These same factors can also impact smaller facilities, including those in our study. Our study used bed size as a proxy for hospital size; however, it should be noted that there is no universal or Canadian definition of a small or large hospital. Despite this, the results from our study of smaller hospitals were similar to what has been observed among larger tertiary care centres.

Screening was conducted to identify clients/patients/residents who were colonized and/or infected with specific AROs. The utility of screening and additional precautions must be weighed against the associated increased healthcare costs, morbidity and mortality of the infection. While it is not a control measure on its own, screening is necessary to apply further infection control measures such as placement and precautions (16). In our study, 500 patients (13.7%) were on additional IPAC precautions, and of those, 11.5% were on additional precautions for reasons other than the selected infection types that were under surveillance. Infection prevention and control Canada reported in 2019 that targeted screening was associated with lower rates of MRSA infection (6), and all hospitals in our study screened for MRSA on admission and most also screened during the patient's stay. Our study also demonstrated that 9.1% of hospitals screened for ESBL at admission and 16.4% of hospitals screened during a patient's stay. This is consistent with prior observations that only a minority of hospitals perform active screening for ESBLs (12), as there is a lack of consensus about the value of screening cultures for resistant gram negative bacilli (such as ESBL-producing bacteria) (16). The majority (69%) of hospitals screened for CPO and no infections were identified, which may indicate that current levels of IPAC activities are effective. It could also indicate that those infected with CPO are less likely to be in a smaller community hospital and more likely to be at a larger tertiary care centre. Despite an overall increase in VRE infections in Canada (17) not all hospitals are screening for VRE at admission (5,18), although 71% of the hospitals in our study did so. It is unclear whether all individuals or only high-risk individuals (e.g. surgical patients, intensive care unit patients, patients with a history of colonization) derive more benefit from screening (18). Further, other studies have shown that relaxation of some screening protocols may not lead to increasing infection incidence in a hospital setting, advocating that cost effectiveness exercises, with targeted screening and isolation precautions, are crucial (18,19).

Limitations

The main limitation of this study is that prevalence on a single day does not enable a complete understanding of an ARO's burden and may not be reflective of AMR and AMU time-series trends for each hospital. Furthermore, aggregate infection rates, such as that for pneumonia, may be affected due to seasonal variation. As this study was conducted prior to the coronavirus 2019 pandemic, it is unknown how the changes associated with the pandemic may impact the generalizability of our results. Another limitation of the study is that hospitals were recruited to participate in this study using a convenience sampling method, which can sometimes result in an unrepresentative sample; for example, there was a lack of participation from hospitals located in Canada's three territories. These hospitals may differ from the hospitals that participated in the survey in important ways, thus impacting the generalizability of our results to facilities in those regions. We recommend that future point prevalence studies improve methodologies and recruitment to align with international standards to enhance national representation and international comparability.

Conclusion

These data provide information on the prevalence of resistant infections caused by MRSA, VRE, ESBL-producing organisms and CPOs, as well as CDI, among adult inpatients in smaller, northern and rural Canadian hospitals, and complement information published by a Canadian network of larger tertiary care centres (20). The findings point to the need for continued study of antimicrobial-resistant pathogens in all Canadian healthcare

settings, as rural and community hospitals may represent an important reservoir of AROs.

Authors' statement

ST — Conceptualization of data analysis, interpretation of data, writing of original draft, revision of manuscript, supervision
DGT — Conceptualization of study, design of study
BK — Data analysis, interpretation of data, writing of original draft, revision of manuscript
DS — Revision of manuscript
TL — Revision of manuscript
JM — Writing of original draft, interpretation of data, revision of manuscript
GG — Design of study, revision of manuscript
CF — Design of study, revision of manuscript
KB — Design of study, revision of manuscript
JE — Design of study, revision of manuscript
JH — Design of study, revision of manuscript
JS — Conceptualization of study, revision of manuscript, supervision

Competing interests

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

S1: Hospital survey questions
S2: Patient questionnaire

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Appendix

Appendix A1: Definitions relating to selected infections

Appendix A2: Case definitions relating to selected antimicrobial-resistant organisms

Appendix A1: Definitions relating to selected infections

An infection is considered to be present if a patient is symptomatic or receiving antimicrobial therapy for the treatment of an infection at the time of the hospital census. Isolates recovered by 8:00 a.m. on the date of the census are eligible for the prevalence survey; please allow one week for laboratory follow-up prior to data submission.

Urinary tract infection (UTI)

Patient must meet Criteria 1a and Criteria 1b:

Criteria 1a

The patient has at least one of the following signs/symptoms:

- Fever >38°C (applicable to patients ≤65 years without an indwelling catheter)
- Suprapubic tenderness with no other recognized cause
- Costovertebral angle pain or tenderness with no other recognized cause
- Urinary urgency (applicable to patients without an indwelling catheter)
- Urinary frequency (applicable to patients without an indwelling catheter)
- Dysuria with no other recognized cause

Criteria 1b

- Positive urine culture $\geq 10^5$ CFU/ml with no more than two species of microorganisms identified

Skin and soft tissue infection (SSTI)

Patient must meet Criteria 1a and Criteria 1b:

Criteria 1a

The patient has at least one of the following signs/symptoms:

- Patient has purulent drainage, pustules, vesicles, or boils
- Patient has at least two of the following signs or symptoms with no other recognized cause: pain or tenderness, localized swelling, redness, or heat

Criteria 1b

The patient has at least one of the following:

- Organisms cultured from aspirate or drainage from affected site. Note that normal skin flora must be a pure culture. This includes: Diphtheroids, *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp.
- Organisms cultured from blood
- Positive laboratory test performed on infected tissue or blood (e.g. antigen tests for herpes simplex, varicella zoster, *Haemophilus influenzae*, or *Neisseria meningitidis*)
- Multinucleated giant cells seen on microscopic examination of affected tissue
- Diagnostic single antibody titer (IgM) or four-fold increase in paired sera (IgG) for pathogen

Bloodstream infection (BSI)

Patient must meet Criteria 1; or meet Criteria 2a, Criteria 2b, and Criteria 2c.

Criteria 1

- Recognized pathogen cultured from at least one blood culture, unrelated to infection at another site

Criteria 2a

The patient has at least one of the following:

- Fever >38° (core)
- Chills (applicable to patients aged ≥1 year)
- Hypotension

Criteria 2b

- A common skin contaminant cultured from ≥2 blood cultures drawn on separate occasions. This includes: Diphtheroids, *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp.

Criteria 2c

- Positive laboratory results are unrelated to infection at another site

Surgical site infection (SSI)

Patient must meet Criteria 1a and Criteria 1b.

Criteria 1a

The patient has at least one of the following:

- Surgical procedure in the past 30 days
- Surgical procedure in the past 90 days and had an implantable foreign device permanently placed during the surgery

Criteria 1b

The patient has at least one of the following:

- Purulent drainage from superficial or deep incision
- Organism identified from an aseptically obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for the purposes of clinical diagnosis/ treatment
- At least one of the following pain or tenderness, localized swelling, redness, or heat and incision deliberately opened by surgeon/attending physician and non-culture based testing is not performed Surgeon/attending physician diagnoses
- Spontaneous dehiscence or incision deliberately opened or aspirated by a surgeon/attending physician and organism is identified by a culture or non-culture based method which is performed for purposes of clinical diagnosis and treatment and at least one of the following: fever (>38°), localized pain or tenderness
- Abscess/other evidence of infection involving a deep incision found on gross anatomical oar histopathological examination or imaging test
- Infection involves any part of the anatomy deeper than the fascial/muscle layers that was opened/manipulated during operation and at least one of the following: purulent drainage from a drain placed into organ/space, organisms identified from an aseptically obtained fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for the purposes of clinical diagnosis or treatment, abscess/infection involving organ/space found on gross anatomical or histopathological exam, or imaging test suggestive of infection

Pneumonia (PNEU)

Patient must meet Criteria 1a, Criteria 1b, Criteria 1c, and Criteria 1d. Note that patients without underlying pulmonary or cardiac disease (e.g. respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging test is acceptable.

Criteria 1a

- Fever >38°

Criteria 1b

- Leukopenia (≤4,00 WBC/mm^3) or leukocytosis (≥12,000 WBC/mm^3)

Criteria 1c

Two or more serial chest imaging test results with at least one of the following:

- Infiltrate
- Consolidation
- Cavitation

Criteria 1d

For adults ≥70 years, altered mental status with no other recognized cause, and at least one of the following:

- New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
- New onset or worsening cough, or dyspnea, or tachypnea
- Rales or bronchial breath sounds
- Worsening gas exchange (e.g. O_2 desaturations, PaO_2/ FiO_2 ≤240), increased oxygen requirements, or increased ventilator demand)

Clostridioides (formally *Clostridium*) *difficile* infection (CDI)

Patient must meet Criteria 1a and Criteria 1b; or Criteria 2; or Criteria 3. Note that diarrhea is defined as one of the following: any patient with six or more watery/unformed stools in a 36-hour period; or an adult patient with three or more watery/unformed stools in a 24-hour period that is new or unusual for the patient.

Criteria 1a

- Diarrhea or fever, abdominal pain and/or ileus

Criteria 1b

- Laboratory confirmation of a positive toxin assay or positive polymerase chain reaction for *C. difficile* (without reasonable evidence of another cause of diarrhea)

Criteria 2

- Diagnosis of pseudomembranes on sigmoidoscopy or colonoscopy (or after colectomy) or histological/pathological diagnosis of CDI

Criteria 3

- A diagnosis of toxic megacolon (adult patients only)

Appendix A2: Case definitions relating to selected antimicrobial-resistant organisms

Methicillin-resistant *Staphylococcus aureus* (MRSA)

- Isolation of *Staphycococcus aureus* from any site
- Resistance of isolate to oxacillin

Vancomycin-resistant *Enterococci* (VRE)

- Isolation of *Enterococcus faecalis* or *faecium*
- Resistance of isolate to vancomycin (minimum inhibitory concentration, MIC ≥8 ug/m)

Extended-spectrum beta-lactamase-producing bacteria (ESBL)

Definitions are given for *Escherichia coli* and *Klebsiella pneumoniae*. Additional ESBLs are to be defined by the reporting facility and indicated as an ESBL on the patient form.

- Isolation of *Escherichia coli* or *Klebsiella pneumoniae* from any site
- MIC testing: a decrease of >3 doubling dilutions in an MIC for either cefotaxime or ceftazidime tested in combination with 4 µg/ml clavulanic acid, versus its MIC when tested alone
- Disk diffusion testing: a ≥5 mm increase in a zone diameter for either antimicrobial agent tested in combination with clavulanic acid versus its zone when tested alone

Carbapenemase-producing organisms (CPOs): *Enterobacteriaceae* spp. and *Acinetobacter* spp.

All *Enterobacteriaceae* spp. and *Acinetobacter* spp. that demonstrate resistance to carbapenem-class antimicrobials (defined below) should be investigated for the production of carbapenemase.

Carbapenem-resistance is defined as:

- *Enterobacteriaceae* carbapenem-resistant organism (CRO):
  - Imipenem, meropenem, or doripenem resistance: (MIC ≥2 µg/ml) or (≤22 mm disk diffusion)
  - Ertapenem resistance: (MIC ≥1 µg/ml) or (≤21 mm disk diffusion)
- *Acinetobacter* CRO:
  - Imipenem or meropenem resistance: (MIC ≥8 µg/ml) or (≤15 mm disk diffusion)

Carbapenemase-producing organism (CPO):

- Organisms (e.g. *Enterobacteriaceae* spp. and *Acinetobacter* spp.) identified as a CPO must meet hospital or provincial definitions. CPOs do not need to meet the CRO definitions, above, and supersede CRO status if applicable

Antimicrobial susceptibilities of *Neisseria gonorrhoeae* in Canada, 2020

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Abstract

Background: The Gonococcal Antimicrobial Surveillance Programme is a passive surveillance system that has monitored antimicrobial resistance in *Neisseria gonorrhoeae* in Canada since the 1980s. This article summarizes the demographics, antimicrobial resistances and NG-MAST (*N. gonorrhoeae* multiantigen sequence typing) for cultures collected in 2020.

Methods: The National Microbiology Laboratory (NML) in Winnipeg received resistant *N. gonorrhoeae* cultures from provincial and territorial public health laboratories. Agar dilution was used to determine the minimum inhibitory concentrations to ten antimicrobials for all cultures received at NML, according to Clinical and Laboratory Standards Institute guidelines. The NG-MAST typing was also determined for each culture.

Results: A total of 3,130 *N. gonorrhoeae* cases were cultured across Canada in 2020; a 36% decrease from 2019 (n=4,859). The level of decreased susceptibility to cefixime increased significantly between 2016 and 2020 to 2.8% (p=0.0054). Decreased susceptibility to ceftriaxone declined significantly between 2016 (1.8%) and 2020 to 0.9% (p=0.001), and there was no significant change with azithromycin between 2016 (7.2%) and 2020 (6.1%). The proportion of cultures with an azithromycin minimum inhibitory concentrations of ≥1 mg/L increased significantly from 11.6% in 2016 to 15.3% in 2020 (p=0.0017). The most common NG-MAST type in Canada for 2020 was sequence type (ST)-11461, while ST-12302 was most commonly associated with azithromycin resistance and ST-16639 with cephalosporin decreased susceptibility.

Conclusion: Antimicrobial resistance in *N. gonorrhoeae* remains an important public health concern and continued surveillance is imperative to monitor trends to ensure the recommended therapies will be the most effective.

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Introduction

Neisseria gonorrhoeae is the causative agent of gonorrhoeae, which is the second most reported bacterial sexually transmitted infection (STI) in Canada. In 2019, there were 35,443 cases reported in Canada; more than double the number of cases reported in 2014 (1). Similarly, the incidence of infections has increased from 45.9/100,000 to 94.3/100,000 during that timeframe (2).

Due to the ability of *N. gonorrhoeae* to evolve and develop resistance to antimicrobials that are used to treat infections, the World Health Organization released a global action plan to control the spread and impact of antimicrobial resistance (AMR) *N. gonorrhoeae* in 2012 and the Canadian Antimicrobial Resistance Surveillance System advised caution with regards to multidrug-resistant gonorrhea in 2020 (3–5). Of particular concern are isolates with either decreased susceptibility to third-generation cephalosporins or resistance to azithromycin, which are part of the currently recommended treatment regimen of ceftriaxone (250 mg intramuscularly plus azithromycin 1 g orally) (6). In Canada, there were two cases of cephalosporin-resistant *N. gonorrhoeae* between 2017 and 2020 and several cases of high-level azithromycin resistance (1,7,8).

Since the 1980s, the Gonococcal Antimicrobial Surveillance Programme has run as a passive national surveillance program. Isolates that are submitted to this program undergo antimicrobial susceptibility testing and are characterized using *N. gonorrhoeae* multiantigen sequence typing (NG-MAST). The NG-MAST uses highly variable regions of the *porB* gene (PIB porin) and the *tbpB* gene (subunit B of transferrin-binding protein) alleles for molecular epidemiology of *N. gonorrhoeae*. The NG-MAST is a molecular typing method and can be used in outbreak investigations and to support treatment failure investigations. It has also shown a close association between a subset of sequence types (STs) and antimicrobial resistance, including azithromycin resistance and ST-12302 in Canada (9–11).

Gonorrhea most often presents as urethritis in males and cervicitis in females, though females are more likely to be asymptomatic (12). If cases of gonorrhoea are untreated, the bacterium can enter the blood and other sterile sites causing disseminated gonococcal infections (DGI). While uncommon, DGI cases can have severe morbidity, causing arthritis, dermatitis, migratory polyarthralgia, tenosynovitis and, in rare cases, endocarditis (13,14).

Antimicrobial resistant *N. gonorrhoeae* is continually evolving and new resistances can rapidly emerge. Continued surveillance of antimicrobial susceptibility and STs of *N. gonorrhoeae* is necessary to identify clusters, inform treatment guidelines and mitigate the impact of resistant gonorrhea. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which was declared by the World Health Organization in early 2020, decreased the testing capacity of laboratories across Canada for *N. gonorrhoeae* culture; the number of isolates analyzed compared to previous years greatly decreased. This article summarizes the antimicrobial susceptibility trends and sequence typing of *N. gonorrhoeae* cultures in Canada for 2016–2020.

Materials and methods

Surveillance

Surveillance of *N. gonorrhoeae* AMR in Canada consists of a voluntary passive laboratory system where provincial and territorial partners send *N. gonorrhoeae* cultures to the National Microbiology Laboratory (NML). Isolates cultured between January 1 and December 31, 2020, were received from Alberta, British Columbia, Manitoba, New Brunswick, Northwest Territories, Nova Scotia, Ontario, Québec and Saskatchewan. In 2020, a total of 3,130 *N. gonorrhoeae* isolates were cultured in Canada: 1,628 viable cultures that were resistant to at least one antibiotic were submitted to NML for antimicrobial susceptibility testing and molecular typing; 1,089 cultures were tested by provincial and territorial laboratories and antimicrobial susceptibility testing results were submitted to NML. The remaining 413 presumed susceptible cultures that were tested by provincial and territorial laboratories in 2020 were not submitted to NML but were included in the final denominator used throughout this article. The total number of cultures from each province or territory and the number of cultures with resistance to at least one antimicrobial are given in **Table S1**. The main denominator used throughout this article is 3,130, unless otherwise noted.

Isolate testing

All *N. gonorrhoeae* cultures received by NML (n=1,628) were tested for antimicrobial susceptibility using the agar dilution method to determine their minimum inhibitory concentrations (MICs) for ten antimicrobials (penicillin, tetracycline, erythromycin, spectinomycin, ciprofloxacin, ceftriaxone, cefixime, azithromycin, ertapenem and gentamicin). Interpretation of results are made in accordance with the Clinical and Laboratory Standards Institute, except for ceftriaxone and cefixime, which used the World Health Organization guidelines and erythromycin, ertapenem and gentamicin, which were based on publications (4,15–19). Penicillin, tetracycline, erythromycin and azithromycin were all resistant at a MIC ≥2 mg/L. Ciprofloxacin was resistant at a MIC of at ≥1 mg/L, gentamicin at a MIC of ≥32 mg/L, and spectinomycin at a MIC of ≥128 mg/L. Ceftriaxone has decreased susceptibility at a MIC ≥0.125 mg/L, cefixime has decreased susceptibility at a MIC of ≥0.25 mg/L, and ertapenem is non-susceptible at ≥0.063 mg/L (**Table S2**). Additional testing for the presence of β-lactamase was performed on all cultures received by NML and polymerase

chain reaction detection of the *tetM* plasmid was done when tetracycline MICs were ≥16 mg/L. Isolates were categorized as susceptible, resistant, multidrug-resistant (MDR; either decreased susceptibility or resistance to one recommended therapy plus at least two other antibiotics) or extensively drug-resistant (XDR; decreased susceptibility/resistance two currently recommended therapies plus resistance to at least two other antibiotics).

Cultures were also analyzed for molecular genotyping using NG-MAST (10). Sanger sequencing of both strands were assembled using SeqMan Pro 15 (DNAStar, Madison, Wisconsin, United States). Sequences were submitted to the PubMLST *Neisseria* spp. database to determine STs. Due to the decommissioning of the previous NG-MAST website (http://www.ng-mast.net), which resulted in the deletion of several thousand previously identified STs, some of the STs in this article contain updated allelic profiles from previous years.

Data analysis

Demographic information submitted with the *N. gonorrhoeae* isolates included age, sex, isolation site, province and date of collection. Multiple isolates collected from the same patient within four weeks and with the same NG-MAST ST were considered to be duplicates. Determination of the isolate to be deemed a duplicate was based on a hierarchy of isolation sites, with isolates taken from a sterile site being first priority for inclusion (and marked as DGI), a throat isolate being second priority, followed by rectum, then the urogenital tract. For each figure, the denominator used is included in the footnote(s). The AMR trends for azithromycin, cefixime and ceftriaxone were analysed at both the provincial or territorial level and at the national level, while the correlation of the most common NG-MAST STs with AMR is also examined. Statistical significance of trends was assessed using the Cochran Armitage test of trend, with a *p*-value of <0.05 considered significant.

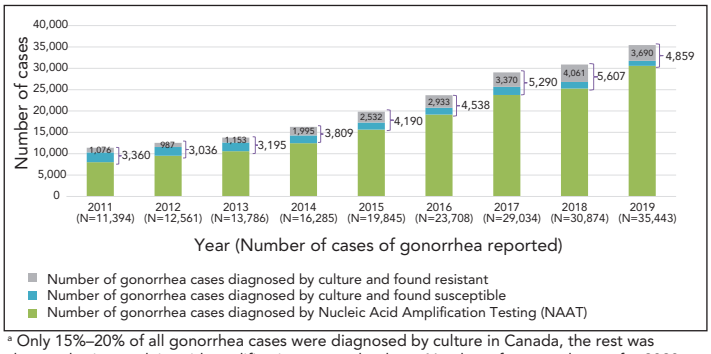
Results

Isolates tested, demographics and isolation sites

Of the 3,130 isolates from across Canada in 2020, 70.1% had resistance to at least one antimicrobial (Table S1). In Canada over 80% of gonorrhoea cases were diagnosed using nucleic acid amplification tests (**Figure 1**), while the remaining ~20% cases were cultured (20). The technology for the prediction of antimicrobial susceptibility from a nucleic acid amplification test is complex and is currently offered as a laboratory-developed test by some research and reference laboratories, but the current gold standard requires culture.

In 2020, of those cultures sent to NML (n=2,679), 70.2% (n=1,880/2,679) came from individuals between the ages of 21 and 40 years, 21.9% (n=586/2,679) from individuals 41 years of age and older and 7.9% (n=213/2,679) from individuals younger than 21 years of age. The majority of isolates (82.9%; n=2,220/2,679), came from males, 16.6% (n=446/2,679) from females and 0.5% (n=13/2,679) came from either gender diverse or patients whose gender was not given. Most common overall isolation site for males was penis/urethra (60.9%, n=1,352/2,220) while for females it was the throat (32.1%, n=143/446). For more details on ages of patients and isolation sites see **Table S3**.

Figure 1: *Neisseria gonorrhoeae* cases in Canada, 2011 to 2019[a]

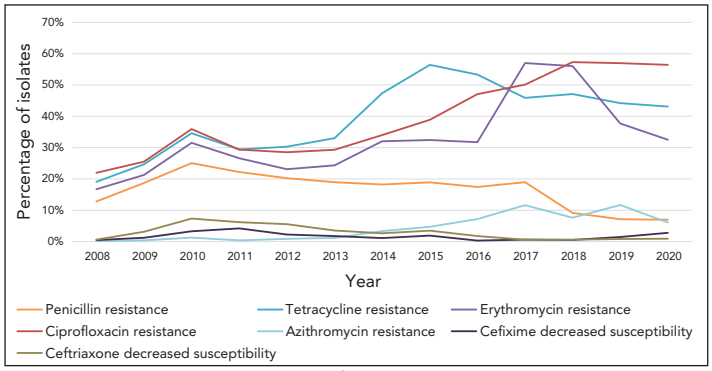


[a] Only 15%–20% of all gonorrhea cases were diagnosed by culture in Canada, the rest was detected using nucleic acid amplification test technology. Number of reported cases for 2020 had not yet been determined at the time of publication

Antimicrobial resistance trends in antimicrobials not included in the recommended treatment guidelines 2016–2020

National trends of gonococcal antimicrobial susceptibilities for 2008–2020 indicated that of the antimicrobials that were not currently part of the recommended treatment regimens, ciprofloxacin was the only one to have seen a continuing increase in the level of resistance in recent years, increasing from 22.0% in 2008 to 56.5% in 2020. Penicillin resistance peaked in 2010 at 25.1% but fell to 7.0% in 2020. Tetracycline resistance decreased from 56.4% in 2015 to 43.1% in 2020. Erythromycin resistance fell from its peak at 57.0% in 2017 to 32.5% in 2020 (**Figure 2**).

Figure 2: Percentage of antimicrobial resistance of *Neisseria gonorrhoeae* tested in Canada, 2008–2020[a,b]



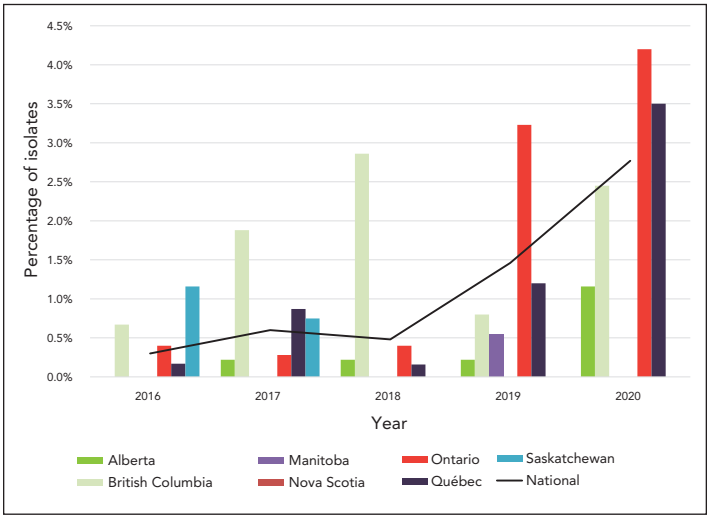
[a] Percentages are based on the total number of isolates tested nationally: 2008=3,907; 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607; 2019=4,859; 2020=3,130

[b] Due to some provinces not testing all seven antimicrobials in 2017, 2018 and 2019 penicillin denominators were 3,267, 3,883, 3,822 and 2,409, respectively; erythromycin denominators were 2,879, 3,418, 3,446 and 2,025, respectively; and tetracycline denominator in 2020 was 2,409

Cefixime antimicrobial resistance in Canada, 2016–2020

Cefixime decreased susceptibility (CeDS, MIC ≥0.25 mg/L) has seen a significant increase (p=0.0054) from 0.30% in 2016 to 2.8% in 2020, which is almost double from 1.5% in 2019 (**Figure 3**). The proportion of strains with higher MICs (≥0.25 mg/L) increased significantly during this timeframe as well (p=0.0054), see **Table S4** for complete break down of the proportion of MICs. The MDR strains with CeDS also increase significantly (p<0.0001) (**Figure S1**).

Figure 3: Percentage of *Neisseria gonorrhoeae* cultures with decreased susceptibility to cefixime by province, 2016–2020[a,b]



[a] Provinces included in this figure are only those that submitted at least one culture to the National Microbiology Laboratory that had decreased susceptibility to cefixime
[b] Denominators used for the calculations of the percentages are the number of cultures tested in each province (data in Table S1)

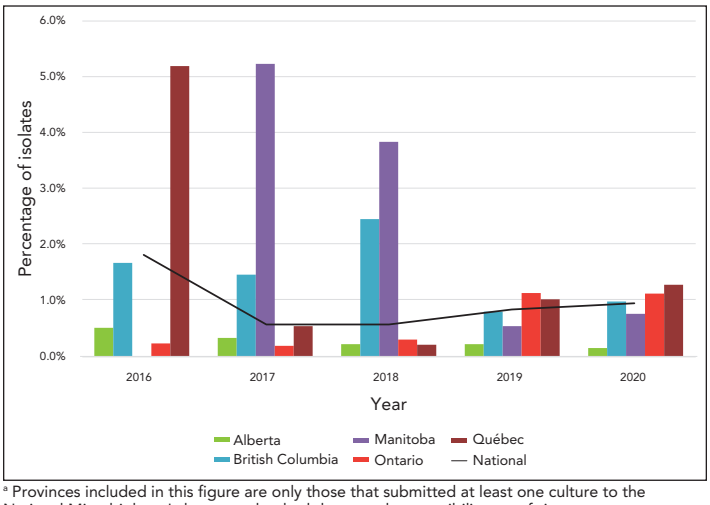
Ceftriaxone antimicrobial resistance in Canada, 2016–2020

Ceftriaxone decreased susceptibility (CxDS, MIC ≥0.125 mg/L) decreased significantly, falling from 1.8% in 2016 to 0.9% in 2020 (p=0.001) (**Figure 4**). The proportion of MDR isolates with CxDS decreased significantly (p<0.0001) as well, from 18.2% in 2016 to 4.6% in 2020. The proportion of MDR isolates with both CeDS and CxDS increased significantly (p<0.0001) (Figure S1) from 1.2% in 2016 to 10.0% in 2020.

Azithromycin antimicrobial resistance in Canada, 2016–2020

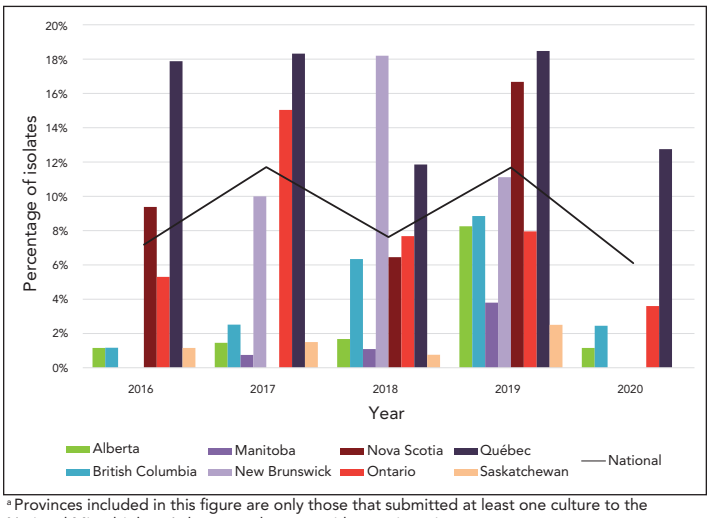
Azithromycin resistance (AziR) did not change significantly from 2016 to 2020 for cultures that had a MIC ≥2 mg/L as shown in **Figure 5**. For cultures that had a MIC ≥1 mg/L, there was a significant increase (p=0.0017) from 11.6% in for 2016 to 15.3% in 2020 (**Figure 6**).

Figure 4: Percentage of *Neisseria gonorrhoeae* cultures with decreased susceptibility to ceftriaxone by province, 2016–2020[a,b]



[a] Provinces included in this figure are only those that submitted at least one culture to the National Microbiology Laboratory that had decreased susceptibility to ceftriaxone
[b] Denominators used for the calculations of the percentages are the number of cultures tested in each province (Table S1)

Figure 5: Percentage of azithromycin-resistant *Neisseria gonorrhoeae* cultures by province, 2016–2020[a,b]

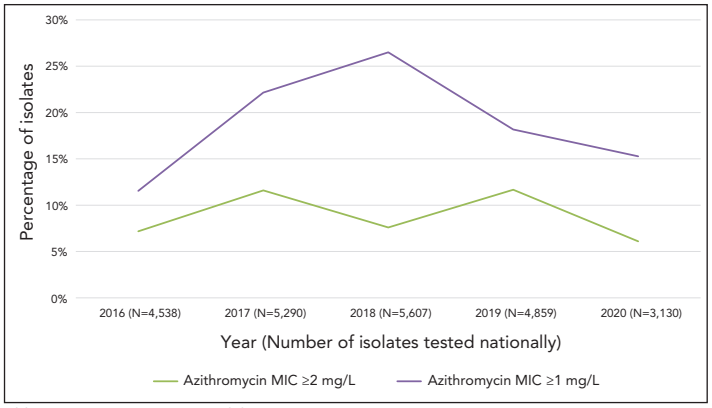


[a] Provinces included in this figure are only those that submitted at least one culture to the National Microbiology Laboratory that was azithromycin resistant
[b] Denominators used for the calculations of the percentages are the number of cultures tested in each province (Table S1). Newfoundland and Labrador had one azithromycin resistant isolate in 2019

The number of MDR cultures that were AziR increased significantly from 78.3% in 2016 to 97.0% in 2020 (p<0.0001) (Figure S1). Between 2016 and 2020, there was a significant decrease in the number of MDR cultures (p=0.0117) from 8.9% to 6.3% (**Figure S2**). There was no significant change in the number of XDR cultures between 2016 (n=1) and 2020 (n=2) (**Figure S3**). A full list of all XDR cases found in Canada is given in **Table S5**.

Within Canada over the past five years there has been a significant increase (<0.0001) in DGI cases from 0.03% (n=6/23,708) in 2016 to 0.20% (n=71/35,443) in 2020.

Figure 6: Trends the percentage of azithromycin minimum inhibitory concentrations for *Neisseria gonorrhoeae* at the susceptibility breakpoint[a]

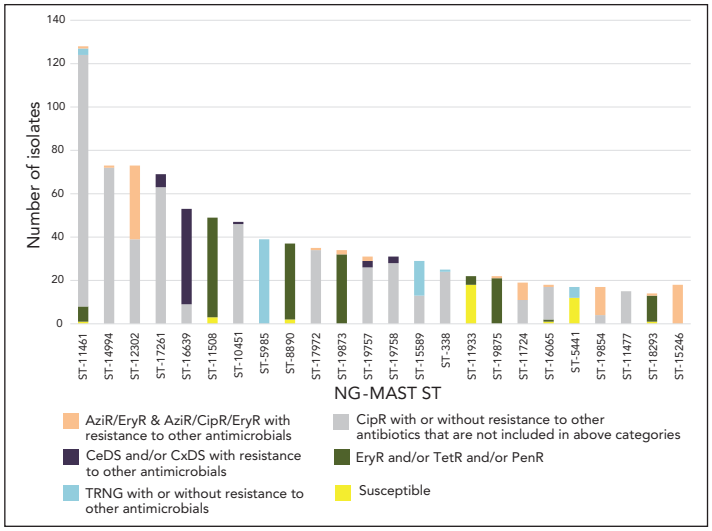


Abbreviation: MIC, minimum inhibitory concentration
[a] Denominators used for the calculations of the percentages are the number of cultures tested in each province (Table S1). Disseminated gonococcal infections cases in Canada, 2016–2020

NG-MAST sequence type trends in Canada, 2016–2020

In total, 1,590 cultures were successfully typed for NG-MAST in 2020. The most frequently detected NG-MAST sequence type in Canada was ST-11461 (n=128), followed by ST-14994 (n=73) and ST-12302 (n=73). As shown in **Figure 7**, ST-12302, ST-11724, ST-19854 and ST-15246 all have high proportions of the cultures that are AziR. The ST-16639 has a high proportion of cultures with either CeDS or CxDS. The number of isolates for each ST that were from each province and territory is shown in **Figure S4**, while **Figure S5** shows the trends of some common STs over time. Of note is the sharp decrease in the number of ST-12302 and ST-14994 in 2020 (Figure S5).

Figure 7: Distribution of resistance characterization within *Neisseria gonorrhoeae* NG-MAST sequence types, 2020, n=1,590[a]



Abbreviations: AziR, azithromycin resistance; CeDS, cefixime decreased susceptibility; CipR, ciprofloxacin resistance; CxDS, ceftriaxone decreased susceptibility; EryR, erythromycin resistance; NG-MAST, *N. gonorrhoeae* multiantigen sequence typing; ST, sequence type; PenR, penicillin resistant; TerR, tetracycline resistant; TRNG, tetracycline resistant *Neisseria gonorrhoeae*
[a] Does not include nine isolates that were non-typeable. This graph represents 915 isolates. The remaining 674 isolates are dispersed among 279 sequence types containing one to 14 isolates each

Discussion

On March 11, 2020, the World Health Organization declared the outbreak of the coronavirus, SARS-CoV-2, a global pandemic (21,22). This global emergency had a cascading effect on all aspects of public health and infectious disease surveillance. From the laboratory perspective, due to the redistribution of laboratory personnel in response to the SARS-CoV-2 pandemic, STI laboratory testing numbers dropped dramatically across Canada, with multiple jurisdictions suspending their STI testing entirely at times throughout 2020 (22,23). This redistribution of labour led to a decrease in the total number of *N. gonorrhoeae* cultures collected in public health laboratories across Canada by 36% between 2019 and 2020; from 4,859 cultures in 2019 to 3,130 in 2020 (Table S1). While the number of reported gonorrhea cases in Canada in 2020 has not yet been reported, multiple countries have reported estimates on 1) the impact on surveillance of gonorrhea AMR, 2) adherence to recommended treatment guidelines and 3) under-reporting of cases of STIs in 2020 due to the lockdowns and reassignment of laboratory staff (24–26). The full effect of the SAR-CoV-2 pandemic on the surveillance of *N. gonorrhoeae* AMR will not be fully known for several years (27).

Decreased susceptibility to cefixime had been declining in Canada and Europe since the early 2010s (28–30). While more recent data from Europe has not yet been published, Canada has seen a rapid and significant increase in the level of gonococcal isolates with CeDS since 2018 (Figure 3). What is driving this increase is unclear, although there has been an increase in ST-16639, and the majority of these cultures have a cefixime MIC ≥0.25 mg/L. This ST was first detected in Canada in 2019 (n=38) and increased in 2020 (n=53). This trend in ST-16639 isolates should be carefully monitored going forward to inform public health actions.

Another factor that could be contributing to this increase in CeDS is a possible increase in the use of oral therapy, specifically using the combination therapy of 800 mg cefixime plus 1 g azithromycin during the various lockdowns that occurred across Canada in 2020. Because cefixime is an oral medication (versus the intramuscular injection delivery required for ceftriaxone) it is simpler for delivery to patients during times of limited health services and telehealth appointments.

The national level of AziR in Canada did not differ significantly between 2017 and 2020, although there was some variability from year to year. Part of this annual variability is due to geographical variability in AziR, with some regions having now updated their treatment protocols in response to these data (31). The effects of these updated treatment recommendation on the AziR rates in those regions will be determined with continued surveillance. Much of the increase in AziR levels between 2013 and 2018 was driven by ST-12302, which has a strong association with low-level resistance to azithromycin (11). Since 2017, the

number of ST-12302 cultures sent to NML has decreased steadily, which could be a factor in the plateauing of AziR.

While the percentage of cultures with azithromycin MICs at or above the break point of 2 mg/L has remained steady since 2017, the number of *N. gonorrhoeae* cultures with a MIC of 1 mg/L has increased significantly during that time (Figure 6). The cause of this shift is unclear, though in NML's whole genome sequencing data, when looking at the single-nucleotide polymorphisms that are associated with AziR, many strains contain the mosaic *mtrR* promoter, which is associated with decreased susceptibility to azithromycin in *N. gonorrhoeae* (32). While there is potentially an ongoing shift in azithromycin MIC in Canada, being driven by the prominence of the mosaic *mtrR* promoter, other jurisdictions, most notably Australia, have set their breakpoint for azithromycin at 1 mg/L, which is also the epidemiological cut-off value from European Committee on Antimicrobial Susceptibility Testing (33,34). While Canada has not seen an increase in reported treatment failures for gonorrhea, due to dual therapy being the recommended treatment method, this rise in azithromycin MIC 1 mg/L is of concern and should be monitored.

Since 2016, there has been a national increase in the number of DGI cases. While this increase is uneven across Canada, more emphasis on detection, investigation and culturing of these cases should be made. What differentiates an uncomplicated *N. gonorrhoeae* infection from one that becomes a DGI is still unclear, although there is some evidence that it is linked to certain *N. gonorrhoeae* virulence factors, particularly *porB* protein structures type "A", due to its role in the interaction of the complement system (35). This can lead to the ability of *N. gonorrhoeae* to spread to sterile sites throughout the body, which can cause far greater morbidity. Provinces and territories across Canada should consider more closely monitoring and tracking these serious cases.

Limitations

An important limitation to consider when interpreting the data presented in this article is that submission of isolates is voluntary and is not standardized across the country; therefore, the overall interpretation of the results is difficult due to the limitations related to the isolates available for testing. Only a subset of laboratory isolates from each province may have been submitted for testing; thus, this article does not reflect true incidence or rates of antimicrobial resistance in Canada.

Due to the SAR-CoV-2 pandemic and the reallocation of laboratory resources that followed, there was a decrease in the number of *N. gonorrhoeae* cultures that were grown across Canada and submitted to NML. This might have led to some trends being over- or under-reported due to the differing surveillance capabilities in each of the provinces and territories throughout the pandemic.

Conclusion

Though the number of isolates collected decreased in 2020 in comparison to previous years, *N. gonorrhoeae* AMR remains an important public health concern. In the past five years, there has been a significant increase in the proportion of cultures with decreased susceptibility to cefixime, a significant increase in the number of DGI cases across the country, and a change in the most prevalent NG-MAST ST. Significant changes were not seen with antimicrobials. Continued surveillance of *N. gonorrhoeae* AMR in Canada is imperative to monitor these trends, as well as to detect clonal outbreaks, to identify new or emerging types of antimicrobial resistance and to help to ensure that national treatment guidelines will continue to advise effective treatment regimens. Enhancing surveillance to include linked epidemiological and laboratory data would address the limitations regarding data representativeness and interpretation in the current passive surveillance system. The Enhanced Surveillance of Antimicrobial Resistant Gonorrhea was initiated in 2014 and has been implemented to fill this gap.

Authors' statement

RT — Formal analysis, validation, investigation, data curation, visualization, writing–original draft, review and editing of final version
PS — Formal analysis, validation, investigation, data curation, visualization
BL — Resources, methodology, writing–review and editing
MD — Resources, methodology, writing–review and editing
LH — Resources, methodology, writing–review and editing
SP — Resources, methodology, writing–review and editing
PVC — Resources, methodology, writing–review and editing
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None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

Table S1: Summary of the *Neisseria gonorrhoeae* cultures, submitted antimicrobial resistance testing results, and laboratory data received by the National Microbiology Laboratories from participating provinces and territory, 2016–2020
Table S2: *Neisseria gonorrhoeae* agar dilution antimicrobial testing ranges and minimum inhibitory concentration interpretations
Table S3: Age of patient and isolation site of the *Neisseria gonorrhoeae* cultures tested at the National Microbiology Laboratory, 2020 (n=2,679)
Table S4: Cefixime susceptibilities of *Neisseria gonorrhoeae* isolates tested by the National Microbiology Laboratory, 2016–2020
Figure S1: Percentage MDR-GC cultures in Canada between 2016 and 2020 broken down by whether they are resistant to azithromycin or if they have decreased susceptibility to either cefixime or ceftriaxone
Figure S2: Trends of multi-drug resistant *Neisseria gonorrhoeae* in Canada from 2016 to 2020
Figure S3: Trends of extensively drug-resistant *Neisseria gonorrhoeae* in Canada from 2016 to 2020
Table S5: All extensively drug-resistant *Neisseria gonorrhoeae* strains isolated in Canada (N=29)
Figure S4: Provincial distribution within *Neisseria gonorrhoeae* NG-MAST sequence types, 2020 (N=1,590)
Figure S5: Trends of prevalent NG-MAST sequence types of *Neisseria gonorrhoeae* isolates tested by the National Microbiology Laboratory, 2016–2020

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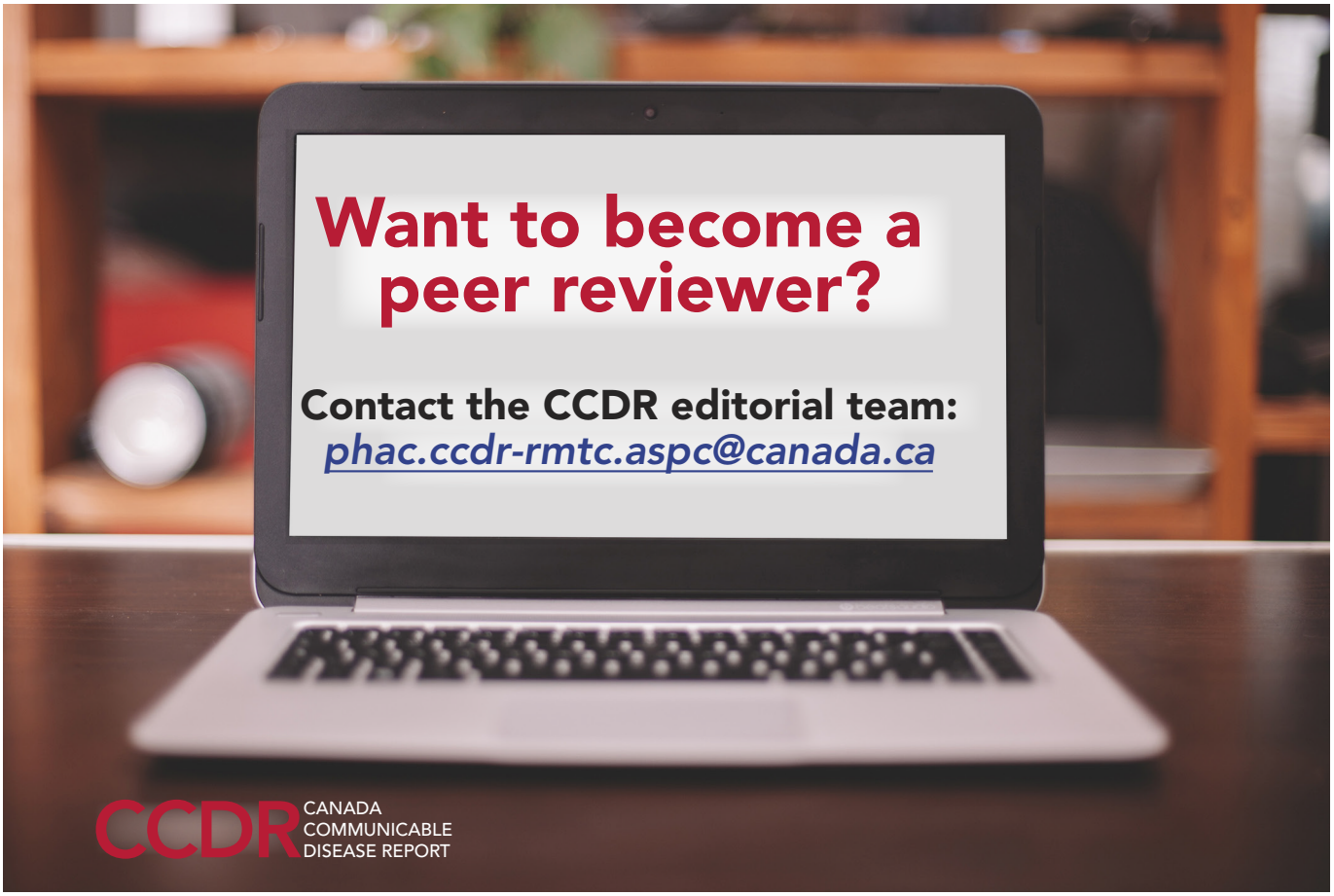

Summary of the National Advisory Committee on Immunization (NACI) Rapid Response: Updated interim guidance on Imvamune in the context of ongoing monkeypox outbreaks

Nicole Forbes[1], Oliver Baclic[1], Robyn Harrison[2], Nicholas Brousseau[3] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: During the period of monkeypox community transmission and restricted vaccine supply in the summer of 2022, Canadian provinces and territories and a number of vaccine stakeholders indicated the need for consistent national guidance on pre-exposure vaccination (including the identification of priority populations for pre-exposure vaccination programs) and guidance on the potential use of dose-sparing strategies.

Methods: The National Advisory Committee on Immunization (NACI) High Consequence Infectious Disease Working Group reviewed data on the status of the monkeypox outbreak along with additional published and non-published evidence regarding the safety, immunogenicity and protection offered by Imvamune®. NACI approved updated recommendations on September 16, 2022, and on September 23, 2022 it released updated interim guidance on the use of Imvamune in the context of the ongoing monkeypox outbreak.

Results: During periods of adequate vaccine supply, NACI recommended that Imvamune pre-exposure vaccination should be offered as a two-dose primary series, with at least 28 days between the two sub-cutaneous doses. When supply is limited, guidance was provided for the use of dose sparing strategies, including extended dosing intervals and fractional intradermal dosing to maximize vaccine coverage for those at highest risk of exposure to the monkeypox virus.

Conclusion: The updated NACI recommendations provide additional guidance on the use of Imvamune for the management of the 2022 monkeypox outbreak in Canada and may be considered to maximize vaccine coverage in outbreak settings when supply is limited.

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Introduction

On June 10, 2022, in the context of a rapidly evolving monkeypox outbreak, National Advisory Committee on Immunization (NACI) provided options for the use of the Imvamune® vaccine (Modified vaccinia Ankara Bavarian Nordic; MVA-BN) for post-exposure vaccination against monkeypox (1). NACI recommended that a single dose of the Imvamune vaccine may be offered to people with high-risk exposures to a probable or confirmed case of monkeypox, or within a setting where transmission is happening; a second dose could be offered after 28 days only if an assessment indicated an ongoing risk of exposure (1).

Canadian jurisdictions experiencing ongoing monkeypox outbreaks built on the foundation of the early NACI guidance on the use of Imvamune. Specifically, jurisdictions with active monkeypox outbreaks expanded eligibility for Imvamune vaccine administration beyond post-exposure use based in part on the limited feasibility of case and contact identification with this outbreak.

The Public Health Agency of Canada (PHAC), together with the provinces and territories, identified the need for national guidance on pre-exposure vaccination, including identification of priority populations for pre-exposure vaccination programs and guidance on the potential use of dose-sparing strategies (i.e. extended dosing intervals and/or fractional intradermal dosing).

The 2022 monkeypox outbreaks in Canada, the United States and Europe have primarily affected men who identify as men who have sex with men (MSM) and who have reported recent sex with one or multiple partners (2). The majority of cases reported no contact with a person known to have a confirmed monkeypox infection (3–5). The severity of disease reported in the 2022 Canadian outbreaks has been generally low, with fewer reported hospitalizations, intensive care unit (ICU) admissions and deaths (case fatality rate of less than 0.1%) compared with historical outbreaks (5–8). At least 25% of cases were reported to have a concomitant sexually transmitted infection (3,7,9–11).

For the purposes of the NACI Statement, MSM is defined as: man or Two-Spirit identifying individual who has sex with another person who identifies as a man, including but not limited to individuals who self-identify as transgender, cis-gender, Two-Spirit, gender-queer, intersex and non-binary and who also identify as gay, bisexual or pansexual.

Methods

On August 22, 2022, the NACI High Consequence Infectious Disease Working Group (HCID WG) was convened to discuss and review data on the evolving monkeypox outbreak. Input was sought from and provided by the Public Health Ethics Consultative Group, Canadian Immunization Committee, NACI's Vaccine Safety Working Group and the National Emergency Strategic Stockpile. That same date, Montréal Public Health and Ontario Ministry of Health presented emerging evidence on the ongoing monkeypox outbreaks, including epidemiological trends and Imvamune vaccine programs to the HCID WG. Three groups representing 2SLGBTQI+ communities and one group representing sex workers were consulted to provide stakeholder input on the acceptability of vaccine strategies.

The HCID WG reviewed data on the current status of the monkeypox outbreak in Canada and globally, along with additional evidence included in published scientific literature and from the manufacturer, regarding the safety, immunogenicity and protection offered by Imvamune. Modelling information provided by PHAC on the impact of dose sparing strategies when vaccine supply is limited was also reviewed.

Results

By September 16, 2022, nine Canadian provinces and territories had publicly reported 1,363 cases of monkeypox (3). Over 95% of confirmed cases have been in men 18–44 years of age who self-identified as gay, bisexual and other MSM and as having multiple and/or new sex partners; 52% reported living with human immunodeficiency virus (HIV). In response to the outbreak, PHAC had distributed over 110,000 doses of Imvamune vaccine to provinces and territories, and over 70,000 people had been vaccinated with at least one dose as of August 28, 2022 (12). The epidemiology of Canadian and international outbreaks has helped identify individuals and groups at highest risk of exposure to the virus. Men who have sex with men and individuals who have sex with MSM have the highest risk of being exposed to the monkeypox virus, provided they have multiple sex partners, have had a recent sexually transmitted infection or engage in sexual contact at sex-on-premise venues. Individuals who self-identify as sex workers, regardless of self-identified sex or gender, and individuals who volunteer or work at sex-on-premise venues may also be at higher risk of exposure to the monkeypox virus.

Available post-marketing data on Imvamune safety collected until September 2022 provided assurances that the vaccine was well tolerated when administered prophylactically (13,14). In Canada, the majority of adverse events following immunization reported to the passive surveillance system were non-serious and primarily include injection site reactions and fatigue (*personal communication, Public Health Agency of Canada; Surveillance of adverse events following immunization with Imvamune. August 17, 2022*).

The HCID WG did not identify any direct evidence on the efficacy or effectiveness of a two-dose primary series of Imvamune (given as either pre or post-exposure vaccination) against monkeypox infection, transmission or severe disease. Emerging evidence suggested that individuals vaccinated with one dose of Imvamune and who remained at high risk of exposure following vaccination could be at risk of infection post-vaccination (13,15).

Real world, experimental and modelling data provided evidence that extended two-dose intervals and intradermal vaccine administration could provide protection from monkeypox infection at an individual level while maximizing vaccine coverage for those at highest risk of monkeypox exposure (16–19).

A smaller intradermal (ID) dose, administered between layers of the skin, is expected to generate a similar immune response to a full dose administered subcutaneously (SC) but requires technical

skill and careful planning in order to prevent vaccine dose wastage and to ensure safety given the multi-dose vial vaccine preparations with limited shelf life once opened (16). Intradermal administration of vaccine (for dose sparing) thus poses feasibility challenges. Broad and safe deployment of ID doses may be optimal when used for second doses but not for first doses. In addition, there is a large body of evidence regarding the on-label (SC), administration of Imvamune. Internal PHAC modelling based on Canadian supply projections suggested that expanding vaccine coverage by extending dose intervals of the Imvamune vaccine and using 1-full (SC) and 1-fractional (ID) dose could have short-term public health benefits in preventing infections while vaccine supply is constrained. This unique potential solution stems from what is known about different vaccination strategies, principles of vaccinology, and feasibility of vaccination programs.

Recommendations

Following the review of available evidence, NACI made the following recommendations.

Pre-exposure vaccination

1.1 In the context of an active monkeypox outbreak, NACI recommends that immunization using the Imvamune vaccine should be offered to individuals with highest risk of monkeypox. After considering current and projected outbreak epidemiology, NACI recommends the following individuals/groups be considered for vaccination with Imvamune:

MSM and individuals who have sex with MSM, and who meet at least one of the following criteria:

- Having two or more sexual partners or being in a relationship where at least one of the partners has other sexual partners
- Having had a confirmed sexually transmitted infection acquired in the last year
- Engage in sexual contact in sex-on-premise venues

OR

- Individuals who self-identify as sex workers regardless of self-identified sex/gender

OR

- Staff or volunteers in sex-on-premise venues where workers may have contact with fomites potentially contaminated with monkeypox, without the use of personal protective equipment

The NACI continues to recommend pre-exposure vaccination with Imvamune vaccine for those working in research laboratory settings with replicating orthopoxviruses as outlined in the June 10, 2022 *NACI Rapid Response, Updated interim guidance on Imvamune® in the context of ongoing monkeypox outbreaks*.

1.2. Those with prior documented history of monkeypox infection need not be vaccinated. **(Strong NACI recommendation)**

2. In the context of the ongoing monkeypox outbreak and limited vaccine supply, dose sparing strategies should be considered in order to expand vaccination coverage to a broader population currently considered for pre-exposure vaccination. **(Strong NACI recommendation)**

2.1. Among immunocompetent adults currently considered for pre-exposure vaccination, the first dose of Imvamune can be prioritized in order to extend the potential protective impact broadly across populations most at risk of exposure.

Second doses should be offered as soon as demand for first doses among eligible individuals has been met. Individuals should receive their second dose at least 28 days after the first dose, provided they are at ongoing risk of exposure. This may result in an extended interval strategy, where the second dose is offered beyond the minimum authorized interval (28 days).

Individuals considered moderately to severely immunocompromised and currently eligible for pre-exposure vaccination should be prioritized to receive two doses of the Imvamune vaccine administered at the authorized interval (28 days between doses).

2.2. NACI recommends that, in the context of limited Imvamune vaccine supply, off-label ID administration (0.1 mL per dose) can be used among immunocompetent adults when given as a second dose following a first dose given subcutaneously, provided dose sparing and safe administration practises are feasible.

Individuals who are younger than 18 years of age, at risk of keloid scars, or moderately to severely immunocompromised should be offered Imvamune vaccine using the subcutaneous route of administration only.

Personnel involved in preparing and administering the vaccine should be provided adequate training before implementing intradermal administration. Jurisdictions should have protocols to minimize the risk of dose wastage and to reduce the potential of contamination of the vials if single-dose vials are to be used for multiple doses. If a vial is used for multiple doses, it should be discarded after six hours following first puncture.

3. NACI recommends that, when supply is not constrained, Imvamune pre-exposure vaccination should be offered as a two-dose primary series, with at least 28 days between first and second SC doses, for individuals currently eligible for pre-exposure vaccination. **(Strong NACI recommendation)**

Post-exposure vaccination

4. NACI continues to recommend the use of Imvamune as a post-exposure vaccination (also known and referred to as post-exposure prophylaxis) to individuals who have had high risk exposure(s) to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. A post-exposure vaccine dose should be offered as soon as possible, preferably within four days of last exposure but can be considered up to 14 days of last exposure. It should not be offered to individuals who are symptomatic and who meet the definition of suspect, probable or confirmed case. **(Strong NACI Recommendation)**

A summary table of the recommended immunization schedule is provided in **Appendix**.

Conclusion

The updated NACI recommendations identify groups at risk of monkeypox during the 2022 ongoing outbreak in Canada that are eligible for pre-exposure vaccination and provide additional strategies on the use of Imvamune that may be considered in order to maximize vaccine coverage when vaccine supply is limited. The future course monkeypox epidemiology remains unknown; thus, as the current outbreak evolves and new risk factors or groups at higher risk are identified, the criteria for those who should be vaccinated may change.

Authors' statement

NF — Writing, original draft, review, editing
OB — Writing, original draft, review, editing
RH — Writing, review, editing
NB — Writing, review, editing

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Competing interest

None.

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Appendix: Summary table (immunization schedule)

Table A1: Immunization schedule for Imvamune® in the context of the 2022 monkeypox outbreak

Dose number	Pre-exposure vaccination[a,b]		Post-exposure vaccination[a,b]	
	Immunocompetent adults	Moderately to severely immunocompromised and/or younger than 18 years of age and/or increased risk of keloid scars	Immunocompetent adults	Moderately to severely immunocompromised and/or younger than 18 years of age and/or increased risk of keloid scars
Dose 1	0.5 mL, SC	0.5 mL, SC	0.5 mL, SC, within 4 days since exposure, can be considered up to 14 days	0.5 mL, SC within 4 days since exposure, can be considered up to 14 days
Dose 2	0.5 mL, SC, 28 days after dose 1 (supply not constrained) OR 0.5 mL SC administered ≥28 days after dose 1 (constrained supply) OR 0.1 mL, ID (constrained supply only)	0.5 mL, SC 28 days after dose 1	0.5 mL, SC (if at ongoing risk of exposure)	0.5 mL, SC (if at ongoing risk of exposure)

Abbreviations: ID, intradermal; SC, subcutaneous

[a] Immunocompetent individuals recommended for Imvamune pre-exposure or post-exposure vaccination should receive a single dose if they have previously been vaccinated with a live replicating 1st or 2nd generation smallpox vaccine (i.e. as a booster dose). However, individuals considered moderately to severely immunocompromised should receive two doses, regardless of previous smallpox vaccination

[b] Pre-exposure or post-exposure vaccination is not indicated for individuals who meet the definition of suspect, probable or confirmed monkeypox case or with prior history of infection with monkeypox

In the context of constrained supply, for immunocompetent individuals, the first dose can be prioritized; this may result in an extended interval strategy, where the second dose is offered beyond the minimum authorized interval of 28 days. For post-exposure vaccination, the second dose is only administered if the person is at ongoing risk of exposure.

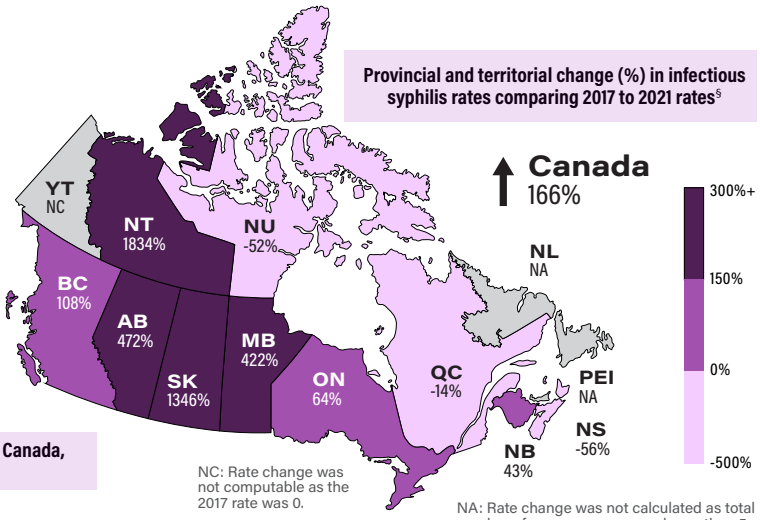
Imvamune given as pre-exposure or post-exposure vaccination should not be delayed due to recent receipt of a messenger ribonucleic acid (mRNA) coronavirus disease 2019 (COVID-19) vaccine. If vaccine timing can be planned (i.e. prior to employment within a research laboratory), NACI recommends that Imvamune be given at least four weeks after or before an mRNA vaccine for COVID-19. Refer to the June 10, 2022, NACI Statement for details on co-administration guidance.

Infectious syphilis and congenital syphilis in Canada*, 2021

11,268 cases
of infectious syphilis† were reported in 2021, for a **rate of 30 per 100,000** population

Rate increased by ▲ **20%**
between 2020 and 2021 following a period of **decreased access to STBBI services** in the context of the COVID-19 pandemic ‡

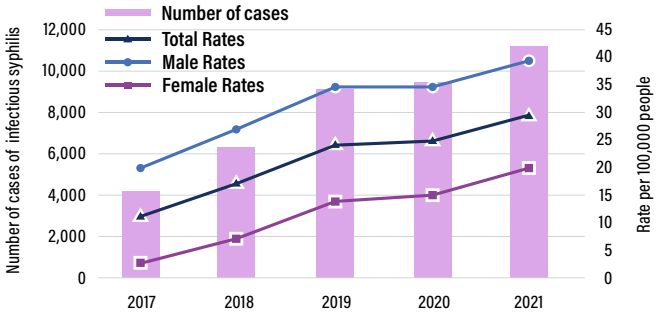
Provincial and territorial change (%) in infectious syphilis rates comparing 2017 to 2021 rates§



NC: Rate change was not computable as the 2017 rate was 0.

NA: Rate change was not calculated as total number of cases per year was lower than 5

Number of cases and rates of infectious syphilis by sex in Canada, from 2017 to 2021



There were
96 CASES
of confirmed early congenital syphilis† in 2021 compared to only 7 cases in 2017. An increase of 1271%.

Nationally, **34% of cases were among females** in 2021

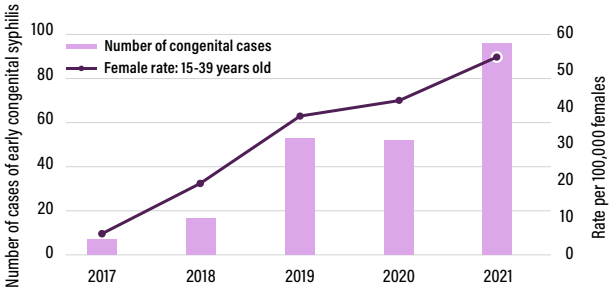
Compared to 2017, the 2021 infectious syphilis rate was **729%** higher for females and **96%** higher for males.

Cases among gbMSM** represent **30% of total cases in 2021.**

People aged 25 to 39 years old had the highest rate of infectious syphilis in 2021, but those **less than 20 years old** had the highest rate increase from 2017 to 2021.

Social and structural determinants of health and health inequities play a role in the inequitable occurrence of syphilis across different populations ††.

Number of confirmed congenital syphilis cases and reported infectious syphilis rates among females aged 15-39 years in Canada, from 2017 to 2021



* Data were obtained directly from provinces and territories (PTs). Nine PTs submitted data for the full calendar year of 2021. Two PTs (PE and NL) did not provide any data and two PTs (NB and NS) provided partial counts; annual counts were estimated. ***Data for 2021 are preliminary.***

† Infectious syphilis includes the primary, secondary and early latent (less than one year after infection) stages of infection, during which syphilis is transmissible. Early congenital syphilis is defined as a laboratory confirmation of infection with Treponema pallidum occurring within the first 2 years of birth. Case definitions for diseases under national surveillance. Can Comm Dis Rep 2000;26(S3). Retrieved July 2022, from https://www.canada.ca/en/public-health/services/diseases/syphilis/health-professionals/national-case-definition.html

‡ Survey of the impact of COVID-19 on the ability to provide STBBI prevention, testing and treatment including harm reduction services in Canada. Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control. 2021. https://www.canada.ca/en/public-health/services/publications/diseases-conditions/survey-impact-covid-19-delivery-stbbi-prevention-testing-treatment.html

**gbMSM: Gay, bisexual and other men who have sex with men.

†† Aho J, Lybeck C, Tetteh A, Issa C, Kouyoumdjian F, Wong J, Anderson A, Popovic N. Rising syphilis rates in Canada, 2011–2020. Can Comm Dis Rep 2022;48(2/3):52–60.

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

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Canada

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Response to letter: "Circular logic and flawed modelling compromises non-pharmaceutical intervention paper's conclusions"

To the Editor:

Grant *et al*. have raised criticisms of our recent article in *Canada Communicable Disease Report* (1), mostly in terms of our exploration of effects of non-pharmaceutical interventions (NPIs). We emphasize that the article explores the combined effects of NPIs and vaccinations on the outcomes of the pandemic until April 2022. Grant *et al*. contend that the article is not impartial and does not use robust data, but we reject these claims. Model inputs are derived either from the scientific literature (based on a scan/review of coronavirus disease 2019 [COVID-19] literature conducted by the Public Health Agency of Canada [PHAC] each day since February 2020) or from fitting to surveillance and other data (see Table A5 of the Supplemental material). Grant *et al*. state that assumptions used in the model are incorrect (but do not specify what, in their view, the errors are). In our view, the model used for the counterfactual analysis in the article is credible, relying on robust data and methodologies, and has undergone independent and critical peer-review three times in order to be published in high impact and reputable scientific journals (2–4). Grant *et al*. state that we use circular reasoning, and that there is inappropriate assignment of causality between NPIs and incidence. We reject these claims also, as explained in the following responses.

Grant *et al*. state that restrictive NPIs (such as school and business closures, stay at home orders, curfews, quarantine) are "not part of existing pandemic plans". In support of this statement, they cite a World Health Organization publication (Global Influenza Program 2019) (5). However, in that publication, and in other Canada-specific documents (Government of Canada 2019) (6) it is clear that restrictive NPIs are indeed part of pandemic plans that were in place before COVID-19. The position of Grant *et al*. is that the utility of NPIs is, and has been, questionable. They state that the most robust studies to date (in their words "those randomized, cluster randomized trials and robust case-control studies") have shown only weak effects of NPIs. However, with the exception of a study on mask use that did not test the role of masks in source control of SARS-CoV-2 infection (7) (in which the authors state the findings "should not be used to conclude that a recommendation for everyone to wear masks in the community would not be effective in reducing SARS-CoV-2 infection"), the studies cited by Grant *et al*. are not randomized trials or case-control studies, but retrospective analyses of NPI stringency compared against surveillance data. For a respiratory virus, reduction in the rate of transmission is the only possible outcome of restrictive measures that reduce daily rates of contact between members of the public, as long as the public complies with the measures (as did the majority in Canada) (8). The rising waves of COVID-19 cases resulted in increased hospitalisations and strain on intensive care unit capacity that in turn drove re-implementation of restrictive NPIs, following which cases and hospitalisations declined again as shown in Figure 1 in the article. Some studies have indeed found weak associations between NPIs and incidence, but there are many reasons for this including the use of statistical methods that may be suboptimal, issues with surveillance data and measurement of NPIs, and complex patterns of implementation and lifting of NPIs. The Rees *et al*. article cited in our article (9) did find a robust and logical relationship between NPI stringency and incidence in Canada, as did another cited in the article.

Grant *et al*. claim that we confuse the use of case fatality rate (CFR) and infection fatality rate (IFR), deliberately or due to ignorance. We are fully aware of the differences between CFR and IFR, and of the importance of this in the context of COVID-19 when approaching one third of infections have likely been asymptomatic. At the start of the pandemic, values were cited as CFR until it became clear that asymptomatic infection occurred, after which the appropriate metric was IFR. We are aware of a range of estimates of IFR conducted at different time points, and for different populations, particularly regarding population age—older aged populations tend to have more co-morbidities and higher IFR. The literature cited by Grant *et al*. does not support their argument and better aligns with our estimates. The study they cite by Ioannidis *et al*. (10) looked at IFR estimates for a range of countries with very different age demographics—IFR in European countries similar to Canada (England, Belgium, Spain, Italy) was frequently estimated at greater than 1%. One study from Denmark they cite (11) focused on those younger than 70 years of age and thus cannot be used for comparison purposes. Another from Denmark they cite (12) explores IFR in the Danish population during the wave caused by the low-virulence Omicron variant, when a high proportion of infections were vaccine breakthrough cases—circumstances that would be expected to yield an extremely low IFR estimate. Again, this study is not an appropriate comparator. In the study by the COVID-19 Forecasting Team (13) cited by Grant *et al*., the estimates for IFR in Canada ranged from more than 1% to 0.67% during 2020 to early 2021, which is consistent with our own studies (3,4,14), so we do not understand how Grant *et al*. can state that an IFR of 1% is a "massive overestimate". While

IFR likely decreased during the first year of the pandemic as therapies improved (as indicated by the study of the COVID-19 Forecasting Team) (13), IFR subsequently increased due to the emergence of the more virulent Alpha and Delta variants, and the combined impact of these factors are accounted for in counterfactual modelling. It is clear in the methods, and by viewing Table 3, that the model fully accounts for asymptomatic infections, and the model outputs of symptomatic (likely to be "cases") and asymptomatic infections (unlikely to be "cases") are explicitly stated. Grant *et al*. appear to assume that estimates of IFR cited in the article come from a simple calculation of data presented on reported cases and deaths in Table 1 of the article, but it is explicit in the table that the number of cases recorded in surveillance underestimate the true number of infections, and citations are provided for IFR estimates.

Grant *et al*. state that we relied on "flawed and discredited mathematical models" citing an article by Ioannidis *et al*. (15). This article reviewed outcomes of model-based forecasting, which is not the type of model used in our study. It is true that models parameterized with incorrect parameter values, or fit to data that are unsound, will likely produce inaccurate results. However, forecasts by good models often do not come to pass, particularly if, based on the forecasts, policies change to increase control of the epidemic. The model used for the counterfactual analysis is an agent-based computational model that simulates actions and interactions of individuals and is particularly suited for studying the effectiveness of different scenarios of interventions (in contrast to forecasts) that are highly dependent on community and population dynamics, such as the effectiveness of NPIs and vaccines.

Grant *et al*. claim that the model "presumes efficacy of NPIs to prove that NPIs have efficacy" and that "this circular reasoning alone should have disqualified this paper at the stage of peer review". In the paper, we do not "presume" efficacy of NPIs. We do indeed cite articles that support the efficacy of NPIs, and we visually compare incidence and NPI stringency (in Figure 1), but we then model impacts of implementation and lifting of NPIs in Canada. In the model, NPIs have an impact on contacts between agents (i.e. members of the public) or transmission probability when contacts occur, which is informed by estimates from the scientific literature (a scan and review of COVID-19 literature is conducted by PHAC each day), from Canadian data sources (e.g. hospital occupancy, vaccine uptake, open-source mobility data) or from fitting to surveillance data. For example, restrictive closures were modelled on the reduction in mobility from open-access, population-level data associated with changes in the stringency index, and associated reductions of contact rates were based on surveys of the Canadian public that have been conducted at multiple time points during the pandemic. The model inputs (all described in the Supplemental material) therefore reflected changes in NPIs at various times of the pandemic according to what actually occurred, while the model outputs assessed the efficacy of these NPIs on the epidemic. There is not, therefore, a circular argument associated with us selecting unrealistically high effectiveness values for NPIs in the modelling because simple effectiveness values for NPIs are not model inputs.

Grant *et al*. suggest our worst-case upper bound estimate of 800,000 deaths in the counterfactual analysis is unreasonable. They estimate that this would mean an IFR of 3% and a death rate fourteen times higher than that seen in Sweden. We emphasize that this worst-case counterfactual estimate obtained in the model does not include vaccination and accounts for waning of post-infection immunity acquired in wave 1 (according to current estimates of waning of immunity against infection and severe outcomes) allowing a large wave of reinfections associated with the more virulent Delta wave to occur (see Figure 4). Overall IFR in this counterfactual scenario remains 1% as can be estimated from the model output data in Table 3. It is not correct to compare this counterfactual estimate with observed data from Sweden where both NPIs and vaccinations were implemented.

Grant *et al*. appear to assume that Figure 1 in the article, which compares the timelines of variations in stringency of NPIs and incidence of COVID-19, is used to attribute causality of incidence to NPI stringency. However, Figure 1 is merely a pictorial description of the timeline of the epidemic and implementation and release of NPIs. It is a simplification as, of course, there were inter-provincial variations in the timing of implementation and release of different NPIs. There is no attempt to infer causality from this diagram; causality is inferred from more detail statistical analyses cited in the article (8,16).

Grant *et al*. claim that we did not consider other explanations, including the lower death rates in British Columbia compared to Québec when stringency was higher in the latter province and that death rates are affected by factors such as age structure, obesity rate, population density and economic disparity. In our experience, stringency and mortality rates varied amongst provinces and territories according to a number of factors including the number of cases detected initially during the pandemic, the intrinsic within-province or territory characteristics of transmission, healthcare capacity etc. This article looked at Canada as a whole rather than dissecting regional variations, but in the article we point out the value of future jurisdiction-by-jurisdiction analyses. Some interprovincial differences in fatality rates are associated with epidemics in long-term care, that were more severe in some provinces than others, and it should be noted that some inter-provincial disparities are due to differences in completeness of reporting of cases and deaths. Reporting of deaths in Québec was likely more complete than other provinces (17). The epidemics that occurred in long-term care are not considered in, nor do they inflate, outputs from counterfactual modelling because the model represents the baseline number of infections, hospitalisations and deaths excluding outbreaks such as those seen in long-term care facilities, hospitals and

other localized outbreaks (see the Supplemental material). The counterfactual modelling is therefore a conservative estimate of the efficacy of NPIs and vaccination in Canada. Further, the mortality rate that was used in the counterfactual modelling was derived from national surveillance data of the first 200,000 cases reported in Canada; this inherently takes into account some of the complexities that Grant *et al*. has pointed out including age structure, population density, socioeconomic disparity and comorbidities such as obesity that varies across Canada.

Grant *et al*. criticize the article for choosing inappropriate comparator nations ("two isolated islands [New Zealand and Australia] and a country without functional land borders [South Korea]") and state that "the authors…..conveniently forget that these countries have subsequently had massive outbreaks". The zero-COVID approach to managing COVID-19 was presented in our article as an alternative that was adopted by certain countries or jurisdictions. It was made clear that this approach was only possible under certain circumstances as stated by Grant *et al*. Those that did adopt this approach had fewer deaths per capita than countries that did not, up to early 2022 when the Omicron variant emerged, and NPIs in these countries were lifted. After NPIs were lifted, and transmission of COVID-19 was unrestricted, there was an expected significant increase in infections and deaths in these countries, as occurred in many countries including Canada with the lifting of NPIs. It is made clear in the article that "as the Omicron variant emerged, most of these countries experienced major outbreaks…" once NPIs were lifted. Hospitalisations and deaths occurred in zero-COVID countries during the Omicron waves because, despite high levels of vaccine uptake, many people remained unvaccinated and, of course, while the vaccines are very effective against severe outcomes, they are not 100% effective. Even so, to date the rates of deaths in Australia and New Zealand (circa 57 and 39 per 100,000 population at the time of writing) are substantially lower than in Canada (at the time of writing 118 per 100,000) and in the Unites States (at the time of writing 311 per 100,000).

Grant *et al*. criticise the authors for not considering unintended consequences of NPIs. It is made clear in the article that exploring COVID-19 cases and deaths is our starting point for exploring counterfactuals, but the article shows the potentially catastrophic impact of COVID-19 in Canada had public health measures and vaccination not been implemented as they were. As mentioned in the article, future studies are needed to explore the full range of consequences of COVID-19, long-COVID and unintended consequences of NPIs, which are beyond the scope of this paper. One way of exploring the full impact is by excess deaths. While there is a perception that deaths due to unintended consequences of NPIs may be substantial, there is not much evidence, with some exceptions such as the impact on overdose deaths in British Columbia. In the zero-COVID countries, deaths were generally lower than in years prior to the pandemic, possibly due to NPIs reducing transmission of a range of other infectious diseases (18,19). When analyses have found significant excess deaths over and above reported deaths, these have been mostly attributable to under-reporting of COVID-19 deaths, rather than to deaths due to unintended consequences of NPIs (18). It should also be recognized that delays in diagnosis and treatment for non-COVID-19 illnesses such as cancer were likely due to hospital capacity being overwhelmed with COVID-19 patients. It has been argued that late re-implementation of restrictions to control transmission contributed to non-COVID-19 deaths due to deferral of routine diagnostic and surgical procedures (20–22).

Grant *et al*. consider that the author team, as members of PHAC, would actually have a competing interest in producing a favourable evaluation of the management of the epidemic in Canada because of our responsibility for decision-making. This perception is not correct. During a pandemic, PHAC officials, and the Chief Public Health Officer (23), have a key role in providing advice—evidence-based recommendations and best practice guidance, and all the authors were involved in contributing to the development and communication of this scientific information. In addition, the PHAC has key roles in acting as a central national focus for liaison with domestic and international partners and for facilitating public health action. With the exception of measures at our international borders, the decisions on implementation of NPIs and administration of vaccines have always been the responsibility of provincial and territorial governments in consultation with their own public health advisors. While PHAC developed guidance and recommendations to facilitate responses by provinces and territories, the overall pattern of changes in NPIs during the pandemic, as described in Figure 1, comes from decisions made at the provincial and territorial level. In this article, we therefore comment on what occurred as informed observers of the implementation and lifting of NPIs—not as architects. We emphasize that this article aims to describe what could have happened with lower levels of use of NPIs and of vaccine uptake. It shows that outcomes in terms of COVID-19 cases, hospitalizations and deaths may have been far worse than actually occurred by comparing against counterfactuals in a modelling study and comparing against outcomes in other countries. It does not explore whether or not management of the pandemic in Canada was optimal, and we were explicit that further study of that is needed.

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Is there protective immunity after an Omicron infection?

Source: Emerging Science Group of the Public Health Agency of Canada. Evidence Brief on Protective Immunity Post Infection with Omicron. July 26, 2022. Full report available from: ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca

Background: Although the literature is well-established on protection and waning of immunity following infection with previous SARS-CoV-2 strains and COVID-19 vaccination, little is known about protective immunity following Omicron infection. Assessment of this must also consider key Omicron sublineages (BA.1, BA.2, BA.4 and BA.5), as each sublineage has a unique complement of mutations. A review of existing evidence was conducted to answer a series of questions. When there is a history of Omicron infection with one strain what is the risk of reinfection with the **same** Omicron strain or reinfection with a **different** Omicron strain? How does the risk of reinfection vary by the history of vaccination and/or infection prior to the first Omicron infection? What are the trends in *in vitro* immunogenicity studies, measuring neutralizing antibodies and T and B cell activity, after an Omicron infection?

Methods: Targeted keyword searching was conducted within twenty databases to identify all relevant studies on COVID-19. The database was then filtered for articles on Omicron prior to use of the following search terms to identify potentially relevant citations: reinfect*, recurrent, re-positive, longitudinal, immun*, neutraliz* and neutralis*. The search netted 1,721 citations up to July 26, 2022. Real-world data on reinfections post Omicron infection and immunogenicity studies on Omicron more than 14 days post diagnosis were included. Animal studies and immunogenicity measurements fewer than 14 days after diagnosis with COVID-19 were excluded. Data were extracted from relevant studies into evidence tables to address each of the questions and then summarized. For this article, only the observational studies were referenced.

Results: Twenty-three studies were identified, including six observational studies and 17 *in vitro* studies.

- The six observational studies included three test negative case-control studies and three retrospective cohort studies. Of those, none was peer-reviewed: five were pre-prints and one was a Letter to the Editor.
- The 17 *in vitro* studies examined immune responses 0.5–3 months after an Omicron infection, which corresponds to the peak immune response time.

Previous infection with one Omicron strain was associated with significant protection against reinfection with other Omicron strains, but this varied by how different the strains were from each other and by vaccine status.

- In all studies, prior infection with the BA.1 Omicron strain offered more than 95% protection against reinfection with another BA.1 Omicron strain and more than 85% protection against reinfection with a BA.2 Omicron strain (1–6).
- Prior infection with a BA.1 or BA.2 Omicron infection offered 76% protection against a BA.4/BA.5 reinfection (5).

Protective immunity from reinfection is greater when there is a history of COVID-19 vaccination rather than a history of a previous infection prior to the initial Omicron infection.

- Immunity from vaccination prior to the first Omicron infection reduced the risk of Omicron reinfection by 96% (6).
- Immunity from previous infection prior to the first Omicron infection reduced the risk of Omicron reinfection by 72% (2–4).
- One Canadian study found the risk of reinfection with Omicron BA.2 following a BA.1 infection was the same for those who had two or three mRNA COVID-19 vaccinations (4); however, there were a disproportionate number of reinfections among individuals who were unvaccinated (3,4), of which a disproportionate number were younger than 20 years old (2).

Trends in immunogenicity studies

Studies on immune markers, such as neutralizing antibodies and T and B cell activity, do not directly equate with protection but they do indicate the immune system is primed to respond to a pathogen. Immunogenicity studies were consistent with observational studies.

- Infection with Omicron BA.1 neutralized subsequent BA.1 infections most efficiently, followed by BA.2, BA.2.13 and BA.2.12.1.
- Omicron BA.4 and/or BA.5 were most resistant to neutralization by both BA.1 and BA.2 convalescent sera (i.e. samples from people recovered from COVID-19).
- Convalescent sera from people who were infected with the Omicron strain and who were also vaccinated had higher neutralizing antibody responses against Omicron sublineages compared to convalescent sera from people who were infected with the Omicron strain and who were unvaccinated.
- The level of B cell responses significantly increased when there was a history of two or three-dose vaccination as well as an Omicron infection, compared to those with two or three-dose vaccination who had not been infected with the Omicron strain.

Conclusion: After an initial Omicron infection, the level of protective immunity against an Omicron reinfection varied from 72%–96%, depending on how closely related the two Omicron strains were and the previous vaccination history. Observational evidence was limited by the small number of studies, the lack of peer review, short follow-up times and the risk of bias inherent to retrospective studies. The findings from *in vitro* immunogenicity studies findings were consistent with the observational studies; however, they were limited in that they were short-term and could only provide indirect evidence of protection. Peer-reviewed prospective studies and longer-term immunogenicity studies are needed.

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