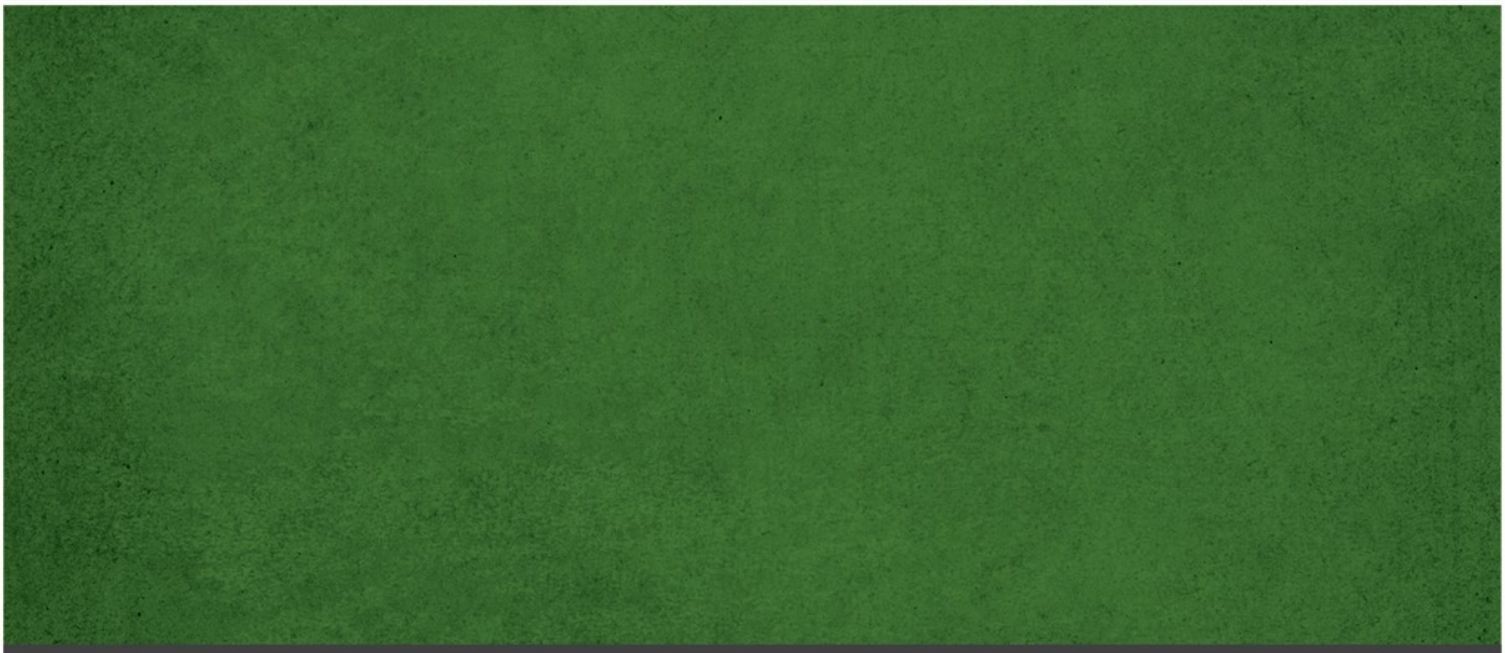
CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM

2017 REPORT



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Également disponible en français sous le titre:

Système canadien de surveillance de la résistance aux antimicrobiens – rapport de 2017

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This publication is available in alternative formats upon request.

Publication date: November 10th, 2017

Cat.:
ISSN:
Pub.:

CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM – 2017 REPORT

Glossary

AMR	Antimicrobial resistance
AMU	Antimicrobial use
BSI	Bloodstream infection
CA-CDI	Community-associated *Clostridium difficile* Infections
CAHI	Canadian Animal Health Institute
CCS	Canadian CompuScript
CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
CARSS	Canadian Antimicrobial Resistance Surveillance System
CCHS	Canadian Community Health Survey
CDH	Canadian Drugstore and Hospital
CDI	*Clostridium difficile* infection
CDTI	Canadian Disease and Therapeutic Index
CIDSC	Communicable and Infectious Disease Steering Committee
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CNISP	Canadian Nosocomial Infection Surveillance Program
CPE	Carbapenemase-producing Enterobacteriaceae
CPO	Carbapenamase-producing organisms
CRE	Carbapenem-resistant Enterobacteriaceae
CTBRS	Canadian Tuberculosis Reporting System
DDD	Defined Daily Dose
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESAG	Enhanced Surveillance for Antimicrobial Resistant Gonorrhea
ESBL	Extended-spectrum ß-lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
GLASS	Global Antimicrobial Resistance Surveillance System
GNB	Gram-negative Bacilli
HA-CDI	Healthcare-associated *Clostridium difficile* infection
HA-MRSA	Healthcare-associated methicillin-resistant *Staphylococcus aureus*
kg	Kilogram
MDR	Multidrug-resistant
MDR-TB	Multidrug-resistant Tuberculosis
mg/L	Milligrams per liter
MIA	Medically important antimicrobials
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSM	Men who have sex with men
NAAT	Nucleic Acid Amplification Test
NML	National Microbiology Laboratory
NIHB	Non-Insured Health Benefits
OIE	World Organisation for Animal Health
PCU	Population Correction Unit
PHAC	Public Health Agency of Canada
TB	Tuberculosis
VRE	Vancomycin-resistant enterococci
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant tuberculosis

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Message from the Chief Public Health Officer and the President of the Public Health Agency of Canada

Antimicrobial resistance (AMR) continues to be one of the most significant public health threats facing the world today. Drug resistant infections threaten healthcare as we know it, as it erodes our ability to prevent and treat infections. In Canada, although overall rates of AMR have remained stable in recent years, they are still well above levels we saw in the early 2000s. Collective and continued efforts to reduce the rates of AMR and preserve the effectiveness of existing antimicrobials are essential to ensuring our ability to fight infectious diseases.

September 2017 marked the release of *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action* (Framework). The Framework resulted from collaborative efforts on the part of the federal government, provinces and territories and other key partners in the human and animal health sectors. It was designed to guide efforts across sectors to address AMR and antimicrobial use (AMU), with a focus on four key components: surveillance, stewardship, infection prevention and control, and research and innovation. The Canadian Antimicrobial Resistance Surveillance System (CARSS) provides a foundation of evidence upon which to build even greater integration.

Through the synthesis and analysis of information from PHAC's surveillance systems and laboratory reference services, CARSS provides an integrated picture of AMR and AMU in Canada. Making progress towards addressing the gaps identified in last year's report, the CARSS-2017 Report provides more surveillance data on AMR in priority organisms and on infections occurring in the community. It also presents new information on AMU among non-physician prescribers and expanded AMR surveillance in food-producing animals.

PHAC relies on relationships and the collective efforts of many partners to provide a more comprehensive view of AMR/AMU in Canada. We thank all contributors for their time and continued support, and we look forward to new and continued collaborations to improve AMR and AMU surveillance in Canada.

Dr. Siddika Mithani
President, Public Health Agency of Canada

Dr. Theresa Tam
Chief Public Health Officer of Canada

Introduction

The Canadian Antimicrobial Resistance Surveillance System (CARSS) is Canada's national surveillance system for reporting on antimicrobial resistance (AMR) and antimicrobial use (AMU). CARSS integrates and synthesizes information from Public Health Agency of Canada (PHAC) surveillance systems and laboratory reference services, covering both human and food-producing animal populations. CARSS aims to provide evidence to support policy and programming to foster prudent AMU, and to prevent, limit, and control AMR in Canada. It is a core component of *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action*[1].

The CARSS-2017 Report provides a snapshot of 2015 and 2016 AMR and AMU data in Canada. In addition, it presents new information on antimicrobial-resistant infections occurring in the community setting, antimicrobial prescribing practices among dentists, AMR and AMU on sentinel turkey farms, and AMU in companion animals.

In 2014, the Public Health Network's Communicable and Infectious Disease Steering Committee (CIDSC) and PHAC reviewed a proposed list of microorganisms that have shown resistance to antimicrobials. From this list, the CIDSC AMR Task Group identified the microorganisms of greatest importance to public health in Canada, and as such, of priority for national surveillance[2]. The technical information presented on the priority microorganisms in each CARSS publication may adapt in response to data availability and evolving AMR information needs, as established through ongoing consultation with stakeholders. In this way, CARSS endeavors to be flexible and responsive to issues related to AMR and AMR surveillance in Canada.

International comparisons between Canada and other countries with respect to AMR can only be made when data are presented at the national level, and are collected using comparable methodologies. While some Canadian data on antimicrobial resistant microorganisms are collected and reported in a way that allows for international comparison, most are not. Despite this challenge, CARSS-2017 Report aims to provide an international perspective on AMR and AMU, where appropriate, to give greater context to the surveillance findings for Canada.

Although PHAC surveillance systems are producing useful, reliable data on AMR and AMU, there are areas for improvement. CARSS-2017 Report describes the current limitations of Canada's AMR and AMU surveillance and provides an update on efforts planned or underway to address existing surveillance gaps.

CARSS-2017 Report is divided into two parts. Part one is an executive summary that highlights AMR and AMU surveillance findings in Canada. Part two is a technical annex that provides a detailed look at AMR and AMU surveillance data. The technical annex has an AMR section that focuses on each priority microorganism and describes the surveillance methods used. The technical annex's AMU section provides information on antimicrobials intended for people. Data on human AMU focuses on the amount of antimicrobials dispensed through community pharmacies, prescriber specialization breakdown, hospital purchasing of antimicrobials, and indications for antimicrobial use.

EXECUTIVE SUMMARY

Antimicrobial resistance and antimicrobial use

From 2011 to 2016, Canada reported AMR rates that were similar to or lower than rates reported by many other developed countries[3-5]. While Canadian AMR infection rates relating to antimicrobial-resistant organisms have fluctuated over recent years, upward trends were seen in the rate of methicillin-resistant *Staphylococcus aureus* (MRSA) blood stream infection (BSI) in pediatric hospitals, and the rate of vancomycin-resistant *Enterococcus* (VRE) BSI in adult hospitals. In addition, the rate of drug-resistant gonorrhea increased between the years 2014 and 2015. Conversely, rates of healthcare-associated *Clostridium difficile* infection (CDI) decreased over time.

Examining human antimicrobial use in the community in Canada, the rate of prescriptions dispensed was relatively stable between 2013 and 2016 and slightly lower than the rates observed between 2010 and 2012. Newfoundland and Labrador had the highest rate of prescriptions dispensed in the community in 2016; British Columbia had the lowest. In 2015, Canada was 13th lowest among 31 countries in consumption of antimicrobials, a slightly worse showing than in 2014 when Canada placed 12th among 31 countries in antimicrobial consumption[5]. The antimicrobial prescribing rate among physicians and dentists is generally stable, following an increase seen in prescribing by dentists from 2010 to 2012. In terms of antimicrobial use in the hospital setting, the purchasing of antimicrobials remained stable between 2010 and 2016. In 2016, Manitoba, Prince Edward Island, and Newfoundland and Labrador had the highest antimicrobial purchasing rates per capita; Ontario and Alberta had the lowest rates. Of concern, hospitals in 2016 purchased more antimicrobials considered “last resort” (e.g., daptomycin) than in previous years[6].

The key findings on AMR and AMU surveillance are presented below.

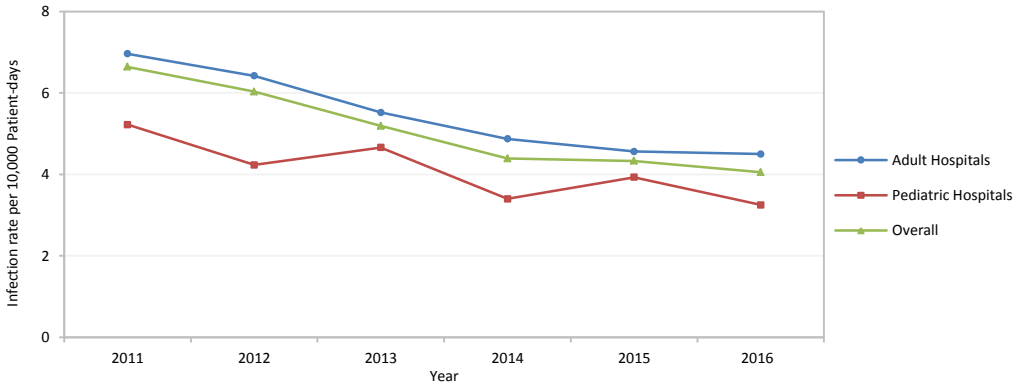
Antimicrobial resistance

The promotion of standardized infection prevention and control techniques, in combination with antimicrobial stewardship, contribute to reducing the spread of infections, inappropriate prescribing, and in turn, help prevent the development of AMR in Canada. However, despite the relatively low rates of AMR observed in Canada, there are areas of concern[7].

Clostridium difficile (*C. difficile*), the bacteria responsible for *C. difficile* infection (CDI), may be a consequence of standard drug treatments routinely prescribed for unrelated infections, as *C. difficile* bacteria are naturally resistant to many antimicrobials and spread rapidly once competing microorganisms have been eliminated by these drugs[8]. In 2016, rates of healthcare-associated CDI (HA-CDI) in Canada continued to decline. The overall rate of HA-CDI decreased from 6.64 cases per 10,000 patient-days in 2011 to 4.05 cases per 10,000 patient-days in 2016 (Figure 1). When types of hospitals were compared, the 2016 rate of HA-CDI continued to be higher in adult hospitals than in pediatric hospitals (4.50 and 3.25 cases per 10,000 patient-days, respectively). Surveillance of community-

associated (CA)-CDI in sentinel hospitals began in 2015 and will continue for three years. First year surveillance data (2015) showed that 37% of all CDI reported among patients admitted to sentinel hospitals were community-associated. This proportion is similar to other proportions of CA-CDI that have been reported in the literature[5].

Figure 1: Rate of healthcare-associated *C. difficile* infection, 2011-2016

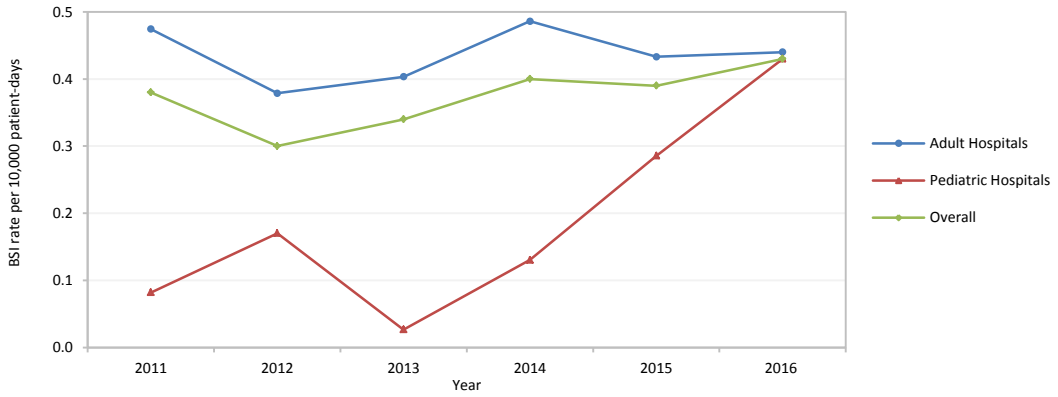


A critical indicator for AMR in Enterobacteriaceae is resistance to the carbapenem class of antimicrobials. Infections caused by carbapenemase-producing Enterobacteriaceae (CPE) are generally multidrug-resistant, have limited treatment options, and are associated with poor health outcomes, making them a serious public health concern worldwide[9]. Globally, infection rates of CPE and other carbapenemase-producing organisms have increased over time[4, 5], while rates of CPE infections in sentinel Canadian hospitals have remained low and relatively stable. From 2011 to 2014, the overall rate of CPE infections in sentinel hospitals decreased from 0.013 cases to 0.007 cases per 10,000 patient-days. In 2015, this rate increased very slightly to 0.008 cases per 10,000 patient-days. In contrast, the number of CPE isolates voluntarily reported to provincial public health laboratories increased from 4 in 2009 to 779 in 2016. The greatest annual increase (1.8 fold) occurred between 2015 and 2016. This discrepancy between sentinel hospital and laboratory surveillance findings may be due to increased cases of CPE infection in the community or among hospitals not represented in the group of hospitals under surveillance; increased awareness of and reporting of CPE; and/or other factors not yet identified.

First described in 1961, methicillin-resistant *Staphylococcus aureus* (MRSA) is a *S. aureus* that has acquired resistance to anti-staphylococcal β-lactam antibiotics (e.g., methicillin, oxacillin, and cefazolin). While MRSA has historically been associated with hospitals and other healthcare settings (healthcare-associated MRSA [HA-MRSA]), community-associated MRSA (CA-MRSA) is increasingly being observed as a cause of illness in Canada and elsewhere[3-5]. The overall rate of MRSA infection in sentinel hospitals in Canada increased from 2.84 cases to 3.13 cases per 10,000 patient-days between 2011 and 2016. However, this rate remained below the 2009 rate of 3.78 cases per 10,000 patient-days. When hospitalized cases were compared by area of acquisition, the overall rate of HA-MRSA infection decreased between 2011 and 2016 (from 1.93 to 1.69 cases per 10,000 patient-days, respectively), while the overall rate of CA-MRSA infection increased during the same time period (from 0.56 to 0.96 cases per 1,000 admissions). From 2011 to 2016, the rate of CA-MRSA infection in pediatric hospitals was consistently higher than the rate in adult and mixed-patient hospitals (e.g., 1.56, 1.02, and 0.75 cases per 1,000 patient admissions in 2016, respectively). The rate of HA-MRSA blood stream infection (BSI) in

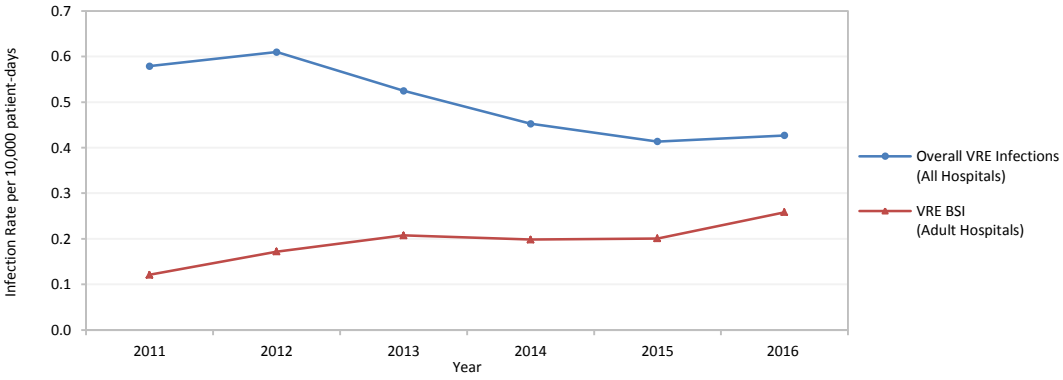
adult hospitals was relatively stable from 2011 to 2016 (0.47 to 0.44 cases per 10,000 patient-days), whereas the rate of HA-MRSA BSI in pediatric hospitals increased more than fivefold (rising from 0.08 to 0.43 cases per 10,000 patient-days between 2011 and 2016) (Figure 2). This increase in pediatric BSI is concerning and requires closer monitoring.

Figure 2: Rate of healthcare-associated MRSA blood stream infection (BSI), 2011-2016



Vancomycin-resistant enterococci (VRE) infections have limited treatment options, and are the focus of international surveillance efforts[3-5,7]. VRE in Canada has historically been associated with healthcare facilities, and the burden of VRE in the community is unknown. The overall rate of VRE infection in Canada increased sharply between 2007 (0.10 cases per 10,000 patient-days) and 2012 (0.61 cases per 10,000 patient-days), and then declined to 0.41 cases per 10,000 patient-days in 2015 (Figure 3). The rate increased slightly in 2016 to 0.44 cases per 10,000 patient-days. When compared by type of hospital and site of infection, the rate of VRE BSI in sentinel adult hospitals more than doubled between 2011 (0.12 cases per 10,000 patient-days) and 2016 (0.26 cases per 10,000 patient-days).This finding points to the need for ongoing monitoring of this microorganism in Canada.

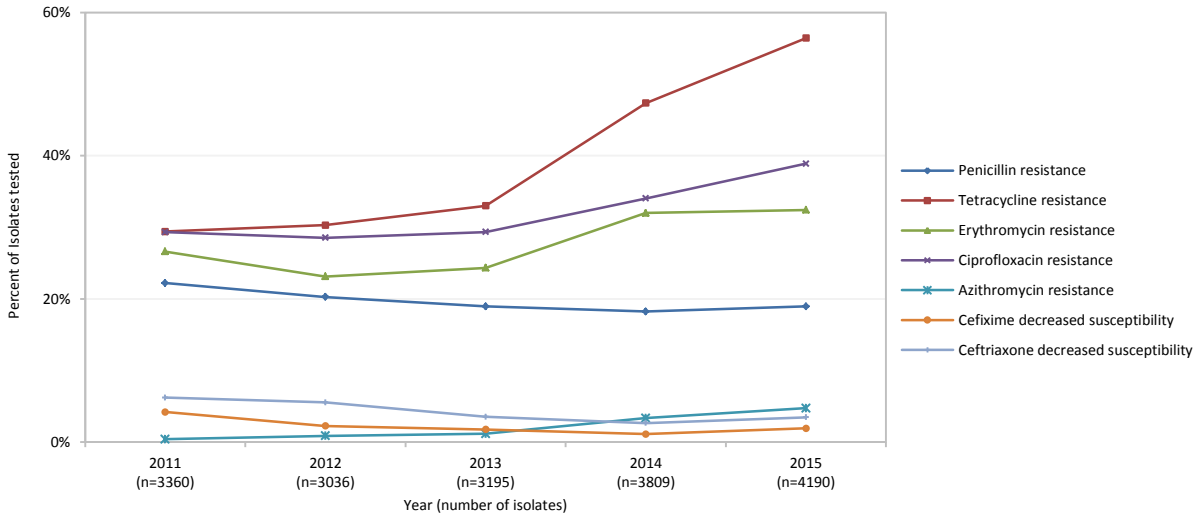
Figure 3: Rate of overall VRE infection and VRE blood stream infection, 2011-2016



Gonorrhea (caused by *Neisseria gonorrhoeae*) is one of the most commonly reported bacterial sexually transmitted infections (STI) in Canada[10]. The overall rate of gonorrhea more than doubled, from 21.8 cases per 100,000 population in 2001 to 55.4 cases per 100,000 population in 2015. The treatment and control of gonorrhea are major public health challenges worldwide[7,11], due to the emergence and spread of AMR in *N. gonorrhoeae.* In Canada, the proportion of *N. gonorrhoeae* isolates resistant to many

antimicrobials continued to rise in 2015 (Figure 4). Between 2014 and 2015, the proportion of cultured isolates resistant to at least one antimicrobial increased from 52% to 60%. Between 2010 and 2015, the proportion of azithromycin-resistant *N. gonorrhoeae* increased from 1.3% to 4.7%. When the proportion of antimicrobial-resistant *N. gonorrhoeae* strains obtained from isolates is at a level of 5% or more, or when an unexpected increase below 5% is observed in key populations with high rates of gonococcal infection, the World Health Organization recommends that countries review and modify their national guidelines for STI treatment and management[11], a best practice that Canada implements. Isolates with decreased susceptibility to cefixime or ceftriaxone, two cephalosporin class antimicrobials used to treat gonorrhea, also increased between 2014 and 2015 (from 1.1.% to 1.9% and 2.7% to 3.5%, respectively). From 2012 to 2014, there was a very small proportion of isolates in Canada observed to be both resistant to azithromycin and to have decreased susceptibility to cephalosporins (cefixime or ceftriaxone), the currently recommended dual therapy treatment for gonorrhea (0.2% in 2012, 0.3% in 2013, and 0.03% in 2014, respectively). The United Kingdom reported the world's first dual therapy treatment failure in 2015[12]. While Canada has had no reported treatment failures resulting from resistance to azithromycin and decreased susceptibility to cephalosporins, these findings highlight the need for ongoing monitoring of drug-resistant *N. gonorrhoeae,* and the appropriate use of antimicrobials to help maintain the effectiveness of current treatment regimens.

Figure 4: Percent of gonorrhea isolates demonstrating resistance/decreased susceptibility to selected antibiotics, 2011-2015



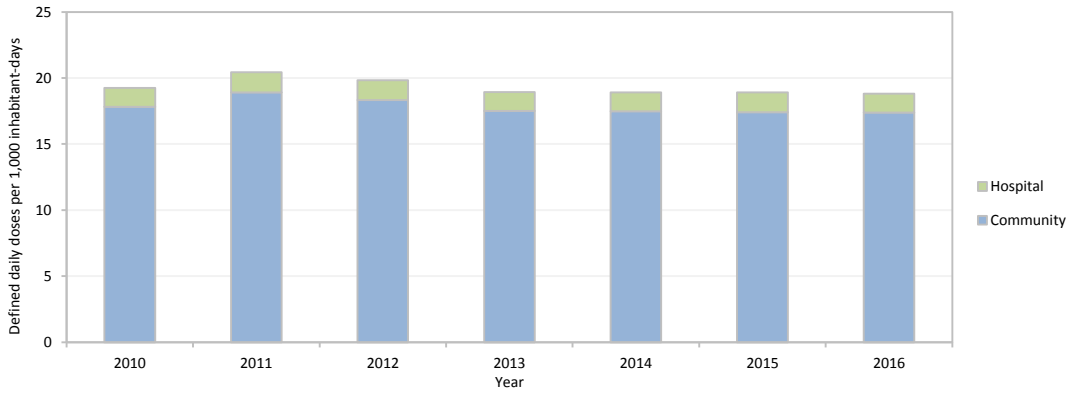
Antimicrobial use in humans

The use of antimicrobials is a major factor in the emergence and spread of resistant microorganisms. Prudent AMU is recognized as a core element in managing the risks of AMR to preserve the effectiveness of antimicrobials and slow the development of drug-resistant organisms. Programs and policies that highlight education, awareness-raising, as well as professional and regulatory oversight help foster rational prescribing and use of antimicrobials in humans. AMR and AMU surveillance provide data for action to guide antimicrobial stewardship efforts[13].

Antimicrobial use in the community

In Canada, the majority of antimicrobials used by humans are available by prescription only. In 2016, an estimated 92% of doses of antimicrobials were dispensed in the community, while the remaining proportion (8%) was purchased for use in hospitals (Figure 5). The proportion of community dispensed antimicrobials did not change from previous years[14]. In 2016, an estimated 22.6 million prescriptions were dispensed in Canada, with a total expenditure of nearly 700 million dollars. The rate of antimicrobial prescriptions dispensed in the community setting was relatively stable between 2013 and 2016 (approximately 625 prescriptions per 1,000 inhabitants) and slightly lower than the rates observed between 2010 and 2012 (598 to 547) prescriptions per 1,000 inhabitants). In 2016, amoxicillin was the most frequently prescribed antimicrobial (25% of prescriptions), followed by azithromycin (10% of prescriptions). In 2016, the rate of prescriptions dispensed in adults 60 years and older was 86 prescriptions per 1,000 inhabitants, nearly 1.5 times higher than rates in the 0 to 14 year and 15 to 59 year age groups (598 and 547 prescriptions per 1,000 inhabitants, respectively). Amoxicillin, ciprofloxacin, and cephalexin were the antimicrobials most commonly prescribed in the oldest age group.

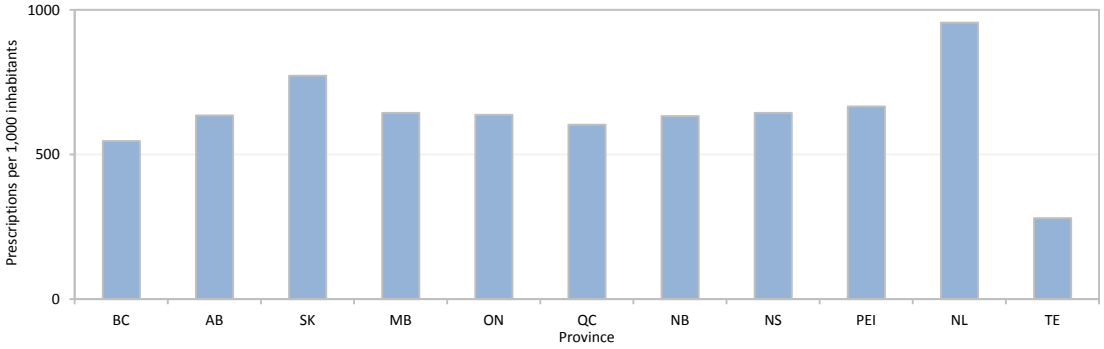
Figure 5: Defined daily doses (DDDs) per 1,000 inhabitant-days in Canada, from hospital purchase and community prescription data, 2011-2016



In 2015, the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) reported the overall consumption of antimicrobials for systemic use (J01) in both hospital and community settings for participating European countries[5]. ESAC-Net is a good candidate for human AMU comparisons to Canada, as ESAC-Net represents one of the largest, internationally standardized AMU data sources and uses methods comparable to Canada. Comparing 2015 outpatient consumption in Europe with 2015 Canadian community consumption (community pharmacist dispensing), Canada ranked 13th out of 31 countries (ranked from lowest to highest consumption), a slightly worse showing than in 2014 when Canada was 12th among 31 countries in community consumption of antimicrobials.

When data were compared by province in Canada, Newfoundland and Labrador had the highest prescription rate (955 prescriptions per 1,000 inhabitants) in 2016, a finding also observed in previous years. Prescription rates were lowest in British Columbia and among individuals covered by the Non-Insured Health Benefits (NIHB) program in the Territories (Figure 6). The reasons for these provincial differences are currently being explored. While use of most antimicrobials was higher in Newfoundland and Labrador than in other provinces, amoxicillin was prescribed at particularly high rates (data not shown).

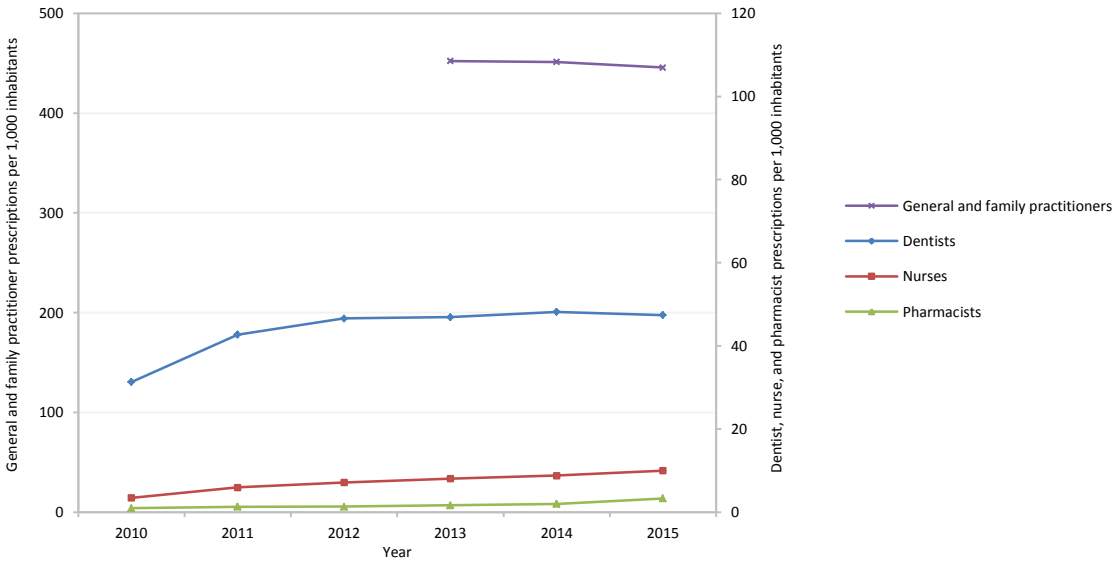
Figure 6: Canadian variation in prescription rates per 1,000 individuals among provinces and NIHB-covered individuals in the territories, 2016



Note: BC = British Columbia, AB = Alberta, SK = Saskatchewan, MB = Manitoba, ON = Ontario, QC = Québec, NB = New Brunswick, NS = Nova Scotia, PEI = Prince Edward Island, NL = Newfoundland and Labrador, TE = Territories (Yukon, Northwest Territories, and Nunavut)

In 2016, family physicians accounted for 65% of all prescriptions dispensed by community pharmacies in Canada. The most commonly prescribed antimicrobials by all physicians in private practice were amoxicillin, azithromycin, and cephalexin. As seen in previous years, antimicrobials were most often prescribed for respiratory infections, followed by genito-urinary system infections, and skin and soft tissue infections. In 2015, physicians in private practice wrote 446 antimicrobial prescriptions per 1,000 inhabitants, while the rate for dentists was 47 prescriptions per 1,000 inhabitants (Figure 7). Data in 2015 showed a downward trend in the antimicrobial prescribing rate of physicians and a generally stable rate for dentists, following an increase seen in prescribing by dentists from 2010 to 2012.

Figure 7: Prescriptions dispensed in the community by general and family practitioners, dentists, nurses, and pharmacists, 2010-2015



Antimicrobial use in the hospital setting

In 2016, 8% of antimicrobial doses in Canada were purchased for use in the hospital setting (Figure 5); this proportion was unchanged from previous years. The rate of antimicrobial purchasing by hospitals varied throughout Canada during the surveillance period. In 2016, Manitoba, as well as Prince Edward Island and Newfoundland and Labrador combined, had the highest antimicrobial purchasing rates per

capita (2.7 and 2.3 defined daily doses [DDDs] per 1,000 inhabitant-days, respectively). Ontario and Alberta had the lowest rates (1.0 and 1.3 DDDs per 1,000 inhabitant-days, respectively).

Cephalosporins were the most purchased antimicrobial drug class by hospitals in Canada in 2016, similar to previous years, followed by fluoroquinolones. While the rate of cephalosporin purchasing remained relatively stable from 2010 to 2016, the rate of purchasing of fluoroquinolones decreased by 43% during the same time period (0.25 to 0.17 DDDs per 1,000 inhabitant-days). Between 2010 and 2016, the purchasing rate for two drug classes, penicillin combinations (e.g., penicillins with an enzyme inhibitor) and β-lactamase sensitive penicillins (e.g., penicillin G), increased by 41% (0.09 to 0.15 DDDs per 1,000 inhabitant-days) and 34% (0.05 to 0.07 DDDs per 1,000 inhabitant-days), respectively. Of concern, hospital purchasing of daptomycin, one of the "last resort" antibiotics, increased in 2016. Daptomycin is generally reserved for use in the treatment of life-threatening *S. aureus* and *Enterococcus* infections[6]. The reason for this increase is not known.

Antimicrobial use in food-producing and companion animals

Just as use of antimicrobials in humans can lead to the development and persistence of AMR, use of antimicrobials in food-producing and companion animals may also contribute to antimicrobial-resistant bacteria. Such bacteria may then be transferred to humans through direct contact with animals, as well as foodborne or waterborne routes. Surveillance of antimicrobial use in animals, crops, and people provides important data to guide antimicrobial stewardship efforts and to contain AMR in Canada.

In 2016, approximately 1.0 million kilograms of medically important antimicrobials were distributed for sale for use in animals by the Canadian Animal Health Institute (CAHI) member companies. This volume was approximately 14% lower than 2007 and 17% lower than 2015. These reported quantities do not include antimicrobials imported for 'own use' or as active pharmaceutical ingredients intended for further compounding. Additionally, there were 0.6 million kilograms of ionophores and chemical coccidiostats distributed for use in animals (these antimicrobials are not considered medically important). In 2016, 99% of the antimicrobials distributed were intended for use in food-producing animals and 1% was intended for use in companion animals (based on kilograms of active ingredient).

The overall quantity of fluoroquinolones distributed for use in animals decreased by approximately 56% between 2015 and 2016. Fluoroquinolones are classified as "of very high importance to human medicine" by Health Canada's Veterinary Drugs Directorate. Fluoroquinolones are licensed for use in certain animal species in Canada and have warnings on their labels recommending against extra-label use due to AMR concerns and guidelines for use only after failure of an initial treatment[15].

Between 2012 and 2016, there were provincial differences in the kilograms of active ingredient of antimicrobials distributed for sale by CAHI member companies, and year-to-year differences within provinces in the quantities distributed. The provinces with the greatest declines since 2015 (as relative percentages of their 2015 kilogram total) were New Brunswick, Manitoba, Nova Scotia, Newfoundland and Labrador, Saskatchewan, and Québec (decrease of >15% of total kilograms each). The only province

with an increase in total kilograms of active ingredient distributed for sale was Prince Edward Island (approximately 20% increase in kilograms).

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) collects and reports information from member countries on antimicrobial agents intended for use in animals. ESVAC is a good candidate for animal AMU comparisons to Canada, as ESVAC is the only current multinational source of quantitative surveillance data on antimicrobial agents intended for use in animals. Canada uses reporting metrics similar to ESVAC, with the notable exception that Canada includes beef cows in the denominator. Using the latest ESVAC data (2015) and the latest Canadian data (2016), out of 31 countries, Canada was the fifth highest for consumption of antimicrobials measured as milligram of drug per kilogram of animal (equivalent to milligram per population corrected unit)[16]. In 2016, Canada had higher consumption than the reported average for the participating European countries. Canada would report more antimicrobials per kilogram of animal if the currently unknown quantities of antimicrobials imported for 'own use' or as active pharmaceutical ingredients for further compounding were included.

PHAC conducts farm level surveillance to describe trends in farm AMR and AMU, and investigates associations between farm AMU and AMR to provide sound data for human health risk assessments. Farm level surveillance indicated that a change in antimicrobial use policies on broiler chicken farms across Canada appeared to have achieved the desired goal of reducing the use of antimicrobial agents in classes considered of very high importance to human medicine, in particular the use of the antimicrobial ceftiofur (a third generation cephalosporin).

Addressing surveillance data gaps

CARSS-2017 Report provides a good overview of the current situation of AMR and AMU in Canada. There are strong data for specific AMR pathogens from large, tertiary hospitals. An added strength is the representation of AMR in foodborne bacteria from food-producing animals and food of animal origin. In addition, AMU information for both humans and animals has improved over time. For example, the reporting of AMU among Indigenous populations in Canada is now addressed in a more fulsome analysis, and PHAC has acquired farm level data on how and why antimicrobials are used.

However, there are gaps that need to be addressed to increase the depth, breadth, and quality of AMR and AMU surveillance in Canada. For example, there are limited data on antimicrobial-resistant organisms in the community. There are also limited data on AMR in smaller, non-academic hospitals; Indigenous populations; AMR in long term-care facilities; and no or limited data for northern healthcare settings. In addition, there are no or limited data on the appropriateness of antimicrobials that are prescribed.

AMR data along the food chain for animals and humans are restricted to specific bacterial organisms (e.g., *Salmonella*). The livestock species covered include the major meat-producing animals in Canada (e.g., cattle, pigs, broiler chickens, and turkeys), while no on-going surveillance is currently underway for other animal production areas (e.g., aquaculture, veal, and sheep). Farm level AMU data are currently limited to sentinel farms in swine and poultry.

Since the release of the first CARSS report in 2015, PHAC has collaborated with a range of partners representing public health, health care, agriculture, and other sectors, to address identified gaps and improve AMR and AMU surveillance in Canada. PHAC surveillance programs have many initiatives planned, under way, or recently completed to collect new data or to enhance the use of existing AMR or AMU data. Examples of such initiatives include:

- a point prevalence study on AMR and AMU in smaller community, rural, and Northern based hospitals, and long term-care facilities;
- an AMU 'Rapid Response' module in the Canadian Community Health Survey (CCHS) to provide answers to common questions on AMU and information on personal antibiotic stewardship practices;
- a three-year study of hospitalized cases of community-associated *Clostridium difficile*;
- turkey and nursery pig surveillance studies to examine AMU and AMR on farms; and
- a five-year study that will provide a greater understanding of how food production practices contribute to the development of AMR of human health concern.

Next steps and conclusion

The evolving epidemiology of AMR in Canada, and the growing threat of AMR globally, underscore the need for ongoing monitoring of this public health event. PHAC continues to address AMR and AMU surveillance gaps in partnership with other federal departments, the provinces and territories, non-governmental organizations, professional associations, and academia. To this end, PHAC is implementing a number of initiatives over the next several years to enhance surveillance information, with the goals of improving Canada's ability to respond to emerging AMR threats, and supporting antimicrobial stewardship efforts by providing better evidence for decision-making.

Global problems require global solutions. Work is currently under way by PHAC to harmonize its surveillance methods in order to participate in international programs stemming from the Global Action Plan on Antimicrobial Resistance. These programs include the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) and the World Organization for Animal Health's global database on antimicrobial agents intended for use in animals. The first data contributions to GLASS by PHAC occurred in 2017, with the submission of 2015 human *Salmonella* data. Full participation is targeted for 2019. In addition to taking part in global programs, PHAC is committed to working with its international partners in other ways to identify common approaches and best practices to prevent, limit, and control the development and spread of AMR in Canada and worldwide.

TECHNICAL ANNEX

Antimicrobial resistance and use

The following technical annex provides a detailed view of 2015 and available 2016 data on the priority organisms monitored under PHAC's surveillance systems. The antimicrobial resistance (AMR) section focuses on PHAC's nine priority organisms and surveillance methods to provide a description of the current situation of AMR in Canada. As the AMR landscape is dynamic, the priority organisms listed in the technical annex may adapt with each publication in response to evolving AMR information needs and data availability. These priorities are established through consultation with experts and stakeholders across Canada. The priority organisms listed in the following CARSS-2017 AMR technical annex include:

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae and *Acinetobacter* spp.
- *Staphylococcus aureus*
- *Enterococcus* spp.
- *Streptococcus pyogenes* and *pneumoniae*
- *Neisseria gonorrhoeae*
- *Mycobacterium tuberculosis*
- *Salmonella enterica* serovars Typhi and Paratyphi
- Non-typhoidal *Salmonella enterica*

The AMR monitored in the animal/food/retail sector includes:

- *Escherichia coli*
- *Campylobacter* spp.
- *Salmonella enterica*

The antimicrobial use (AMU) section provides information on antimicrobials intended for use in humans, animals, and crops. With regards to antimicrobials intended for use in humans, data sources include antimicrobials dispensed through community pharmacies, prescriber specialization breakdown, as well as hospital purchasing and use. Animal data include antimicrobials distributed for sale, farm level data providing indications for antimicrobial use, and an international comparison of antimicrobial distribution/sales data.

The following surveillance systems provided AMR/AMU results for this report:

1. The *Canadian Nosocomial Infection Surveillance Program* (CNISP)

   Established in 1994, CNISP is a collaborative effort between PHAC and sentinel hospitals participating as members of the Canadian Hospital Epidemiology Committee (CHEC), a subcommittee of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada. This program conducts surveillance on select antimicrobial-resistant organisms and

healthcare-associated infections in over 60 largely university-affiliated, acute-care hospitals in all provinces. No data are collected from the three territories.

2. The *Canadian Integrated Program for Antimicrobial Resistance Surveillance* (CIPARS)

   Established in 2002, CIPARS monitors AMU in animals and humans, as well as AMR in *Salmonella* in humans, animals, animal feed, and retail food. Antimicrobial resistance in *Campylobacter* and *Escherichia coli* are monitored in animals and food of animal origin. The focus of CIPARS is on bacteria and antimicrobials of public health importance; veterinary pathogens other than *Salmonella* are not covered. The Canadian Animal Health Institute (CAHI) voluntarily provides CIPARS with data on the quantities of antimicrobial agents distributed by their member companies. Health Canada's Pest Management Regulatory Agency (PMRA) collects annual Canadian sales data from all pesticide manufacturers for antimicrobials intended for use on crops and provides these data to CIPARS.

3. The *Canadian Tuberculosis Reporting System* (CTBRS)

   The CTBRS is a case-based surveillance system that uses data submitted by the provincial and territorial public health authorities and maintains information on people diagnosed with active tuberculosis.

4. The *Antimicrobial-resistant Neisseria gonorrhoeae Surveillance System*

   The *Antimicrobial-resistant Neisseria gonorrhoeae Surveillance System* has monitored antimicrobial susceptibilities of *N. gonorrhoeae* since 1985, through collaboration between the National Microbiology Laboratory (NML) and provincial laboratories.

5. The *National Surveillance of Invasive Streptococcal Disease*

   The *National Surveillance of Invasive Streptococcal Disease* is a passive surveillance system that monitors antimicrobial susceptibilities in *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolated from sterile sites such as blood and spinal fluid. The surveillance is conducted through collaboration between the NML, provincial laboratories, the University of Manitoba, and the Canadian Antimicrobial Resistance Alliance.

In addition to the systems outlined above, PHAC's NML supports all AMR surveillance programs, providing data on molecular characterization and antimicrobial resistance. The NML also provides laboratory reference services to all provinces and territories, which assists with the detection of novel and emerging AMR organisms.

Human AMU data include information on prescriptions dispensed by retail pharmacies in Canada, antimicrobials purchased by Canadian hospitals, and diagnoses for which physicians have recommended an antimicrobial in the community. Four datasets are accessed describing human AMU, and are presented in three sections: Community AMU, AMU by diagnosis, and Hospital AMU.

1. Community AMU

   The data presented are from two datasets: the Canadian CompuScript (CCS) dataset (purchased from IQVA), and Health Canada's Non-Insured Health Benefits (NIHB) program. The CCS includes data collected from 60% of pharmacies in Canadian provinces, which are extrapolated to the universe of nearly 10,000 Canadian pharmacies. Data included are prescriptions dispensed by antimicrobial product, and the number of units dispensed by product.

   The NIHB program data were acquired in order to present a picture of use among Indigenous populations in Canada. This dataset includes prescription counts and the number of units dispensed by product for all prescriptions dispensed under the program.

2. AMU by diagnosis

   The Canadian Disease and Therapeutic index (CDTI) dataset, purchased from IQVA, provides information about the patterns and treatments of disease encountered by office-based physicians (specialists and general practitioners, including those with offices in hospitals). Data from 652 physicians were available in 2016, and projection methods were used to extrapolate to the universe of approximately 55,092 Canadian physicians. At visits to these physicians during data collection periods, the physicians record all diagnoses made, as well as all drug products that are recommended (whether or not a prescription for that product is provided).

3. Hospital AMU

   The Canadian Drugstore and Hospital (CDH) database, purchased from IQVA, provides a measure of the dollar value and unit volume of pharmaceutical products purchased by nearly all Canadian hospitals. Data about purchases from pharmaceutical manufacturer warehouses/wholesalers are collected from over 650 hospitals, and are extrapolated to represent purchases made by over 740 hospitals across Canada.

Clostridium difficile

Clostridium difficile (*C. difficile*) has been reported as the most frequent cause of healthcare-associated infectious diarrhea in Canada[17]. Transmission of *C. difficile* is often through contact with contaminated surfaces, as *C. difficile* spores are naturally resistant to commonly-used disinfectants[18]. Although *C. difficile* is not traditionally considered to be an antimicrobial-resistant organism, *C. difficile* infection (CDI) can be a consequence to antibiotic therapies routinely prescribed for unrelated infections, often resulting in a competitive advantage over susceptible organisms[4]. A notable example is the emergence of the North American pulse-field type 1 (NAP-1) strain of *C. difficile*, which demonstrated increased virulence and resistance to fluoroquinolones. To date, resistance of *C. difficile* to currently recommended antimicrobial therapies for CDI (i.e., metronidazole and vancomycin) is not a concern.

Methods

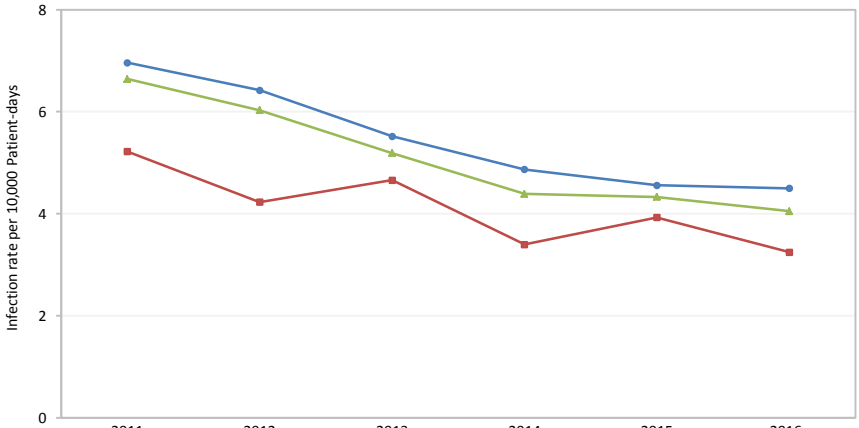
National surveillance data on healthcare-associated CDI (HA-CDI) have been collected prospectively by PHAC since 2007, and represent all non-recurrent inpatient healthcare-associated infections attributable to a sample of largely university-affiliated, acute-care hospitals in all provinces (no data are collected from the three territories). A minimum dataset is completed for inpatients diagnosed with CDI (demographics, clinical information, previous hospitalizations, source of infection, and ward type). A two-month targeted surveillance is conducted each year, and includes an expanded minimum dataset (e.g., antibiotic treatments and outcome), linkages to laboratory results (e.g., molecular characterization and susceptibility testing) and a review of the patient outcome at 30 days (i.e., alive or not). Pediatric inpatients are included as part of targeted surveillance year round.

Patients diagnosed with CDI are epidemiologically classified as healthcare-associated or community-associated. Cases are considered healthcare-associated if any of the following four criteria are met: (1) the patient had been admitted for three days or more prior to the onset of symptoms; (2) the patient had been previously hospitalized within four weeks; (3) the patient had two or more visits to any of the following locations within the previous four weeks: oncology, dialysis, day surgery, day hospital, transfusion clinic, interventional radiology, or emergency; and (4) the patient had at least one visit to the emergency department for 24 hours or more within the previous four weeks. Cases are considered community-associated if the patient had been admitted for less than three days prior to the onset of symptoms, with no history of hospitalization or any other healthcare exposure within the previous 12 weeks. Patients diagnosed with CDI who do not meet the definition for either healthcare-associated or community-associated are considered indeterminate cases, and are excluded from this report.

Healthcare-associated *C. difficile* in Canada

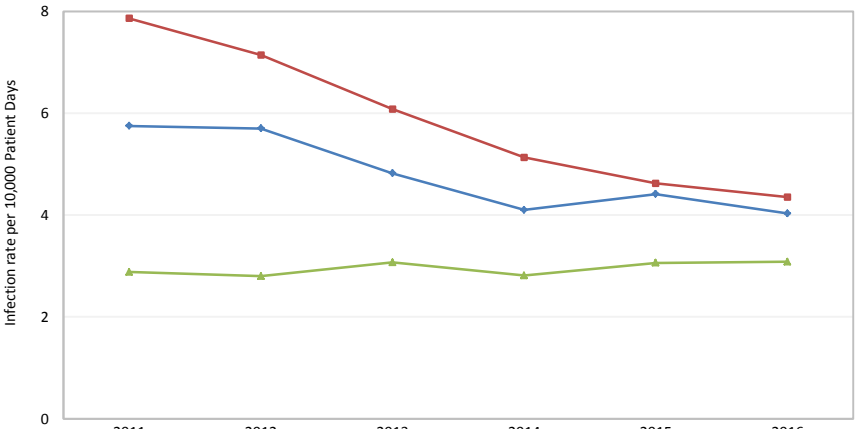
The overall rate of HA-CDI continued to decline, from 6.64 cases per 10,000 patient-days in 2011 to 4.05 in 2016 ($p < 0.001$). Stratified by hospital type, the 2016 rates of HA-CDI in the 33 adult-only hospitals continued to be greater than those in the eight pediatric-only hospitals (4.50 and 3.25 per 10,000 patient-days, respectively, $p < 0.001$) (Figure 8). Despite having the highest overall regional rates in 2016, the central provinces (Ontario and Québec) continued to see declines (Figure 9).

Figure 8: Rate of healthcare-associated *C. difficile* infection (CDI), 2011-2016



	2011	2012	2013	2014	2015	2016
Adult Hospitals	6.96	6.42	5.52	4.87	4.56	4.50
Pediatric Hospitals	5.22	4.23	4.66	3.40	3.93	3.25
Overall	6.64	6.03	5.19	4.39	4.33	4.05

Figure 9: Rate of healthcare-associated *C. difficile* infection (CDI) by region, 2011-2016



	2011	2012	2013	2014	2015	2016
West	5.75	5.7	4.82	4.1	4.41	4.03
Central	7.86	7.14	6.08	5.13	4.62	4.35
East	2.88	2.8	3.07	2.81	3.06	3.08

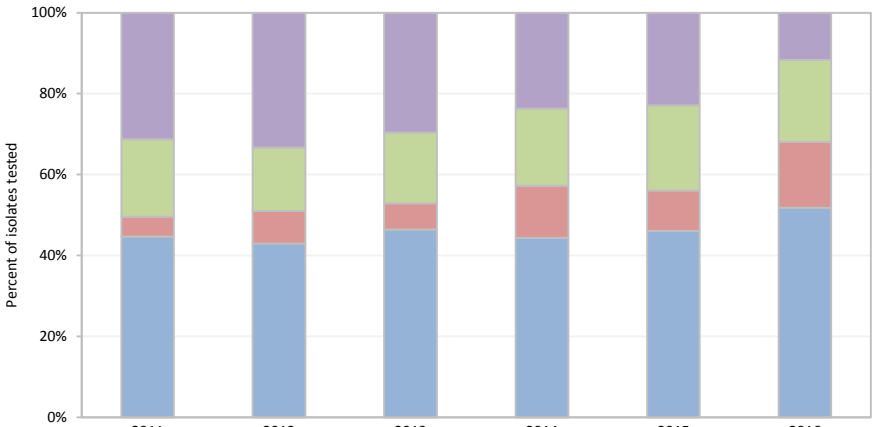
Note: West = British Columbia, Alberta, Saskatchewan, and Manitoba. Central = Ontario and Québec. East = New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador.

In 2015, there were 2,930 cases of HA-CDI among 62 reporting hospitals. The mean age was 64 years, and slightly more were male (51%). Most patients (89%) were alive at 30 days following diagnosis. The percentage of deaths in adults attributable to HA-CDI continued to decline (5.0% in 2011 to 3.0% in 2016, p = 0.087). No deaths attributable to HA-CDI were reported by pediatric-only hospitals.

As part of targeted surveillance in 2016, 455 isolates were submitted to PHAC. For the first time since the inception of the surveillance, NAP-4 was the dominate strain of *C. difficile* (20% of all isolates tested). The proportion of NAP-1 decreased between 2011 and 2016 (31% vs. 12%, respectively, p <0.001) (Figure 10).

When stratified by hospital type, NAP-4 was the dominate strain in pediatric-only hospitals (28% in 2015), followed by NAP-11 (12%) (Figure 11).

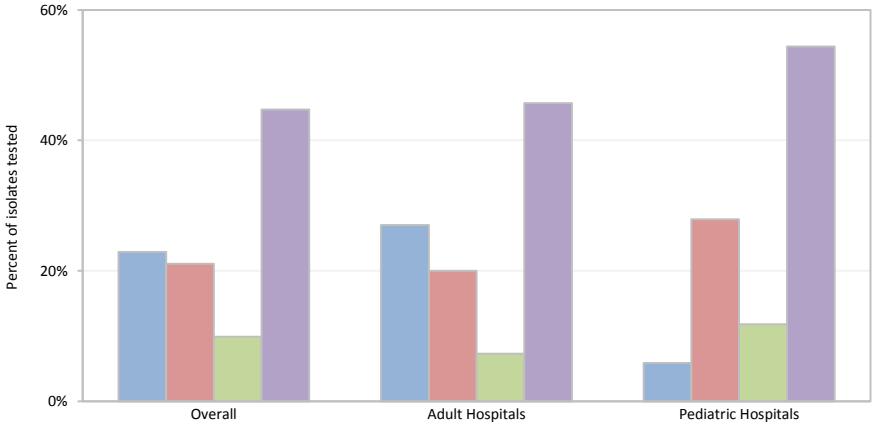
Figure 10: Overall HA-CDI strain types, 2011-2016



	2011 (n=486)	2012 (n=492)	2013 (n=513)	2014 (n=482)	2015 (n=503)	2016 (n=455)
NAP-1	31.3%	33.3%	29.6%	23.7%	22.9%	11.7%
NAP-4	19.1%	15.7%	17.5%	19.1%	21.1%	20.2%
NAP-11	4.9%	8.1%	6.4%	12.9%	9.9%	16.3%
Other	44.7%	42.9%	46.5%	44.3%	46.1%	51.8%

Note: Strains reported as other NAP types include: NAP-2, NAP-3, NAP-5, NAP-6, NAP-7, NAP-8, NAP-9, NAP-10, NAP-12, and strains not assigned a NAP type.

Figure 11: Overall HA-CDI strain types by hospital type, 2015

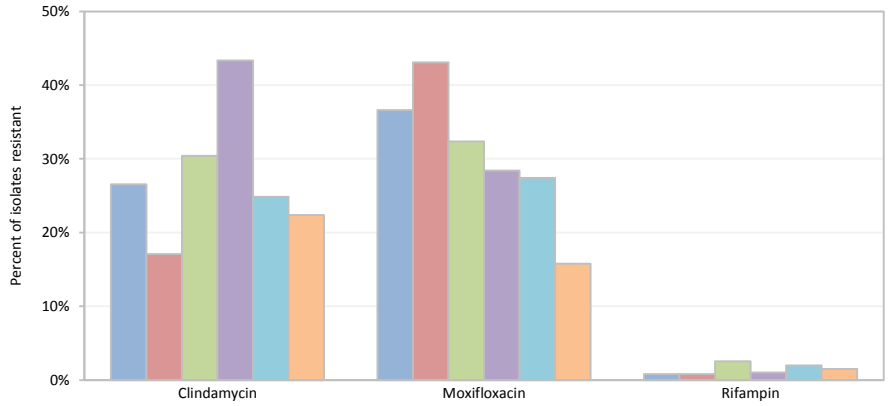


	Overall (n=503)	Adult Hospitals (n=300)	Pediatric Hospitals (n=68)
NAP-1	22.9%	27.0%	5.9%
NAP-4	21.1%	20.0%	27.9%
NAP-11	9.9%	7.3%	11.8%
Other	44.7%	45.7%	54.4%

Note: Strains reported as other NAP types include: NAP-2, NAP-3, NAP-5, NPA-6, NAP-7, NAP-8, NAP-9, NAP-10, and NAP-12 and strains not assigned a NAP type.

The overall proportion of resistance for clindamycin and moxifloxacin decreased from 27% and 37% of all isolates tested in 2011, to 22% and 16% in 2016, respectively. In contrast, resistance to rifampin increased from 0.8% in 2011 to 1.5% in 2016 ($p<0.001$) (Figure 12).

Figure 12: HA-CDI overall resistance patterns, 2011-2016



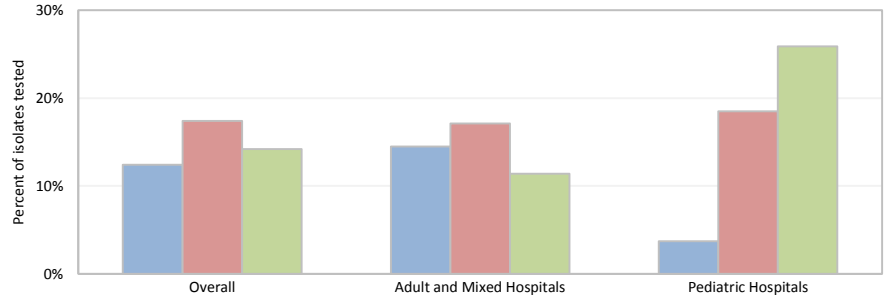
	Clindamycin	Moxifloxacin	Rifampin
2011	26.5%	36.6%	0.8%
2012	17.1%	43.1%	0.8%
2013	30.4%	32.4%	2.5%
2014	43.4%	28.4%	1.0%
2015	24.9%	27.4%	2.0%
2016	22.4%	15.8%	1.5%

Text Box 1: Pilot Project - Surveillance for community-associated *Clostridium difficile* infection

In 2015, a three-year pilot project was begun to assess the burden, risk factors, and outcomes of community-associated CDI (CA-CDI) through genome sequencing and epidemiologic data collection. Epidemiologic data were collected from 49 hospitals on all inpatients, outpatients, and emergency room patients diagnosed with CA-CDI. Laboratory stool samples were collected between March 1 and April 30 for adult patients, and all year for pediatric patients. Patients diagnosed with CDI were epidemiologically classified as CA-CDI if the patient had been admitted for less than three days prior to the onset of symptoms, and had no history of hospitalization or any other healthcare exposure within the previous 12 weeks.

The 2015 results from this pilot indicate 37% of all CDI were considered CA-CDI in 2015. Overall, the North American pulse-field type 4 (NAP-4) appeared to be the dominant strain of CA-CDI (17%). However, NAP-11 was identified as the most common strain in pediatric-only hospitals (26%), followed by NAP-4 (19%) (Figure A).

Figure A: CA-CDI strain types by hospital type, 2015



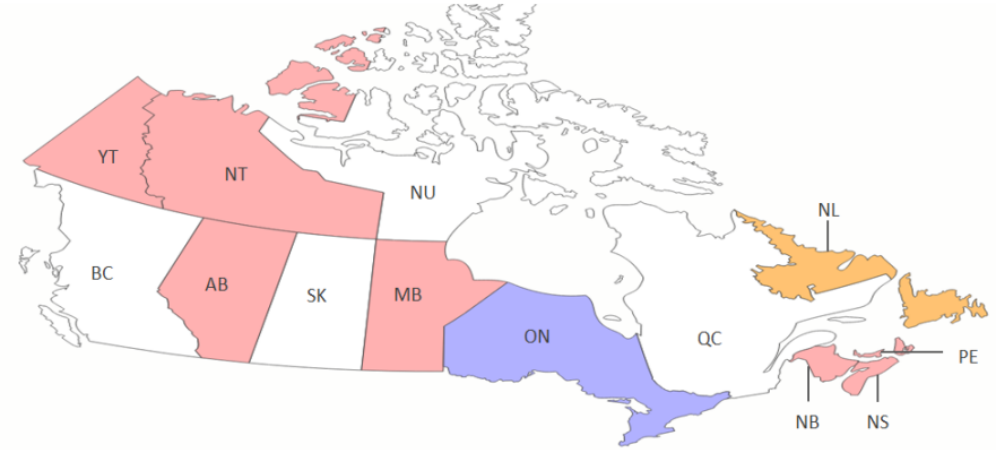
	Overall	Adult and Mixed Hospitals	Pediatric Hospitals
NAP-1	12.4%	14.5%	3.7%
NAP-4	17.4%	17.1%	18.5%
NAP-11	14.2%	11.4%	25.9%

In 2015, the predominant strain type observed in CA-CDI is different than CNISP HA-CDI, where NAP-1 is the predominant strain type in adult and mixed hospitals and NAP-4 is the predominant strain type in pediatric hospitals.

Text Box 2: Canadian Notifiable Disease Surveillance System (CNDSS): Reportable CDI

Nationally notifiable diseases are infectious diseases that have been identified by the federal government and provinces and territories as priorities for monitoring and control efforts. The CNDSS collects notifiable disease data provided voluntarily by provinces and territories, which include the counts of confirmed cases in a given year by age and sex. For certain diseases, the CNDSS has data that date back to 1924. The information collected and managed by CNDSS is used as a benchmark to identify trends of diseases at the national level. CDI (formerly called *Clostridium difficile*-associated Diarrhea) was added to the notifiable disease list in 2009; however, national participation has been variable (Figure A). CNDSS does not distinguish between healthcare-associated or community-associated CDI in its reporting.

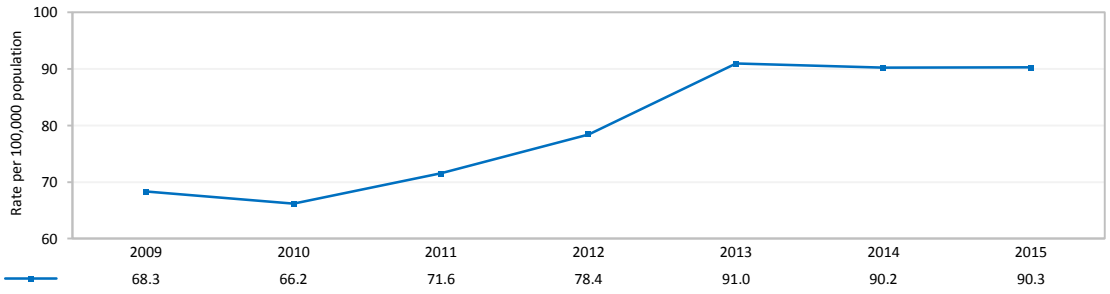
Figure A: The chronology of the participating provinces and territories in reporting CDI to CNDSS



	2009	2010	2011	2012	2013	2014	2015
First year of reporting CDI	MB, NT		PE	AB, NS	YT		NB
First year of reporting CDI Hospital Outbreaks	ON						
First year of reporting CDI Aggregate Data	NL						

As of 2015, seven of 13 provinces and territories are included in calculating rates of CDI at the national level. Data from Ontario and Newfoundland are excluded in the CNDSS analysis, as the reporting of CDI in those provinces is not consistent with that of other provinces and territories. Figure B below captures the rates of CDI from 2009 to 2015. Among reporting jurisdictions, CDI rates appear to be rising; increasing 32% from 2009 to 2015 (68.3 to 90.3 reported cases per 100,000 population).

Figure B: Rate of reported CDI per 100,000 population, 2009-2015



Note: Data from Ontario represent hospital outbreaks and are excluded. Aggregate data from Newfoundland and Labrador does not include age and sex breakdown and are excluded. CDI associated diarrhea was reported by Manitoba and the Northwest Territories from 2009-2015, Prince Edward Island from 2011-2015, Nova Scotia and Alberta from 2012-2015, the Yukon from 2013-2015, and New Brunswick in 2015.

Carbapenem-resistant Enterobacteriaceae and *Acinetobacter* spp.

Enterobacteriaceae are gram-negative bacilli (GNB) found in both healthcare and community settings, and include species such as *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp. These organisms are known to colonize the gastrointestinal tract of healthy individuals, but can also cause infection. Susceptibility to commonly prescribed antimicrobials varies among Enterobacteriaceae species. An example of this is the production of extended-spectrum β-lactamase (ESBL), an enzyme that deactivates commonly used third-generation cephalosporins, rendering this antimicrobial therapy ineffective[19].

Carbapenems, a type of broad-spectrum antimicrobial, are an effective treatment for infections caused by ESBL-producing organisms. However, antimicrobial resistance to carbapenems is a growing concern. One mechanism of resistance to carbapenems is the production of carbapenemase (i.e., an enzyme that deactivates carbapenem antimicrobials). Infections caused by carbapenemase-producing organisms (CPOs), including carbapenemase-producing Enterobacteriaceae (CPE), have limited treatment options and are associated with poor outcomes[20]. Additional GNB outside of the Enterobacteriaceae family that have also demonstrated resistance via carbapenemase production include carbapenemase-producing *Acinetobacter* spp. (CPA).

Methods

National surveillance data on CPO, including both Enterobacteriaceae and *Acinetobacter* spp., have been prospectively collected by PHAC since 2010, and represent all newly-identified CPO infections and colonizations in a sample of largely university-affiliated, acute-care hospitals in all provinces (no data are collected from the three territories). Isolates that are identified as carbapenem-resistant by the reporting hospital are submitted for additional testing to identify carbapenemase producers. Isolates found to be a CPO are epidemiologically linked to the patient and a minimum dataset is completed (e.g., demographics, clinical information, ward type, site of positive culture, source of infection, comorbidities, and outcome at 30 days).

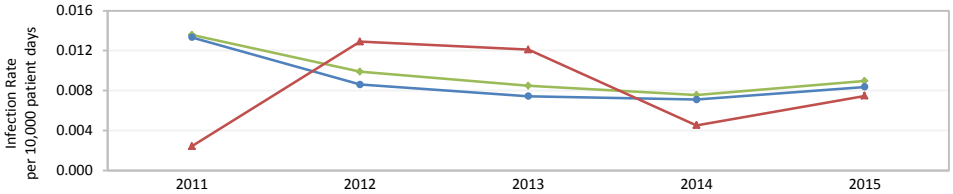
In addition, national surveillance specific to CPE has been conducted by PHAC since 2013, in collaboration with the Canadian Public Health Laboratory Network (CPHLN). Provincial health laboratories voluntarily submit: (1) CPE isolates, or (2) standardized aggregate data on CPE isolates. All surveillance submissions represent both infections and colonizations, and exclude duplicate isolates and environmental samples to the extent possible.

Carbapenemase-producing Enterobacteriaceae and *Acinetobacter* spp. in Canada: Hospital Surveillance

Due to relatively small numbers, rates include both infections and colonizations identified in hospital inpatients. The overall rate of CPO in 2011 was 0.014 per 10,000 patient-days, and declined to 0.009 in 2015 ($p=0.012$). Incidence of CPE in 2011 was 0.013 per 10,000 patient-days, and declined to 0.008 in

2015 (p=0.006); CPA incidence in 2011 was 0.002 per 10,000 patient-days, increased to 0.013 in 2012 (p<0.001), then declined to 0.007 in 2015 (p=0.002) (Figure 13).

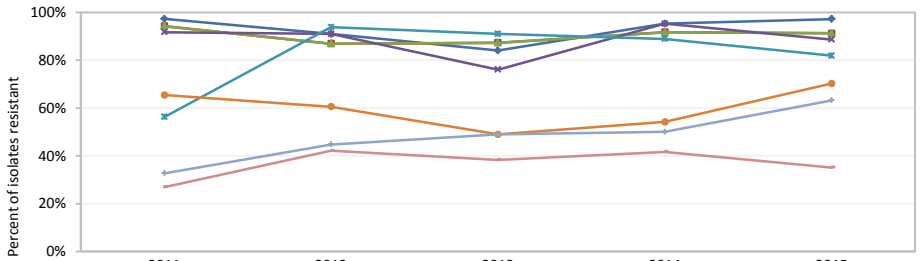
Figure 13: Overall incidence of CPO (CPE & CPA) per 10,000 patient-days, 2011-2015



	2011	2012	2013	2014	2015
CPO	0.014	0.010	0.008	0.008	0.009
CPE	0.013	0.009	0.007	0.007	0.008
CPA	0.002	0.013	0.012	0.005	0.007

In 2015, 60 patients were identified as infected or colonized with CPO from 58 reporting hospitals. The majority of these patients (52%) were 65 years of age or older and 70% were male. Outcome at 30 days was available for 55% of patients, for whom a crude mortality of 27% was observed. Isolates were identified as CPE for 92% of patients, compared to 8% CPA. Only one patient was identified as having both CPE and CPA. The most common CPE pathogen was *Klebsiella pneumonia* (34%), followed by *Escherichia coli* (27%), and the most common CPA pathogen was *Acinetobacter baumannii* (4%). Antibiotic susceptibility testing was available for 95% of CPO in 2015, of which resistance to ceftriaxone, ampicillin, cefazolin, ertapenem, meropenem, ciprofloxacin, gentamicin, and piperacillen-tazobactam was observed at 97%, 91%, 91%, 89%, 82%, 70%, 63%, and 35%, respectively (Figure 14).

Figure 14: Selected CPO antimicrobial resistance patterns, 2011-2015



	2011 (n=52)	2012 (n=38)	2013 (n=47)	2014 (n=48)	2015 (n=57)
Ceftriaxone*	97.2%	90.9%	84.0%	95.2%	97.1%
Ampicillin	94.2%	86.8%	87.2%	91.7%	91.2%
Cefazolin	94.2%	86.8%	87.2%	91.7%	91.2%
Ertapenem*	91.7%	90.9%	76.0%	95.2%	88.6%
Meropenem*	56.3%	93.8%	90.9%	88.9%	81.8%
Ciprofloxacin	65.4%	60.5%	48.9%	54.2%	70.2%
Gentamicin	32.7%	44.7%	48.9%	50.0%	63.2%
Pip-Taz	26.9%	42.1%	38.3%	41.7%	35.1%

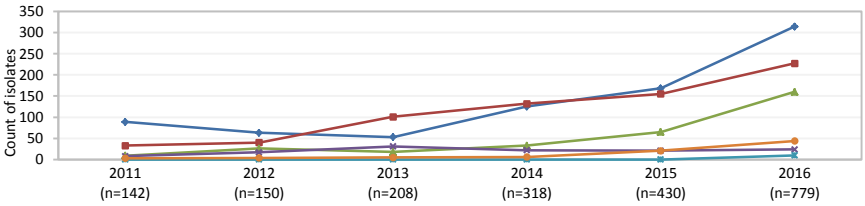
*Note: Total tested for ceftriaxone and ertapenem: 2011 (n=36); 2012 (n=22); 2013 (n=25); 2014 (n=21); 2015 (n=35); total tested for meropenem: 2011 (n=16); 2012 (n=16); 2013 (n=22); 2014 (n=27); 2015 (n=22). Pip-Taz = piperacillin-tazobactam

Surveillance of carbapenemase-producing Enterobacteriaceae in Canada: Provincial Health Laboratories

In 2016, 779 CPE isolates were submitted to provincial health laboratories. This represents a 1.8 fold increase from 2015 (n=430). Between 2008 and 2016, a total of 2,106 CPE isolates were submitted, and

in general, the numbers of CPE reported by the provinces doubled every two years. In 2016, isolates producing *Klebsiella pneumoniae* carbapenemase (KPC) continued to be the most common CPE, followed by isolates producing New Delhi Metallo-β-lactamase (NDM) (40% and 29%, respectively). From 2014 to 2016, there was a 4.8 fold increase in reports of OXA-48-like isolates (33 to 160 isolates). From 2015 to 2016, there was a 2.5 fold increase in OXA-48-like containing isolates (65 to 160 isolates). The number of reported cases of *Serratia marcescens* carbapenemase (SME)-producing organisms has been stable since 2014 (Figure 15).

Figure 15: Count of CPE isolates by resistance gene, 2011-2016

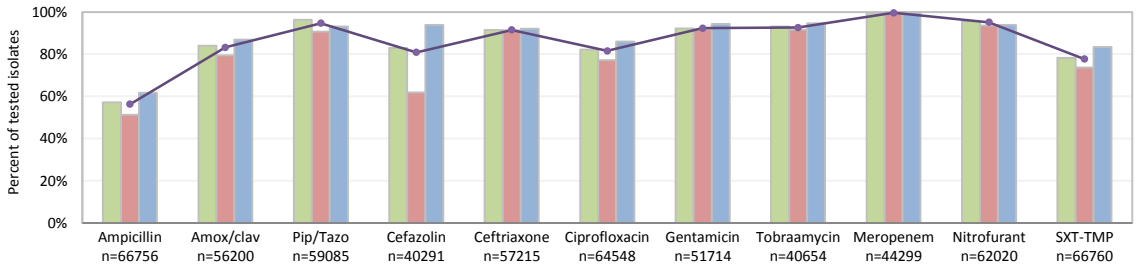


	2011 (n=142)	2012 (n=150)	2013 (n=208)	2014 (n=318)	2015 (n=430)	2016 (n=779)
KPC	89	63	53	125	168	314
NDM	33	40	101	132	155	227
OXA-48-like	9	26	18	33	65	160
SME	8	17	31	22	21	24
OXA-48/NDM	0	0	0	0	0	10
Other	3	4	5	6	21	44

Text Box 3: Antimicrobial susceptibilities of *Escherichia coli* in Canadian hospitals through the analysis of annual susceptibility profile summaries: A pilot study

To improve the understanding of AMR in Canadian hospitals, a pilot study was conducted to collect existing AMR data from hospital susceptibility profiles (antibiograms). Twenty three acute-care hospitals from seven provinces submitted hospital antibiogram information on *E. coli* for the calendar year 2015. Overall and regional susceptibility rates are presented in Figure A. The regional differences were minor — the percent susceptible was lowest in Central Canada, compared to Western and Eastern Canada.

Figure A: Susceptibility results of *E.coli* from participating sentinel hospitals, 2015



	Ampicillin n=66756	Amox/clav n=56200	Pip/Tazo n=59085	Cefazolin n=40291	Ceftriaxone n=57215	Ciprofloxacin n=64548	Gentamicin n=51714	Tobraamycin n=40654	Meropenem n=44299	Nitrofurant n=62020	SXT-TMP n=66760
West	57.2%	84.0%	96.3%	83.0%	91.5%	82.2%	92.2%	93.2%	99.5%	95.6%	78.2%
Central	51.3%	79.4%	90.7%	61.9%	91.3%	77.2%	91.7%	91.5%	99.7%	93.6%	73.7%
East	61.7%	86.9%	93.1%	93.9%	92.0%	86.0%	94.4%	94.7%	99.9%	93.9%	83.4%
National	56.3%	83.2%	94.7%	80.9%	91.5%	81.6%	92.3%	92.6%	99.5%	95.1%	77.7%

Note: West = British Columbia (n=4), Alberta (n=6) & Saskatchewan (n=2), Central = Ontario (n=7) & Québec (n=2), East = New Brunswick (n=1), Prince Edward Island (n=1); n = number of isolates tested nationally; TMP-SMX = Trimethoprim-sulfamethoxazole; Amox/Clav = Amoxicillin-clavulanate; Pip/Tazo = Piperacillin-tazobactam

Despite a lack of standardized antibiogram data for analysis, the antibiogram information represents a potentially rich and unleveraged data source for AMR surveillance and stewardship. The datasets analysed in this pilot study may give a more accurate reflection of susceptibility rates due to their large size. Moving forward, PHAC will attempt to improve representation (data from all provinces) and to standardize the timeframe (calendar year), patient status (e.g., inpatient; adult vs. pediatric), and specimen type for antibiograms submitted.

Text Box 4: Screening for Carbapenemase-producing Enterobacteriaceae (CPE) in agri-food samples, 2011-2015

Background:

Carbapenems are categorized as very important to human medicine and are used to treat very severe, often multidrug-resistant infections, usually in hospitalized patients. The developing global emergence of carbapenemase-producing Enterobacteriaceae (CPE) outside of the healthcare system, including possible food chain dissemination, is an antimicrobial resistance concern. There are no carbapenem products approved for use in animals in Canada.

Methods:

Screening for carbapenem resistance in *Salmonella* and *E. coli* isolates from all core agri-food surveillance components (i.e., retail, slaughter house, and farm), as well as animal clinical *Salmonella* isolates, has occurred since 2013. Isolates meeting minimum inhibitory concentration criteria for ceftiofur and ceftriaxone were screened further for carbapenemase production by disk diffusion. Beginning in 2016, meropenem (a carbapenem antimicrobial) was added to the panel of antimicrobials to detect antimicrobial resistance. Because carbapenemase production could be missed using the regular screening approach, selective media (ChromID®CARBA) was used for primary bacterial isolation of samples collected through targeted studies of imported retail seafood, imported dried spices, and dried imported chicken pet treats. A subset of retail meat samples was also tested for the presence of CPE using this selective media approach.

Results:

By the end of 2015, over 13,000 core surveillance isolates had been screened for CPE. To date, no CPE have been identified in the domestic food chain (i.e., retail, slaughter house, and farm). Over 3,000 samples from targeted studies and retail surveillance have been screened using selective media. Of these, CPE have been detected from nine samples: two imported clam products were identified with the NDM-1 gene in *Enterobacter cloacae*, six seafood products contained the IMI gene in *Enterobacter* spp., and a novel VCC-1 gene was found in a *Vibrio cholerae* isolate recovered from imported shrimp[19].

Conclusions:

With the global dissemination of CPE representing a growing concern in non-healthcare settings, the increased sensitivity of selective media methodology enabled detection of rare and emerging resistance genes. Detection of CPE in the Canadian agri-food sector, and retail meat and other products, has been limited thus far to imported seafood products.

Text Box 5: Carbapenemase-producing Enterobacteriacae in human isolates from Canada

Many carbapenemase-producing Enterobacteriacae (CPE) demonstrate multidrug resistance which severely limits treatment options. These organisms remain a global concern, and Canada continues to monitor their occurrence in animals, animal-derived food animals, and people.

All human *Salmonella* isolates have been tested for antimicrobial susceptibility since 2010, and no CPE have been identified. In 2016, meropenem (a carbapenem antimicrobial) was added to the susceptibility plate used to test all isolates for susceptibility.

In addition to testing human isolates, PHAC is collaborating with the Canadian Public Health Laboratory Network (CPHLN) to support the voluntary reporting of CPE. In some provinces, CPE testing is done within the provincial public health laboratories and reported to PHAC (i.e., British Columbia, Ontario, and Québec) and for other provinces (as well as some additional isolates from British Columbia and Québec), PHAC provides the testing support.

Staphylococcus aureus

Staphylococcus aureus (*S. aureus*) is a bacterium commonly found in the nose, groin, and skin of healthy individuals. While infections caused by *S. aureus* are largely associated with the skin and soft tissues, bacterial pneumonia and/or blood stream infections are not uncommon.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a *S. aureus* that has acquired resistance to anti-staphylococcal β-lactam antibiotics (e.g., methicillin, oxacillin, and cefazolin. The transmission of MRSA is most frequently through direct skin-to-skin contact, or through contact with a contaminated item or surface. While MRSA has historically been associated with hospitals and other healthcare settings (HA-MRSA), community-associated MRSA (CA-MRSA) is increasingly common.

Methods

National surveillance data on MRSA in humans has been prospectively collected by PHAC since 1995, and represents all newly-identified MRSA infections in a sample of largely university-affiliated, acute-care hospitals in all provinces (no data are collected from the three territories). Non-screening MRSA isolates (i.e., MRSA infections) are epidemiologically linked to an inpatient and a minimum dataset is then completed (e.g., demographics, clinical information, and site of positive culture, source of infection as per epidemiological definition, and outcome at 30 days). A three-month (January through March) targeted surveillance is conducted each year, and includes linkages to laboratory results (e.g., strain typing and susceptibility testing). Targeted surveillance is conducted year round on all necrotizing fasciitis, necrotizing pneumonia, and blood stream infections (BSI). Sentinel hospital sites can opt into completing targeted surveillance. Screening isolates testing positive for MRSA without infection (i.e., colonization) and related epidemiologic data are not currently collected.

The source of MRSA infection (i.e., HA and CA) is attributed through epidemiological definition and best clinical judgement. HA-MRSA infection is defined as MRSA being identified on or after the third calendar day of admission, or as having exposure to any healthcare setting (including long-term care, rehabilitation facilities, or clinics) in the previous 12 months. CA-MRSA infection is defined as MRSA identified before the third calendar day of admission, as well as having: (1) no previous history of the organism; (2) no prior exposure to healthcare settings; and (3) no reported use of medical devices.

Methicillin-resistant *Staphylococcus aureus* in Canada

The overall rate of MRSA infection increased from 2.84 cases per 10,000 patient-days in 2011 to 3.13 in 2016 ($p=0.06$). Similarly, the overall rate for MRSA blood stream infection increased from 0.56 cases per 10,000 patient-days in 2011 to 0.84 in 2016 ($p<0.001$) (Figure 16). This increase appears to be driven by the western provinces (i.e., British Columbia, Alberta, Saskatchewan, and Manitoba) (Figure 17).

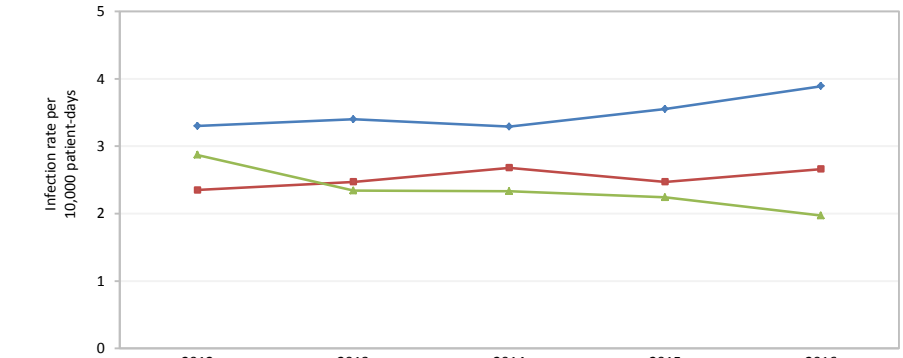
In 2015, there were 2,103 MRSA infections among 61 reporting hospitals. The mean age was 53 years, males represented 56% of infections, and 63% were epidemiologically linked to a healthcare setting. All-

cause mortality was monitored at 30 days from diagnosis. In 2015, 10% of patients with MRSA infection died; however, when patient deaths were stratified by site of infection, 20% of those with MRSA blood stream infection died (down from 28% in 2011), compared to 7% for all other non-blood stream MRSA infections.

Figure 16: Overall Incidence of MRSA Infection, 2011-2016

	2011	2012	2013	2014	2015	2016
All MRSA Infections	2.84	2.80	2.83	2.89	3.01	3.13
MRSA BSI	0.56	0.51	0.53	0.64	0.72	0.84

Figure 17: Overall incidence of MRSA Infection by region, 2012-2016

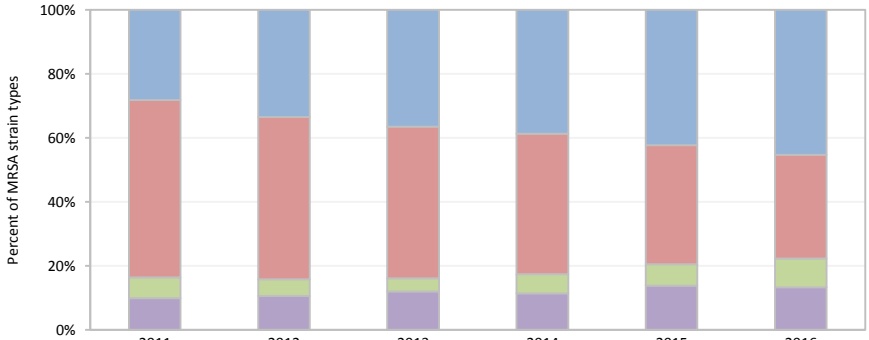


	2012	2013	2014	2015	2016
West	3.30	3.40	3.29	3.55	3.89
Central	2.35	2.47	2.68	2.47	2.66
East	2.87	2.34	2.33	2.24	1.97

Note: West = British Columbia, Alberta, Saskatchewan, and Manitoba. Central = Ontario and Québec. East = New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador.

As part of targeted surveillance, the 2016 laboratory analysis of MRSA strain types shows that the overall proportion of epidemic MRSA strain type 10 (CMRSA10) surpassed the overall proportion of epidemic MRSA strain type 2 (CMRSA2) for the second year in a row (45% vs. 32%) (Figure 18). However, CMRSA2 continues to demonstrate the largest proportion of MRSA blood stream infections, representing 43% of all tested blood isolates in 2015, compared against 37% of CMRSA10. While the literature[20] attributes CMRSA2 to healthcare settings and CMRSA10 to community settings, the higher proportion of CMRSA10 in relation to CMRSA2 may be correlated to increasing rates of CA-MRSA and decreasing rates of HA-MRSA.

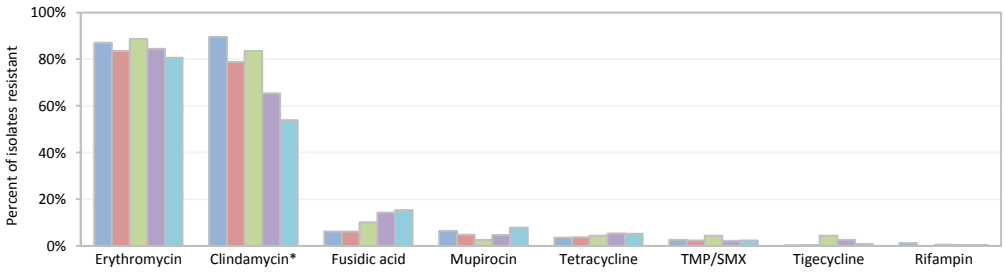
Figure 18: MRSA Epidemic Strain Types, 2011-2016



	2011 (n=584)	2012 (n=534)	2013 (n=587)	2014 (n=688)	2015 (n=716)	2016 (n=664)
CMRSA10	28.3%	33.5%	36.5%	38.7%	42.3%	45.3%
CMRSA2	55.3%	50.7%	47.4%	43.9%	37.2%	32.4%
CMRSA7	6.5%	5.2%	4.1%	6.0%	6.7%	9.0%
Other	9.9%	10.6%	12.0%	11.4%	13.8%	13.3%

The proportion of MRSA isolates resistant to erythromycin, mupirocin, tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), tigecycline, and rifampin has remained relatively unchanged, while resistance to fusidic acid has more than doubled since 2011 (6.3% to 15.3% in 2015). Resistance to clindamycin continues to decrease from 90% in 2011 to 54% in 2015. No resistance to linezolid, daptomycin, and vancomycin was detected in 2015 (Figure 19).

Figure 19: Antimicrobial resistance of MRSA isolates, 2011-2015



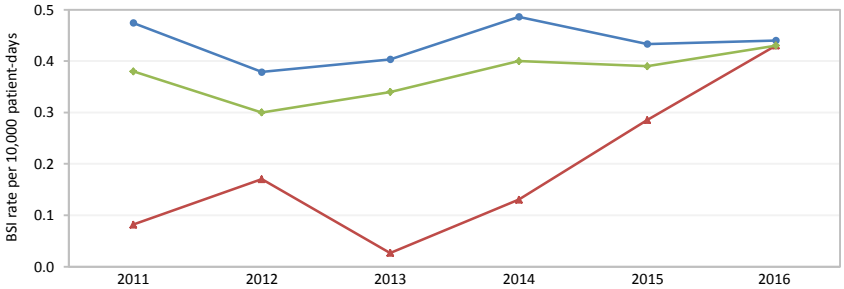
	Erythromycin	Clindamycin*	Fusidic acid	Mupirocin	Tetracycline	TMP/SMX	Tigecycline	Rifampin
2011 (n=527)	87.1%	89.5%	6.3%	6.5%	3.6%	2.7%	0.4%	1.3%
2012 (n=517)	83.6%	78.9%	6.2%	4.8%	3.7%	2.3%	0.4%	0.0%
2013 (n=558)	88.7%	83.5%	10.2%	2.7%	4.5%	4.5%	4.5%	0.5%
2014 (n=634)	84.4%	65.4%	14.4%	4.7%	5.4%	2.2%	2.7%	0.5%
2015 (n=496)	80.6%	53.8%	15.3%	7.9%	5.2%	2.4%	0.8%	0.4%

*Note: Total tested for clindamycin:2011 (n=381); 2012 (n=374); 2013 (n=418); 2014 (n=572); 2015 (n=496)

Healthcare-associated methicillin-resistant *Staphylococcus aureus*

For MRSA infections attributed to healthcare settings, the overall rate decreased from 1.93 cases per 10,000 patient-days in 2011 to 1.69 in 2016 ($p < 0.001$). Blood stream infections (BSI) attributed to HA-MRSA, however, showed a fivefold increase in pediatric hospitals, rising from 0.08 per 10,000 patient-days in 2011 to 0.43 in 2016 ($p < 0.001$). Comparatively, the rate of HA-MRSA blood stream infections in adult hospitals remained relatively stable between 0.38 and 0.49 since 2012. In 2016, the overall rate of HA-MRSA blood stream infection was 0.43 cases per 10,000 patient-days (Figure 20).

Figure 20: Incident rate of HA-MRSA blood stream infection, 2011-2016



	2011	2012	2013	2014	2015	2016
Adult Hospitals	0.47	0.38	0.40	0.49	0.43	0.44
Pediatric Hospitals	0.08	0.17	0.03	0.13	0.29	0.43
Overall	0.38	0.30	0.34	0.40	0.39	0.43

Community-associated methicillin-resistant *Staphylococcus aureus*

For MRSA infections attributed to the community (CA-MRSA), the overall rate steadily increased from 0.56 cases per 1,000 admissions in 2011 to 0.96 in 2016. This trend is consistent when measured by 10,000 patient-days (0.71 to 1.29). The rate of CA-MRSA in pediatric hospitals was consistently higher than that of adult hospitals and mixed hospitals (1.56, 1.02, and 0.75 cases per 1,000 admissions in 2016, respectively).

Enterococcus spp.

Enterococci bacteria are commonly present as part of the normal gastrointestinal flora of both humans and animals, and are known to cause infections on rare occasions. To date, the majority (90%) of human enterococcal infections are caused by two species: *Enterococcus faecalis* and *Enterococcus faecium*. Enterococci demonstrate a high degree of intrinsic antimicrobial resistance to commonly prescribed antibiotics, rendering most antibiotic therapies ineffective. Enterococci are also known to rapidly acquire and transfer antimicrobial resistance through horizontal exchange[22].

Vancomycin has long been considered a reliable antibiotic option for the treatment of infections caused by multidrug-resistant *Enterococcus*. The acquisition of high-level vancomycin resistance by enterococci has since left clinicians with limited therapeutic options[23]. While literature suggests that infections caused by vancomycin-resistant enterococci (VRE) in Canada are almost exclusively associated with healthcare facilities, information regarding the transmission of VRE in the community is unknown. Historical monitoring by PHAC did not identify VRE along the Canadian food chain between 2003 and 2011[24].

Methods

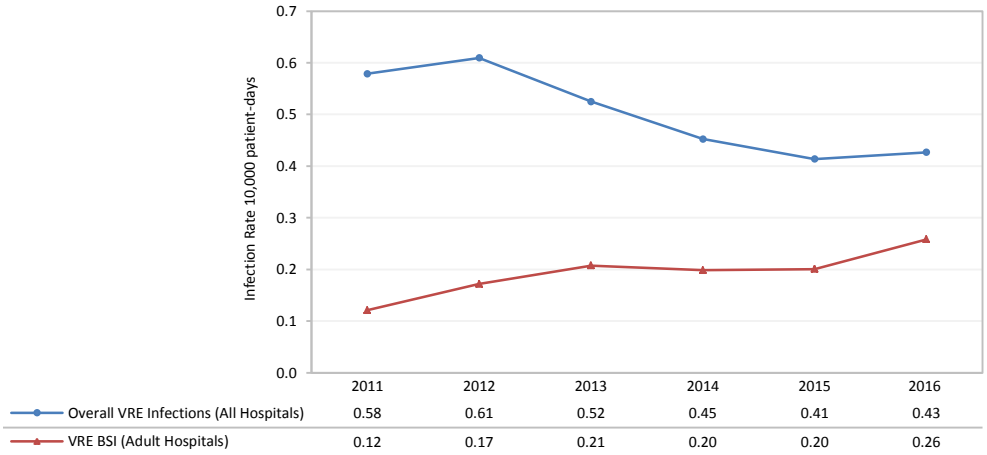
National laboratory-confirmed surveillance data on VRE in humans have been collected prospectively by PHAC since 1999, and represent all newly-identified VRE infections (*E. faecalis* and *E. faecium*) in a sample of largely university-affiliated, acute-care hospitals in all provinces (no data are collected from the three territories). Non-screening VRE isolates (i.e., VRE infections) are epidemiologically linked to an

inpatient and a minimum dataset is then completed (e.g., demographics, clinical information, site of positive culture, source of infection). Targeted surveillance is conducted on all VRE blood stream infections, and includes additional laboratory testing (e.g., strain type and susceptibility testing) and an expanded minimum dataset (e.g., medical procedures, devices, antimicrobial therapies, ICU admissions, and outcomes). Screening isolates testing positive for VRE without infection (i.e., colonization) and related epidemiologic data are not currently reported.

Vancomycin-resistant enterococci in Canada

Between 2011 and 2016, the overall infection rate of VRE in Canada declined from 0.58 cases per 10,000 patient-days to 0.43 in 2016 ($p < 0.001$). The rate of VRE blood stream infection (BSI) in adult hospitals, however, more than doubled, from 0.12 cases per 10,000 patient-days in 2011 to 0.26 in 2016 ($p = 0.001$) (Figure 21).

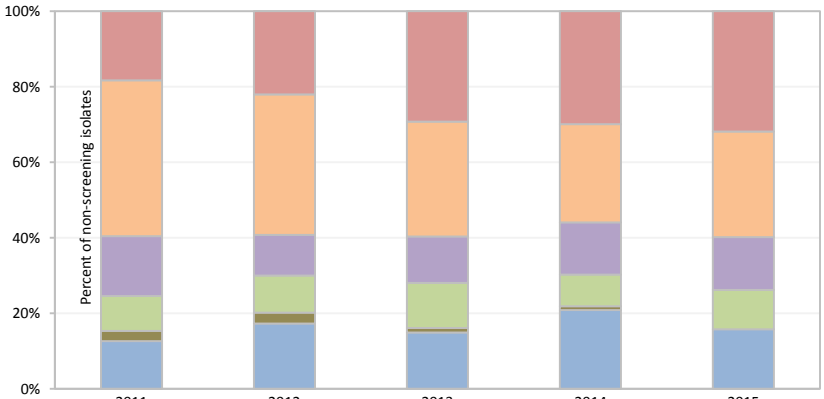
Figure 21: Rate of VRE infection, 2011-2016



In 2015, there were 271 VRE infections among 53 reporting hospitals. Half (50%) were age 65 years or older; slightly more infections were reported in males (54%); and nearly all cases (95%) were healthcare-associated. Blood isolates remained the most common VRE culture (32%), followed by urine (28%), skin/soft tissue/burn (14%), surgical wound (10%), and other (16%) (Figure 22). The crude mortality for patients with VRE blood stream infection was 39%.

As part of targeted surveillance, 75 VRE isolates were submitted in 2015. Of these, all VRE blood stream infections were identified as *VanA Enterococcus faecium*. Multiple-locus sequence typing (MLST) was performed, which identified VRE type ST117, ST412, and ST18 (18.3%, 16.9%, and 15.5% of all isolates tested, respectively). All 2015 isolates were resistant to ampicillin and penicillin.

Figure 22: Site of non-screening VRE cultures, 2011-2015



	2011 (n=403)	2012 (n=417)	2013 (n=335)	2014 (n=311)	2015 (n=279)
Blood	18.4%	22.1%	29.3%	29.9%	31.9%
Urine	41.2%	37.2%	30.4%	26.0%	28.0%
Skin/Soft tissue/Burn	15.9%	10.8%	12.2%	13.8%	14.0%
Surgical wound	9.2%	9.8%	11.9%	8.4%	10.4%
Rectum	2.7%	2.9%	1.2%	1.0%	0.0%
Other	12.7%	17.3%	14.9%	20.9%	15.8%

Streptococcus pyogenes and *pneumoniae*

Streptococcus is a genus of bacteria that is capable of causing life-threatening invasive disease in susceptible individuals[25]. While most infections are non-invasive and respond well to common antimicrobials, invasive infections caused by *Streptococcus* (e.g., *Streptococcus pneumoniae* and *Streptococcus pyogenes*) can result in meningitis, blood stream infection, and toxic shock syndrome[26]. As *Streptococcus pneumoniae* (*S. pneumoniae*) and *Streptococcus pyogenes* (*S. pyogenes*) can be resistant to antimicrobial therapy, invasive infections caused by antimicrobial-resistant *Streptococcus* (ARS) can be difficult to treat[27]. Prevention of infection by some serovars of *S. pneumoniae* can be achieved by immunization with pneumococcal vaccines[28].

Methods

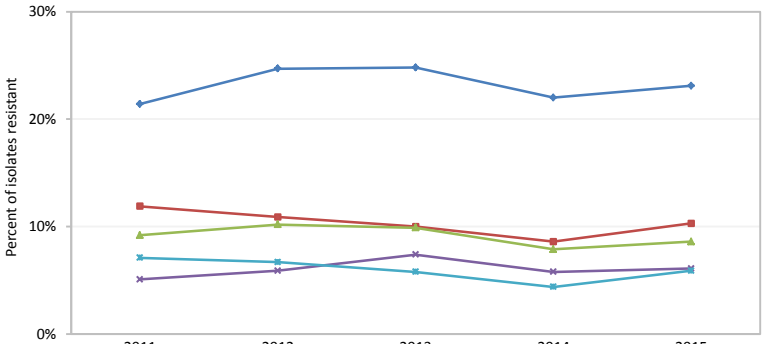
National laboratory surveillance data on *Streptococcus,* including both *S. pneumoniae* and *S. pyogenes*, have been collected by PHAC since 2010, through collaboration with the Laboratoire de santé publique du Québec, Alberta Provincial Laboratory for Public Health, and the Toronto Invasive Bacterial Diseases Network. Provincial public health laboratories voluntarily submit: (1) invasive *Streptococcus* isolates and epidemiologic information directly, or (2) standardized aggregate data on *S. pneumoniae*.

Antimicrobial susceptibility testing on *S. pneumoniae* has been conducted since 2011, through collaboration with the University of Manitoba and the Canadian Antimicrobial Resistance Alliance. Provincial health laboratories in eight participating jurisdictions identify *S. pneumoniae* isolates taken from sterile-sites, and voluntarily submit eligible isolates.

Multidrug-resistant *S. pneumoniae* in Canada

Between 2011 and 2015, rates of antimicrobial resistance among *S. pneumoniae* remained stable. In 2015, 23% of 1,132 tested isolates were resistant to clarithromycin, followed by penicillin (10%), doxycycline (9%), trimethoprim-sulfamethoxazole (6%), and clindamycin (6%). All isolates were susceptible to vancomycin, ertapenem, daptomycin, linezolid, and tigecycline (Figure 23). Between 2014 and 2015, multidrug resistance (MDR) to three or more classes of antimicrobials increased from 4.9% to 6.7%.

Figure 23: Selected *S. pneumoniae* antimicrobial resistance patterns, 2011-2015

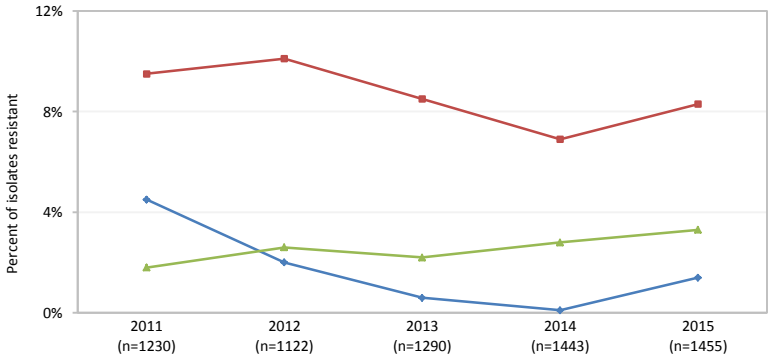


	2011 (n=1133)	2012 (n=1128)	2013 (n=1061)	2014 (n=1125)	2015 (n=1132)
Clarithromycin	21.4%	24.7%	24.8%	22.0%	23.1%
Penicillin	11.9%	10.9%	10.0%	8.6%	10.3%
Doxycycline	9.2%	10.2%	9.9%	7.9%	8.6%
Trimethoprim-sulfamethoxazole	5.1%	5.9%	7.4%	5.8%	6.1%
Clindamycin	7.1%	6.7%	5.8%	4.4%	5.9%

Multidrug-resistant *S.pyogenes* (Group A streptococcus) in Canada

Between 2014 and 2015, antimicrobial resistance to erythromycin increased from 6.9% to 8.3%; resistance to clindamycin increased from 2.8% to 3.3%; and resistance to chloramphenicol increased from 0.1% to 1.4% (Figure 24). All isolates were susceptible to penicillin and vancomycin.

Figure 24: Invasive S. pyogenes antimicrobial resistance patterns, 2011-2015



	2011 (n=1230)	2012 (n=1122)	2013 (n=1290)	2014 (n=1443)	2015 (n=1455)
Chloramphenicol	4.5%	2.0%	0.6%	0.1%	1.4%
Erythromycin	9.5%	10.1%	8.5%	6.9%	8.3%
Clindamycin	1.8%	2.6%	2.2%	2.8%	3.3%

Neisseria gonorrhoeae

Neisseria gonorrhoeae (*N. gonorrhoeae*) is the causative agent of gonorrhea. It is the second most common sexually transmitted infection reported in Canada[29, 30], and can cause both symptomatic and asymptomatic infection. Additionally, *N. gonorrhoeae* has acquired resistance, making treatment and control of gonococcal infection complicated. An increase in resistance to azithromycin, combined with decreased susceptibility to cephalosporins, prompted Canada to adopt combination therapy (i.e., the administration of two antibiotics) as standard treatment in 2013[31]. To date, combination therapy has not resulted in treatment failure for gonorrhea in Canada; however, combination treatment failure has been reported by the United Kingdom[32].

Methods

National surveillance data on *N*. *gonorrhoeae* is passively collected by PHAC through collaboration with provincial public health laboratories. Provincial public health laboratories submit: (1) all resistant *N. gonorrhoeae* isolates for additional testing, or (2) all *N. gonorrhoeae* isolates if antimicrobial susceptibility testing is not done. The submission of isolates is voluntary and not standardized across the country. Epidemiological information includes the age and sex of the patient, as well as the anatomical location of the infection. Total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportion.

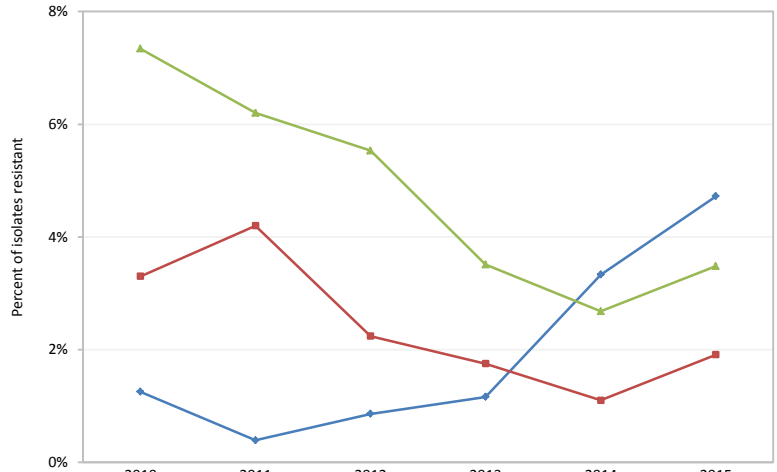
Drug-resistant *Neisseria gonorrhoeae* in Canada

The overall rate of gonorrhea continues to increase in Canada, from 35 cases per 100,000 population in 2006, to 55 in 2015 ($p < 0.001$). As in previous years, the rate of reported cases of gonorrhea was higher in males than females (63% vs. 37%); however, females accounted for the most cases in youth ages 19 years and under.

In 2015, 19,845 cases of gonorrheal infection were reported to PHAC, 4,190 (21%) of which were cultured. Of those cultured, 2,530 were found to be resistant to at least one antibiotic. This represents a 1.2 fold increase from 52% in 2014 to 60% in 2015 ($p<0.001$).

The percent of *N. gonorrhoeae* isolates that demonstrated resistance and decreased susceptibility to antimicrobials currently recommended as preferred therapy (i.e., azithromycin, ceftriaxone, and cefixime) is increasing; most notably to azithromycin. The proportion of azithromycin-resistant *N. gonorrhoeae* isolates, defined as a minimum inhibitory concentration (MIC) ≥ 2.0 milligrams per litre (mg/L), increased from 1.3% in 2010 to 4.7% in 2015 ($p < 0.001$). Conversely, a decreasing proportion of *N. gonorrhoeae* isolates demonstrated decreased susceptibility to cephalosporins (cefixime and ceftriaxone); cefixime (MIC ≥ 0.25 mg/L) decreased from 3.3% in 2010 to 1.9% in 2015 ($p < 0.001$), and ceftriaxone (MIC ≥ 0.125 mg/L) decreased from 7.3% in 2010 to 3.5% in 2015 ($p < 0.001$) (Figure 25).

Figure 25: Percentage of N. gonorrhoeae isolates demonstrating resistance to azithromycin, and decreased susceptibility to cefixime and ceftriaxone, 2010-2015

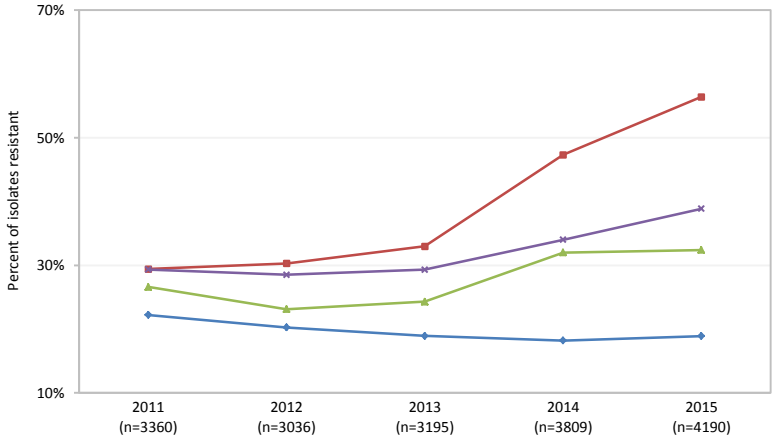


	2010 (n=2970)	2011 (n=3360)	2012 (n=3036)	2013 (n=3195)	2014 (n=3809)	2015 (n=4190)
Azithromycin (≥2 mg/L)	1.3%	0.4%	0.9%	1.2%	3.3%	4.7%
Cefixime (≥0.25 mg/L)	3.3%	4.2%	2.2%	1.8%	1.1%	1.9%
Ceftriaxone (≥0.125 mg/L)	7.3%	6.2%	5.5%	3.5%	2.7%	3.5%

Since 2012, 18 isolates of *N. gonorrhoeae* that demonstrated both resistance to azithromycin and decreased susceptibility to either cefixime or ceftriaxone has been identified. Despite the small numbers, this is of concern as it represents a threat to the success of currently recommended dual therapy treatment options.

Additional testing included antimicrobial susceptibility testing of *N. gonorrhoeae* isolates to penicillin, erythromycin, tetracycline, and ciprofloxacin; illustrated in Figure 26.

Figure 26: Percentage of *N. gonorrhoeae* isolates demonstrating resistance to penicillin, tetracycline, erythromycin, and ciprofloxacin, 2011-2015

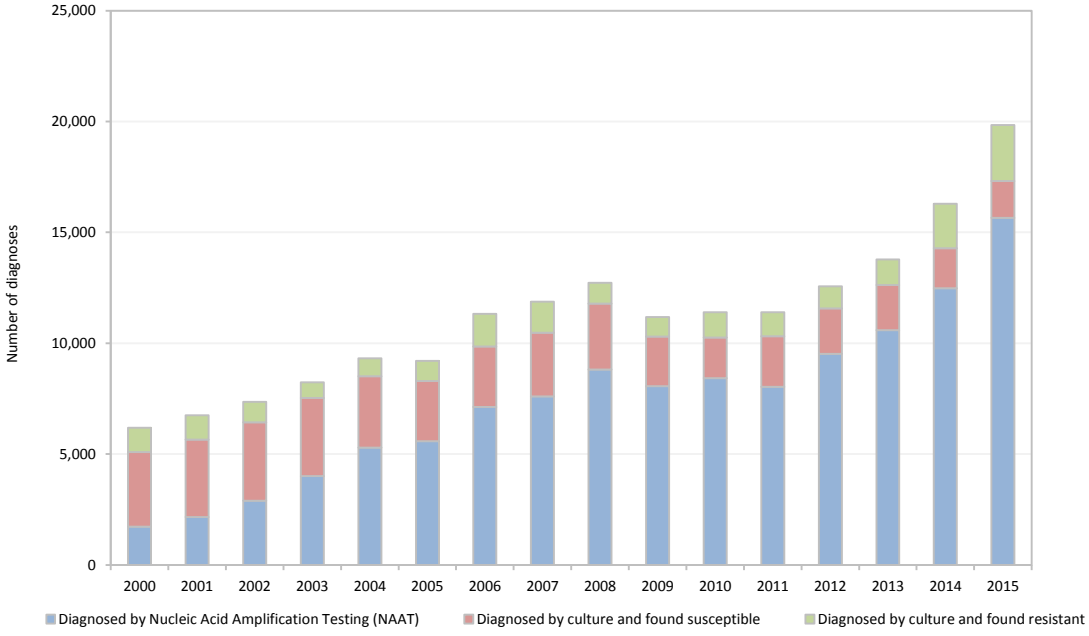


	2011 (n=3360)	2012 (n=3036)	2013 (n=3195)	2014 (n=3809)	2015 (n=4190)
Penicillin Resistance	22.2%	20.3%	18.9%	18.2%	18.9%
Tetracycline Resistance	29.4%	30.3%	33.0%	47.3%	56.4%
Erythromycin Resistance	26.6%	23.1%	24.3%	32.0%	32.4%
Ciprofloxacin Resistance	29.3%	28.5%	29.3%	34.0%	38.9%

Nucleic Acid Amplification Test (NAAT)

In regards to gonorrhea, the continued shift in diagnostic practice from cultures to NAAT has presented a challenge to laboratories monitoring the antimicrobial susceptibility of *N. gonorrhoeae*, as cultures are currently required for antimicrobial susceptibility testing. Over 70% of gonococcal infections in Canada are now diagnosed using NAAT, and therefore antimicrobial susceptibility data in these jurisdictions are not available (Figure 27).

Figure 27: Distribution of gonorrhea diagnosis methods, 2000-2015



Text Box 6: Enhanced Surveillance of Antimicrobial Resistant Gonorrhea

In 2015, STI clinics at five sites across Canada participated in the Enhanced Surveillance of Antimicrobial Resistant Gonorrhea (ESAG) and provided epidemiologic and treatment data. Data included gonorrhea-positive cultures collected from 657 patients, along with those patients' treatment information. The majority of cases at the five participating sites were prescribed either the preferred or alternative therapies as proposed by the Canadian Guidelines on Sexually Transmitted Infections[29]. The definitions for preferred or alternative therapies are shown in Table A.

Among men who have sex with men (MSM), 95% were prescribed either the preferred or alternative therapy proposed by the Canadian Guidelines on Sexually Transmitted Infections for their anogenital infections (Table B). For pharyngeal infections among MSM, 92% were prescribed either the preferred or alternative therapy proposed by the Canadian Guidelines on Sexually Transmitted Infections. Among other adults, including females, transgender, and males who did not meet the definition of MSM, there was a high level of adherence to the guidelines (93%) for anogenital infections, and a lower level (76%) for pharyngeal infections.

Table A: Treatment guidelines for anogenital and pharyngeal infections – preferred and alternative treatments

Treatment		MSM	Other Adults
Anogenital	Preferred	Ceftriaxone 250 mg IM + azithromycin 1 g PO	Ceftriaxone 250 mg IM + azithromycin 1 g PO OR Cefixime 800 mg PO + azithromycin 1 g PO
	Alternative	Cefixime 800 mg PO +azithromycin 1 g PO OR Spectinomycin 2 g IM + azithromycin 1g PO OR Azithromycin 2 g PO	Spectinomycin 2 g IM + azithromycin 1g PO OR Azithromycin 2 g PO
Pharyngeal	Preferred	Ceftriaxone 250 mg IM + azithromycin 1 g PO	Ceftriaxone 250 mg IM + azithromycin 1 g PO
	Alternative	Cefixime 800 mg PO +azithromycin 1 g PO	Cefixime 800 mg PO +azithromycin 1 g PO OR Azithromycin 2 g PO

Table B: Prescribed treatment for gonorrhea infections by sexual behaviour, ESAG (2015)

	Anogenital		Pharyngeal	
Treatment	MSM	Other Adults	MSM	Other Adults
Preferred or Alternative	95.4%	93.4%	92.4%	76.4%
Other	4.1%	6.3%	7.6%	18.2%
No treatment information	0.5%	0.3%	0.0%	5.5%

Mycobacterium tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that affects primarily the lungs, but can also affect any part of the body. It is transmitted by the inhalation of airborne droplets produced by an individual with infectious pulmonary and/or laryngeal TB when coughing, sneezing, talking, or spitting. A susceptible individual usually requires prolonged exposure before becoming infected. Globally, a number of issues have increased the prevalence of drug-resistant TB, including incorrect or inappropriate prescription of anti-TB drugs; unavailability of drugs; inadequate supervision; and uncommonly, malabsorption of these drugs. In Canada, anti-TB drugs are divided into two broad groups: first and second-line drugs. Four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) are classified as first-line drugs because all are effective, can be taken orally, and are well-tolerated. A standard course of TB treatment lasts between six and nine months and typically includes a combination of isoniazid, rifampin, ethambutol, and pyrazinamide.

As resistant strains of TB bacteria emerge, drug treatment options become fewer, the duration of treatment increases to between 18 and 24 months (or possibly longer), and adverse drug reactions to second- and third-line drugs become a greater risk. Second-line drugs, used to treat those individuals resistant to one or more of the first-line drugs described above, may be less effective and more toxic than first-line TB drugs. The second-line TB drugs include the fluoroquinolones (levofloxacin, moxifloxacin, and ofloxacin) and injectable agents (amikacin, capreomycin, and kanamycin). Certain TB strains are developing resistance to second-line drugs, thereby reducing the availability of effective treatment options for TB. A number of new drugs, such as bedaqualine, delamanid, pretomanid, and sutezolid, are being investigated as potential add-on therapy to the current regimen used to treat resistant infections[33].

Methods

Data for this report have been collected by PHAC using a case-based surveillance system that maintains information on people diagnosed with active TB disease. Provincial and territorial public health authorities voluntarily submit data on all new and re-treatment cases of active TB disease that meet the Canadian case definition. Individuals diagnosed with active TB disease are said to have drug-resistant TB if the strain of TB causing disease is resistant to one or more of the four first-line drugs. Table 1 describes TB drug resistance patterns as defined in the Canadian Tuberculosis Standards.

Table 1: Definitions of TB drug resistance patterns

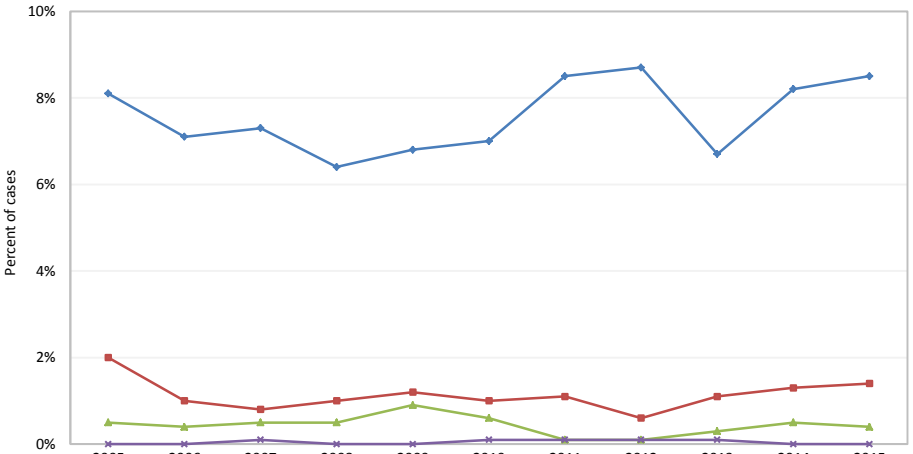
Resistance pattern	Definition
Monoresistance	Resistance to one first-line anti-tuberculosis drug only (isoniazid, rifampin, ethambutol or pyrazinamide).
Polyresistance (other patterns)	Resistance to more than one first-line anti-tuberculosis drug, not including the combination of isoniazid and rifampin.
Multidrug-resistant tuberculosis (MDR-TB)	Resistance to isoniazid AND rifampin with or without resistance to other anti-tuberculosis drugs
Extensively drug-resistant tuberculosis (XDR-TB)	Resistance to isoniazid AND rifampin AND any fluoroquinolone AND at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Drug-Resistant Tuberculosis in Canada

Between 2005 and 2015, both the number of reported TB cases and the annual Canadian incidence rate remained relatively stable. Overall, there were 17,975 cases of active TB disease reported for an average of 1,627 cases reported annually. Over the same period, the incidence rate ranged from a low of 4.5 per 100,000 population in 2014 to a high of 5.1 per 100,000 population in 2005 and 2006.

Between 2005 and 2015, 79 % of all reported TB cases in Canada had a positive culture result. Of these cases, 98% had sensitivity results reported, and 9% of these were found to be drug-resistant (i.e., resistant to at least one of the first-line TB drugs). Isoniazid was the drug for which resistance was most frequently reported. Since 2011, the proportion of all cases with resistance to pyrazinamide has been increasing (Figure 28).

Figure 28: Percent of culture-positive TB cases resistant to each of the four first-line TB drugs, Canada, 2005-2015

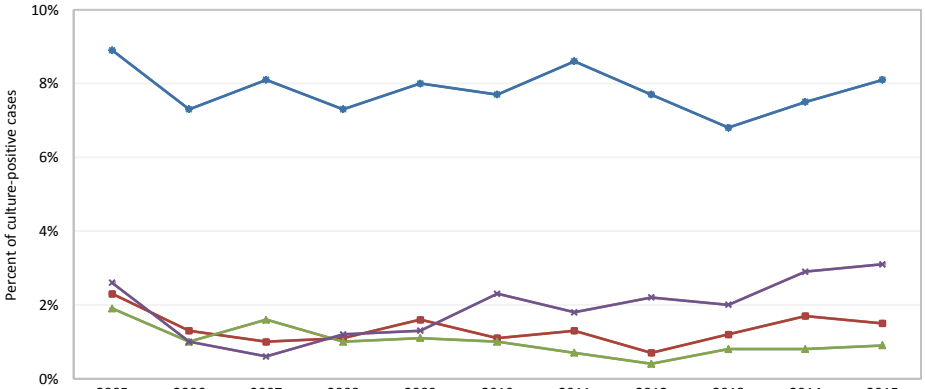


	2005 (n=1208)	2006 (n=1303)	2007 (n=1237)	2008 (n=1320)	2009 (n=1261)	2010 (n=1259)	2011 (n=1319)	2012 (n=1336)	2013 (n=1355)	2014 (n=1344)	2015 (n=1322)
Monoresistant	8.1%	7.1%	7.3%	6.4%	6.8%	7.0%	8.5%	8.7%	6.7%	8.2%	8.5%
Multidrug-resistant	2.0%	1.0%	0.8%	1.0%	1.2%	1.0%	1.1%	0.6%	1.1%	1.3%	1.4%
Other	0.5%	0.4%	0.5%	0.5%	0.9%	0.6%	0.1%	0.1%	0.3%	0.5%	0.4%
Extensively drug-resistant	0.0%	0.0%	0.1%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%

Overall, there has been little change over time in the proportion of cases showing any drug resistance and multidrug-resistance. Between 2005 and 2015, of the cases with sensitivity results, 8% were monoresistant; 0.4% were polyresistant; 1% were MDR-TB; and < 0.1% were XDR-TB. The percentage of cases with XDR-TB remained between 1% and 2% for the period 2005 and 2015. In the years 2014 and 2015, there were no XDR-TB cases reported in Canada (Figure 29).

These data highlight the unique aspects of TB in Canada, including the disproportionate effect on Indigenous people and immigrants to Canada from areas of the world with high rates of TB disease. From 2005 to 2015, 14,044 cases were reported with both resistance status and origin. Of these, 9% were resistant to at least one of the first-line TB drugs. Foreign-born TB cases accounted for 83% of cases with drug-resistant strains, whereas 12% of cases were Canadian-born, non-Indigenous individuals and 5% were Canadian-born, Indigenous individuals.

Figure 29: Percent of reported culture-positive TB cases by resistance profile, 2005-2015



	2005 (n=1146)	2006 (n=1250)	2007 (n=1232)	2008 (n=1319)	2009 (n=1214)	2010 (n=1250)	2011 (n=1307)	2012 (n=1331)	2013 (n=1305)	2014 (n=1299)	2015 (n=1253)
Isoniazid	8.9%	7.3%	8.1%	7.3%	8.0%	7.7%	8.6%	7.7%	6.8%	7.5%	8.1%
Rifampicin	2.3%	1.3%	1.0%	1.1%	1.6%	1.1%	1.3%	0.7%	1.2%	1.7%	1.5%
Ethambutol	1.9%	1.0%	1.6%	1.0%	1.1%	1.0%	0.7%	0.4%	0.8%	0.8%	0.9%
Pyrazinamide	2.6%	1.0%	0.6%	1.2%	1.3%	2.3%	1.8%	2.2%	2.0%	2.9%	3.1%
Isoniazid	8.9%	7.3%	8.1%	7.3%	8.0%	7.7%	8.6%	7.7%	6.8%	7.5%	8.1%
Rifampicin	2.3%	1.3%	1.0%	1.1%	1.6%	1.1%	1.3%	0.7%	1.2%	1.7%	1.5%
Ethambutol	1.9%	1.0%	1.6%	1.0%	1.1%	1.0%	0.7%	0.4%	0.8%	0.8%	0.9%
Pyrazinamide	2.6%	1.0%	0.6%	1.2%	1.3%	2.3%	1.8%	2.2%	2.0%	2.9%	3.1%

Of the 2,711 Canadian-born Indigenous cases reported between 2005 and 2015, 2% were found to have strains of TB that were resistant to at least one of the first-line TB drugs. All the strains were found to be mono-resistant, primarily to isoniazid. Of the 1,588 Canadian-born non-Indigenous cases, 9% were drug-resistant strains. Of these 149, 93% were mono-resistant; 5% were MDR-TB; and less than 1% were identified as XDR-TB.

Of the 9,745 foreign-born cases reported between 2005 and 2015, 11% were resistant to one or more of the first-line TB drugs. Of these, 80% were mono-resistant; 14% were MDR-TB; 5% were poly-resistant; and <0.5% were XDR-TB.

The more severe forms of drug resistance (MDR-TB and XDR-TB) were reported primarily among foreign-born cases with a small percentage reported in the Canadian-born, non-Indigenous population. Of the 158 MDR-TB cases, 96% were among the foreign-born, and the remaining 4% were among the Canadian-born, non-Indigenous population. Between 2005 and 2015, five XDR-TB cases were reported, four were among foreign-born individuals, and one was a Canadian-born individual.

In Canada, drug-resistant TB remains below international levels. However, of the TB cases reported each year, the proportion with any drug resistance continues to remain between 8% and 9%, and between 1% and 2% are found to have MDR-TB. Fortunately, XDR-TB remains rare in Canada, with the last case reported in 2013.

Salmonella enterica serovars Typhi and Paratyphi

Enteric fever is caused by *Salmonella enterica* serovars Typhi (*S.* Typhi) and Paratyphi (*S*. Paratyphi). It is an enteric febrile illness characterized by fever, rash, and diarrhea (or constipation). Children usually present with milder symptoms compared to adults. Serious complications, such as myocarditis or intestinal perforation, can also occur.

Humans are the only reservoir for typhoidal *Salmonella*. Infection usually occurs from consumption of food or water that has been contaminated by an ill person or a chronic asymptomatic carrier. Among Canadians, enteric fever is usually acquired during international travel.

The first line for empiric therapy is a fluoroquinolone, with ciprofloxacin being the most commonly used[34]. However, when deciding on the optimal empiric therapy, antimicrobial resistance patterns in the travel destination countries should be considered. When fluoroquinolone resistance is suspected, injectable third-generation cephalosporins are the empiric treatment of choice. Azithromycin is being increasingly used to treat enteric fever because of the emergence of multidrug-resistant strains.

Methods

Provincial public health laboratories submit all *S.* Typhi, *S*. Paratyphi A, and *S*. Paratyphi B for antimicrobial susceptibility testing, and provide associated data including age and gender of the patient, as well as the anatomical site of the infection. The Yukon, Northwest Territories, and Nunavut forward their isolates to one of the provincial laboratories. Antimicrobial drug susceptibility testing was performed using automated broth microdilution and breakpoints established by the Clinical Laboratory Standards Institute, whenever available. The antimicrobials in the susceptibility panel for 2015 were: amoxicillin-clavulanic acid, ceftiofur, ceftriaxone, ciprofloxacin, ampicillin, azithromycin, cefoxitin, gentamicin, nalidixic acid, streptomycin, trimethoprim-sulfamethoxazole, chloramphenicol, sulfisoxazole, and tetracycline. In 2016, the panel was updated to include meropenem (a carbapenem antimicrobial) and ceftiofur was removed from the panel.

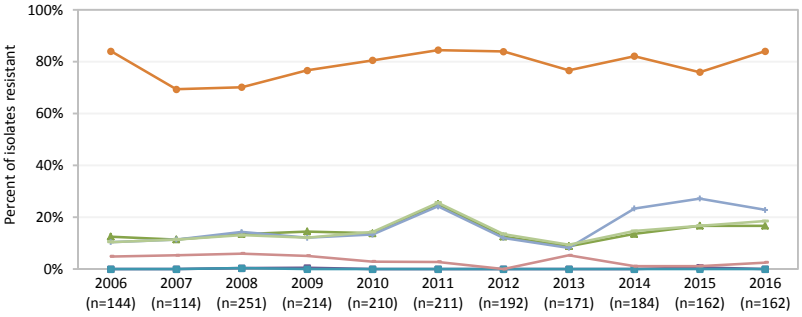
Drug-resistant *Salmonella* Typhi and *Salmonella* Paratyphi in Canada

In 2016, 162 typhoidal isolates were tested for antimicrobial susceptibility; *S*. Typhi (n=137), *S*. Paratyphi A (n=22), and *S*. Paratyphi B[i] (n=3). The majority of typhoidal isolates tested in 2016 were from residents of Ontario, British Columbia, Alberta, and Québec.

In 2016, 84% of typhoidal isolates were resistant to nalidixic acid (Figure 30) and 14% were resistant to ciprofloxacin. No isolates were resistant to ceftriaxone or azithromycin in 2016. A total of 14% of isolates were susceptible to all antimicrobials tested, whereas 19% were multi-class-resistant (i.e., resistant to ≥ 3 classes of antimicrobials) in 2016.

[i] *Salmonella* Paratyphi B does not include *S*. Paratyphi B var. L (+) tartrate (+), formerly called *S*. Paratyphi var. Java.

Figure 30: Resistance to selected antimicrobials among human typhoidal *Salmonella* in Canada, 2006-2016



	2006 (n=144)	2007 (n=114)	2008 (n=251)	2009 (n=214)	2010 (n=210)	2011 (n=211)	2012 (n=192)	2013 (n=171)	2014 (n=184)	2015 (n=162)	2016 (n=162)
Ampicillin	12.5%	11.4%	13.5%	14.5%	13.8%	25.1%	12.5%	8.8%	13.6%	16.7%	16.7%
Ceftriaxone	0.0%	0.0%	0.4%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.0%
Gentamicin	0.0%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Nalidixic acid	84.0%	69.3%	70.1%	76.6%	80.5%	84.4%	83.9%	76.6%	82.1%	75.9%	84.0%
Streptomycin	10.4%	11.4%	14.3%	12.1%	13.3%	24.2%	12.0%	8.2%	23.4%	27.2%	22.8%
Tetracycline	4.9%	5.3%	6.0%	5.1%	2.9%	2.8%	0.0%	5.3%	1.1%	1.2%	2.5%
Trimethoprim-sulfamethoxazole	10.4%	11.4%	13.1%	12.1%	14.3%	25.6%	13.5%	9.4%	14.7%	16.7%	18.5%

Non-typhoidal *Salmonella enterica*

Non-typhoidal salmonellosis is a food-borne gastrointestinal disease caused by a gram-negative bacterium belonging to the Enterobacteriaceae family. It is one of the primary causes of bacterial diarrheal disease in Canada[35]. Most cases of salmonellosis are mild and resolve without treatment; however, it can be life-threatening in some cases. The severity of the disease depends on the susceptibility of the individual and the serovar of *Salmonella*. Antimicrobial-resistant *Salmonella* have been found throughout the food chain, including isolates resistant to antimicrobials of importance to human medicine and multidrug-resistant isolates.

Methods

Provincial public health laboratories submit all or a subset of their *Salmonella* isolates for antimicrobial susceptibility testing; the four largest provinces (British Columbia, Alberta, Ontario, and Québec) submit isolates detected during the first 15 days of each month. Along with the isolates, data about age and gender of the patient, as well as the anatomical site of positive cultures are collected.

Routine antimicrobial susceptibility testing was performed on five frequently isolated non-typhoidal serovars in 2015 and 2016: *S*. Enteritidis, *S*. Heidelberg, *S*. Newport, *S*. Typhimurium, and *S*. 4,[5],12:i:-. In addition, a small subset of the other *Salmonella* serovars submitted were also tested for antimicrobial susceptibility. All isolates were tested using automated broth microdilution and breakpoints established by the Clinical Laboratory Standards Institute, whenever available. The antimicrobials in the susceptibility panel used in 2015 were: amoxicillin-clavulanic acid, ceftiofur (a third generation cephalosporin used in veterinary medicine), ceftriaxone, ciprofloxacin, ampicillin, azithromycin, cefoxitin, gentamicin, nalidixic acid, streptomycin, trimethoprim-sulfamethoxazole, chloramphenicol, sulfisoxazole, and tetracycline. In 2016, the panel was updated to include meropenem (a carbapenem antimicrobial) and ceftiofur was removed from the panel.

Drug-resistant non-Typhoidal *Salmonella* in Canada

In 2016, a total of 2,405 non-typhoidal *Salmonella* human isolates were submitted to PHAC for antimicrobial susceptibility testing, the majority of which were submitted by Ontario (38%) followed by Québec (17%), Alberta (13%), and British Columbia (10%). *Salmonella* Enteritidis was the most common serovar associated with human disease submitted for susceptibility testing, followed by *S*. Typhimurium and *S*. Heidelberg.

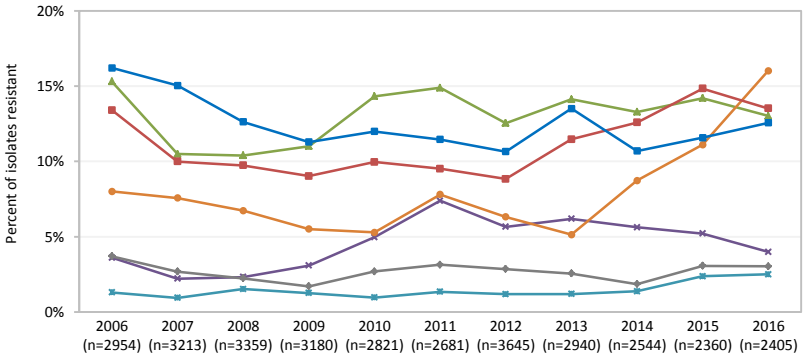
In 2016, the majority of the non-typhoidal *Salmonella* isolates tested for antimicrobial resistance were recovered from stool samples (81%), followed by blood (6%), and urine (4%) (Table 2).

Table 2: Total number of non-typhoidal *Salmonella* isolates submitted for antimicrobial susceptibility testing by sample source and serovar in Canada, 2016

Sample Source	Enteritidis	Heidelberg	4,[5],12:i:-	Newport	Typhimurium	Other serovars
Blood	62	54	6	3	13	17
Stool	979	207	140	156	279	194
Urine	34	20	6	7	8	23
Other	2	2	2	0	0	3
Unknown	88	32	1	19	23	25
Total	1165	315	155	185	323	262

In 2016, 33% of human non-typhoidal *Salmonella* isolates were resistant to one or more antimicrobials tested and 11% of isolates were resistant to three or more antimicrobial classes (i.e., multi-class-resistant). In 2016, nalidixic acid was the antimicrobial to which the largest proportion of isolates were resistant (16%), followed by streptomycin (14%), ampicillin (13%), and tetracycline (13%). Twelve isolates (0.5%) were resistant azithromycin in 2016, 2% of isolates were resistant to ciprofloxacin, and 4% of isolates were resistant to ceftriaxone. No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel. The trend in resistance to nalidixic acid increased significantly from 2013 to 2016 ($p < 0.001$) (Figure 31).

Figure 31: Resistance to selected antimicrobials among human non-typhoidal *Salmonella* in Canada, 2006-2016



	2006 (n=2954)	2007 (n=3213)	2008 (n=3359)	2009 (n=3180)	2010 (n=2821)	2011 (n=2681)	2012 (n=3645)	2013 (n=2940)	2014 (n=2544)	2015 (n=2360)	2016 (n=2405)
Ampicillin	15.3%	10.5%	10.4%	11.0%	14.3%	14.9%	12.5%	14.1%	13.3%	14.2%	13.0%
Ceftriaxone	3.6%	2.2%	2.3%	3.1%	5.0%	7.4%	5.7%	6.2%	5.6%	5.2%	4.0%
Gentamicin	1.3%	0.9%	1.5%	1.3%	1.0%	1.3%	1.2%	1.2%	1.4%	2.4%	2.5%
Nalidixic acid	8.0%	7.6%	6.7%	5.5%	5.3%	7.8%	6.3%	5.1%	8.7%	11.1%	16.0%
Streptomycin	13.4%	10.0%	9.7%	9.0%	10.0%	9.5%	8.8%	11.5%	12.6%	14.8%	13.5%
Tetracycline	16.2%	15.0%	12.6%	11.3%	12.0%	11.5%	10.6%	13.5%	10.7%	11.6%	12.6%
Trimethoprim-sulfamethoxazole	3.7%	2.7%	2.2%	1.7%	2.7%	3.1%	2.9%	2.6%	1.8%	3.1%	3.0%

Resistance in Enteric Bacteria from Animal and Food Sources

PHAC monitors antimicrobial resistance in selected bacterial organisms in animals and food sources across Canada. The organisms include *E. coli*, *Campylobacter*, and *Salmonella* that exist in food animal sources and can be transmitted to people. The contamination of animals and animal products with antimicrobial-resistant bacteria has been identified as a source for human infection with resistant organisms, and these organisms are a frequent cause of food-borne outbreaks.

Many individuals infected with food-borne *E. coli*, *Salmonella,* and *Campylobacter* will develop diarrhea, fever, and abdominal cramps. In most cases, the illness is self-limited and antimicrobial treatment is not required. Some vulnerable individuals (e.g., the elderly, very young children, and individuals with underlying medical conditions) may need to be treated and hospitalized if the diarrhea is severe. Pregnant women are also at increased risk of complications related to these organisms.

Methods

Samples for bacterial isolation are collected at three points along the food chain: (1) healthy animals on farm, (2) healthy animals at slaughter, and (3) meat at retail food stores. Susceptibility testing of veterinary clinical isolates of *Salmonella* (i.e., *Salmonella* from sick animals or their environment) and *Salmonella* isolates from animal feed was also performed. Sampling focused on the major meat producing animal species consumed in Canada: chicken(s), pigs/pork, cattle/beef, and turkey(s). Table 3 indicates which enteric bacteria were isolated from which animal species along the food chain in 2015 and 2016.

Table 3: Zoonotic bacteria routinely tested for antimicrobial resistance by animal species and point along the food chain, 2015-2016

	Farm	Slaughter	Retail Meat
Chicken(s)	*E. coli* *Campylobacter* *Salmonella*	*E. coli* *Campylobacter* *Salmonella*	*E. coli* *Campylobacter* *Salmonella*
Pigs (pork)	*E. coli* *Salmonella*	*E. coli* *Campylobacter* *Salmonella*	*E. coli* *Salmonella*^
Cattle (beef)	N/A	*E. coli* *Campylobacter*	*E. coli*
Turkey(s)*	*E. coli* *Campylobacter* *Salmonella*	N/A	*E. coli* *Campylobacter* *Salmonella*

^Pork is tested for the presence of *Salmonella,* but due to low recovery rates, the *Salmonella* results are not routinely reported
*In 2015, ggeneric *E. coli*, *Campylobacter*, and *Salmonella* from turkeys on farm were only collected in British Columbia and were not included in the routine analysis; in 2016, farm turkey isolates were collected in British Columbia, Ontario and Québec

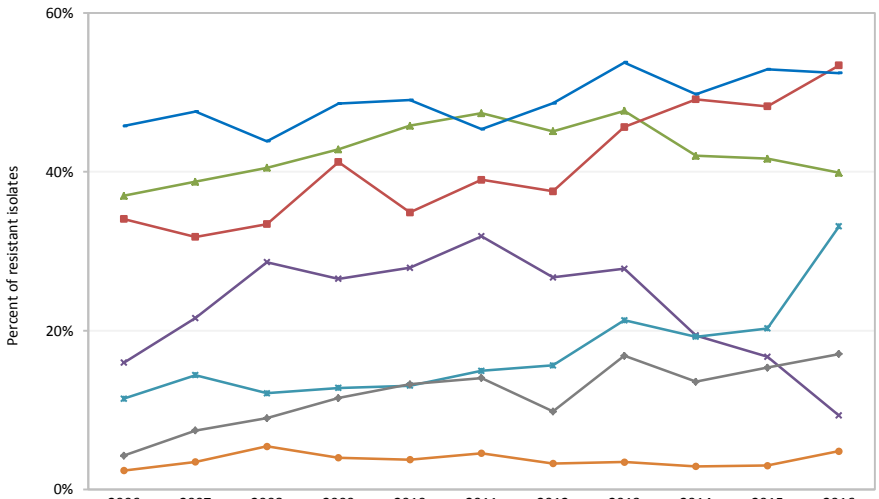
Resistance varies along the food chain, even within a single animal species. Because human exposure to food animals or their products is highest via the consumption of retail meat, the data described below for generic *E. coli, Campylobacter,* and *Salmonella* are only from retail meat surveillance. In 2015, retail meat samples were collected from British Columbia, Alberta, Ontario, and Québec. Samples were also collected from New Brunswick, Nova Scotia, and Prince Edward Island during the first half of the year.

Because there was not a full year of sampling from this region, the results are not included here. In 2016, retail meat samples were collected from British Columbia, Alberta, Ontario, and Québec.

1a. Generic *Escherichia coli* from Chicken

Over half of the generic *E. coli* isolates obtained from chicken retail samples in 2016 were found to be resistant to streptomycin (53%) and tetracycline (52%), followed by sulfisoxazole (46%) and ampicillin (40%) (Figure 32). Resistance to ceftriaxone further decreased in 2016 to 9%, continuing the significant trend from 2013 to 2016 ($p < 0.001$). In contrast, resistance to gentamicin increased significantly in 2016 to 33% up from 20% in 2015 ($p < 0.001$). No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel.

Figure 32: Resistance to selected antimicrobials among generic *Escherichia coli* isolates from chicken meat samples collected from retail stores, 2006-2016

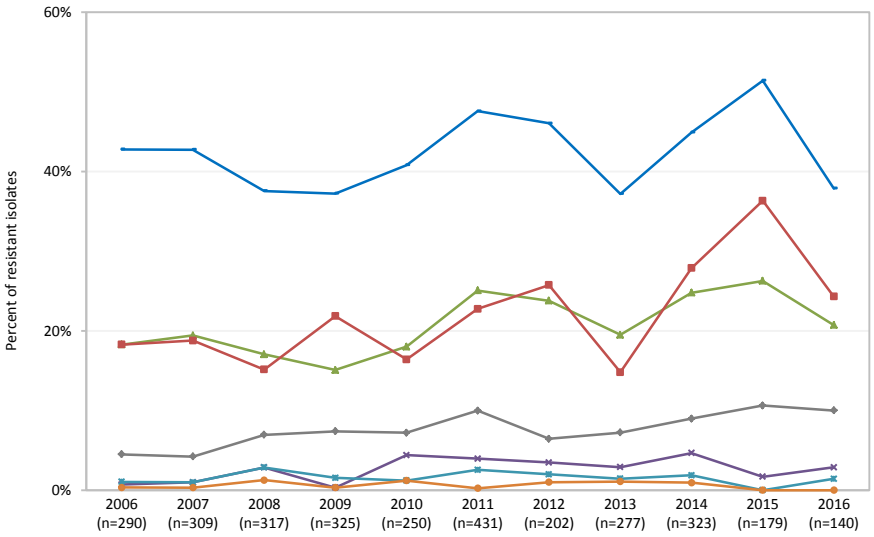


	2006 (n=376)	2007 (n=431)	2008 (n=479)	2009 (n=626)	2010 (n=559)	2011 (n=549)	2012 (n=397)	2013 (n=493)	2014 (n=619)	2015 (n=365)	2016 (n=311)
Ampicillin	37.0%	38.7%	40.5%	42.8%	45.8%	47.4%	45.1%	47.7%	42.0%	41.6%	39.9%
Ceftriaxone	16.0%	21.6%	28.6%	26.5%	27.9%	31.9%	26.7%	27.8%	19.4%	16.7%	9.3%
Gentamicin	11.4%	14.4%	12.1%	12.8%	13.1%	14.9%	15.6%	21.3%	19.2%	20.3%	33.1%
Nalidixic acid	2.4%	3.5%	5.4%	4.0%	3.8%	4.6%	3.3%	3.4%	2.9%	3.0%	4.8%
Streptomycin	34.0%	31.8%	33.4%	41.2%	34.9%	39.0%	37.5%	45.6%	49.1%	48.2%	53.4%
Tetracycline	45.7%	47.6%	43.8%	48.6%	49.0%	45.4%	48.6%	53.8%	49.8%	52.9%	52.4%
Trimethoprim-sulfamethoxazole	4.3%	7.4%	9.0%	11.5%	13.2%	14.0%	9.8%	16.8%	13.6%	15.3%	17.0%

1b. Generic *Escherichia coli* from Pigs (Pork)

Resistance to streptomycin and tetracycline decreased significantly in 2016 compared to 2015 ($p = 0.028$ and $p < 0.006$, respectively) (Figure 33). Three percent of isolates were resistant to ceftriaxone and no isolates were resistant to nalidixic acid. No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel.

Figure 33: Resistance to selected antimicrobials among generic *Escherichia coli* isolates from pork meat samples collected from retail stores, 2006-2016

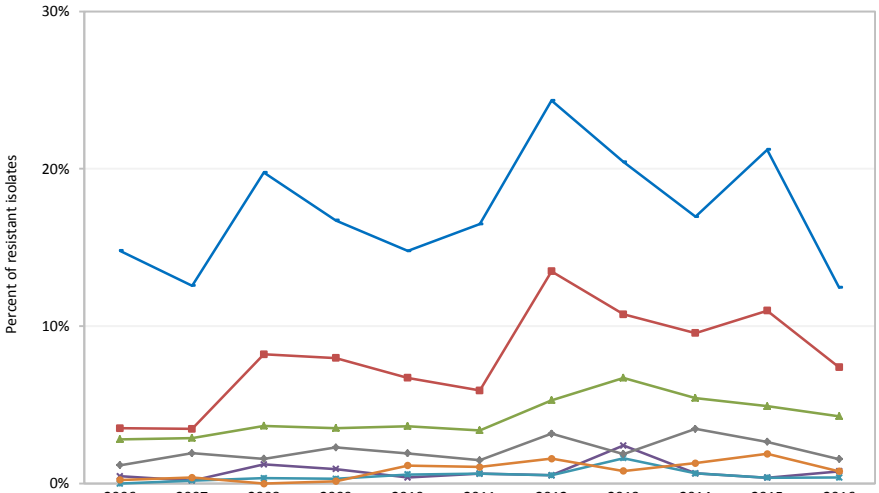


	2006 (n=290)	2007 (n=309)	2008 (n=317)	2009 (n=325)	2010 (n=250)	2011 (n=431)	2012 (n=202)	2013 (n=277)	2014 (n=323)	2015 (n=179)	2016 (n=140)
Ampicillin	18.3%	19.4%	17.0%	15.1%	18.0%	25.1%	23.8%	19.5%	24.8%	26.3%	20.7%
Ceftriaxone	0.7%	1.0%	2.8%	0.3%	4.4%	3.9%	3.5%	2.9%	4.6%	1.7%	2.9%
Gentamicin	1.0%	1.0%	2.8%	1.5%	1.2%	2.6%	2.0%	1.4%	1.9%	0.0%	1.4%
Nalidixic acid	0.3%	0.3%	1.3%	0.3%	1.2%	0.2%	1.0%	1.1%	0.9%	0.0%	0.0%
Streptomycin	18.3%	18.8%	15.1%	21.8%	16.4%	22.7%	25.7%	14.8%	27.9%	36.3%	24.3%
Tetracycline	42.8%	42.7%	37.5%	37.2%	40.8%	47.6%	46.0%	37.2%	44.9%	51.4%	37.9%
Trimethoprim-sulfamethoxazole	4.5%	4.2%	6.9%	7.4%	7.2%	10.0%	6.4%	7.2%	9.0%	10.6%	10.0%

1c. Generic *Escherichia coli* from Cattle (Beef)

The most common resistance among generic *E. coli* isolates from beef in 2016 was to tetracycline, with 13% of all isolates resistant to this antimicrobial (Figure 34). Two isolates were resistant to ceftriaxone (<1%), one isolate was resistant to gentamicin (<1%), and two isolates were resistant to nalidixic acid (<1%). No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel.

Figure 34: Resistance to selected antimicrobials among generic *Escherichia coli* isolates from beef meat samples collected from retail stores, 2006-2016

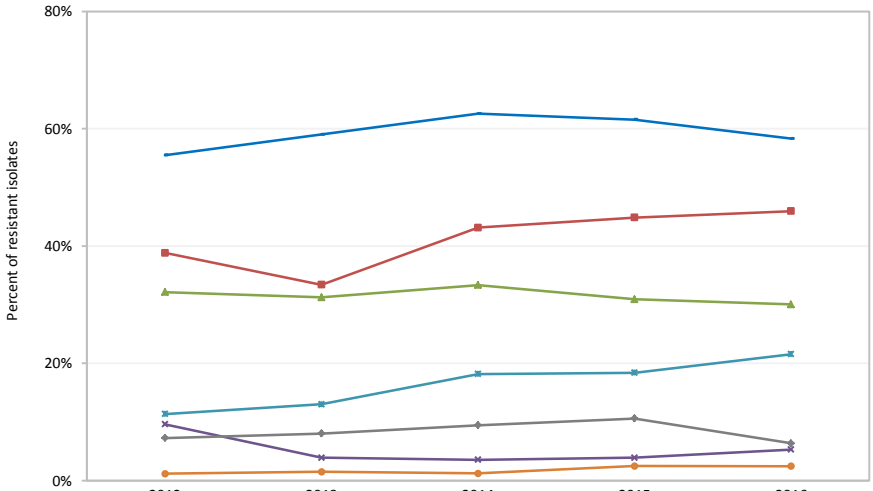


	2006 (n=426)	2007 (n=517)	2008 (n=572)	2009 (n=652)	2010 (n=521)	2011 (n=473)	2012 (n=378)	2013 (n=372)	2014 (n=460)	2015 (n=264)	2016 (n=257)
Ampicillin	2.8%	2.9%	3.7%	3.5%	3.6%	3.4%	5.3%	6.7%	5.4%	4.9%	4.3%
Ceftriaxone	0.5%	0.2%	1.2%	0.9%	0.4%	0.6%	0.5%	2.4%	0.7%	0.4%	0.8%
Gentamicin	0.0%	0.2%	0.3%	0.3%	0.6%	0.6%	0.5%	1.6%	0.7%	0.4%	0.4%
Nalidixic acid	0.2%	0.4%	0.0%	0.2%	1.2%	1.1%	1.6%	0.8%	1.3%	1.9%	0.8%
Streptomycin	3.5%	3.5%	8.2%	8.0%	6.7%	5.9%	13.5%	10.8%	9.6%	11.0%	7.4%
Tetracycline	14.8%	12.6%	19.8%	16.7%	14.8%	16.5%	24.3%	20.4%	17.0%	21.2%	12.5%
Trimethoprim-sulfamethoxazole	1.2%	1.9%	1.6%	2.3%	1.9%	1.5%	3.2%	1.9%	3.5%	2.7%	1.6%

1d. Generic *Escherichia coli* from Turkey

Fifty-eight percent of all *E. coli* isolates from turkey meat were resistant to tetracycline in 2016, followed by streptomycin (46%), sulfisoxazole (30%), and ampicillin (30%) (Figure 35). Five percent of isolates were resistant to ceftriaxone, one isolate was resistant to ciprofloxacin and one isolate was resistant to azithromycin. No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel.

Figure 35: Resistance to selected antimicrobials among generic *Escherichia coli* isolates from turkey meat samples collected from retail stores, 2012-2016

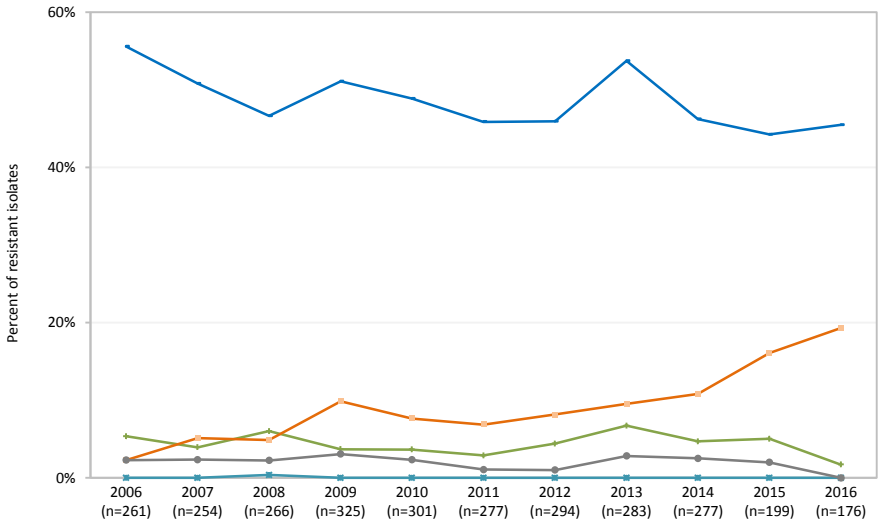


	2012 (n=510)	2013 (n=461)	2014 (n=561)	2015 (n=359)	2016 (n=283)
Ampicillin	32.2%	31.2%	33.3%	30.9%	30.0%
Ceftriaxone	9.6%	3.9%	3.6%	3.9%	5.3%
Gentamicin	11.4%	13.0%	18.2%	18.4%	21.6%
Nalidixic acid	1.2%	1.5%	1.2%	2.5%	2.5%
Streptomycin	38.8%	33.4%	43.1%	44.8%	45.9%
Tetracycline	55.5%	59.0%	62.6%	61.6%	58.3%
Trimethoprim-sulfamethoxazole	7.3%	8.0%	9.4%	10.6%	6.4%

2a. *Campylobacter* spp. from Chicken

In 2016, 45% of *Campylobacter* spp. isolates from retail chicken were resistant to tetracycline (Figure 36). Resistance to ciprofloxacin was detected in 19% of isolates and no isolates were resistant to telithromycin; both ciprofloxacin and telithromycin are considered to be of very high importance in human medicine.

Figure 36: Resistance to selected antimicrobials among *Campylobacter* spp. isolates obtained from chicken meat samples collected from retail stores, 2006-2016

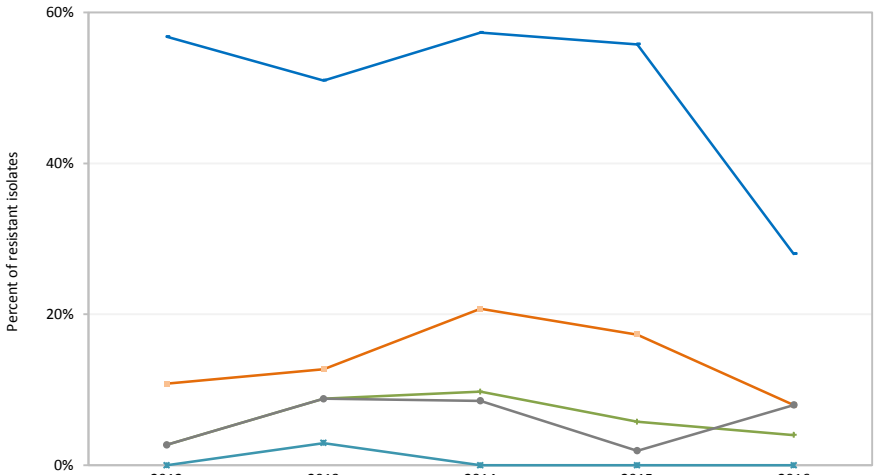


	2006 (n=261)	2007 (n=254)	2008 (n=266)	2009 (n=325)	2010 (n=301)	2011 (n=277)	2012 (n=294)	2013 (n=283)	2014 (n=277)	2015 (n=199)	2016 (n=176)
Azithromycin	5.4%	3.9%	6.0%	3.7%	3.7%	2.9%	4.4%	6.7%	4.7%	5.0%	1.7%
Ciprofloxacin	2.3%	5.1%	4.9%	9.8%	7.6%	6.9%	8.2%	9.5%	10.8%	16.1%	19.3%
Gentamicin	0.0%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Telithromycin	2.3%	2.4%	2.3%	3.1%	2.3%	1.1%	1.0%	2.8%	2.5%	2.0%	0.0%
Tetracycline	55.6%	50.8%	46.6%	51.1%	48.8%	45.8%	45.9%	53.7%	46.2%	44.2%	45.5%

2b. *Campylobacter* spp. from Turkey

In 2016, 28% of *Campylobacter* spp. isolates from retail turkey meat were resistant to tetracycline, a significant decrease relative to 2015 ($p = 0.029$) (Figure 37). Resistance to ciprofloxacin was detected in 8% of isolates and two isolates were resistant to telithromycin.

Figure 37: Resistance to selected antimicrobials among *Campylobacter* spp. isolates obtained from turkey meat samples collected from retail stores, 2012-2016

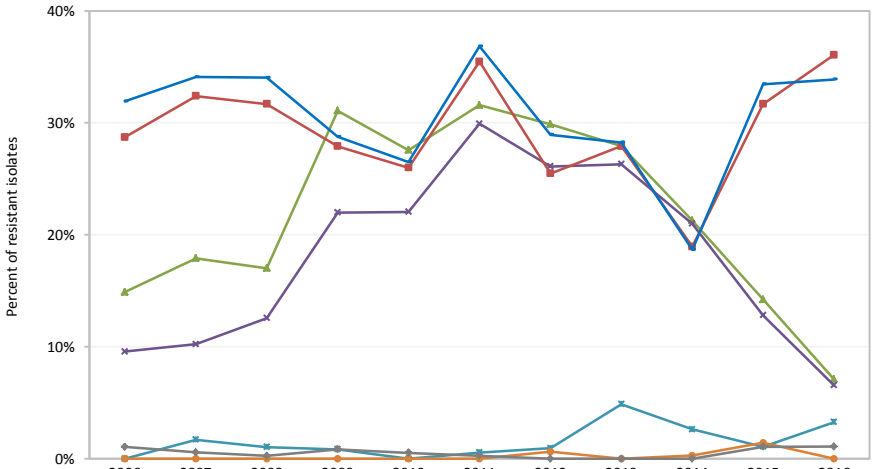


	2012 (n=74)	2013 (n=102)	2014 (n=82)	2015 (n=52)	2016 (n=25)
Azithromycin	2.7%	8.8%	9.8%	5.8%	4.0%
Ciprofloxacin	10.8%	12.7%	20.7%	17.3%	8.0%
Gentamicin	0.0%	2.9%	0.0%	0.0%	0.0%
Telithromycin	2.7%	8.8%	8.5%	1.9%	8.0%
Tetracycline	56.8%	51.0%	57.3%	55.8%	28.0%

3a. *Salmonella* in Chicken

In 2016, 39% of all *Salmonella* isolates recovered from retail chicken were resistant to one or more antimicrobials tested, and 6% of isolates were multi-class-resistant (i.e., resistant to three or more antimicrobial classes). Thirty-six percent of retail chicken *Salmonella* isolates were resistant to streptomycin, followed by tetracycline (34%), and ampicillin, amoxicillin-clavulanic acid, and ceftriaxone (7% each) (Figure 38). The declining trends in resistance to ampicillin and ceftriaxone seen from 2011 to 2016 were found to be significant ($p < 0.001$). In 2016, no resistance was observed to azithromycin or ciprofloxacin, representing two antimicrobials used in human medicine for treating severe and invasive salmonellosis along with treatment during pregnancy and for immunocompromised individuals. No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel. Among retail chicken meat, the most common *Salmonella* serovars associated with resistance to third-generation cephalosporins were *S*. Heidelberg and *S*. Kentucky.

Figure 38: Resistance to selected antimicrobials among *Salmonella* isolates from chicken meat samples collected at retail stores, 2006-2016



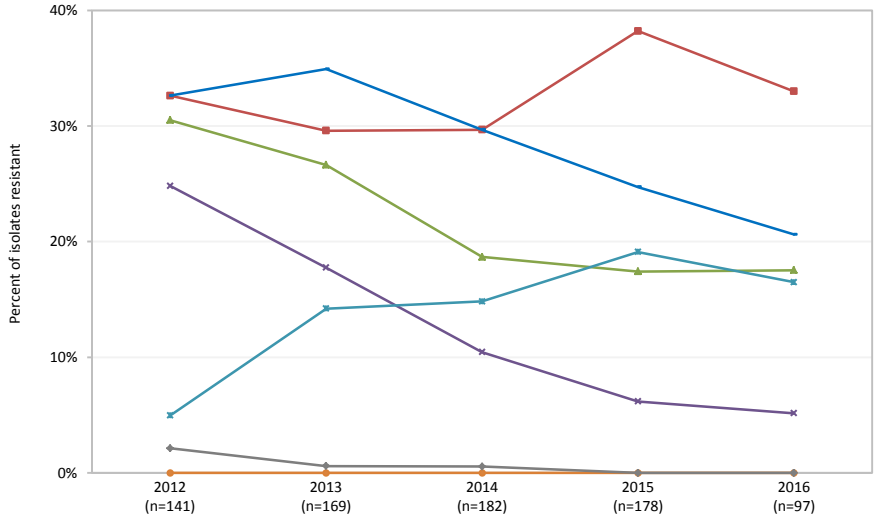
	2006 (n=94)	2007 (n=352)	2008 (n=382)	2009 (n=473)	2010 (n=381)	2011 (n=361)	2012 (n=318)	2013 (n=308)	2014 (n=343)	2015 (n=281)	2016 (n=183)
Ampicillin	14.9%	17.9%	17.0%	31.1%	27.6%	31.6%	29.9%	27.9%	21.3%	14.2%	7.1%
Ceftriaxone	9.6%	10.2%	12.6%	22.0%	22.0%	29.9%	26.1%	26.3%	21.0%	12.8%	6.6%
Gentamicin	0.0%	1.7%	1.0%	0.8%	0.0%	0.6%	0.9%	4.9%	2.6%	1.1%	3.3%
Nalidixic acid	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.0%	0.3%	1.4%	0.0%
Streptomycin	28.7%	32.4%	31.7%	27.9%	26.0%	35.5%	25.5%	27.9%	19.0%	31.7%	36.1%
Tetracycline	31.9%	34.1%	34.0%	28.8%	26.5%	36.8%	28.9%	28.2%	18.7%	33.5%	33.9%
Trimethoprim-sulfamethoxazole	1.1%	0.6%	0.3%	0.8%	0.5%	0.3%	0.0%	0.0%	0.0%	1.1%	1.1%

3b. *Salmonella* in Turkey

In 2016, 45% of all *Salmonella* isolates recovered from retail turkey meat were resistant to one or more antimicrobials tested, and 15% of isolates were multi-class-resistant (i.e., resistant to three or more antimicrobial classes). Thirty-three percent of retail turkey *Salmonella* isolates were resistant to streptomycin, followed by tetracycline (21%), and sulfisoxazole (19%) (Figure 39). No resistance was observed to azithromycin or ciprofloxacin, antimicrobials used in human medicine for treating severe and invasive salmonellosis. No resistance to meropenem was detected in 2016, the first year this antimicrobial was included in the testing panel.

Resistance among *Salmonella* isolates is strongly dictated by serovar; some serovars are much more likely to demonstrate resistance than others. Although turkeys and chickens are both poultry species, the serovars recovered from turkey meat are very different from those that are detected in retail chicken meat. As such, the resistance profiles observed in turkey are also different. Among retail turkey meat, the most common *Salmonella* serovar associated with resistance to third-generation cephalosporins was *S*. Heidelberg. Resistance to this important class of antimicrobials was also observed in isolates of *S*. Agona.

Figure 39: Resistance to selected antimicrobials among *Salmonella* isolates from turkey meat samples collected at retail stores, 2012-2016



	2012 (n=141)	2013 (n=169)	2014 (n=182)	2015 (n=178)	2016 (n=97)
Ampicillin	30.5%	26.6%	18.7%	17.4%	17.5%
Ceftriaxone	24.8%	17.8%	10.4%	6.2%	5.2%
Gentamicin	5.0%	14.2%	14.8%	19.1%	16.5%
Nalidixic acid	0.0%	0.0%	0.0%	0.0%	0.0%
Streptomycin	32.6%	29.6%	29.7%	38.2%	33.0%
Tetracycline	32.6%	34.9%	29.7%	24.7%	20.6%
Trimethoprim-sulfamethoxazole	2.1%	0.6%	0.5%	0.0%	0.0%

Text Box 7: Fluoroquinolone resistance in *Escherichia coli* and *Salmonella*

Fluoroquinolones are a class of antimicrobial considered to be of very high importance to human medicine (Category I) that is commonly used in people to treat a variety of infections. Although the majority of resistance to fluoroquinolones has been observed in *Campylobacter* isolates, the rare occurrence of ciprofloxacin (a fluoroquinolone) resistance in *E. coli* and *Salmonella* has been noted.

Among agri-food isolates, 27 fluoroquinolone-resistant *E. coli* isolates were recovered between 2011 to 2015; ten isolates were from 2015 and were from chickens (n=3), chicken meat (n=2), ground beef (n=1), and ground turkey (n=4). In 2016, nine additional fluoroquinolone-resistant *E. coli* isolates were recovered; these isolates were from chickens (n=3), turkeys (n=1), chicken meat (n=3), and turkey meat (n=1). Between 2011 and 2015, ciprofloxacin resistance was detected in 24 *Salmonella* isolates from agri-food sources; 11 were from 2015 and most were recovered from healthy chickens (n=3) and sick cattle (n=7). In 2016, 14 additional fluoroquinolone-resistant *Salmonella* were detected and most (n=12) were from sick cattle.

Nearly all *S*. Kentucky isolates were fully susceptible to all antimicrobials tested in 2002. Beginning in 2004/2005, resistance to streptomycin and tetracycline began to emerge, and then in 2009/2010, resistance to β-lactam antimicrobials (e.g., amoxicillin-clavulanic acid, ceftiofur, cefoxitin, ampicillin, and ceftriaxone) started to appear, often in conjunction with resistance to streptomycin and tetracyclines. More recently, these resistant isolates have also shown resistance to nalidixic acid, which is a quinolone and can be an indicator of emerging resistance to fluoroquinolones. Since 2011, 45 *S*. Kentucky isolates from agri-food sources were resistant to nalidixic acid; nearly three quarters of these were from 2015. In 2016, no *S*. Kentucky isolates were resistant to nalidixic acid.

Resistance to ciprofloxacin was observed for the first time in agri-food *S*. Kentucky isolates in 2015; this finding also marked the first time fluoroquinolone resistance was detected in any *Salmonella* recovered from chicken. No *S*. Kentucky isolates from agri-food were resistant to ciprofloxacin in 2016. In 2015, 32 *S*. Kentucky isolates from healthy chickens on farm were resistant to all β-lactam antimicrobials tested; three quarters were also resistant to nalidixic acid. This same resistance pattern was also seen in two *S*. Kentucky isolates recovered from retail chicken meat samples. All but one agri-food *S*. Kentucky isolates with this resistance pattern in 2015 were from British Columbia. British Columbia is the only region where participating broiler chicken farms have reported the use of enrofloxacin (a fluoroquinolone); however, there has been no reported use in British Columbia or any other region in Canada since 2013. In 2016, there were 38 *S*. Kentucky isolates resistant to all β-lactams tested (except meropenem); none of these isolates was resistant to nalidixic acid.

Fluoroquinolone-resistant non-typhoidal *Salmonella* isolates from humans were mainly serovars Kentucky, Enteritidis, and Typhimurium. There were 127 of these isolates between 2011 and 2015; 17 non-typhoidal human ciprofloxacin-resistant human isolates were from 2015. An additional 41 human non-typhoidal *Salmonella* isolates were resistant to ciprofloxacin in 2016. Unexpectedly, in 2015, most of the resistant isolates from humans were *S*. Kentucky (n=9). This finding is important and something to watch over time, as *S*. Kentucky is a very common serovar in chicken, but is rarely recovered from humans. In contrast to the resistance patterns observed in animal and food derived *S*. Kentucky isolates, only five of all *S*. Kentucky isolates from humans between 2011 and 2015 were resistant to ceftriaxone and just one of these were also resistant to nalidixic acid. Of the *S*. Kentucky isolates from humans between 2011 and 2015, two-thirds were resistant to ciprofloxacin or nalidixic acid. All of the *S*. Kentucky isolates from humans in 2016 (n=12) were resistant to ciprofloxacin or nalidixic acid. Previous analysis of *S*. Kentucky isolates concluded that Canadian human infections were not acquired from domestically produced food[36]. The same study observed that of those patients with travel history, all had had travelled to Africa. This is similar to previous work in Europe that linked infection with ciprofloxacin-resistant *S*. Kentucky to travel to countries in Africa[37]. In 2016, most of the fluoroquinolone-resistant isolates from humans were *S.* Enteritidis (n=20); there were 12 resistant *S*. Kentucky isolates from humans in 2016.

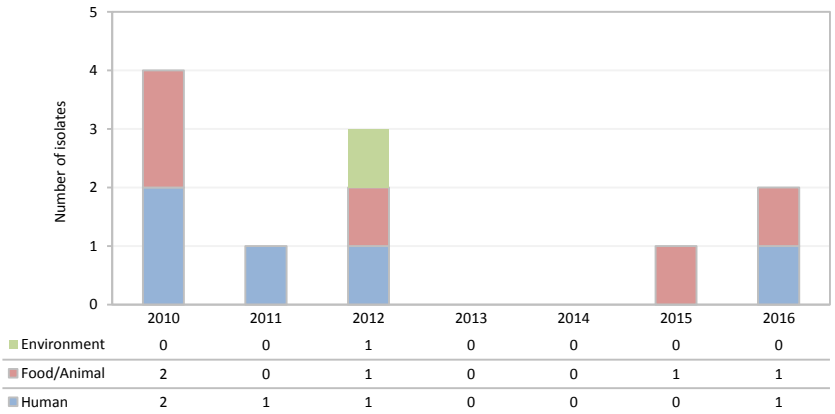
Text Box 8: Screening for colistin resistance in humans, animals, and food products

Colistin is a polymyxin antimicrobial (polymyxin E), and is considered to be of very high importance to human medicine[15]. Resistance to colistin may be mediated by the MCR-1 gene which was first reported in November 2015 in China[38]. Since then, screening efforts in surveillance programs have expanded, the global reporting of colistin resistance has increased, and the MCR-2 gene[39] was discovered.

Since 2015, *Salmonella* and *E. coli* from all agri-food surveillance components (i.e., retail, slaughter house, farm) as well as animal clinical *Salmonella* isolates were tested for colistin resistance. Retrospective testing of isolates from the same agri-food surveillance components and supported targeted research studies were tested for resistance to colistin if they met minimum inhibitory concentration criteria for resistance to ciprofloxacin and ceftriaxone. Human isolates were tested using similar inclusion screening criteria. Any isolates meeting phenotypic screening criteria were tested for the presence of the MCR gene variants using PCR methodologies.

Of the tested samples and isolates, four *E. coli* and one *S.* Typhimurium from humans have been detected with the MCR-1 gene. Five *E. coli* isolates from food (two retail ground beef; one retail veal meat; two imported seafood products) and one *E. coli* isolate from sewage contained the MCR-1 gene (Figure A).

Figure A: Number of isolates testing positive for the MCR-1 gene, 2010-2016*



	2010	2011	2012	2013	2014	2015	2016
Environment	0	0	1	0	0	0	0
Food/Animal	2	0	1	0	0	1	1
Human	2	1	1	0	0	0	1

*Note: Since these results are derived from a number of sources, no inference of year-to-year trend can be made.

Canadian surveillance programs and targeted studies identified the MCR-1 gene conferring resistance to colistin in retrospective and prospective testing of human, agri-food, and environmental samples. The presence of colistin resistance in isolates derived from domestic food animals, imported seafood, environment, and human patients with varied travel histories highlights the importance of continued monitoring efforts.

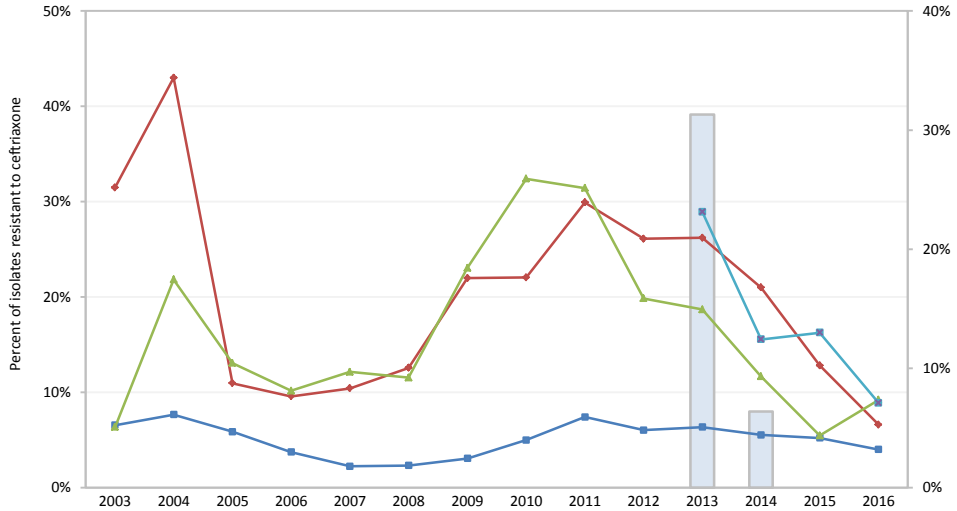
Text Box 9: Ceftriaxone resistance in Non-Typhoidal *Salmonella* and generic *Escherichia coli*

Ceftriaxone is a Category I antimicrobial[15] (very high importance to human medicine) that is used to treat a variety of human infections. Although ceftriaxone is not used in animals, similar drugs (e.g., ceftiofur) are used to treat and prevent a range of animal infections. In most situations, if an organism is resistant to one of these drugs, it will also be resistant to the other.

In 2015, a reduction in reported use of ceftiofur on broiler chicken farms and changing resistance to ceftriaxone in *Salmonella* from humans, chickens, and chicken meat were observed (Figure A). In mid-2014, the poultry industry implemented a national ban on the use of Category I antimicrobials for disease prevention purposes. Consistent with the timing of this ban, reported ceftiofur use in broiler chickens continued to decrease and dropped to 0% among participating flocks in 2015. Reported ceftiofur use remained at 0% in 2016. Over the same time period, a concurrent decline was observed in resistance to ceftriaxone in *Salmonella* from multiple surveillance components. Similar trends have been observed in *E. coli* (data not shown). Most ceftriaxone resistance in humans has been observed in isolates of *Salmonella* Heidelberg. In 2016, resistance to ceftriaxone in *Salmonella* Heidelberg isolates from humans dropped to 16%, down from 27% in 2015 (data not shown).

The industry-led initiative to eliminate use of ceftiofur and all other Category I antimicrobials in poultry for disease prevention has appeared to have had the desired effect. Data have shown a reduction in reported use of ceftiofur in broiler chicken as well as reduced resistance in both *E. coli* and *Salmonella* from chickens and chicken meat. This trend will be monitored in coming years and the impact of this important intervention on resistance in *Salmonella* from humans will also continue to be examined.

Figure A: Reduction in reported use of ceftiofur on farm and changing resistance to ceftriaxone in non-typhoidal *Salmonella* from humans and chicken sources, 2003-2016



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Flocks reporting use of ceftiofur											31.3%	6.4%	0.0%	0.0%
Human Non-Typhoidal Salmonella	6.6%	7.7%	5.9%	3.7%	2.2%	2.3%	3.1%	5.0%	7.4%	6.0%	6.4%	5.5%	5.2%	4.0%
Retail chicken Salmonella	31.5%	43.0%	11.0%	9.6%	10.4%	12.6%	22.0%	22.0%	29.9%	26.1%	26.2%	21.0%	12.8%	6.6%
Slaughter house chicken Salmonella	6.3%	21.8%	13.1%	10.2%	12.1%	11.5%	23.0%	32.4%	31.4%	19.8%	18.7%	11.7%	5.5%	9.2%
Farm chicken Salmonella											23.1%	12.4%	13.0%	7.1%

Text Box 10: Increasing numbers of highly-drug-resistant *Salmonella*

Multidrug resistance (MDR) occurs when the bacteria are resistant to multiple antimicrobial agents. These types of bacteria pose the greatest threat to public health as often there are few or no treatment options left.

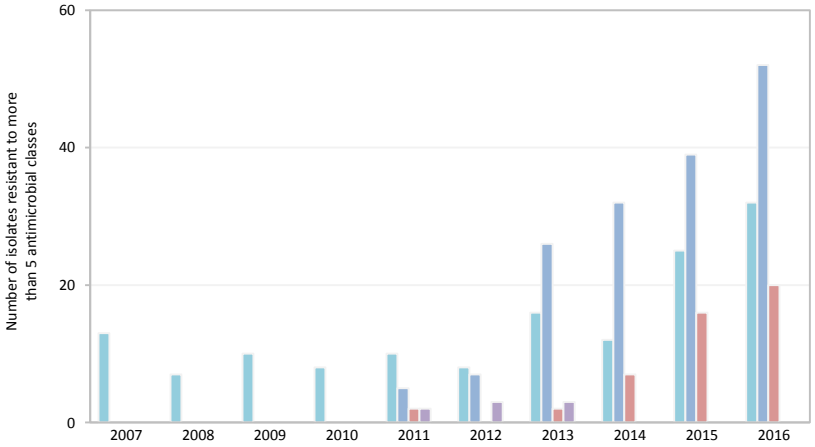
Depending on the year, susceptibility of *Salmonella* isolates is tested for six to seven different antimicrobial classes. The number of drug classes tested depends on the configuration of the test panel used in a particular surveillance year. In 2016, seven antimicrobial classes were tested.

More often, bacteria that are resistant to the greatest number of antimicrobial classes have been recovered from sick people and animals, who may have already been treated with antibiotics. PHAC is paying particular attention to those bacteria resistant to more than five antimicrobial classes (Figure A).

Between 2006 and 2010, no agri-food *Salmonella* isolates were resistant to more than five classes. Since 2011, a small but increasing number of highly-resistant isolates have been recovered. Most of these have been recovered from clinically sick cattle; and most of these have been *S.* Dublin (106/161; 66%) and *S.* Typhimurium (42/161; 26%). Just one agri-food isolate (*S.* Typhimurium) has shown resistance to all seven classes tested: one isolate from a clinical cattle sample submitted in 2014. While this trend is important to monitor, the results need to be interpreted with caution. PHAC does not receive all clinical *Salmonella* isolates from agri-food sources (many laboratories do not submit clinical isolates), and some submissions are likely clustered around disease outbreak events, and thus may represent repeat submissions from the same animal or farm. No highly-resistant *Salmonella* isolates have been detected from chicken sources.

The number of highly-resistant *Salmonella* isolates from humans has also increased. Four human isolates have shown resistance to all seven antimicrobial classes tested: two *S.* 4,[5],12:i:- (in 2012 and 2016), one *S.* Newport (in 2014), and one *S.* Kentucky (in 2015). Figure A provides some evidence that highly-resistant isolates may be becoming more frequent in humans and animals in Canada, and is a trend that will continue to be monitored.

Figure A: Number of isolates resistant to more than five antimicrobial classes, by species, 2007-2016



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Human (non-typhoidal)	13	7	10	8	10	8	16	12	25	32
Cattle	0	0	0	0	5	7	26	32	39	52
Pork	0	0	0	0	2	0	2	7	16	20
Turkey	0	0	0	0	2	3	3	0	0	0
Chicken	0	0	0	0	0	0	0	0	0	0

Antimicrobial use in Canada

Human antimicrobial use

Methods

All data presented are for antimicrobials within the J01 class, as described by the World Health Organization[30]. These are the antibacterials for systemic use. Antimicrobials classified in other groups (e.g., D01 antifungals for dermatological use, A01AB anti-infectives and antiseptics for local oral treatment) have been excluded from these analyses.

Human AMU data include information on prescriptions dispensed by retail pharmacies in Canada, antimicrobials purchased by Canadian hospitals, and diagnoses for which physicians have recommended an antimicrobial in the community. Four datasets are accessed describing human AMU, and are presented in three sections: Community AMU, AMU by diagnosis, and Hospital AMU. All data received are reviewed, cleaned, and analysed by PHAC.

1. Community AMU

   The data presented are from two datasets: the Canadian CompuScript (CCS) dataset (purchased from IQVA), and Health Canada's Non-Insured Health Benefits (NIHB) claims data. The CCS includes data collected from 60% of pharmacies in Canadian provinces (no territorial data are available), which are extrapolated to the universe of nearly 10,000 pharmacies. Data included are prescriptions dispensed by antimicrobial product, and the number of units dispensed by product.

   The NIHB claim data were acquired in order to present a picture of use among Indigenous populations in Canada, and provide estimates of AMU in the territories among Indigenous peoples. This dataset includes prescription counts and the number of units dispensed by product for all prescriptions dispensed under the program.

2. AMU by diagnosis

   The Canadian Disease and Therapeutic index (CDTI) dataset, purchased from IQVA, provides information about the patterns and treatments of disease encountered by office-based physicians (specialists and general practitioners, including those with offices in hospitals). Data from 652 physicians were available in 2016 and projection methods were used to extrapolate data to the universe of approximately 55,092 physicians in Canada. At visits to these physicians during data collection periods (2 days each quarter), the physicians record all diagnoses made, as well as all drug products that are recommended (whether or not a prescription for that product is provided).

3. Hospital AMU

   The data in this section arise from The Canadian Drugstore and Hospital (CDH) database purchased from IQVA. The CDH provides a measure of the dollar value and unit volume of pharmaceutical products purchased by nearly all Canadian hospitals. Hospitals in this context include general hospitals, long term care facilities, psychiatric, pediatric/maternity, government, cancer, and specialized hospitals. Federal prisons are excluded. Data about purchases from pharmaceutical manufacturer warehouses/wholesalers are collected from over 650 hospitals and are extrapolated to represent the purchases made by over 740 hospitals across Canada. The provinces of Prince Edward Island (PEI) and Newfoundland and Labrador were grouped due to the small volume of purchases within each province. British Columbia, Nunavut, Yukon, and North West Territories have been grouped together, as the supply of pharmaceutical purchases to this province and the territories are captured as one and cannot be further broken down by the respective province or territory. CDH provides the estimated value of antimicrobials purchased by various hospitals sectors and does not necessarily represent administered antimicrobials. In addition, returns are included, and the database is always adjusting for corrections; therefore, the history of data can change.

The data in this section are presented using four different metrics, each presenting a slightly different picture of antimicrobial use. These metrics are:

1. Kilograms of active agent. This metric allows for comparisons across different datasets, where prescriptions or dose counts may be inappropriate (e.g., comparing human and animal use, where a herd prescription is not appropriate to compare to a single prescription for a human). It is a crude measurement of the weight of active ingredient dispensed or purchased. It should be noted that this metric can change greatly based upon the products being used in a setting, as pharmacodynamics play a considerable role. For example, a product that requires a larger (i.e., heavier) dose does not necessarily promote selection for resistance at a higher rate than a product that requires a small dose.

2. Defined Daily Doses (DDDs) per population. This is a standardized metric for human drug use, allowing for comparisons to be made between populations. The standardized daily dose for each antimicrobial is set by the World Health Organization, and reflects a normal single-day dosage for an adult. Overall measures presented here are calculated by dividing the total number of active kilograms for each product by the standardized daily dose. These values are then divided out by population measures for comparability over time and between provinces. Adjustments are not made for prescriptions dispensed to children here; national measures are presented as if all prescriptions were dispensed to an adult. Where data are broken down by age categories for comparison purposes, DDDs are not presented for the 0-14 age group.

3. Prescriptions per population. This metric provides the best information for looking at prescriber behaviours. DDDs can fluctuate when higher doses or longer durations are prescribed, or when population dynamics change (i.e., differences in the proportion of children/adults, as a child's dose may be a fraction of the standardized measure set for adults). The prescriptions per

population measure is not influenced by these factors and is easily understood. Therefore, it is often the first choice for comparisons within a country over time. However, it may not be the best option for international comparisons of AMU, as volume of product is not considered.

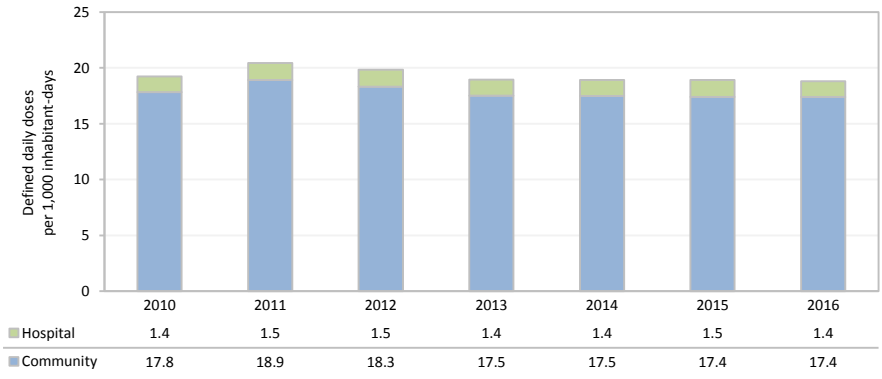
4. Defined Daily Doses (DDDs) per prescription. This metric is calculated by dividing the DDDs per product by the number of prescriptions for that same product. This metric allows for an assessment of how prescriptions are changing over time; an increasing DDD per prescription measure may indicate that the average prescription is being written for a longer duration, or a stronger strength of the product.

National Antimicrobial Use

In Canada, antimicrobial use has varied slightly since 2010, with lowest per capita usage in 2016 and highest in 2011 (Figure 40). Between 2013 and 2016, very little variation was seen in antimicrobial use overall, following declines seen since 1995[14]. The vast majority of antimicrobial use in Canada in humans occurs in the community setting, with approximately 92% of defined daily doses (DDDs) in 2016 dispensed through pharmacies, compared to 8% purchased by hospitals.

In 2016, 206,262 kilograms (kg) of antimicrobial ingredients were dispensed through pharmacies and 40,752 kg were purchased by hospitals, for a total of 247,014 kg and an expenditure of approximately $766 million ($674 million in the community and $92 million in hospital purchasing).

Figure 40: Defined daily doses per 1,000 inhabitant-days in Canada, from hospital purchase and community dispensation data, 2010-2016



	2010	2011	2012	2013	2014	2015	2016
Hospital	1.4	1.5	1.5	1.4	1.4	1.5	1.4
Community	17.8	18.9	18.3	17.5	17.5	17.4	17.4

National Pharmacy Dispensing

Methods

The data presented here arise from two datasets: the Canadian CompuScript (CCS) dataset and Health Canada's Non-Insured Health Benefits (NIHB) claims data. The CCS includes data collected from 60% of pharmacies in Canadian provinces, and these data are extrapolated to the universe of nearly 10,000 pharmacies. Data included are prescriptions dispensed by antimicrobial product and the number of units

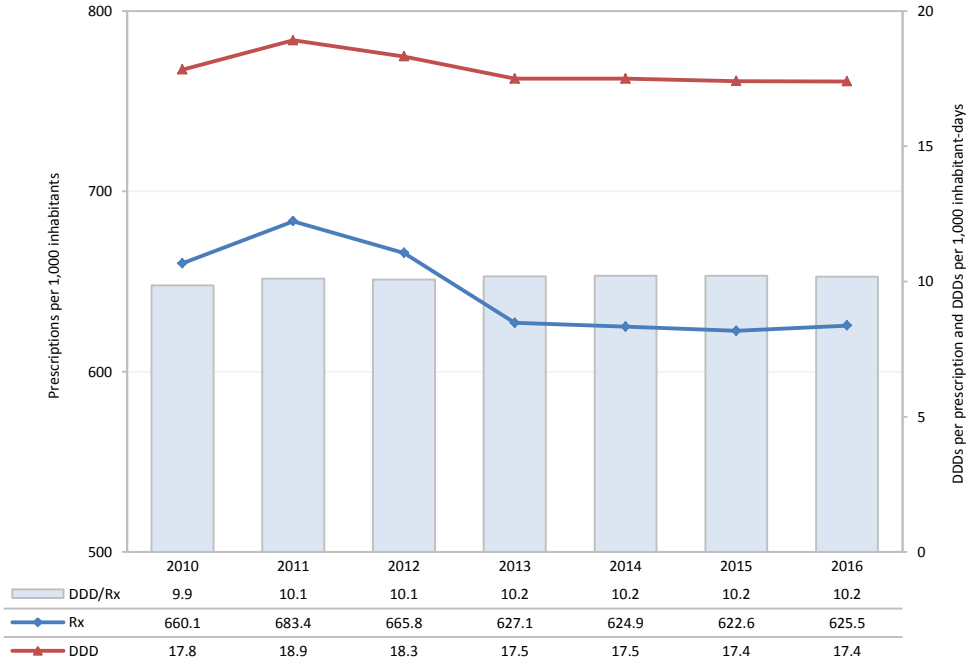
dispensed by product. This dataset can be broken down by patient age or by the specialty of the prescriber (but not both at once, due to small cell sizes and privacy concerns).

The NIHB claims data were acquired in order to present a picture of use among Indigenous populations in Canada. This dataset includes prescription counts and the number of units dispensed by product for all prescriptions dispensed under the program. As the prescriptions dispensed under this program in the provinces are included in the CCS dataset, these are excluded from the national information presented, and only NIHB prescribing from the territories are included.

Antimicrobial dispensations in the community

In 2016, 625 prescriptions were dispensed in the community setting per 1,000 inhabitants (Figure 41). This measure remained quite stable between 2013 and 2016, following a decline of 38 prescriptions per 1,000 inhabitants between 2012 and 2013, and previous large declines seen since 1995. Similar trends in the DDDs have occurred over time (Figure 41). DDDs per prescription increased slightly from 2010 to 2016.

Figure 41: Total measures of community antimicrobial use in Canada 2010-2016; defined daily doses (DDDs) per prescriptions, prescriptions (Rx) per 1,000 inhabitants, and DDDs per 1,000 inhabitant-days



	2010	2011	2012	2013	2014	2015	2016
DDD/Rx	9.9	10.1	10.1	10.2	10.2	10.2	10.2
Rx	660.1	683.4	665.8	627.1	624.9	622.6	625.5
DDD	17.8	18.9	18.3	17.5	17.5	17.4	17.4

The most frequently prescribed antimicrobials in Canada have remained stable over time (Table 4). Amoxicillin continues to be the most frequently prescribed product, accounting for approximately 26% of prescriptions in 2016, followed by azithromycin and cephalexin. The antimicrobials with the greatest number of defined daily doses dispensed have also remained stable over recent years (Table 5). Amoxicillin accounted for nearly 29% of DDDs dispensed in 2016, followed by doxycycline and clarithromycin.

Table 4: Prescriptions per 1,000 inhabitants for the ten most commonly prescribed antimicrobials in Canada, 2010-2016

Antimicrobial	Rank*	2010	2011	2012	2013	2014	2015	2016
Amoxicillin	1	158.75	170.25	163.17	160.23	166.32	161.28	164.35
Amoxicillin and enzyme inhibitor	6	18.12	23.74	25.04	27.43	29.87	33.72	36.95
Azithromycin	2	54.07	58.35	59.92	56.19	56.83	59.44	63.23
Cephalexin	3	44.86	48.50	49.52	50.79	51.12	50.98	52.27
Ciprofloxacin	4	62.21	63.39	61.40	58.23	56.08	55.47	52.02
Clarithromycin	7	64.07	66.93	62.12	52.85	46.72	39.61	34.87
Clindamycin	10	23.51	23.19	22.73	22.60	22.40	21.99	21.37
Doxycycline	9	14.47	15.79	16.66	18.59	20.38	23.05	24.76
Nitrofurantoin	5	29.45	31.77	34.22	34.06	35.86	38.03	38.26
Sulfamethoxazole and trimethoprim	8	33.63	31.92	29.55	30.75	29.47	30.27	30.50
TOTAL		660.09	683.37	665.79	627.09	624.90	622.60	625.50

*Ranked from the highest prescribing to the lowest prescribing in 2016

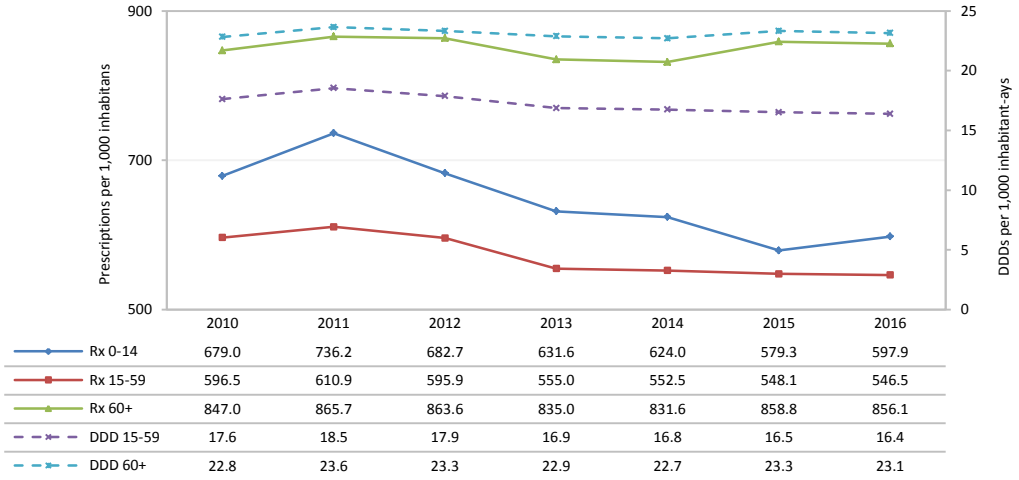
Table 5: Defined daily doses per 1,000 inhabitant-days for the ten antimicrobials with highest DDDs dispensed in Canada, 2010- 2016

Antimicrobial	Rank*	2010	2011	2012	2013	2014	2015	2016
Amoxicillin	1	4.63	5.03	4.83	4.82	5.05	4.94	5.03
Amoxicillin and enzyme inhibitor	4	0.65	0.86	0.91	1.01	1.11	1.27	1.40
Azithromycin	7	0.77	1.02	1.00	0.85	0.85	0.89	0.93
Cephalexin	5	0.90	0.97	0.98	1.01	1.02	1.02	1.04
Ciprofloxacin	6	1.19	1.22	1.17	1.11	1.07	1.06	0.99
Clarithromycin	3	2.70	2.82	2.64	2.28	2.03	1.75	1.54
Doxycycline	2	1.13	1.23	1.31	1.40	1.50	1.68	1.79
Minocycline	10	1.03	0.98	0.87	0.82	0.75	0.68	0.61
Nitrofurantoin	8	0.70	0.74	0.78	0.76	0.78	0.81	0.80
Sulfamethoxazole and trimethoprim	9	0.77	0.75	0.69	0.68	0.67	0.65	0.64
TOTAL		17.83	18.92	18.32	17.50	17.49	17.41	17.39

*Ranked from the greatest to least DDDs in 2016

While overall prescription rates have remained relatively stable since 2010 following a substantial decline from 1995 to 2010[41], patterns of use have changed among age groups in Canada, as seen during the 2010 to 2016 time frame (Figure 42). Prescription rates for children 0-14 years have been on a downward trend since 2011, while prescription rates for those 60+ have been more variable. Similar to previous years, both prescription and DDD rates were highest in 2016 for the 60+ age group. Prescription rates for the 15-59 age group remained stable during 2013 to 2016, but at a lower rate than those seen from 2010 to 2012. Note that DDDs are not presented for the 0-14 age group for comparison, as this measure is not considered to be appropriate for children due to the definition of a defined daily dose (a standard measure for the dose per day for typical usage of the antimicrobial in an adult).

Figure 42: Patterns of antimicrobial use by age group as dispensed by Canadian pharmacies, by prescriptions (Rx) per 1,000 inhabitants and defined daily doses (DDDs) per 1,000 inhabitant-days 2010-2016



The five most commonly prescribed antimicrobials differed slightly among the age groups (Table 6). While amoxicillin was the most commonly prescribed product across the age groups, the remaining products and/or rankings varied.

Table 6: Prescriptions per 1,000 inhabitants for the top five most commonly prescribed antimicrobials per age group in Canada, 2010-2016

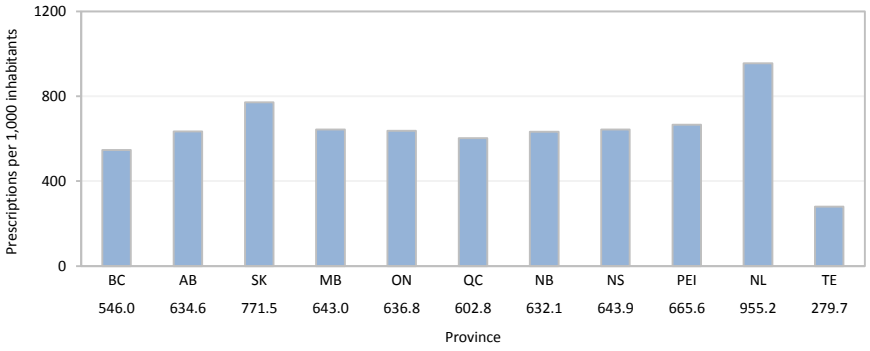
Age group	Antimicrobial	Rank*	2010	2011	2012	2013	2014	2015	2016
0 - 14	Amoxicillin	1	315.76	354.51	339.46	321.19	339.22	315.68	333.11
	Amoxicillin and enzyme inhibitor	5	26.25	32.41	31.55	32.79	33.32	33.36	32.41
	Azithromycin	2	70.14	79.45	74.91	66.12	64.46	64.79	71.60
	Cephalexin	4	36.96	40.55	45.30	44.84	44.05	34.81	36.62
	Clarithromycin	3	80.80	91.31	81.27	64.72	55.09	44.73	39.62
	TOTAL		678.96	736.16	682.73	631.65	624.02	579.29	597.95
15 - 59	Amoxicillin	1	124.96	131.73	124.84	123.89	127.54	124.75	125.16
	Azithromycin	2	49.31	52.25	53.81	50.31	51.17	52.53	55.85
	Cephalexin	3	41.43	44.41	44.32	45.43	45.82	46.41	46.85
	Ciprofloxacin	4	57.09	57.96	55.42	51.90	49.64	48.61	44.92
	Nitrofurantoin	5	25.93	27.97	30.63	31.28	33.22	34.86	34.71
	TOTAL		596.51	610.87	595.95	555.04	552.48	548.06	546.47
60 +	Amoxicillin	1	136.15	141.60	141.61	145.03	149.36	151.05	150.42
	Azithromycin	4	55.89	60.30	66.67	65.94	67.29	74.58	77.05
	Cephalexin	3	62.37	67.61	68.53	71.01	71.41	75.15	77.76
	Ciprofloxacin	2	128.82	129.84	126.14	119.82	114.78	113.16	106.78
	Nitrofurantoin	5	63.25	67.15	69.81	66.58	68.36	72.56	73.33
	TOTAL		847.01	865.71	863.57	835.00	831.58	858.78	856.15

*Ranked by prescribing in 2016

Provincial / Territorial Pharmacy Dispensing

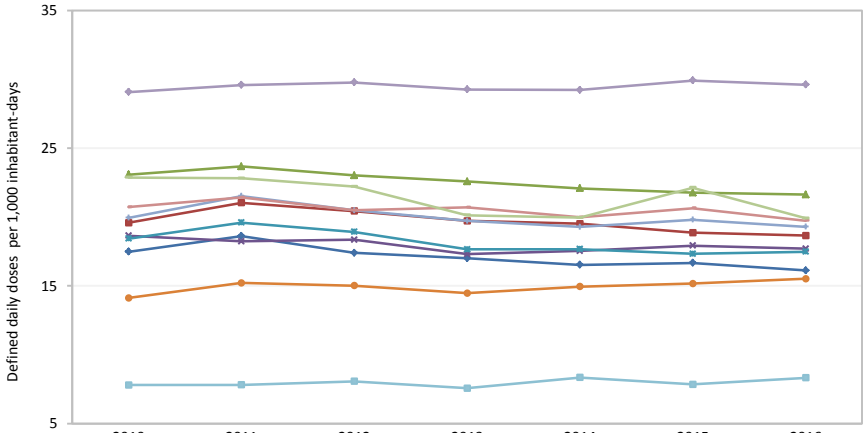
At the provincial level in 2016, prescription rates were variable with the highest prescription rates in Newfoundland and Labrador (954 prescriptions per 1,000 inhabitants). Prescription rates were lowest in British Columbia (545 prescriptions per 1,000 inhabitants) and among NIHB-covered individuals in the Territories (280 prescriptions per 1,000 inhabitants) (Figure 43). The relative ranking of antimicrobial use among the provinces has remained quite stable over time (Figure 44).

Figure 43: Canadian variation in prescription rates per 1,000 individuals among provinces and NIHB-covered individuals in the territories, 2016



Note: BC = British Columbia, AB = Alberta, SK = Saskatchewan, MB = Manitoba, ON = Ontario, QC = Québec, NB = New Brunswick, NS = Nova Scotia, PEI = Prince Edward Island, NL = Newfoundland and Labrador, TE = Territories (Yukon, Northwest Territories, and Nunavut)

Figure 44: Defined daily doses per 1,000 inhabitant-days in Canadian provinces, 2010-2016



	2010	2011	2012	2013	2014	2015	2016
BC	17.5	18.6	17.4	17.0	16.5	16.7	16.1
AB	19.6	21.0	20.4	19.7	19.5	18.9	18.6
SK	23.1	23.7	23.0	22.6	22.1	21.8	21.6
MB	18.6	18.2	18.4	17.3	17.5	17.9	17.7
ON	18.4	19.6	18.9	17.6	17.7	17.3	17.5
QC	14.1	15.2	15.0	14.5	14.9	15.2	15.5
NB	19.9	21.5	20.5	19.7	19.3	19.8	19.3
NS	20.7	21.4	20.5	20.7	20.0	20.6	19.7
PE	22.9	22.8	22.2	20.1	20.0	22.1	19.9
NL	29.1	29.6	29.8	29.3	29.2	29.9	29.6
TE	7.8	7.8	8.1	7.6	8.3	7.8	8.3

Note: BC = British Columbia, AB = Alberta, SK = Saskatchewan, MB = Manitoba, ON = Ontario, QC = Québec, NB = New Brunswick, NS = Nova Scotia, PEI = Prince Edward Island, NL = Newfoundland and Labrador, TE = Territories (Yukon, Northwest Territories, and Nunavut)

Table 7: Defined daily doses per 1,000 inhabitant-days for the top ten antimicrobials in Canadian Provinces, 2016

Antimicrobial	Rank*	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NF	TE
Amoxicillin	1	4.15	5.30	6.54	5.30	5.64	3.86	4.88	5.02	5.99	9.33	2.85
Amoxicillin and enzyme inhibitor	4	1.13	1.63	1.32	1.48	1.17	1.73	1.77	1.46	1.80	2.17	0.64
Azithromycin	7	0.55	0.85	1.18	1.17	1.06	0.89	0.96	0.58	0.82	1.79	0.29
Cephalexin	5	1.17	1.30	1.96	1.43	1.18	0.29	1.21	1.51	1.34	1.90	0.60
Ciprofloxacin	6	0.93	0.94	0.94	0.99	0.87	1.21	0.81	0.91	0.89	2.59	0.36
Clarithromycin	3	1.48	1.65	1.24	0.83	1.29	2.07	1.42	1.63	1.62	2.00	0.66
Doxycycline	2	2.53	2.26	4.18	2.20	1.39	1.14	2.46	2.99	2.65	2.48	1.21
Minocycline	10	0.64	1.00	0.24	0.57	0.38	0.83	0.58	0.87	0.39	0.72	0.04
Nitrofurantoin	8	0.91	0.73	1.16	0.72	0.98	0.40	0.92	1.13	0.87	1.10	- -
Sulfamethoxazole and trimethoprim	9	0.66	0.66	0.98	0.99	0.65	0.41	0.81	0.88	0.88	1.30	0.50
TOTAL		16.12	18.65	21.63	17.70	17.48	15.52	19.29	19.73	19.91	29.60	8.32

*Ranked from greatest to least DDDs at the national level in 2016

Note: BC = British Columbia, AB = Alberta, SK = Saskatchewan, MB = Manitoba, ON = Ontario, QC = Québec, NB = New Brunswick, NS = Nova Scotia, PEI = Prince Edward Island, NL = Newfoundland and Labrador, TE = Territories (Yukon, Northwest Territories, and Nunavut)

Prescribing Practices by Specialization

Information regarding the specialization of the professional who wrote the antimicrobial prescription was available from the community prescribing dataset from 2012 to 2016. A total of 32 different medical and non-medical specializations were identified, including a catch-all "all other specialty" group[ii]. To facilitate the review of the data, these specializations were further categorized into eight broader groupings[iii]: general and family practitioners; dermatologists; pathologists, radiologists and nuclear medicine; emergency medicine; pediatrics; medicine; surgery; and all other specialities.

Sixty-five percent of all prescriptions dispensed by community pharmacies were prescribed by general and family practitioners in 2016, followed by "all other specialities" (22.1%), and medicine (5%). The most commonly prescribed antimicrobials by the community prescribers group were amoxicillin, azithromycin, and cephalexin. Amoxicillin was among the top three drugs prescribed by all groups with the exception of medicine; the other two antimicrobials varied by specialty group (Table 8).

[ii] All other specialties includes: nurses, dentists, pharmacists.

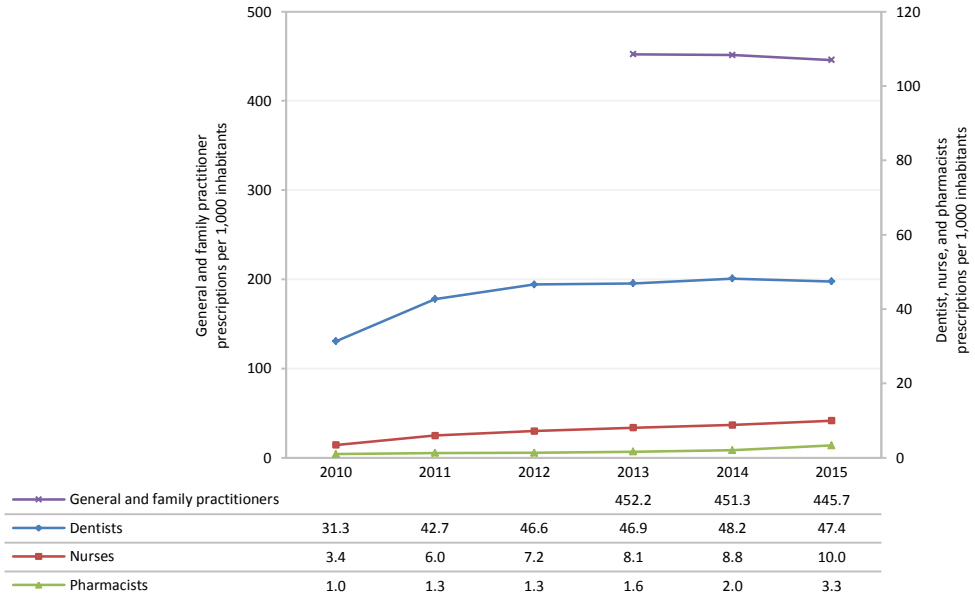
[iii] Family physicians and general practitioners; dermatologists; pathologists, radiologist and nuclear medicine; emergency medicine; pediatrics; medicine: allergists, immunologists, bacteriologists, cardiologists, endrocrinologists, gastroenterologists, geriatrics, hematologists, internists, nephrologists, neurologists, oncologists, otolaryngologists, psychiatrists and respirologists, rheumatologists; surgery: anaesthesiologists, general surgery, obstetrician & gynecologists, opthalmologists, orthopedic surgery, plastic surgeons, thoracic/cardiac surgery and urologist; and all other specialties.

Table 8: Prescriptions per 1,000 inhabitants for the top three antimicrobials prescribed by each specialty group

Specialty	Antimicrobial	2013	2014	2015	2016
All other specialties	Amoxicillin	55.16	56.17	56.93	58.57
	Clindamycin	12.61	12.40	12.10	11.64
	Penicillin V	11.01	9.78	9.75	9.31
General and family practitioners	Amoxicillin	91.52	96.15	91.00	92.08
	Azithromycin	43.79	44.44	46.24	48.19
	Cephalexin	34.38	34.88	35.05	35.74
Dermatologist	Doxycycline	2.22	2.51	2.84	2.73
	Minocycline	2.29	2.06	1.74	1.44
	Tetracycline	0.79	0.70	0.68	0.64
Pathologists, radiologists and nuclear medicine	Amoxicillin	0.38	0.41	0.42	0.44
	Ciprofloxacin	0.11	0.11	0.11	0.10
	Azithromycin	0.08	0.07	0.07	0.08
Emergency Medicine	Cephalexin	0.64	0.72	0.75	0.83
	Amoxicillin	0.52	0.59	0.55	0.58
	Ciprofloxacin	0.47	0.51	0.55	0.51
Medicine	Amoxicillin	4.76	4.67	4.48	4.81
	Sulfamethoxazole and trimethoprim	3.59	3.53	3.90	4.38
	Azithromycin	3.37	3.65	3.78	4.22
Paediatrician	Amoxicillin	5.95	6.40	6.02	6.15
	Azithromycin	1.09	0.98	0.97	1.10
	Cephalexin	1.04	1.06	0.90	0.92
Surgery	Ciprofloxacin	5.50	5.31	5.00	4.71
	Cephalexin	4.01	4.14	4.20	4.24
	Nitrofurantoin	2.81	2.86	2.75	2.55

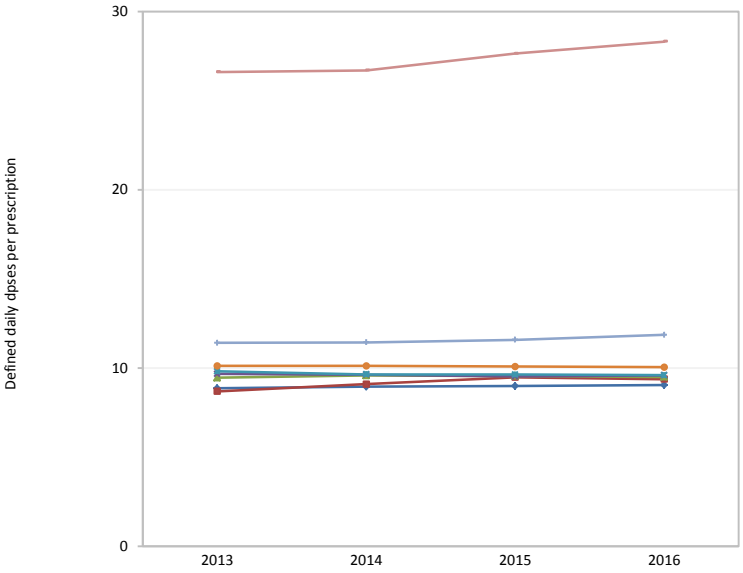
From 2013 to 2015, specific information about the prescribers in the "all other specialties" grouping were available. The most common prescribers identified in this grouping were dentists, with much smaller proportions provided by nurses, and pharmacists (Figure 45). The prescribing rate among dentists increased from 2010 to 2013, and remained relatively stable from 2013 to 2016. The reason for this increase is not known at this time. An increase in prescribing by nurses and pharmacists also occurred from 2010 to 2015, which may reflect growth in the nurse practitioner population[42] and increasing scope of practice among pharmacists[43].

Figure 45: Prescriptions dispensed in the community by general and family practitioners, dentists, nurses, and pharmacists, 2010-2015



When looking at the amount of antimicrobial dispensed per prescription, dermatologists had the highest levels in 2016, with approximately 28 DDDs per prescription (Figure 46). This is likely due to long-term prescriptions for antibiotics used to treat skin infections and conditions such as acne. The medicine and community practitioners group followed at 12 and 10 DDDs per prescription, respectively.

Figure 46: Defined daily doses per prescription for prescriptions dispensed by specialty groups, 2013-2016



	2013	2014	2015	2016
Emergency medicine	8.9	9.0	9.0	9.0
Paediatricians	8.7	9.1	9.5	9.4
All other specialties	9.5	9.6	9.6	9.5
Pathologists, radiologists and nuclear medicine	9.7	9.6	9.5	9.6
Surgery	9.8	9.6	9.6	9.6
Community practitioners	10.1	10.1	10.1	10.0
Medicine	11.4	11.4	11.6	11.9
Dermatologists	26.6	26.7	27.6	28.3

Antimicrobial use in Indigenous and non-Indigenous Populations

In Canada, province and territories are responsible for providing health care services, guided by the provisions of the *Canada Health Act.* Indigenous people in Canada may access insured services through provincial governments and territorial governments. However, there are a number of health-related services that are not insured by provincial and territorial plans, including prescription medications such as antimicrobials. Health Canada's Non-Insured Health Benefits (NIHB) program provides coverage for a limited range of services for Indigenous people when they are not insured elsewhere.

Methods

The community dispensing data (CSC dataset) used in this report includes prescriptions covered under the NIHB program if they were dispensed within the provinces. However, this dataset does not include

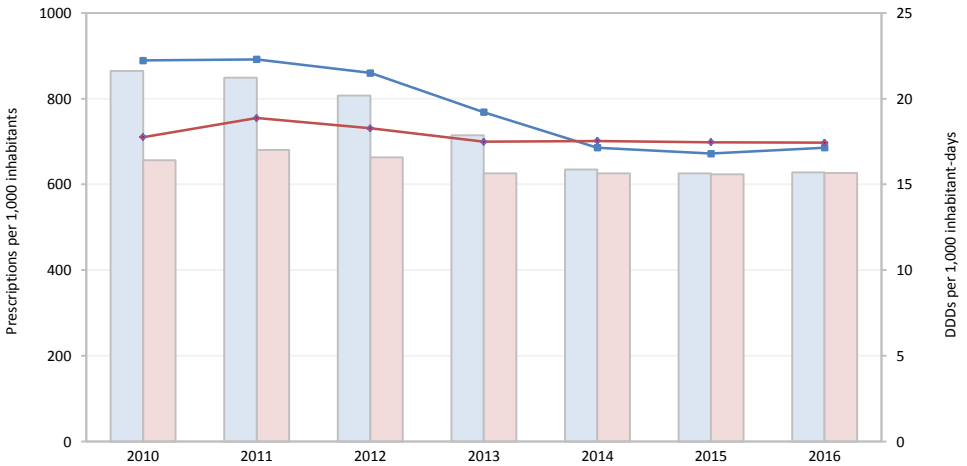
prescriptions dispensed in the territories. To better understand antimicrobial use within the Indigenous communities in Canada, Health Canada provides data on antimicrobial prescriptions covered by the NIHB program by province or territory of client residence. These data are integrated into the national and provincial level results in this report.

To avoid duplication of measures and allow for a comparison between NIHB-covered individuals and the general population, provincial NIHB claims were excluded from the overall dispensation data. It should be noted that while the NIHB data only cover Indigenous people, not all Indigenous people access these services and their use may be captured among the general community dispensing data. However, these data present the best opportunity to compare the antimicrobial use between Indigenous and non-Indigenous peoples in Canada.

Antimicrobial Use among Indigenous and Non-Indigenous populations

Overall, antimicrobial use in the Indigenous and non-Indigenous populations was very similar in 2016, with approximately 626 and 628 prescriptions dispensed per 1,000 inhabitants, respectfully. While use remained relatively stable in the non-Indigenous population in Canada from 2010 to 2016, use in the Indigenous population declined to approximately the same level as in the non-Indigenous population in 2016 (Figure 47).

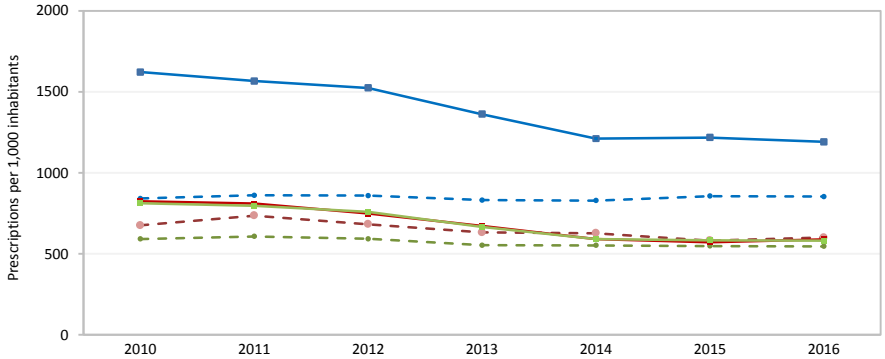
Figure 47: Defined daily doses per 1,000 inhabitant-days and prescriptions (Rx) per 1,000 inhabitants for Indigenous (NIHB) and non-Indigenous populations (non-NIHB), 2010-2016



	2010	2011	2012	2013	2014	2015	2016
NIHB Rx	864.6	848.9	806.8	714.6	635.0	626.0	628.3
non-NIHB Rx	656.3	680.6	663.4	626.0	625.8	623.7	626.7
NIHB DDD	22.2	22.3	21.5	19.2	17.1	16.8	17.1
non-NIHB DDD	17.8	18.9	18.3	17.5	17.5	17.5	17.4

The decline in use in the Indigenous population from 2010 to 2016 can be attributed to reductions in all age groups (Figure 48), although the most dramatic decline occurred in the 60+ age group. The 60+ age group displayed the highest prescription rates however, and had much higher prescription rates than did the non-Indigenous population. In contrast, prescription rates in the 0-14 and 15-59 age groups were very similar in 2016 in Indigenous and non-Indigenous populations.

Figure 48: Prescriptions per 1,000 inhabitants for Indigenous (NIHB) and non-Indigenous (non-NIHB) populations, by age group, 2010-2016



	2010	2011	2012	2013	2014	2015	2016
non-NIHB 0 - 14	675.5	735.6	682.2	632.1	627.4	581.6	600.3
non-NIHB 15 - 59	592.1	607.2	592.6	553.0	552.5	548.2	546.6
non-NIHB 60 +	841.7	860.8	858.7	831.1	828.8	856.2	853.7
NIHB 0 - 14	823.2	809.4	748.9	672.1	591.2	570.5	588.5
NIHB 15 - 59	811.8	796.5	759.3	666.0	591.9	583.4	580.7
NIHB 60 +	1621.5	1565.7	1523.6	1361.7	1211.4	1217.9	1191.3

Antimicrobial Recommendations by Diagnoses

Methods

The data presented here arise from the Canadian Disease and Therapeutic index (CDTI) dataset. The CDTI provides information about the patterns and treatments of disease encountered by office-based physicians (specialists and general practitioners, including those with offices in hospitals).

These data are actively collected from a group of sample physicians that represent all major specialties across Canada. Data from 652 physicians were available in 2016 and projection methods were used to extrapolate data to the universe of approximately 55,092 physicians in Canada. At visits to these physicians during data collection periods, the physicians actively record all diagnoses made, as well as all drug products that are recommended (whether or not a prescription for that product is provided).

It is important to note that the information contained in this analysis is for antimicrobials for which a physician has provided a recommendation or prescription, and does not represent actual prescriptions dispensed by pharmacists or consumed by the patient. Furthermore, diagnosis neither visits with antimicrobial recommendations nor the number of diagnoses can be translated into the total number of patients, as some patients may have visited multiple times within the data collection periods, and patients may have received more than one diagnosis at a visit.

The information included in this analysis provides a view of antimicrobial recommendation practices which may require further study for decision making.

Antimicrobial recommendations

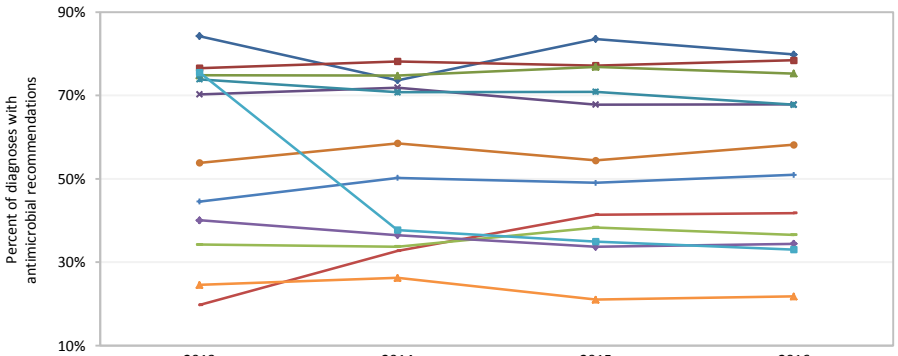
In 2016, more than 335 million diagnoses were made by practitioners outside of hospitals in Canada, resulting in slightly less than 25 million antimicrobial recommendations. It should be noted that antimicrobial recommendations are not necessarily linked to a prescription for a number of reasons: the physician may mention an antimicrobial but not provide a prescription, a patient may refuse an antimicrobial prescription, or a patient may choose not to fill a prescription received.

An antimicrobial was mentioned in 7.4% of visits for all diagnoses combined. However, the proportion of visits with antimicrobial recommendations varied by visit type (Table 9) and by diagnosis (Figure 49).

Table 9: Five diagnostic classes for which antimicrobials were most likely to be recommended, and proportion of visits with an antimicrobial recommendation, 2013-2016

Diagnostic class	Proportion of visits with an antimicrobial recommendation			
	2013	2014	2015	2016
Diseases of the respiratory system	32.01	31.56	30.06	30.58
Diseases of the genito-urinary system	22.37	21.82	22.68	22.42
Infective parasitic diseases	13.74	14.29	18.06	15.35
Diseases of the skin and subcutaneous tissue	16.02	15.38	15.42	13.98
Central nervous system diagnoses	14.77	13.61	12.77	14.45

Figure 49: Proportion of specific diagnoses given an antimicrobial recommendation, 2013-2016[iv]



	2013	2014	2015	2016
Pneumonia	84.2%	73.6%	83.5%	79.8%
Cystitis	76.5%	78.2%	77.2%	78.4%
Bronchitis	74.8%	74.8%	76.9%	75.2%
Sinusitis	70.3%	71.9%	67.8%	67.8%
Cellulitis	73.9%	70.7%	70.9%	67.7%
Otitis media	53.8%	58.5%	54.4%	58.2%
Tonsillitis	44.5%	50.2%	49.0%	50.9%
Syphilis & gonorrhea	19.8%	32.7%	41.4%	41.8%
Parasitic diseases	34.2%	33.7%	38.3%	36.5%
Pharyngitis	40.1%	36.5%	33.7%	34.4%
Carbuncle/furuncle	75.5%	37.7%	34.9%	33.0%
U.R.T.I.	24.5%	26.2%	21.0%	21.8%

[iv] Note: Syphilis & gonorrhea diagnosis also includes "other unspecified venereal disease". In Canada, it is expected that 100% of syphilis & gonorrhea diagnoses will be treated with an antimicrobial

Hospital Purchasing

Methods

The data in this section arise from The Canadian Drugstore and Hospital (CDH) database purchased from IQVA. The CDH provides a measure of the dollar value and unit volume of pharmaceutical products purchased by nearly all Canadian hospitals. Hospitals in this context include general hospitals, long term care facilities, psychiatric, pediatric/maternity, government, cancer, and specialized hospitals. Federal prisons are excluded. Data about purchases from pharmaceutical manufacturer warehouses/wholesalers are collected from over 650 hospitals and are extrapolated to represent the purchases made by over 740 hospitals across Canada. The provinces of Prince Edward Island (PEI) and Newfoundland and Labrador were grouped due to the small volume of purchases within each province. British Columbia, Nunavut, Yukon, and North West Territories have been grouped together as the supply of pharmaceutical purchases to this province and the territories are captured as one and cannot be further broken down by the respective province or territory. CDH provides the estimated value of antimicrobials purchased by various hospitals sectors and does not necessarily represent administered antimicrobials. In addition, returns are included, and the database is always adjusting for corrections; therefore, the history of data can change.

Antimicrobial purchasing in Canadian hospitals

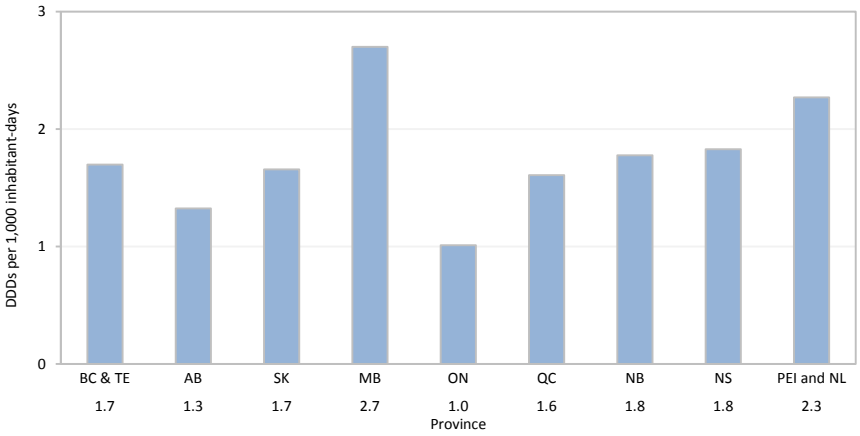
In 2016, 40,752 kilograms of antimicrobials were purchased by various hospital sectors across Canada at a cost of approximately $92 million. The amount purchased by various hospital sectors declined from $119 million in 2010 to $92 million in 2016, a decrease of nearly 30%. When adjusted for the number of inhabitant-days that occurred in 2016, this amounts to approximately 1.4 DDDs of antimicrobial purchased per 1,000 inhabitant-days, a rate that remained fairly stable over the 2010 to 2016 period of surveillance.

The defined daily doses (DDD) per 1,000 inhabitant-days for the antimicrobials purchased by hospitals varied throughout Canada. Manitoba, and PEI and Newfoundland and Labrador combined, were the provinces that had the highest antimicrobial purchasing rates in 2016 (2.7 and 2.3 DDD per 1,000 inhabitant-days, respectively); whereas Ontario and Alberta had the lowest rates (1.0 and 1.3 DDD per 1,000 inhabitant-days, respectively) (Figure 50).

When compared to previous years, cephalosporins remained the most purchased antimicrobial drug class in Canada in 2016, with a rate of 0.38 DDD per 1,000 inhabitant-days, followed by fluoroquinolones. These two drug classes consistently remained the two most prominent drug class purchases over the surveillance period. Although purchasing rates for cephalosporins remained relatively consistent from 2010 to 2016, there was a 43% decrease in the purchasing rate for fluoroquinolones (0.25 to 0.17 DDD per 1,000 inhabitant-days (Table 10). Two drug classes that showed increases in purchasing rates during the surveillance period were combinations of penicillins, which demonstrated a 41% increase from 2010 to 2016 (0.09 to 0.15 DDD per 1,000 inhabitant-days), and sensitive penicillins, which demonstrated a 34% increase (0.05 to 0.07 DDD per 1,000 inhabitant-days).

Overall DDD per 1,000 inhabitant-days for antimicrobials purchased throughout Canada remained relatively stable from 2010 to 2016 (Table 10).

Figure 50: Defined daily doses (DDD) per 1,000 inhabitant-days for antimicrobials purchased by hospitals in Canada, by province and territories, 2016



Note: BC = British Columbia, AB = Alberta, SK = Saskatchewan, MB = Manitoba, ON = Ontario, QC = Québec, NB = New Brunswick, NS = Nova Scotia, PEI = Prince Edward Island, NL = Newfoundland and Labrador, TE = Territories (Yukon, Northwest Territories, and Nunavut)

Table 10: Defined daily doses per 1,000 inhabitant-days by drug class, classified by importance level for human medicine, purchased by hospitals in Canada, by province and territories, 2010-2016

Drug Class	2010	2011	2012	2013	2014	2015	2016
Critically Important							
J01GB - Aminoglycosides	0.038	0.035	0.035	0.031	0.028	0.023	0.020
J01DH - Carbapenems	0.035	0.040	0.033	0.026	0.033	0.047	0.049
J01CA - Penicillins with extended spectrum	0.129	0.132	0.132	0.135	0.135	0.126	0.120
J01XA - Glycopeptide antibacterials	0.015	0.018	0.016	0.015	0.024	0.013	0.026
J01FA - Macrolides	0.132	0.147	0.135	0.125	0.118	0.139	0.140
J01AA - Tetracyclines	0.085	0.103	0.085	0.092	0.100	0.107	0.100
J01MA - Fluroquinolones	0.249	0.250	0.250	0.259	0.234	0.255	0.174
J01XB - Polymyxins	0.001	0.001	0.001	0.002	0.001	0.002	0.002
J01DB - J01DE - Cephalosporins	0.391	0.412	0.398	0.363	0.348	0.368	0.379
J01XX - Other antibacterials*	0.004	0.005	0.007	0.009	0.010	0.010	0.011
Highly Important							
J01BA - Amphenicols	0.000	0.000	0.000	0.000	0.000	0.000	0.000
J01FF - Lincosamides	0.043	0.044	0.043	0.041	0.037	0.035	0.034
J01CF - β-lactamase-resistant penicillins	0.050	0.053	0.052	0.050	0.052	0.049	0.047
J01XC - Steroid antibacterials	0	0	0	0	<0.001	<0.001	<0.001
J01GA -Streptomycins	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01EE - Trimethoprim with sulphonamides	0.063	0.063	0.062	0.061	0.057	0.058	0.058
J01CE - β-lactamase sensitive penicillins	0.049	0.060	0.109	0.075	0.076	0.075	0.074
Important							
J01CR - Combinations of penicillins	0.089	0.108	0.116	0.118	0.135	0.139	0.152
J01DI -Other cephalosporins and penems	<0.001	0	0	0	0	0	<0.001
J01EA - Trimethoprim	0.001	0.002	0.001	0.001	0.001	0.001	0.001
J01XD - Imidazole derivatives	0.005	0.007	0.006	0.006	0.003	0.003	0.002
J01XE - Nitrofurantoin	0.031	0.034	0.034	0.032	0.032	0.030	0.031
Total	1.41	1.52	1.52	1.44	1.42	1.49	1.42

*Includes, but not limited to, linezolid, daptomycin, fosfomycin

For the overall 2010 to 2016 surveillance period, ciprofloxacin was the most commonly purchased antimicrobial. However, it went from the number one to the fifth most purchased antimicrobial in 2016, preceded by azithromycin, cefazolin, ceftriaxone, and amoxicillin (Table 11). The ciprofloxacin purchasing rate decreased by 30% from 2010 to 2016 (0.13 to 0.10 DDD per 1,000 inhabitant-days).

Table 11: The average defined daily doses per 1,000 inhabitant-days for the top ten antimicrobials purchased by hospitals in Canada, 2010-2016

Antimicrobial	Rank*	2010	2011	2012	2013	2014	2015	2016
Amoxicillin	3	0.09	0.13	0.09	0.10	0.10	0.10	0.10
Amoxicillin and enzyme inhibitor	9	0.04	0.05	0.05	0.05	0.07	0.10	0.08
Azithromycin	4	0.08	0.09	0.09	0.09	0.08	0.11	0.11
Cefazolin	2	0.12	0.12	0.12	0.10	0.09	0.11	0.11
Cefoxitin	7	0.11	0.10	0.08	0.06	0.07	0.07	0.06
Ceftriaxone	5	0.06	0.08	0.08	0.09	0.10	0.10	0.11
Ciprofloxacin	1	0.13	0.13	0.14	0.16	0.14	0.16	0.10
Doxycycline	6	0.08	0.09	0.08	0.08	0.09	0.10	0.09
Penicillin G	8	0.04	0.05	0.10	0.07	0.07	0.07	0.07
Sulfamethoxazole and trimethoprim	10	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Total		0.81	0.87	0.90	0.87	0.87	0.94	0.89

*Ranked from greatest to least DDDs at the national level for combined years from 2010 to 2016

Large differences in the purchasing of specific antimicrobials by hospitals were observed throughout the country. Ceftriaxone was the only antimicrobial consistently identified among the top five antimicrobials purchased by all provincial and territorial hospitals. Manitoba's largest number of DDDs purchased per 1,000 inhabitant-days was driven by the purchases of amoxicillin (0.42 DDD per 1,000 inhabitant-days), cefoxitin (0.34 DDD per 1,000 inhabitant-days), and sulfamethoxazole and trimethoprim (0.28 DDD per 1,000 inhabitant-days). The top antimicrobial purchased in each province varied with azithromycin identified as the top antimicrobial in Alberta, Saskatchewan, and Ontario, doxycycline in British Columbia and the Territories, amoxicillin in Prince Edward Island and Newfoundland and Labrador, cefazolin in Nova Scotia, and penicillin G in New Brunswick and Québec (Table 12). The reasons for the differences in antimicrobial use between province and territories are not well understood, but are likely (at least in part) due to different hospital sectors' (i.e., long term care vs. acute-care) drug formularies, case-mixes, and different treatment protocols.

Table 12: Defined Daily doses per 1,000 inhabitant days for the top ten antimicrobials purchased by hospitals in Canada, 2016

Antimicrobial	Rank	AB	BC & TE	MB	NB	NS	ON	PEI & NFLD	QC	SK
Amoxicillin	4	0.07	0.12	0.42	0.07	0.07	0.08	0.24	0.07	0.12
Amoxicillin and enzyme inhibitor	7	0.08	0.07	0.14	0.11	0.08	0.05	0.11	0.12	0.07
Azithromycin	1	0.17	0.15	0.17	0.09	0.11	0.10	0.12	0.06	0.18
Cefazolin	2	0.12	0.07	0.04	0.20	0.20	0.10	0.16	0.13	0.09
Cefoxitin	9	0.04	0.11	0.34	0.05	0.06	0.03	0.02	0.06	0.09
Ceftriaxone	3	0.12	0.17	0.20	0.13	0.12	0.09	0.19	0.06	0.20
Ciprofloxacin	5	0.09	0.07	0.11	0.12	0.12	0.07	0.20	0.13	0.16
Doxcxyline	6	0.10	0.26	0.10	0.09	0.08	0.06	0.10	0.05	0.08
Penicillin G	8	0.00	0.00	0.00	0.25	0.23	0.01	0.15	0.23	0.00
Sulfamethoxazole and Trimethoprim	10	0.05	0.06	0.28	0.04	0.05	0.04	0.09	0.05	0.08
Total		0.85	1.09	1.80	1.15	1.11	0.63	1.39	0.96	1.07

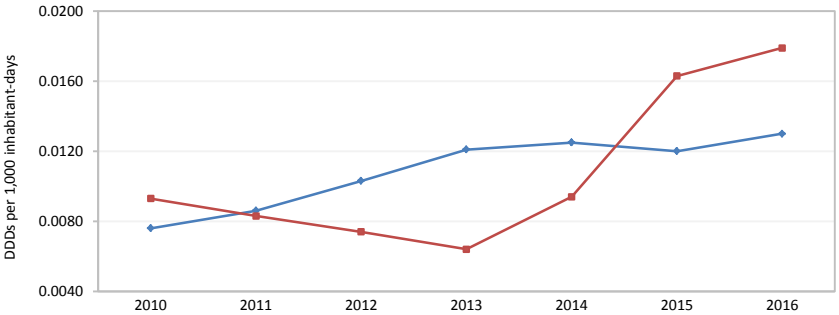
*Ranked from greatest to least DDDs at the national level for 2016

Text Box 11: Increasing use of antimicrobials of high importance

The World Health Organization has published a list of "reserve group" antibiotic products, which includes products that are intended to be used only in instances where all alternatives have failed.
The list of antimicrobials of last resort is defined as follows: atrenozam; daptomycin; fosfomycin by intravenous route of administration; 4th generation cephalosporins (cefepime, cefpirome, cefozopran); 5th generation cephalosporins (ceftaroline); and polymyxins (colistin, polymixin B, tigecycline).

Despite direction to prescribe these products only when alternatives have failed, the use of these products has been increasing in the community setting in Canada, where last resort treatment is expected to be uncommon (Figure A). In the hospital setting, the use of these products has remained relatively stable from 2013 to 2016, following a period of increase from 2010 to 2013.

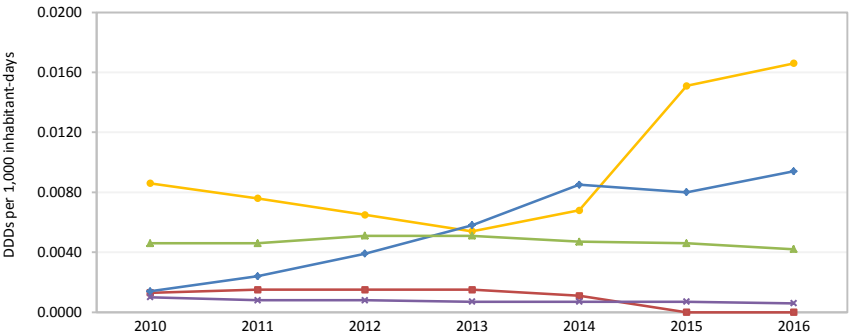
Figure A: Defined daily doses per 1,000 inhabitant-days purchased by hospitals and dispensed by community pharmacies for antimicrobials of high importance, 2010-2016



	2010	2011	2012	2013	2014	2015	2016
Hospital purchasing	0.0076	0.0086	0.0103	0.0121	0.0125	0.0120	0.0130
Community dispensing	0.0093	0.0083	0.0074	0.0064	0.0094	0.0163	0.0179

The increases in use of these products is driven mainly by an increase in the use of colistin (Figure B). Increases in the use of daptomycin have also been seen from 2010 to 2016. In contrast to colistin use, daptomycin use is primarily in the hospital setting in Canada, with >99% of DDDs in Canada purchased by hospitals year over year from 2010 to 2016.

Figure B: Defined daily doses per 1,000 inhabitant-days purchased by hospitals and dispensed by community pharmacies for antimicrobials of high importance, by antimicrobial, 2010-2016



	2010	2011	2012	2013	2014	2015	2016
Cefepime	0.0013	0.0015	0.0015	0.0015	0.0011	0.0000	0.0000
Colistin	0.0086	0.0076	0.0065	0.0054	0.0068	0.0151	0.0166
Daptomycin	0.0014	0.0024	0.0039	0.0058	0.0085	0.0080	0.0094
Linezolid	0.0046	0.0046	0.0051	0.0051	0.0047	0.0046	0.0042
Tigecycline	0.0010	0.0008	0.0008	0.0007	0.0007	0.0007	0.0006

No use of aztreozam, cefpirome, cefozopran, polymixin B, or intravenous fosfomycin has been identified in the Canadian antimicrobial use datasets from 2010 to 2016. This may indicate zero use of these products in Canada, or may indicate very low levels of use (so low that they may allow for the identification of prescribers and/or patients after data extrapolation).

Text Box 12: Quantitative Antimicrobial Use Surveillance amongst hospitals participating in the Canadian Nosocomial Infection Surveillance Program (CNISP): Pilot Study Results, 2009 to 2013

Background: Antimicrobial resistance (AMR) is a serious and growing issue with global ramifications. Antimicrobial utilization (AMU) is of particular importance in understanding the emergence of AMR. The aim of this pilot study was to assess the feasibility and identify the gaps/limitations of surveying AMU among inpatients in acute tertiary care hospitals across Canada.

Objective: To identify trends and patterns of AMU in acute-care hospitals in Canada.

Methods: A total of 28 CNISP hospitals (21 adult, four mixed, and three pediatric) across ten provinces participated in a five-fiscal year pilot surveillance study. Complete adult AMU data was obtained on 65 antimicrobials from 23 CNISP hospital pharmacies. A descriptive epidemiologic analysis was conducted and nationally stratified by bed size, categorized as follows: ≤ 200, 201-500, or >500 beds.

Results: Overall AMU in sites with ≤ 200 beds decreased from 667 to 592 DDD/1,000 patient-days between 2009-2013. In sites with 201-500 and >500 beds, increases in AMU of 585 to 604 and 597 to 599 DDD/1,000 patient-days, respectively, were demonstrated between 2009-2013. There were no significant differences in the mean AMU during the 5-fiscal year period amongst the stratified bed sizes (p=0.99) (Figure A).
The top antimicrobials used are listed in Figure B. CNISP sites with ≤ 200 beds, on average, most utilized ciprofloxacin, meropenem, piperacillin tazobactam and vancomycin compared to the other bed size groups. Whereas, on average, hospitals with 201-500 beds utilized ampicillin the most and those hospitals with >500 beds had the highest utilization of cefazolin and metronidazole (Figure C).

Conclusions: These national findings illustrate the differences in AMU by bed size and various shifts in trends that have occurred over the five year study period. These results emphasize the need for active ongoing surveillance of AMU within hospitals to monitor trends and lay the groundwork for further improvements in the AMU surveillance protocol and to establish specific Canadian benchmarks for AMU.

Figure A: DDD per 1,000 patient-days for the total antimicrobial usage in CNISP hospitals, stratified by bed size, 2009-2013 (fiscal years)

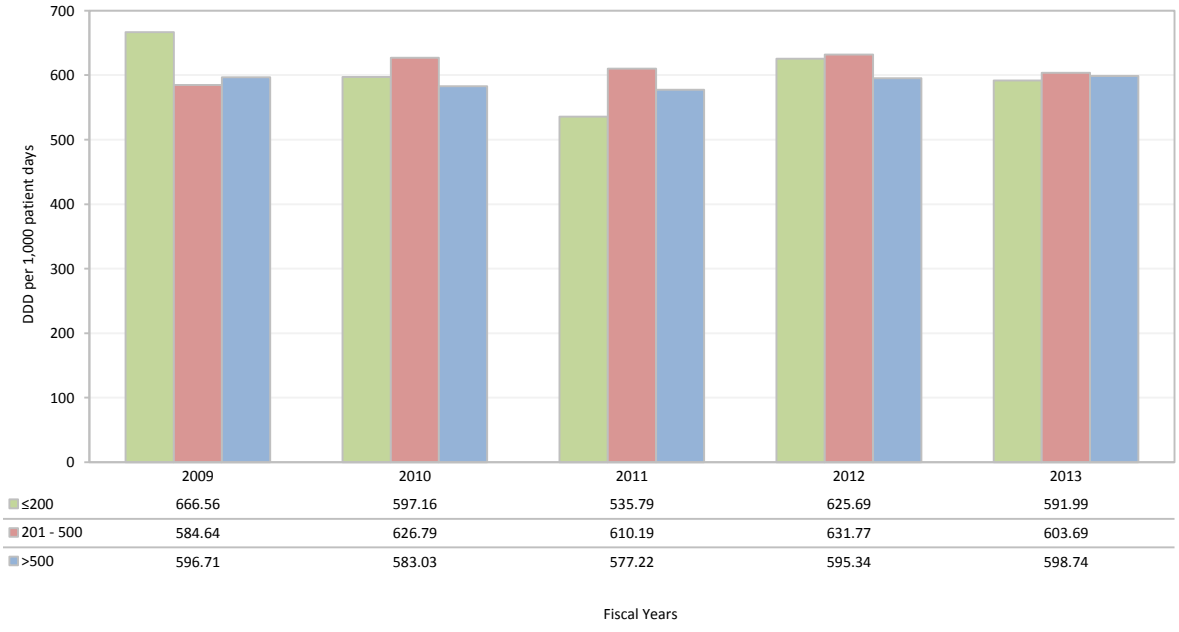


Figure B: DDD per 1,000 patient-days for the (A) five out of the top ten antimicrobials and (B) the remaining five of the top ten antimicrobials used in CNISP hospitals stratified by bed size, 2009-2013 (fiscal years)

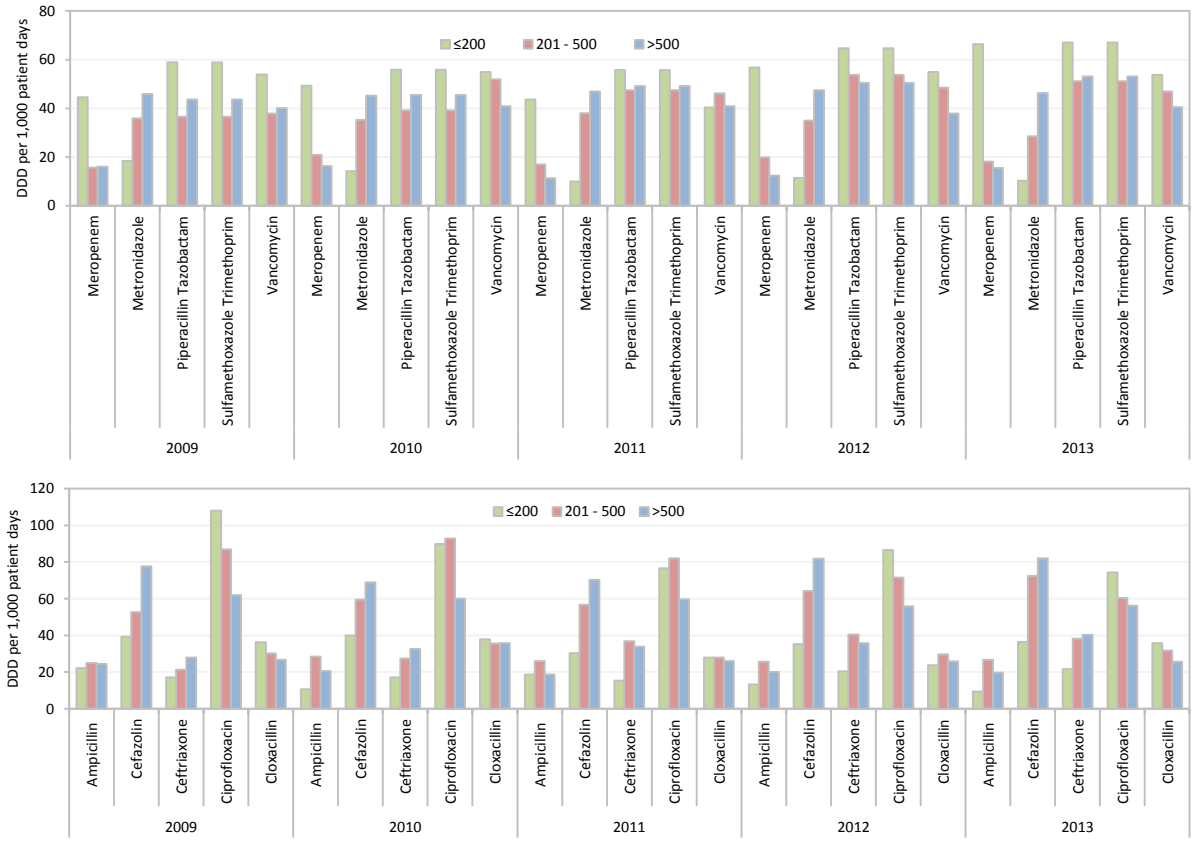
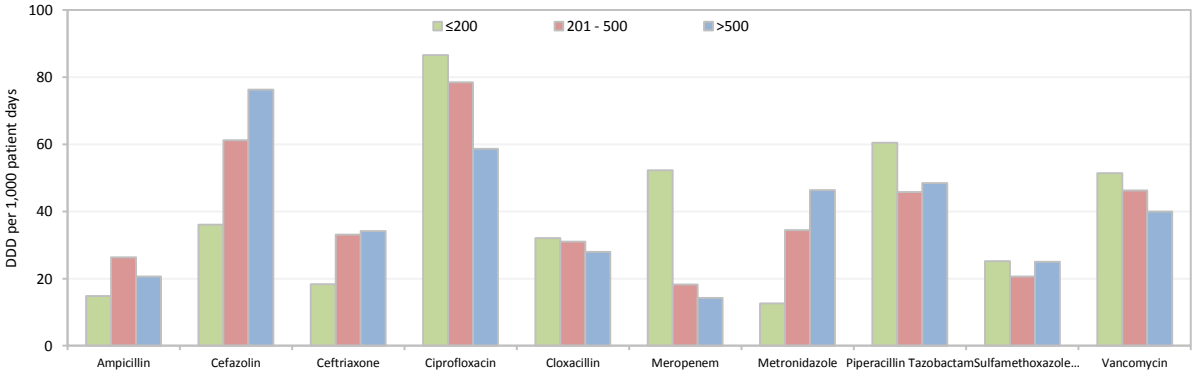


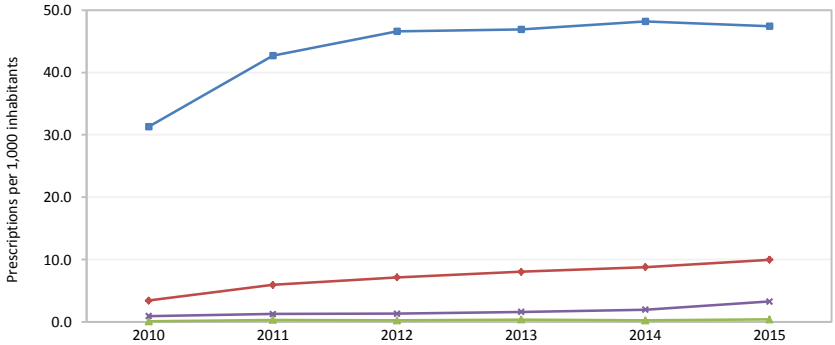
Figure C The average DDD per 1,000 patient-days for the top ten antimicrobials used in the CNISP hospitals stratified by bed size, 2009-2013 (fiscal years)



Text Box 13: Increases in prescribing by non-physician prescribers

In 2016, specific information regarding the specialty of some prescribers among the "all other specialties" group was available in the community prescription database. These specialties included dentists, nurses, optometrists, and pharmacists. Among these specialties, the majority of antimicrobials were prescribed by dentists (Figure A). Since 2010, increases in prescribing have been seen in all four of the non-traditional prescriber groups. Prescribing by nurses, optometrists, and pharmacists remained low in 2015, together accounting for approximately 2% of prescribing in 2015. In contrast, prescribing by dentists accounted for nearly 8% of prescriptions in 2015.

Figure A: Prescriptions dispensed per 1,000 inhabitants prescribed by dentists, nurses, optometrists, and pharmacists in the community setting 2010-2015



	2010	2011	2012	2013	2014	2015
Dentists	31.3	42.7	46.6	46.9	48.2	47.4
Nurses	3.4	6.0	7.2	8.1	8.8	10.0
Optometrists	0.1	0.3	0.3	0.4	0.3	0.4
Pharmacists	1.0	1.3	1.3	1.6	2.0	3.3

Among dentists, the most common antimicrobials prescribed varied from the most common antimicrobials prescribed among all practitioners (Table A). While amoxicillin and amoxicillin with enzyme inhibitor were among the highest volume products dispensed through dentist prescriptions (similar to all prescribers), penicillin V, metronidazole, erythromycin, and tetracycline were not as commonly used among the overall prescriber data.

Table A: Defined daily doses per 1,000,000 inhabitant-days[v] top five antimicrobials prescribed by dentists, nurses, optometrists, and pharmacists dispensed by community pharmacies, 2010-2015

Specialty	Antimicrobial	Rank	2010	2011	2012	2013	2014	2015
Dentists	Amoxicillin	1	505.41	807.39	870.99	907.24	959.79	957.13
	Amoxicillin and enzyme inhibitor	4	11.03	18.09	22.36	26.03	30.64	34.76
	Clindamycin	2	86.79	109.08	114.40	115.13	119.28	114.72
	Doxycycline	5	14.74	18.57	19.60	19.15	18.58	18.03
	Penicillin V	3	94.19	88.74	101.15	93.37	83.08	78.26
	TOTAL		766.48	1108.14	1196.42	1221.06	1269.95	1256.19
Nurses	Amoxicillin	1	51.90	95.28	104.43	122.95	134.33	146.21
	Amoxicillin and enzyme inhibitor	5	2.96	6.84	9.13	11.88	14.46	17.70
	Cephalexin	4	5.73	11.41	14.50	17.04	17.85	19.35
	Clarithromycin	3	10.72	20.74	24.80	22.91	21.28	21.35
	Doxycycline	2	8.42	13.54	14.67	16.53	18.98	22.54
	TOTAL		114.42	209.68	243.01	273.16	294.97	330.85
Optometrists	Amoxicillin	2	1.42	5.54	3.08	6.01	2.63	4.86
	Amoxicillin and enzyme inhibitor	3	0.07	0.23	0.33	0.39	0.49	1.05
	Cephalexin	4	0.20	0.38	0.54	0.53	0.46	0.64
	Clindamycin	5	0.21	0.83	0.26	0.47	0.23	0.43
	Doxycycline	1	0.15	0.90	2.14	2.99	3.61	5.08
	TOTAL		2.73	9.80	8.59	13.23	8.89	13.88
Pharmacists	Amoxicillin	1	4.79	9.80	10.97	17.92	20.04	30.77
	Azithromycin	4	0.86	1.97	2.32	2.19	3.52	6.36
	Ciprofloxacin	2	0.94	1.67	1.94	2.10	2.52	8.12
	Clarithromycin	5	1.80	3.33	3.21	4.45	8.15	5.58
	Doxycycline	3	1.20	2.48	2.98	4.30	6.24	7.25
	TOTAL		28.48	37.53	41.42	52.68	63.93	85.83

[v] Note increase in denominator from 1,000 to 1,000,000 inhabitant-days.

Antimicrobial use in animals

The Canadian Animal Health Institute (CAHI) voluntarily provides data regarding antimicrobials distributed for sale for use in animals. CAHI has been providing these data on an annual basis since 2006. At the time of writing, some of the CAHI member companies re-stated their 2014 and 2015 data. Hence, the data included in this report differ slightly from the CAHI data presented previously. PHAC also collects information about antimicrobial use in animals through surveillance of volunteer sentinel farms for grower-finisher pigs, broiler chicken, and turkeys.

Recent changes to regulatory oversight of antimicrobials in animals restrict who can import medically-important antimicrobials (MIAs). The new regulations will prevent importation of MIA for own use in food animals and will require an establishment license for individuals seeking to import active pharmaceutical ingredients for MIA drugs. Reporting of sales volumes by manufacturers and importers of animal antimicrobial drugs will become mandatory and will be tracked annually[44].

Antimicrobial Use in Production and Companion Animals

In 2016, approximately 1.0 million kilograms of MIAs were distributed for sale for use in animals by CAHI member companies. This volume was approximately 14% lower than 2007 and 17% lower than 2015. There were 0.6 million kg of ionophores and chemical coccidiostats distributed for use in animals; these antimicrobials are not considered medically important and are not included in further analyses or international comparisons.

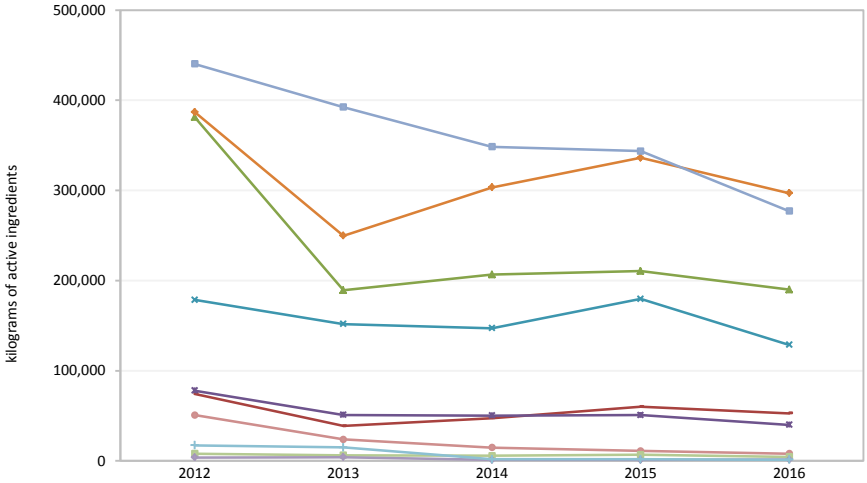
In 2016, 99% of the antimicrobials distributed were intended for use in food-producing animals (including horses) and 1% was intended for use in companion animals, based on kilograms of active ingredients.

The overall quantity of fluoroquinolones distributed for use in animals decreased by 56% between 2015 and 2016. Fluoroquinolones are classified as “of very high importance to human medicine”[16]. Fluoroquinolones are licensed for use in certain animal species in Canada and have warnings on their labels recommending against extra-label use in other animal species due to AMR concerns as well as guidelines for use only after failure of an initial treatment.

Between 2012 and 2016, there were provincial differences in the quantities of antimicrobials distributed for sale by CAHI member companies (based on kilograms of active ingredients), and year-to-year differences within provinces in the quantities distributed. The provinces with the greatest declines since 2015 (as relative percentages of their 2015 kg total) were New Brunswick, Manitoba, Nova Scotia, Newfoundland and Labrador, Saskatchewan, and Québec (approximate decrease of >15% of total kg each). The only province with an increase in total kg active ingredient distributed for sale was Prince Edward Island (approximately 20% increase in kg) (Figure 51). These provincial differences may be related to different numbers and types of animals in each province, differences in disease pressure, differences in antimicrobial use, or other management practices. The quantities reported per province

reflect the quantities distributed to veterinary clinics, feed mills, and over-the-counter outlets by CAHI member companies. There may be subsequent re-distribution of antimicrobials across provincial borders after this point.

Figure 51. Quantity of medically important antimicrobials (kilograms) distributed for sale for use in animals, by province, 2012-2016

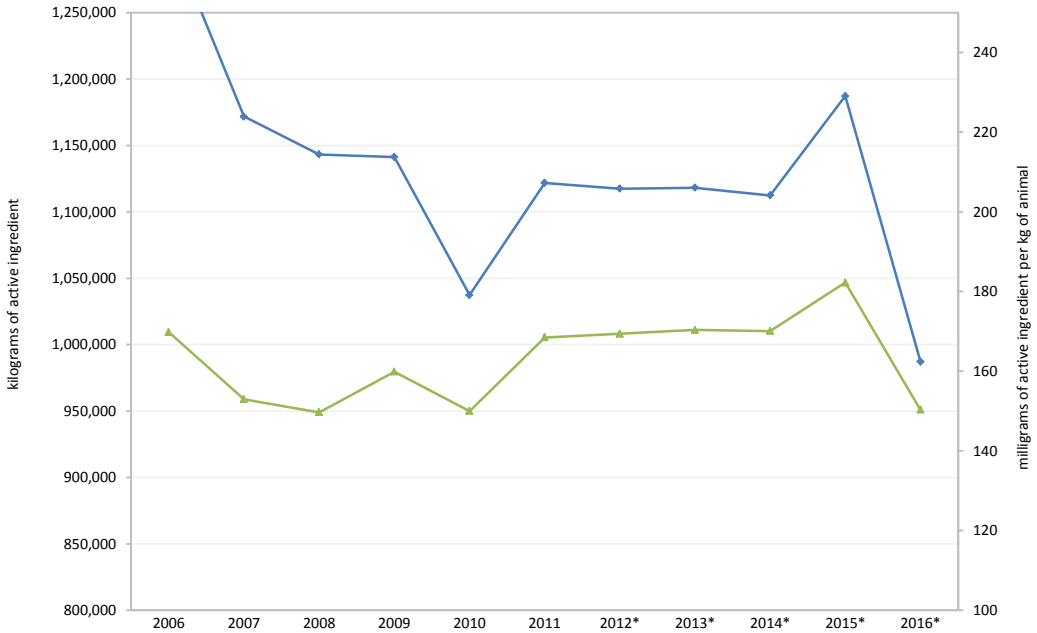


	2012	2013	2014	2015	2016
BC	74,376	38,680	47,351	60,067	52,738
AB	381,193	189,245	206,573	210,475	189,870
SK	77,971	50,961	50,333	50,708	39,976
MB	178,577	151,675	147,088	179,660	128,715
ON	386,917	249,621	303,240	336,049	296,916
QC	440,364	392,312	348,387	343,544	276,971
NS	50,797	23,850	14,696	11,092	8,066
NB	7,959	6,172	5,782	6,780	4,463
PE	3,781	4,164	1,134	1,147	1,378
NL	17,322	15,023	1,883	1,740	1,357

Notes: Data Source: Canadian Animal Health Institute. This figure does not account for provincial differences in numbers or types of animals. There may be subsequent distribution of antimicrobials across provincial borders after being distributed to the veterinary clinics. Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding.

The overall quantity of antimicrobials distributed is more meaningful when a denominator is applied to indicate how many animals these antimicrobials could potentially be given to. Additionally, animal species on average weigh very different amounts (e.g., a chicken is much lighter in weight than a cow). Hence the denominator needs to account for both the number of animals and their weights. This combination is referred to as the animal biomass, otherwise known as the 'population correction unit' or 'PCU'. This is a common metric for reporting quantities of antimicrobials intended for use in animals; particularly for international comparisons. Antimicrobial distribution data adjusted by this denominator means that we are reporting the milligrams of antimicrobials distributed per kilogram of animal in Canada (i.e., mg antimicrobial/kg animal). With this in mind, for production animals, the overall quantity of medically-important antimicrobials per kilogram of animals in Canada decreased by 2% since 2007 and decreased by 17% since 2015 (using European animal weight standards) (Figure 52). Over the past five years there has been an 11% decline.

Figure 52: Medically-important antimicrobials distributed for use in animals over time; measured as kilograms of active ingredient and milligrams of active ingredient per kilogram of animal, 2007-2016



	2006	2007	2008	2009	2010	2011	2012*	2013*	2014*	2015*	2016*
Total (kg)	1,310,373	1,171,796	1,143,187	1,141,213	1,037,313	1,121,715	1,117,457	1,118,097	1,112,340	1,187,136	987,157
Total (mg/PCU—European weights)	170	153	150	160	150	168	169	170	170	182	150

*Notes: Indicates data excluding antimicrobials sold for use in companion animals.
Data Sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-Food Canada, Equine Canada, European Surveillance of Veterinary Antimicrobial Consumption.
The population data used for live horses was from 2010 and for fish was from 2015; more recent population data for these animal species were unavailable at the time of writing. Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding.

Route of administration

CAHI data show that in 2016, antimicrobials were predominantly distributed for use in animals in feed (76%). Other less frequent routes of administration included water, injection, oral/topical, and intramammary (12%, 9%, 3%, <1% respectively). Similar to the CAHI data, findings from farm surveillance (i.e., grower-finisher pigs, broiler chickens and turkeys) indicate that the majority of antimicrobials were administered through feed.

Indication for Antimicrobial Use in Animals

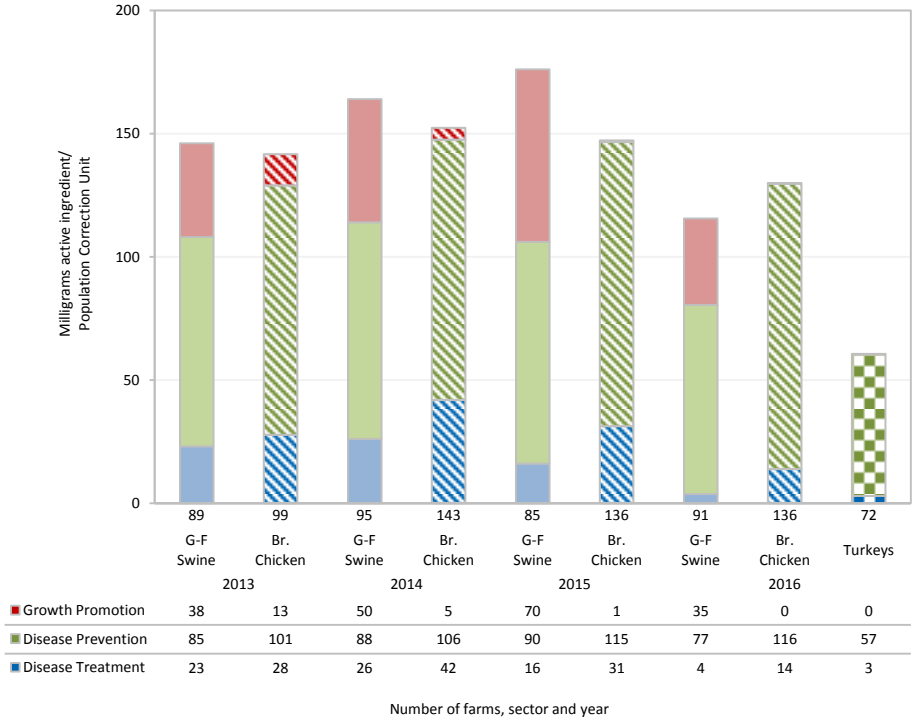
In Canada, antimicrobials are used in animals to treat disease, prevent disease, or to promote growth (i.e., production claims), though there is pending action to remove the growth promotion claims of medically important antimicrobials[47]. In 2016, 11% and 7% of participating pig and chicken farmers, respectively, reported no use of antimicrobials; 13% of participating turkey farmers also reported not using antimicrobials.

In 2016, the proportion of antimicrobials used for disease prevention increased to 66% and 89% on grower-finisher pig and broiler chicken farms, respectively (Figure 53). The trend in use in broiler chicken between 2014 and 2016 was towards more disease prevention (69% to 89%) and less for growth promotion (3% to 0%). Between 2014 and 2015, there was an increase in overall use in grower-finisher

pigs with an increase in use for growth promotion, 40% in 2015 compared to 30% in 2014. In 2016, overall use in grower-finisher pigs decreased and use for growth promotion dropped back to 30%.

For the first time in 2016, turkey farmers also reported their antimicrobial use. The overall quantity was lower than both grower-finisher pigs and broiler chickens. Ninety-three percent of use was for disease prevention and less than 1% for growth promotion.

Figure 53: Trends in the proportion of antimicrobials used on grower-finisher pig, broiler chicken and turkey sentinel farms, excluding ionophores and coccidiostats, by reason for use, based on estimates of milligrams of use per kg of animal, 2013-2016

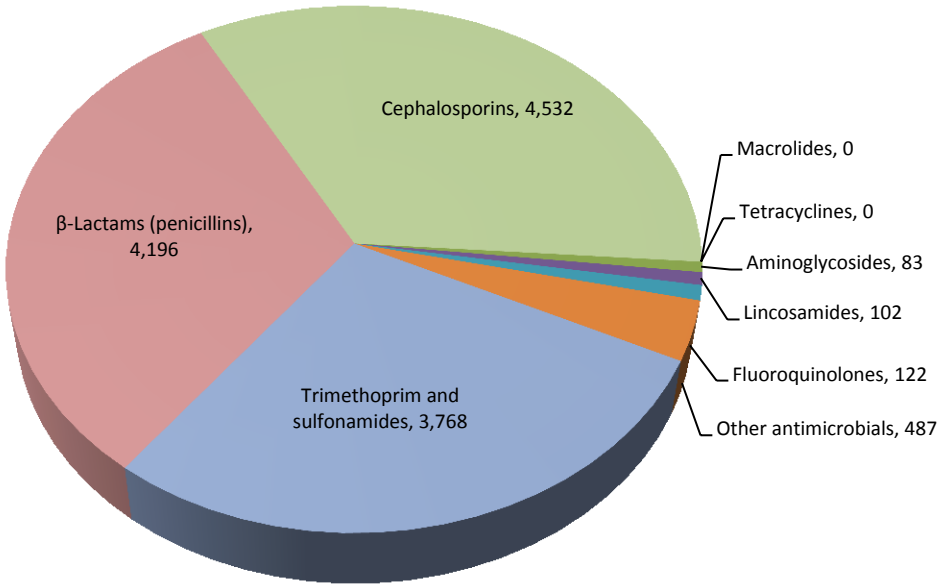


Among grower-finisher pig farms in 2016, 22% reported use of tetracyclines and lincosamides for growth promotion. This represents a slight decline in tetracycline use for growth promotion from 25% in 2015. While both are regarded to be medically important antimicrobials by Health Canada, lincosamides are classified as drugs of high importance to human medicine.

Antimicrobial use in companion animals

In 2016, the predominant classes of antimicrobials used in companion animals were cephalosporins, β-lactams, and trimethoprim-sulfas (Figure 54). All three of these classes are antimicrobials of high importance to humans according to the classification system of the Veterinary Drugs Directorate, Health Canada[15].

Figure 54. Relative quantities of antimicrobial classes distributed for use in companion animals (percentages based on kg active ingredient), 2016.

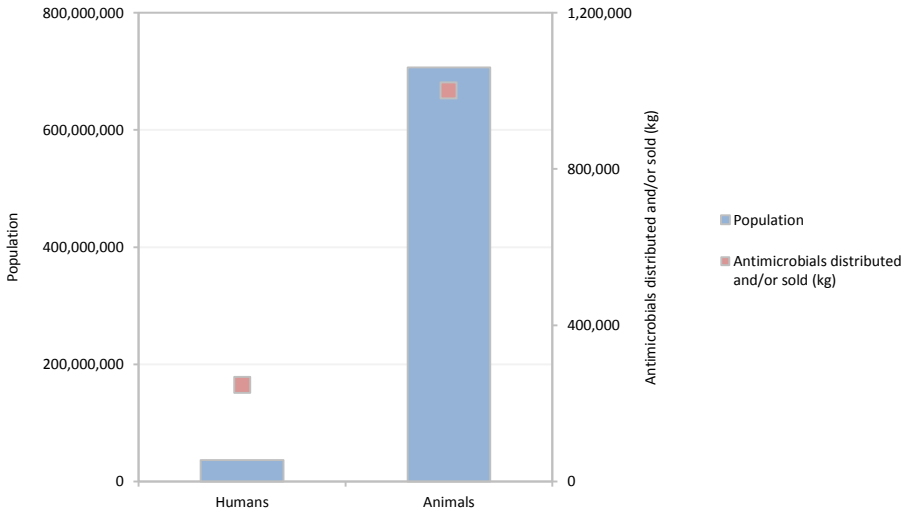


Note: Data Sources: Canadian Animal Health Institute. Antimicrobial sales were assigned to animal type according to label claim and in the situation where mixed species was indicated on the label, the manufacturer assigned the kg to either "Companion animal" or "Production animal". Values do not include antimicrobials imported under the "own use" provision or imported as active pharmaceutical ingredients used in compounding. "Other antimicrobials" for 2016 included: avilamycin, bacitracins, bambermycin, chloramphenicol, chlorhexidine gluconate, florfenicol, fusidic acid, nitarsone, nitrofurantoin, nitrofurazone, novobiocin, polymixin, tiamulin, and virginiamycin.

Integration of Human and Non-Human Antimicrobial Use

When measured by kilograms of active ingredient, approximately 78% of antimicrobials distributed or sold in 2016 were intended for production animals, 20% were for humans, 1% for crops[46] and 1% for companion animals. For context, there were approximately 19 times more animals in Canada in 2016 than people; which is an underestimate of the number of animals because the statistics on fish are reported as kg of fish, not number of live animals and hence cannot be included. After adjusting for underlying populations and average weights (i.e., mg drug/kg animal or mg drug/kg human), there were roughly 1.5[44] times more antimicrobials distributed for use in animals (using European standard weights) than in humans (Figure 55).

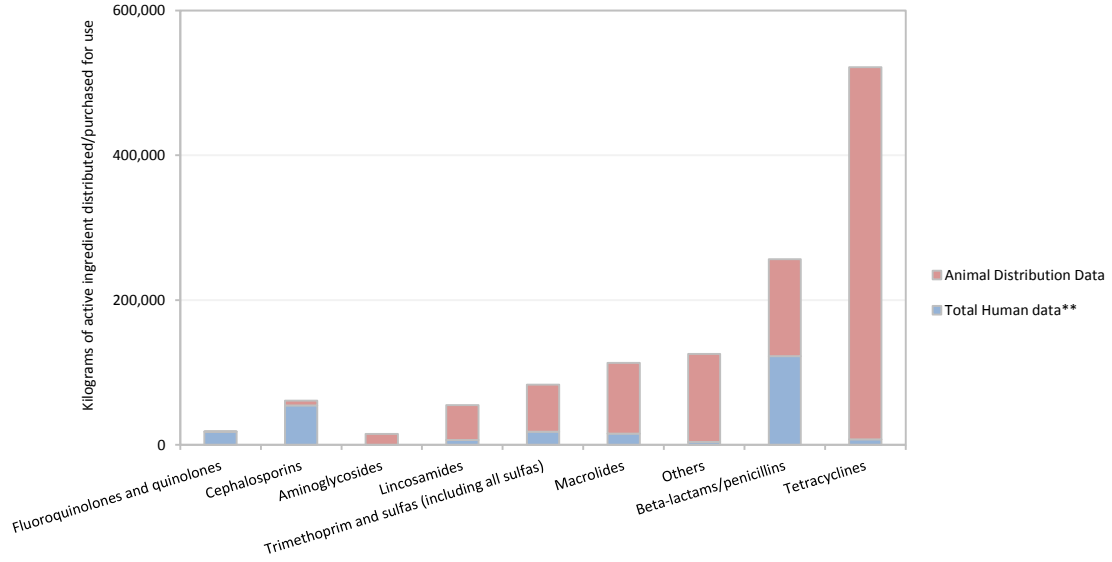
Figure 55: Population sizes and kilograms of antimicrobial agent distributed and/or sold in human and animals in Canada, 2016



Notes: Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada, and IQVA. Animal distribution data do not include own use imports or active pharmaceutical ingredients use in compounding. Ionophores and chemical coccidiostats were excluded. The numbers of animals in this figure are an underestimate as the number of fish are not included (fish are reported as kg, not as live numbers of animals).

Similar antimicrobials are used in humans and animals; however, some antimicrobial classes are sold or distributed more for use in humans than animals and vice-versa. In humans, the predominant classes of antimicrobials sold (by kg active ingredient in descending order) were β-lactams, cephalosporins, and fluoroquinolones (Figure 56). In animals, the predominant classes of antimicrobials were tetracyclines, β-lactams, and other antimicrobials: avilamycin, bacitracins, bambermycin, chloramphenicol, chlorhexidine gluconate, florfenicol, fusidic acid, nitrofurantoin, nitrofurazone, novobiocin, polymixin, tiamulin, and virginiamycin.

Figure 56. Kilograms of medically important antimicrobials distributed and/or sold for use in animals and humans by antimicrobial class, 2016.



Notes: Data Sources: Canadian Animal Health Institute and IQVA. Values for the animal data do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. Other antimicrobials for the animal data included: avilamycin, bacitracins, bambermycin, chloramphenicol, chlorhexidine gluconate, florfenicol, fusidic acid, nitrofurantoin, nitrofurazone, novobiocin, polymixin, tiamulin, and virginiamycin. Other antimicrobials for the human data included: bacitracin, chloramphenicol, colistin, colistimethate, daptomycin, fixadomycin, fosfomycin, fusidic acid, linezolild, methenamine, metronidazole, nitarsone, nitrofurantoin, polymyxin B, quinupristin/dalfopristin,and vancomycin.**includes human hospital and retail pharmacy data.

International Comparisons

Priority Antimicrobial Resistant Organisms

International comparisons between Canada and other countries with respect to antimicrobial resistance (AMR) identified in specific organisms can only be made when data are presented at the national level and are of comparable surveillance methodology. While some Canadian data on antimicrobial resistant organisms are collected and reported in a way that warrants international comparison (e.g., Mycobacterium tuberculosis, *Salmonella* spp.), most are not (e.g., methicillin-resistant *Staphylococcus Aureus*, vancomycin-resistant Enterococci, *Clostridium difficile*).

To address this limitation, Canada participated in the World Health Organization's (WHO) 68th World Health Assembly, in which the global action plan on antimicrobial resistance was adopted. As a result, the Global Antimicrobial Resistance Surveillance System (GLASS) was implemented, designed to standardize the data collection and reporting of AMR by priority organisms, allowing for the most robust international comparisons to date.

The organisms identified by the WHO for GLASS surveillance closely align to the organisms identified by PHAC as priority pathogens in Canada; *Shigella* spp. being the only pathogen identified by GLASS that PHAC does not consider a first tier priority organism (Table 13). The first data contributions to GLASS by PHAC occurred in 2017, with the submission of the 2015 *Salmonella* spp. data. Work is currently underway by PHAC to harmonize additional PHAC surveillance methods for increased GLASS data contributions. Full participation is targeted for 2019.

Table 13: Comparison of PHAC first tier and GLASS priority organisms

PHAC first tier organisms	GLASS priority organisms
Clostridium difficile	
Extended-spectrum β-lactamase (ESBL)-producing organisms	*Escherichia coli* *Klebsiella pneumonia*
Carbapenem resistant organisms (*Acinetobacter* spp. & Enterobacteriaceae spp.)	*Acinetobacter baumannii* *Escherichia coli* *Klebsiella pneumonia*
Enterococcus spp.	
Neisseria gonorrhoeae	*Neisseria gonorrhoeae*
Streptococcus pyogenes (Group A Streptococcus) and *pneumoniae*	*Streptococcus pneumoniae*
Salmonella spp.	*Salmonella* spp.
Staphylococcus aureus	*Staphylococcus aureus*
Mycobacterium tuberculosis	
Campylobacter spp.	
-	*Shigella* spp.

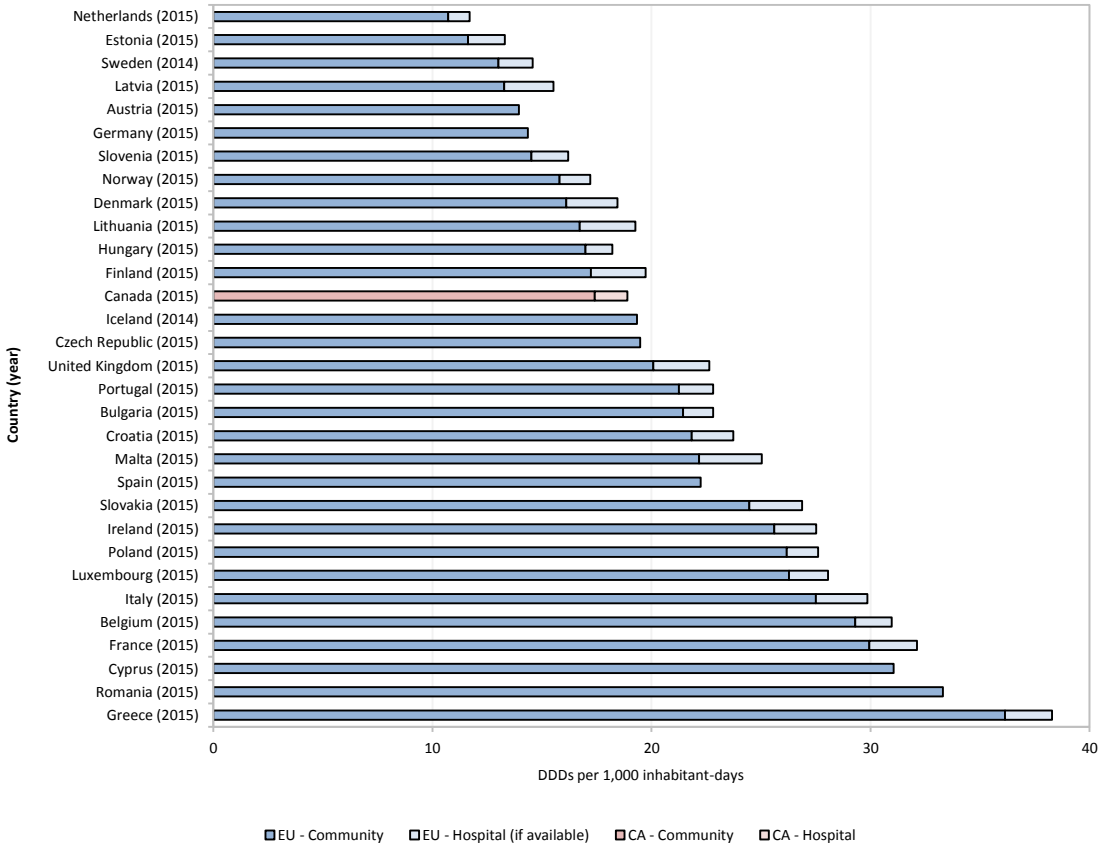
Antimicrobial Use in Humans

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) reports the overall consumption of antibacterials for systemic use (J01) in both hospital and community settings from participating European countries. ESAC-Net is a good candidate for human AMU comparisons to Canada,

as ESAC-Net represents one of the largest internationally standardized AMU data sources, and reports in defined daily doses (DDDs) per 1,000 inhabitant-days.

Comparing 2015 outpatient AMU in Europe with 2015 Canadian community pharmacy dispensation, Canada ranks 13th out of 31 countries (countries ranked by increasing consumption); however, comparing 2015 hospital AMU in Europe with 2015 Canadian hospital purchasing data, Canada ranks 6th out of 24 countries (Figure 57) (countries ranked by increasing consumption). Note that ESAC-Net was unable to report hospital AMU data for seven European countries, and that 2014 data were used for two.

Figure 57: J01 Antimicrobial consumption (DDDs per 1,000 inhabitant-days), Canada (CA) and Europe (EU)



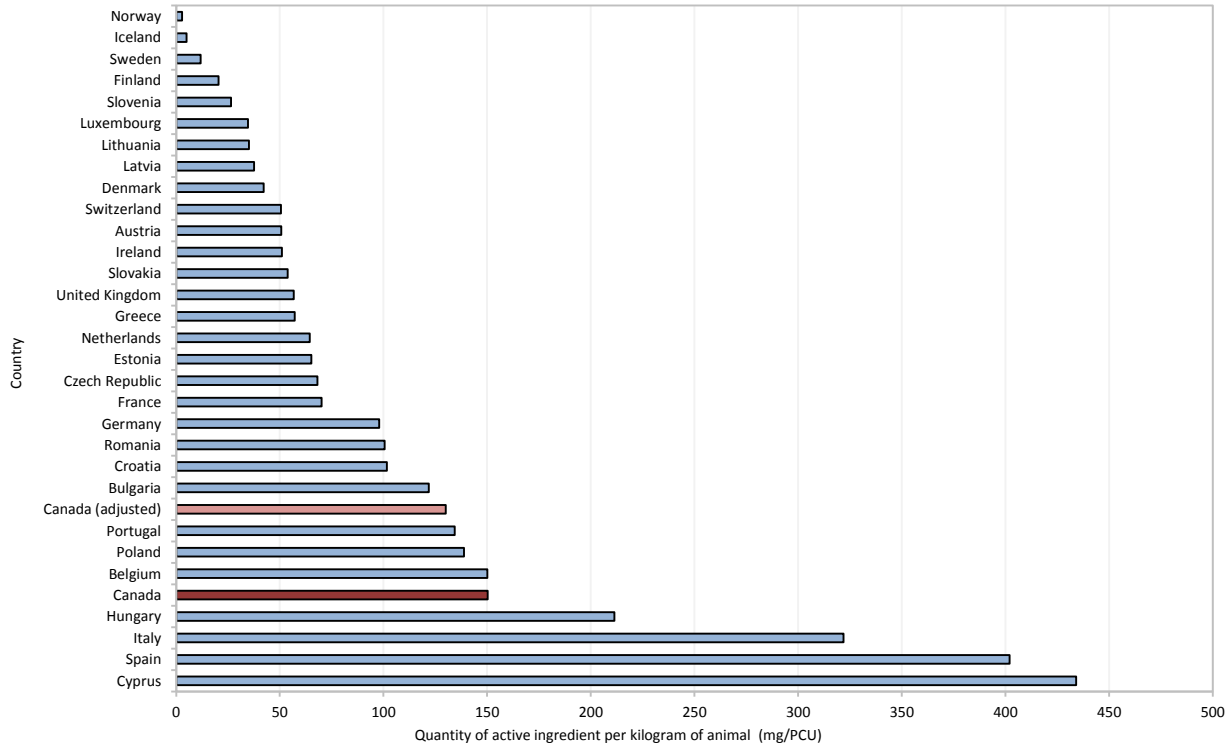
Antimicrobial use in Animals

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) collects and reports information from member countries on antimicrobial agents intended for use in animals[16]. ESVAC is a good candidate for animal AMU comparisons to Canada, as ESVAC is the only current multinational source of quantitative surveillance data on antimicrobial agents intended for use in animals. Canada uses reporting metrics similar to ESVAC, with the notable exception that Canada includes beef cows in the denominator. In 2015, a total of 30 European countries provided animal antimicrobial consumption data to ESVAC[Error! Bookmark not defined.].

Using the latest ESVAC data (2015)[Error! Bookmark not defined.] and the latest Canadian data (2016), out of 31 countries, Canada was the fifth highest for consumption of antimicrobials measured as mg of drug/kg of animal (equivalent to mg/population corrected unit) (Figure 58). Data from all countries shown are using the same average weights at treatment. However, Canadian average weights in many production classes are heavier than European average weights. As per stakeholder request, based on preliminary analysis, the lighter red column for Canada indicates where Canada would rank if Canadian average weights at treatment were used in the calculations.

In 2016, Canada had higher consumption than the reported average for the participating European countries. Canada would report more antimicrobials per kg animal if the currently unknown quantities of antimicrobials imported for 'own use' or as active pharmaceutical ingredients for further compounding were included.

Figure 58: Sales of antimicrobials (adjusted by populations and weights) for Canada (2016) and countries participating in the European Surveillance of Veterinary Antimicrobial Consumption (2015)



Note: Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-Food Canada, Equine Canada, European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). PCU = population correction unit. The Canadian data used for live horses were from 2010 and fish from 2015; more recent data were unavailable. For the Canadian data, values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. The PCU denominator was harmonized to the greatest extent possible with ESVAC[47]. ESVAC denominator does not include beef cows, whereas in Canada beef cows are a significant population and are included. The ESVAC approach excludes companion animal data.

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