CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM – REPORT 2016

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Data to 2014

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Glossary

AMR	Antimicrobial resistance
AMU	Antimicrobial use
AST	Antimicrobial susceptibility testing
BCCDC	British Columbia Centre for Disease Control
BSI	Bloodstream infection
CA	Community-associated
CAHI	Canadian Animal Health Institute
CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
CARA	Canadian Antimicrobial Resistance Alliance
CARSS	Canadian Antimicrobial Resistance Surveillance System
CDI	*Clostridium difficile* infection
CIDSC	Communicable and Infectious Disease Steering Committee
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CNDSS	Canadian Notifiable Disease Surveillance System
CNISP	Canadian Nosocomial Infection Surveillance Program
CPHLN	Canadian Public Health Laboratory Network
CPO	Carbapenemase-producing organisms
CRA	Carbapenem-resistant *Acinetobacter*
CRE	Carbapenem-resistant Enterobacteriaceae
CTBLSS	Canadian Tuberculosis Laboratory Surveillance System
DDD	Defined daily doses
DID	Daily doses per 1000 inhabitants per day
EARS-NET	European Antimicrobial Resistance Surveillance Network
EIP	Emerging Infections Program
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESAG	Enhanced Surveillance of Antimicrobial Resistant Gonorrhea
ESBL	Extended-spectrum ß-lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
GAS	Group A Streptococcus
GNB	Gram-negative Bacilli
HA	Healthcare-associated
HA-CDI	Healthcare-associated *Clostridium difficile* infection
HA-MRSA	Healthcare-associated methicillin-resistant *Staphylococcus aureus*
HO-CDI	Hospital-onset *Clostridium difficile* infection
HUS	Hemolytic Uremic Syndrome
ICU	Intensive Care Unit
iGAS	Invasive Group A streptococcal diseases

INH	Isoniazid
IPD	Invasive pneumococcal disease
IV	Intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	Multidrug-resistant
MDR-TB	Multidrug-resistant Tuberculosis
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSM	Men who have sex with men
NARMS	National Antimicrobial Resistance Monitoring System for Enteric Bacteria
NHS	National Health Service
NHSN	National Healthcare Safety Network
NIHB	Non-Insured Health Benefits
NML	National Microbiology Laboratory
PCR	Polymerase chain reaction
PCU	Population Correction Unit
PCV13	13-valent pneumococcal conjugate vaccine
PFGE	Pulsed-field gel electrophoresis
PHAC	Public Health Agency of Canada
PHN	Public Health Network
RMP	Rifampin
SSTI	Skin and soft tissue infection
STI	Sexually transmitted infection
TB	Tuberculosis
TMP-SMX	Trimethoprim-sulfamethoxazole
US CDC	United States Centers for Disease Control and Prevention
UTI	Urinary tract infections
VRE	Vancomycin-resistant Enterococci
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB

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

Antimicrobial resistance (AMR) continues to be a serious public health issue in Canada and internationally. Common and treatable infections may once again become deadly. This reality is illustrated by the recent detection of the mcr-1 colistin resistant gene in isolates from animal, food, and human sources in Canada, the United States and elsewhere in the world.

Last year, the inaugural "*Canadian Antimicrobial Resistance Surveillance System (CARSS) Report 2015"* presented integrated surveillance data from nine of the Public Health Agency of Canada (PHAC)'s existing surveillance systems and laboratory reference services[1] to provide information on AMR and AMU in Canada, with the aim to support decision-making by health professionals and policy makers.

This second report reflects a year of momentum, building on the first report by increasing the depth and breadth of surveillance data and analysis.

Highlights of this report include the identification of priority organisms to help focus surveillance efforts; results of a pilot of enhanced surveillance of antimicrobial-resistant gonorrhea to better support the response to the resurgence of gonorrhea reported in recent years; and outcomes of a feasibility study of "AMR-Net", a web-based application that was used to collect and analyze community-level AMR information and which could serve to educate healthcare professionals and Canadians about AMR trends in the community. The report also identifies surveillance gaps which future CARSS reports will strive to fill to enable us to provide a more comprehensive picture of AMR and AMU in Canada.

PHAC's surveillance efforts can only be successful with the contributions and collaboration of its partners, the provinces and territories, healthcare professionals, veterinarians, associations and organizations, communities and individuals. These partners provide data and advice essential to making CARSS the national focal point for AMR and AMU surveillance data in Canada. We thank all contributors for their time, expertise and continued support.

Dr. Siddika Mithani
President, Public Health Agency of Canada

Dr. Gregory Taylor
Chief Public Health Officer of Canada

[1] The Canadian Nosocomial Infection Surveillance Program; the Canadian Integrated Program for Antimicrobial Resistance Surveillance; FluWatch; the Canadian Tuberculosis Laboratory Surveillance System; the Canadian Tuberculosis Reporting System; the Antimicrobial-resistant Neisseria gonorrheoeae Surveillance System; the national surveillance of invasive Streptococcal disease; the Canadian HIV Strain and Drug Resistance Surveillance Program; data on antimicrobial uptake purchased through IMS Health Canada Inc.; and laboratory references services provided by the National Microbiology Laboratory.

Executive Summary

Introduction

The establishment of CARSS is a key commitment made in the *Federal Action Plan on AMR and AMU in Canada: Building on the Federal Framework for Action*. CARSS provides an integrated picture of AMR/AMU in Canada based on available surveillance data from PHAC's nine surveillance systems and laboratory reference services which track the identified priority organisms. The inaugural CARSS report issued in 2015 provided information on AMR/AMU in Canada until 2013. This year's report demonstrates the Government of Canada's continued commitment to leading activities to prevent, limit and control the emergence and spread of AMR as described in *Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*.

One of the key accomplishments this year has been the work with federal/provincial/territorial partners to develop a list of priority organisms of concern for AMR. The list was developed by leveraging the expertise of the federal/provincial/territorial Pan-Canadian Public Health Network's (PHN's) Communicable and Infectious Disease Steering Committee (CIDSC). Working with PHAC, a task group identified and prioritized AMR organisms of concern in Canada; identified where sufficient surveillance data are being collected and where gaps may exist; and made recommendations to address some of those gaps. The list of priority organisms is an important step in determining the data that need to be collected from all surveillance partners in Canada.

Since the release of the CARSS 2015 report, PHAC has invested significant effort in AMR/AMU surveillance including the implementation of two pilot initiatives to address gaps in community settings identified in the initial CARSS report and the spring 2015 Auditor General of Canada report "*Antimicrobial Resistance"*. The Enhanced Surveillance of Antimicrobial Resistant Gonorrhea (ESAG) pilot was undertaken in response to the high levels of resistance to antimicrobials used for treating gonorrhea. ESAG assessed the feasibility of obtaining surveillance data to improve the understanding of the current levels and trends of resistant gonorrhea in Canada. It aimed to provide stronger evidence to guide the development of treatment guidelines and public health interventions to minimize the spread of antimicrobial resistant gonorrhea. The AMR-Net pilot was undertaken to determine the feasibility of obtaining and analyzing existing antimicrobial susceptibility data in the community; to improve PHAC's ability to respond to emerging threats and support stewardship efforts by informing evidence-based decision making. The results of the two pilot initiatives confirmed the feasibility of collecting data in community settings.

Antimicrobial resistance and antimicrobial use

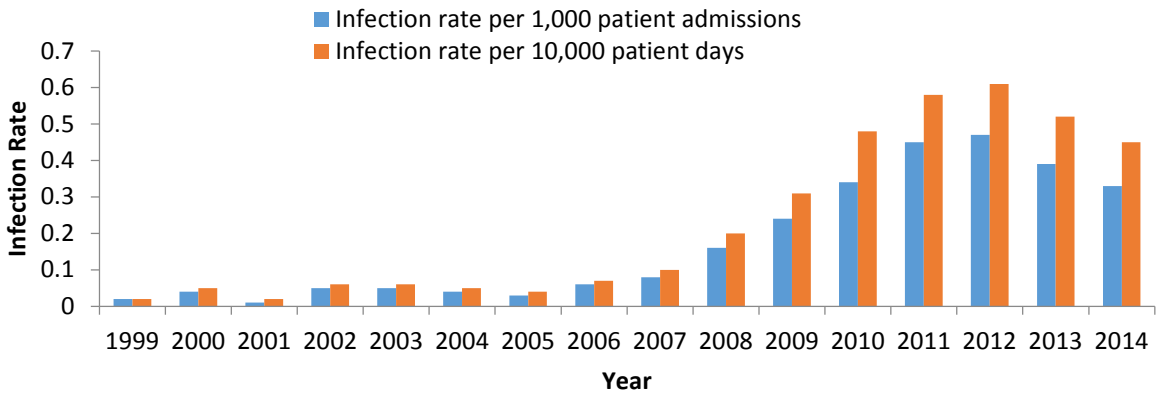
Antimicrobial resistance is the ability of microorganisms (including bacteria, fungi, viruses and parasites) to become resistant to treatment by antimicrobial drugs, such as antibiotics[2]. Resistance can develop naturally over time as microorganisms evolve, mutate and multiply. Microorganisms, especially bacteria, are also able to transfer their resistant traits to other microorganisms, increasing the spread of AMR. The scope of resistance is accelerated by excessive and/or unnecessary use of antimicrobial drugs used to treat bacterial infections, such as inappropriate prescribing practices by health professionals and patients not taking prescribed drugs as directed.

Antimicrobial resistance

Antimicrobial resistance significantly impedes our ability to fight infectious diseases, leading to more hospitalizations and/or increased hospital stays. This results in increased health care costs and costs to society in the form of time away from work, increased disability claims and loss of productivity.

Antimicrobial resistance is now occurring in every reporting country in the world. Globally, bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*, are demonstrating a reported range of resistance of between 5% and 80% of tested strains. Current surveillance in Canada is showing generally stable rates of resistance and in some cases a decline of infection rates of select AMR organisms in recent years. For example, rates of hospitalized methicillin-resistant *Staphylococcus aureus* (MRSA) infection have declined 25% since 2008, and declines in each of the past two years for vancomycin-resistant Enterococci (VRE) infections have been observed. That said, incidence rates of MRSA and VRE have not decreased to levels seen before 2007 when increases in resistance began, indicating that more work needs to be done to reverse the problem.

Incidence rates of vancomycin-resistant Enterococcus infections per 1,000 patient admissions and per 10,000 patient days, 1999 to 2014

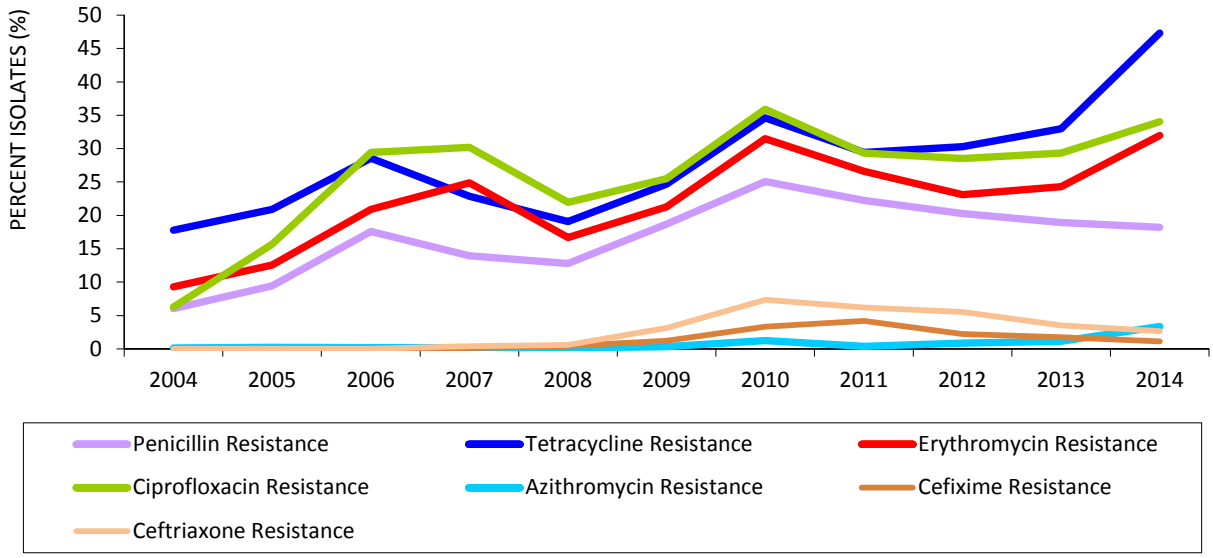


[2] An antimicrobial is a natural, semisynthetic or synthetic substance that is capable of killing or inhibiting the growth of microbes. The term antimicrobial will be used throughout this document to refer to antibiotics, antivirals, antifungals and anti-parasitics.

Although Canada is not seeing the same general level of resistance as some other countries, there are areas of concern. For example, available data indicate that more than one third of gonorrhea cases are resistant to each of ciprofloxacin, erythromycin and tetracycline. In recent years, there has been a small proportion of cases (<0.3%) resistant to both azithromycin and cephalosporins (ceftriaxone and cefixime) the currently recommended dual therapy treatment[3] for gonorrhea. Canada demonstrates higher azithromycin resistance levels to *N. gonorrhoeae* (3.3% in 2014) than the United States which reported 0.6% in 2013 and the United Kingdom which reported 1.6% in 2013[4,5].

If the rate of resistance continues to increase, it would threaten the success of the currently recommended dual therapy treatment regimen. This shows the need for ongoing monitoring of AMR to help maintain the effectiveness of current treatment regimens and to guide their modification when appropriate.

Percentage of gonorrhea isolates resistant to antibiotics, 2004 to 2014



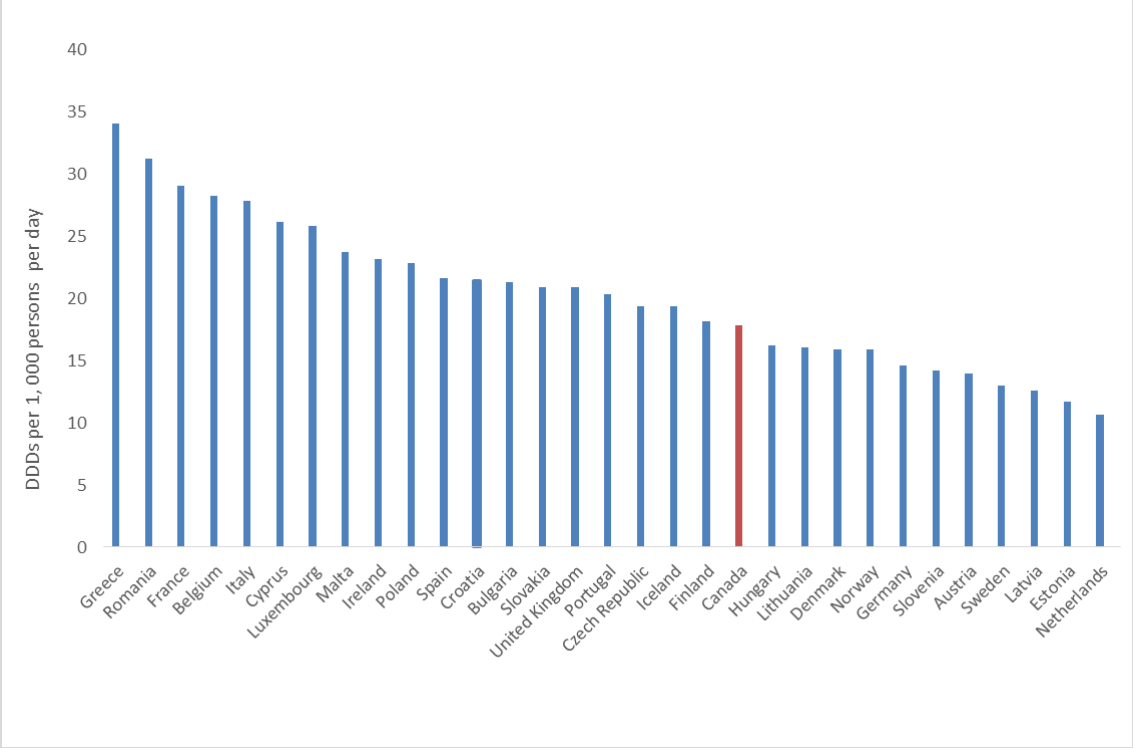
Antimicrobial use in humans

In Canada, the majority of antimicrobials used by humans are available by prescription only. Over the last 13 years, the volume of antimicrobial prescriptions in humans has remained relatively stable. In 2014, 23 million prescriptions were dispensed, with 93% dispensed by community pharmacies. The overall expenditure on antimicrobials in Canada was $786M, with community dispensing accounting for 87% and hospital purchases accounting for 13% of this amount.

[3] Public Health Agency of Canada National Microbiology Laboratory. National surveillance of antimicrobial susceptiblities of *Neisseria gonorrhoeae* annual summary 2014. Ottawa ON: PHAC; 2015.
[4] Public Health Agency of Canada. *Salmonella Enterica Spp*. Pathogen safety data sheet: Infectious substances. [Internet] Ottawa ON: PHAC; [updated 2011 Feb 18; cited 2016 Mar 23]. http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/salmonella-ent-eng.php#note7.
[5] Summary of the statement on international travellers and Typhoid by the Committee to Advice on Tropical Medicine and Travel CATMAT. Can Comm Dis Rep. 2014;40-4. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/14vol40/dr-rm40-04/dr-rm40-04-tropmed-eng.php.

Antimicrobials were most often recommended for treating respiratory infections. Eighty-two percent (82%) of acute sinusitis diagnoses, 77% of acute bronchitis diagnoses, and 74% of pneumonia diagnoses resulted in a recommendation for an antimicrobial. Further work is required to assess the appropriateness of practitioner antimicrobial recommendations and adherence to clinical guidelines for specific antimicrobials for first-line treatments. An example would be the treatment of lower urinary tract infections where ciprofloxacin is recommended more often than the guidelines suggested trimethoprim-sulfamethoxazole or nitrofurantoin. In 2014, a total of 30 European countries provided information to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) on antimicrobials consumed in their community. When these data were compared with the 2014 Canadian outpatient antimicrobial consumption rate, Canada (17.8 defined daily dosage (DDD)s per 1,000 persons per day) ranked 12th out of 31 countries by increasing level of AMU, with almost half the level of use reported by Greece (country with highest use, 34 DDDs per 1,000 persons per day)[6].

Outpatient antimicrobial use (defined daily dosage (DDD) per 1,000 persons per day) reported in Canada and in 30 European countries

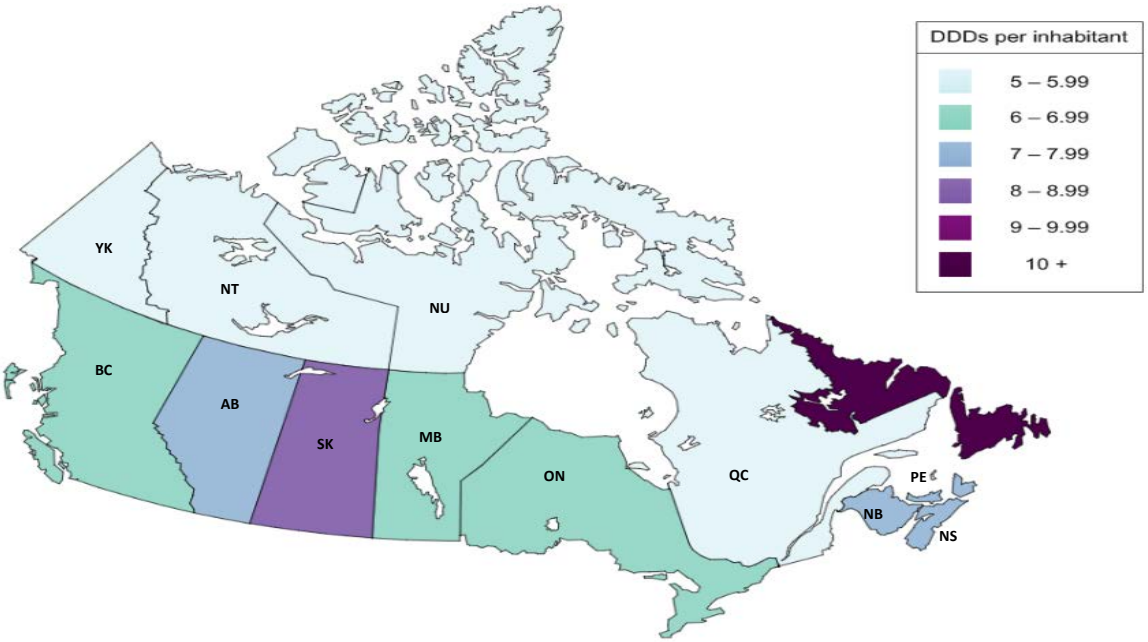


There is significant variation in the rates of antimicrobial prescribing within Canada. Differences observed in prescriptions filled for parenteral (injection and intravenous) antimicrobials through community pharmacies likely reflect differences in provincial policies regarding the payment for outpatient parenteral antimicrobials. In contrast to the large variation observed among the top five

[6] European Centre for Disease Prevention and Control (CDC) Antimicrobial consumption rates by country. [Internet] Solna Sweden: ECDC; 2016. [updated 2016 March 22; cited 2016 March 23]. http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx.

antimicrobials purchased by hospitals, commonalities are observed among the antimicrobials dispensed in the community across provinces and territories. For example, amoxicillin and clarithromycin were among the top five antimicrobials dispensed with the highest levels of defined daily doses (DDDs) per inhabitant in every province and territory. Further analysis is required to determine the reason for the observed differences.

Total antimicrobials dispensed through community pharmacies within provinces or territories in Canada, 2014[7]



Antimicrobial use in animals

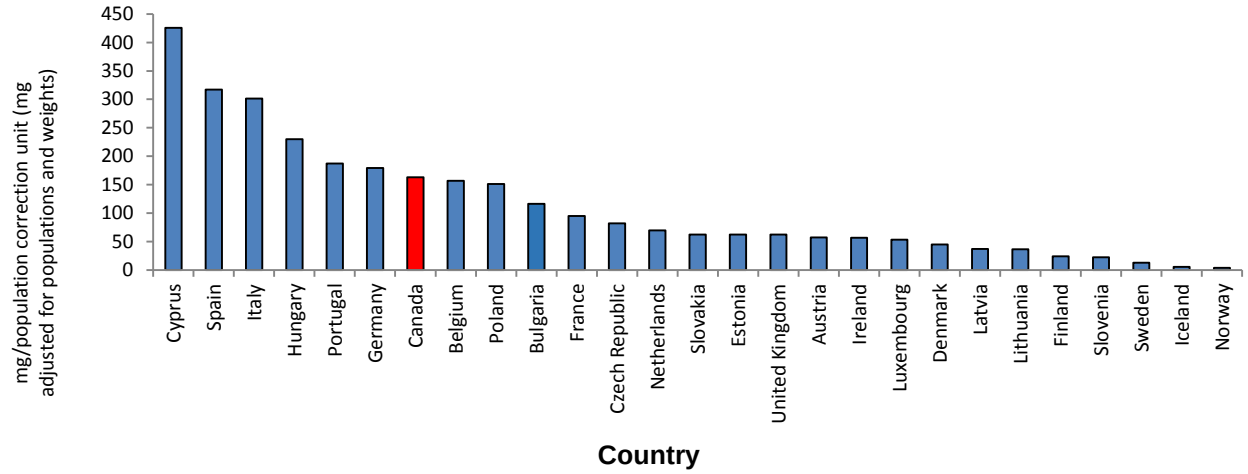
There is increasing evidence that the use of antimicrobial agents in veterinary medicine and livestock production is an important contributing factor to the emergence and persistence of AMR in bacteria in humans. The spread of organisms with resistance traits from animals to humans necessitates the assessment of human health risks associated with AMU in food-producing animals.

Canada is a major source of food-producing animals for domestic and international markets, with approximately 19 times the number of animals than humans in the country. The majority (73%) of antimicrobials distributed to animals were in the same classes as those antimicrobials used in human medicine. In 2014, approximately 82%[8] of antimicrobials important to human medicine were distributed and/or sold for use in food-producing animals. Antimicrobials are used in food-producing animals (e.g., chickens, pigs and cattle) for the treatment and prevention of disease, and to improve feed efficiency/promote growth.

[7] BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario; QC: Quebec; NB: New Brunswick; NS: Nova Scotia; PE: Prince Edward Island; NL: Newfoundland and Labrador; TE: Territories (includes: NT: Northwest Territories, NU: Nunavut, YU: Yukon).
[8] 82% (intended for food-producing animals) calculated by dividing amount distributed and/or sold for use in food-producing animals by total amount distributed and/or sold for use in humans, food-producing animals, companion animals, and crops; 18% (for humans), less than 1% for companion animals and less than 1% for crops.

In Canada, as in many other countries, AMR is monitored in chicken, pork and beef for *Escherichia coli, Campylobacter* and *Salmonell*a as a way to measure the potential movement of AMR priority organisms from animals to humans. In comparison to the countries participating in the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) network, Canada ranked 7th highest out of 27 countries for increasing levels of antimicrobial sales adjusted by populations and weights[9]. Canada's total milligrams distributed, adjusted by population, was 44 times that used in Norway (country with the lowest sales) and less than half of that reported by Cyprus (the country with the highest sales).

Antimicrobial sales for animals (quantity adjusted by populations and weights) for Canada (2014) and countries participating in the European Surveillance of Veterinary Antimicrobial Consumption Network (2013)



Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada and European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Own use importation and active pharmaceutical ingredient importation are not included for the Canadian data.
Ionophores and chemical coccidiostats were excluded. The denominator was harmonized with ESVAC to the best extent possible, acknowledging different sources of data on populations of animals. ESVAC approach excludes companion animal data from the numerator. The Canadian denominator includes beef cattle, an animal type not included by ESVAC.
Data from all countries shown are using the same average weights at treatment. However, Canadian average weights in a few production classes are heavier than European average weights.

AMR priority organisms

PHAC's surveillance systems are essential tools in its efforts to protect Canadians from the health risks associated with AMR. Surveillance data inform the understanding of transmission routes and help assess the magnitude and trends of related morbidity and mortality. In this context, PHAC identified 138 infectious pathogens (microorganism that can cause disease) worldwide that have exhibited resistance, and from these used a multi-step approach to assess and determine the AMR pathogens of relevance to Canada. The criteria used included the incidence, communicability/transmissibility, preventability, treatability, clinical impact and mortality.

[9] The denominator used to adjust the sales data is equivalent to the biomass of the population. In the European Surveillance of Veterinary Antimicrobial Consumption, this is labelled the "Population Correction Unit" or "PCU".

Subsequently the PHN's CIDSC established a task group to determine the pathogens of greatest importance to public health in Canada. Led by PHAC, it included epidemiologists, infectious diseases and public health experts from across the country, and federal/provincial/territorial experts.

Although it was recognized that resistance can occur in all types of organisms including viruses, fungi and parasites, the task group focused on bacteria in humans and animals as it relates to human health. The group identified the following organisms as the first order of priority for surveillance purposes, which should be, or currently are, under surveillance in Canada:

- *Clostridium difficile*
- Extended-spectrum β-lactamase (*ESBL)* - producing organisms[10]
- Carbapenem-resistant organisms[11] *(Acinetobacter +* Enterobacteriaceae spp.*)*
- Enterococcus spp.
- *Neisseria gonorrhoeae*
- *Streptococcus pyogenes (*Group A *Streptococcus)* and *pneumoniae*
- *Salmonella* spp.
- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*
- *Campylobacter* spp.

[10] Extended-spectrum β-lactamase (ESBL)-producing organisms: Enterobacteriaceae spp. (*Klebsiella, E. coli), Pseudomonas*, Others to consider: *Providencia stuartii*, *Citrobacter*, *Serratia*, *Proteus*, Enterobacter.
[11] ‡Carbapenem-resistant organisms (CROs): Enterobacteriaceae spp. (*Klebsiella, E. coli), Pseudomonas, Acinetobacter*.

Organisms transmitted in healthcare settings

PHAC's surveillance systems currently monitor the following priority bacteria transmitted mainly in healthcare settings:

Clostridium difficile (C. difficile) is an important healthcare-associated infection that causes significant morbidity and mortality. While largely responsive to current standard treatments, the infection spreads rapidly because it is naturally resistant to many drugs used to treat other infections. Most cases occur in patients taking high doses of specific antibiotics or taking antibiotics over long periods of time, those who have underlying medical conditions, or those who have had invasive medical procedures. Following a decade of increasing rates of *C. difficile* in hospitalized patients, rates declined in 2014 from 5.2 cases per 1,000 patient admissions to 3.4 cases per 1,000 patient admissions.

Carbapenem resistant Organisms (CRO) and Carbapenem-resistant Enterobacteriaceae (CRE) can cause infections in the urinary tract, respiratory system, bloodstream or in wound infections of vulnerable patients (such as the very young, elderly or immune-compromised). The carbapenem group of antimicrobials is most often a last line of treatment for Enterobacteriaceae and is usually reserved for multidrug-resistant Enterobacteriaceae. The emergence of CRE and a related group called Carbapenemase-producing organisms (CPO) have become serious public health concerns internationally because there are few alternative treatments available when resistance to this group of antimicrobials occurs. In Canada, both the CRE and CPO rates have remained consistently low since 2010 but continue to be closely monitored given the increasing rates in other countries.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common causes of healthcare-associated infections in Canada. Methicillin is one of the first-line antibiotics used to treat *Staphylococcus aureus* infections. MRSA can cause serious and sometimes fatal infections in the hospital setting. With resistance to methicillin, vancomycin has now become the primary antimicrobial used to treat MRSA infections. As a result, resistance to vancomycin needs to be monitored to inform action to preserve this treatment option. Since 2008, the overall MRSA infection rates in hospitals have decreased by 25%, but have not declined to rates seen in the early 2000s.

Vancomycin-resistant Enterococci (VRE) can cause a range of infections in the urinary tract, bloodstream and surgical wounds of hospital patients. Vancomycin is generally prescribed to treat serious infections caused by organisms that are resistant to other antimicrobials. As such, resistance to vancomycin further limits therapeutic options. VRE infection rates increased sharply from 2007 (0.10 cases per 10,000 patient days) to 2012 (0.61 cases per 10,000 patient days) before decreasing in 2013 and 2014 (to 0.45 cases per 10,000 patient days). Despite recent decreases in Canada, VRE infections are increasing in prevalence worldwide and therefore, continue to be a global health threat that could arise again in Canada.

Organisms transmitted in community settings

The following priority bacterial organisms transmitted primarily in community settings are being monitored through PHAC's surveillance systems:

Streptococcus pneumoniae (S. pneumoniae) causes a severe form of infection that can lead to pneumonia and meningitis most often diagnosed in young children and the elderly. *S. pneumoniae* has shown resistance to penicillin and the erythromycin group of drugs. The national annual incidence rate of invasive pneumococcal disease and the resistance to a number of antimicrobials used to treat *S. pneumoniae* have decreased since 2010 with the implementation of childhood immunization programs using a 13-valent pneumococcal conjugate vaccine.

Group A *Streptococcus* (GAS) can cause invasive diseases such as necrotizing fasciitis (flesh-eating disease) and non-invasive diseases such as strep throat and scarlet fever. From 2009 to 2013, the national incidence rate of invasive GAS cases increased from 4.0 to 4.7 per 100,000 population, with the highest incidence seen in infants less than one year of age and in seniors 60 years of age and older. In 2014, all samples of invasive GAS responded to first-line antimicrobials, while resistance to second-line antimicrobials either remained relatively unchanged or declined. The serious nature of the infections caused by GAS requires that AMR be closely monitored to ensure effective treatments remain available.

***Neisseria gonorrhoeae* (gonorrhea)** can cause genital/reproductive tract inflammation and damage, and potentially, infertility. Between 2004 and 2013, the rate of reported cases of gonorrhea increased 43.1% (from 27.4 to 39.3 per 100,000 population), particularly in females. Coupled with the increase in cases, *N. gonorrhoeae* has developed resistance to a range of antimicrobials used to treat it. In 2014, 18.2% of isolates were resistant to penicillin; 47.3% were resistant to tetracycline; 32.0% were resistant to erythromycin; and 34.0% were resistant to ciprofloxacin. There has also been decreased susceptibility to cefixime, ceftriaxone or azithromycin, threatening the availability of treatment options.

***Mycobacterium tuberculosis* (TB)** rates in Canada are among the lowest in the world; however, it disproportionately affects Indigenous people and the foreign-born individuals from areas of the world with high rates of TB. Overall, there was no notable change in the resistance to first-line medications in Canada from 2004 to 2014 and resistance levels remain low (8% resistance to one drug and 1% multidrug-resistance) and below international levels. Although AMR TB is not a major problem in Canada, the potential for the emergence of more cases in Canada exists due to increasing levels in other countries and ease of international travel.

Organisms transmitted in animals

The following priority bacteria transmitted through animals are monitored through PHAC's Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) system:

Escherichia coli (E. coli) are extremely common bacteria, as they inhabit the gastrointestinal tract of healthy animals and humans. They are considered to be good indicators of antimicrobial selection pressure, can carry resistance genes that can be spread to other bacteria, and, in some cases, may cause illness themselves. In 2014, the proportion of chicken, swine and cattle samples (on farm, at slaughter and at retail) positive for generic *E. coli* were 96%, 55% and 56% respectively. Following the May 2014 industry ban of the preventive use of antimicrobials considered of very high importance to human medicine, including ceftiofur, a third generation cephalosporin, CIPARS observed a decrease in resistance to third generation cephalosporins in *E. coli* from chickens and chicken meat. For example, 28% of isolates from chicken meat were resistant to third generation cephalosporins in 2013 but only 19% in 2014. PHAC also observed a decrease in the use of ceftiofur in broiler chicken flocks from 31% in 2013 to 6% in 2014.

Campylobacter are a major cause of foodborne diarrhoeal illness in humans. The majority of *Campylobacter* infections are mild, but can be severe or even fatal among very young children, the elderly and immune-compromised individuals. In 2014, the proportion of chicken, swine and cattle samples (on farm, at slaughter and at retail) positive for *Campylobacter* were 25%, 73% and 87% respectively. CIPARS observed a decrease, corresponding with the industry ban on the preventive use of antimicrobials of very high importance to human health, in the number of farms reporting fluoroquinolone use from 2/99 in 2013 to 0/142 in 2014.

***Salmonella* spp**. Salmonellosis is one of the most common and widely distributed foodborne diseases, with tens of millions of human cases occurring worldwide every year. Caused by over 2,500 different types of *Salmonella*, the majority of infections cause mild gastroenteritis but can be severe in the young, the elderly and the immune-compromised. In 2014, the proportion of chicken and swine samples (on-farm, at slaughter and at retail) positive for *Salmonella* spp. were 34% and 16% respectively. As in *E. coli* there was a decrease in resistance to third generation cephalosporins in non-typhoidal *Salmonella* from chickens and chicken meat in 2014 compared to 2013. For example, 22% of isolates from chickens sampled on-farm were resistant to third generation cephalosporins in 2013 but only 12% in 2014. By comparison, resistance to third generation cephalosporins in *Salmonella* from pigs was below 5% in 2014.

Surveillance data gaps

PHAC in collaboration with provinces and territories has identified gaps in surveillance which require addressing in order to provide a comprehensive picture of AMR/AMU in Canada. Of most importance is the lack of data regarding the resistance of a number of priority pathogens of concern to the health of Canadians. This includes resistant *E. coli*, *Neisseria gonorrhoeae*, and *Shigella*. Other gaps include limited data on AMR in smaller, non-academic hospitals, no data for rural and northern healthcare settings and First Nations and Inuit communities, and limited data on AMR in the community, outpatient clinics, long-term care facilities, and physicians' and dentists' offices.

As resistant microbes are generally found where AMU is more prevalent, identifying and addressing gaps in AMU data is critical to mitigating the threat of AMR. PHAC obtains information on prescriptions dispensed by retail pharmacies, antimicrobials purchased by hospitals, and diagnoses for which physicians have recommended an antimicrobial in the community[12]. While there is some understanding of prescribing patterns in hospital and community settings, other information gaps limit the ability to assess appropriate indications of use and identify potential areas of overprescribing.

Currently, there is limited data on AMU in animals as well as some gaps in the surveillance of AMR in animals and the food chain. There is a lack of information on the quantities of antimicrobials imported for own use or as active pharmaceutical ingredients for compounding by veterinarians and used in food-producing animals. The introduction of new federal regulations for veterinary oversight of AMU is anticipated to open new sources for some of these data after regulations are passed in December 2016.

Finally, there is a significant gap in understanding the linkages between AMU and the observed patterns of resistance and the spread of pathogens in Canada.

[12] Human AMU data is purchased by the Public Health Agency of Canada from Information Management Solutions (IMS) Health Canada Inc.

Identifying AMR surveillance data gaps for priority organisms

Priority organism	Collection of surveillance data	
	Community setting	Hospital setting
Clostridium difficile	○	●
Enterobacteriaceae spp., *E. coli, Klebsiella (*BSI)	Captured in hospital settings	◒
Enterococcus spp. and *Staphylococcus aureus* (BSI)	Captured in hospital settings	◒
Staphylococcus aureus (other infection sites)	◒	◒
Streptococcus pyogenes and *pneumoniae*	◒	◒
	◒	◒
Neisseria gonorrhoeae	◒	Captured in community settings
Mycobacterium tuberculosis	●	●
Salmonella spp.	●	●
Campylobacter spp.	◒	◒

● MEETS SURVEILLANCE DATA REQUIREMENTS

◒ PARTIALLY MEETS SURVEILLANCE DATA REQUIREMENTS

○ DOESN'T MEET SURVEILLANCE DATA REQUIREMENTS

Next steps/conclusion

PHAC has made significant progress strengthening its surveillance systems in order to provide a comprehensive and integrated public health picture of AMR and AMU in Canada. Ongoing surveillance gaps present a challenge to developing a comprehensive picture in both the community and hospital settings. PHAC is committed to working with provincial and territorial governments, and other partners to address surveillance gaps. The identification of the increasing resistance of microorganisms to antimicrobials, and questions regarding the appropriate use of antimicrobials, demonstrate the necessity for continued vigilance in order to address the issue of AMR and AMU in Canada. Expanding surveillance activities to collect quality data regarding health professional prescribing practices, infection rates, and resistance patterns for priority organisms, particularly in the community setting, will be the priority of PHAC's work over the coming year.

AMR is a global problem that cannot be solved without global collaboration. PHAC will continue to work with its international partners such as the World Health Organization (WHO) to identify and measure common indicators as well as share best practices for stewardship to tackle AMR in Canada.

Technical annex

Antimicrobial resistance and antimicrobial use

The following technical annex provides a more detailed view of the surveillance data on the priority organisms surveilled under PHAC's surveillance systems. The AMR section focuses on priority organism and describes the surveillance methods, the situation in Canada and an international perspective. The priority organisms listed in the following AMR section includes: *Clostridium difficile*, multidrug-resistant Enterobacteriaceae and *Acinetobacter*; methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococcus spp.; drug-resistant *Streptococcus*, *Neisseria gonorrhoeae*, *Salmonella typhi*, non-Typhoidal *Salmonella*, and Tuberculosis.

The AMU section provides information on human and animal antimicrobial usage. It gives details on the human aspect for the amount of antimicrobials dispensed through community pharmacies, prescriber specialization breakdown as well as hospital purchasing and use. The animal aspect is presented by antimicrobials distributed for sale, indication for use and international comparison.

Antimicrobial resistance in Canada

Clostridium difficile

Clostridium difficile (C. difficile) is a gram-positive, spore-forming, anaerobic bacillus and is the most frequent cause of healthcare-associated infectious diarrhea in Canada and other developed countries. There has been a marked increase in *C. difficile* infection (CDI) incidence and mortality across the United States, Canada and Europe during the last decade (1). Most cases of CDI occur in patients who are elderly and who have other underlying medical conditions. *C. difficile* spreads rapidly in healthcare settings by direct contact because it is naturally resistant to many antimicrobials used to treat other infections. *C. difficile* spores in the environment also tend to be resistant to most commonly-used disinfectants. It is estimated that 1.5% of all hospitalized patients will develop CDI during the course of their hospitalization. Approximately 15% of these will develop severe disease and 6% of severe CDI cases will die from the infection (2, 3).

While resistance to current standard treatments for CDI (vancomycin, metronidazole) is not a concern at present, the extensive use of antimicrobials in hospitals to treat patients often creates a competitive advantage for *C. difficile.* A virulent strain of *C. difficile*, the North American pulsed-field (NAP) type 1 (NAP1) which emerged in 2000 was found to be resistant to fluoroquinolones, a class of antimicrobials commonly used to treat other infections in both the hospital and community settings. NAP1 has spread throughout North America and Europe and is responsible for increasing CDI rates, hospital outbreaks and more severe disease especially in the elderly (3). Whereas NAP1 appears to be most prevalent in adult cases of CDI, NAP4 was found to be the most common type found in pediatric cases with CDI between one and 18 years of age (4).

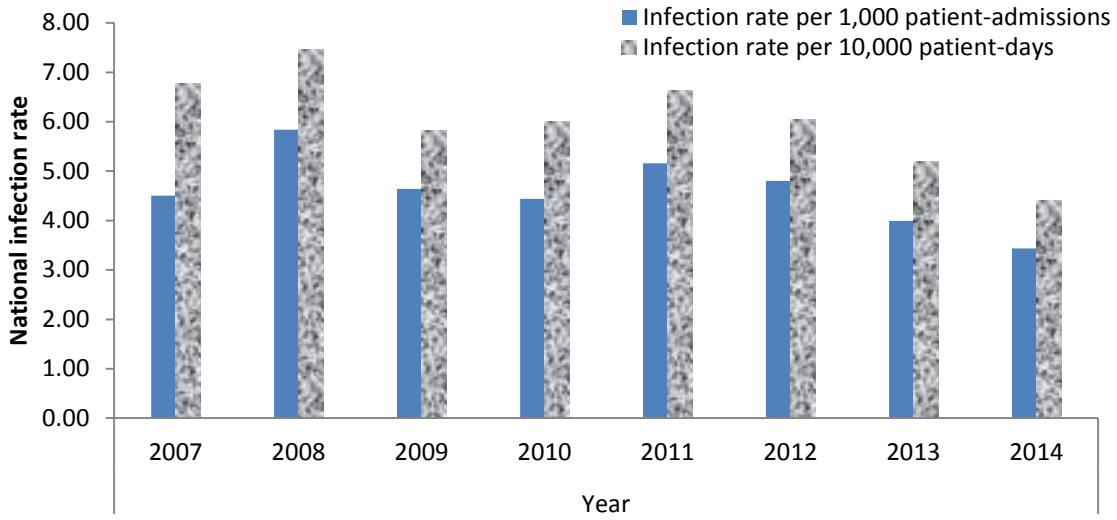
Methods

PHAC has collected information on healthcare-associated (HA)-CDI through the Canadian Nosocomial Infection Surveillance Program (CNISP) since 2005. As of 2014, CNISP collected information in 58 major hospitals in 10 provinces. Infection Control Professionals complete a standardized patient questionnaire through concurrent or retrospective chart review once a possible CDI case is identified by the hospital's laboratory. Detailed patient information including outcome information (admitted to intensive care unit for complications related to HA-CDI, underwent colectomy or died) was submitted to PHAC for each identified case of HA-CDI. Attributable mortality was provided from March 1st to April 30th each year. Whenever possible, frozen stool specimens from patients with laboratory confirmed HA-CDI were forwarded to the National Microbiology Laboratory (NML) for *C. difficile* isolation and molecular characterization. Stool specimens in adult patients 18 years of age and older with HA-CDI were submitted between March 1st and April 30th of each year whereas the stool specimens of children aged one year to less than 18 years were submitted year round to NML.

CDI in Canada

In 2008, the infection rate peaked at 5.8 cases per 1,000 patient admissions and 7.5 cases per 10,000 patient days. Since 2011, the rates have been slowly declining from 5.2 cases per 1,000 patient admissions to 3.4 in 2014. Similarly, since 2011, the infection rates per 10,000 patient days have fallen from 6.6 cases to 4.4 in 2014 (**Figure 1**).

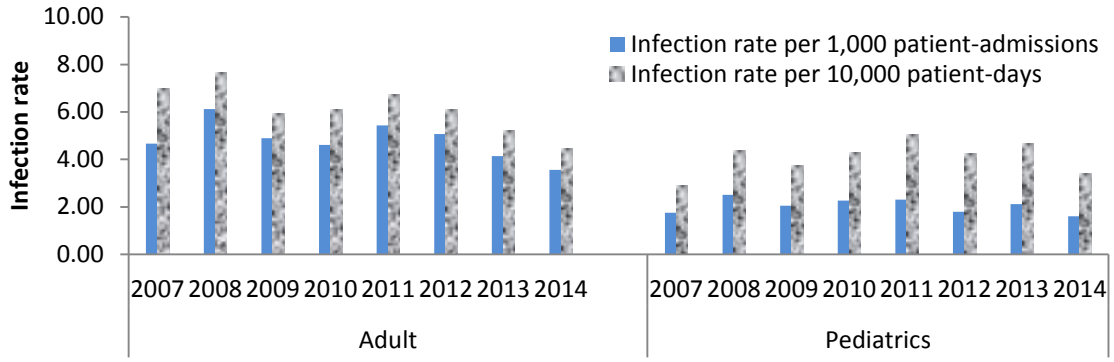
Figure 1: Healthcare-associated CDI national rates, 2007 to 2014



In 2014, mean age for adults (n= 2,599) was 68.1 years (range: 18 years to 102 years) and 51% (n = 1,324) were males. The mean age for the pediatric cases (n= 133) was 7.5 years (range: 1 year to 17 years) and 56% (n = 74) were males.

Adults continue to have higher reported rates than pediatric age groups[13]. Since 2011 the rates for adults appear to be declining whereas the pediatric rates appear to be relatively more stable (**Figure 2**)[14].

Figure 2: Healthcare-associated CDI rates, adults vs. pediatric cases, 2007 to 2014



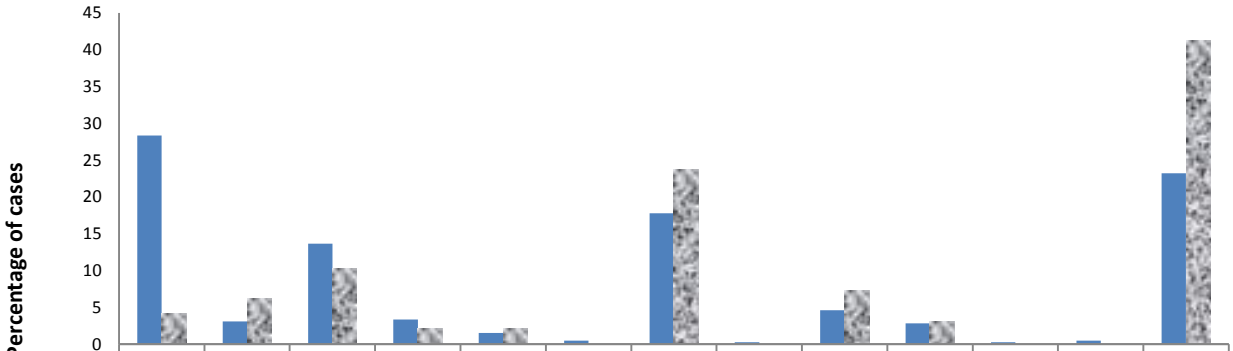
[13] Pediatric cases are defined as individuals >= 1 year and < 18 years of age.

[14] The reporting adult sites did include a small number of children cases as they were unable to separate the adult specific denominator from some of the 'mixed' hospitals (i.e.; Adult and pediatric patients). Denominator values used in the calculation of pediatric rates are based on data from pediatric centres only (9 in all) in 2014.

Data on outcomes, 30 days after the date of first positive *C. difficile* test, were available for 512 adult cases and 107 pediatric cases in 2014. Of the 512 adults, 11.9% (n = 61) were reported to have died. CDI was reported to have contributed to but was not the cause of death for 19 cases and CDI was the cause of death for 6 cases. The causal relationship between CDI and death was not known for 15 cases. For the remaining 21 cases, CDI was not related to the individual's death. For the 107 pediatric cases, there was one death and CDI was not related to that outcome.

In 2014, the results of strain typing were reported for 388 adult cases and 97 pediatric cases. For the adult cases, 28.4% of *C. difficile* strains were the North American Pulsed Field Type 1 (NAP1) strain whereas only 4.1% of the pediatric cases were strain type NAP1 where 23.7% of the pediatric cases were NAP4 (**Figure 3**).

Figure 3: HA-CDI strain types comparing adults and pediatric cases, 2014



	NAP1	NAP10	NAP11	NAP12	NAP2	NAP3	NAP4	NAP5	NAP6	NAP7	NAP8	NAP9	Unassigned
ADULTS	28.4	3.1	13.7	3.4	1.5	0.5	17.8	0.3	4.6	2.8	0.3	0.5	23.2
PEDIATRIC	4.1	6.2	10.3	2.1	2.1	0.0	23.7	0.0	7.2	3.1	0.0	0.0	41.2

Antibiogram results were available for 2,290 adult cases and 518 children diagnosed between 2007 and 2014. Susceptibility results were reported for the following antimicrobial agents: clindamycin, metronidazole, moxifloxacin, rifampin, tigecycline and vancomycin. For adults, between 2007 and 2014, no resistance to metronidazole or tigecycline was reported and one case was found to be non-susceptible to vancomycin. In 2009, 63.3% of adult cases were found to be resistant to moxifloxacin. Between 2009 and 2014, the percentage of cases found to be resistant has been slowly declining and by 2014, 34.3% of the reported cases were resistant to moxifloxacin. In 2009, 37.5% of the reported cases were resistant to clindamycin and resistance level fell to a low for the period of 13.4% of reported cases by 2012. However, in 2013, 30.7% of cases were found to be resistant to clindamycin and this went up to 41.3% again in 2014.

Compared with adults, resistance to clindamycin was reported more frequently among children. In 2009, 62% of reported cases were resistant and although there was a dramatic decline observed in 2010 to 13.5%, from 2011 to 2014 the proportion of cases showing resistance increased to 51.5%. In children, the proportion of cases resistant to moxifloxacin has been lower than in adults. In 2009, 14.3% of children were resistant to moxifloxacin. Between 2010 and 2012 the rate remained relative stable but in 2013, 5.0% of reported cases were resistant to moxifloxacin. In 2014 the proportion increased slightly to 5.2%.

International perspective

The lack of internationally-recognised standardized surveillance case definitions for CDI across countries hampers the interpretation of CDI epidemiology. In the United States, *C. difficile* surveillance is performed through two systems: the Emerging Infections Program (EIP) which is an active, population- and laboratory-based surveillance system across diverse United States (USA) geographic locations. The EIP started in 2009 and currently runs in 10 EIP sites with approximately 11.7 million people under surveillance. On the other hand; hospital data are collected through the National Healthcare Safety Network (NHSN) since 2013 (5).

Comparing Canadian and the United States CDI rates is somewhat difficult as the United States data are calculated with population estimates as opposed to the Canadian national rates that are reported in patient days. However, the declining rates reported in Canada were also seen in the United States. A 10% decrease in hospital-onset CDI (HO-CDI[15]) was reported between 2011 and 2013 in the United States (6). In 2010, the overall United States HA-CDI[16] rates ranged from 58.5 to 94.8/100,000 population across seven EIP sites (7). In 2011, the average reported rate across 10 sites was 92.8 cases/100,000 population (8). Also, the NAP1 strain was more prevalent in the HA-CDI than among community-associated infections (30.7% vs. 18.8%, P<0.001) in 2011 (8). Deaths related to *C. difficile* increased 400% between 2000 and 2007 in the United States. About half of CDI cases occur in people less than 65, yet more than 90% of deaths are reported in people ≥ 65 (9).

In England and Wales, voluntary surveillance for CDI has been conducted since 1990. National Health Service (NHS) acute trust mandatory reporting, in people aged ≥65 years, was introduced in January 2004. Since 2007, mandatory NHS acute trust surveillance was enhanced to include all patients ≥2 years and for all *C. difficile* infections. As per Public Health England, the overall mandatory "trust apportioned CDI"[17] rates have decreased between 2007-2008 (89.6 per 100,000 bed days) and 2014-2015 (15.1 per 100, 000 bed days). However, there has been a 2.9% increase between 2013-2014 (14.7 per 100,000 bed days) and 2014-2015. As seen in Canada and USA, there is a notable declining trend in the proportion of reported HO-CDI (≥3 days post-admission) from 78.8% in 2007-2008 to 57.4% in 2014-2015 in the United Kingdom (10).

[15] HO-CDI if the positive specimen was collected > 3 calendar days after hospital admission or in a long-term acute care hospital.

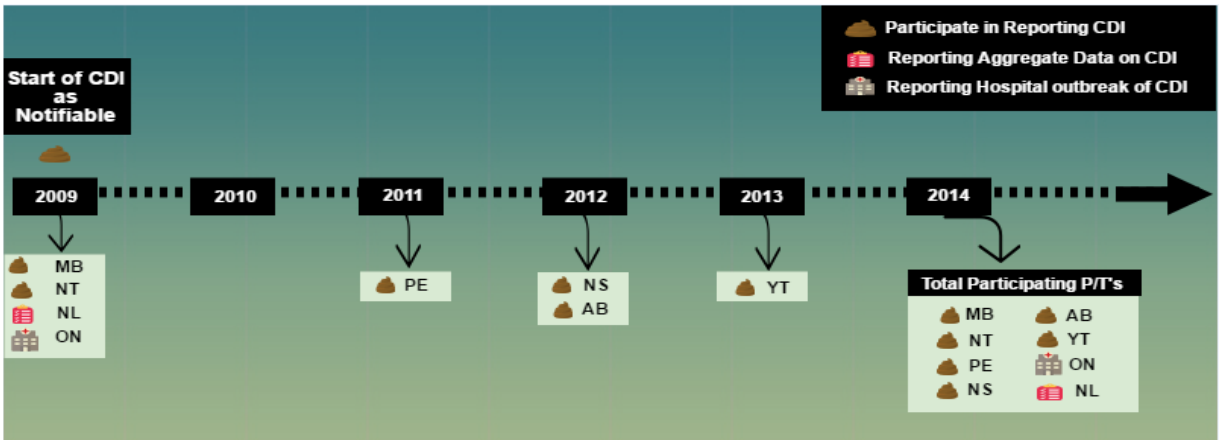
[16] HA- CDI: comprises HO-CDI, community-onset healthcare facility-associated CDI and nursing home onset CDI

[17] *Trust apportioned C. difficile*: Any NHS patient specimens taken on the fourth day of admission onwards (e.g. day four when day one equals day of admission) at an acute trust (including cases with unspecified specimen location) for inpatients, day-patients, emergency assessment, or unspecified patient category. Records with a missing admission date (where the specimen location is acute trust or missing and the patient category is inpatients, day-patients, emergency assessment, or unspecified) are also included.

Text Box 1: Canadian Notifiable Disease Surveillance System (CNDSS): *Clostridium difficile* Infection (CDI)

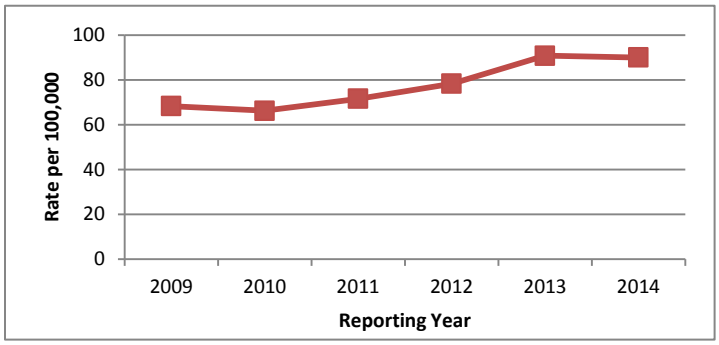
Nationally notifiable diseases are communicable diseases that have been identified by the federal government and all provinces and territories as priorities for monitoring and control efforts. The CNDSS collects notifiable disease data, which includes the count, age, sex and year, provided voluntarily by the provinces and territories (P/T). For certain diseases, the CNDSS has data that dates back to 1924. The information collected and managed by CNDSS is used as a benchmark and to identify trends of diseases at the national level and stratified by age group and sex. In 2009, CDI was included in the notifiable disease list; however, the participating P/T has increased over the years and chronology, as well as the current participating P/T can be viewed in Figure A.

Figure A: The Chronology of the participating Provinces and Territories in reporting CDI to CNDSS



Despite the increasing number of P/Ts participating in reporting CDI to CNDSS, as of 2013, only 6 P/Ts are included in the reporting of CDI at the national level. Ontario and Newfoundland are excluded in the CNDSS analysis as the reporting of CDI is not consistent with the remaining P/Ts. The figure below captures the rates of CDI from 2009 to 2014. Among the P/T reporting, CDI rates appear to be rising with a 32% increase from 2009 to 2014 (68.31 per 100,000 reported cases to 90.02 per 100,000 reported cases).

Figure B: CDI rate per 100,000 of reported cases of CDI in Canada from 2009 to 2014



NOTE: ON reports on hospital outbreaks only and NL reports aggregated data only. These data are not included here. CDI associated diarrhea was reported by MB and NT from 2009-2014, PE from 2011-2014, NS and AB from 2012-2014 and YT from 2013-2014.

Multidrug-resistant Enterobacteriaceae and *Acinetobacter*

Enterobacteriaceae are gram-negative bacilli (GNB) commonly encountered in both the healthcare settings and in the community; and include species such as *Escherichia coli*, *Klebsiella* species (spp.) and *Enterobacter* spp. These organisms are normal flora in the gastrointestinal tract in healthy humans (referred to as colonization), but can cause infections in vulnerable individuals, including urinary tract, respiratory, bloodstream, and wound infections. Enterobacteriaceae have mixed susceptibility to commonly-prescribed antimicrobials. One form of resistance occurs when GNB acquire the ability to produce extended-spectrum β-lactamases (ESBL), an enzyme class that renders it resistant to commonly-used extended-spectrum (third-generation) cephalosporins (e.g., ceftazidime, cefotaxime and ceftriaxone) as well as beta-lactam-lactamase inhibitor combinations (e.g., piperacillin-tazobactam, etc.) (11).

Another form of resistance involves the carbapenem group of antimicrobials which is a relatively safe and generally effective treatment for ESBL as well as other highly resistant gram-negative organisms and there are few alternative treatments available when resistance to carbapenem occurs. Enterobacteriaceae that have acquired resistance to carbapenems are called carbapenem-resistant Enterobacteriaceae (CRE). Some CRE are also carbapenemase-producing organisms (CPO) by virtue of their ability to produce enzymes, called carbapenemases, which break down carbapenems (11). There are other GNB outside of the Enterobacteriaceae family that have also shown resistance to carbapenems including *Acinetobacter* spp. and *Pseudomonas* spp.

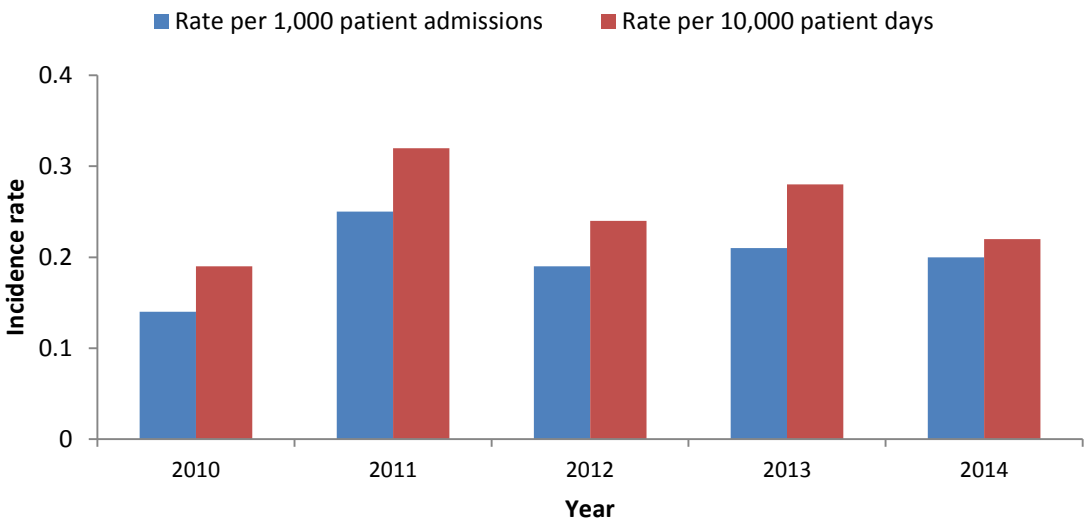
Methods

CNISP has been collecting data on CRE and CPO in hospitalized patients since 2010 (12). Participation in this surveillance has increased from 33 CNISP hospitals in 2010 to 58 CNISP hospitals in 2014. All CRE and CRA identified in the participating hospitals are submitted to NML for further testing. If an isolate was determined to be a carbapenemase producer by NML, a detailed patient questionnaire was completed. Detailed patient information included patient demographics, where the culture was obtained (urine, wound, etc.), travel history and whether or not the patient had died.

Carbapenem-resistant Enterobacteriaceae in Canada

Between 2010 and 2014, there were a total of 652 CRE cases collected from the CNISP sites. The CRE rate did not change significantly from 2010 (0.19 per 10,000 patient days) to 2014 (0.22 per 10,000 patient days); however, there were two high peaks in 2011 and 2013, in which the incidence rate nearly doubled from that of 2010 to reach an incidence rate of 0.32 per 10, 000 patient days in 2011 and 0.28 per 10,000 patient days in 2013 (**Figure 4**). The increase in both years was largely due to an ongoing outbreak at one individual hospital and was not reflective of a national trend.

Figure 4: National CRE incidence rates per 10,000 patient days and 1,000 admissions, 2010 to 2014



Carbapenemase-producing organisms in Canada

Between 2010 and 2014, CNISP hospitals reported a total of 301 CPO isolates, representing 273 individuals. Among those individuals, 25 (9.1%) harbored at least two CPOs. Nationally, the incidence of CPO has remained stable from 2010 (0.10 per 10,000 patient days) to 2014 (0.11 per 10,000 patient days) (**Figure 5**).

Figure 5: National CPO incidence rates per 10,000 patient days and 1,000 admissions, 2010 to 2014

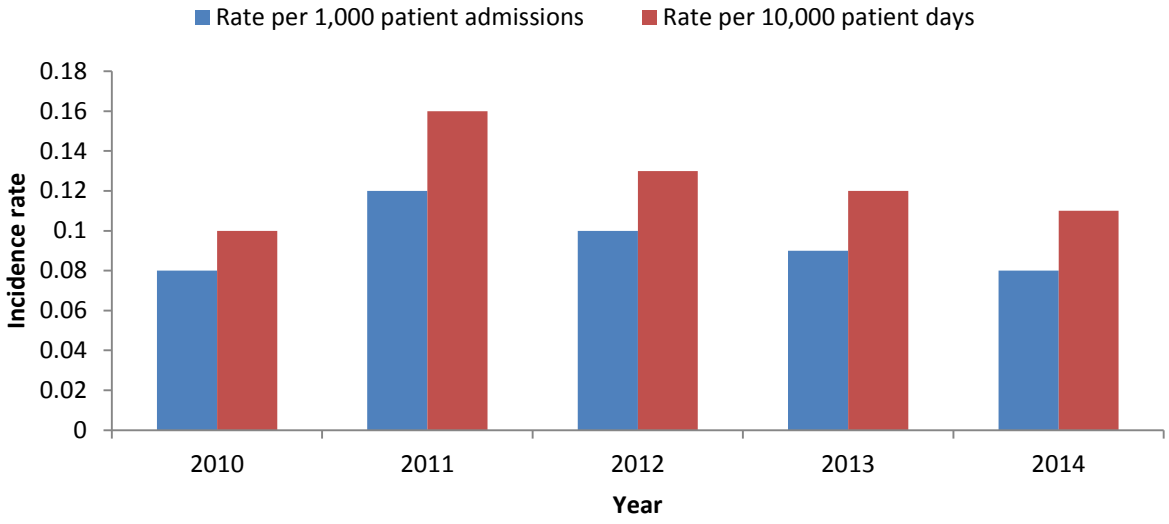
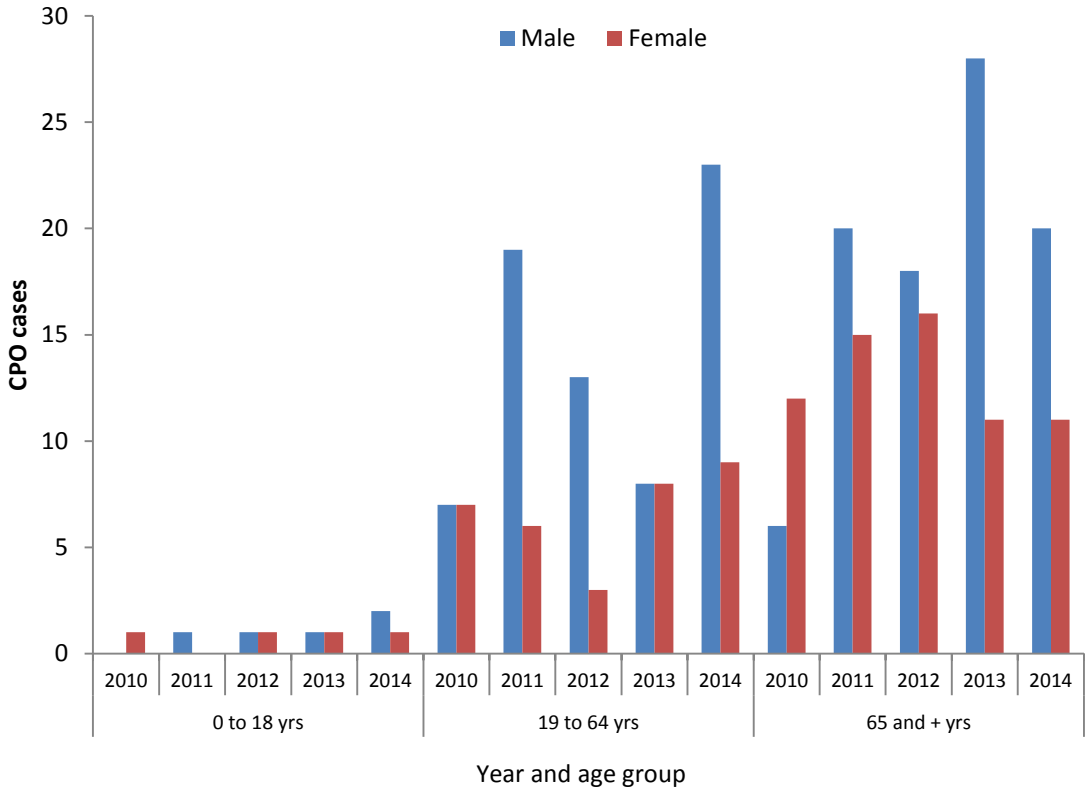


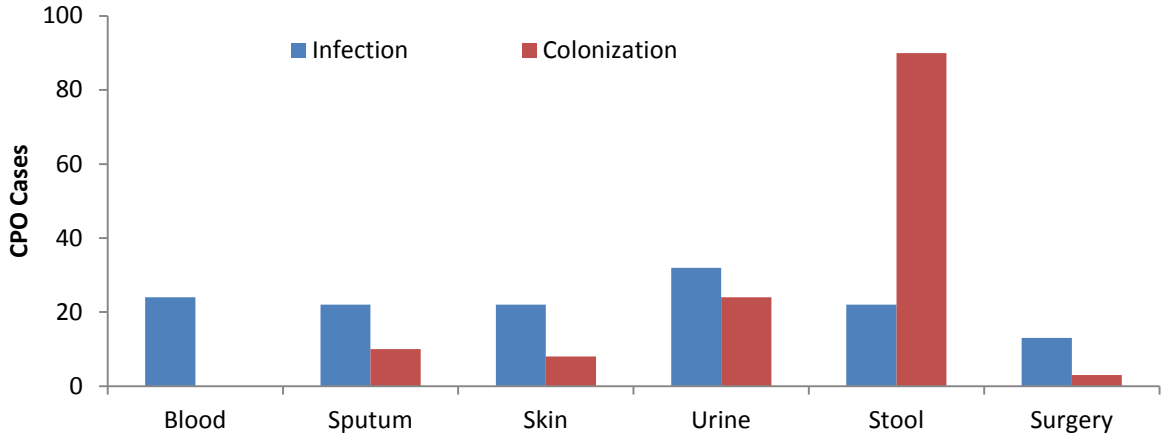
Figure 6 shows the distribution of reported CPO cases by gender and age over the 2010 to 2014 period for 269 individuals. Overall, males represented 62% of all cases (n=167) and individuals 65 and over (n=158) represented 58% of all CPO cases.

Figure 6: Total CPO cases by age group and sex, 2010 to 2014



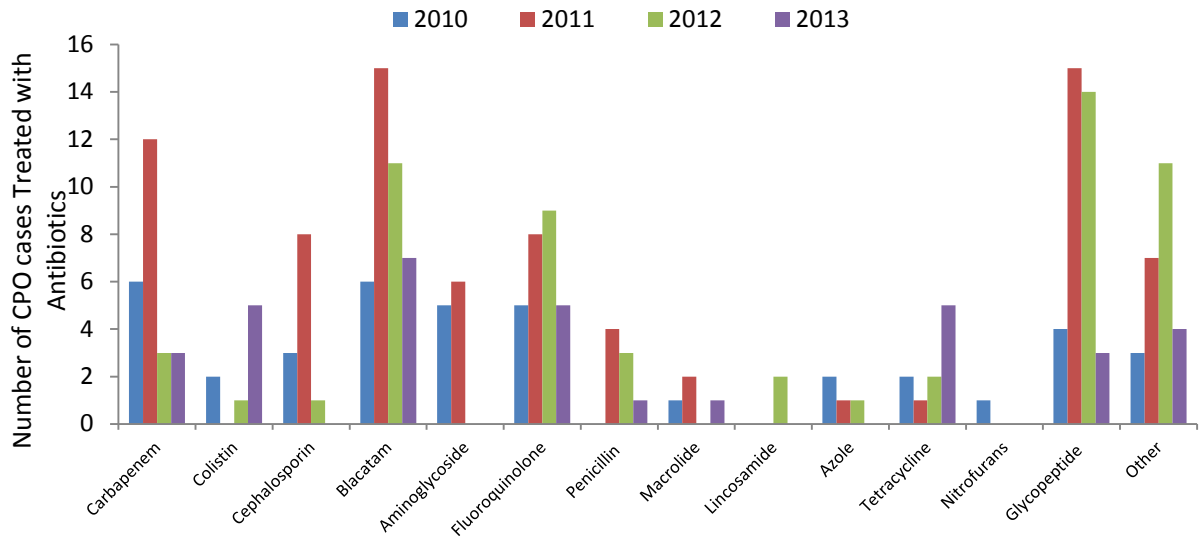
Among the 273 individuals harboring CPO's from 2010 to 2014, 105 (38.8%) were infections, 131 (48%) were in patients who harbored the bacteria without showing signs of infection (colonization) and the status was unknown for 38 (13.9%) cases. The majority of the reported CPO isolates was captured from rectal/stool swabs (n=91). Rectal and stool specimens represented 46% of all reported CPO cases which represents 22% of CPO infections and 69.5% of CPO-colonized cases. The highest number of CPO infections (n=106) were isolated in urine (n=72, 67%), followed by blood (n=24, 23%) then sputum, skin, stool and surgical sites (**Figure 7**).

Figure 7: The total colonized and infected CPO cases by infection sites, 2010 to 2014[18]



From 2010 to 2014 the proportion of patients who died at 30 days after the date of first positive CPO culture has remained relatively stable ranging from 15% in 2010 to 12% in 2014. Death is reported as 'all-cause mortality' and is not necessarily attributable to the CPO infection. Treatment data were available for 2010 to 2013 for 122 out of the 206 individuals harboring CPOs (59.2%). The most commonly-prescribed antimicrobials from 2010 to 2013 were *B*-lactams (32.0%) followed by glycopeptides (29.5%), fluoroquinolones (22.0%) and carbapenems (19.7%). In 2013, the use of colistin and tetracycline to treat CPO infections increased; whereas, the use of *B*-lactams and glycopeptides decreased from 2010 to 2013 (**Figure 8**). Collection of antimicrobial treatment data was discontinued in 2014.

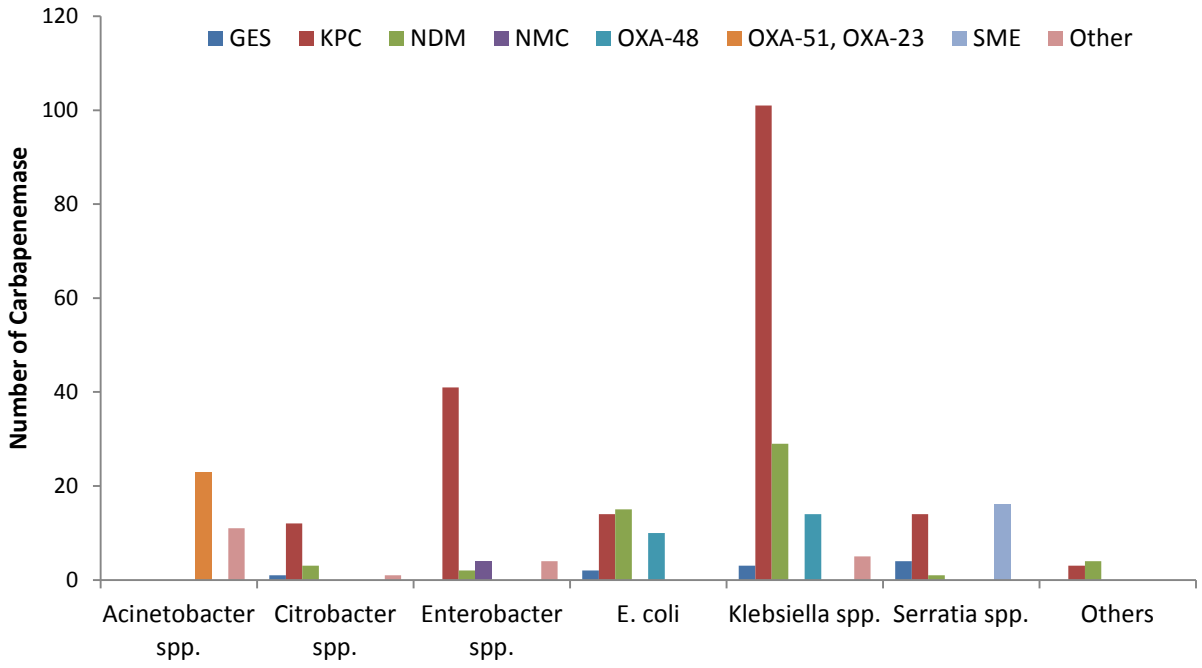
Figure 8: CPO patients treated with the following antimicrobials, 2010 to 2013



[18] Multiple infection sites can be reported for one patient and therefore the number of infection sites exceeds the number of patients identified as having a CPO infection or colonization.

A total of 303 isolates that tested positive for a carbapenemase gene (n=303) by both polymerase chain reaction (PCR) and Etest at the National Microbiology Laboratory (NML) were summarized in **Figure 9** based on the corresponding type of Enterobactericeae and *Acinetobacter* species. Certain carbapenemases are specific to certain genera. SME are exclusive to *Serratia* spp., to be more specific *Serratia marcescens* and OXA-51, OXA-23 unique to *Acinetobacter baumannii* and NMC to *Enterobacter cloacae*. This was further supported by the results of the lab data collected from 2010 to 2014, where SME was only identified in *Serratia* spp. OXA51-OXA 23 in *Acinetobacter* spp. and NMC in *Enterobacter* spp. *Klebsiella-pneumoniae* carbapenemase (KPC) carbapenemase-producing organisms expands to several genera such as *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia* and *E. coli*. (13, 14). It is dominant in *Klebsiella species* which is expected as it was originally assumed to be unique to *K. pneumoniae.* The GES enzymes are dominant in *Pseudomonas aeruginosa*; however, they have been observed in many other genera of the Enterobacteriaceae family including *Klebsiella*, *Citrobacter*, *Serratia* spp. and *E. coli* (13–15). In these isolates, the New Delhi metallo-beta-lactamase (NDM) and oxacillinase (OXA)-48 enzymes are most commonly found in *Klebsiella pneumoniae* and *E. coli*; however, since this gene can easily spread from one microorganism to another by horizontal gene transfer, it is also seen in other species (16).

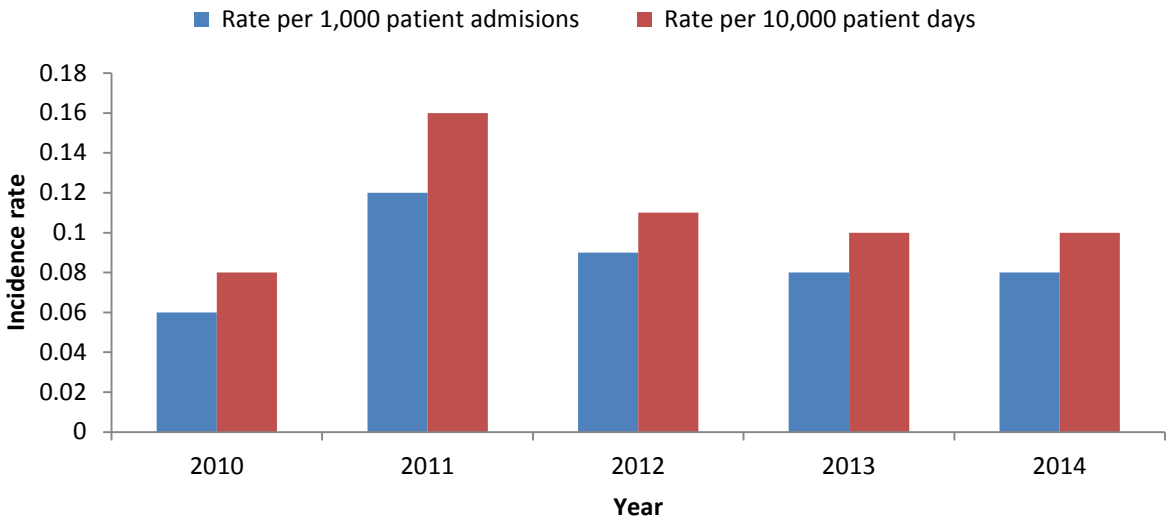
Figure 9: Distribution of the CPO harboring carbapenemase, 2010 to 2014



Carbapenemase-producing Enterobacteriaceae (CPE)

Between 2010 and 2014, CNISP reported on 270 isolates harboring CPE. The overall CPE rates have increased by approximately 33% from 2010 (0.06 per 1,000 patient admissions) to 2014 (0.08 per 1,000 patient admissions). However there was a high peak in 2011, in which the incidence rate doubled compared to 2010 (0.12 per 1,000 patient admissions) (**Figure 10**).

Figure 10: National CPE infection and colonization rates per 10,000 patient days and 1,000 patient admissions, 2010 to 2014



Text Box 2: Carbapenemase-producing Enterobacteriaceae (CPE) in Canada; The Canadian Public Health Laboratory Network (CPHLN) data

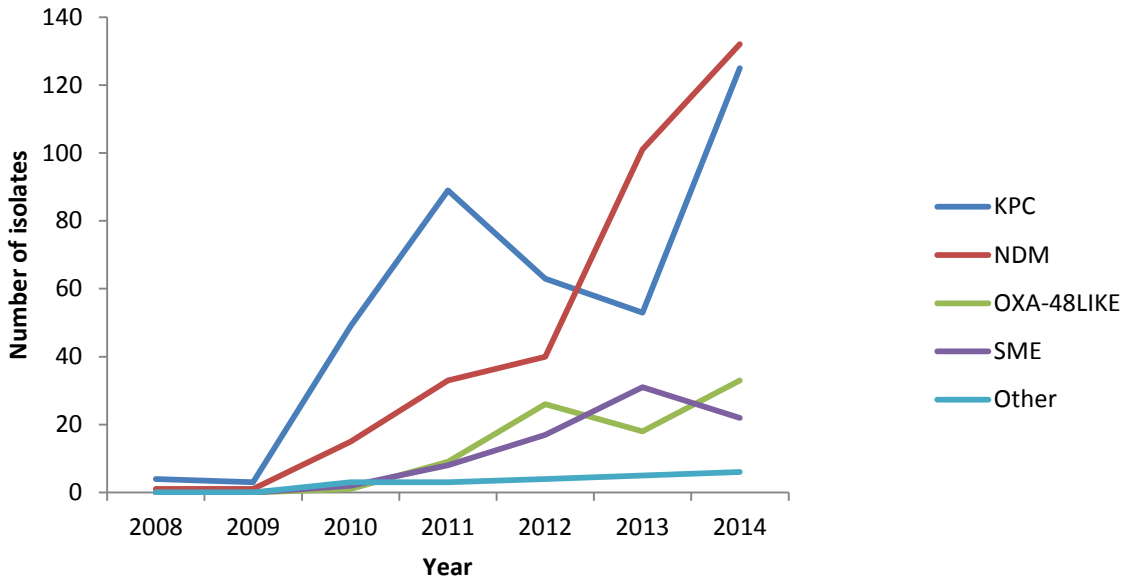
In 2013, the NML in collaboration with the Canadian Public Health Laboratory Network (CPHLN) began voluntary reporting of non-duplicate carbapenemase-producing Enterobacteriaceae (CPE) at six-month intervals to better understand the emergence of CPE in Canada. Provinces which had their own testing for the major carbapenemases (British Columbia, Ontario, and Quebec) submitted total numbers of CPE identified, whereas the NML provided the testing data for the other provinces along with some additional data for Quebec and British Columbia.

Limitations for this reporting included the possibility of underreporting of CPE as it is not reportable in most provinces. The dataset represents patient colonizations and infections and the increased numbers could be a result of increased screening at healthcare sites. SME was reported for Ontario from 2013 onwards and the Quebec data represent reporting from 2010 onward.

Between 2008 and 2014, a total of 897 CPE isolates have been reported, and in general the numbers of CPE reported by the provinces have doubled every two years. In 2014, the number of NDM and KPC has been almost equally reported and represent the most common CPEs in Canada. Since 2013 we have observed an increase in reports of OXA-48 isolates from 18 to 33 isolates in 2014. It is also interesting to note the elevated numbers of SME carbapenemases identified from *Serratia marcescens*, which seem to be unique for Canada.

CPE are a growing concern globally as many of these isolates display a multidrug resistance phenotype with some isolates pan-resistant. This phenotype severely limits treatment options for infections. Continued timely reporting of these isolates in Canada by the CPHLN will continue to provide baseline information on CPE in Canada.

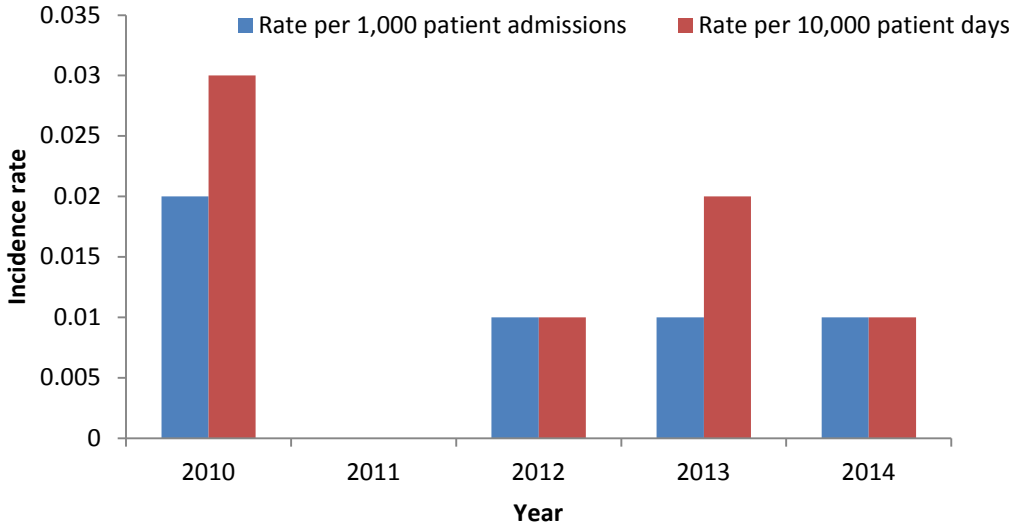
Figure A: Carbapenemase-producing Enterobacteriaceae (CPE) in Canada: the Canadian Public Health Laboratory Network (CPHLN) data, 2008 to 2014



Carbapenemase-producing *Acinetobacter* (CPA)

Between 2010 and 2014, CNISP reported on 31 isolates harboring CPA. Following a peak in CPA incidence rates in 2010 (0.02 per 1,000 patient admissions, 0.03 per 10,000 patient days), the overall CPA rates per 1,000 patient admissions remained stable since 2012 (0.01 per 1,000 patient admissions) (**Figure 11**).

Figure 11: National CPA infection and colonization rates per 10,000 patient days and 1,000 patient admissions, 2010 to 2014



Text Box 3: Emergence of *mcr-1* encoding colistin resistance in *E. coli* in Canada

A recent report from China indicated the detection of the *mcr-1* colistin resistance gene in *E. coli* and *K. pneumoniae* isolates from animal, food and human sources (a). These reports are of concern because colistin is one of the antibiotic choices of last resort for treating multidrug-resistant Gram-negative infections.

In Canada, screening for the *mcr-1* gene at PHAC's NML was initiated in December 2015, and to date, three *E. coli* isolates have been identified with the gene. One isolate (from 2011) was from a human case in Ontario who had previously lived in Egypt (b) and this isolate was also resistant to carbapenems (an OXA-48 producer). The other two isolates (from 2010) were found in retail ground beef samples purchased in Ontario through the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) and these isolates were also multidrug resistant.

The *mcr-1* gene has been added to the NML's routine platform of testing for surveillance and research isolates, including the prospective testing of isolates from the Canadian Nosocomial Infection Surveillance Program (CNISP), CIPARS, and laboratory reference work.

References

a) Liu, Y-Y, Wang, Y, Walsh, TR et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. Lancet Infect Dis 2015; 16(2):161–168. http://dx.doi.org/10.1016/S1473-3099(15)00424-7.

b) Ellis C, Chung C, Tijet N, et al. OXA-48-like Carbapenemase-producing Enterobacteriaceae in Ottawa, Canada. Diagn Microbiol Infect Dis 2013; 76: 399–400.

International perspective

Carbapenem resistance is under regular surveillance by the European Antimicrobial Resistance Surveillance Network (EARS-NET). AMR data are expressed as a percentage of resistant isolates out of all isolates with susceptibility information on carbapenem resistance for a specific pathogen. In Europe, between 2011 and 2014, carbapenem resistance significantly increased for *K. pneumoniae* (6.0% in 2011 to 7.3% in 2014), yet it remained relatively stable at 0.1% for *E. coli*. From 2011 until 2014, significantly increasing resistance trends to carbapenems were observed in seven countries (Bulgaria, Croatia, France, Germany, Italy, Portugal and Spain) for *K. pneumoniae*. Yet, in 2014, national resistance to carbapenem was 0.0 % in Estonia, Finland, Iceland, Norway and Sweden for *K. pneumoniae*. Also, no carbapenem resistance for *E. coli* was observed in Croatia, Cyprus, the Czech Republic, Estonia, Finland, Hungary, Iceland, Latvia, Lithuania, Malta, the Netherlands, Norway, Slovakia, Slovenia or Sweden. Resistance to a combination of antimicrobials including carbapenem remained low in *E. coli* (less than 0.1%) in 2014. On the other hand, approximately 5.7% of all *K. pneumoniae* isolates were resistant to the combination of fluoroquinolone, third-generation cephalosporins, aminoglycosides and carbapenem (17).

In 2015, the United States Centers for Disease Control and Prevention (US CDC) changed the CRE surveillance definition to include Enterobacteriaceae with resistance to carbapenem or those with carbapenemase production. Previous definition targeted carbapenemase-producing CRE and included resistance to carbapenems (excluding ertapenem) and third-generation cephalosporins (18). In 2013, the US CDC declared that the CRE threat level was urgent (immediate public health threat requiring aggressive intervention). In the United States, in the first half of 2012, at least one serious CRE case was found in 4% of the short-stay hospitals. On the other hand, 18% of the long-term acute-care hospitals had one case. Each year, almost 600 deaths result from carbapenem-resistant *Klebsiella* spp. and *E. coli* (the most common types of CRE in the United States. In 2012, 11% of *Klebsiella* spp. and 2% of *E. coli* were resistant to carbapenem in United States hospitals (9).

As per the EARS-NET 2014 report, carbapenem resistance in Europe was mediated by metallo-beta-lactamases (e.g., Verona integron-encoded metallo-β-lactamase and NDM enzymes) or serine-Carbapenemase (e.g., KPC enzymes) (17). It has been shown that CRE strains carrying plasmid-encoded carbapenemase enzymes like NDM and KPC have the ability to rapidly disseminate and therefore represent a public health concern (19). Additionally, OXA-48-like enzymes, a family with carbapenemase-like activity, have also been found to reduce carbapenem susceptibility (17). The latter family has shown great ability to spread and cause hospital outbreaks. This can be explained by the high-transfer efficiency of the plasmid-containing OXA-48-like genes.

In the United States, from 2010 to 2015, 52 CRE isolates (collected from 43 patients) produced OXA-48-like carbapenemase, *K. pneumoniae* isolates which accounted for 81% of patients followed by *E. coli* isolates (16% of patients) (19). In Europe, only three countries (Iceland, Montenegro and the former Yugoslav Republic of Macedonia) reported no CPE cases in 2013. Greece, Italy and Malta reported that CPE are regularly isolated from patients in most hospitals, corresponding to an endemic situation (20).

Methicillin-resistant *Staphylococcus aureus*

Staphylococcus aureus (*S. aureus*) is a common gram-positive bacterium normally found on the skin of healthy individuals. The bacteria can also be found in the interior of the nose and the groin region of healthy individuals without causing disease (colonization). *S. aureus* can cause a variety of infections, most notably in the skin and soft tissue, bone and bloodstream (BSI). *S. aureus* that have acquired resistance to β-lactam antimicrobials (e.g., penicillins such as oxacillin, methicillin and dicloxacillin) are called methicillin-resistant *Staphylococcus aureus* (MRSA) (21).

S. aureus, including MRSA is one of the most common causes of healthcare-associated infections in Canada and is spread from person to person through direct contact and by contact with contaminated surfaces. Initially, MRSA was found mainly in healthcare settings but over the past decade, community-associated MRSA (CA-MRSA) has been increasing in Canada, especially in certain populations (e.g., Indigenous peoples, homeless people and intravenous drug users). MRSA can cause serious infections such as BSI in the hospital setting, which can lead to death. In the community it causes mostly skin and soft tissue infections.

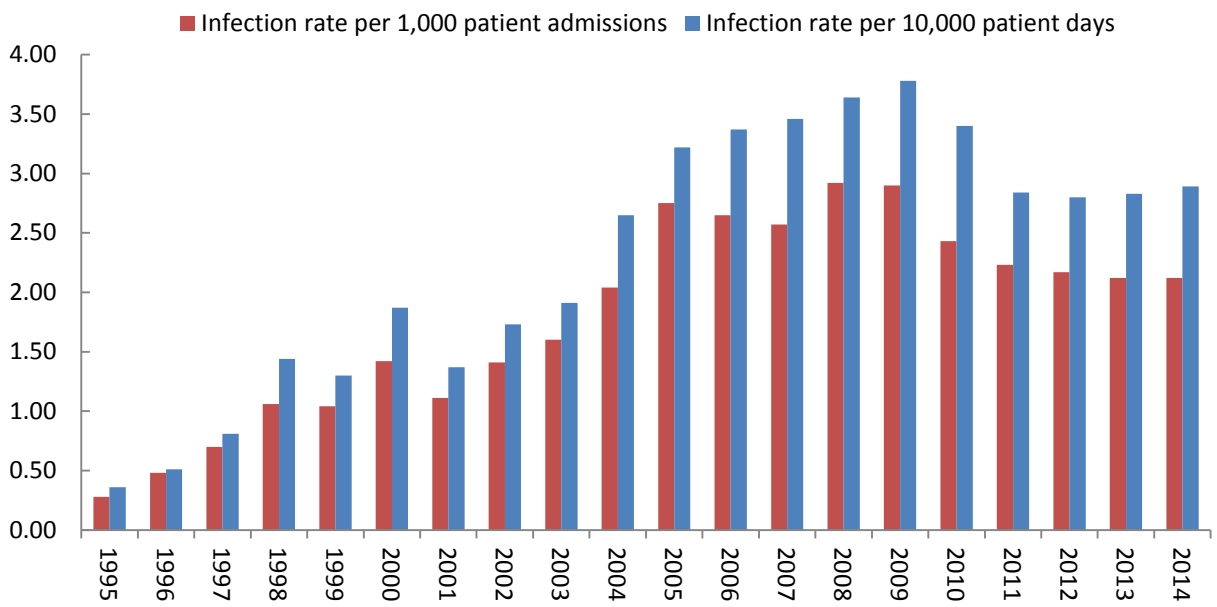
Methods

PHAC has collected information on MRSA infections in hospitalized patients through CNISP since 1995. Hospitals participating in CNISP report screening specimens, clinical isolates (anatomical sites other than blood) and blood isolates. Screening specimens represent colonized cases and are isolated from nose, perineal, groin, axillary or other screening sites. Colonizations are reported from each site as an aggregate number with information on where MRSA was acquired. Individuals from whom MRSA was recovered from a clinical isolate or a positive blood culture are classified as either a clinical infection or bacteremia respectively. Case information include demographics and clinical information, previous hospitalization within the past 12 months, site of positive culture, where MRSA was presumed to have been acquired (either in the community or in the hospital), and outcome within the first 30 days following positive identification of MRSA culture. One MRSA clinical isolate for each clinically infected case collected between January 1st and March 31st of each calendar year are sent by participating hospitals to NML for molecular testing. One blood isolate from cases occurring at any time during the surveillance year are also sent to the NML for molecular testing.

MRSA in Canada

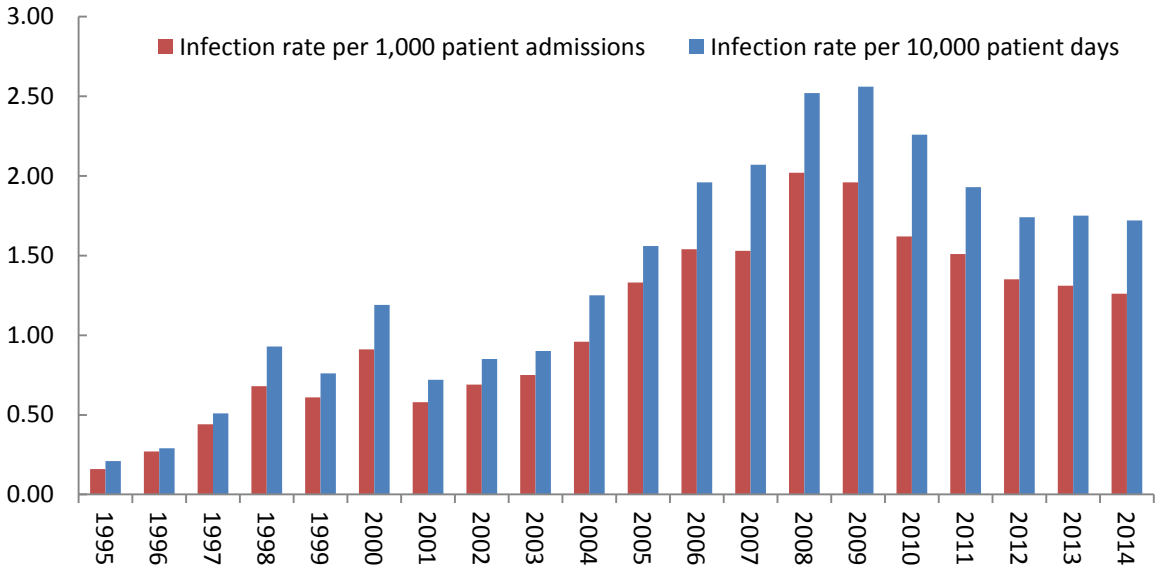
Data on MRSA infections in hospitalized patients presented here were reported to CNISP and were further classified into healthcare-associated (HA), community-associated (CA) and MRSA blood stream infections (BSI). In 2014, the rate of all MRSA infections in patients was 2.12 per 1,000 patient admissions and 2.89 per 10,000 patient days (**Figure 12**). Overall MRSA infection rates continued to rise from 1995 until 2008. Since 2008, there has been a decrease of approximately 25% in MRSA infection rates (2.92 per 1,000 patient admissions and 3.64 per 10,000 patient days in 2008).

Figure 12: National MRSA infection rates, 1995 to 2014



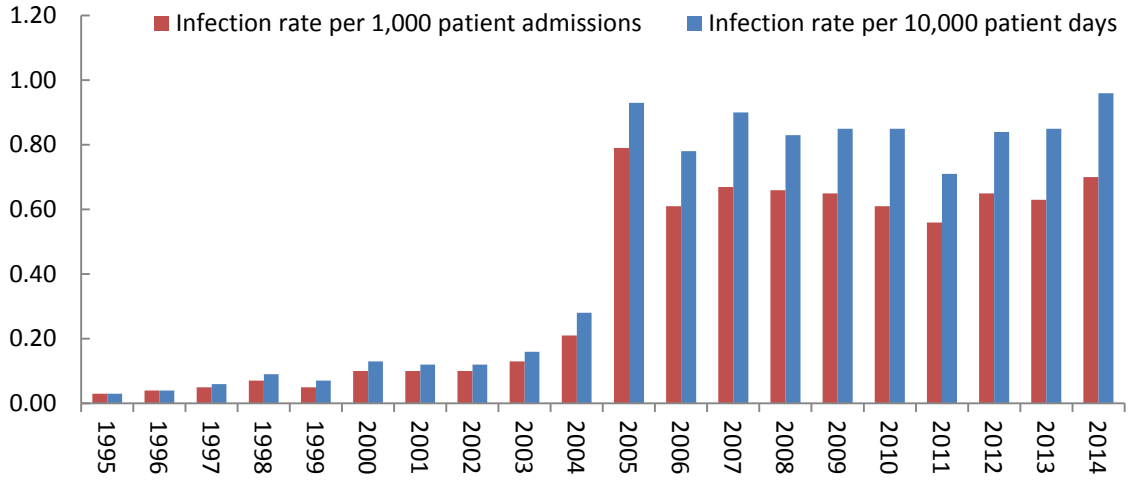
Since 2008, the most dramatic reduction seen in MRSA infection rates was among those infections identified as healthcare-associated. HA-MRSA infection rates continued to rise from 1995 until about 2008; however, since 2008 there has been approximately a 30% decrease in HA-MRSA infections rates. In 2008, HA-MRSA infection rates were 2.02 per 1,000 patient admissions and 2.52 per 10,000 patient days in 2008 and in 2014 were 1.26 per 1,000 patient admissions and 1.72 per 10,000 patient days respectively (**Figure 13**).

Figure 13: National HA-MRSA infection rates, 1995 to 2014



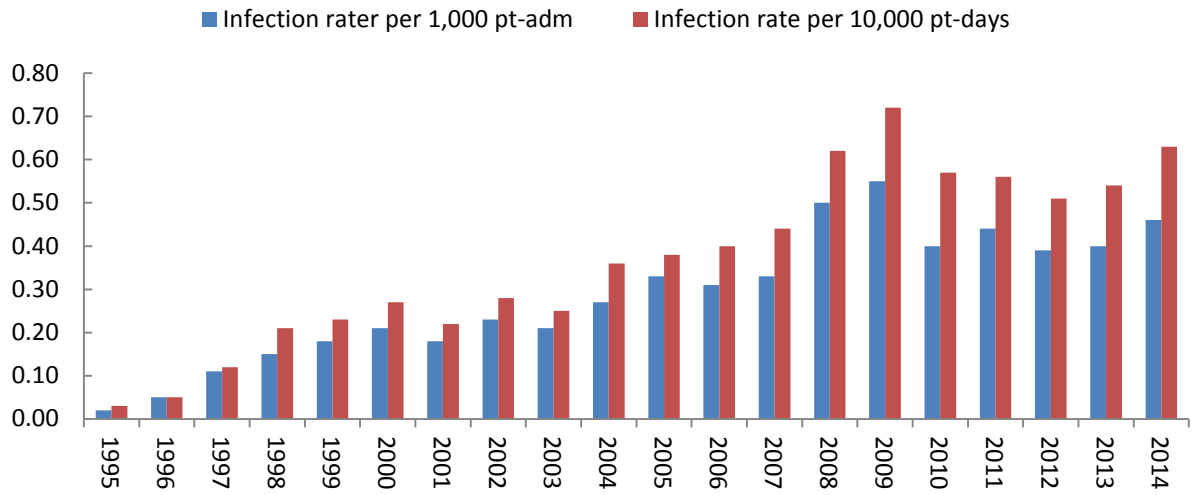
CA-MRSA infection rates remained relatively low until 2005 when a dramatic increase (greater than 400%) was observed. In 2004, CA-MRSA rates were 0.21 per 1,000 patient admissions and 0.28 per 10,000 patient days and in 2005 they were 0.79 and 0.93 respectively. However, since 2005 CA-MRSA infection rates have remained relatively consistent (**Figure 14**).

Figure 14: National CA-MRSA infection rates, 1995 to 2014



National trends of MRSA-BSI infection from 1995 to 2014 saw rates slowly increasing until 2009. Since then MRSA-BSI rates have remained relatively stable (**Figure 15**).

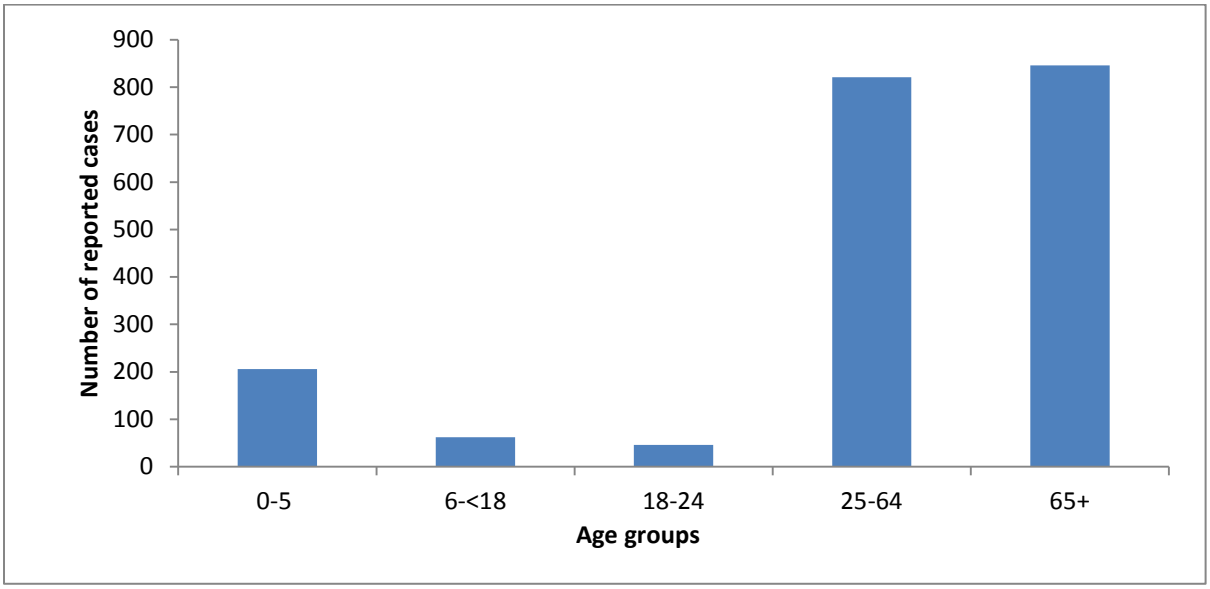
Figure 15: National MRSA-BSI infection rates, 1995 to 2014



In 2014, 444 (22%) of MRSA infections were from blood and 1,537 (78%) were from clinical sources other than blood. Skin and soft tissue infections (SSTI) represented the largest proportion (728, 43%) of MRSA infections, followed by surgical site (214, 37%), and respiratory (297, 15%) identified from clinical sources other than blood—37% when blood isolates were included.

The majority of cases were seen in those ≥ 25 years. Males with MRSA infections represented 59% of all cases. (**Figure 16**)

Figure 16: Age of patients with MRSA infection, 2014



Among the patients with reported MRSA infections, 80% of all hospitalized patients with reported MRSA infections in 2014 survived; whereas, only 10% of the patients had died at 30 days following diagnosis. However, of those patients identified as having a MRSA-BSI, 23% had died at 30 days following diagnosis with MRSA-BSI compared to only 6% of those with a clinical (non-blood) infection. Death is reported as 'all-cause mortality' and not necessarily attributable to the MRSA infection. Therefore, it is not known whether the deaths observed were directly related to their MRSA infection.

Table 1 describes MRSA epidemic strain types identified from blood and clinical non-blood isolates submitted annually for cases with a clinical/blood MRSA infection. Three strain types, CMRSA-2, CMRSA-10 and CMRSA-7 together accounted for almost 90% of all strain types identified over the seven-year surveillance period. CMRSA-2 (corresponds to USA100/800) is most commonly attributed as a healthcare-associated genotype while CMRSA-7 (corresponds to USA400) and CMRSA-10 (corresponds to USA300) are attributed to community-associated genotypes. Between 2008 and 2014, CMRSA-2, the strain type most typically associated with hospital settings, remains the most predominant strain type identified nationally in both clinical and blood isolates followed by CMRSA-10 and CMRSA-7, the two strain types most commonly associated with community settings. In both clinical and blood isolates the proportion of CMRSA-10 has been steadily increasing since 2008.

Table 1: The three most common MRSA epidemic strain types identified in clinical and blood MRSA infections, 2008 to 2014

Strain type	Blood infections							Clinical non-blood Infections						
	2008 (%)	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)
CMRSA-2 (USA100/800)	127 (53.8)	163 (58.6)	165 (58.9)	157 (54.7)	123 (50.2)	133 (46.7)	162 (49.2)	218 (53.2)	173 (52.6)	197 (54.1)	160 (54.4)	149 (51.2)	145 (47.9)	128 (38.6)
CMRSA-7 (USA400)	15 (6.4)	6 (2.2)	7 (2.5)	16 (5.6)	7 (2.9)	15 (5.3)	17 (5.2)	29 (7.1)	15 (4.6)	22 (6.0)	25 (8.5)	21 (7.2)	10 (3.3)	23 (6.9)
CMRSA-10 (USA300)	63 (26.7)	79 (28.4)	72 (25.7)	84 (29.3)	89 (36.3)	101 (35.4)	110 (33.4)	112 (27.3)	99 (30.1)	109 (29.9)	80 (27.2)	90 (30.9)	113 (37.3)	137 (41.3)

Although intravenous vancomycin is one of the primary antimicrobials recommended for treatment of MRSA, both linezolid (IV and oral) and daptomycin (IV) are used within Canadian healthcare settings. Other antimicrobials that are treatment options for specific sites of MRSA infections include: telavancin (intravenous [IV]) for SSTIs, doxycycline for SSTIs, Trimethoprim-sulfamethoxazole (TMP-SMX) (IV) as well as clindamycin (IV and oral) for treating SSTIs and pneumonia (22).

In rare cases, *S. aureus* may become resistant to vancomycin, the antimicrobial most frequently used to treat serious MRSA infections. This leaves few treatment options available as vancomycin-resistant *S. aureus* (VRSA) identified to date were also resistant to oxacillin and other classes of antimicrobials. Although VRSA has been identified in the United States and the United Kingdom, there have been no identified cases in Canada to date (23). There have also been no documented resistance to tigecycline, linezolid or daptomycin in the CNISP isolates tested from 2008 to 2013. The proportion of tested MRSA isolates across Canada that were resistant to ciprofloxacin, erythromycin and clindamycin has remained

relatively unchanged over this period (Table 2). There has been a slight decrease in the proportion of tested isolates that were resistant to tetracycline and TMP-SMX.

Antimicrobial susceptibility patterns can vary widely by geographical region. In Canada, resistance in MRSA to ciprofloxacin, erythromycin and clindamycin is slightly higher in the eastern regions, while resistance to tetracycline and TMP-SMX is lower in the east compared to the rest of Canada (24).

Table 2: Antimicrobial resistance of MRSA isolates (clinical and blood), 2008 to 2013

Antimicrobial	Clinical Isolates						Blood Isolates					
	2008 (N=376) (%)	2009 (N=312) (%)	2010 (N=631) (%)	2011 (N=288) (%)	2012 (N=274) (%)	2013 (N=298) (%)	2008 (N=234) (%)	2009 (N=241) (%)	2010 (N=277) (%)	2011 (N=249) (%)	2012 (N=236) (%)	2013 (N=260) (%)
Clindamycin	241 (64.1)	146 (46.8)	223 (61.8)	180 (62.5)	150 (54.7)	178 (59.7)	152 (65.0)	109 (45.2)	188 (67.9)	163 (65.5)	137 (58.1)	103 (39.6)
Erythromycin	324 (86.2)	279 (89.4)	306 (84.8)	240 (83.3)	221 (80.7)	268 (89.9)	197 (84.2)	217 (90.0)	246 (88.8)	226 (90.8)	207 (87.7)	228 (87.7)
Ciprofloxacin	324 (86.2)	278 (89.1)	309 (85.6)	249 (86.5)	223 (81.4)	257 (86.2)	196 (83.8)	223 (92.5)	249 (89.9)	217 (87.1)	202 (85.6)	222 (85.4)
Fusidic Acid	16 (4.3)	16 (5.1)	31 (8.6)	19 (6.6)	17 (6.2)	27 (9.1)	19 (8.1)	14 (5.8)	21 (7.6)	14 (5.6)	13 (5.5)	30 (11.5)
Gentamicin	28 (7.4)	22 (7.1)	11 (3.0)	13 (4.5)	6 (2.2)	16 (5.4)	16 (6.8)	6 (2.5)	11 (4.0)	5 (2.0)	2 (0.8)	12 (4.6)
Mupirocin	48 (12.8)	22 (7.1)	34 (9.4)	31 (10.8)	29 (10.6)	17 (5.7)	23 (9.8)	18 (7.5)	19 (6.9)	30 (12.0)	15 (6.4)	12 (4.6)
Tetracycline	30 (8.0)	20 (6.4)	17 (4.7)	7 (2.4)	7 (2.6)	12 (4.0)	22 (9.4)	9 (3.7)	13 (4.7)	13 (5.2)	12 (5.1)	13 (5.0)

International perspective

In the United States, invasive MRSA infections are monitored through the EIP which is an active, population- and laboratory-based surveillance system across diverse United States geographic locations in addition to NHSN which collects hospital data (25). The United States rates are reported using population estimates unlike Canada's rates that are reported in hospital patient admissions and patient days.

Comparing the Canadian MRSA rates to those in the United States is difficult due to use of different methodologies; however, the overall declining trend noticed in Canada has also been reported in the United States. The healthcare-associated[19] United States MRSA rates (both hospital and community onset) dropped by 32.5 % from 2007 to 2008 (27.1 cases per 100,000 population) until 2013 (18.3 cases per 100,000 population) (26). For MRSA bacteremia, the Canadian MRSA-BSI has remained relatively stable since 2009, whereas, MRSA-BSI were reduced by 73% from 2001 to 2009 in intensive care unit (ICU) patients with central lines in the United States (27). Also, an overall 8% decrease in the United States hospital-onset MRSA bacteremia was reported between 2011 and 2013 (28).

In contrast to Canada and the United States, MRSA cases have been increasing elsewhere. In Denmark, for example, the highest reported rate for new MRSA cases[20] was in the year 2014 (52.7 per 100,000 population). The number of new MRSA cases in 2014 (n=2,965) represented a 42% increase compared to 2013 (n=2,092) and was as five times as in 2007 (n=663). In 2014, MRSA bacteremia in Denmark comprised 2.9 % out of all *S. aureus* bacteremia increasing from 1.7% in 2013. It is of note that Denmark reports on MRSA bacteremia only (blood isolates only), this has been voluntarily up until 2006 (29).

In Denmark, the highest proportions of drug resistance were seen in penicillin (77%), fusidic acid (15%), erythromycin (8%), clindamycin (8%) and norfloxacin (6%) in 2014. Additionally, between 2005 and 2014, resistance to erythromycin (5% to 8%), clindamycin (4% to 8%), fusidic acid (10% to 15%) and norfloxacin (3% to 6%) has increased (29). On the other hand, in Canada, the top four drugs to which resistance was reported from MRSA blood isolates were cefoxitin (99.6%), erythromycin (87.7%), ciprofloxacin (85.4%) and clindamycin (39.6%) in 2013. Also, resistance to *S. aureus* bacteremia has increased for ciprofloxacin, erythromycin and fusidic acid from 83.8%, 84.2% and 8.1% in 2008 to 85.4%, 87.7% and 11.5% in 2013 respectively. Resistance to clindamycin has decreased from 65% to 39.6% within the same time period. Resistance to linezolid was not seen across the surveillance periods in either country.

[19] ABCs invasive MRSA epidemiological classification: isolation of MRSA from a normally sterile site. MRSA cases are classified to either: 1- Hospital-onset (HO): MRSA culture was obtained ≥ day 4 of hospitalization, where admission is hospital day 1.
2- Healthcare-associated community-onset (HACO) if the culture was obtained in an outpatient setting or before the fourth calendar day of hospitalization and had one of more of the following: A) a history of hospitalization, surgery, dialysis, or residence in a long-term care facility in the previous year, or B) the presence of a central vascular catheter (CVC) within two days prior to MRSA culture healthcare-associated cases comprise both HO and HACO.
3- Community-associated (CA) if none of the previously mentioned criteria are met.
HCA: Healthcare-associated invasive MRSA infection; sum of patients that are classified as either the HO or HACO classes.

[20] New MRSA case: Any person found positive for MRSA strain for the first time (either infected or colonized).

Vancomycin-resistant Enterococci

Enterococci are part of the normal intestinal flora of both humans and animals, but may also cause a range of illnesses. Many infecting strains originate from the patient's intestinal flora. From here, they can spread and most commonly cause urinary tract infections (UTIs), BSIs, intra-abdominal infections and surgical wound infections in hospitalized patients. *Enterococcus faecalis* (*E. faecalis)* and *Enterococcus faecium (E. faecium)* are the most prevalent species cultured from humans, accounting for more than 90% of clinical isolates (30).

The naturally high level of antimicrobial resistance found in Enterococci makes infections difficult to treat (29). The acquisition of vancomycin resistance by Enterococci has affected treatment options and fueled debate regarding screening and infection control practices for this organism (31,32). VRE, particularly *E. faecium* strains, are frequently resistant to all or a majority of antibiotics that are typically effective treatment for vancomycin-susceptible Enterococci. This leaves clinicians treating VRE infections with limited therapeutic options.

Methods

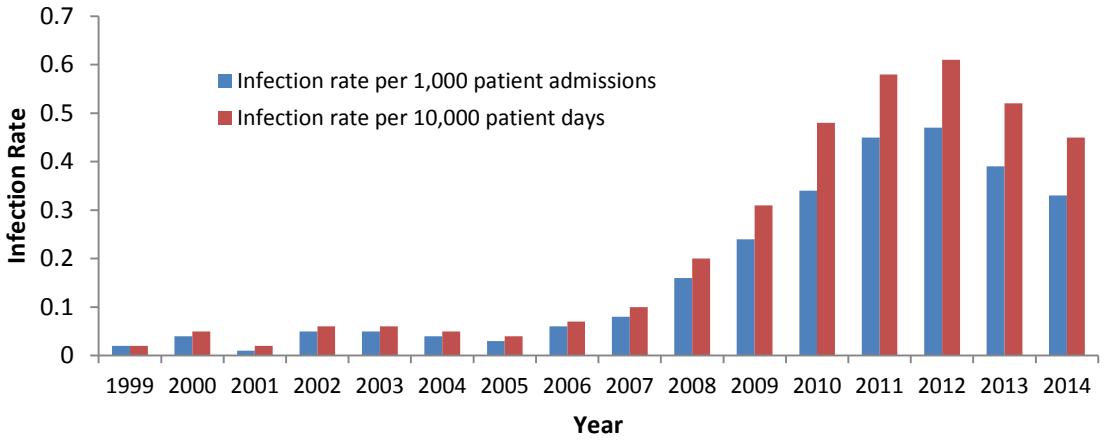
PHAC has been collecting information on hospitalized patients with VRE[21] through CNISP since 1999. Infection Control Professionals complete a standardized patient questionnaire through concurrent or retrospective chart review once a VRE is identified by the hospital laboratory. The questionnaire includes patient demographics and clinical information, previous hospitalization within the past 12 months, site of positive culture, where VRE was presumed to have been acquired (community or hospital), and whether the patient had concurrent infection with methicillin-resistant *Staphylococcus aureus* (MRSA). All specimens of VRE infected cases are sent by participating hospitals to NML for molecular testing. Polymerase chain reaction (PCR) was used to determine the presence of vancomycin resistant genes *van A, B, C, D, E, G* and *L.* Multilocus sequence typing and broth microdilution using Gram-Positive Sensititre panels were completed only for bloodstream infection specimens to determine genetic relatedness and antimicrobial susceptibility, respectively.

VRE in Canada

Between 1999 and 2007, the infection rates of VRE remained relatively stable at 0.10 cases per 10,000 patient days. Between 2008 and 2012, the rates began a steady increase, reaching a peak of 0.61 cases per 10,000 patient days in 2012. In 2014, the rate settled back to 0.45 cases per 10,000 patient days (**Figure 17**).

[21] For a full explanation of the Canadian Nosocomial Infection Surveillance Program refer to: Public Health Agency of Canada. *Vancomycin-resistant enterococci infections in Canadian acute-care hospitals: Surveillance report January 1, 1999 to December 31, 2011*. Ottawa ON: Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada; 2013.

Figure 17: Incidence rates of vancomycin-resistant *Enterococcus* infections per 1,000 patient admissions and per 10,000 patient days, 1999 to 2014

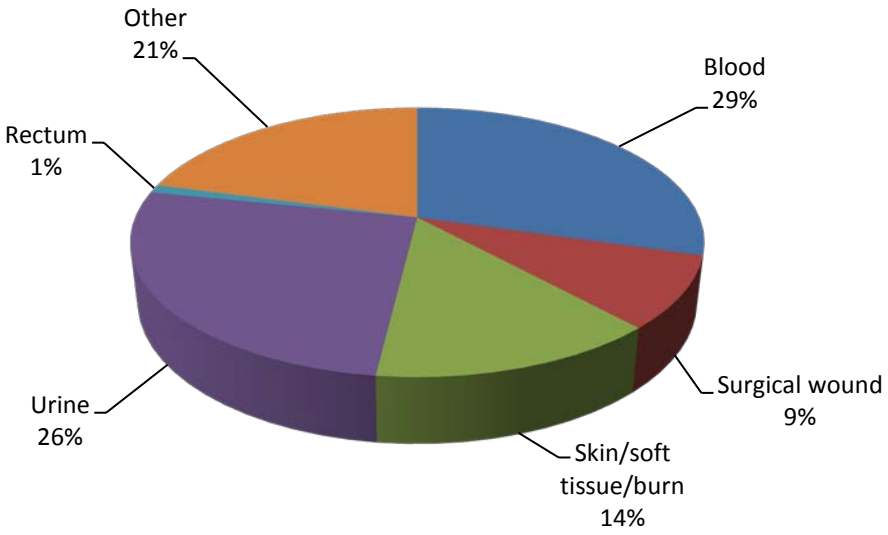


In 2014, 54 hospitals reported a total of 294 VRE infections to PHAC for an infection rate of 0.45 per 10,000 patient days. The molecular characterization of the infecting organism was known for 60% (n = 175) of the reported cases and of these 175 cases, 99% (n = 173) were *E. faecium* and 1% (n=2) were *E. faecalis*. *Van A* was the predominant gene identified in 98% (n=172) of the VRE infections.

Of the 294 reported cases, 85% were healthcare-associated within the reporting hospital. The remaining 15% were distributed between, healthcare-associated - any other healthcare facility/setting (outside of the reporting hospital), community-associated and unknown**.**

Figure 18 identifies the site of VRE infection for cases reported in 2014. It shows that BSIs were the most frequently-reported site, followed closely by infections identified in urine. Previously reported data indicate that VRE BSI rates are slowly increasing over time.

Figure 18: Site of VRE infections for diagnosed cases, 2014



In 2014, VRE was recovered from multiple sites for 16 cases. Blood in combination with another site was the most common presentation for individuals infected at two or more sites. Of the cases of reported VRE, 52% percent (n=153) of the reported cases were over the age of 65 and 1% (n=3) was less than 19 years of age. Males accounted for 52% (n=152) of reported VRE infections.

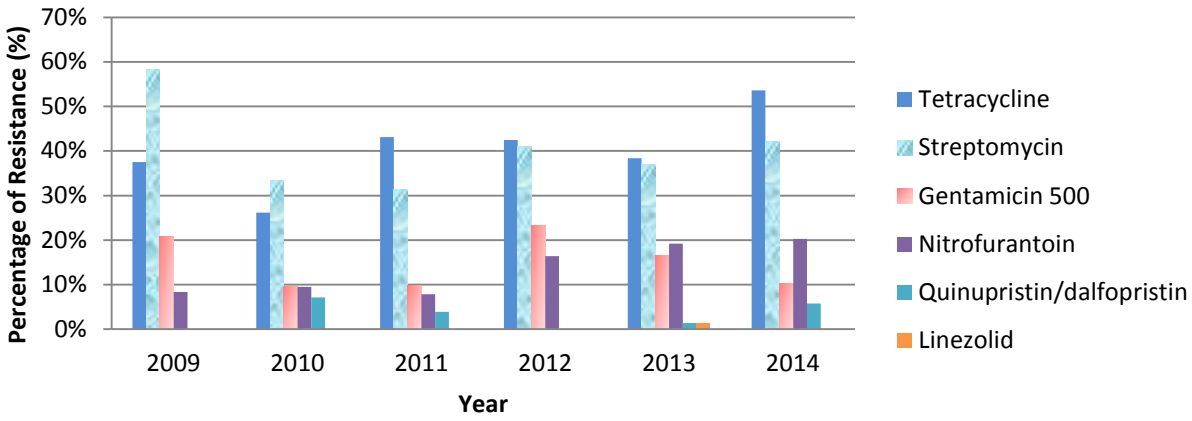
Susceptibility results for 12 antimicrobial agents were available for 368 cases diagnosed with VRE BSI between 2009 and 2014 (**Figure 19**). The agents reported include: ampicillin, ciprofloxacin, erythromycin, gentamicin 500, levofloxacin, linezolid, nitrofurantoin, penicillin, quinupristin/dalfopristin, rifampin, high-level streptomycin and tetracycline.

Of the cases tested between 2009 and 2014, nearly all were resistant to ampicillin, ciprofloxacin, erythromycin, levofloxacin and penicillin. The proportion of cases exhibiting resistance to these antibiotics has remained stable over the surveillance period. Between 2009 and 2013, resistance to rifampin has been slowly increasing; however, the proportion fell from 95% in 2013 to 78% 2014. Since 2011, resistance to nitrofurantoin has also been steadily increasing from 8% of cases in 2011 to 20% in 2014.

Between 2009 and 2010, there was a noticeable decrease in the proportion of cases exhibiting resistance to streptomycin, however, since 2010, resistance has remained consistent. Resistance to tetracycline has fluctuated between 38% of cases to 54% of cases over the surveillance period. Gentamicin 500 resistance peaked in 2012 with 23% of tested cases exhibiting resistance, however by 2014, the proportion fell to 10%.

Only a few cases were found to be resistant to linezolid and quinupristin/dalfopristin between 2009 and 2014. Out of the 368 cases tested for resistance, one was determined to be resistant to linezolid and ten were resistant to quinupristin/dalfopristin.

Figure 19: Proportion of VRE BSI cases resistant to the specific antimicrobials, 2009 to 2014



For 2014, outcome at 30 days following the date of positive blood culture was unknown or the information was not provided for 3% (n= 2) of VRE BSI cases. Of the remaining 62 cases for which data were available, 36% (n=23) of patients were still alive and in hospital and 34% (n=22) had been discharged or transferred at 30 days follow-up. Twenty-seven percent (n = 17) of VRE BSIs reported to CNISP in 2014 died.

International perspective

Since the first description of VRE in a clinical isolate in Europe in 1988, VRE are increasing in prevalence worldwide. According to the National Healthcare Safety Network from 2009 to 2010, 35.5% of enterococcal hospital-associated infections were resistant to vancomycin, ranking as the second most common cause of nosocomial infections in the United States (33). Each year, around 20,000 VRE cases are reported among inpatients and result in approximately 1,300 deaths (9).

In 2012, a majority of European countries reported vancomycin resistance in *E. faecium* below 5%, whereas only few countries reported estimates above 10% (34). As per EARSS-NET, the mean VRE proportions increased from 6.2% in 2011 to 7.9% in 2014 in Europe. In 2014, resistance frequency ranged from 0% in Estonia, Finland, Iceland and Malta to 45.1% in Ireland. Increasing trends were seen in Bulgaria, Croatia, Denmark, Hungary, Ireland, Italy, Slovakia and United Kingdom from 2011 until 2014 (17).

Most of the global VRE cases result from *van A* which is mostly carried by *E. faecium* (35).

Drug-resistant *Streptococcus*

The bacterium *Streptococcus pneumoniae* is the cause of invasive pneumococcal disease (IPD), a severe form of infection that can lead to pneumonia with bacteremia and meningitis. The burden of the disease is highest in young children and the elderly. *S. pneumoniae* can also cause otitis media (middle ear infection), sinusitis, peritonitis and rare cases of endocarditis (36). Prevention of infection by some serotypes of *S. pneumoniae* can be achieved by immunization with pneumococcal vaccines (37). *Streptococcus pyogenes* can cause invasive group A streptococcal diseases (iGAS) such as streptococcal toxic shock syndrome, necrotizing fasciitis ("flesh-eating" disease) and bacterial sepsis, as well as non-invasive diseases like pharyngitis ("strep throat"), scarlet fever, rheumatic fever and skin infections such as impetigo (36).

Methods

Provincial public health laboratories submit invasive *Streptococcus* isolates to the NML for serotyping, including information on patient age, gender, clinical source and date of collection; whereas the Laboratoire de santé publique du Québec, Alberta Provincial Laboratory for Public Health and the Toronto Invasive Bacterial Diseases Network submit serotyping data on invasive *S. pneumoniae* isolates that have been identified in their laboratories. The data were aggregated by age into <2 year, 2-14 year, 15-49 year, 50-64 year and ≥65 year age groups; and regionally into Western (British Columbia, Alberta, Saskatchewan, Manitoba, Yukon Territories, Northwest Territories and Nunavut); Central (Ontario and Quebec) and Eastern (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador) regions of Canada. Submission of isolates is voluntary and not standardized across the country.

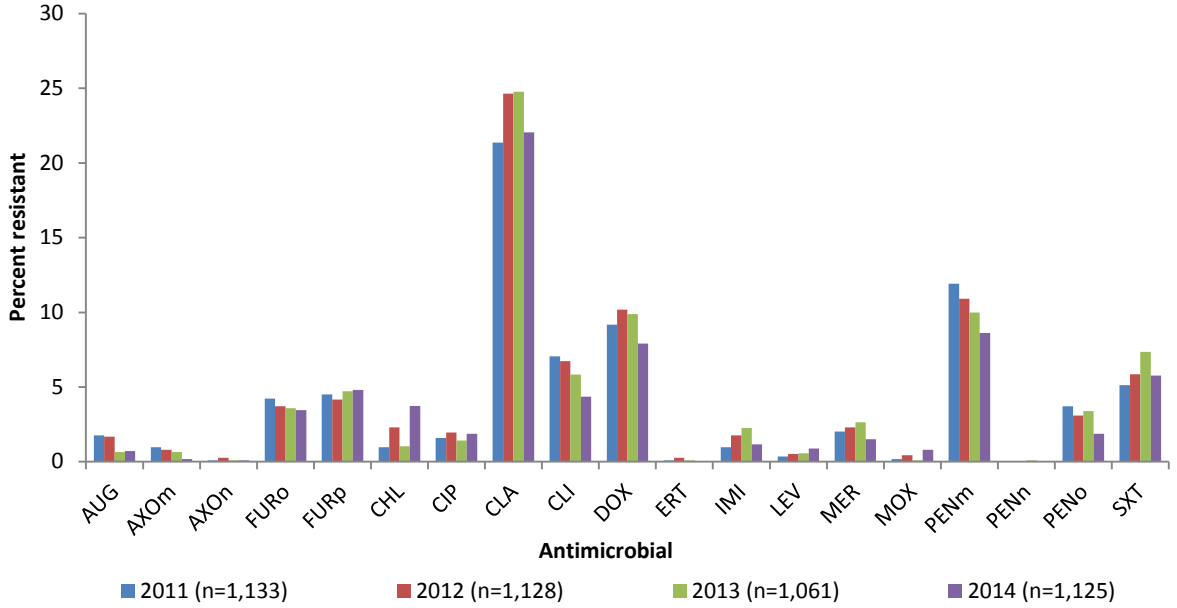
In 2011, the NML began a collaboration with the University of Manitoba – Health Sciences Centre - Canadian Antimicrobial Resistance Alliance (CARA) to provide antimicrobial susceptibility testing (AST) for *S. pneumoniae* isolates submitted called SAVE (*S. pneumoniae* Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada After the Introduction of PCV13). All sterile-site isolates from any age group causing invasive pneumococcal disease submitted by 8 participating jurisdictions (Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, Prince Edward Island, New Brunswick, Newfoundland and Labrador) are included in the study.

Drug-resistant *S. pneumoniae* in Canada

In Canada, since the implementation of routine immunization programs with 13-valent pneumococcal conjugate vaccine (PCV13) beginning in 2010, the national annual incidence rate of IPD has decreased from 9.6 cases per 100,000 population in 2011 to 8.9 cases per 100,000 population in 2014. During this time, the average annual incidence rate was highest in people aged 60 years and older (21.8 cases per 100,000 population), followed by infants less than one year (18.4 cases per 100,000 population) and children aged one to four years (12.8 cases per 100,000 population).

Resistance of *S. pneumoniae* to penicillin has decreased from 12% in 2011 to 9% in 2014 (**Figure 20**) and resistance to clindamycin declined from 7% to 4% over the same period. Resistance to doxycycline (8%) has remained relatively stable since 2010. Resistance to clarithromycin, which can be used in community-acquired pneumonia, decreased from 25% in 2013 to 22% in 2014 and TMP-SMX resistance has remained stable at 6%. To date, there has been no resistance reported to linezolid, tigecycline or vancomycin. Carbapenem resistance among *S. pneumoniae* is less common being detected at levels less than 2% in 2014.

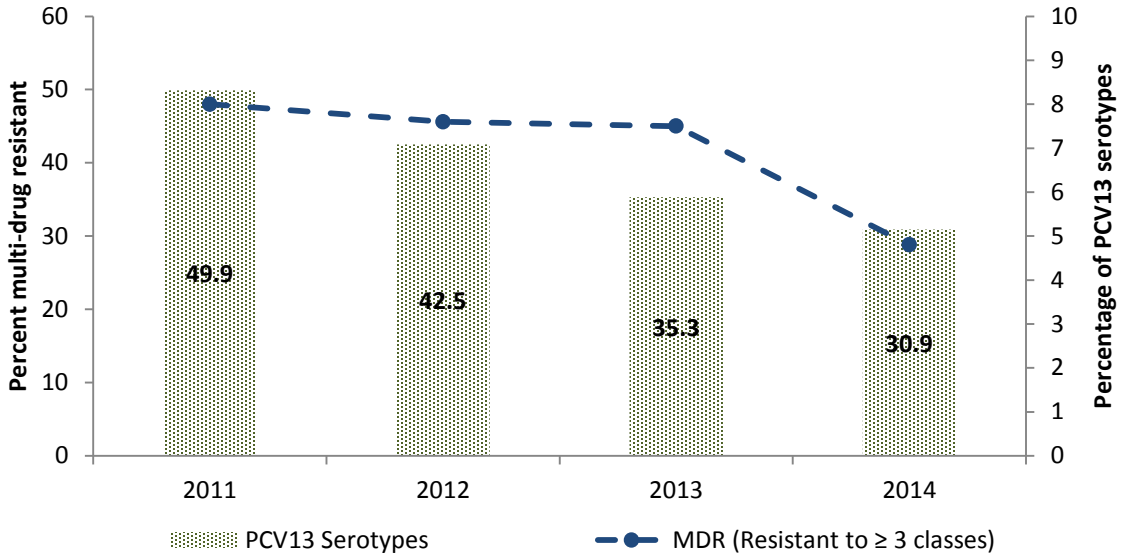
Figure 20: Antimicrobial resistance of *Streptococcus pneumoniae* isolates, 2011 to 2014[22]



Beginning in 2010, PCV13 was introduced in Canada, which included protection against the multidrug-resistant (MDR) serotype, 19A. The vaccine-induced decline of PCV13 serotypes (including the MDR serotype 19A) has driven a concurrent decline in overall AMR in pneumococci (**Figure 21**) (38). PCV13 serotypes have declined from 50% of the isolates in 2011 to 31% in 2014. Resistance to three or more classes of antimicrobials has also declined from 8% to 5% over the same time period. The impact of the pneumococcal vaccine on resistant strains illustrates the importance of vaccines as part of a strategy to mitigate the impact of AMR.

[22] AUG = amoxicillin/clavulanic acid; PENm = penicillin using the parenteral meningitis CLSI interpretive standard; PENn = penicillin using the parenteral non-meningitis interpretive standard; PENo = penicillin using the oral penicillin V interpretive standard; LEV = levofloxacin; MOX = moxifloxacin; AXOm = ceftriaxone using the parenteral meningitis interpretive standard; AXOn = ceftriaxone using the parenteral non-meningitis interpretative standard; FURo = cefuroxime using the oral interpretative standard; FURp = cefuroxime using the parenteral interpretative standard; ETP = ertapenem; IMI = imipenem; MER = meropenem; CIP = ciprofloxacin; CLA = clarithromycin; CLI = clindamycin; CHL = chloramphenicol; DOX = doxycycline; SXT = trimethoprim/sulfamethoxazole. Non susceptibility was not observed for daptomycin (no interpretative standard), linezolid, tigecycline (no interpretative standard), or vancomycin. EUCAST[EUCAST, 2015] interpretative breakpoints were used for CIP, all others according to CLSI[CLSI, 2015].

Figure 21: Multidrug resistance and proportion of PCV13 serotypes of pneumococci, 2011 to 2014

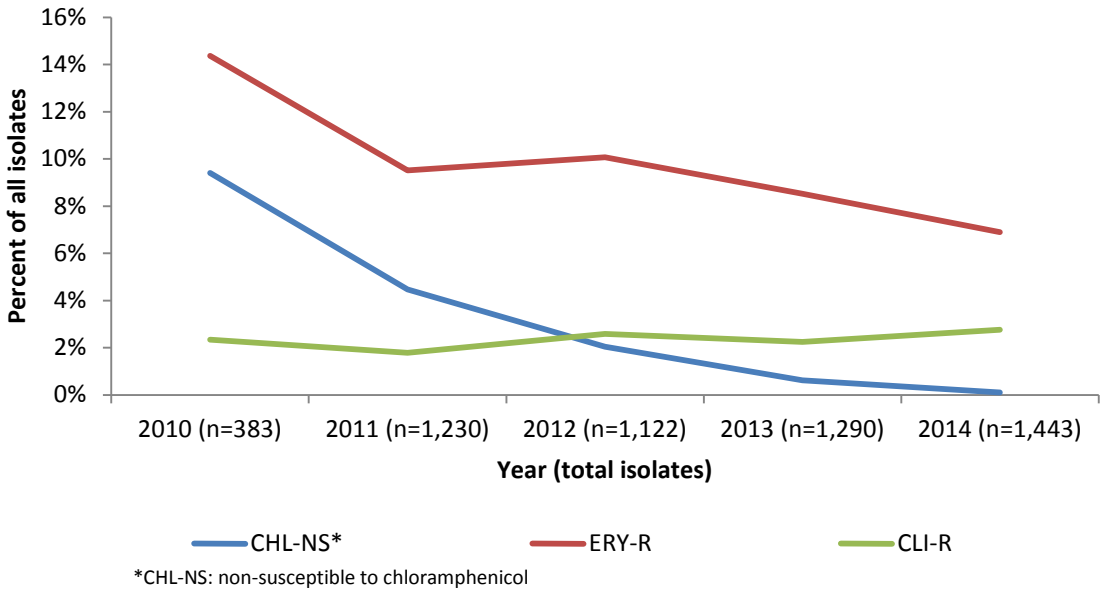


Drug-resistant *S. pyogenes* in Canada

From 2009 to 2013, the national incidence rate of iGAS in Canada has increased significantly ($p<0.0001$) from 4.0 to 4.7 cases per 100,000 population with an average annual incidence rate of 4.5 cases per 100,000 population (range: 4.0-4.9). The average annual incidence rate per 100,000 population was highest in infants less than one year of age (9.4 cases, range: 8.7-9.8), followed by the over 60 age group (7.2 cases, range: 6.6-7.6).

The most predominant types of iGAS in 2014 were *emm* types 1 and 89 accounting for 28% and 10% of the isolates tested, respectively. The majority of iGAS was isolated from blood samples (69%), followed by synovial fluid (8%). All iGAS were susceptible to penicillin and vancomycin. Resistance to clindamycin, a second-line drug for treatment, has remained relatively unchanged from 2010 to 2014 with about 2% of isolates resistant to this antimicrobial, while resistance to erythromycin and non-susceptibility to chloramphenicol has decreased from 14% to 7% and 9% to 0.1%, respectively, over the same time period (**Figure 22**).

Figure 22: Antimicrobial resistance of invasive *Streptococcus pyogenes* (GAS), 2010 to 2014



*CHL-NS: non-susceptible to chloramphenicol

International perspective

Similar to Canada, the overall IPD rate has declined in the United States from 2011 to 2014 (11.8 cases per 100,000 population to 8.7 cases per 100,000 population, respectively). In the United States, IPD rates in people ≥65, compared to the relatively stable rates in Canada, have increased from 35 cases per 100,000 population to 40.9 cases per 100,000 population between 2011 and 2014. As seen in Canada, for children less than five years, the United States rates have decreased from 12 cases per 100,000 population in 2011 to 8.4 cases per 100,000 population in 2014.

In the United States, between 2011 and 2014, resistance to erythromycin was detected in 28.4% of the overall IPD isolates increasing from 26.2% in 2011 to 30.2% in 2014. Tetracycline resistance was lower at 11.5% decreasing from 13.2% in 2011 to 11.7% in 2014. TMP-SMX resistance was on average 10.7% decreasing from 14.3% in 2011 to 9.7% in 2014 (39,40).

The top three drugs to which resistance was found in Canada were clarithromycin (23.2%) followed by penicillin (10.4%) and then doxycycline (9.3%). In 2014, resistance to penicillin in Canada (8.6%) was higher compared to the United States (2%) and the United Kingdom (0.5%) (41).

Invasive GAS rates were stable in the United States from 2009 until 2013 (3.6 to 3.7 cases per 100,000 population) in contrast to the significant increase seen in Canada (42, 43). Yet, in 2014, United States rates increased by 13% to 4.4 cases per 100,000 population (44).

The 2013 US CDC antibiotic resistance threats report indicated that from 2010 to 2011; 10% of the GAS isolates were erythromycin-resistant (9). From 2010 to 2014 a decline in iGAS resistance to erythromycin (14.4% to 6.9%) was seen in Canada**.** Clindamycin resistance was higher in the United States (3.4%) compared to Canada (2%) from 2010 to 2011**.**

Neisseria gonorrhoeae

Neisseria gonorrhoeae (N. gonorrhoeae) causes gonorrhea, a highly infectious sexually transmitted infection. It commonly results in genital infection that may be symptomatic or asymptomatic. Other sites of infection are also possible. If untreated or inappropriately treated, it may cause genital/reproductive tract inflammation and damage as well as infertility. The treatment and control of gonorrhea is complicated because *N. gonorrhoeae* develops resistance to the antimicrobials used to treat it, including penicillins, tetracyclines, macrolides and quinolones. Recently, isolates with resistance to azithromycin and decreased susceptibility to cephalosporins are emerging and threatening the last available treatment options. The Canadian Guidelines on Sexually Transmitted Infections updated recommendations for the use of combination gonorrhea therapy with 250 milligrams ceftriaxone intramuscularly and azithromycin 1 grams orally as the first-line treatment for uncomplicated anogenital and pharyngeal infections in adults (45).

Methods

Provincial public health laboratories submit *N. gonorrhoeae* isolates to the NML as part of the passive National *Neisseria gonorrhoeae* Surveillance Program, including information on age and gender of the patient as well as the anatomical site of infection. Laboratories submit isolates when resistance to one antimicrobial has been identified or if the provincial laboratories do not perform any antimicrobial susceptibility testing. Submission of isolates is voluntary and is not standardized across the country. Total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportion. Antimicrobial susceptibility testing was conducted using agar dilution for the following antimicrobials: penicillin, tetracycline, erythromycin, spectinomycin, ciprofloxacin, ceftriaxone, cefixime, azithromycin, ertapenem and gentamicin.

Gonorrhea in Canada

Gonorrhea is the second most commonly reported bacterial sexually transmitted infection in Canada. Between 2004 and 2013, the rate of reported cases of gonorrhea increased by 43.1%, from 27.4 to 39.3 per 100,000 population, particularly in females. In 2013, as in previous years, the rate of reported cases of gonorrhea was higher in males than females (47.4 vs. 31.1 per 100,000 population). Females between the ages of 15 and 24 years and males between the ages of 20 and 29 accounted for the highest rates of gonorrhea in 2013 (46).

Of the 3,809 *N. gonorrhoeae* isolates cultured in public health laboratories across Canada in 2014, a total of 1,955 (52.4%) were found to be resistant to at least one antibiotic tested (47).

Isolates with decreased susceptibility to ceftriaxone (minimum inhibitory concentration [MIC] greater or less than 0.125 milligrams per litre) have declined from 7.3% (n=218/2,970) in 2010 to 2.7% (n=101/3,809) in 2014. Those with decreased susceptibility to cefixime (MIC greater or less than 0.25 milligrams per litre) have declined from 4.2% (n=140/3,360) in 2011 to 1.1% (n=42/3,809) in 2014. The proportion of azithromycin-resistant (MIC greater or less than 2 milligrams per litre) *N. gonorrhoeae* isolates increased from 0.4% (n=11/3,106) in 2009 to 3.3% (n=127/3,809) in 2014, including 38 isolates from an outbreak (**Figure 23**). In 2014, 34.0% (n=1,296/3,809) of the isolates were resistant to ciprofloxacin; 32.0% (n=1,219/3,809) were resistant to erythromycin; 18.2% (n=693/3,809) were resistant to penicillin and 47.3% (n=1,809/3,809) were resistant to tetracycline (**Figure 24**) (47).

Since 2012, isolates with resistance to azithromycin and decreased susceptibility to cephalosporins (cefixime and ceftriaxone) have been observed in *N. gonorrhoeae* isolates in Canada, with a total of 0.2% (n=7/3,036) in 2012, 0.3% (n=8/3,195) in 2013 and 0.03% (n=1/3,809) in 2014. Despite the small numbers, this is of concern as it represents a threat to the success of currently recommended dual therapy treatment options (47).

Figure 23: Percentage of gonorrhea isolates resistant to azithromycin, decreased susceptibility to cefixime and ceftriaxone, 2009 to 2014*

*MIC Interpretative standards: azithromycin (US CDC, 2014); cefixime and ceftriaxone (48)

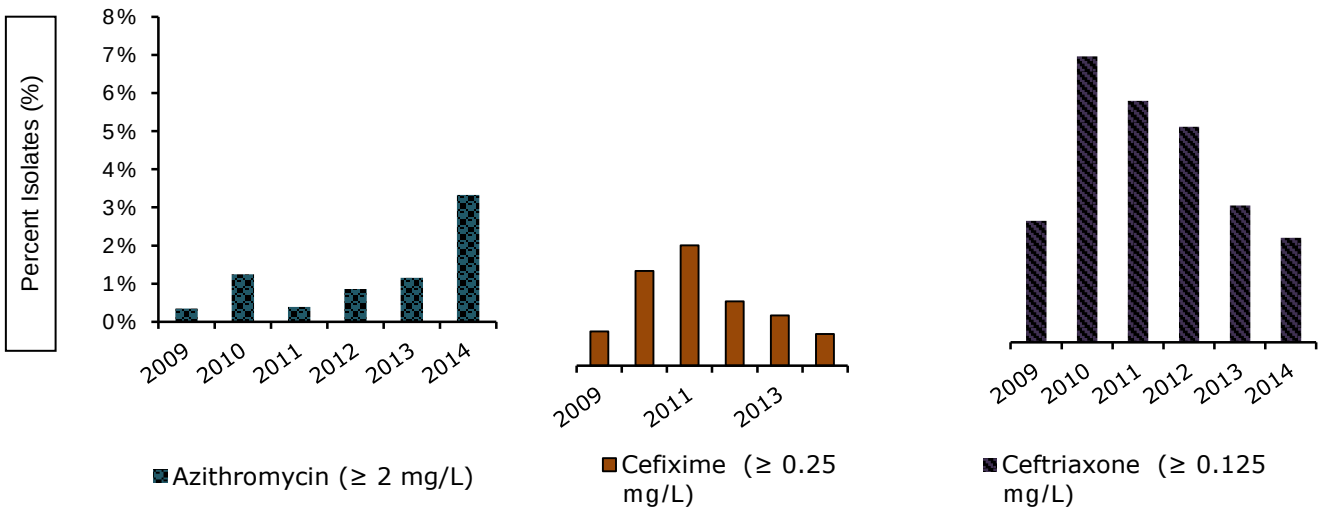
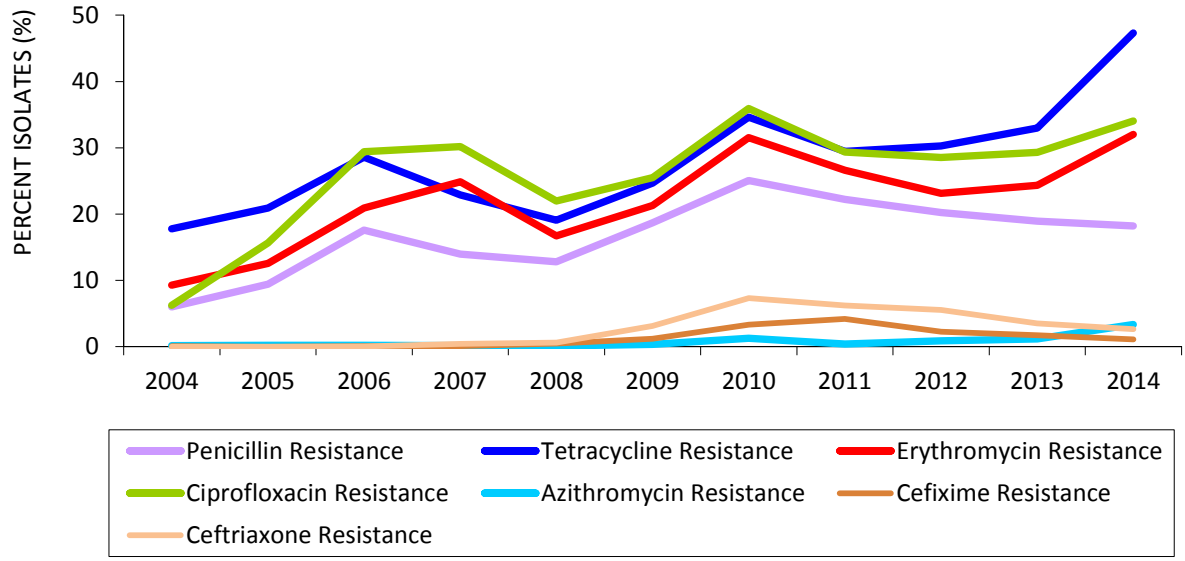


Figure 24: Percentage of gonorrhea isolates resistant to antibiotics, 2004 to 2014



International perspective

The decrease in the proportion of isolates with elevated MICs to the cephalosporins observed in Canada was also reported in the United States and the United Kingdom. In the United States isolates with decreased cefixime susceptibility declined from 1.4% in 2011 to 0.4% in 2013 and decreased ceftriaxone susceptibility declined from 0.4% in 2011 to 0.05% in 2013 (49). The United Kingdom reported that the proportion of isolates with decreased cefixime susceptibility declined from 6.3% in 2010 to 1.3% in 2013 and decreased ceftriaxone susceptibility declined from 0.3% in 2009 to 0.1% in 2013 (50). In Canada, *N. gonorrhoeae* azithromycin resistance levels were higher than in the United States (MIC greater or less than 2 milligrams per litre), which ranged from 0.2% to 0.6% between 2009 and 2013 and in the United Kingdom (MIC greater or less than 1 milligrams per litre), which reported 1.6% in 2013 (51,52). Australia reported 2.1% azithromycin resistance among their isolates in 2013 (50).

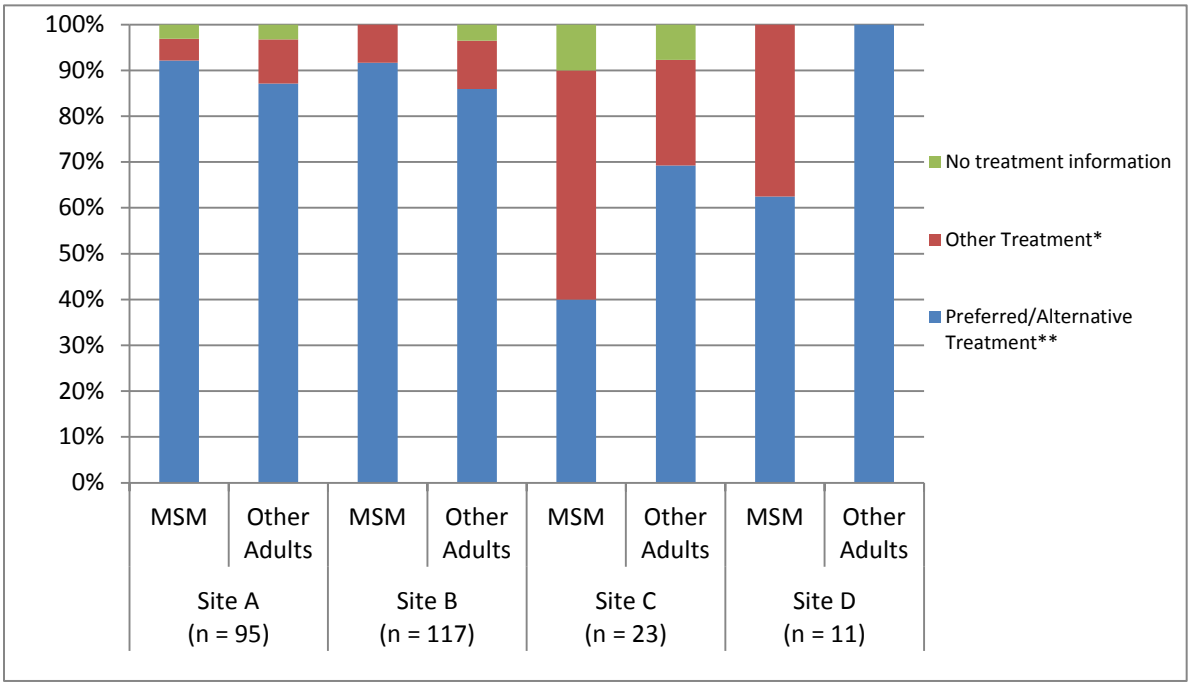
Text Box 4: Enhanced Surveillance of Antimicrobial Resistant Gonorrhea (ESAG) Pilot

In 2014, STI clinics at four sites across Canada participated in the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea pilot and provided treatment data. Preliminary data included that gonorrhea-positive cultures were obtained for 179 infections at Site A, 167 infections at Site B, 25 infections at Site C and 14 infections at Site D and included in the sampling frame. Among the 385 infections with positive gonorrhea cultures, the majority of cases at four participating sites were prescribed either the preferred or alternative therapies as proposed by the Canadian Guidelines on Sexually Transmitted Infections (46).

Among men who have sex with men (MSM), 40-92 % were prescribed either the preferred or alternative therapy proposed by the Canadian Guidelines on Sexually Transmitted Infections for their anogenital infections (**Figure A**). For pharyngeal infections among MSM, 50-100% 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, 69-100% were prescribed either the preferred or alternative therapy proposed by

the Canadian Guidelines on Sexually Transmitted Infections for anogenital infections. In this group, 83-89% were prescribed the preferred or alternative therapy for pharyngeal infections.

Figure A: Prescribed treatment for cases with anogenital infections by sexual behaviour, ESAG (2014)



* Other treatment consists of monotherapy or combination therapy. Combination therapy could include acceptable alternatives to azithromycin or the antibiotics recommended as preferred/alternative treatments, but dosage information was not available.
** The preferred and alternate treatment for anogenital infections vary between MSM and other adults (e.g., women and men who have sex with women exclusively), but they include ceftriaxone 250 mg IM plus azithromycin 1 g PO; cefixime 800 mg PO plus azithromycin 1 g PO; spectinomycin 2 g IM plus azithromycin 1 g PO; or azithromycin 2 g PO.

Drug-resistant *Salmonella Typhi*

Enteric fever is caused by *Salmonella* serotypes *Typhi* and *Paratyphi*. It is an enteric febrile illness characterized by fever, rash, diarrhea (more common in children) or constipation (more common in adults). Children usually present with milder symptoms compared to adults. Serious systemic manifestations can also occur (e.g., myocarditis). Three percent of patients might present with bleeding due to intestinal perforation (51).

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 (52). In Canada, enteric fever is usually acquired during travel and the destination of travel is the strongest predictor of *S. Typhi* risk with travel to South Asia[23] posing the highest risk.

[23] South Asia is defined as Afghanistan, Bangladesh, Bhutan, India, Nepal, Maldives, Pakistan and Sri Lanka. Among these countries, the large majority (≥ 90%) of cases of typhoid among travelers were reported from India, Pakistan and Bangladesh.

The first line for empiric therapy is a fluoroquinolone with ciprofloxacin being the most commonly used (53). However, when deciding on the optimal empiric therapy, antimicrobial resistance patterns in the travel destination countries should be considered (51). 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 (53).

Methods

Provincial public health laboratories submit all *Salmonella Typhi*, *Paratyphi A* and *Paratyphi B* to the NML for antimicrobial susceptibility testing, 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. Laboratories submit isolates as part of the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). Antimicrobial drug susceptibility testing was performed using broth microdilution and breakpoints established by the Clinical Laboratory Standards Institute whenever available. The antimicrobials in the susceptibility panel include the following antimicrobials: amoxicillin-clavulanic acid, ceftiofur, ceftriaxone, ciprofloxacin, ampicillin, azithromycin, cefoxitin, gentamicin, kanamycin, nalidixic acid, streptomycin, trimethoprim-sulfamethoxazole, chloramphenicol, sulfisoxazole and tetracycline.

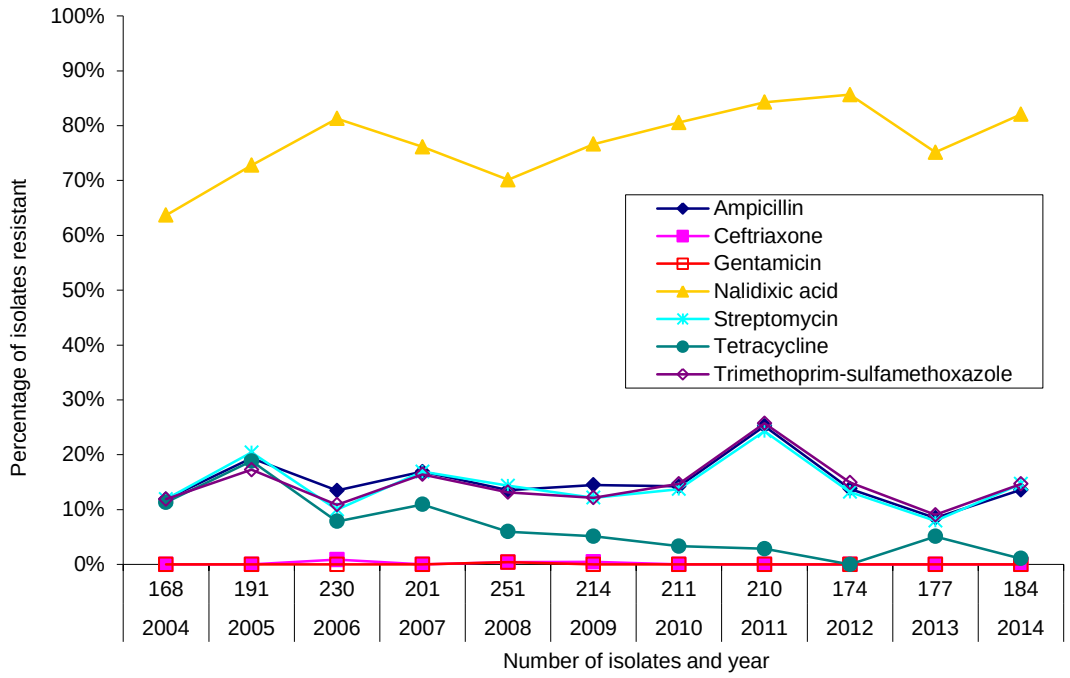
Drug-resistant *Salmonella Typhi* in Canada

In Canada, the rate of typhoidal *Salmonella* infection has ranged from a low of 0.5 cases per 100,000 population in 2003 to a high of 0.7 cases per 100,000 population in 2008. Between 2009 and 2011, rates of *S. Typhi* infections have been very low in Canada ranging between 0.39 and 0.53 cases per 100,000 population respectively (54). A total of 184 typhoidal isolates were tested for antimicrobial susceptibility in 2014 by the Canadian Integrated Programs for Antimicrobial Resistance Surveillance (CIPARS); *S. Typhi* (n=148), *S. Paratyphi* A (n=29) and *S. Paratyphi* B [24] (n=7). The majority of these typhoidal isolates tested in 2014 were from residents of Ontario, British Columbia and Alberta.

Antimicrobial resistance for *Salmonella* (typhoidal and non-typhoidal serotypes) has been monitored by CIPARS since 2002. Similar to previous years, the majority of typhoidal isolates (82%) were resistant to nalidixic acid (**Figure 25**). Ciprofloxacin resistance has increased significantly in Canada from zero percent in 2003 to 17% in 2013 and 14% in 2014. No resistance to ceftriaxone or azithromycin was reported in 2014. A total of 18% (33/184) of isolates were susceptible to all antimicrobials tested whereas 16% were multiclass-resistant (resistant to ≥ 3 classes of antimicrobials).

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

Figure 25: Antimicrobial resistance trends for different antimicrobials tested against typhoidal *Salmonella*, 2004 to 2014



International perspective

In 2014, the World Health Organization (WHO) estimated that almost 21 million cases of *S. Typhi* infections with related 222,000 deaths occur worldwide annually (55). Almost 90% of these deaths occur in Asia. The annual incidence rate of blood culture-confirmed cases in Asian urban slums is estimated to be 180–494 per 100,000 for children between five and 15 years old and similar or higher rates occur in children younger than five years old in these areas (56). Resistance to nalidixic acid and decreased susceptibility to ciprofloxacin is becoming endemic in the Indian subcontinent and in Southeast Asia (57).

In the United States, around 300 culture-confirmed cases of *S.* Typhi and 100 cases of *S.* Paratyphi serotypes are reported annually. As seen in Canada, the vast majority of cases (greater than 80% of *S. Typhi* and greater than 90% of *S. Paratyphi A*) are among travelers to South Asia. On the other hand, the risk of *S.* Typhi infection has declined in some travel destination countries. As a result, US CDC removed pre-travel typhoid vaccination recommendations for travel to Eastern Europe and the Middle East (53). Resistance to *S.* Typhi has been declared a serious threat by the US CDC. Resistance to ciprofloxacin has increased significantly in the United States from 20% in 1999 to more than 70% in 2011. From 2009 to 2011, approximately 67% of *S.* Typhi infections were resistant or partially resistant to ciprofloxacin. On the other hand, US CDC reports that until 2013 no resistance to azithromycin or ceftriaxone was seen in the United States for *S.* Typhi (58).

Drug-resistant Non-typhoidal *Salmonella*

Methods

Provincial public health laboratories submit all *Salmonella*, *Paratyphi A* and *Paratyphi B* to the NML for antimicrobial susceptibility testing, 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. Laboratories submit isolates as part of the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS).

Antimicrobial drug susceptibility testing was performed using broth microdilution and breakpoints established by the Clinical Laboratory Standards Institute whenever available. The antimicrobials in the susceptibility panel include the following antimicrobials: amoxicillin-clavulanic acid, ceftiofur, ceftriaxone, ciprofloxacin, ampicillin, azithromycin, cefoxitin, gentamicin, kanamycin, nalidixic acid, streptomycin, trimethoprim-sulfamethoxazole, chloramphenicol, sulfisoxazole and tetracycline.

Drug-resistant non-Typhoidal *Salmonella* in Canada

In 2014, a total of 2,496 non-typhoidal *Salmonella* human isolates were submitted to PHAC for antimicrobial susceptibility testing, the majority of which were submitted by Ontario (35%) followed by Quebec (17%), British Columbia (11%) and Alberta (11%). *Salmonella* Enteritidis was the most common serotype associated with human disease submitted for susceptibility testing, followed by *S.* Heidelberg and *S.* Typhimurium.

The majority of the *Salmonella* isolates were recovered from stool samples (83%), followed by blood (5%) and urine (4%) (**Table 3**).

Table 3: Total number of non-typhoidal *Salmonella* spp. isolates submitted for antimicrobial susceptibility testing by sample source and serotype in Canada, 2014

Sample source	*S.* Enteritidis	*S.* Heidelberg	*S.* 4,[5],12:i:-	*S.* Newport	*S.* Typhimurium	Other serotypes
Blood	59	42	4	6	10	7
Stool	1013	267	128	173	308	184
Urine	29	27	2	10	10	20
Other	11	4	1	0	1	2
Unknown	106	22	3	12	27	8
Total	**1218**	**362**	**138**	**201**	**356**	**221**

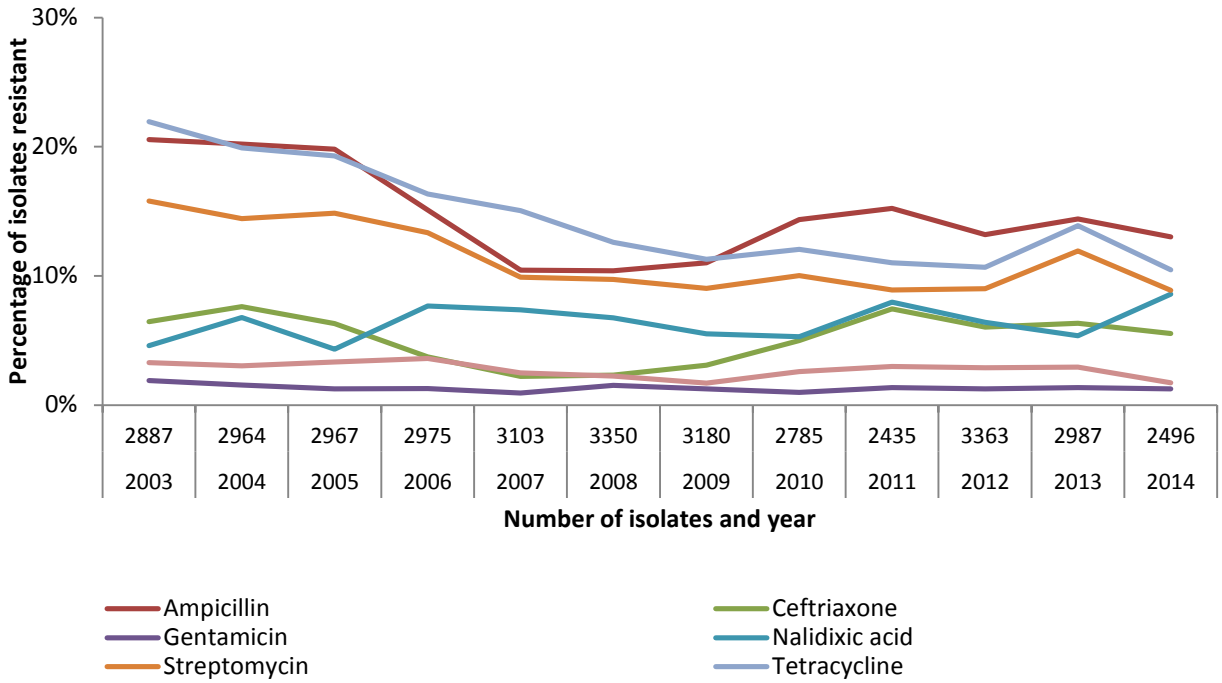
In 2014, 75% of all human non-typhoidal *Salmonella* isolates were susceptible to all antimicrobials tested, with 7% of isolates exhibiting resistance to three or more antimicrobial classes (multiclass-resistant) (**Table 4**). Ampicillin was the antimicrobial for which a larger proportion of isolates were resistant (8%), followed by tetracycline (7%), streptomycin (6%) and gentamicin (6%). No resistance to azithromycin was reported in 2014 and only 1% of isolates were resistant to ciprofloxacin, both antimicrobials used in treatment of severe human infections. Over time, resistance to most antimicrobials has been decreasing since 2004 (**Figure 26**), with the exception of resistance to nalidixic acid which has nearly doubled between 2013 (5%) and 2014 (9%). Most of the nalidixic-resistant isolates

from humans are *Salmonella* Enteritidis and the increase in resistance to this antimicrobial is likely associated with the large number of Enteritidis cases observed in 2014.

Table 4: Resistance (%) among non-typhoidal *Salmonella* and percentage of isolates distributed among common *Salmonella* serotype recovered from humans, chicken and pigs in Canada, 2014

Antimicrobial	Human (%)	Chicken (%)	Pigs (%)
	Clinical	Food chain	Food chain
Amoxicillin-clavulanic acid	5	17	3
Ampicillin	13	17	31
Azithromycin	0	0	2
Cefoxitin	5	16	3
Ceftiofur	6	16	3
Ceftriaxone	6	17	4
Chloramphenicol	4	0	14
Ciprofloxacin	1	0	0
Gentamicin	1	2	2
Nalidixic acid	9	0	0
Streptomycin	9	26	42
Sulfisoxazole	0	7	44
Tetracycline	10	30	62
Trimethoprim-sulfamethoxazole	2	0	6
Fully susceptible	75	56	33
Multiclass resistant	7	6	44
Number of isolates	***2497***	***694***	***325***
Enteritidis	49	24	0
Heidelberg	15	18	0
Kentucky	0	24	1
Typhimurium	14	3	22
Other	22	30	77

Figure 26: Resistance to selected antimicrobials among human non-typhoidal *Salmonella* spp. in Canada, 2003 to 2014



International perspective

The US CDC has reported that they have observed resistance to ceftriaxone in about 3% of non-typhoidal *Salmonella* tested and some level of resistance to ciprofloxacin in about 3%. Multidrug resistance (greater than five classes) has been observed in approximately 5% of non-typhoidal *Salmonella* tested by the US CDC (9).

Text Box 5: Multiclass resistance in *Salmonella* 4,[5],12:i:- in humans and along the food chain in Canada

The prevalence of *Salmonella* 4,[5],12:i:- in humans has increased over the past ten years and this serotype now ranks among the top five reported in the United States and Canada (59,60). More recently, an increase in the proportion of *S*. 4,[5],12:i:- isolates with resistance to ampicillin, streptomycin, sulfonamide and tetracycline (ASSuT) has been observed. A marked increase in ASSuT-resistant *S*. 4,[5],12:i:- infections in Europe pre-dated the emergence in North America. In Europe, the majority of multidrug-resistant isolates were phage types DT193 and DT120. Infections in Europe with the DT193 strains have been associated with exposure to pigs or pork products (61). In the United States, the CDC has investigated multiple outbreaks and clusters associated with ASSuT-resistant 4,[5],12:i- with a pulsed-field gel electrophoresis (PFGE) pattern JPXX01.1314 (identical to DT193) (59). In Canada, molecular work has shown that the majority of the ASSuT-resistant isolates belonged to sequence type 34, which has been described previously in many European countries and has been linked to food-producing animals, specifically pork (59,61).

Results

In 2014, 182 *S*. 4,[5],12:i:- isolates from humans were submitted for susceptibility testing by CIPARS. Of

these isolates, 37% demonstrated resistance to ASSuT+ (including those isolates with resistance to other antimicrobials except chloramphenicol) (**Table A**). Among the ASSuT+-resistant isolates, 41 were DT193; only one susceptible isolate was DT193. Sixty-nine *S*. 4,[5],12:i:- isolates were recovered from pigs and submitted for susceptibility testing by CIPARS in 2014; 72% of these isolates were from clinical submissions and not from healthy pigs or pork products sampled along the food chain. Among all isolates from pigs, 70% demonstrated resistance to ASSuT+ (**Table A**). Among the resistant isolates, 79% were DT193; 2 of the 4 susceptible 4,[5],12:i:- isolates from pigs were DT193. Human cases of *S*. 4,[5],12:i:- were observed in all regions of Canada in 2014. However, ASSuT+ isolates were only observed in pigs and pork products in Ontario and Quebec. Although this multidrug-resistant phenotype of *S*. 4,[5],12:i:- was recovered from healthy pigs on farm, the majority of isolates were recovered from sick pigs suggesting that this serotype is an important pathogen for pigs as well as humans.

Conclusions

The number of *S*. 4,[5],12:i:- human infections in Canada remains high and the proportion of cases exhibiting multidrug resistance continues to increase. While the human cases are distributed across the country, pig infections with the same strain appear to be clustered in Ontario and Quebec. Further studies and ongoing surveillance are needed to determine whether there is a link between the human and animal cases and what factors might be contributing to the rise in prevalence of the serotype and emergence of multidrug resistance. CIPARS is collaborating with the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) in the United States to better understand domestic sources of this infection and the international spread of this resistant pattern.

Table A: ASSuT resistance among *Salmonella* 4,[5],12:i:- from pigs/pork and humans in Canada, 2014

	Human	Pigs			
	Clinical	Farm	Slaughter	Retail	Clinical
Fully susceptible (%)	28	6	50	0	4
ASSuT+ pattern (%)	37	63	50	0	74
Number of isolates tested	138	16	2	1	50

Drug-resistant Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that primarily affects the lungs but can also affect any part of the body. It is transmitted by the inhalation of airborne infectious droplet nuclei 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. Adolescents and adults are most likely to transmit TB infection, although young children can sometimes be infectious (62).

Individuals diagnosed with active TB disease are said to have drug-resistant TB if the strain of TB causing their disease is resistant to one or more of the four first-line drugs. The following resistance patterns are of concern: Mono-resistance—defined as resistance to one first-line anti-TB drug only (isoniazid, rifampin, ethambutol or pyrazinamide); Polyresistance (other patterns)—defined as resistance to more than one first-line anti-TB drug, not including the isoniazid and rifampin combination; Multidrug-resistant *tuberculosis* (MDR-TB)—defined as resistance to isoniazid and rifampin with or without resistance to other anti-tuberculosis drugs; and Extensively drug-resistant *TB (XDR-TB)*—defined as resistance to isoniazid (INH), rifampin (RMP), any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin).

TB is a major public health problem that affects millions of people around the globe, predominantly in low- and middle-income countries (63). TB, however, remains a persistent health threat in high-income countries, particularly among the poorest, most vulnerable segments of the population (64). Globally, the improper prescription of anti-TB drugs, their proper prescription but unavailability, inadequate supervision or, uncommonly, the malabsorption of these drugs has increased the prevalence of drug-resistant TB (62).

Methods

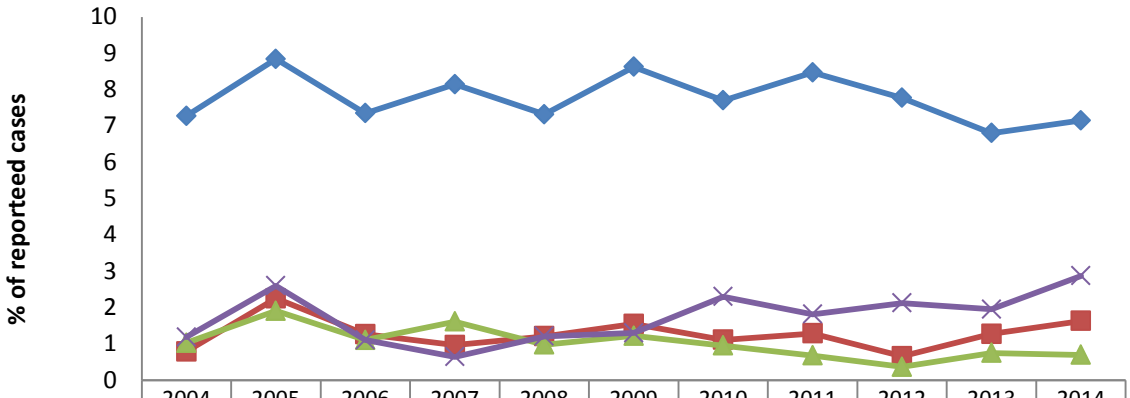
PHAC collects information on tuberculosis in Canada through the Canadian Tuberculosis Laboratory Surveillance System (CTBLSS) and the Canadian Tuberculosis Reporting System (CTBRS). CTBLSS is an isolate-based surveillance system developed to collect timely data on tuberculosis (TB) drug resistance across Canada. Participating laboratories include members of the Canadian Tuberculosis Laboratory Technical Network representing all provinces and territories. Participating laboratories submit drug susceptibility test results for all first-line TB drugs (isoniazid, ethambutol, rifampin, and pyrazinamide) and the results for at least one of the fluoroquinolones (levofloxacin, Moxifloxacin, or ofloxacin), and the injectable agents (amikacin, capreomycin and kanamycin). CTBRS is 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 their disease is resistant to one or more of the four first-line drugs.

Drug-resistant Tuberculosis in Canada

Canada has one of the lowest TB disease rates in the world (63). Between 2004 and 2014, both the number of reported TB cases and the overall Canadian incidence rates have remained relatively stable (**Figure 27**). Overall, between 2004 and 2014, there were 17,902 cases of active TB disease reported to the CTBRS for an average of 1,627 cases reported annually. Over the same period, the incidence rate remained relatively stable between 4.4 cases to 5.0 cases per 100,000 population.

Between 2004 and 2014, 80% (14,338) of all reported TB cases in Canada were culture-positive. Of these 98% (14,047) were tested for resistance. Nine percent (9%, 1,268 cases) of the culture-positive cases were found to be resistant to at least one of the first-line anti-tuberculosis drugs. Isoniazid resistance was the most common pattern of first-line drug resistance reported (**Figure 27**).

Figure 27: Percentage culture-positive TB cases resistant to each of the four first-line medication, 2004 to 2014

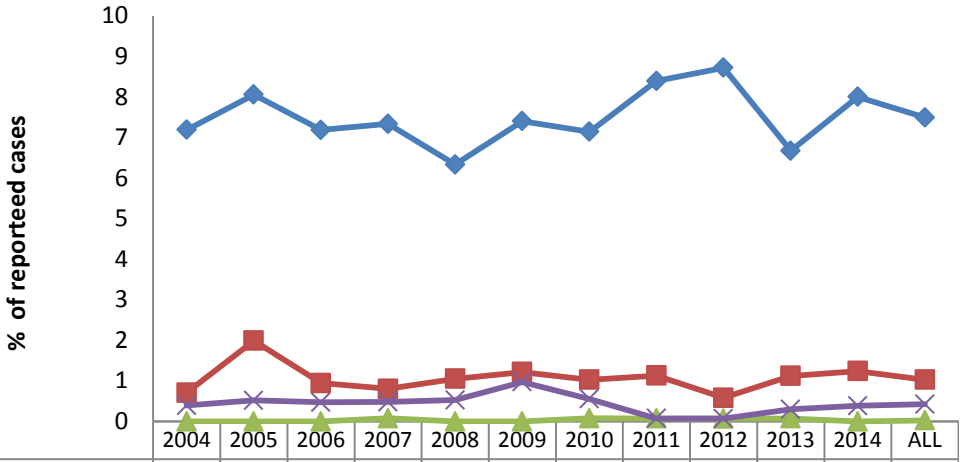


	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
% INH Resistance	7.3	8.8	7.3	8.1	7.3	8.6	7.7	8.5	7.8	6.8	7.1
% RMP Resistance	0.8	2.3	1.3	1.0	1.2	1.5	1.1	1.3	0.7	1.3	1.6
% EMB Resistance	1.0	1.9	1.1	1.6	1.0	1.2	1.0	0.7	0.4	0.8	0.7
% PZA Resistance	1.2	2.6	1.1	0.6	1.2	1.3	2.3	1.8	2.1	2.0	2.9

Reporting year

Between 2004 and 2014, of the culture-positive cases tested for resistance (n=14,047), 8% (n = 1,070) were monoresistant, 0.5% (n = 60) were identified as polyresistant, 1% (n=150) were MDR-TB and less than 0.1% (n=5) were XDR-TB (**Figure 28**). The percentage of cases with MDR-TB has remained between 1% and 2% for the period 2004 and 2014 (Figure 28).

Figure 28: Percentage of culture-positive TB cases by resistant patterns, 2004 to 2014



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	ALL
Monoresistance	7.2	8.1	7.2	7.3	6.3	7.4	7.1	8.4	8.7	6.7	8.0	7.5
MDR-TB	0.7	2.0	0.9	0.8	1.1	1.2	1.0	1.1	0.6	1.1	1.2	1.0
XDR TB (included in MDR-TB Count)	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0
Other patterns (non mdr non xdr)	0.4	0.5	0.5	0.5	0.5	1.0	0.6	0.1	0.1	0.3	0.4	0.4

Geographic distribution[25]

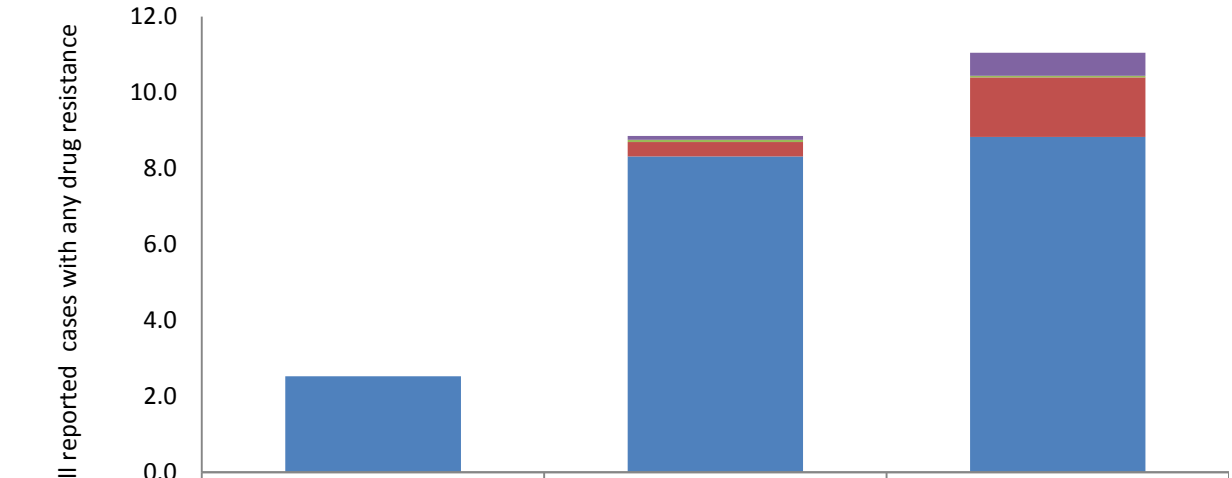
Data from the CTBLSS show that every province and territory in Canada reported at least one case of drug-resistant TB between 2004 and 2014 (65). As well, Alberta, British Columbia, Manitoba, Ontario and Quebec have all reported cases of MDR-TB. Of the five XDR-TB cases reported between 2004 and 2014, three were reported from Ontario and one each from Manitoba and Quebec.

Between 2004 and 2014, of the reported cases with drug resistant TB (i.e., resistance to at least one of the first-line antimicrobials), 46% (n= 585) were females and 54% (n = 683) were males. Ten percent of females and 9% of males tested had TB that was resistant to at least one of the first-line TB drugs. For both males and females, 1% of the cases tested had TB that was resistant to both INH and RMP. Among the XDR-TB cases, four of the five cases were female. For all cases, the majority, 42% (n = 541) were between the ages of 25 and 44.

Two percent (n = 69) of the Canadian-born Indigenous cases, 9% (n = 141) of the Canadian-born non-Indigenous cases and 11% (n = 1,047) of the foreign-born cases were resistant to at least one of the first-line antimicrobials (**Figure 29**). The foreign-born cases accounted for 83% (n=1,047) of all resistant cases, 97% (n=145) of the MDR-TB cases and four of the five XDR-TB cases.

[25] For this section the data from the Canadian Tuberculosis Laboratory Surveillance System are used. All other sections use the surveillance data from the Canadian Tuberculosis Reporting System.

Figure 29: Percentage of all TB cases by type of drug resistance across origin, 2004 to 2014

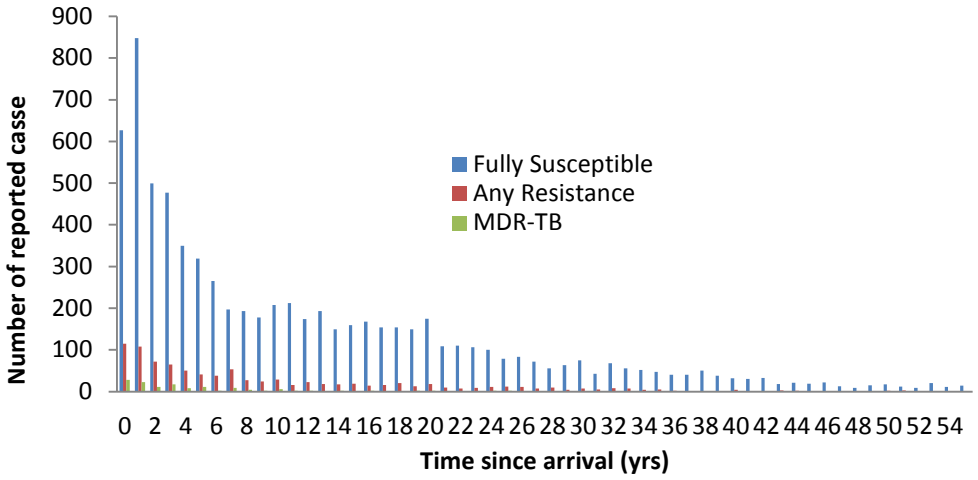


	Canadian-born Aboriginal (n = 69)	Canadian-born non-Aboriginal (n=141)	Foreign-born (n = 1,047)
Other Patterns	0.0	0.1	0.6
XDR TB	0.0	0.1	0.0
MDR-TB	0.0	0.4	1.6
Monoresistant	2.5	8.3	8.8

Origin

Among the foreign-born, drug-resistant TB cases presented earlier after arrival in Canada than drug-susceptible TB cases (**Figure 30**). Of the susceptible cases for which year of arrival was recorded (n = 7,517), 42% arrived in Canada within five years of the TB diagnosis compared to 60% of MDR-TB cases (n = 144).

Figure 30: Time from arrival in Canada to diagnosis for foreign-born, culture-positive tuberculosis cases by drug susceptibility pattern



Between 2004 and 2014, drug-resistant TB was reported slightly more often in cases with a past history of TB (re-treatment cases) as compared with those with no prior history of disease (new cases). Of 12,901 new active TB cases reported, 0.9% (n = 114) were MDR-TB whereas for the 907 re-treatment case 3.8% (n = 35) were MDR-TB. This difference in proportions is significant ($p < 0.001$).

As routine testing of TB cases for resistance to fluoroquinolones (levofloxacin, moxifloxacin and ofloxacin) or injectable agents (amikacin, kanamycin and capreomycin) is not done in Canada, the epidemiology of second-line drug resistance has not been clearly described. Testing is typically considered where resistance to INH and RMP has been established. Of the 155 cases resistant to both INH and RMP, 142 were tested for resistance to at least one fluoroquinolone and one of the injectable agents. Of these 142, 10% (n = 15) were also resistant to a fluoroquinolone and 13% to at least one of the three injectable agents.

Final treatment outcome was assessed for cases diagnosed between 2006 and 2013. For these cases (n = 10,525) treatment outcome was reported for 92% (n = 9,730) of cases. Eighty-four percent of cases were sensitive to all four first-line medications, 83% of the monoresistant cases and 79% of the MDR-TB cases were reported as cured or had completed treatment. At the time the outcome data were reported to PHAC, 3% of the fully-sensitive cases were still on treatment whereas 11% of the MDR-TB cases were still on treatment. Death was recorded as the final outcome for 10% of the fully-sensitive cases and 4% of the MDR-TB cases.

The duration of treatment varied depending on the reported pattern of drug resistance. For cases that were fully sensitive (n = 7,332) the mean duration of treatment was 8.7 months (95% CL: 8.6 – 8.8 months). For those cases with any resistance, excluding the MDR-TB cases, (n = 588), the duration of treatment was 10.8 months. Finally, of those cases resistant to INH and RMP for ± 0.3 months which outcome data were available (n = 72) the mean duration of treatment was 23 months ± 1 month (95% CL: 21 – 24 months).

International perspective

The WHO estimates that, globally, in 2014, 9.6 million people fell ill with TB and 1.5 million of those with TB died. An estimated 480,000 people developed MDR-TB and an estimated 9.7% of people with MDR-TB had XDR-TB. An estimated 3.3% of new and 20% of previously treated cases had MDR-TB. These estimates remained unchanged from those reported in 2012. Globally, in 2014, of the individuals diagnosed with MDR-TB or rifampicin-resistant tuberculosis, 75% lived in the European Region, India, South Africa or China (63).

In 2014, the reported TB incidence rate in the United States was 3.4 per 100,000 population, which was lower than the Canadian rate for the same year (66). Between 2004 and 2014, in the United States, 1% of all reported new cases and 5% of re-treatment cases were diagnosed with MDR-TB. These percentages are comparable to the proportions reported in Canada. Between 2009 and 2014, there were 15 XDR-TB cases reported in the United States representing less than 0.1% of all reported culture-positive cases in that period. This is also similar to what was observed in Canada, where less than 0.1% (n=5) of cases reported between 2004 and 2014 were XDR-TB (67).

The burden of TB in Canada among the foreign-born reflects the global TB patterns. Between 2004 and 2014, there were 17,902 reported cases of active TB disease in Canada, of which 67% (n=11,942) were foreign-born. Of all the foreign-born cases, 46% were from three countries, China, India and the Philippines—countries identified by the World Health Organization as High Burden TB countries. The remaining cases came from over 180 different countries. Of those reported cases with MDR-TB, 96% (n=149) were foreign-born and 56% (n=84) case were born in the Philippines (n=26) China (n=22), India (n=20) and Vietnam (n=16) (68).

Text Box 6: AMRNet - A community-based antimicrobial resistance surveillance pilot project

Background: An important gap in national and provincial antimicrobial resistance surveillance is the ability to capture AMR data for community and out-patient populations. These data are required to improve our ability to understand AMR trends at local, regional, provincial and national levels, better respond to emerging threats and support stewardship efforts by informing evidence-based decision-making. Across Canada, private and public laboratories conduct large-scale, high-throughout antimicrobial susceptibility testing on a wide variety of bacterial organisms on a daily basis. Canadian laboratories are therefore uniquely positioned to provide key data and information to support community-level AMR surveillance.
Objective: To conduct a pilot study to assess the feasibility of capturing and analyzing existing antimicrobial susceptibility data generated by frontline laboratories.
Results: PHAC, in collaboration with the British Columbia Centre for Disease Control (BCCDC) and BC LifeLabs Medical Laboratory Services, collected and analyzed community-level AMR information for the years 2008 to 2013. The data provided by BC collaborators included information related to patient age, gender, specimen source, organism and antimicrobial susceptibility data. As part of the pilot project, data were analysed for *Campylobacter* spp., *Escherichia coli* and methicillin-resistant *Staphylococcus aureus*. In addition, a web-based application (AMRNet) is being developed which will help educate healthcare professionals and the public about trends in resistance in the community.
Conclusions: PHAC has determined that the information captured via the AMRNet pilot is promising and warrants further engagement of key surveillance partners to support broader national implementation of community-based surveillance of AMR infections.

Resistance in foodborne bacteria

PHAC monitors antimicrobial resistance in selected bacterial organisms in food sources across Canada. These include *E. coli*, *Salmonella* and *Campylobacter* species which are prevalent in food-animal sources and impact on human health. 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.

Most individuals infected with food-borne *E. coli*, *Salmonella* and *Campylobacter* species will develop diarrhea, fever and abdominal cramps. In most cases, the illness is self-limited and treatment is not required. Some vulnerable individuals, such as the elderly, very young children, and individuals with underlying medical conditions; may need to be hospitalised if the diarrhea is severe. Pregnant women are also at increased risk of complications related to these organisms. Some strains of *E. coli*, such as *E. coli* O157:H7 or enterohemorrhagic *E. coli* (EHEC) can cause a life-threatening condition known as hemolytic uremic syndrome (HUS). Individuals with HUS can develop permanent kidney damage and potential death.

Methods

The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) monitors antimicrobial resistance in three zoonotic bacteria: generic *Escherichia coli*, *Campylobacter* and *Salmonella*. Samples are collected at three points along the food chain: 1) from healthy animals on farm, 2) from healthy animals at slaughter and 3) meat at retail food stores. CIPARS focuses sampling on the major meat commodities consumed in Canada: chicken, pork and beef. **Table 5** indicates which zoonotic bacteria were isolated from which animal species along the food chain in 2014. Additionally, clinical *Salmonella* isolates from humans and animals are also tested for antimicrobial resistance.

Table 5: Zoonotic bacteria routinely tested for antimicrobial resistance by animal species and point along the food chain, CIPARS 2014

	Farm	Slaughter	Retail Meat
Chicken	*E. coli* *Campylobacter* *Salmonella*	*E. coli* *Campylobacter* *Salmonella*	*E. coli* *Campylobacter* *Salmonella*
Pigs	*E. coli* *Salmonella*	*E. coli* *Campylobacter* *Salmonella*	*E. coli*
Cattle	N/A	*E. coli* *Campylobacter*	*E. coli*

Generic *Escherichia coli*

Chicken

Generic *E. coli* are found everywhere as they inhabit the gastrointestinal tract of animals and humans and therefore act as good indicators of antimicrobial resistance selection pressure. In 2014, a total of 1,294 samples from chickens were submitted for bacterial and antimicrobial susceptibility testing. The

proportion of samples positive for generic *E. coli* has remained consistent, with 96% of all samples collected in 2014 found to be positive (**Table 6**).

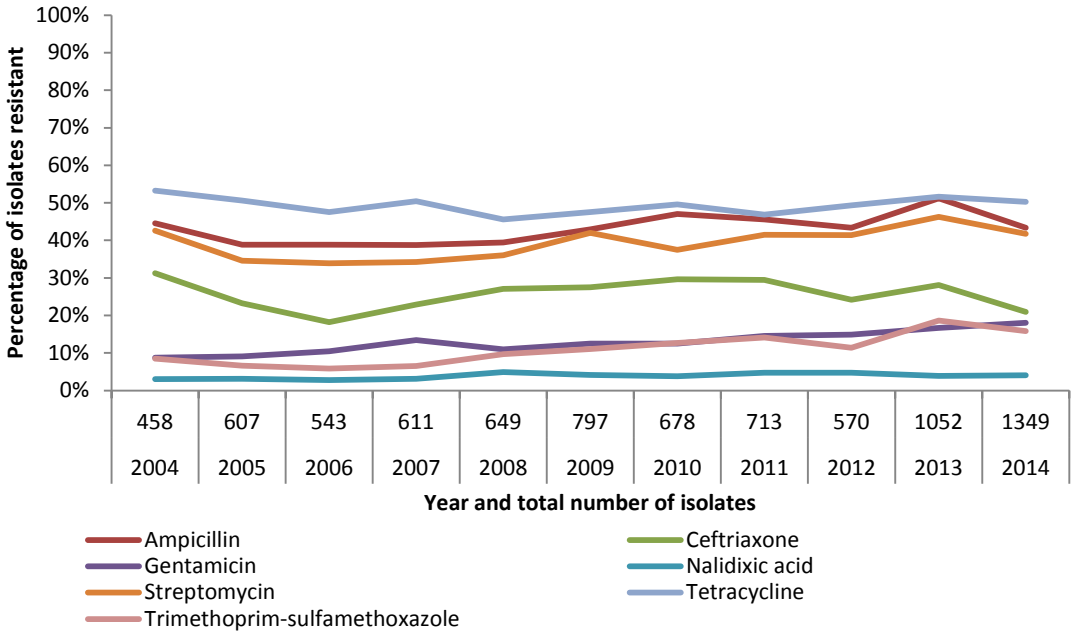
Table 6: Total number of chicken samples across the food chain submitted for bacterial testing and the proportion of samples positive for generic *Escherichia coli*, 2004-2014[26]

Year	No. of isolates recovered / No. of samples submitted for testing	Percentage of isolates recovered
2004	739/752	98%
2005	914/934	98%
2006	543/558	97%
2007	612/636	96%
2008	649/699	93%
2009	799/836	96%
2010	679/737	92%
2011	714/752	95%
2012	621/648	96%
2013	963/1003	96%
2014	1238/1294	96%
Total	**8471/8 849**	**96%**

Approximately half of the generic *E. coli* isolates obtained from chicken samples along the food chain were found to be resistant to tetracycline, followed by ampicillin (43%) and streptomycin (42%) (**Figure 31**). Resistance to ceftriaxone decreased between 2004 (31%) and 2014 (21%), while resistance to gentamicin and trimethoprim-sulfamethoxazole increased during this time period from 9% to 18% and 9% to 16%, respectively.

[26] In 2004 only, the number of isolates recovered is higher than the number of isolates undergoing antimicrobial susceptibility testing as the number of generic *E. coli* isolates cultured from chicken samples at retailers was higher than the desired sample size. For budgetary reasons, susceptibility testing was only performed on a subset of isolates those years. From 2005 onwards, only approximately 50% of the retail chicken samples are cultured for *E. coli* (systematic random selection).

Figure 31: Resistance to selected antimicrobials among generic *Escherichia coli* isolates from chicken samples collected from farms (broiler), slaughter and retail stores in Canada, 2004-2014



In 2014, all provinces/regions participating in the CIPARS broiler chicken farm program reported a decrease in the use of ceftiofur, a third-generation cephalosporin, compared to 2013. This corresponded with decreased levels of third-generation cephalosporin resistance among generic *E. coli* from broiler chickens. In 2014, the Canadian chicken industry implemented a policy eliminating the preventive use of antimicrobials considered of very high importance to human medicine, including third-generation cephalosporins, and this intervention is likely responsible for most of the decrease in third-generation cephalosporin use reported in broiler flocks.

Swine

Swine samples were collected at different stages along the food chain: sentinel grower-finisher swine farms, federally-inspected at slaughter and at retail stores across the country. Over time the recovery rates for generic *E. coli* among swine samples collected along the food chain has ranged from 50% (2005) to 62% (2004), with 55% of all swine samples collected in 2014 found to be contaminated with this organism (**Table 7**).

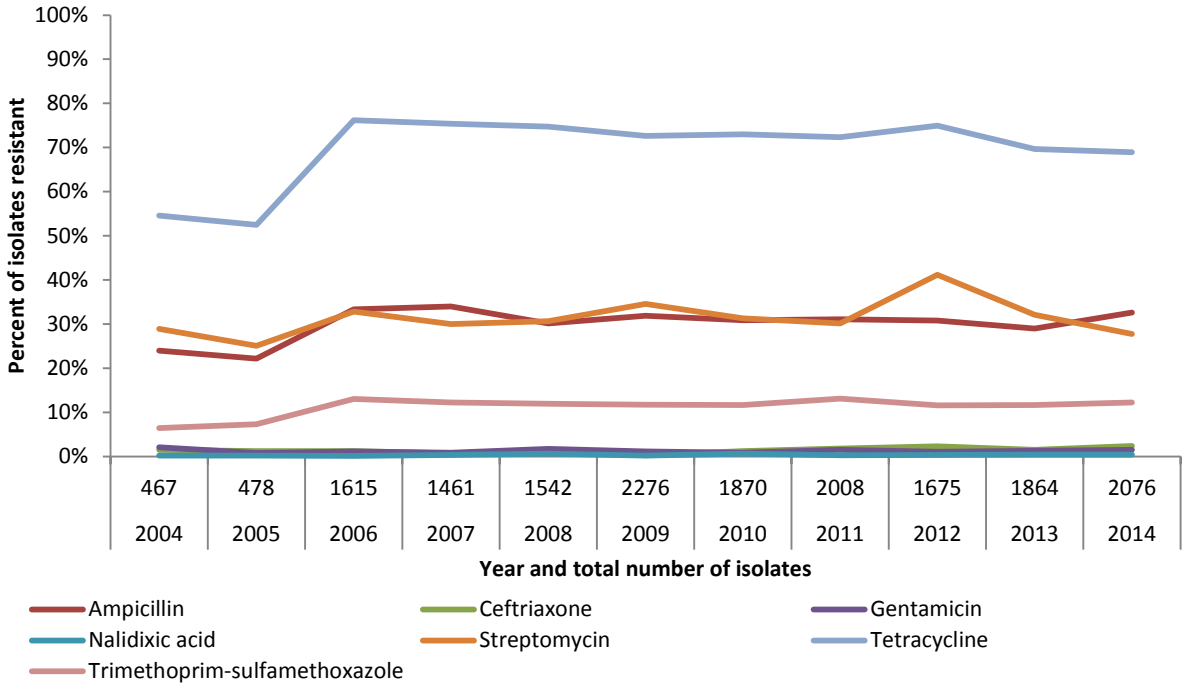
Table 7: Total number of swine samples across the food chain submitted for bacterial testing and the proportion of samples positive for generic *Escherichia coli*, 2004 to 2014[27]

Year	No. of positive samples / No. of samples submitted	Percent positive (recovery)
2004	467/751	62%
2005	479/961	50%
2006	641/1133	57%
2007	4746/1326	56%
2008	819/1492	55%
2009	1076/1876	57%
2010	915/1702	54%
2011	1076/1907	56%
2012	832/1497	56%
2013	904/1507	60%
2014	1024/1852	55%
Total	**8979/16004**	**56%**

Sixty-nine percent of all *E. coli* isolates from pigs were resistant to tetracycline in 2014. Two percent of isolates were resistant to ceftriaxone and gentamicin and less than 1% were resistant to nalidixic acid (**Figure 32**). Since surveillance of grower-finisher pigs on farm began in 2006, the level of resistance in *E. coli* from pigs has remained relatively stable.

[27] CIPARS farm swine surveillance recovers up to three isolates per positive sample. Therefore, the number of positive samples in the table above is smaller than the number of *E. coli* undergoing antimicrobial susceptibility testing in the figure below since CIPARS farm swine surveillance was implemented (2006).

Figure 32: Resistance to selected antimicrobials among generic *Escherichia coli* isolates obtained from swine samples collected from farms (grower-finisher), slaughter and retailers in Canada, 2004 to 2014



Cattle

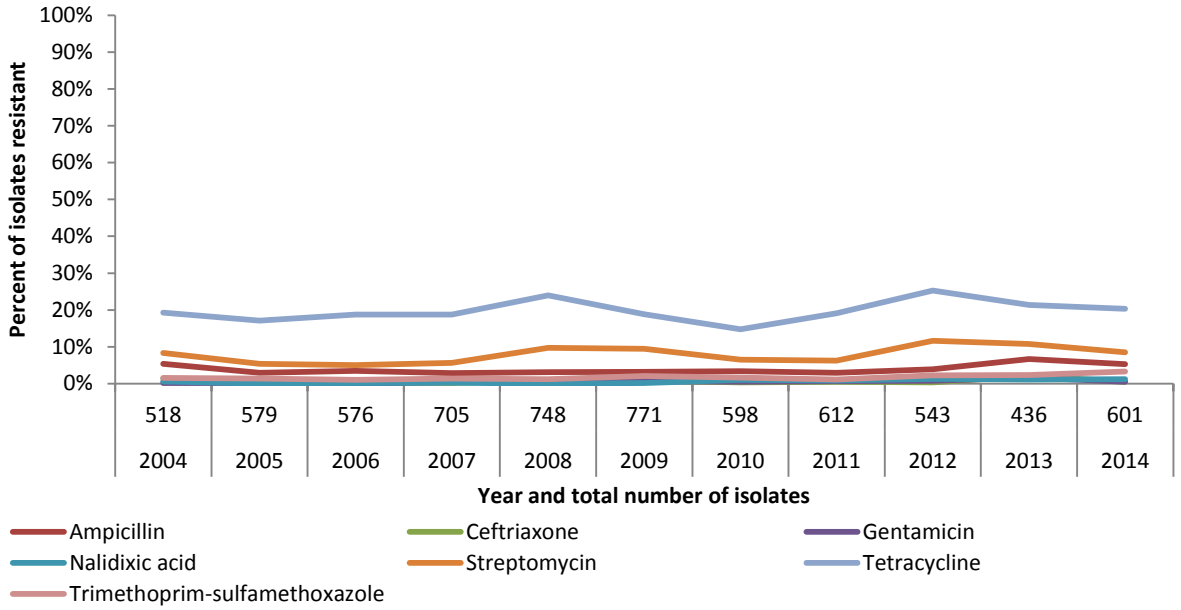
Samples cultured for *E. coli* were collected at slaughter and retail level. Currently there is no surveillance of cattle at the farm level. This should be taken into consideration when reviewing to recovery rates below (**Table 8**).

Table 8: Total number of cattle samples, number of isolates recovered and the percentage of isolates recovered for generic *Escherichia coli* from slaughter and retailers, 2004 to 2014

Year	No. of isolates recovered / No. of samples submitted	Percentage of isolates recovered (Recovery)
2004	518/692	75%
2005	579/758	76%
2006	576/767	75%
2007	690/877	79%
2008	748/980	76%
2009	772/1048	74%
2010	590/912	65%
2011	612/937	65%
2012	571/849	67%
2013	413/740	56%
2014	605/1076	56%
Total	**6674/9636**	**69%**

Similar to that observed among chicken and swine samples, the largest proportion of generic *E. coli* isolates were resistant to tetracycline, with 20% of all isolates resistant to this antimicrobial in 2014 (**Figure 33**). Very little (≤ 0.3%) resistance was observed to ceftriaxone and the antimicrobials gentamicin and nalidixic acid.

Figure 33: Resistance to selected antimicrobials among generic *Escherichia coli* isolates obtained from cattle samples collected from slaughter and retailers in Canada, 2004 to 2014



Campylobacter species

Chicken

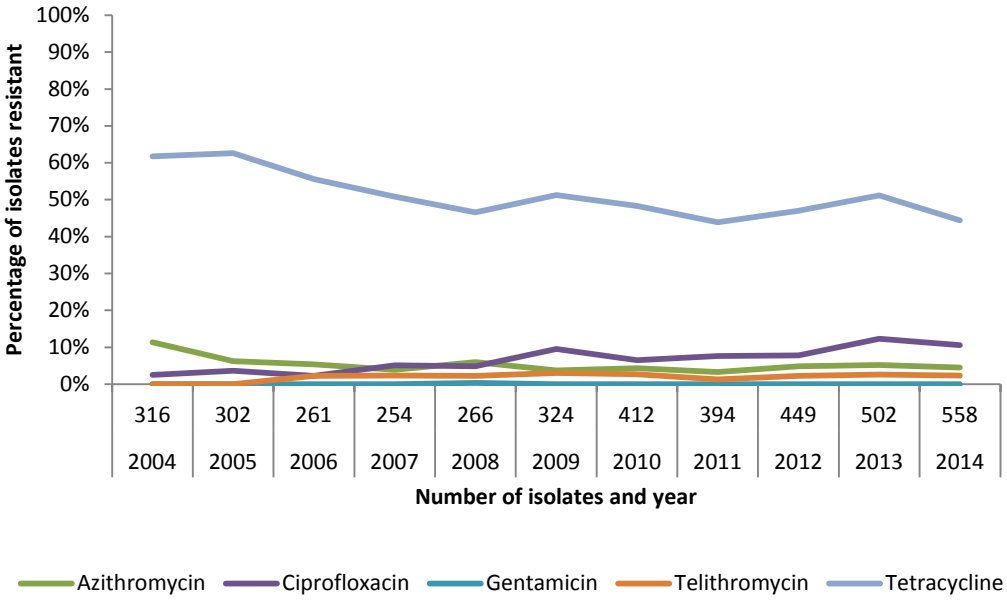
Testing for *Campylobacter* spp. contamination is carried out on chicken samples collected from farms (broiler chickens), at slaughter and retail outlets across Canada. Total recovery rates are presented below (**Table 9**). In 2014, 26% (294/1149) of retail, 27% (187/683) of abattoir and 16% (93/564) of farm chicken samples were positive for *Campylobacter*.

Table 9: Total number of chicken samples, number of *Campylobacter* isolates recovered and percentage of isolates recovered from farm (broiler chicken), slaughter and retail in Canada, 2004 to 2014

Year	No. of isolates recovered / No. of samples submitted	Percentage of isolates recovered (recovery)
2004	320/676	47%
2005	307/784	38%
2006	261/761	34%
2007	263/857	30%
2008	268/958	28%
2009	349/1164	30%
2010	386/1369	28%
2011	398/1669	24%
2012	449/1562	29%
2013	489/1857	26%
2014	563/2273	25%
Total	**4037/13930**	**29%**

In 2014, 44% of *Campylobacter* spp. isolates were resistant to tetracycline (**Figure 34**). Resistance to ciprofloxacin reported in 2014 (11%) was higher than resistance observed in 2004 (4%) and was consistent across all points along the food chain—retail (11%; 30/277), slaughter (11%; 20/188) and farm (10%; 9/93).

Figure 34: Resistance to selected antimicrobials among *Campylobacter* spp. isolates obtained from chicken samples collected from farms (broiler), slaughter and retailers in Canada, 2004 to 2014



Danofloxacin and enrofloxacin are fluoroquinolones approved for use in livestock in Canada, specifically for treating respiratory disease in cattle and pigs (there are no approved uses in chicken). When data about ciprofloxacin resistance in *Campylobacter* spp. recovered from chicken samples were examined at the regional level, it was noticed that trends varied considerably between provinces/regions and decreases in reported fluoroquinolone use in some provinces appeared to coincide with observed decreases in ciprofloxacin resistance.

Swine

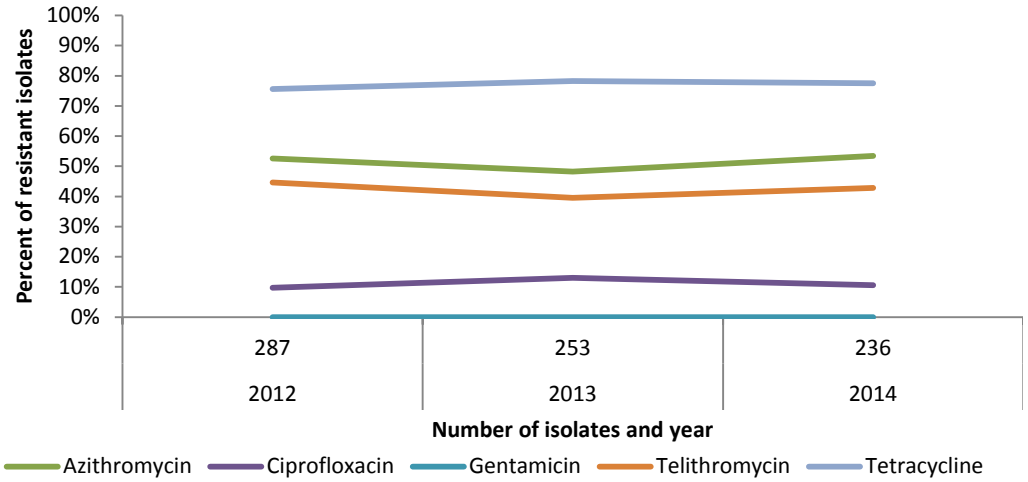
Samples from pigs for *Campylobacter* spp. detection are only collected at slaughter level and testing for *Campylobacter* only started in 2012. Retail samples are not tested for *Campylobacter* due to the low levels detected during the beginning of surveillance. *Campylobacter* is commonly isolated from pigs at slaughter (**Table 10**); most of the isolates from pigs are *Campylobacter coli*.

Table 10: Total number of swine samples, number of *Campylobacter* spp. isolates recovered and percentage of isolates recovered from slaughter samples in Canada, 2012 to 2014

Year	No. of isolates recovered/ No. of samples submitted	Percentage of Isolates recovered (Recovery)
2012	289/370	78%
2013	236/315	75%
2014	237/326	73%
Total	**762/1011**	**75%**

In 2014, 78% of isolates were resistant to tetracycline, followed by azithromycin (53%) and telithromycin (43%). Eleven percent of isolates were resistant to ciprofloxacin (**Figure 35**).

Figure 35: Resistance to selected antimicrobials among *Campylobacter* spp. isolates obtained from swine samples collected at slaughter in Canada, 2012 to 2014



Cattle

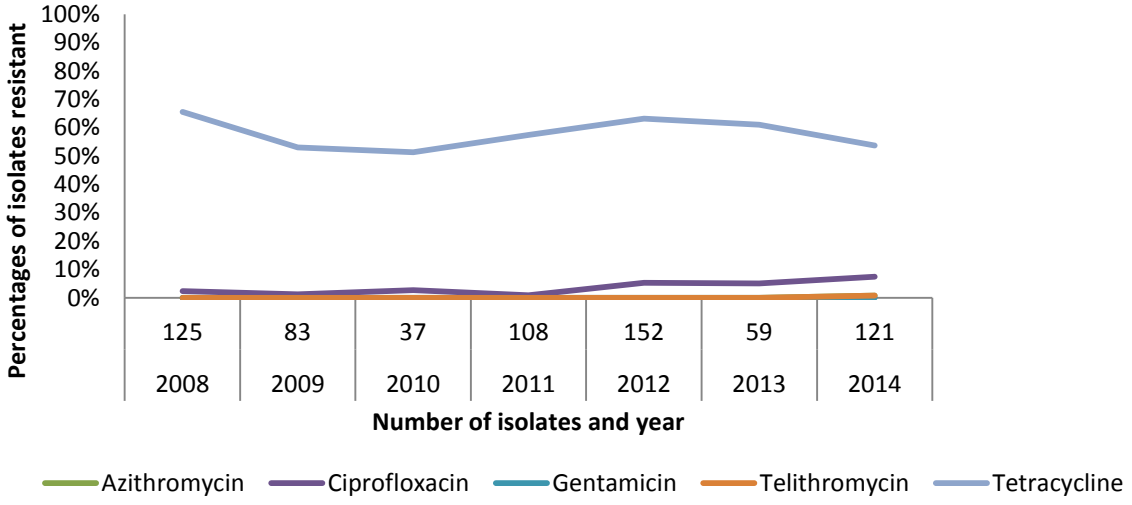
Campylobacter spp. have been isolated from cattle samples collected at slaughter level since 2008. Similar to *Campylobacter* spp. in swine, this organism is not tested for among beef samples collected at the retail meat level due to low detection levels identified at the beginning of the Surveillance Program. Recovery rates for *Campylobacter* spp. among cattle samples has ranged from 53% in 2010 to 92% in 2012, with 87% of all samples testing positive for *Campylobacter* spp. in 2014 (**Table 11**).

Table 11: Total number of cattle samples, number of *Campylobacter* spp. isolates recovered and percentage of isolates recovered from slaughter samples in Canada, 2008 to 2014

Year	No. of isolates recovered/ No. of samples submitted	Percentage of isolates recovered (Recovery)
2008	129/182	71%
2009	86/126	68%
2010	37/70	53%
2011	108/142	76%
2012	152/166	92%
2013	54/152	36%
2014	123/142	87%
Total	**689/980**	**70%**

Antimicrobial resistance in *Campylobacter* spp. isolates recovered from cattle samples is mainly to tetracycline, with 54% of isolates resistant to this antimicrobial in 2014 (**Figure 36**). Resistance to azithromycin and telithromycin was reported for the first time in 2014, although less than 1% of isolates were resistant to these antimicrobials. Resistance to ciprofloxacin has increased between 2008 and 2014 from 2% to 7% during this time period.

Figure 36: Resistance to selected antimicrobials among *Campylobacter* spp. isolates recovered from cattle sampled at slaughter in Canada, 2008 to 2014



Salmonella spp.

Chicken

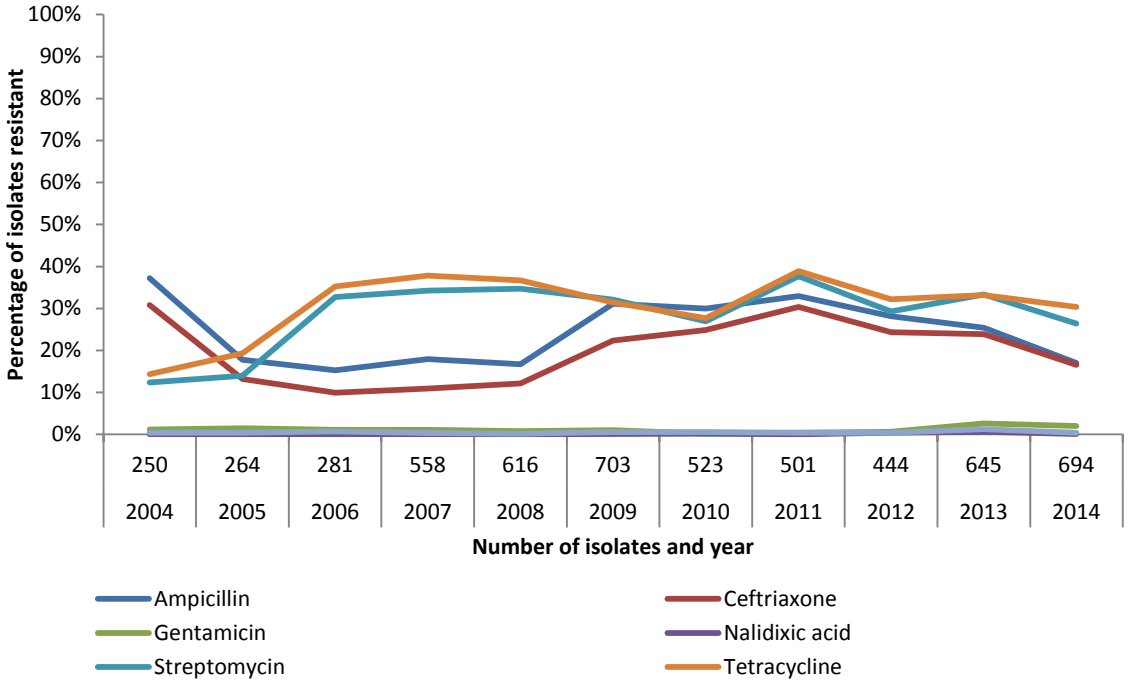
Testing for *Salmonella* spp. is carried out on chicken samples collected from farms, at slaughter and retailers. In 2014, 34% of all chicken samples collected in Canada were found to be contaminated with *Salmonella* spp. (**Table 12**). Among the *Salmonella* recovered from chicken, *S.* Enteritidis and *S.* Kentucky were the main serotype identified, with *S.* Heidelberg being the third most common serotype.

Table 12: Total number of chicken samples, number of *Salmonella* spp. isolates recovered and percentage of isolates recovered from farms (broiler chicken), slaughter and retail stores in Canada, 2004 to 2014

Year	No. of isolates recovered / No. of samples submitted	Percentage of isolates recovered (Recovery)
2004	250/1553	16%
2005	278/1898	15%
2006	293/1045	28%
2007	556/1665	33%
2008	616/1810	34%
2009	704/1935	36%
2010	523/1614	32%
2011	505/1674	30%
2012	444/1550	29%
2013	624/1924	32%
2014	700/2050	34%
Total	**5493/18718**	**29%**

In 2014, 56% of all *Salmonella* isolates recovered from chicken along the food chain were fully susceptible to all antimicrobials tested, with 6% of isolates classified as multiclass-resistant (resistant to three or more antimicrobial classes). Thirty percent of chicken *Salmonella* isolates were resistant to tetracycline, followed by streptomycin (26%) and ampicillin, amoxicillin-clavulanic acid and ceftriaxone (17% each) (**Figure 37**). In 2014, no resistance was observed to azithromycin or ciprofloxacin, two antimicrobials used in human medicine for treating severe and invasive salmonellosis.

Figure 37: Resistance to selected antimicrobials among *Salmonella* spp. isolated from broiler chicken samples collected at farms, slaughter and retail stores in Canada, 2004 to 2014



Among retail chicken meat and slaughter houses chicken, the most common *Salmonella* serotype associated with resistance to third-generation cephalosporin was *S.* Heidelberg. Further information on third-generation cephalosporin resistance in non-typhoidal *Salmonella* is provided in the section entitled *Integration of AMU and AMR Across the Food chain*.

Swine

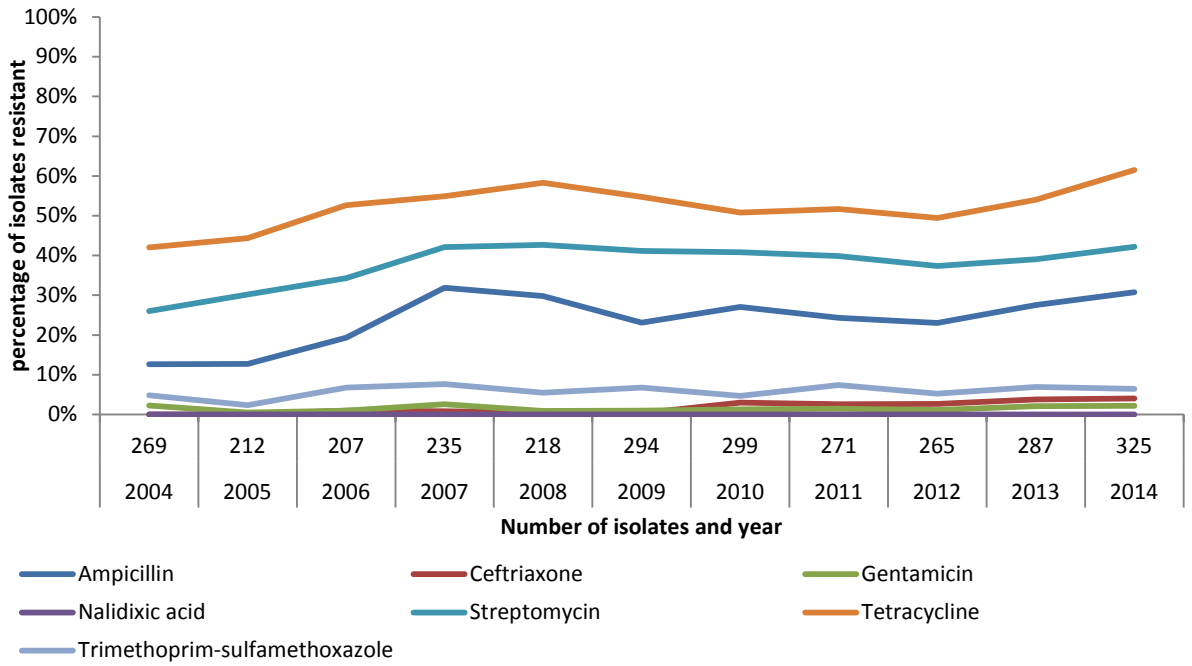
Recovery of *Salmonella* spp. among swine samples obtained from farms (grower-finisher), at slaughter and retailers has decreased over time from 38% observed in 2004 to 16% in 2014 (**Table 13**). The majority of the *Salmonella* isolates were identified as *S.* Typhimurium, and unlike chicken products, *S.* Enteritidis, *S.* Heidelberg and *S.* Kentucky were rarely identified among samples tested.

Table 13: Total number of *Salmonella* spp. isolates recovered from swine samples, total number of samples submitted and percentage of isolates recovered along the food chain in Canada, 2004 to 2014

Year	No. of isolates recovered/ No. of samples submitted	Percentage of isolates recovered (Recovery)
2004	270/703	38%
2005	212/486	44%
2006	206/750	27%
2007	207/1508	14%
2008	221/1675	13%
2009	286/2038	14%
2010	296/1910	16%
2011	276/2095	13%
2012	263/1683	16%
2013	277/1668	17%
2014	332/2015	16%
Total	**2846/16531**	**17%**

In 2014, 33% of all *Salmonella* isolates recovered from swine samples along the food chain were susceptible to all antimicrobials tested and 44% were identified as multiclass-resistant. The majority of the isolates, 62%, were resistant to tetracycline, followed by sulfisoxazole (44%) and streptomycin (42%). No resistance has been observed to nalidixic acid since the beginning of the surveillance period. Resistance to ampicillin, streptomycin and tetracycline increased between 2004 and 2014 (**Figure 38**).

Figure 38: Resistance to selected antimicrobials among *Salmonella* spp. isolates recovered from swine samples at farms, slaughter and retail stores in Canada, 2004 to 2014



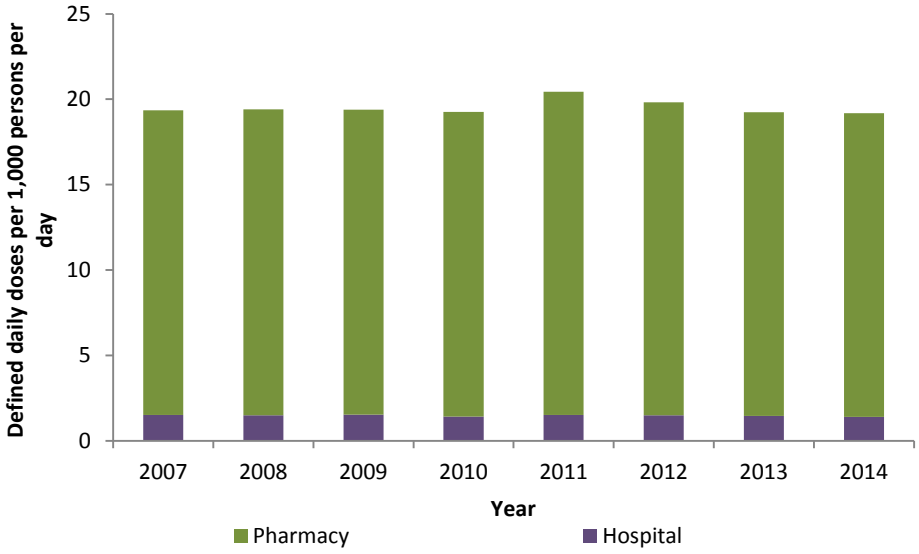
Antimicrobial use in Canada

Antimicrobial use in humans

In Canada, antimicrobial use in humans has remained relatively stable over the last 8 years (**Figure 39**), with only slight changes observed in the total antimicrobials purchased by hospitals (4% decrease) and no changes within the total antimicrobials dispensed by community pharmacies in 2014 compared to 2013. Antimicrobial dispensing in the community continues to account for the majority of all antimicrobial use (AMU) (93%), with a total of 17.8 defined daily doses (DDDs) dispensed per 1,000 inhabitants per day (DIDs) compared to 1.4 DIDs purchased by hospitals.

This accounts for a total of 240,939 kilograms of active ingredients and $786 million spent on antimicrobials in 2014. Changes in the levels of use for individual antimicrobials were observed, with different trends noted in hospital and community settings.

Figure 39: Defined daily doses of antimicrobials per 1,000 population-days dispensed through community pharmacies or purchased by hospitals in Canada, 2007 to 2014



Community utilization

Pharmacy dispensations

On average, 65% of Canadians filled a prescription for an antimicrobial for bacterial infections in 2014 (**Figure 40**) resulting in a total of 23 million prescriptions dispensed. Prescriptions for amoxicillin represented the largest proportion of all antimicrobials dispensed (26%), followed by azithromycin (9%) and ciprofloxacin (8%). Total antimicrobial use in the community at the national level has remained stable between 2013 and 2014 as measured by DDDs per inhabitant, prescriptions per inhabitant and DDDs per prescription (**Table 14**). However, between 2007 and 2014, there has been a slight increase in DDDs per prescription and a decrease in the prescriptions per inhabitant.

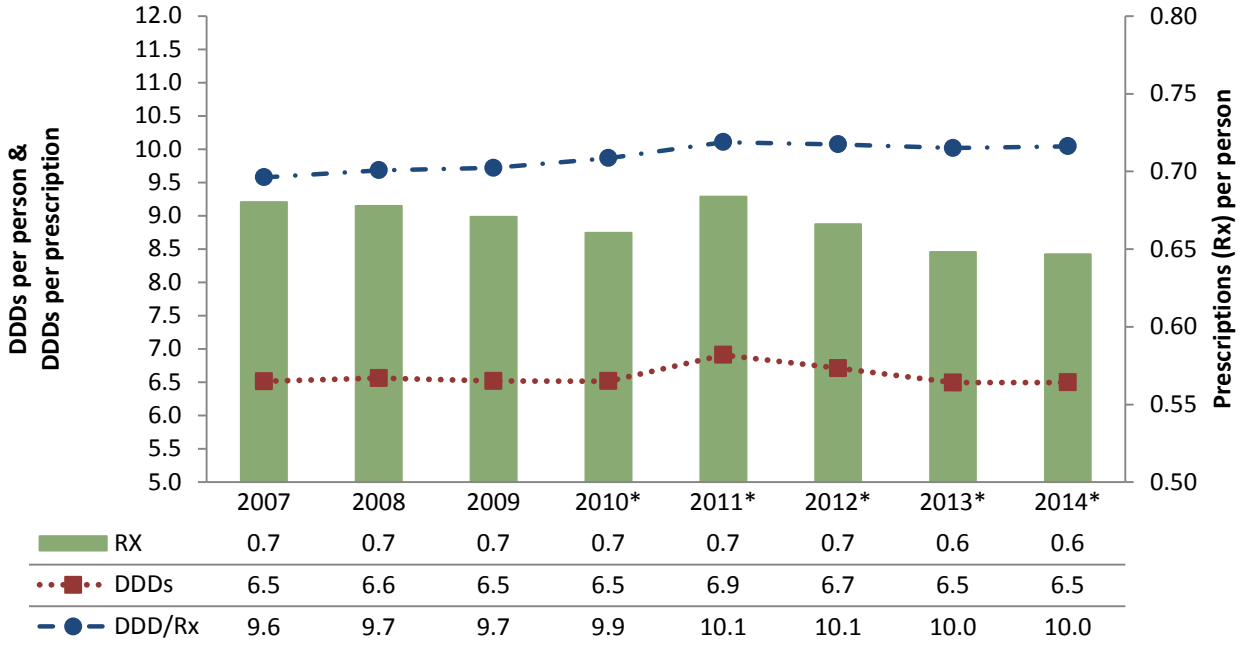
The majority of antimicrobials used in the Canadian outpatient population in 2014 were drugs for oral administration – at the national level, more than 213 prescriptions and 237 DDDs of oral antimicrobials were dispensed for every parenteral antimicrobial prescription.

Table 14: Total consumption for the top 10 antimicrobials* dispensed by community pharmacies (DDDs per 1,000 inhabitants) in Canada, 2007 to 2014

Antimicrobial	Rank	2007	2008	2009	2010	2011	2012	2013	2014
Amoxicillin	1	1597.2	1624.1	1641.8	1691.4	1836.3	1768.9	1758.9	1843.5
Amoxicillin and enzyme inhibitor	4	244.5	262.0	271.6	239.0	314.7	333.9	368.5	405.8
Azithromycin	7	284.4	288.0	289.4	282.7	370.6	367.7	308.9	310.3
Cephalexin	6	342.6	348.6	337.4	330.0	354.1	358.7	368.9	371.1
Ciprofloxacin	5	439.6	442.8	425.2	434.4	444.1	428.2	405.8	390.8
Clarithromycin	2	982.5	997.6	1009.0	985.6	1028.8	965.6	830.6	743.0
Doxycycline	3	313.0	336.6	346.9	411.5	449.9	477.8	510.1	548.0
Minocycline	9	371.6	370.9	349.2	374.4	357.8	319.6	299.4	275.4
Nitrofurantoin	8	211.7	226.4	241.9	256.2	271.4	284.5	283.8	292.5
Sulfamethoxazole and trimethoprim	10	287.5	285.2	282.8	279.3	274.9	254.1	248.3	245.3
TOTAL		**3477.4**	**5182.2**	**5195.2**	**5284.5**	**5702.6**	**5559**	**5383.2**	**5425.7**

***** Ranked from greatest to least DDDs at the national level in 2014.

Figure 40: Total antimicrobials dispensed through community pharmacies over time in Canada, as measured by defined daily doses per prescription, defined daily doses per inhabitant and prescriptions per inhabitant, 2007 to 2014[28]

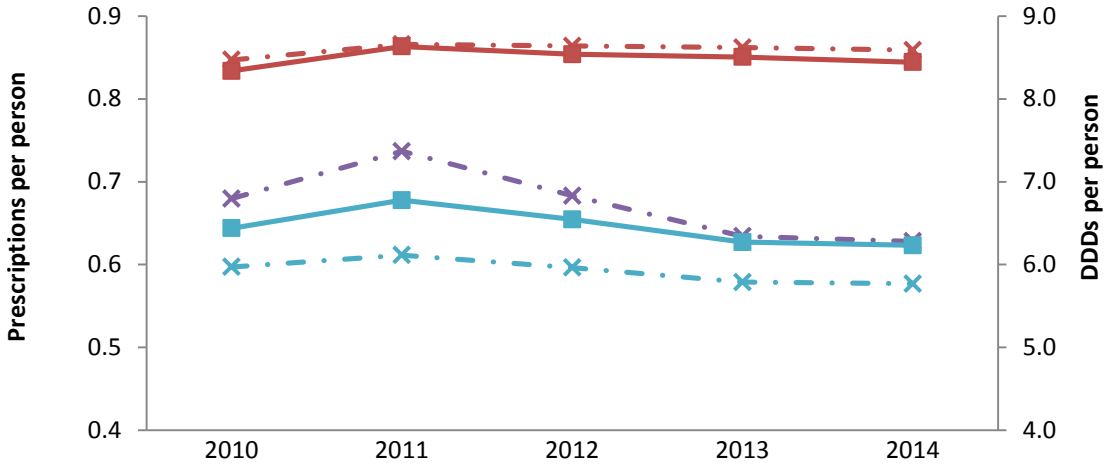


	2007	2008	2009	2010*	2011*	2012*	2013*	2014*
RX	0.7	0.7	0.7	0.7	0.7	0.7	0.6	0.6
DDDs	6.5	6.6	6.5	6.5	6.9	6.7	6.5	6.5
DDD/Rx	9.6	9.7	9.7	9.9	10.1	10.1	10.0	10.0

Interestingly prescribing rates among children (≤ 14 years old) have decreased 8% in 2014 compared to 2010 and 1% compared to 2013 (**Figure 41**). In 2014, on average, 63% of children between the ages of 0 and 14 years received an antimicrobial. Fifty-four percent of these prescriptions were for amoxicillin, followed by azithromycin (10%) and clarithromycin (9%). Compared to 2010, amoxicillin and enzyme inhibitor dispensing rates in 2014 increased 27%, while rates for amoxicillin alone increased 8% compared to 2010.

[28] Data from 2007 to 2009 include only oral products, 2010 to 2014 data include oral and parenteral products.

Figure 41: Patterns in antimicrobial use by age group, as dispensed by Canadian pharmacies, 2010 to 2014



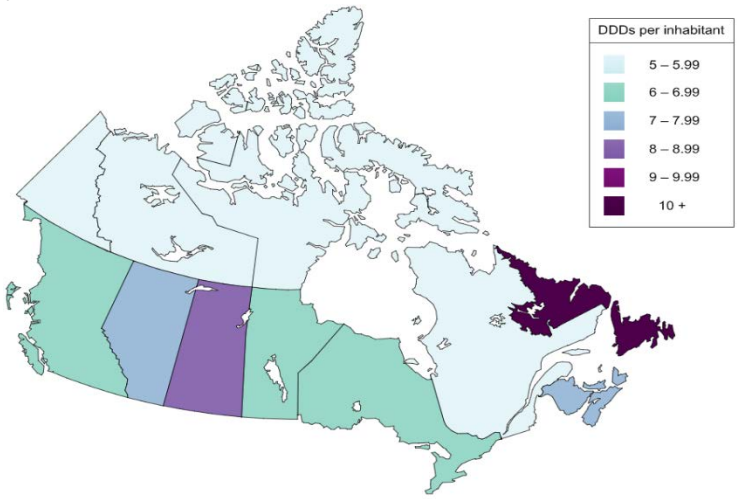
	2010	2011	2012	2013	2014
Rx 0-14	0.7	0.7	0.7	0.6	0.6
Rx 15-59	0.6	0.6	0.6	0.6	0.6
Rx 60+	0.8	0.9	0.9	0.9	0.9
DDD 15-59	6.4	6.8	6.5	6.3	6.2
DDD 60+	8.3	8.6	8.5	8.5	8.4

Year

In 2014, 58% of adults (15-59 years old) received an antimicrobial prescription compared to 86% of seniors (60 years and older). Although declines in prescribing rates have been observed between 2010 and 2014 in younger age groups (8% in children and 3% in adults), these declines have not been observed among seniors. Additionally, adults received more doses per prescription than seniors (approximately 11 days of treatment per prescription, compared to 10 days of treatment for seniors).

Variation in antimicrobial use was observed across Canadian provinces and territories, with Newfoundland and Labrador displaying higher DDDs per inhabitant. In 2014, Newfoundland and Labrador had more than 33% higher DDDs per inhabitant than Saskatchewan (next highest) (**Figure 42**).

Figure 42: Total antimicrobials dispensed through community pharmacies within provinces or territories in Canada, 2014[29]



Provincial/territorial variation in the total antimicrobials dispensed at the individual drug level was particularly pronounced for amoxicillin in 2014 (with a high of 3.4 DDDs per inhabitant in Newfoundland and Labrador and a low of 1.3 DDDs per inhabitant in Quebec) (**Table 15**). Amoxicillin and clarithromycin were the only two drugs identified among the top five antimicrobials dispensed with higher DDDs per inhabitant in every province and territory. Ciprofloxacin was among the top five antimicrobials dispensed in British Columbia (#5), Quebec (#4) and Newfoundland and Labrador (#3).

[29] BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario; QC: Quebec; NB: New Brunswick; NS: Nova Scotia; PE: Prince Edward Island; NL: Newfoundland and Labrador; TE: Territories (includes: Northwest Territories, Nunavut, Yukon).

Table 15: Total defined daily doses per 1,000 population per day of top antimicrobials dispensed by community pharmacies in Canada in 2014, by province and territories[30]

Antimicrobial	Rank[31]	AB	BC	MB	NB	NL	NS	ON	PE	QC	SK	TE
Amoxicillin	1	2026.2	1533.6	2004.0	1820.7	3360.0	1904.9	2090.9	1771.2	1321.7	2377.7	1072.7
Amoxicillin and enzyme inhibitor	4	497.5	337.7	443.7	462.5	654.8	416.3	326.9	781.8	504.6	346.9	179.8
Azithromycin	7	298.5	181.7	423.3	330.2	539.2	207.8	356.1	309.4	280.4	391.9	127.7
Cephalexin	6	483.5	425.3	504.6	464.3	658.8	543.9	403.9	544.8	110.5	730.2	235.2
Ciprofloxacin	5	397.5	374.8	404.4	337.8	1018.0	367.6	340.8	366.0	449.6	375.6	145.0
Clarithromycin	2	877.4	689.5	452.2	766.0	1073.9	831.4	696.6	838.4	819.5	583.3	215.7
Doxycycline	3	675.3	837.5	592.3	585.6	649.8	798.9	433.4	727.6	339.2	1464.7	319.2
Minocycline	9	436.0	288.4	255.3	260.8	302.6	386.0	191.0	218.1	345.5	99.6	
Nitrofurantoin	8	277.6	353.1	225.9	325.7	339.5	413.1	352.8	316.8	139.0	428.9	
Sulfamethoxazole & trimethoprim	10	264.3	268.3	329.9	322.3	537.8	388.3	238.3	407.9	152.5	421.0	175.0
TOTAL	**0**	**6233.8**	**5289.9**	**5635.6**	**5675.9**	**9134.4**	**6258.2**	**5430.7**	**6282**	**4462.5**	**7219.8**	**2470.3**

[30] BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario; QC: Quebec; NB: New Brunswick; NS: Nova Scotia; PE: Prince Edward Island; NL: Newfoundland and Labrador; TE: Territories (includes: Northwest Territories, Nunavut, Yukon).

[31] Ranked from greatest to least DDDs at the national level in 2014.

Text Box 7: Antimicrobial consumption among Indigenous communities in Canada

In Canada, provinces and territories are responsible for providing health care services, guided by the provisions of the *Canada Health Act*. First Nations and Inuit people access insured services through provincial and territorial governments. However, there are a number of health-related services that are not insured by provinces, territories or other private insurance plans. Health Canada's Non-Insured Health Benefits (NIHB) Program provides coverage for a limited range of services for First Nations and Inuit (including antimicrobial prescriptions) when they are not insured elsewhere.

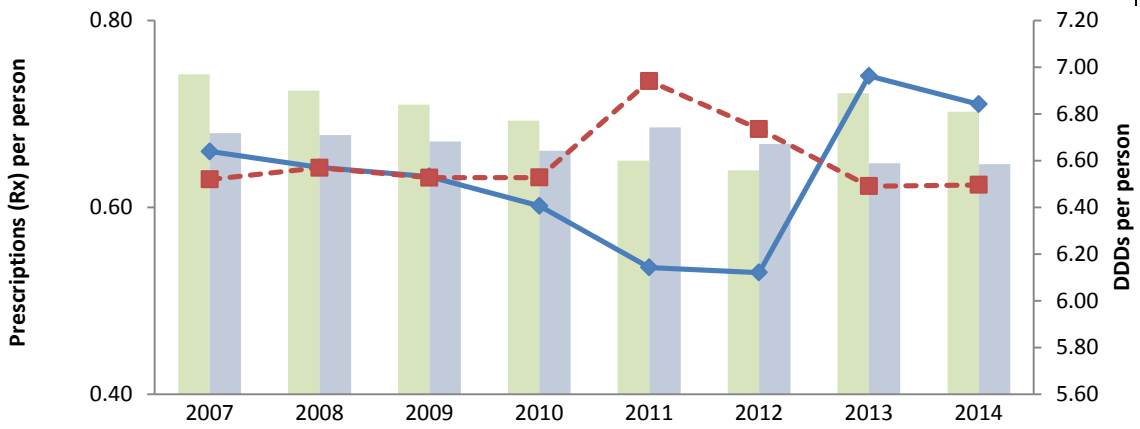
The community dispensing data presented in this report includes prescriptions covered under the NIHB program, with the exception of the Territories. To better understand antimicrobial use within the Indigenous communities, Health Canada provided data on antimicrobial prescriptions covered under the NIHB program. These were excluded from the community dispensing data to allow a true comparison of antimicrobial use between Indigenous and Non-Indigenous communities. Data cleaning and analysis followed methods used for other human antimicrobial use analyses.

Overall, antimicrobial use within the Indigenous and Non-Indigenous populations was similar, with an average of 70% and 65% of people receiving an antimicrobial through a community pharmacy, respectively. Total amounts of antimicrobials dispensed to Indigenous populations have decreased during this time period, with a 19% decrease for total prescriptions per inhabitant and a 4% decrease during this time period for total defined daily doses per inhabitant.

Children (aged 0-14 years) observed a 30% reduction in prescriptions per inhabitant for antimicrobials dispensed to Indigenous populations between 2002 and 2014 (**Figure B**). Lower reductions were observed among antimicrobial dispensing rates within the adult (aged 15-59 years) and elderly (aged 60 years or older) members of Indigenous populations. Total antimicrobial dispensed, as measured by DDD per inhabitant decreased across all age groups (**Figure C**). Age information for Non-Indigenous populations is available as of 2010. Prescribing rates and total antimicrobials dispensed for this population remained stable among all age groups during 2010 to 2014.

PHAC and Health Canada will continue to work together to monitor outpatient antimicrobial consumption among Canadians to assist in identifying areas requiring education or stewardship programs.

Figure A: Outpatient consumption of antimicrobials among Indigenous (NIHB) and Non-Indigenous (Non-NIHB) populations in Canada, 2002 to 2014



	2007	2008	2009	2010	2011	2012	2013	2014
RX NHIB	0.74	0.73	0.71	0.69	0.65	0.64	0.72	0.70
RX Non-NIHB	0.68	0.68	0.67	0.66	0.69	0.67	0.65	0.65
DDDs NHIB	6.64	6.57	6.53	6.41	6.14	6.12	6.96	6.84
DDDs Non-NIHB	6.52	6.57	6.53	6.53	6.94	6.73	6.49	6.50

Figure B: Total prescriptions per person dispensed in Canada, by age group and population, 2007 to 2014

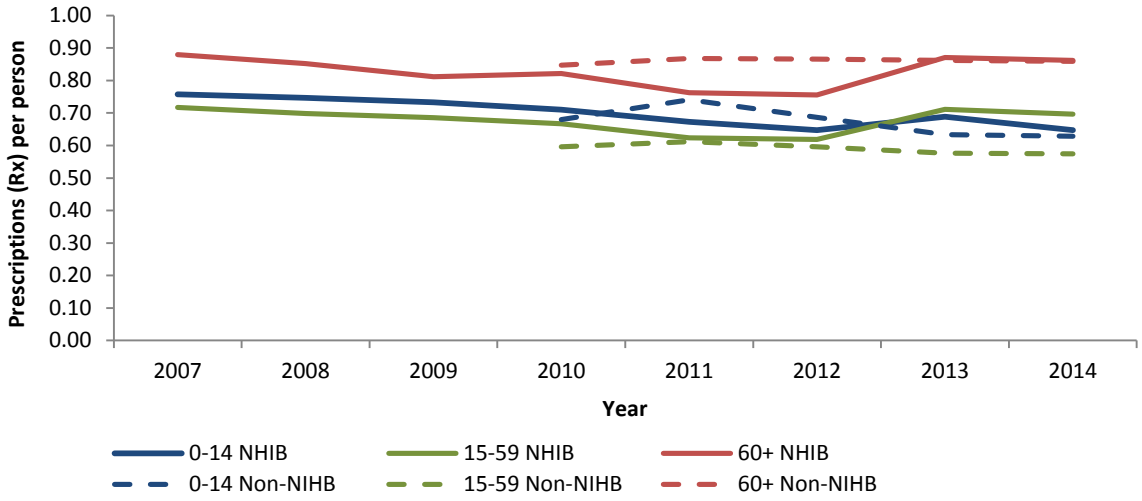
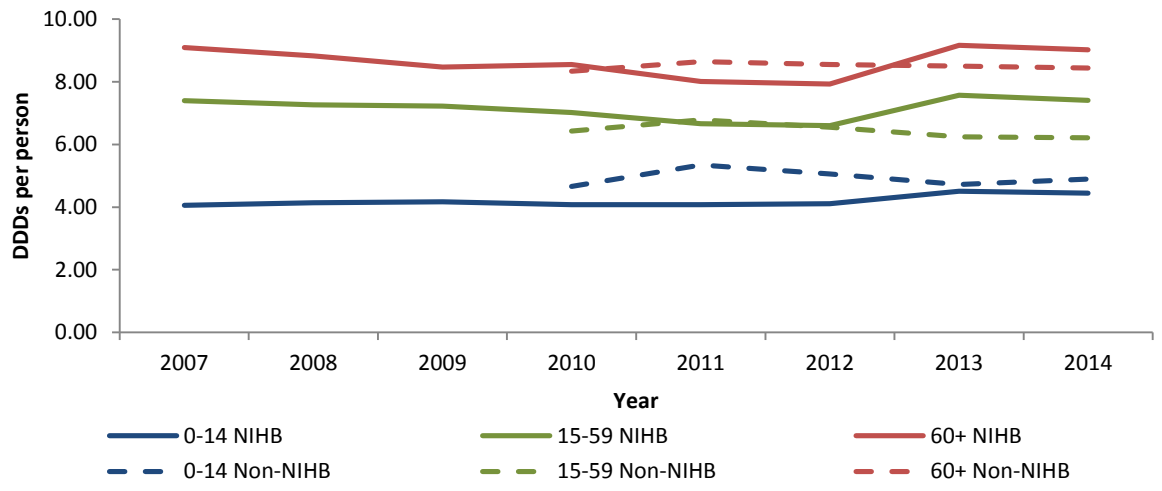


Figure C: Total antimicrobials (DDDs per person) dispensed by community pharmacies in Canada, by age group and population, 2002 to 2014



Prescribing practices by specialization

Information on the specialization of the professional providing a prescription was available in the dispensing data from community pharmacies for 2010 to 2014. A total of 31 different medical and non-medical specializations were identified with an additional category 'all other speciality'[32]. To facilitate the review of the data, these specializations were further categorized into eight broader groupings[33] (family physicians and general practitioners; dermatologists; diagnostics; emergency medicine; pediatrics, medicine; surgery; and all other specialities).

Sixty-six percent of all prescriptions dispensed by community pharmacies were prescribed by "community practitioners" (family physicians and general practitioners), followed by specialties included in the "all other specialties" (21%) and "medicine" (5%). The antimicrobials most commonly prescribed by "community practitioners" were amoxicillin, azithromycin and ciprofloxacin. While amoxicillin was the top antimicrobial prescribed by practitioners within the "all other specialties" and "medicine" categories, clindamycin and penicillin v rounded off the top three drugs prescribed by "all other specialties" and azithromycin and sulfamethoxazole by "medicine" professionals.

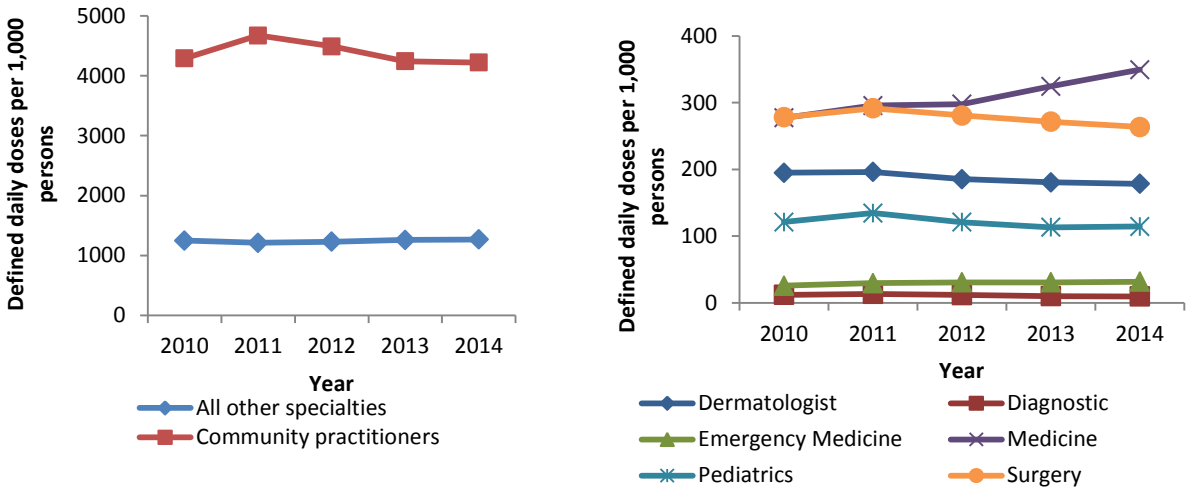
Prescriptions provided by "community practitioners", "all other specialties" and "medicine" professionals represented the largest number of DDDs per 1,000 inhabitants in 2014 (**Figure 43**). While the total amounts of antimicrobials prescribed by the different specializations remained relatively stable over time, compared to 2010, the largest decrease in 2014 for the total antimicrobials prescribed was observed by professionals in the "diagnostic" (21% decrease) category. However, an increase was

[32] All other specialities includes "all other miscellaneous: e.g.,: sports medicine and other specialists" e.g., nurse practitioners.

[33] **Community practitioners**: family physicians and general practitioners; **dermatologists**; **diagnostics:** pathologists, radiologist and nuclear medicine; **emergency medicine**; **pediatrics, medicine:** allergists, immunologists, bacteriologists, cardiologists, endocrinologists, gastroenterologists, geriatrics, hematologists, internist, nephrologist, oncologists, psychiatrists and respirologists; **surgery:** anesthesiologists, general surgery, obstetrician & gynecologists, ophthalmologists, orthopedic surgery, thoracic/cardiac surgery and urologists; and **all other specialities.**

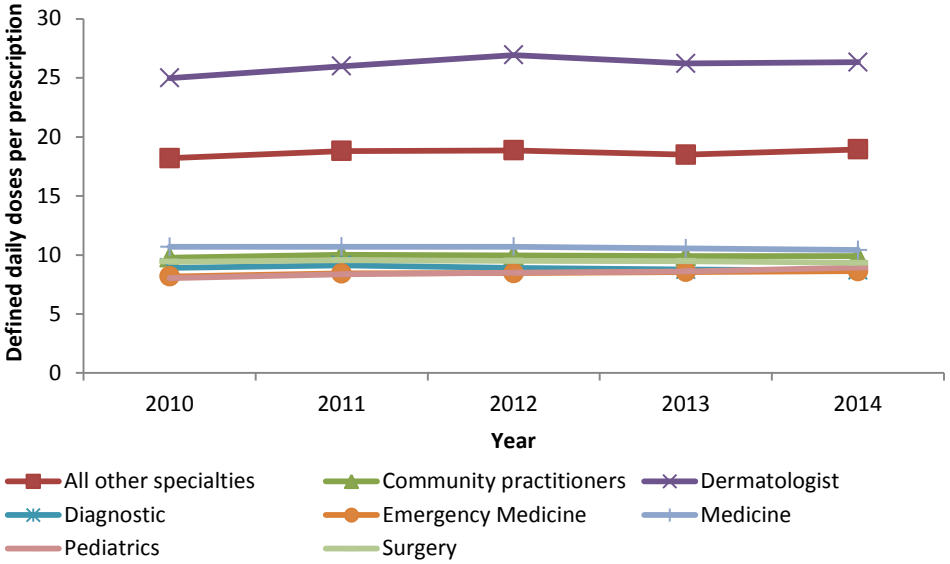
observed in total antimicrobials dispensed for prescriptions in the "medicine" category, increasing 26% in 2014 compared to 2010. These increases were largely due to higher levels dispensed over the five-year period for amoxicillin, azithromycin, cefadroxil, cefazolin, nitrofurantoin and tetracycline.

Figure 43: Total defined daily doses per 1,000 inhabitants for antimicrobials prescribed by different specializations and dispensed by community pharmacies in Canada, 2010 to 2014



When looking at the total amount of antimicrobials provided per prescription, dermatologists had the highest levels with 26 DDDs per prescription, followed by "all other specialties" (19 DDDs per prescription) and "medicine" (10 DDDs per prescription) (**Figure 44**). The larger levels of antimicrobials provided by dermatologists per prescription is consistent with longer treatments provided for skin conditions such as acne. The main drugs prescribed by this specialization included sulfadiazine, doxycycline, tetracycline and trimethoprim products. Prescribing practices have remained stable over the five-year period, with no large changes observed in the total antimicrobials per prescription dispensed by any of the prescriber specializations.

Figure 44: Total defined daily doses per prescription by different specializations and dispensed by community pharmacies in Canada, 2010 to 2014



Antimicrobial recommendations by diagnoses

In 2014, a total of 297 million medical diagnoses were made by community-level practitioners resulting in a little over 23 million antimicrobial recommendations. Antimicrobial recommendations are not necessarily tied to a prescription as the patient may not have agreed with receiving an antimicrobial prescription, may not have filled out a prescription following physician orders to wait a period of time, may have chosen not to fill the prescription, may have received a sample of medication, or was a continuation of a previous prescription renewal.

Eight percent of all diagnoses resulted in an antimicrobial being recommended for treatment in 2014. Forty percent of all antimicrobial recommendations were provided for treating respiratory infections, of which 38% were for treating upper respiratory tract infections, followed by acute bronchitis (21%) and acute sinusitis (14%). Overall, 82% of all diagnoses of acute sinusitis resulted in an antimicrobial being recommended followed by acute bronchitis (77%) and pneumonia (74%) (**Figure 45**).

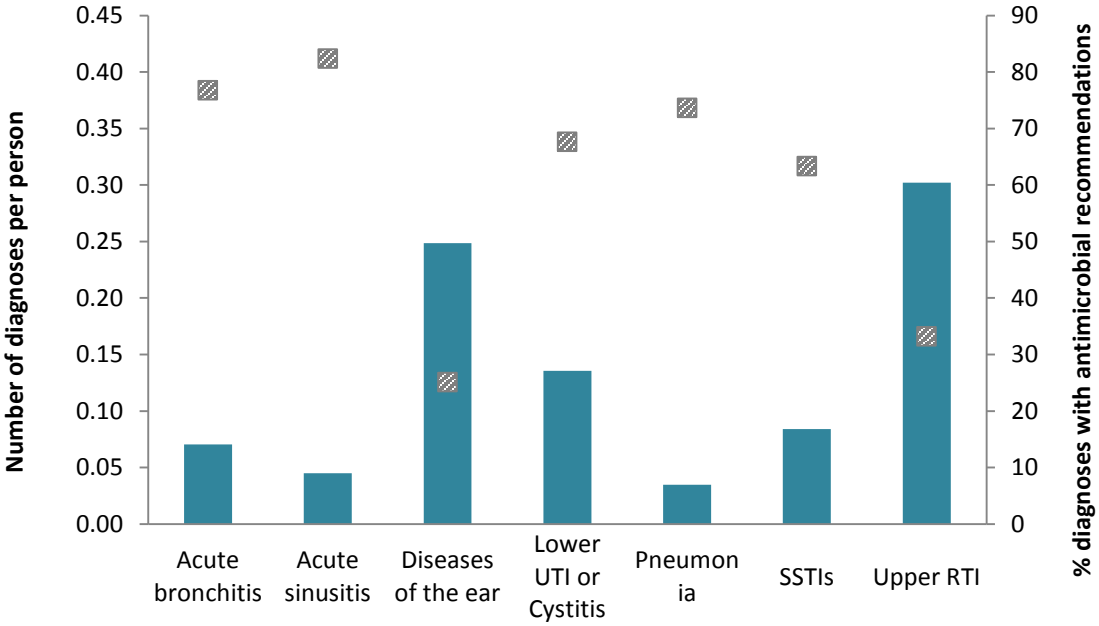
Children (0 to nine years of age) had the highest overall antimicrobial recommendation rate with nearly eight out of 10 children having been recommended an antimicrobial for treatment in 2014. As a result, this age group had the highest proportion of diagnoses resulting in an antimicrobial recommendation (11%). The majority of the recommendations were provided for the treatment of diseases of the ear (42%), followed by upper respiratory tract infections (24%) and skin and soft tissue infections (8%). Amoxicillin was the predominant antimicrobial recommended for the treatment of diseases of the ear (73% of all recommendations) and upper respiratory tract infections (77%).

While people between 10 and 19 years of age had the lowest recommendation rate (0.51 per person) in 2014, they had the second highest proportion of diagnoses resulting in an antimicrobial recommendation (10%). The majority of the recommendations were provided for treating upper respiratory tract infections (32%), diseases of the ear (12%) and acne (8%). Similar to what was observed

in children, amoxicillin was the main antimicrobial recommended for treating diseases of the ear (61%) and upper respiratory tract infections (51%).

Seven out of 10 people in the elderly age group received an antimicrobial recommendation in 2014, mainly for the treatment of lower urinary tract infections or cystitis (16%), acute bronchitis (11%) and skin and soft tissue infections (10%). In 2014, 39% percent of all recommendations provided for treating skin and soft tissue infections were for cephalexin. For treating acute bronchitis, a similar proportion of recommendations were made for azithromycin (27%) and clarithromycin (25%). Similarly, ciprofloxacin (41%) and nitrofurantoin (41%) were recommended for treating lower urinary tract infections or cystitis.

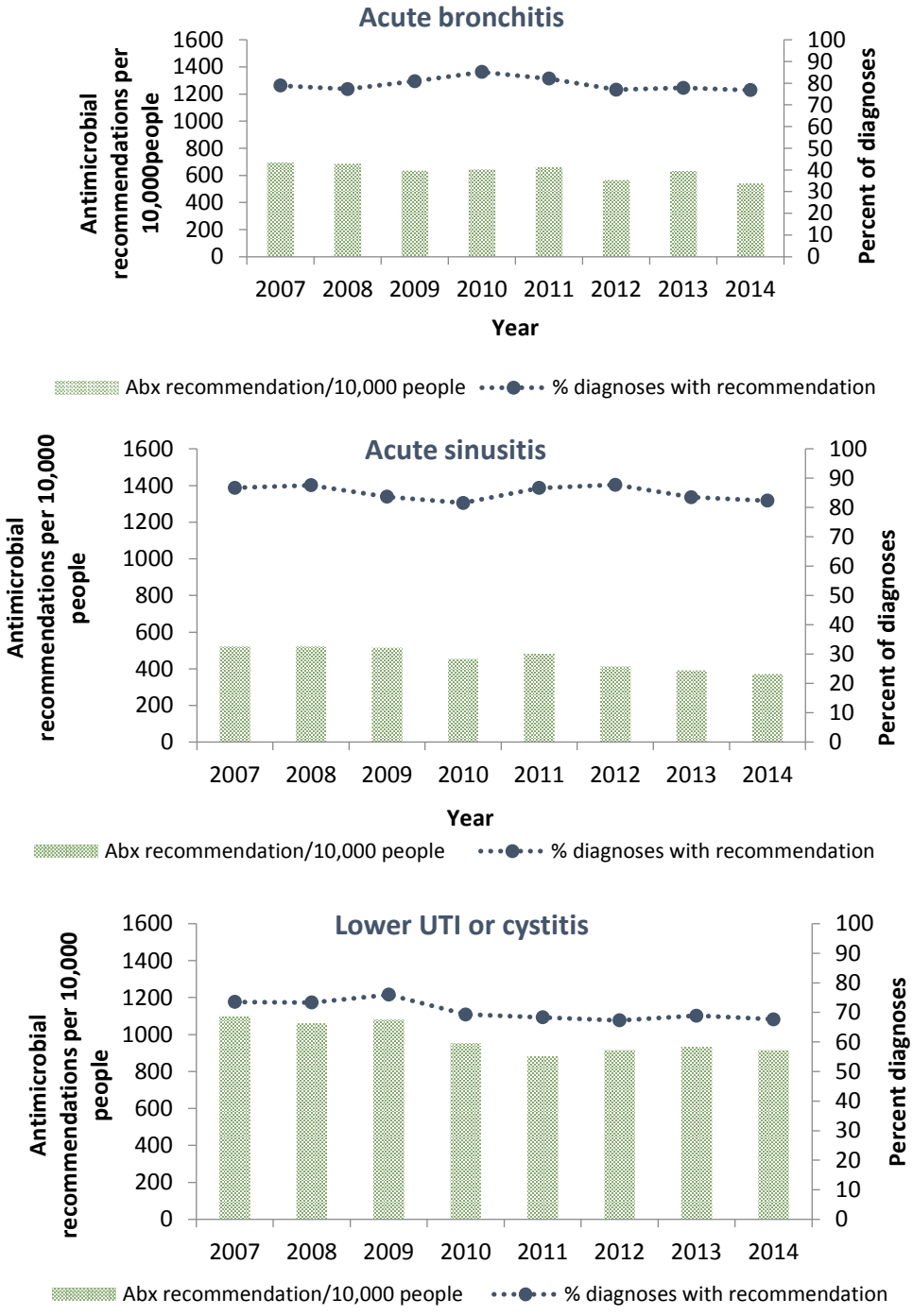
Figure 45: Number of specific diagnoses per person and the percentage of those diagnoses with recommendations for an antimicrobial in Canada, 2014[34]

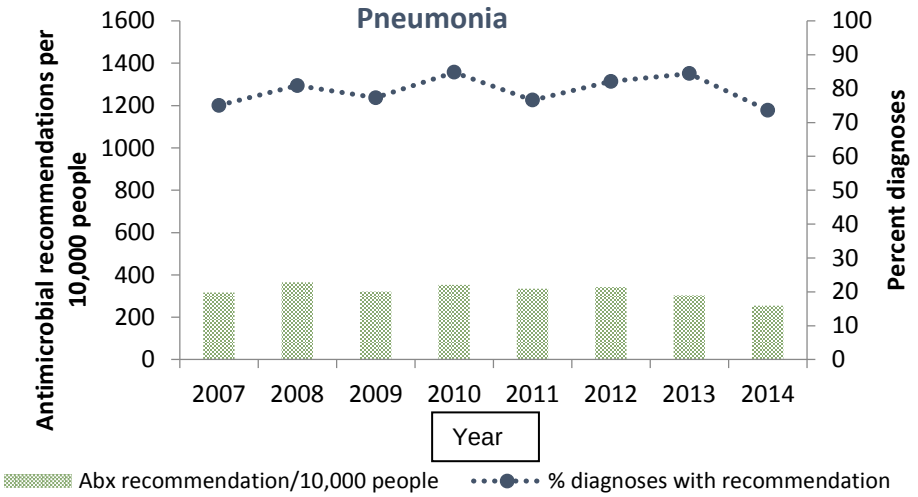


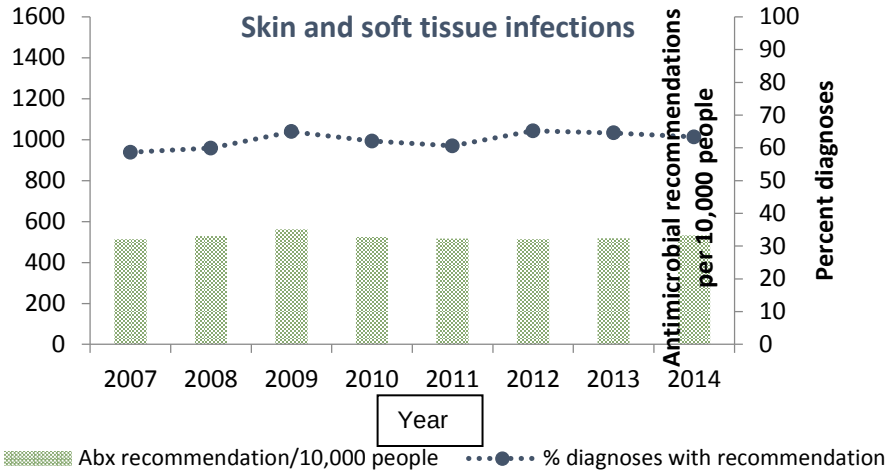
On average, the percentage of diagnoses for which an antimicrobial was recommended remained stable over time, while the antimicrobial recommendation rates per population decreased (**Figure 46**).

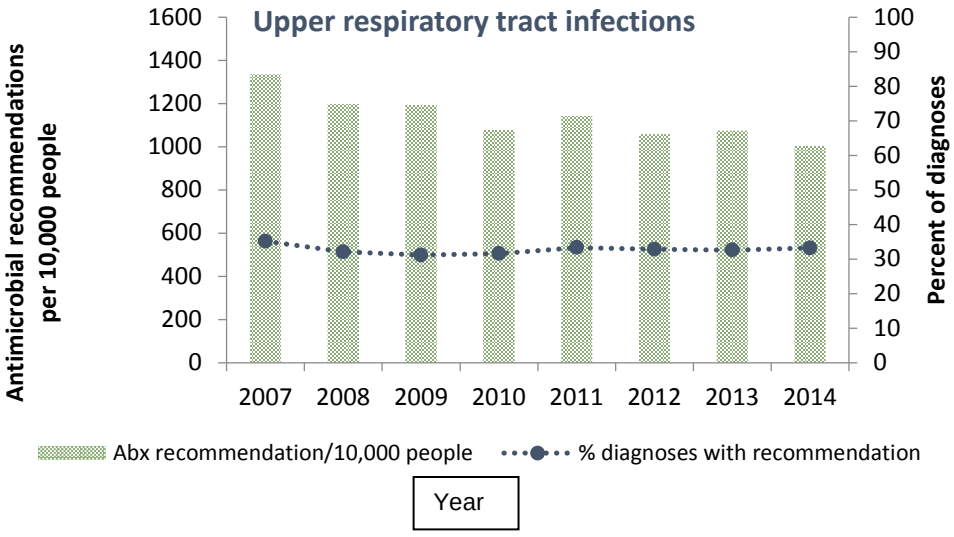
[34] UTI=urinary tract infection; SSTI= skin and soft tissue infection; RIT= respiratory tract infection.

Figure 46: Total antimicrobial recommendation rates and percentage of those diagnoses receiving a recommendation for an antimicrobial from community physicians for selected conditions in Canada, 2007 to 2014




Pneumonia
Antimicrobial recommendations per 10,000 people
Percent diagnoses
1600
1400
1200
1000
800
600
400
200
0
100
90
80
70
60
50
40
30
20
10
0
2007
2008
2009
2010
2011
2012
2013
2014
Year
Abx recommendation/10,000 people
% diagnoses with recommendation


Skin and soft tissue infections
Antimicrobial recommendations per 10,000 people
Percent diagnoses
1600
1400
1200
1000
800
600
400
200
0
100
90
80
70
60
50
40
30
20
10
0
2007
2008
2009
2010
2011
2012
2013
2014
Year
Abx recommendation/10,000 people
% diagnoses with recommendation


Upper respiratory tract infections
Antimicrobial recommendations per 10,000 people
Percent of diagnoses
1600
1400
1200
1000
800
600
400
200
0
100
90
80
70
60
50
40
30
20
10
0
2007
2008
2009
2010
2011
2012
2013
2014
Year
Abx recommendation/10,000 people
% diagnoses with recommendation

Text Box 8 : Physician practices in the treatment of lower urinary tract infections or cystitis in Canada

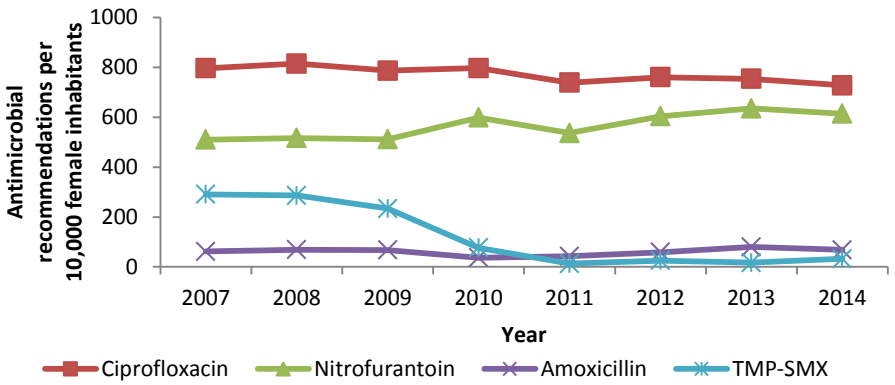
Clinical guidelines for treating acute uncomplicated lower urinary tract infections (UTIs) and cystitis recommend trimethoprim-sulfamethoxazole (TMP-SMX) and nitrofurantoin as first-line therapies (a,c,e). Although fluoroquinolones are effective in treating UTIs, they have not shown added value compared to other antibiotic groups and have the potential to cause secondary infections and the development of resistance (a,e,f). As such, fluoroquinolones should not be used as first-line therapy and should only be used if the recommended first-line antimicrobials cannot be used due to regional resistance patterns, regional availability or allergy history or tolerance problems (g). Beta-lactams and fosfomycin can be considered second-line therapies (69), if resistance rates for TMP-SMX exceed 20% or if first-line drugs are not appropriate (a–c,e,g).

In 2014, 14% of Canadians were diagnosed with lower UTIs or cystitis. Eighty-two percent of those diagnosed were women, the majority (83%) of whom were over 20 years of age. Sixty-eight percent of all lower UTIs diagnosed in 2014 were recommended an antimicrobial for treatment, with the rate of recommendations among women approximately eight times that of males (1,597 recommendations per 10,000 women vs. 213 recommendations per 10,000 men).

In 2014, ciprofloxacin (a fluoroquinolone) was the most commonly recommended antimicrobial for treating these infections among women (46%) followed by nitrofurantoin (38%) and amoxicillin (4%) (**Figure A**). Rates of TMP-SMX recommendations have shown dramatic declines since 2007, with only 2% of those diagnosed with lower UTIs in 2014 having received a recommendation for this antimicrobial. In 2014 nearly half of all UTIs were recommended therapy with ciprofloxacin. This is higher than what has been observed in the United States where 33% of women (h) and 60% of men (d) in different studies received a fluoroquinolone prescription. An additional study carried out in 2014 showed that among patients who received a fluoroquinolone prescription, 94% of these were inappropriate due to no evidence of resistance to other antibiotics (f)

This data highlights the importance of stewardship programs at the outpatient level to reduce the current levels of ciprofloxacin use and enhance adherence to guidelines for treating lower urinary tract infections.

Figure A: Antimicrobials recommended (per 10,000 women) for treatment of lower UTI or cystitis, in Canada, 2007 to 2014



References:

a) Zalmanovichi TA, Green H, Paul M, et al. Antimicrobial agents for treating uncomplicated urinary tract infections in women. Cochrane Database of Systematic Reviews 2010;10. Art. No: CD007182. DOI: 10.1002/14651858. CD007182.pub2.

b) National Institute for Health and Care Excellence (NICE). Urinary tract infections in adults. London: NICE; 2015. https://www.nice.org.uk/guidance/qs90/resources/urinary-tract-infections-in-adults-2098962322117.

c) Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120.

d) Holmer HK, Elman MR, Evans CT, et al. Prescribing without guidance: Antibiotic prescribing for male urinary tract infection (UTI) in primary care. Poster session presented at: IDWeek; 2015 October 7-11; San Diego, CA, USA.

e) Nicolle L, Anderson PAM, Conly J, et al. Uncomplicated urinary tract infection in women. Current practice and the effect of antibiotic resistance on empiric therapy. Can Fam Physician 2006;52:612-618.

f) Nguyen D, Dickter J, Guo R, et al. The misuse of ciprofloxacin in outpatient treatment of acute uncomplicated cystitis (AUC) – a retrospective study. Poster session presented at: IDWeek; 2015 October 7-11; San Diego, CA, USA.

g) National Guideline Clearinghouse (NGC). Guideline synthesis: Diagnosis and management of lower urinary tract infection. In: National Guideline Clearinghouse (NGC). Rockville MD: Agency for Healthcare Research and Quality (AHRQ); 2008 Jan (revised 2012 Mar). http://www.guideline.gov/syntheses/synthesis.aspx?id=35626&search=urinary+tract+infections.

h) Dykehouse L, Dumkov L, Jameson A. Evaluating the need for antimicrobial stewardship efforts in the outpatient setting: A focus on appropriate prescribing for urinary tract infections. Poster session presented at: IDWeek; 2015 October 7-11; San Diego, CA, USA.

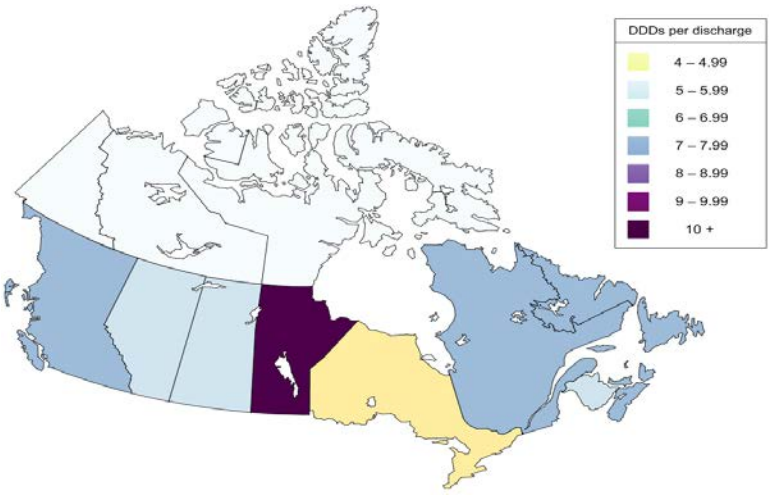
Hospital purchasing and use

In 2014, 38,340 kilograms of antimicrobials were purchased by hospitals across Canada at a cost of $104 million. When adjusted for the number of hospital discharges that occurred in 2014, this amounts to approximately six DDDs of antimicrobial purchased per discharge, a rate that has remained fairly stable over the 2002 to 2014 period of surveillance (**Figure 47**).

Ciprofloxacin was the antimicrobial most commonly purchased in 2014 (10% of all antimicrobial DDDs purchased), followed by amoxicillin, azithromycin, ceftriaxone and doxycycline (7% each) (**Table 16**). Although the purchasing of amoxicillin and ciprofloxacin remained stable between 2008 and 2014, ceftriaxone and doxycycline had the highest increase during the same period. Ceftriaxone purchases increased from 79 DDDs per 1,000 discharges in 2002 to 440 DDDs per 1,000 discharges in 2014 and doxycycline increased from 124 to 417 DDDs per 1,000 discharges during the same time period.

Similar to the variation observed in the community dispensing data, large variations in hospital purchasing of antimicrobials were present in 2014 among the provinces. Manitoba had the largest number of DDDs purchased per discharge than any other province since 2003, 49% higher than Nova Scotia, the province with the next highest number.

Figure 47: Defined daily doses per patient discharge for antimicrobials purchased by hospitals in Canada, by province, 2014



Large differences in the purchasing of specific antimicrobials were observed in Manitoba compared to the other provinces (**Table 17**), particularly amoxicillin (2,302 DDDs per 1,000 discharges compared to 225 DDDs per 1,000 discharges in Nova Scotia), cefoxitin (1,497 DDDs per 1,000 discharges compared to 60 DDDs per 1,000 discharges in Newfoundland and Prince Edward Island) and cephalexin (877 DDDs per 1,000 discharges compared to 93 DDDs per 1,000 discharges in Quebec). Similarly, Nova Scotia purchased larger amounts of imipenem and cilastatin (54 DDDs per 1,000 discharges) compared to Quebec (17 DDDs per 1,000 discharges) which had the second highest levels and Saskatchewan (0.01 DDDs per 1,000 discharges) representing the lowest levels in 2014.

Unlike the community dispensing data where commonalities were observed among the top five antimicrobials dispensed across the provinces, large variations were observed in the antimicrobials purchased by hospitals. Ceftriaxone was the only antimicrobial identified among the top five antimicrobials purchased by all provincial hospitals with the exception of Quebec. More specifically, the top antimicrobial purchased in each province varied with ceftriaxone identified as the top antimicrobial in Alberta, doxycycline in British Columbia, amoxicillin in Manitoba, Newfoundland and Labrador and Prince Edward Island, azithromycin in Saskatchewan, cefazolin in New Brunswick and ciprofloxacin in Ontario, Quebec and Nova Scotia. Nitrofurantoin was identified among the top 10 antimicrobials purchased by hospitals in British Columbia in 2014, but was not identified within the top 10 antimicrobials for any other province. The reasons for the differences in antimicrobial use between provinces are not well understood, but are likely (at least in part) due to different drug formularies and different treatment protocols and variation in sub specialties care units such as Transplantation, Burn and Oncology.

Table 16: The average defined daily doses per 1,000 patient discharges for the top 10 antimicrobials purchased by hospitals in Canada, 2008 to 2014

Antimicrobial	Rank	2008	2009	2010	2011	2012	2013	2014
Amoxicillin	2	351.2	376.5	392.9	407.4	415.2	433.6	455.6
Amoxicillin and enzyme inhibitor	7	149.9	173.5	174.1	210.1	236.5	238.6	314.2
Azithromycin	3	308.0	348.0	356.4	404.7	456.1	481.1	446.5
Cefazolin	6	549.8	584.4	546.3	535.7	541.7	448.2	399.1
Cefoxitin	8	514.9	621.7	468.4	456.5	361.6	264.0	312.4
Ceftriaxone	4	219.3	270.3	272.9	335.0	366.0	413.0	440.0
Ciprofloxacin	1	664.8	649.0	569.4	557.4	599.9	690.6	643.5
Doxycycline	5	474.5	313.3	332.7	410.1	337.4	366.4	417.5
Piperacillin and enzyme inhibitor	9	144.9	202.8	209.4	259.9	270.9	276.7	295.5
Sulfamethoxazole and trimethoprim	10	293.1	302.6	278.2	279.1	274.9	269.8	260.3
TOTAL		**3670.4**	**3842.1**	**3600.7**	**3855.9**	**3860.2**	**3882**	**3984.6**

*Ranked from greatest to least DDDs at the national level in 2014.

Table 17: Defined daily doses per 1,000 patient discharges for the top 10 antimicrobials purchased by hospitals in Canadian provinces, 2014

Antimicrobial	Rank*	BC	AB	SK	MB	ON	QC	NB	NS	PE & NL
Amoxicillin	2	609.5	405.1	518.1	2302.3	290.8	300.6	225.6	360.9	930.0
Amoxicillin and enzyme inhibitor	7	299.6	341.6	160.7	566.4	189.7	489.1	246.3	269.2	422.9
Azithromycin	3	583.2	387.1	721.7	706.0	328.3	522.8	313.2	277.8	420.5
Cefazolin	6	33.5	408.8	272.8	328.6	374.3	575.3	969.1	525.2	574.4
Cefoxitin	8	261.1	137.7	369.4	1497.1	183.0	449.4	162.8	312.7	60.2
Ceftriaxone	4	589.7	539.3	508.6	955.5	403.5	252.1	336.3	400.3	669.7
Ciprofloxacin	1	386.3	478.3	284.8	514.9	504.7	1077.6	556.6	1482.9	680.7
Doxycycline	5	1110.5	446.3	311.5	287.2	366.3	177.9	211.1	341.0	242.7
Piperacillin and enzyme inhibitor	9	314.5	213.5	228.0	235.6	227.7	476.3	262.1	217.8	200.7
Sulfamethoxazole and trimethoprim	10	296.1	279.7	257.5	716.8	215.1	211.5	157.2	284.1	440.3
TOTAL		**4484**	**3637.4**	**3633.1**	**8110.4**	**3083.4**	**4532.6**	**3440.3**	**4471.9**	**4642.1**

*Ranked from greatest to least DDDs at the national level in 2014.

Text Box 9: Antimicrobial use within hospitals participating in the Canadian Nosocomial Infection Surveillance Program (CNISP) – Pilot project

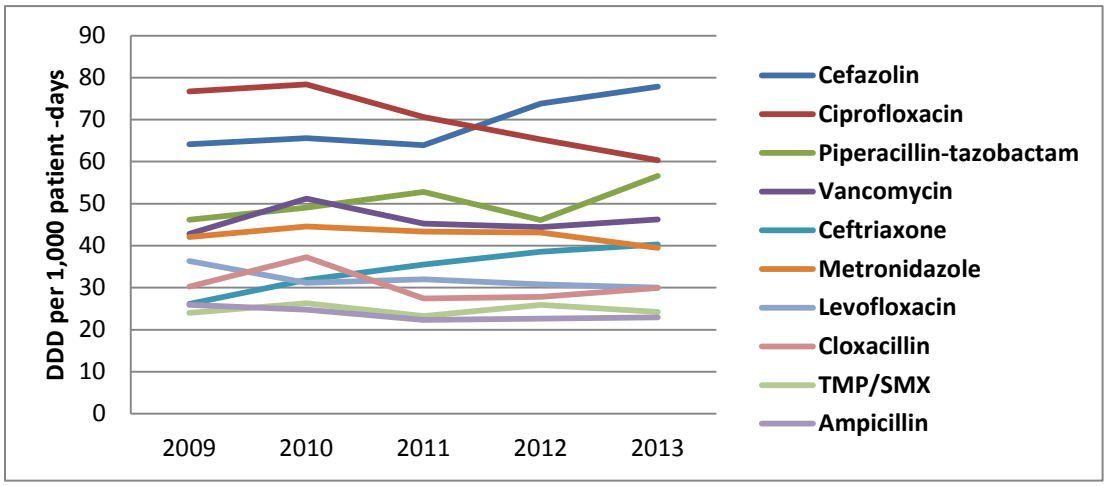
Background: CNISP conducted a 5 year, retrospective, targeted pilot to evaluate the trends of antimicrobial usage in the healthcare setting. AMU data were obtained from 21 (14 adult and seven mixed adult-pediatric) sites for 2009 to 2013 and analyzed using DDD per 1,000 patient days for each antibiotic. The AMU information was collected by fiscal year, April 1st to March 31st of the following year.

Objective: The purpose of this pilot study was to demonstrate the feasibility of AMU data collection and to provide recommendations to further improve the process for data collection and submission.

Results: The total AMU, which included 65 individual antimicrobials, among the participating hospitals has not changed significantly over time, with DDD per 1,000 patient days ranging from 661 in 2009 to 619 in 2013 (p= 0.4922) (**Figure A**). Between 2009 and 2013, the largest increase in use was observed for doxycycline (115%), ertapenem (107%) and amoxicillin-calvulanate (64%), whereas the largest decrease was seen in cefuroxime (-37%) clarithromycin (-28%) and ciprofloxacin (-21%). The number of patient beds within each hospital did not influence the overall levels of use. Hospitals with over 500 beds (seven hospitals) reported a total use in these five years of 573 DDD per 1,000 patient days, whereas hospitals with 201 to 500 (10 hospitals) reported 653 DDD per 1,000 patient days and hospitals of less than 200 beds (four hospitals) reported 1,042 DDD per 1,000 patient days (p = 0.3155).

Limitations: Information on antimicrobials could not be differentiated between parenteral and oral usage, requiring an approximation of DDD for certain antimicrobials. It is important to note that the drug formularies may differ from hospital to hospital and that the AMU data are obtained from an overall hospital perspective per fiscal year (i.e., not collected at an individual patient level and not based on indication). Therefore, the results obtained cannot be used to determine the appropriateness of AMU. Finally, though the CNISP participating sites are considered to be representative of the larger, urban acute care hospitals across Canada, there are limitations with respect to the representativeness of this sample of 21 CNISP sites.

Figure A: Ten most prescribed antimicrobial by DDDs per 1,000 patient days reported by CNISP participating hospitals between 2009 and 2013 in Canada



The Antimicrobial Use Working Group
Canadian Nosocomial Infection Surveillance Program

International perspective

The European Surveillance of Antimicrobial Consumption Network collects information from European member countries to estimate the total antimicrobial consumption in both the community and the hospital sectors.

In 2014, a total of 30 European countries provided information to ESAC-Net on antimicrobials consumed in their community. When these data were compared with the 2014 Canadian outpatient antimicrobial consumption rate, Canada (17.8 DDDs per 1,000 persons per day) ranked 12th lowest out of 31 countries by increasing level of AMU, with almost half the level of use reported by Greece (country with highest use, 34 DDDs per 1, 000 persons per day) (**Figure 48**) (69).

On the other hand, 23 European countries provided information to ESAC-NET on total antimicrobials purchased by their hospitals in 2014. Compared to these data, Canada (1.4 DDDs per 1,000 discharges per day) ranked third lowest out of 24 countries classified by increasing levels of total AMU in hospitals, with nearly half the level of antimicrobials purchased by hospitals in the United Kingdom (2.6 DDDs per 1,000 persons per day) (**Figure 49**) (69).

In the United States, in 2011, healthcare providers prescribed 262.5 million courses of antibiotics (842 prescriptions per 1,000 persons) in community settings. Acute respiratory infections result in the vast majority of inappropriate antibiotic prescriptions in United States outpatient clinics. In 2010, 71% of all outpatient visits for acute bronchitis resulted in an antibiotic prescription. On the other hand, between the mid 1990's and 2008, outpatient antibiotic prescribing rates for children (≤ 14 yrs.) with acute respiratory tract infections decreased by 11% (70).

As such, inappropriate antibiotic use is also seen in United States hospitals, where in 2010, 55.7% of patients discharged from 323 United States hospitals received antibiotics during their hospitalization and antibiotic use could have been improved in almost 37.2% of the reviewed prescription scenarios (70).

Figure 48: Outpatient antimicrobial use (DDD per 1,000 persons per day) reported in Canada and in 30 European countries

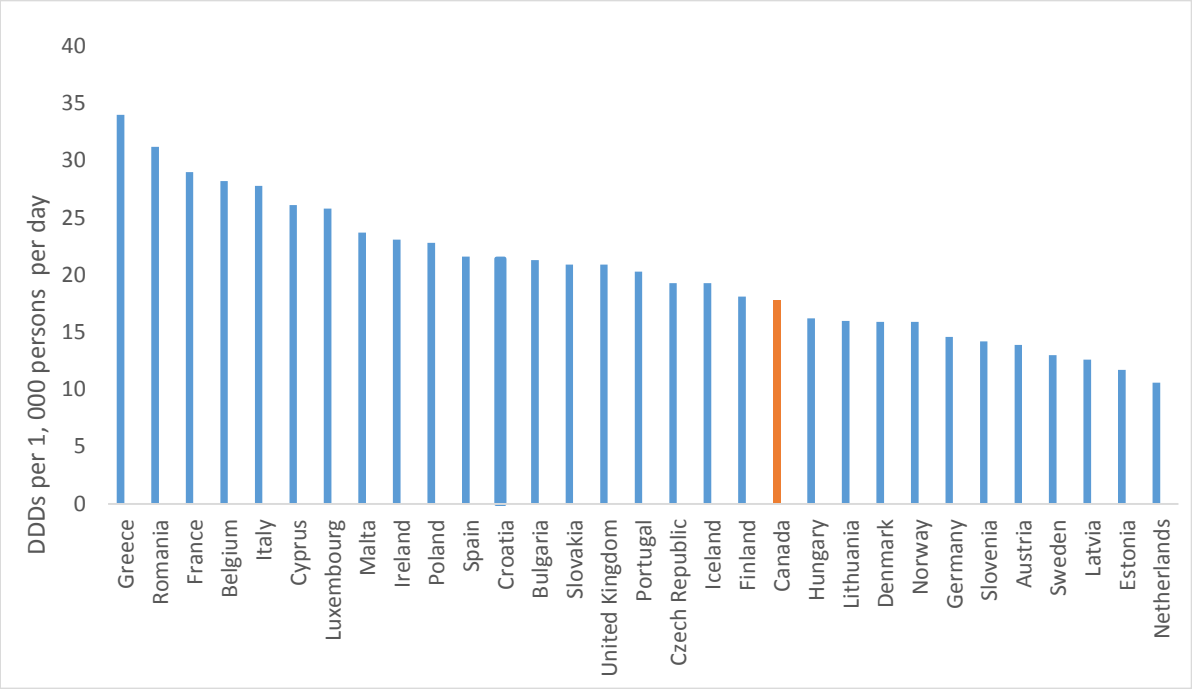
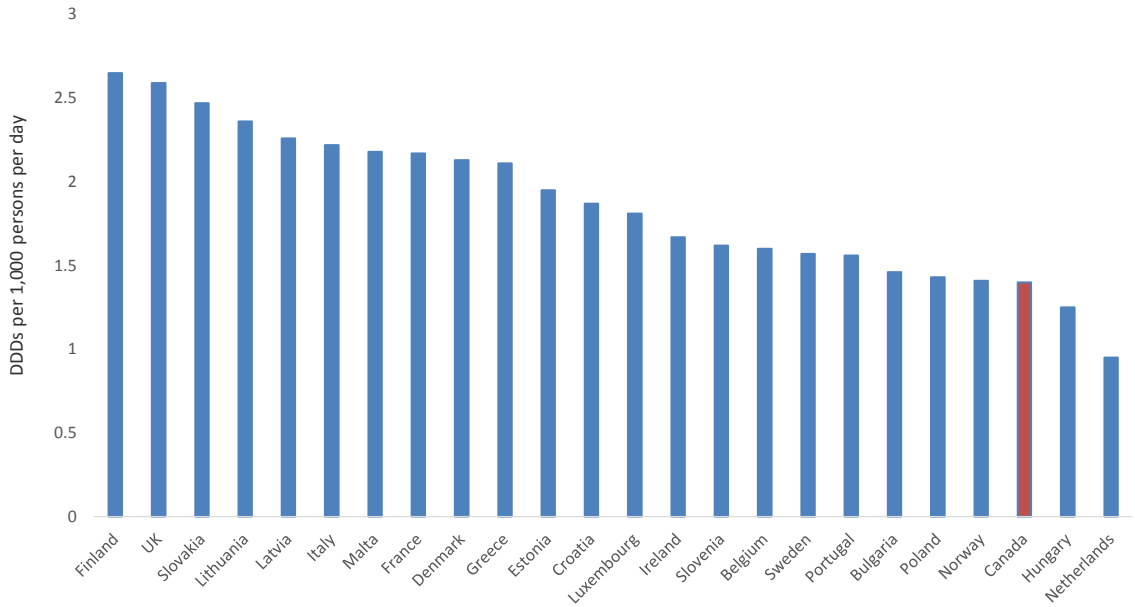


Figure 49: Hospital antimicrobial purchases (DDD per 1,000 persons per day) reported in Canada and in 23 European Countries



Antimicrobial use in animals

Total antimicrobials distributed for sale for use in animals

Information on antimicrobials distributed for sale for use in animals has been voluntarily provided by the Canadian Animal Health Institute (CAHI) since 2006. These data represent quantities of antimicrobials distributed for sale by member companies and do not include quantities of antimicrobials imported for own use or as active pharmaceutical ingredients used in further compounding.

In 2014, 1.5 million kg of antimicrobial active ingredients were distributed for use in animals. This number is 5% higher than in 2013 but 12% lower than reported in 2006. Over the past five years (2010 to 2014), there has been a 1% increase. In Canada, 99% of the antimicrobials distributed in 2014 were intended for use in food-production animals and less than 1% was intended for use in companion animals. Additionally, the majority (73%) of antimicrobials distributed were in the same classes as those used in human medicine. Inappropriate antimicrobial use in food-producing animals is a public health concern as it contributes to emergence of resistant bacteria in animals that can be transmitted to humans through food supply[35].

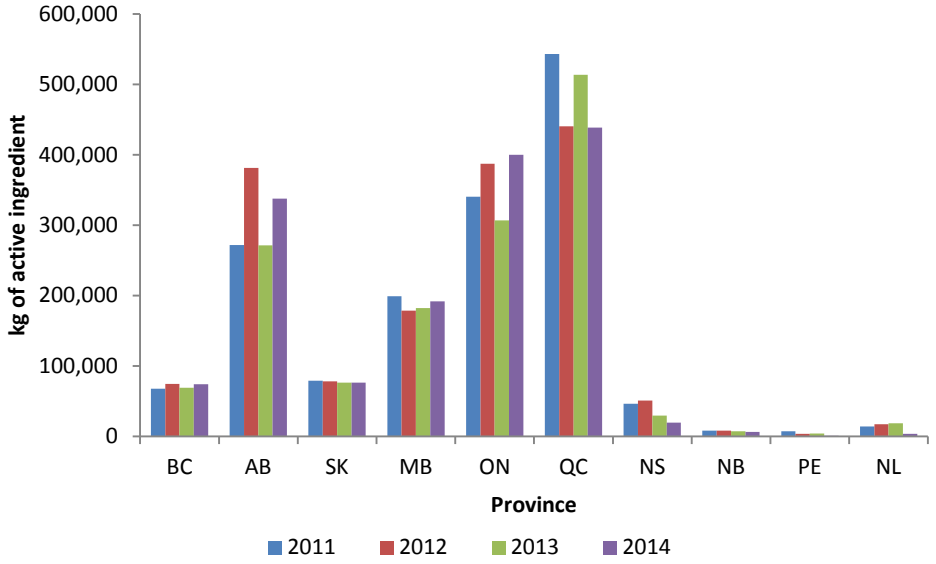
As in previous years, the predominant classes of antimicrobials distributed for use in animals in descending order were the tetracyclines, ionophores, β-lactams, other antimicrobials[36] and the macrolides. Fluoroquinolones are classified as "very high importance to human medicine[37] by Health Canada's 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 antimicrobial resistance concerns. The overall quantity of fluoroquinolones distributed for use in animals increased by 14% between 2013 and 2014, though there has been a 40% increase since 2010 (likely due in part to approval of a new fluoroquinolone indication for use).

Third-generation cephalosporins are also of very high importance to human medicine, are licensed for use in some animal species in Canada and bear the same antimicrobial resistance warning statement on their labels. CAHI data show a decline of 60% in the quantity of cephalosporins distributed for use in animals from 2011 to 2014[38].

There were provincial differences between the quantities and types of antimicrobials distributed and differences within provinces over time such as increases in antimicrobials distributed for sale between 2013 and 2014 were observed for British Columbia, Alberta, Manitoba and Ontario; the most notable increases occurred in Ontario and Alberta. Quebec and the Atlantic provinces all had decreases in antimicrobials distributed for sale between 2013 and 2014. These values do not account for changes in underlying populations or disease pressures. It should be noted that interprovincial distribution of antimicrobials can occur after surveillance data are captured.

[35] Source; CDC: http://www.cdc.gov/narms/animals.html.
[36] Avilamycin, bacitracins, bambermycin, chloramphenicol, florfenicol, nitrofurantoin, nitrofurazone, novobiocin, polymixin, tiamulin and virginiamycin.
[37] Antimicrobials with very high importance are the preferred treatment option for serious infections (those leading to emergency care if left untreated) AND with no or limited alternatives. http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr_ram_hum-med-rev-eng.php.
[38] CAHI provides the information according to a "3 company accounting rule" established by CAHI to comply with the European Union and the United States' anti-competition regulations. In some cases, CAHI added a "90% rule" so as not to infringe on the regulations in the United States.

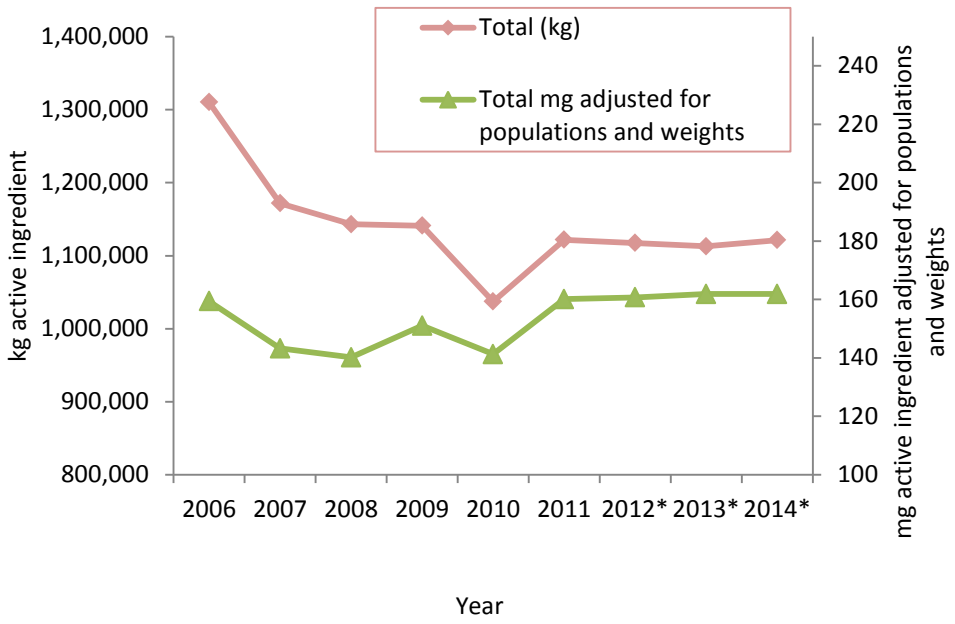
Figure 50: Quantity of antimicrobials (kg) distributed for sale for use in animals, by province, 2011 to 2014



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

As the total quantity of antimicrobials distributed can be highly affected by the numbers and types of animals, adjustments for animal population numbers and weights were made to the national quantities each year. Using this adjustment, the overall quantity of antimicrobials distributed has remained relatively stable over time, with a 3% increase since 2006 and a 1% increase since 2013. Over the past five years (2010 to 2014), there has been a 16% increase. However, neither this adjusted metric nor raw kilogram active ingredient account for different potencies of antimicrobial drugs which is an important factor to consider when evaluating trends in antimicrobial use over time.

Figure 51: Medically-important antimicrobials[39] distributed for use in animals over time; measured as kilogram (kg) active ingredient and milligram (mg) active ingredient, adjusted for populations and weights, 2006 to 2014

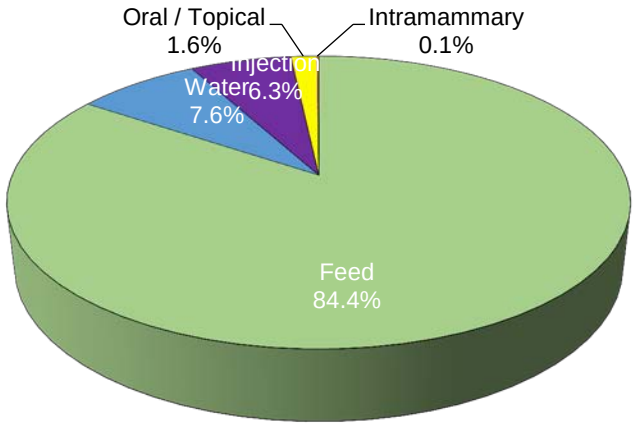


Data sources: CAHI, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada.
*Excluding antimicrobials sold for use in companion animals.
Values do not include own use imports or active pharmaceutical ingredients used in compounding.
Denominator data were calculated using standard weights used by the European Surveillance of Veterinary Antimicrobial Consumption (see *CIPARS 2014 Annual Report – Chapter 3 Antimicrobial Use in Animals* for more details). This Figure includes 2010 data for live horses; last updated in 2010

New for the first time in 2014, CAHI provided the distribution data by pharmaceutical form/intended route of administration (feed, water, injection, oral/topical, intra-mammary). Overall, antimicrobials are predominantly distributed for use in feed for animals (**Figure 52**).

[39] Health Canada classifies antimicrobials according to their importance in human medicine as "very high importance", "high importance", "medium importance", and 'low importance" based on their indications and the availability of alternative drugs. A drug that is indicated for serious infections and has limited or no alternatives or alternatives from the same class is considered more important. (http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr_ram_hum-med-rev-eng.php).

Figure 52: Quantity of antimicrobials (% of total kg) distributed for use in animals, by route of administration, 2014



Data sources: CAHI, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada. *Excluding antimicrobials sold for use in companion animals.
Values do not include own use imports or active pharmaceutical ingredients used in compounding. Denominator data were calculated using standard weights used by the European Surveillance of Veterinary Antimicrobial Consumption (see *CIPARS 2014 Annual Report – Chapter 3 Antimicrobial Use in Animals* for more details). This Figure includes 2010 data for live horses; last updated in 2010

Data source: Canadian Animal Health Institute (CAHI)

Indication for AMU in animals

There are three reasons for AMU in animals in Canada: treatment of disease, prevention of disease and to improve feed efficiency or promote growth (e.g. production claims). The use of antimicrobials as growth promoters is not permitted in the European Union. The United States and Canada are currently taking measures to remove production claims from approved labels for medically-important antimicrobials to promote their judicious use in animals and to limit the emergence and transmission of resistant pathogens from animals to humans through the food supply[40]. Information about reasons for use in production animals is collected through surveillance of volunteer sentinel grower-finisher pig and broiler chicken farms.

Findings from the CIPARS Farm Surveillance Program reveal important differences in the types and relative quantities of antimicrobials used in different food animal sectors (**Figure 53**). In 2014, participating farmers and veterinarians representing approximately 9% of grower-finisher pig herds and 10% of broiler chicken flocks nationally reported no use of antimicrobials by any route of administration. Among participating farms, this represented a slight decrease from 12% in 2013 in swine herds and no change at 10% for both years in broiler chicken flocks. Similar to the CAHI data, in farms that reported using antimicrobials, the majority were administered through feed, rather than by injection or via water.

Overall, the greatest quantity of antimicrobials used (correcting for populations and weights) on sampled grower-finisher pig and broiler chicken farms were for disease prevention–47% and 81%,

[40] Source: http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr-notice-ram-avis-20140410-eng.php.

respectively (**Figure 54**). The trend in use in broiler chicken, comparing 2014 to 2013, was toward more use for disease prevention and less for growth promotion. For the same period in grower-finisher swine, there was an increase in overall use with an increase in use for growth promotion–38% in 2014 compared to 28% in 2013.

For broiler chickens in 2014, 84% of the quantity of the antimicrobials used in feed (adjusted for populations and weights) was primarily for prevention of necrotic enteritis caused by *clostridium perfringens* (macrolides, penicillins, streptogramins, bacitracin and orthosomycin) and coccidiosis (ionophores and chemical coccidiostats). Fourteen percent of flock producers reported use of penicillin, trimethoprim-sulfonamide and tetracyclines in feed for treatment of disease. Only 4% of broiler chicken flock producers reported using antimicrobials for production claims (bacitracin, virginiamycin and penicillin), down from 12% the previous year. Producers reported that the use of antimicrobials in water increased from 7% in 2013 to 14%.

For grower-finisher pig farms reporting in 2014, 15% of the quantity of antimicrobials used in feed (adjusted for populations and weights) was for disease treatment, 47% for disease prevention and 38% for production claims. The majority of antimicrobials used in feed for disease prevention were for respiratory and enteric diseases. Tetracyclines and lincosamides had the highest frequency of use for the prevention of respiratory disease. Reported tetracycline use for the prevention of respiratory disease declined from 30% in 2011 to 22% in 2014, while the frequency of lincosamide use for this reason increased each year from a low of 6% in 2009 to 14% in 2014. For the prevention of enteric disease, 18% of farms reported using macrolides and 17% used lincosamides in 2014.

Therapeutic decisions about which antimicrobials to use at the farm level are based on current disease pressures, availability of non-antimicrobial alternatives to control and prevent disease (e.g., vaccines and bacterins), biosecurity and other operational factors.

Figure 53: Differences in the kilograms of antimicrobial (class) use in feed, adjusted for populations and weights, among production sectors that participate in the CIPARS Farm Surveillance Program, 2014

Data source: CIPARS 2014 Annual Report.

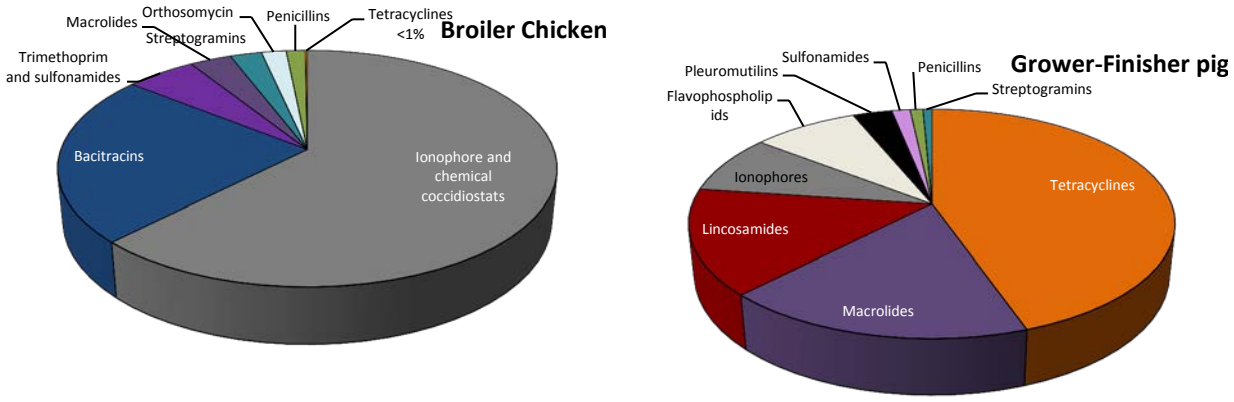
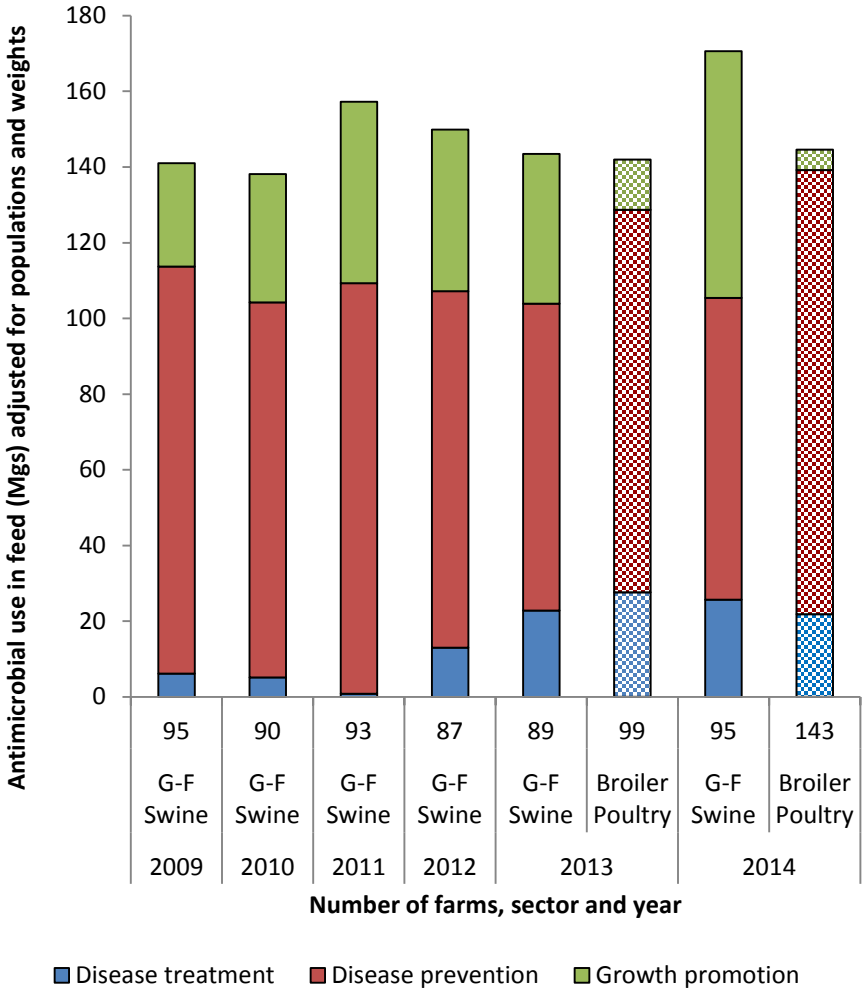


Figure 54: Trends in the proportion of antimicrobials used in feed, excluding ionophores and chemical coccidiostats, by reason for use—based on estimates of milligrams of use adjusted for populations and weights, 2009 to 2014



Data source: CIPARS 2014 Annual Report.

International comparisons for antimicrobial use in animals

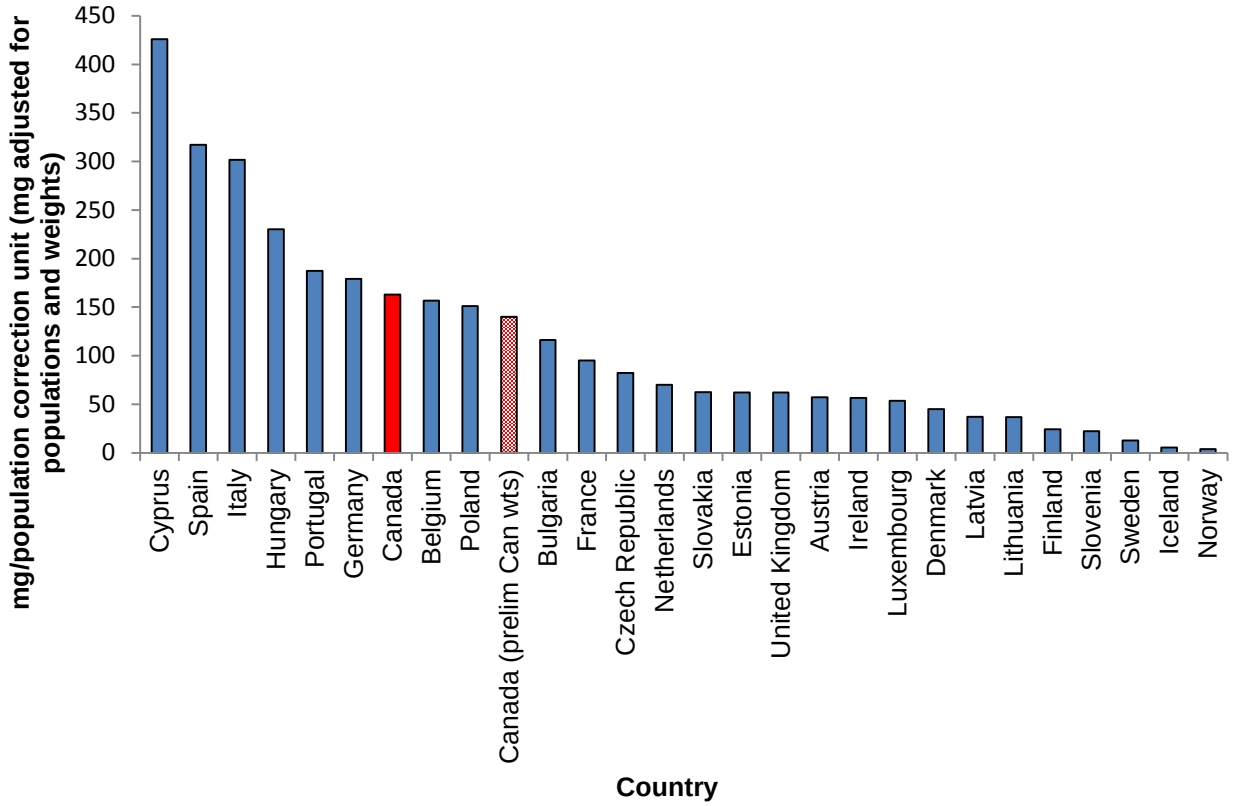
The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) collects and reports information from member countries on antimicrobials intended for use in animals (71). In 2013, 26 member countries participated in ESVAC. When compared to the countries participating in the ESVAC network, Canada ranked 7th highest out of 27 countries by increasing levels of antimicrobial sales adjusted by populations and weights[41] (**Figure 55**).

Canada's total milligrams distributed adjusted by population was 44 times that used in Norway (country with the lowest sales) and less than half of that reported by Cyprus (the country with the highest sales).

[41] The denominator used to adjust the sales data is equivalent to the biomass of the population. In the European Surveillance of Veterinary Antimicrobial Consumption, this is labelled the "Population Correction Unit" or "PCU".

As per a Canadian agri-food industry request, the light red column in **Figure 55** is the relative ranking of Canada when Canadian average weights of animals are used in the calculation instead of European standard weights since some production classes of animals in Canada are heavier than their counterparts in Europe. Canada's position would be further to the left on the Figure (higher mg adjusted by populations and weights) if it was possible to account for the currently unrecorded imports of antimicrobials which fall under own use importation and imports of active pharmaceutical ingredients intended for further compounding. The latest information from an Ipsos/Impact Vet study prepared for CAHI estimated that the lost opportunity value due to these unrecorded imports was 13% of total animal health product sales, but this number is not specific for antimicrobials (personal communication CAHI).

Figure 55: Antimicrobial sales for animals (quantity adjusted by populations and weights) for Canada (2014) and countries participating in the European Surveillance of Veterinary Antimicrobial Consumption Network (2013)



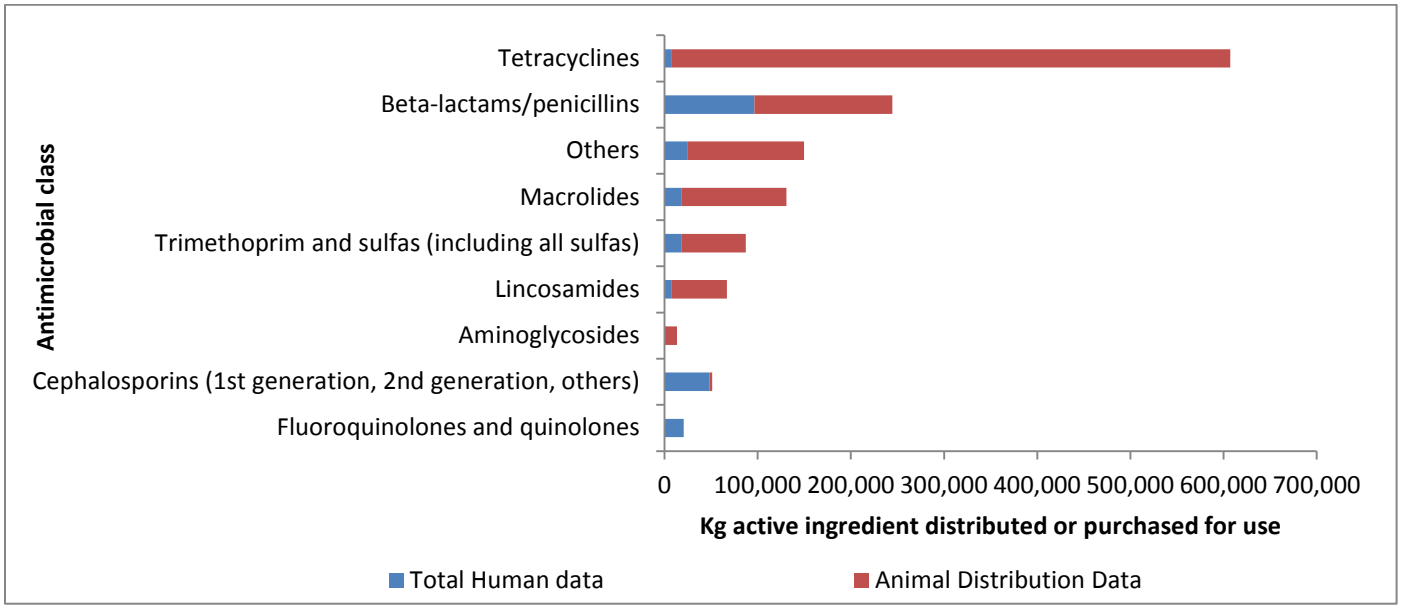
Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada and European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Own use importation and active pharmaceutical ingredient importation are not included for the Canadian data.
Ionophores and chemical coccidiostats were excluded.
The denominator was harmonized with ESVAC to the best extent possible, acknowledging different sources of data on populations of animals. ESVAC approach excludes companion animal data from the numerator.
Data from all countries shown are using the same average weights at treatment. However, Canadian average weights in a few 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.

Integration of human and non-human antimicrobial use data

Canada is a major producer of food animals for domestic and international markets, with approximately 19 times more animals than humans in the country; the majority of which are poultry. In 2014, approximately 1.4 million kg of medically-important antimicrobials were distributed and/or sold for use in humans, animals and crops combined in Canada. For medically-important antimicrobials[42], approximately 82% were intended for production animals, 18% were for humans, less than 1% for companion animals and less than 1% for crops[43]. Adjusting for underlying populations and average weights, in 2014, there was roughly 1.7 times more antimicrobials distributed for use in animals than humans.

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 were tetracyclines, β-lactams and "other" antimicrobials[44].

Figure 56: Kilograms of antimicrobials distributed and/or sold for use in animals and humans by antimicrobial class, 2014



Data sources: Canadian Animal Health Institute, Government of Canada *Human AMU Report* 2014.

The results from the 2014 human AMU data are encouraging as prescribing rates for children (0 to nine years of age) have decreased again this year. However for treating UTIs, ciprofloxacin was most

[42] Values do not include own use imports or active pharmaceutical ingredients used in compounding.
[43] Data provided by Health Canada's Pest Management Regulatory Agency to CIPARS. Personal communication.
[44] "Other antimicrobials" for animals for 2014 included: avilamycin, bacitracins, bambermycin, chloramphenicol, florfenicol, nitrofurantoin, nitrofurazone, novobiocin, polymyxin, tiamulin and virginiamycin. "Other antimicrobials" for humans for 2014 included: bacitracin, chloramphenicol, colistin, daptomycin, ertapenem, fidaxomicin, fosfomycin, fusidic acid, imipenem and cilastatin, linezolid, meropenem, methenamine mandelate, metronidazole, nitrofurantoin and vancomycin.

commonly prescribed drug even though studies have not shown any added value to using this third line therapy. The results from the animal AMU data suggest that more work in stewardship –informed reductions needs to be done to bring Canadian rates down.

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