

Antimicrobial Use among Adult Inpatients in Northern Canada, 2019–2021

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ABSTRACT

Background: Antimicrobial use data from inpatients in northern Canada suitable to inform stewardship programs are limited.

Objective: As a special project of the Canadian Nosocomial Infection Surveillance Program, to describe antimicrobial use for inpatients in northern Canadian acute care hospitals.

Methods: Participating acute care hospitals serving adult or mixed adult and pediatric populations in northern Canada submitted annual data on the use of all systemic antimicrobials from 2019 to 2021. Patient-day denominators were also submitted. Northern Canada was defined as the territories and Statistics Canada's provincial north. Data were analyzed in terms of defined daily doses per 1000 patient days (DDD/1000pd), as per the Anatomical Therapeutic Chemical classification system. Antimicrobials were categorized using the World Health Organization's AWaRe (Access/Watch/Reserve) classification system.

Results: Each year, 42–47 hospitals participated. More than 90% of participating hospitals were in Alberta or British Columbia. There was large variation in overall antimicrobial use between hospitals (e.g., interquartile range 429 to 779 DDD/1000pd in 2021). From 2019 to 2021, there was a 49% relative increase in antimicrobial use, from 401 to 596 DDD/1000pd ($p = 0.11$). Over the same period, the use of third- and first-generation cephalosporins increased by 80% and 64%, respectively; antimicrobials in the "Reserve" category increased from 0.4% to 2% of overall use.

Conclusions: This study represents the largest collection of antimicrobial use data for inpatients in northern Canada to date. From 2019 to 2021, there was an increase in antimicrobial use of 195 DDD/1000pd, largely driven by increases in the use of third- and first-generation cephalosporins. The findings should be interpreted with caution, as results may not be generalizable to all northern hospitals.

Keywords: antimicrobial use, hospital, surveillance

RÉSUMÉ

Contexte : Les données concernant l'utilisation d'agents antimicrobiens chez les patients hospitalisés dans le nord du Canada pouvant éclairer les programmes de gestion sont limitées.

Objectif : Projet spécial de Programme canadien de surveillance des infections nosocomiales visant à décrire l'utilisation d'agents antimicrobiens chez les patients hospitalisés dans des hôpitaux de soins aigus dans le nord du Canada.

Méthodologie : Les hôpitaux de soins aigus ayant participé au projet et qui servent une population adulte ou une population mixte composée d'adultes et d'enfants dans le nord du Canada ont soumis leurs données annuelles concernant l'utilisation de tous les agents antimicrobiens systémiques de 2019 à 2021. Les dénominateurs de jours-patients ont également été soumis. Le nord du Canada était défini comme les territoires et le nord provincial de Statistique Canada. Les données ont été analysées en termes de doses journalières définies par 1000 jours-patients (DJD/1000 jours-patients), selon le Système de classification anatomique, thérapeutique et chimique. Les agents antimicrobiens ont été répartis à l'aide du système de classification AWaRe de l'Organisation mondiale de la Santé : accès aux antibiotiques; antibiotiques à surveiller; antibiotiques de réserve.

Résultats : Chaque année, entre 42 et 47 hôpitaux ont participé. Plus de 90 % de ces hôpitaux se situaient en Alberta ou en Colombie-Britannique. De grandes variations quant à l'utilisation d'agents antimicrobiens de manière générale ont été observées d'un hôpital à l'autre (par exemple, l'intervalle interquartile était de 429 à 779 DJD/1000 jours-patients en 2021). Entre 2019 et 2021, on a observé une augmentation relative de 49 % de l'utilisation d'agents antimicrobiens, qui est passée de 401 à 596 DJD/1000 jours-patients ($p = 0,11$). Pendant la même période, l'utilisation des céphalosporines de troisième et de première génération a augmenté respectivement de 80 % et 64 %; les agents antimicrobiens de la catégorie « Réserve » ont quant à eux augmenté, passant de 0,4 % à 2 % de l'utilisation globale.

Conclusions : Cette étude constitue la plus grande collecte de données sur l'utilisation d'agents antimicrobiens chez les patients hospitalisés dans le nord du Canada à ce jour. Entre 2019 et 2021, on a observé une augmentation de 195 DJD/1000 jours-patients de l'utilisation de ces agents, une augmentation principalement due à une hausse de l'utilisation des céphalosporines de troisième et de première génération. Il convient d'interpréter ces résultats avec prudence, car ils peuvent ne pas être généralisables à tous les hôpitaux du Nord.

Mots-clés : utilisation d'agents antimicrobiens, hôpital, surveillance

INTRODUCTION

Although the use of antimicrobials has contributed to advances in modern medicine,¹ the misuse of these drugs exacerbates selective pressure leading to the emergence and spread of antimicrobial-resistant organisms,² which in turn threaten the ability to prevent and treat common infections. Exposure to antimicrobials may also have negative repercussions for individual patients' health.³⁻⁵

Canada's territories and provincial northern regions represent more than 75% of the country's landmass but only about 6% of its population.⁶ Antimicrobial use data from northern Canadian hospitals are limited. Benchmarks for inpatient antimicrobial use in adults were previously documented for a network of Canadian hospitals⁷; however, no hospitals from northern Canada were included in that work. Canadian northern health systems often differ from their southern counterparts, in terms of accessibility of care, patient mix, and resources available for stewardship activities.^{8,9} Hospitals in Canada's north are generally smaller and provide fewer services for complex, comorbid disease. Although northern communities are not homogeneous, they often differ from southern communities in terms of demographics, socioeconomic factors, health outcomes, resources, rurality, and remoteness.¹⁰⁻¹²

Antimicrobial use is very common among hospitalized patients. In a 2015 global point prevalence study, 34% of inpatients on adult wards were receiving at least 1 antimicrobial.¹³ Data from a point prevalence study of the Canadian Nosocomial Infection Surveillance Program (CNISP) network of Canadian acute care hospitals in 2017 indicated that 40% of hospitalized adults were receiving an antimicrobial.¹⁴ Among various populations of hospitalized adult patients, it has been estimated that 23%–56% of prescriptions may be unnecessary or inappropriate, although these estimates may not be generalizable to northern settings.¹⁵⁻¹⁸

Antimicrobial stewardship programs aim to balance the benefits of antimicrobial use for individual patients against their potentially negative effects. Stewardship programs optimize how and when antimicrobials are used. These programs can reduce antimicrobial use, limit inappropriate prescribing, improve patient outcomes, and reduce costs.¹⁹⁻²² In 2013, implementing an antimicrobial stewardship program became a requirement of accreditation for all Canadian acute care hospitals,²³ although the resources available for stewardship activities vary across the country.^{24,25}

Effective surveillance of antimicrobial use can identify opportunities for interventions, enable evaluation of stewardship programs, generate feedback for clinicians, guide formulary management,²⁶ and promote organizational support for successful stewardship efforts.

Antimicrobial use data for inpatients in northern communities have been published for some but not all jurisdictions.²⁷ Surveillance methods and metrics can differ

among jurisdictions or surveillance programs (e.g., point prevalence studies vs annual surveillance; days-of-therapy or length-of-therapy or quantity vs defined daily doses [DDDs]). To address these differences and data gaps, the CNISP Antimicrobial Use Surveillance Working Group initiated a study of antimicrobial use surveillance in northern Canada with the following objectives: to describe antimicrobial use in acute care hospitals in northern Canada and to provide benchmarking information for northern Canadian stewardship initiatives.

METHODS

Geographic Definition

For the purposes of this work, northern Canada was defined as consisting of the 3 Canadian territories (Yukon, Northwest Territories, and Nunavut) and Statistics Canada's provincial north (the northern regions of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Newfoundland and Labrador).²⁸

Setting and Participating Sites

The CNISP is a collaboration between the Public Health Agency of Canada and the Association of Medical Microbiology and Infectious Disease Canada. As of October 2023, 106 sentinel hospitals, from across all 10 provinces and 1 territory (Nunavut), participate in the CNISP network. The CNISP established a working group for antimicrobial use surveillance in 2007/08. The results of the current study represent northern Canadian hospitals participating in routine CNISP surveillance in recent years, as well as additional hospitals specifically recruited for this project. During data quality checks, outlying results were identified, shared with data submitters, and corrected as necessary. Outlying results were defined as the bottom 5% and top 5% of rates of use of antimicrobials in a given year. As part of this project, each participating hospital received a report comparing rates of antimicrobial use at their hospital to rates of antimicrobial use at all participating sites.

Data Variables and Collection

Adult Inpatients

Adult patients were defined as those at least 18 years of age and those receiving care on wards where the majority of patients were at least 18 years of age. If mixed adult and pediatric hospitals were not able to separate their data by age group, data for pediatric patients could be included in the submitted data. Surveillance covered all acute care inpatient units (including intensive care units) and admissions to emergency departments. Data for non-admitted patients seen in emergency departments and for patients in wards designated as long-term care were excluded. Participating sites provided corresponding adult inpatient-day

denominators (described as “patient days” or “pd”). Estimates of adult inpatient days across the study sites were obtained for each jurisdiction by multiplying the proportion of a jurisdiction’s residents living in northern Canada (obtained from Statistics Canada²⁹) by the total adult inpatient days for the jurisdiction (obtained from the Canadian Institute for Health Information³⁰).

Antimicrobial Use

Participating hospitals provided total antimicrobial use by adult inpatients, separated by type of antimicrobial. Hospitals were asked to submit data in terms of either dispensed or administered antimicrobials and, when possible, to separate their data by administration route (parenteral or oral). With respect to the antimicrobial use data, all systemic antibacterial use was included in surveillance based on the following Anatomical Therapeutic Chemical (ATC) codes: J01, P01AB01 (oral metronidazole), and A07AA09 (oral vancomycin).³¹ Data on antimicrobial use were submitted as quantity of antimicrobials or as DDDs, as per the ATC classification system.³¹ If antimicrobial use data were not submitted in terms of DDDs, the quantity data were centrally converted to DDDs.

Data Analysis

Participating hospitals submitted annual data files, which were then analyzed centrally, as follows. Antimicrobials were categorized using the World Health Organization’s AWaRe (Access/Watch/Reserve) classification system.³² The antimicrobial use data were used to determine the most frequently prescribed antimicrobial agents by drug class. Rates of antimicrobial use were standardized per 1000 patient days (pd), according to the following calculation: (total DDDs / total pd) * 1000, reported as DDDs/1000pd. Bootstrapped standard errors obtained with 10 000 replications were used to calculate 95% confidence intervals (CIs). Friedman tests were used to detect differences across years. All analyses were done using SAS software, version 9.4 (SAS Institute), with *p* values of 0.05 or below considered statistically significant.

A secondary analysis was performed categorizing antimicrobials according to Health Canada’s 2024 reserve list.³³

Ethics Approval

Surveillance of antimicrobial use at participating hospitals is considered a quality improvement activity that is within the mandate of hospital infection prevention and control programs and does not constitute human research requiring formal ethical approval in Canada. Because the surveillance did not involve any alteration in patient care and no patient identifiers or patient-level data were collected, institutional research board approval was not routinely solicited. All data were aggregated, with the lowest level of aggregation being the hospital ward. All data submitted to the CNISP were kept strictly confidential.

RESULTS

Participating Sites

Between 2019 and 2021, a total of 50 sentinel hospitals participated in at least 1 year of surveillance (42–47 hospitals each year) and submitted data eligible for analysis. Thirty-nine of these hospitals provided data for all calendar years. One hospital provided data only for 9 months. Data from 1 hospital for 1 year of the study were omitted, in consultation with the data submitter, due to concerns about data quality. In the absence of a comprehensive list, we estimate that approximately 40% of acute care hospitals in northern Canada were represented in this project (based on unpublished data from the Canadian Institute for Health Information provided to the CNISP). More than 90% of participating hospitals were in northern Alberta or northern British Columbia; data were also submitted from Northwest Territories, Nunavut, and northern Ontario. The total number of inpatient days included in surveillance (1.3 million pd) represented approximately 2% of inpatient days in Canada in 2019–2021 and approximately one-third of inpatient days in northern Canada. Most participating hospitals (48/50, 96%) had fewer than 200 beds, and 5 of the hospitals had an intensive care unit. Participating hospitals contributed a median of 5000 pd per year to surveillance (range 700 to 126 000 pd per year). The characteristics of participating hospitals are summarized in Table 1.

Antimicrobial Use

Overall, from 2019 to 2021, there was a 49% relative increase in use of antimicrobials, from 401 to 596 DDD/1000pd; however, this change was not statistically significant (*p* = 0.11). Antimicrobial use varied substantially among hospitals; for example, in 2021, the interquartile range for overall antimicrobial use was 429 to 779 DDD/1000pd. There was 11-fold variability among the hospitals in overall rate of antimicrobial use in 2021.

Among the 39 hospitals that provided 3 years of data, 25 hospitals had higher rates in 2021 than 2019 and 14 hospitals had lower rates in 2021. There was substantial variation in annual rates of antimicrobial use at individual hospitals over the 3 years. Overall rates of antimicrobial use at a hospital differed by a median of 19% each year (interquartile range 10% to 43%).

The antimicrobial drug classes with the highest use in 2021 were third-generation cephalosporins (139 DDD/1000pd), first-generation cephalosporins (77 DDD/1000pd), penicillins with β-lactamase inhibitors (67 DDD/1000pd), macrolides (64 DDD/1000pd), fluoroquinolones (45 DDD/1000pd), and glycopeptides (27 DDD/1000pd) (Figure 1). These 6 classes of antimicrobials represented 75% of total antimicrobial use in 2021.

Overall use of the 6 most frequently used classes of antimicrobials increased between 2019 and 2021. Third-

TABLE 1. Characteristics of Participating Hospitals

Characteristic	Year; No. of Hospitals ^a		
	2019	2020	2021
No. of hospitals participating	45 ^b	47	42
Jurisdiction			
Northern Alberta	25	27	24
Northern British Columbia	17	17	17
Other ^c	3	3	1
No. of inpatient days	440 000	526 000	361 000
Patient population			
Adult	38	40	37
Mixed adult and pediatric	7	7	5
Teaching hospital			
No	42	44	40
Yes	3	3	2
ICU in hospital			
No	40	42	38
Yes	5	5	5
No. of beds			
≤ 200	44	45	41
201–500	1	1	1
> 500	0	1	0

ICU = intensive care unit.

^aExcept where indicated otherwise.

^bOne hospital provided 9 months of data.

^cNorthwest Territories, Nunavut, and northern Ontario.

and first-generation cephalosporins increased by 80% ($p < 0.001$) and 64% ($p = 0.06$), respectively, and these 2 classes accounted for 47% of the overall increase in antimicrobial use between 2019 and 2021. In addition to the third-generation cephalosporins, statistically significant increases were seen for penicillins with β -lactamase inhibitors ($p = 0.002$) and fluoroquinolones ($p = 0.01$).

In 2021, the most frequently used antimicrobials were ceftriaxone (116 DDD/1000pd), cefazolin (68 DDD/1000pd), azithromycin (58 DDD/1000pd), piperacillin–tazobactam (48 DDD/1000pd), ciprofloxacin (29 DDD/1000pd), and vancomycin (27 DDD/1000pd) (Figure 2). These 6 antimicrobials represented 58% of total antimicrobial use in 2021. At the 31 hospitals where oral use of vancomycin and metronidazole could be separated from parenteral use, 5% of vancomycin use and 42% of metronidazole use was oral.

For many of the most frequently used antimicrobials, use increased significantly ($p < 0.05$) from 2019 to 2021, including ceftriaxone (from 62 to 116 DDD/1000pd), cefazolin (from 37 to 68 DDD/1000pd), azithromycin (from 36 to 58 DDD/1000pd), piperacillin–tazobactam (from 22 to 48 DDD/1000pd), ciprofloxacin (from 24 to 29 DDD/1000pd), clindamycin (from 11 to 25 DDD/1000pd), metronidazole (from 16 to 23 DDD/1000pd), and cefixime (from 12 to 20 DDD/1000pd) (Figure 2).

While absolute use of antimicrobials increased from 2019 to 2021 within each of the AWaRe categories (Figure 3), increases in the percentage of antimicrobial use were

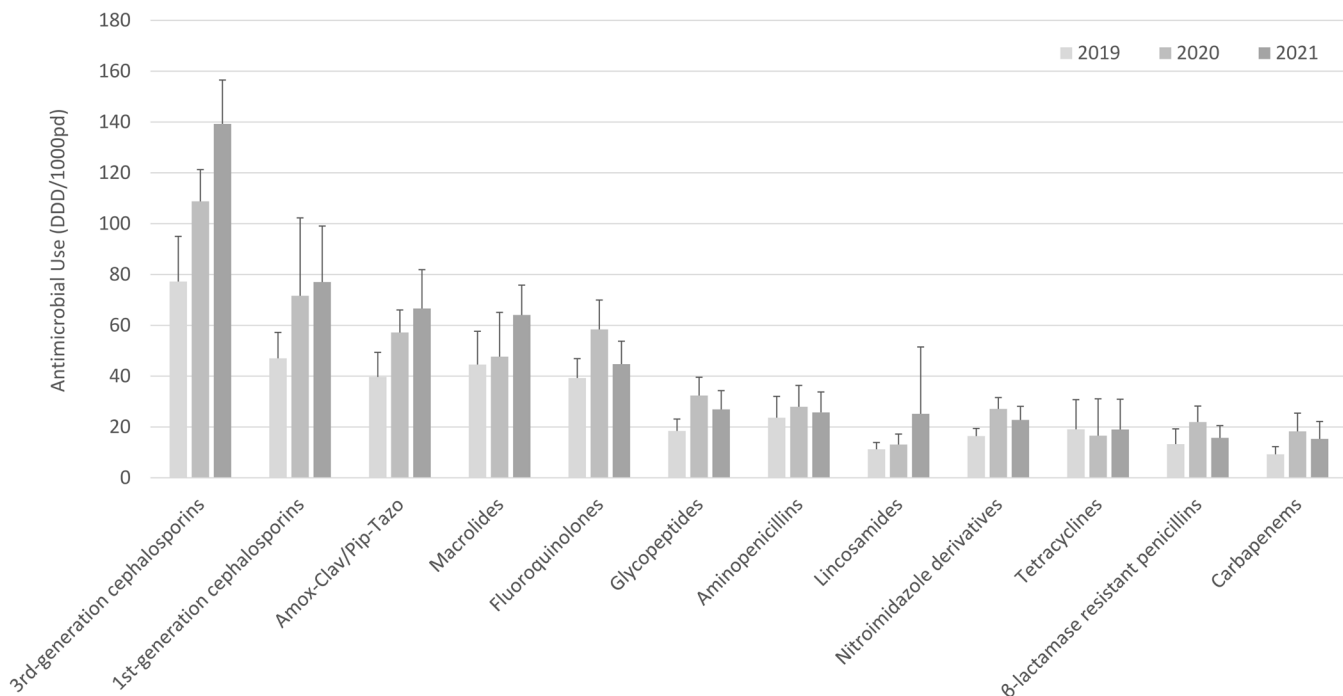


FIGURE 1. Rate of use of the most frequently used antimicrobial drug classes among acute care hospitals in northern Canada, 2019–2021. Data for all years are shown for the 12 drug classes that were most frequently used in 2021; these represented 91% of total antimicrobial use in that year. Error bars represent upper 95% bootstrapped confidence intervals. Amox-Clav = amoxicillin–clavulanic acid, Pip-Tazo = piperacillin–tazobactam, DDD/1000pd = defined daily doses per 1000 patient days.

observed only for the “Watch” and “Reserve” categories. More specifically, use of antimicrobials in the “Watch” category increased from 55% to 59% of total use (from 223 to 352

DDD/1000pd; $p = 0.02$), with ceftriaxone and piperacillin-tazobactam accounting for 61% of this increase. Use of antimicrobials in the “Reserve” category increased from

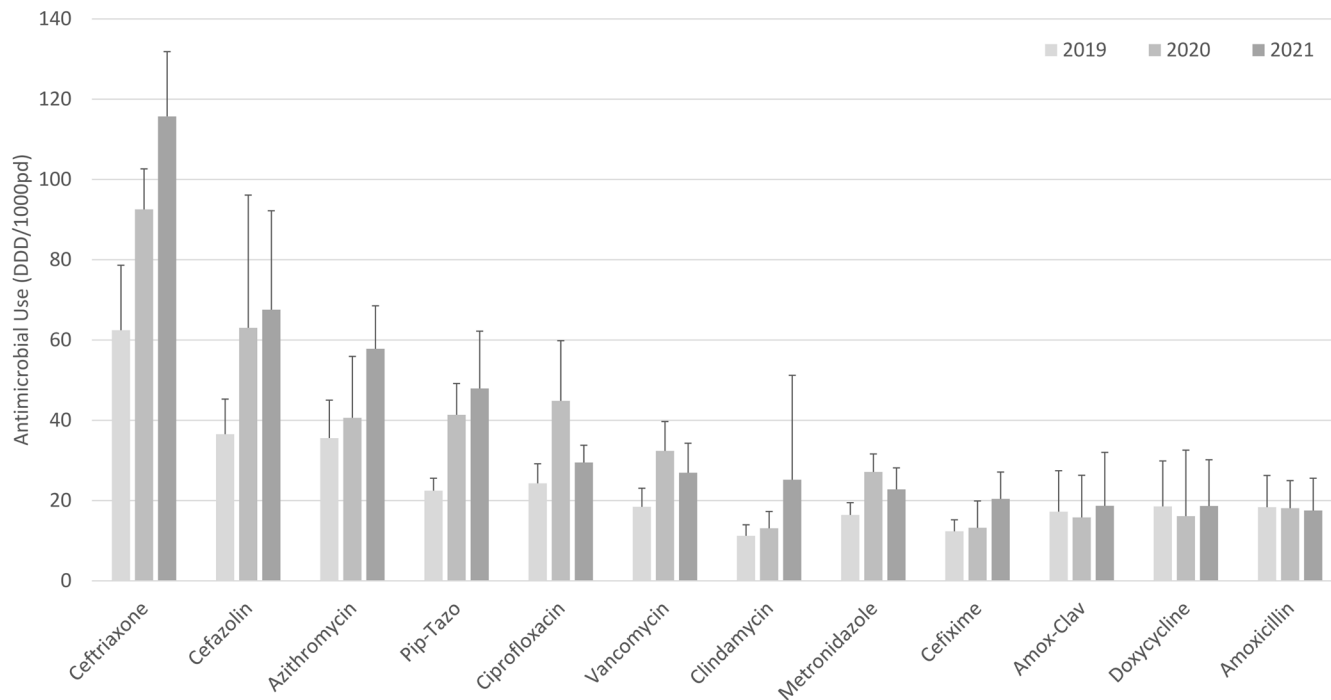


FIGURE 2. Rate of use of the most frequently used antimicrobials among acute care hospitals in northern Canada, 2019–2021. Data for all years are shown for the 12 antimicrobials that were most frequently used in 2021; these represented 79% of total antimicrobial use in that year. Error bars represent upper 95% bootstrapped confidence intervals. Amox-Clav = amoxicillin–clavulanic acid, Pip-Tazo = piperacillin–tazobactam, DDD/1000pd = defined daily doses per 1000 patient days.

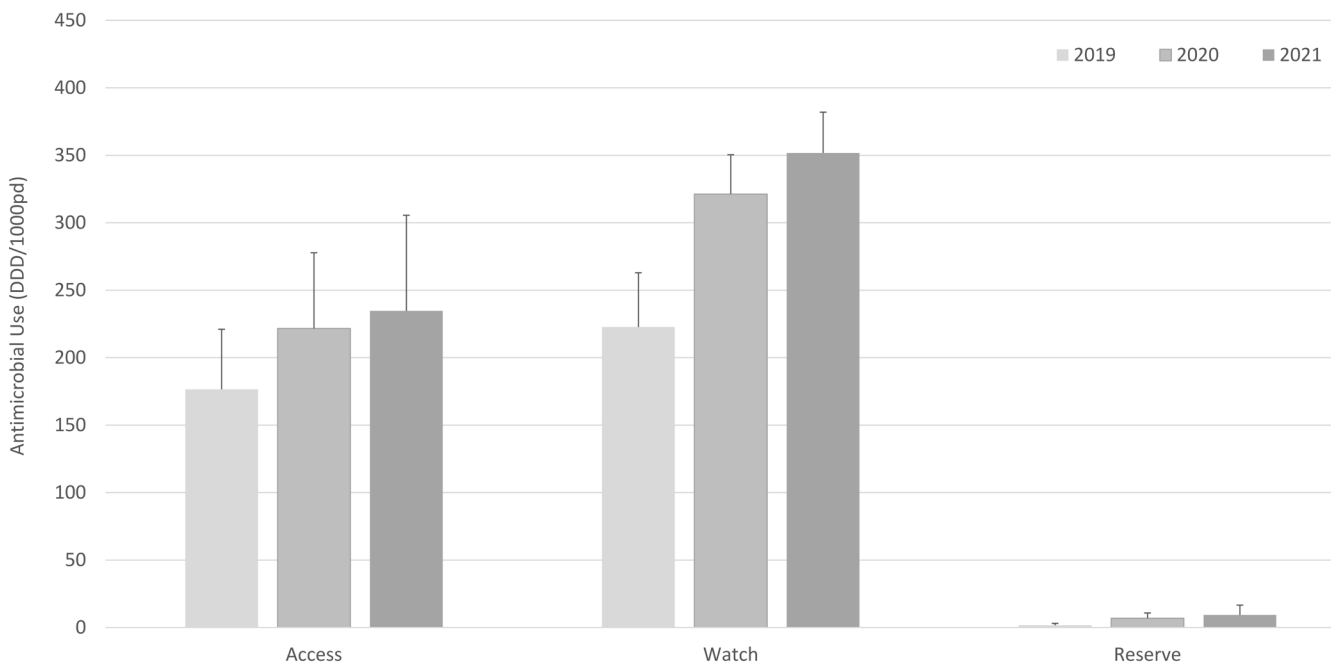


FIGURE 3. Rate of use of antimicrobials by AWaRe (Access/Watch/Reserve) category,³² 2019–2021; antimicrobials not categorized into one of these categories were excluded (about 0.01% of represented antimicrobials). Error bars represent upper 95% bootstrapped confidence intervals. DDD/1000pd = defined daily doses per 1000 patient days.

0.4% to 2% of total use (from 2 to 9 DDD/1000pd; $p = 0.01$). Among antimicrobials in the “Reserve” category, the use of only daptomycin and linezolid totalled more than 1 DDD/1000pd in any year. Total daptomycin use increased from 1 to 8 DDD/1000pd between 2019 and 2021 ($p = 0.04$), and linezolid use increased from 0.4 to 1 DDD/1000pd ($p = 0.09$).

In the secondary analysis, use of antimicrobials on the Health Canada reserve list³³ more than doubled between 2019 and 2021, from 10 to 24 DDD/1000pd ($p = 0.03$). The increase in this group of drugs was due to increases in use of daptomycin and linezolid, as well as a 2-fold increase in the use of meropenem over the study period (from 6 to 12 DDD/1000pd; $p = 0.04$).

DISCUSSION

To our knowledge, these surveillance data represent the largest collection of data on antimicrobials dispensed or administered to hospitalized patients in northern Canada. From 2019 to 2021, there was a 49% relative increase in overall antimicrobial use, from 401 to 596 DDD/1000pd, but this difference was not statistically significant. There was substantial variation in rates of antimicrobial use among hospitals and among years within the same hospital.

Differences in methods, services, and patient populations can make national and international comparisons of rates of antimicrobial use difficult. Using methodology very similar to what was used in the current study, an analysis of CNISP surveillance data of hospitalized adult patients at 22 generally larger hospitals in southern Canada showed that antimicrobial use decreased from 643 to 573 DDD/1000pd between 2009 and 2016.⁷ Similar to the results of our current study, substantial variation was observed among hospitals in the earlier study. Since 2016, among a larger set of CNISP hospitals, overall rates of antimicrobial use have remained relatively stable (525 DDD/1000pd in 2020 across 93 hospitals, including some northern hospital sites).³⁴ Nontertiary, nonspecialized hospitals in Switzerland had antimicrobial use rates similar to those found in our study (538 to 546 DDD/1000 bed-days in 2017).³⁵ One study of 6 smaller community hospitals in North Carolina reported higher rates of antimicrobial use than in our study (ranging from 1000 to > 2000 DDD/1000pd monthly over the period January 2013 to June 2015),³⁶ which suggests variability in antimicrobial use in hospitals of similar size across different countries.

Among the 50 hospitals in our study, there was high variability in overall antimicrobial use rates, with 11-fold variability in 2021 and an interquartile range spanning 350 DDD/1000pd. The high variation in rates of antimicrobial use is not surprising, given that inpatient antimicrobial use rates within the same jurisdiction have been found to vary widely, both in Canada⁷ and in other jurisdictions.³⁷ The small size of many of the participating hospitals, as

well as differences in hospital services and capacity and the presence of intensive care units and specialty services at some hospitals, may explain at least some of the variation observed in our study. Further investigation is required to understand this variability and to optimize antimicrobial stewardship interventions.

In our study, there was a sizable but statistically insignificant increase in overall antimicrobial use between 2019 and 2021. It is notable that our study period included the onset of the COVID-19 pandemic. The pandemic resulted in many changes to the public health and hospital landscapes, which affected antimicrobial use in Canada and internationally. Some of these changes were due directly to the treatment of patients with COVID-19: for example, early in the pandemic, 77% of patients hospitalized with COVID-19 in the United States received at least 1 antimicrobial.³⁸ Other changes were indirect, such as disruptions in stewardship programs,³⁹ disruptions in supply chains, reductions in inpatient days, changes to services provided by hospitals, and fewer opportunities for community transmission of disease. Although some jurisdictions reported lower rates of antimicrobial use during the initial waves of the pandemic,³⁸ a systematic review found that most studies of hospital antimicrobial use reported an increase in use in 2020 compared with 2019.³⁹

In the current study, the increase of 195 DDD/1000pd in antimicrobial use between 2019 and 2021 was largely driven by increases of 80% and 64% in the use of third- and first-generation cephalosporins, respectively. For many participating hospitals, ceftriaxone was the antimicrobial of choice for patients with COVID-19. An increase in ceftriaxone use early in the pandemic was also reported for a large set of 716 hospitals in the United States, where 50% of inpatients with COVID-19 received at least 1 day of ceftriaxone therapy in 2020.³⁸ The US Centers for Disease Control and Prevention have suggested that the increased rate of ceftriaxone use was likely due to “difficulties in distinguishing COVID-19 from community-acquired pneumonia when patients first arrive at a hospital”.⁴⁰ At a hospital in New York, the increase in ceftriaxone use was attributed to the replacement of surgical patients with medical patients.⁴¹ In a Canadian study of antimicrobial prescribing during the first 3 waves of the pandemic at 3 urban hospitals, Elligsen and others⁴² found a transient increase in the prescribing of “respiratory antibiotics” on medical and intensive care wards; in that study, respiratory antibiotic use was aggregated and included ceftriaxone as well as amoxicillin-clavulanate, azithromycin, cefuroxime, levofloxacin, and moxifloxacin.⁴²

Potential reasons for the increase in ceftazolin use are less clear. In 2019, there was an international shortage of ceftazolin due to supply disruptions,^{43,44} which may have reduced use of the drug in that year at some hospitals. No increase in purchasing of ceftazolin was found among a network of 28 Canadian hospitals.⁴⁵

Although use of daptomycin increased significantly in our study, this drug constituted only a small fraction of total antimicrobial use. Higher rates of inpatient use of daptomycin during the first waves of the pandemic were reported in some^{46,47} but not all settings.⁴⁸ Increases in the use of the World Health Organization's "Reserve" category of antimicrobials could be related to treatment of superinfections.

This study had some limitations. Participating hospitals may not be representative of all hospitals in northern Canada. Data were not collected from every northern jurisdiction, and selection and volunteerism biases were likely, due to hospitals voluntarily opting to participate in the project; these biases may have been exacerbated by the burden of the pandemic response. It is notable that the regions with high rates of participation in this project are also the regions with existing centralized infrastructure for collecting antimicrobial use data and/or the regions that already participate in national surveillance of inpatient antimicrobial use. Our surveillance system does not capture data on indication for use or appropriateness of use. The use of data for dispensed medications may not represent the antimicrobials that were administered to patients.⁴⁹ There are technical challenges to obtaining antimicrobial use data from hospitals, and there may be data quality issues at some sites that we were unable to identify or evaluate. During this project, some of the challenges encountered by hospitals considering participation included capture of data in paper records without electronic entry, capture of data by electronic record systems for dispensed antimicrobials on weekdays but not weekends, and absence of an existing method for extracting and validating antimicrobial use data from electronic records. The northern jurisdictions are far from homogeneous, and interjurisdictional variation requires further investigation.

CONCLUSION

This study represents the largest collection to date of antimicrobial use data for inpatients in northern Canada. There was an increase of 195 DDD/1000pd in antimicrobial use from 2019 to 2021, largely driven by 80% and 64% increases in the use of third- and first-generation cephalosporins, respectively. A significant increase in daptomycin use was observed, but this drug accounted for only a small fraction of total antimicrobial use. The findings should be interpreted with caution, as participating hospitals may not be representative of all northern hospitals. High-quality and continued (or regular) surveillance is crucial to support antimicrobial stewardship efforts.

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