CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM—REPORT 2015

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
Système canadien de surveillance de la résistance aux antimicrobiens – Rapport de 2015

To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications@hc-sc.gc.ca

Publication date: March 2015

Cat.: HP37-21/2015E-PDF
ISSN: 2369-0712
Pub.: 140532

CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM—REPORT 2015

TABLE OF CONTENTS

GLOSSARY

AMR	Antimicrobial resistance
AMU	Antimicrobial use
BSI	Bloodstream infection
CAHI	Canadian Animal Health Institute
CA-MRSA	Community-associated Methicillin-resistant *Staphylococcus aureus*
CARSS	Canadian Antimicrobial Resistance Surveillance System
CDI	*Clostridium difficile* infection
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CNISP	Canadian Nosocomial Infection Surveillance Program
CPO	Carbapenamase-producing organisms
CRE	Carbapenem-resistant *Enterobacteriaceae*
CTBLSS	Canadian Tuberculosis Laboratory Surveillance System
CTLTN	Canadian Tuberculosis Laboratory Technical Network
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	Extended-spectrum ß-lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
GAS	Group A *Streptococcus*
GBS	Group B *Streptococcus*
GNB	Gram-negative Bacilli
HA-CDI	Health care-associated *Clostridium difficile* infection
HA-MRSA	Health care-associated Methicillin-resistant *Staphylococcus aureus*
HIV	Human Immunodeficiency Virus
IPD	Invasive pneumococcal disease
IV	Intravenous
LFZ	Laboratory for Foodborne Zoonoses
MDR	Multi-drug-resistant
MDR-TB	Multi-drug-resistant Tuberculosis
MRSA	Methicillin-resistant *Staphylococcus aureus*
NML	National Microbiology Laboratory
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OIE	World Organisation for Animal Health
PCU	Population Correction Unit
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
SSTI	Skin and soft tissue infection
TB	Tuberculosis

TMP-SMX	Trimethoprim-sulfamethoxazole
UTI	Urinary tract infection
VDD	Veterinary Drug Directorate
VRE	Vancomycin-resistant Enterococci
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WHO	World Health Organization
XDR-TB	Extensively drug-resistant Tuberculosis

MESSAGE FROM THE CHIEF PUBLIC HEALTH OFFICER OF CANADA

Antimicrobial resistance is a serious and growing issue. It threatens the world's ability to prevent and treat an ever-increasing range of infections. In Canada alone, total medical care costs associated with antimicrobial resistant infections have been estimated at one billion dollars.

To better understand the problem, surveillance systems, like those stewarded by the Public Health Agency of Canada, provide timely collection and analysis of reliable data on antimicrobial use and resistance. In turn, that data supports health professionals and policy makers in making informed decisions, and in taking concrete action on the prudent use of antimicrobials to mitigate diseases.

That is why strengthening our surveillance platform is critical to informing our understanding of the problem. Better integration of surveillance, as outlined in *Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*, is key. The creation of the Canadian Antimicrobial Resistance Surveillance System (CARSS) which aims to provide an integrated and national picture on antimicrobial use and resistance will help us do just that.

This report is the first step in the creation of CARSS. It represents the first-ever integrated antimicrobial use and resistance surveillance report. It will help integrate existing systems, enhance our surveillance and analysis, and better inform provinces, territories and stakeholders. It highlights analysis informed by the data we receive from our many partners across Canada. It also provides us with important new information: for example, how Canada's use of medically-important antibiotics in animals and humans compares with other countries.

We commend and thank all contributors for their efforts. This report is made possible by the many jurisdictions, organizations and individuals who provide the data that makes CARSS such an important tool in addressing the impacts of antimicrobial resistance. We look forward to consulting with stakeholders over the next year, to help us shape future reports, and to continue building a strong, effective and responsive antimicrobial surveillance system in Canada.

Krista Outhwaite
President, Public Health Agency of Canada

Dr. Gregory Taylor
Chief Public Health Officer of Canada

AT A GLANCE

The Government of Canada is committed to leading activities that will prevent, limit and control the emergence and spread of AMR as described in *Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*. The Canadian Antimicrobial Resistance Surveillance System (CARSS) is an essential component of this work and has been established by the Public Health Agency of Canada (the Agency) to strengthen the coordination and integration of antimicrobial resistance (AMR) and antimicrobial use (AMU) activities and information in Canada. One of CARSS' key responsibilities is to produce an annual report on the status of AMR/AMU in Canada.

This is the first CARSS report. It provides an integrated summary of current and available AMR/AMU information from seven Agency surveillance systems and laboratory reference services. This initial analysis points the way forward for AMR/AMU surveillance in the Agency and provides a benchmark for progress on AMR/AMU moving forward. Future CARSS activities and reports will consider stakeholder feedback, surveillance information needs and gaps, and will include information from other Agency surveillance systems with AMR/AMU components and new surveillance initiatives.

In Canada, AMR and AMU remain a concern due to increased resistance levels detected in pathogenic microbes and antimicrobial use levels that are not declining as needed to preserve the effectiveness of remaining antimicrobials. The threat of AMR is not just a Canadian problem, it is a global problem. Increasing the integration of surveillance will position Canada to continue and improve its contribution to the global AMR mitigation efforts.

Canadian Antimicrobial Resistance Surveillance System (CARSS)

CARSS was created as the national focal point for AMR/AMU surveillance in Canada. It represents an important step in the evolution of the Agency's surveillance programs to act against AMR. CARSS will oversee and champion federal surveillance transformation activities, beginning within the Agency. Through CARSS, the Agency will address the requirements and data needs identified by internal and external stakeholders from a comprehensive integrated perspective. CARSS will work with the Agency's existing surveillance programs to identify new opportunities to collect, share and analyse AMR/AMU data in Canada.

As the overarching AMR/AMU surveillance system for the Agency, CARSS will work nationally and internationally with experts, programs and stakeholders to inform evidence-based actions. Using accurate, relevant and timely data, CARSS will provide an annual, comprehensive, integrated AMR/AMU surveillance report to inform AMR/AMU research and policy on stewardship, innovation and disease prevention.

The AMR/AMU landscape is dynamic and rapidly changing and will require CARSS to adapt to the information needs of stakeholders and decision-makers. As a result, the continued evolution of CARSS will be underpinned by dialogue and consultation with experts and stakeholders across Canada and internationally, ensuring that integration is maximized and that information meets stakeholder needs.

Antimicrobial Use

- Since 2001, AMU (in defined daily doses per 1,000 person-days) has declined in communities and hospitals.
- Since 2006, the total antimicrobials distributed for sale in animals (adjusted for animal population and weight) has remained stable.
- The purchasing of antimicrobials considered "restricted" in the hospital setting has substantially increased over time, particularly in treating Gram-positive infections.
- In 2013, approximately 1.4 times more antimicrobials were distributed for use in animals than humans in Canada (adjusting for population and weight).
- The total antimicrobials distributed for animal use in Canada was 42 times higher than in Norway (the country with the lowest use, ranked number 1). Overall, Canada ranked 21 out of 27 countries based on levels of antimicrobial sales.
- Canada's use of human outpatient antimicrobials was 1.6 times higher than in the Netherlands (the country with lowest use, ranked number 1). Overall, Canada was 11th of 29 countries based on total use of antimicrobials.

Antimicrobial Resistance

- In 2013, resistance to antimicrobials (cephalosporins) used for treating gonorrhoea was present in 3.9% of infections, raising concerns that treatment with these antimicrobials may not be effective.
- Since 2009, methicillin-resistant *Staphylococcus aureus* (MRSA) infection rates have been decreasing, especially in hospital settings. However, current MRSA infection rates continue to exceed those observed in the early 2000s, and MRSA remains a significant cause of infection.
- *Clostridium difficile* infection rates in hospital settings have remained stable since 2007.
- Carbapenems are broad-spectrum antimicrobials usually reserved for use in more severe infections. The annual overall rate of infection resistant to carbapenems (specifically Carbapenem-Resistant *Enterobacteriaceae*) has approximately remained the same.
- Vaccination programs against *Streptococcus pneumoniae* have helped reduce the rate of infection caused by an important multidrug-resistant strain of the bacteria.
- In 2013, resistant *Salmonella* bacteria caused 759 reported human cases of disease (out of a total of 2,987 human *Salmonella* cases).

INTRODUCTION

Since the early twentieth century dramatic improvements to human health have been made as a result of better public health systems, hygiene and infection control, the development of vaccines and, in addition, the extensive use of antimicrobials. As new classes of antimicrobials[a] have been introduced over time, health professionals have more tools in their arsenal to manage and treat infectious diseases, including preventative use in surgeries, chemotherapy and the treatment of immunocompromised patients. Veterinarians have also benefited from the use of antimicrobials in the prevention and treatment of diseases in animals. Since similar classes of antimicrobials are used in both populations antimicrobial selection pressure has been levied in multiple settings leading to the emergence and spread of antimicrobial-resistant organisms.

> “ WE ARE IN A CONSTANT STRUGGLE TO PROTECT OURSELVES FROM THE POTENTIALLY HARMFUL, COMPLEX AND UNSEEN WORLD OF MICROBES. CANADA HAS MADE ADVANCEMENTS IN COMBATING THE MORE HARMFUL MICRO-ORGANISMS. BUT DESPITE ALL OUR PROGRESS, OUR ABILITY TO OVERCOME INFECTIOUS DISEASES REMAINS, AT BEST, LIMITED.[1]
>
> **Dr. David Butler Jones**, Chief Public Health Officer of Canada (2005–2013)

The broader and increased use of antimicrobials in humans and animals has accelerated the development of resistance and made some infections harder to treat with commonly-used antimicrobials. Even more concerning is the ability of some microbes to become resistant to more than one group of antimicrobials which further limits treatment options. As very few new antimicrobials are in development and rates of AMR are increasing, we are now threatened with a return to similar levels of disease and death observed in the early twentieth century.

The Government of Canada has been addressing aspects of AMR for some time. The Agency operates surveillance programs that monitor AMR and AMU in a variety of settings including hospitals, communities, veterinary and agricultural settings; however, existing national surveillance does not provide a complete picture of the state of AMR and AMU in Canada. This limits the ability to effectively monitor the emergence and spread of resistant infections, or to measure the impact of interventions aimed at counteracting loss in antimicrobial effectiveness.

In October 2014, the Government of Canada published *Antimicrobial Resistance and Use in Canada: A Federal Framework for Action* which represented an important step towards meeting the challenge posed by AMR. The Framework describes the Government of Canada’s commitment to lead activities to prevent, limit and control the emergence and spread of AMR.

[a] 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 antiparasitics.

The Agency's existing AMR surveillance systems generate a significant amount of information. When established these systems were designed as standalone systems and integration between systems was not prioritized. To better understand the magnitude and impact of AMR in Canada and to address the threat it poses, the Agency must adapt its surveillance approach so that more comprehensive information is available to inform public health decision-making and implementation of interventions to combat AMR.

The first step towards necessary change is the establishment of CARSS, which will strengthen the coordination and integration of Agency AMR/AMU activities and information. CARSS will also provide leadership on AMR/AMU surveillance, inform and direct the expansion of surveillance activities to areas of greatest need and provide useful and relevant information to stakeholders and the public in support of antimicrobial stewardship interventions to protect the health of Canadians.

SCOPE OF THE REPORT

This first CARSS report integrates currently available Agency AMR/AMU data into a more integrated summary of surveillance information. The data analysis will be used to identify gaps and inform surveillance enhancements. This report is intended to provide Agency AMR/AMU surveillance stakeholders and public health partners with information on current Canadian AMR/AMU surveillance activities and findings. This is also a starting place for future discussions about the way forward for integrated AMR/AMU surveillance in Canada.

BACKGROUND

AMR simply means that the antimicrobial drugs that were once effective against a particular microbe no longer work because the microbe's biological makeup has changed and it has become resistant to treatment. This resistance can occur naturally, or can be acquired when an infection is treated with an antimicrobial that kills only some of the microbes. Those that resist the treatment survive and multiply. Over time, more and more of the resistant microbes remain in our environment, eventually leading to the emergence of new strains of disease-causing microbes that are partially or fully resistant to antimicrobial treatment.

AMR microbes move and spread in the same way as all infectious disease-causing microbes do. Resistant microbes are generally found where AMU is higher and disease conditions are more common (e.g., hospitals). Modern medical and veterinary practice depends on the widespread availability of effective antimicrobials to prevent and treat infections in humans and animals. Without them, our ability to fight infectious disease would be significantly impeded. Actions to mitigate AMR and improve AMU stewardship must be built on a foundation of high-quality and timely surveillance information.

SURVEILLANCE

The Agency's Infectious Diseases Prevention and Control Branch is responsible for managing the systems that currently perform AMR/AMU surveillance. This report includes information from seven Agency surveillance systems (listed below). Moving forward, future reports will respond to stakeholder feedback and surveillance information needs and will include information from other Agency AMR/AMU systems as well as new Agency surveillance initiatives.

1. The *Canadian Nosocomial Infection Surveillance Program* (CNISP), established in 1994, is a collaborative effort between the Agency and sentinel hospitals participating as members of the Canadian Hospital Epidemiology Committee (CHEC), a subcommittee of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada. This program collects data on select antimicrobial-resistant organisms in over 60 largely university-affiliated hospitals in all provinces. The data collected provides clinicians and decision-makers with evidence-based benchmarks, identifies trends and supports the development of national guidance documents to help reduce the transmission of AMR.
2. The *Canadian Integrated Program for Antimicrobial Resistance Surveillance* (CIPARS), established in 2002, monitors AMU in animals and humans, as well as AMR in *Salmonella* in humans, animals and retail food. Antimicrobial resistance in *Campylobacter* and *Escherichia coli* (*E. coli)* are monitored in animals and food of animal origin. The data collected supports antimicrobial stewardship in human and animal health and identifies potential measures to slow the spread of AMR along the food chain. The focus of CIPARS is on bacteria and antimicrobials of public health importance; veterinary pathogens other than *Salmonella* are not covered.

3. *FluWatch* is Canada's national surveillance system that monitors the spread of influenza and influenza-like illnesses on an ongoing basis. *FluWatch* reports contain specific information for health professionals on influenza viruses and antiviral resistance in Canada.
4. The *Canadian Tuberculosis Laboratory Surveillance System* (CTBLSS) monitors drug resistance patterns in *Mycobacterium tuberculosis*. The Agency collaborates with the Canadian Tuberculosis Laboratory Technical Network and participating laboratories (representing all provinces and territories) to monitor this resistance in Canada.
5. The Antimicrobial-resistant *Neisseria gonorrhoeae* Surveillance System has monitored antimicrobial susceptibilities of *N. gonorrhoeae* since 1985. The National Microbiology Laboratory (NML) works in collaboration with provincial laboratories.
6. The national surveillance of Invasive Streptococcal Disease is a passive surveillance system that monitors antimicrobial susceptibilities in *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Streptococcus agalactiae* isolated from sterile sites such as blood and spinal fluid. NML collaborates with provincial laboratories, the University of Manitoba and the Canadian Antimicrobial Resistance Alliance to monitor antimicrobial susceptibilities.
7. The *Canadian HIV Strain and Drug Resistance Surveillance Program* monitors drug resistance in HIV isolates obtained from treatment-naïve individuals with newly diagnosed HIV infection. Five provinces currently participate in this surveillance initiative.

In addition to the systems above, NML and the Laboratory for Foodborne Zoonoses (LFZ) support all Agency AMR surveillance programs and detect new and emerging AMR organisms through laboratory reference services to all provinces and territories.

Human AMU data is purchased by the Agency from IMS Health Canada Inc.[2] These data include information on prescriptions dispensed by retail pharmacies in Canada, antimicrobials purchased by Canadian hospitals, and diagnoses for which physicians have recommended an antimicrobial in the community. This data is received at the provincial level; information for the Yukon, Northwest Territories and Nunavut is not currently included.

THE CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM (CARSS)

The threat posed by AMR simply does not allow the Agency to maintain the status quo. A comprehensive national understanding of AMR/AMU in Canada is required to mitigate the effects of AMR and to increase prudent AMU practices. This report provides the first integration of AMR/AMU surveillance information collected through existing Agency surveillance activities. Before CARSS, reporting was carried out by individual surveillance systems, often with limited explanation or interpretation for key audiences. As a result, the Canadian picture of AMR/AMU is incomplete and our understanding of the success of interventions aimed at counteracting loss in antimicrobial effectiveness due to rising AMR is limited. Integrated and comprehensively translated information will allow the Agency to determine and understand the full AMR/AMU picture, monitor the effectiveness of stewardship interventions, and better position Canada internationally.

The creation of CARSS is a key commitment within the Government of Canada's *Federal Framework for Action on AMR*. CARSS will be a national focal point for AMR/AMU surveillance and its creation is an important step in the evolution of surveillance leading to concrete action on AMR. CARSS will address gaps by working with existing surveillance programs to integrate current surveillance activities, enhance knowledge through additional work on AMR/AMU within the Agency and set strategic priorities. CARSS will begin its work within the Agency with a view to a longer term inclusion of other Federal, Provincial, Territorial, and external partners.

The following are objectives for CARSS:

1. Integrate AMR/AMU surveillance information from within and outside the Agency.
2. Provide an annual integrated report of AMR/AMU in Canada.
3. Provide leadership on AMR/AMU surveillance.
4. Inform and direct strategic AMR/AMU surveillance transformation activities.
5. Create and track performance indicators for AMR/AMU surveillance.

CARSS will be positioned as the overarching AMR surveillance system for the Agency. Because CARSS is being built on the foundation of the current Agency AMR/AMU systems it will be in an excellent position to achieve these objectives. It will work with and support AMR/AMU experts, programs and stakeholders to develop its governance structure. Its surveillance data will inform evidence-based actions and the assessment of AMR mitigation and stewardship interventions. Ultimately the information generated by CARSS will intersect with and inform AMR/AMU research and policy on stewardship, innovation and disease prevention, both domestic and globally.

CARSS will provide information in a timely integrated manner that meets stakeholder needs, working towards including information from beyond the Agency (other Government departments and Provinces and Territories) to complete the AMR/AMU picture. This will require an incremental approach to CARSS and its broader transformation activities. The AMR/AMU landscape is dynamic and rapidly changing with many players. As a result CARSS will be evergreen and adaptable to the AMR/AMU information needs of stakeholders and decision-makers. The adaptation and formation of CARSS will be underpinned by dialogue and consultation with experts and stakeholders across Canada and internationally.

CARSS will oversee and champion federal surveillance transformation activities laid out in the body of this report, and others as they are identified, including actions outlined in the surveillance pillar of the Federal Framework. CARSS will work with stakeholders and Agency programs to identify data gaps. The linkages CARSS establishes with partners and stakeholders will maximize integration and seek to ensure that information meets stakeholder needs. Because CNISP, CIPARS, and other Agency AMR/AMU surveillance programs are components of CARSS, the Agency will address the requirements of stakeholders and data requirements from a comprehensive, rather than an individual program viewpoint.

Future annual AMR and AMU surveillance reports will build on the structure of this initial report. New sections will be added as data from new surveillance initiatives are gathered. The provision of accurate, relevant and timely data on AMR and AMU will serve as an important foundation for the development of best practices and priority setting for decision-makers. Discussion of progress in mitigating AMR and increasing prudent AMU will be a part of the annual CARSS report.

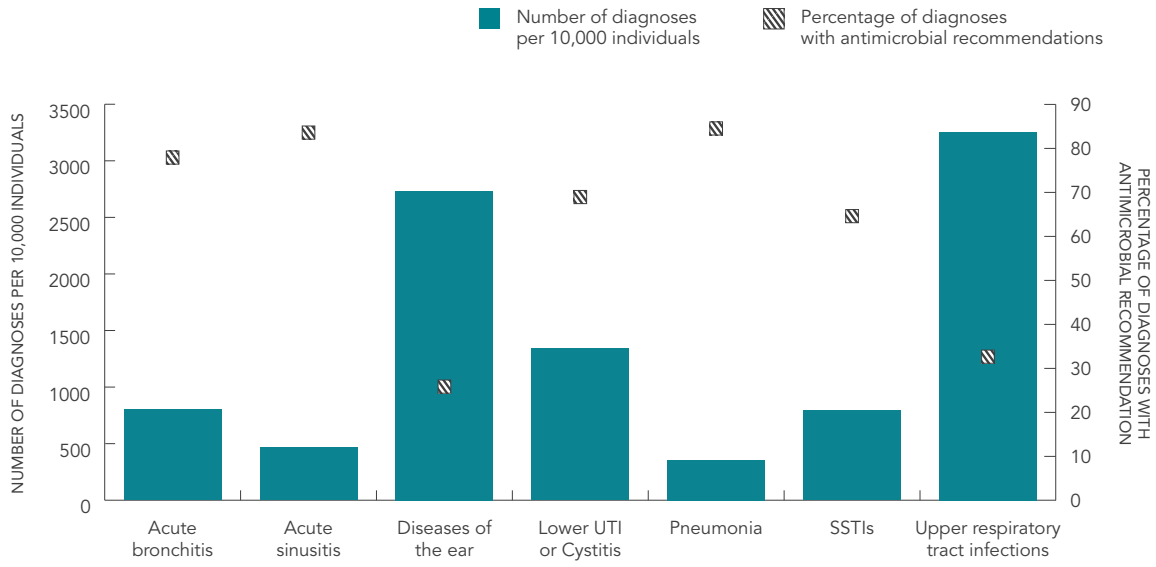
ANTIMICROBIAL USE IN CANADA

ANTIMICROBIAL USE IN HUMANS

In 2013, Canadian community doctors with offices outside of the hospital setting made more than 293 million diagnoses, with 8% of these involved recommending an antimicrobial.[2] Antimicrobials were most commonly recommended for pneumonia, acute bronchitis and acute sinusitis (Figure 1). Although it is not known if there were other comorbidities that guided the physician recommendations (due to data collection methodology), this finding signals possible misuse of antimicrobials since acute bronchitis and sinusitis are often viral rather than bacterial in origin.[3,4]

Compared to 2007 (the first year data was available), in 2013, physician recommendations[b] for antimicrobial treatments decreased from 97% to 84% for upper urinary tract infections, from 58% to 52% for chronic sinusitis, and from 26% to 20% for acne, while recommendations for treating pneumonia increased from 75% to 85%. In 2013, a higher rate of children aged zero to two were recommended antimicrobials than adults aged 20 and older and a higher proportion of female patients were recommended an antimicrobials compared to male patients[2] across all diagnoses.

FIGURE 1: Number of infections diagnosed by doctors in the community per 10,000 individuals and the percentage of these diagnoses with a recommendation for an antimicrobial, 2013[c]



[b] Drug recommendations are not necessarily tied to a prescription as the patient may have been against receiving an antimicrobial prescription or may have not filled out a prescription due to physician orders to wait a period of time or chose not to fill it.

[c] UTI – urinary tract infections; SSTIs – Skin and Soft Tissue Infections

Pharmacy dispensations

Between 2001 and 2013, AMU declined from 208,016 to a total of 200,400 kg dispensed by Canadian community pharmacies (Figure 2).[2] Community pharmacy dispensations represent 70% of all antimicrobials used in Canada. Both the prescription rates (per 1,000 population-days) and mass of active ingredients for antimicrobials dispensed by community pharmacies were at their lowest since the beginning of AMU surveillance in 2000. When examining individual drugs over time, erythromycin and penicillin V had reductions in use while nitrofurantoin, moxifloxacin and azithromycin had increases. Although the reductions far outweighed the increases observed between 2000 to 2013, these changes should continue to be monitored in the event that increases outweigh reductions (e.g., prescriptions for nitrofurantoin increased 139% between 2000 and 2013).

Among all antimicrobials dispensed in 2013, the highest number of prescriptions were provided to the youngest (zero to five years) and oldest (65 years and older) age groups. Yet between 2011 and 2013, the greatest overall reduction was in children in the zero to five year age group, from 1,003 to 872 prescriptions per 1,000 children. The antimicrobials most commonly dispensed in 2013 were amoxicillin, clarithromycin and doxycycline.[2] The decrease in prescriptions to children aligns with suggested guidelines for antimicrobial prescribing in this population.

There is also variation in AMU between provinces and territories. In 2013, Newfoundland and Labrador had the highest amounts of use measured by prescription rates, mass of active ingredients, and defined daily dosage rates. Prescription rates for parenteral (injections and intravenous) products in Québec, New Brunswick and Nova Scotia were more than twice the rate of any other province and were more than 15 times the rates in British Columbia, Manitoba and Ontario. These differences may be due to the fact that patients who were treated at hospital outpatient clinics filled their antimicrobial prescriptions at community pharmacies, rather than at the hospital.

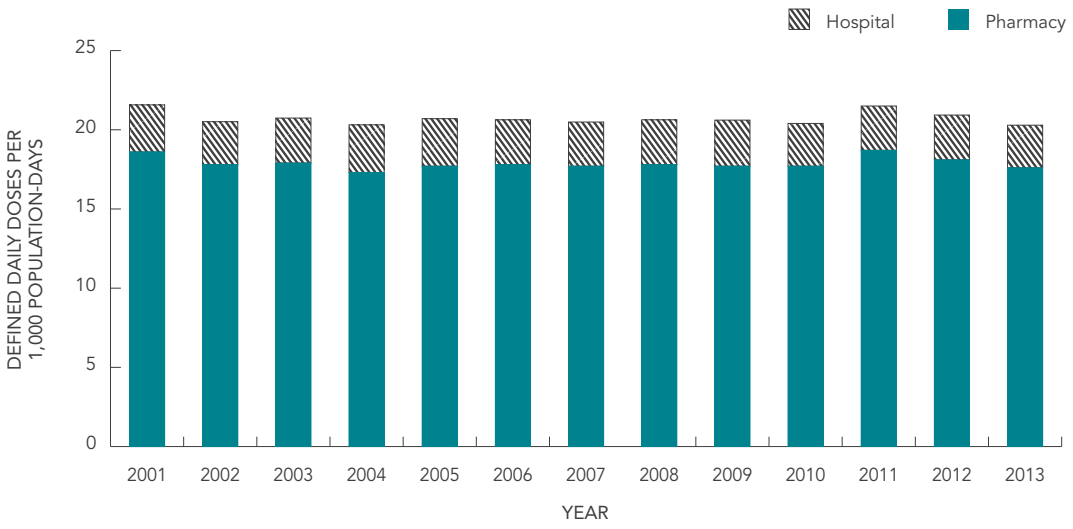
Hospital purchases

Hospital purchases represent 30% of all antimicrobials used in people in Canada.[2] When measured by defined daily doses per 1,000 inhabitant-days there was a slight decrease from 2.97 to 2.69 defined daily doses per 1,000 population-days in antimicrobials purchased in 2001 compared to 2013. These were the lowest levels observed since 2001, the first year with available data on hospital AMU (Figure 2).

In 2013, rates of parenteral (injections and intravenous) antimicrobials purchased by hospitals were nine times higher than oral antimicrobials. The most commonly purchased antimicrobials in 2013 were ceftriaxone, penicillin G and piperacillin with enzyme inhibitor (tazobactam) products.[2] Between 2010 and 2013, there were large increases in hospital purchases of ceftriaxone, piperacillin and tazobactam products, while use of penicillin G decreased by over 60% between 2009 and 2013. These increases are likely due to greater resistance to those antimicrobials that would have otherwise been the first choice for treatment, leading to an increased use of these antimicrobials.[5]

Hospital purchasing of antimicrobials in 2013 varied across provinces and territories. Manitoba had the highest purchase levels while Ontario had the lowest. Ceftriaxone was the highest purchased in the majority of hospitals with the exception of Ontario, Québec and New Brunswick, where penicillin G was the most purchased. Saskatchewan had the lowest proportion of parenteral products purchased (85%) while New Brunswick had the highest (94%), with the remaining products consisting of oral antimicrobials.

FIGURE 2: Defined daily doses per 1,000 population-days dispensed through community pharmacies or purchased by hospitals in Canada, 2001–2013



Antimicrobials of critical importance to human medicine in the hospital

Treatment of severe infectious diseases usually occurs in the hospital setting, often with drugs administered via injection (intravenous or intramuscular). The Agency seeks the expertise of infectious disease physicians, family physicians and pharmacists through the Antimicrobial Use Working Group to assist in the interpretation and development of the Human Antimicrobial Use Report.[2] This group was consulted on how they would cluster antimicrobials to treat Gram-negative and Gram-positive infections in the hospital setting (Table 1). Members categorized critical ("last-recourse") antimicrobials into two groups, "restricted" or "non-restricted" based on their availability and whether they are considered "last recourse" in the treatment of certain infections. The restricted group includes drugs that are available for use but are restricted within the hospital formularies[d] while the non-restricted group includes those that are easily available[e] and widely used in the hospital but still considered to be "last recourse". Other widely-used antimicrobials in hospitals are considered first-line drugs so do not meet the definition of "last recourse" and are not included in either group.

[d] Antimicrobials identified as restricted within formularies can only be dispensed after consultation with an infectious disease specialist. Hospital formularies may vary by hospital.

[e] Depending on the facility, some of the antimicrobials identified as non-restricted might require consultation from an infectious disease specialist. Hospital formularies may vary by hospital.

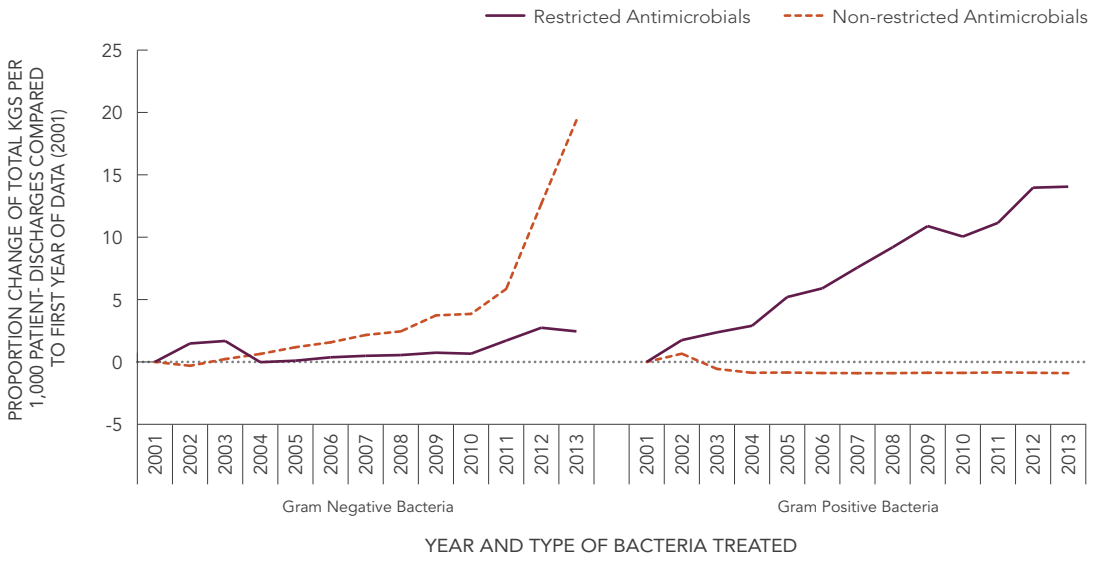
TABLE 1: Identification of critical antimicrobials for treating bacterial infections in the hospital setting by group and type of infection

TYPE OF INFECTION	RESTRICTED	NON-RESTRICTED
Gram-negative bacterial infections	Amikacin Colistin Fosfomycin Imipenem Meropenem Tobramycin Tigecycline	Ertapenem Gentamicin Moxifloxacin Piperacillin-tazobactam
Gram-positive bacterial infections	Daptomycin Linezolid	Vancomycin

The Agency analyses information on antimicrobials purchased by hospitals in Canada. The above grouping was assigned to drugs present in hospital purchasing data and was used to identify purchasing changes over time. Among Gram-negative infections, non-restricted drugs are the main group of antimicrobials used for treatment. Between 2001 and 2003, drugs in the restricted group were used more frequently for treating Gram-negative infections than non-restricted drugs (Figure 3). However since 2003, the use of non-restricted antimicrobials began to increase, with levels in 2013 representing 19 times those of 2001, mainly driven by increases in the purchasing of piperacillin-tazobactam products. Since resistance to these particular antimicrobials in Gram-negative bacterial infections is currently low, non-restricted antimicrobials continue to be effective in combatting infections and should remain the primary choice by physicians for treating these infections in the hospital.

Vancomycin is a non-restricted drug, used primarily for the treatment of Gram-positive infections, with use remaining relatively stable over time. The use of restricted antimicrobials for treating Gram-positive infections has been increasing since 2002 with 2013 use levels 14 times higher than those observed in 2001. Increases in restricted drugs could be due to their increased effectiveness against certain infections, resistance to non-restricted and first-line drugs in Gram-positive infections and changes in clinical practice guidelines or formularies.

FIGURE 3: Proportion change in the total kilograms of restricted and non-restricted antimicrobials per 1,000 patient-discharges purchased by hospitals for the treatment of Gram-positive and Gram-negative infections in Canadian hospitals, 2001–2013



ANTIMICROBIAL USE IN ANIMALS

It is well recognized that the "…use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else".[6] Hence, mitigation of the emergence, spread and impact of AMR requires an understanding of all the settings in which antimicrobial exposure occurs. The World Health Organization (WHO) Advisory Group on Integrated Surveillance of Antimicrobial Resistance, the World Organisation for Animal Health (OIE) and Codex Alimentarius all recommend that countries perform surveillance of antimicrobials used in animals. Some organizations also recommend surveillance in other non-human sectors, such as antimicrobials used on crops. Use of antimicrobials in animals can select for resistance in veterinary pathogens (i.e., those pathogens that cause disease in animals), but can also cause resistance in pathogens that can be transmitted to humans through the food chain (e.g., foodborne *Escherichia coli* and *Enterococcus*) which can exchange resistance genes with other pathogens causing human disease.

Total antimicrobials distributed for animal use

Antimicrobials used in food-production animals represent a large pressure in promoting the development or spread of AMR. Information on antimicrobials distributed for sale for use in animals has been voluntarily provided to CIPARS since 2006 by the Canadian Animal Health Institute (CAHI).[6] In 2013, 1.6 million kg of antimicrobial active ingredients were distributed for use in animals in Canada; 2% lower than in 2012 and 10% lower than reported in 2006. This does not account for different potencies of antimicrobial drugs which can affect interpretation of the data (metric currently under development for Canada).

In 2013, 99.4% of the total antimicrobials distributed for veterinary use in Canada were used in food-production animals, versus 0.6% in companion animals. The majority (68%) of antimicrobials distributed for use in animals were in the same classes as those used in human medicine. The remaining 32% are not found in classes used in human medicine and include the ionophores and chemical coccidiostats.

As in previous years, the predominant classes of antimicrobials distributed for sale in 2013 in descending order were the tetracyclines, ionophores, "other antimicrobials",[f] ß-lactams and the macrolides. Nova Scotia and New Brunswick had a greater than 10% decline in the reported quantity of antimicrobials distributed between 2012 and 2013, while Manitoba and Prince Edward Island showed a more than 10% increase in the same time period. However, it should be noted that subsequent interprovincial distribution of antimicrobials can occur after surveillance data are captured.

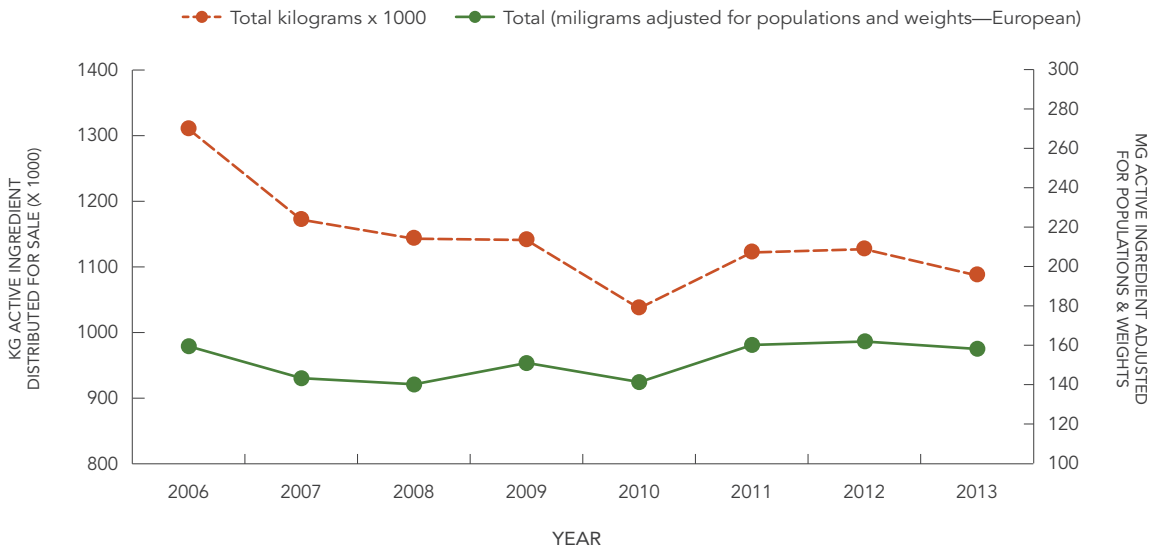
Fluoroquinolones have been classified as of critical importance by the WHO and as "very high importance to human medicine" by Health Canada's Veterinary Drugs Directorate (VDD). Fluoroquinolones are licensed only for certain animal species in Canada and have warnings on their labels recommending against extra-label use due to AMR concerns. The overall quantity of fluoroquinolones distributed for use in animals in 2013 increased by 11% over 2012. Third-generation cephalosporins are also of critical importance and are licensed for use in some animal species in Canada. CAHI data provided to CIPARS shows a decline of 15% in the quantity of cephalosporins used in animals (5,454 kg) from 2012 to 2013, however the data cannot be stratified into specific types of cephalosporins (such as third-generation cephalosporins) due to CAHI accounting rules.[g]

To better understand trends over time, adjustments for animal population numbers and weights were made to the total amounts distributed for animal use. A standard animal weight at treatment (European) was used for each animal production class to determine the "biomass" of the animal population.[8] Using this biomass adjustment, the overall quantity of antimicrobials distributed remained relatively stable over time, with a 1% decrease since 2006 and a 2% decline since 2012 (Figure 4). This stability in quantity of antimicrobials distributed comes at a time when other nations are taking significant measures to decrease the quantities of antimicrobials intended for use in animals, or to restrict certain mass medication use practices, such as use for antimicrobial growth promotion. For example, 18 of 20 countries providing data to the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) between 2010 and 2012 showed a decrease in sales.[8]

[f] Bacitracins, bambermycin, chloramphenicol, clavulanic acid, florfenicol, nitrofurantoin, nitrofurazone, novobiocin, ormethoprim, polymixin, tiamulin and virginiamycin.

[g] 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 the regulations in the United States.

FIGURE 4: Medically-important antimicrobials distributed for use in animals over time; measured as kg active ingredient and mg active ingredient, adjusted for population and weight[h]



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 (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. Information on reasons for AMU in production animals is collected by CIPARS through surveillance of volunteer sentinel grower-finisher pig and broiler chicken farms.[6]

In 2013, 12% of the sampled pig herds and 8% of the sampled chicken flocks reported no use of antimicrobials. This highlights the heterogeneity of use practices by farmers/veterinarians. In farms reporting use of antimicrobials, the majority were administered through feed, rather than by injection or via water. There are also important differences in the types and relative quantities of antimicrobials used in different food animal sectors in the CIPARS farm surveillance program.

Overall, the greatest use of antimicrobials on sampled grower-finisher pig and broiler chicken farms was for disease prevention. For broiler chickens in 2013, 93% of antimicrobials were used in feed, primarily for the prevention of necrotic enteritis (*Clostridium perfringens*—macrolides, penicillins, streptogramins, bacitracin) and coccidiosis (ionophores and chemical coccidiostats). Only 12% of broiler chicken flocks reported using antimicrobials for production claims (bacitracin, virginiamycin, bambermycin and penicillin).

[h] These data do not include quantities of antimicrobials imported under "own-use" provisions (own use importation – OUI) or imported as active pharmaceutical ingredients (API).

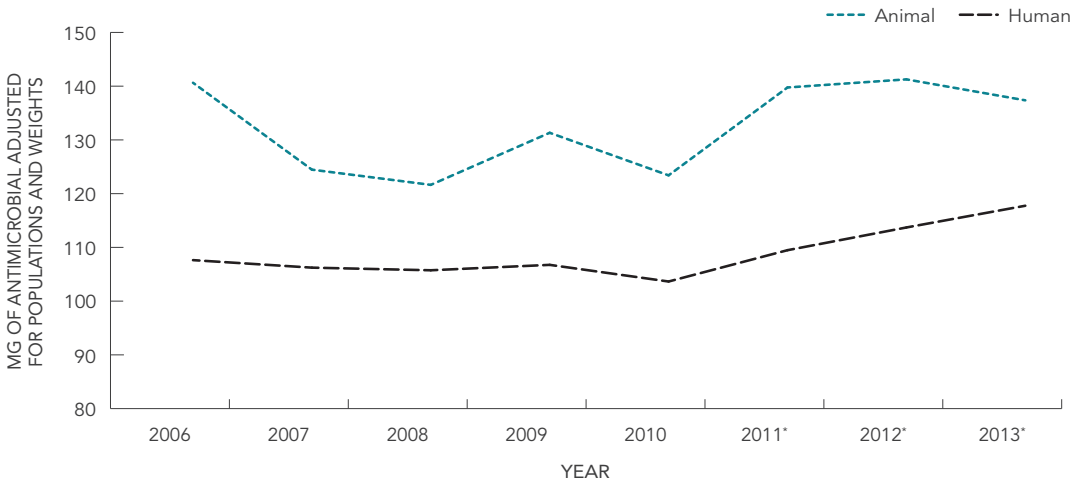
Antimicrobials were administered by participating grower-finisher pig farms via feed for disease treatment (11%), prevention (47%) and production claims (36%). For disease prevention, lincomycin and tylosin were reported mainly for use in the prevention of enteric disease and chlortetracycline for prevention of respiratory disease. Tylosin, ionophores, lincomycin and chlortetracycline were reported as being used for production claims.

INTEGRATION OF HUMAN AND NON-HUMAN ANTIMICROBIAL USE DATA

Canada is a major producer of food animals for domestic and international markets, with approximately 18 times more animals than humans; the majority of which are poultry (approximately 600 million). In 2013, approximately 1.4 million kg of medically-important antimicrobials were distributed and/or sold for use in humans, animals and crops in Canada. Of the medically-important antimicrobials (all classes used in human medicine), 78% were used in production animals; approximately four times more antimicrobials distributed for animals than sold for human use. Of the remaining total medically-important antimicrobials distributed and/or sold for use in Canada, 21% were for use in humans, 1% for companion animals and less than 1% in crops.[i]

Adjusting for underlying population and average weight, in 2013, there were approximately 1.4 times more antimicrobials distributed for use in animals than humans (based on kg active ingredient adjusted by biomass).[6] Since 2006, the quantity of antimicrobials distributed (adjusted by population and weight) for humans increased slightly with few variations year over year to 2013 (Figure 5). Part of this increase is because information for parenteral products provided through community pharmacies was not available prior to 2010. In contrast, the quantity of antimicrobials adjusted by population and weight for animals has a greater degree of variation.

FIGURE 5: Quantity of antimicrobials distributed and/or sold for use in animals and humans, accounting for population and weight (2006–2013)[j]

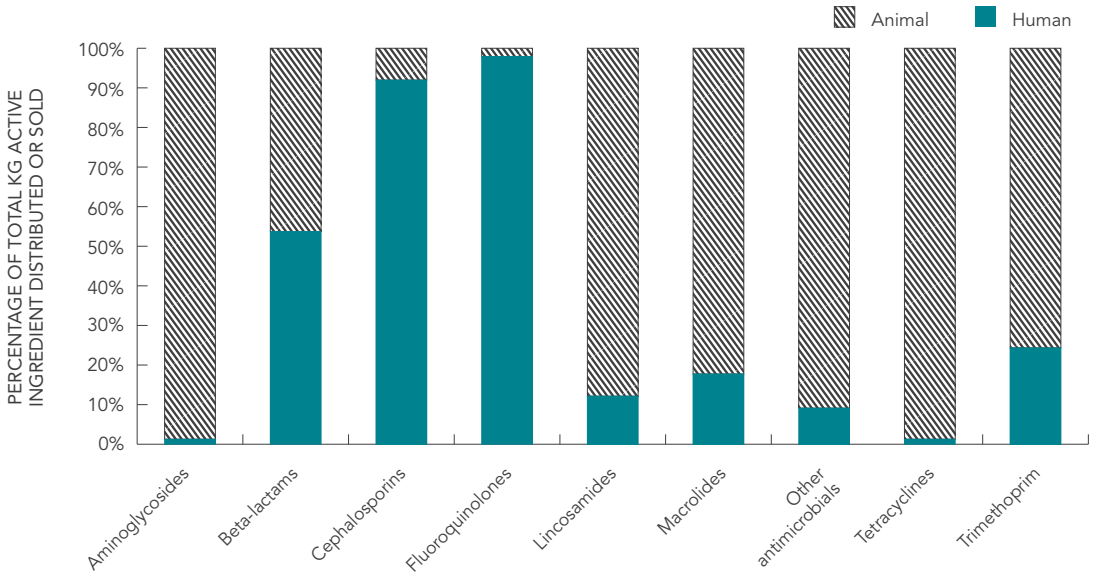


[i] Data provided by Health Canada's Pest Management Regulatory Agency to CIPARS. Personal communication.

[j] * Parenteral products included in human data as of 2010. For animals, these data do not include quantities of antimicrobials imported under "own-use" provisions (own use importation – OUI) or imported as active pharmaceutical ingredients (API).

Because the same or similar antimicrobials are used in humans and animals, AMU in both sectors contributes to the emergence and spread of resistance in bacteria causing human infections. Understanding the overall contribution of each sector's AMU to resistance will help to preserve the effectiveness of antimicrobials for treating and preventing infections in both animals and humans. Some antimicrobial classes are sold or distributed more often for use in humans than animals and vice-versa. In humans, the predominant classes of antimicrobials sold (by kg active ingredient in descending order) are ß-lactams, cephalosporins, fluoroquinolones and macrolides (Figure 6). In animals, they are tetracyclines, "other" antimicrobials,[k] ß-lactams and macrolides.

FIGURE 6: Percentage of total kilograms of antimicrobials distributed and/or sold for use in animals and humans by antimicrobial class in Canada, 2013[l]



[k] "Other antimicrobials" for animals include: bacitracins, bambermycin, chloramphenicol, clavulanic acid, florfenicol, nitrofurantoin, nitrofurazone, novobiocin, ormetoprim, polymixin, tiamulin, virginiamycin.

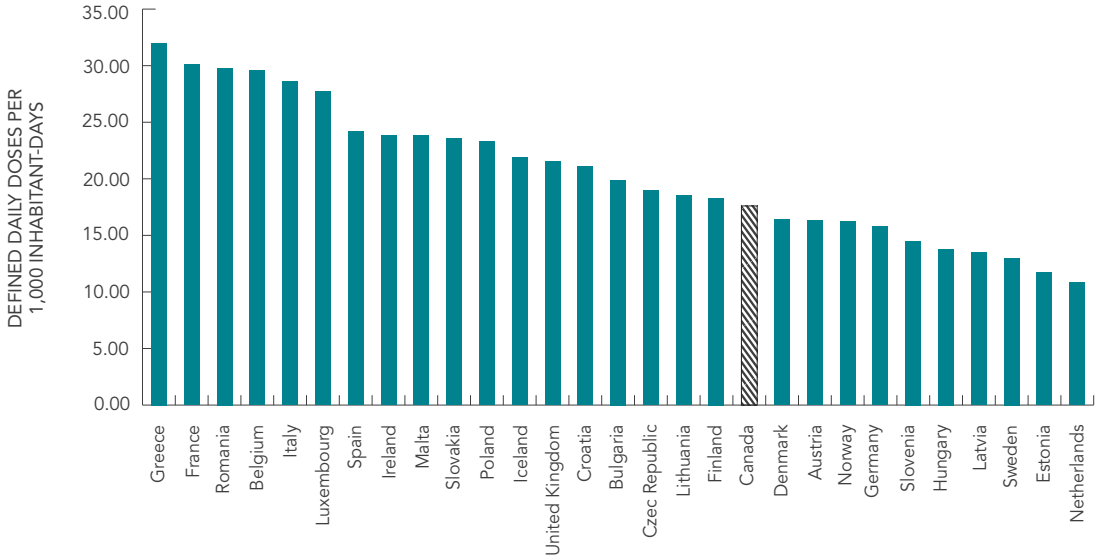
[l] These data do not include quantities of antimicrobials for animals imported under "own-use" provisions (own use importation – OUI) or imported as active pharmaceutical ingredients (API).

INTERNATIONAL COMPARISONS

Human antimicrobial use

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) collects information from the European Union Member Countries to estimate the total amount of outpatient antimicrobials used.[10] A total of 28 countries provided information for 2013. When outpatient AMU in Europe was compared with Canadian community pharmacy dispensation (Figure 7) it was found that Canada has similar levels of AMU as Finland, but slightly higher than Denmark. Canada's overall outpatient use represented 1.6 times the level of use reported by the Netherlands (country with lowest use) and half the level estimated in Greece (country with the highest level of use). Overall, Canada ranked 11th out of the 29 countries classified by increasing levels of total AMU.

FIGURE 7: Outpatient antimicrobial use (DDD per 1,000 inhabitant-days) reported in 28 European countries and Canada, 2013



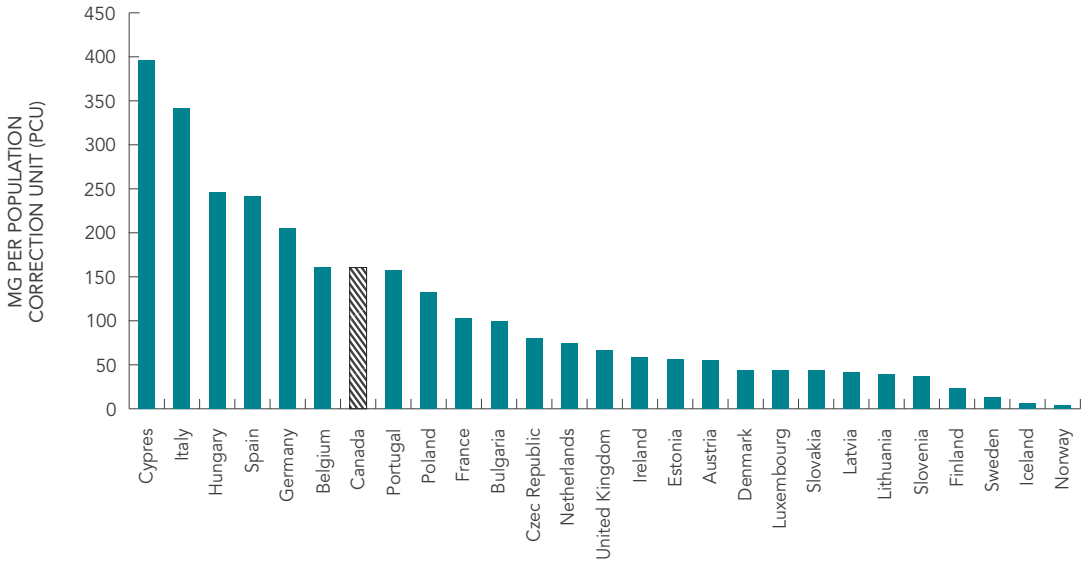
Distribution of antimicrobials for animal use

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) collects and reports information from member countries on antimicrobial agents intended for use in animals.[8] The data available through their reports is focused on food-producing animals. In 2012, a total of 26 member countries provided information on levels of antimicrobial sales.[8] When compared to the countries participating in the ESVAC network, Canada ranked 21 out of 27 countries by increasing levels of antimicrobial sales adjusted by population and weight (Figure 8). Canada's total milligrams distributed adjusted by population was 42 times that used in Norway (country with lowest use) and less than half of that reported by Cyprus (country with highest use). Canada's ranking would increase if we could account for the currently unrecorded imports of antimicrobials which fall under own-use importation (OUI) and imports of Active

Pharmaceutical Ingredients (API) for animal use. The latest information from an Ipsos/Impact Vet study prepared for CAHI estimated that the lost opportunity value due to OUI and API was 13% of total animal health product sales, not just antimicrobials.

One reason for Canada's higher position is that unlike EU countries, Canada still uses antimicrobials for production claims . The Netherlands have significantly reduced AMU by over 50%, from 165 mg per population correction unit (PCU) in 2009[11] to 74.9 mg per PCU in 2012.[8] Canada's total use mirrors that reported by the Netherlands in 2009 prior to their reductions. This suggests that while our commodity sectors are different, a significant reduction of AMU in Canada is possible.

FIGURE 8: Antimicrobial sales for 2012 for animals (quantity adjusted by population and weight) for Canada and countries participating in the European Surveillance of Veterinary Antimicrobial Consumption network[m]



AMU Conclusion

Antimicrobial use is one of the main contributors to the emergence and spread of antimicrobial-resistant organisms. Limiting the selective pressure posed by inappropriate and over use of antimicrobials must be achieved through stewardship-informed reductions in the levels of antimicrobials used in human and animal sectors. It is encouraging to note that Canadian levels of antimicrobials (defined daily doses per 1,000 population-days) dispensed through community pharmacies intended for use in humans were lower in 2013 compared to previous years. Even more encouraging is the fact that the biggest decreases in use were in prescriptions dispensed to children younger than five years of age, which implies that

[m] 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".

prescribers may be following suggested guidelines for this age group. In contrast, the total antimicrobials distributed for animal use remained relatively stable in animals (as measured by the quantity distributed corrected for biomass). This is of concern because similar classes of antimicrobials used to treat and prevent infections in animals are also used in humans.

Food-production animals are, by quantity, the primary sector where antimicrobials are used and represent a large selection pressure for AMR. Based on surveillance of both human and animal AMU, educational campaigns and stewardship programs should continue to stress the need to reduce the proportion of antimicrobials that are provided unnecessarily or in the presence of other available treatments. Although reductions over time have been observed for overall human AMU, it should be determined if this could be the result of using more potent antimicrobials. This has been identified to be the case in the hospital setting, where physicians tend to care for patients with more severe and life-threatening diseases. These potent antimicrobials are considered to be of "last recourse" as other antimicrobials might not have been effective in treating the infection. From hospital purchasing data, large increases in the use of antimicrobials considered of "restricted use" were observed over time, particularly in those used for treating Gram-positive bacteria. The level of use of these antimicrobials should be monitored closely to ensure that these antimicrobials are used properly, preserving their efficacy for treating drug-resistant infections.

Next Steps

The Agency currently reports on antimicrobials dispensed in the community through pharmacies, purchased by hospitals, distributed for animal use, and used in the farm setting (grower-finisher pigs and chickens) and for the first time, antimicrobials sold for use in crops.[n]

Additional human AMU surveillance will be carried out through the collection of AMU data in the hospital setting through a subset of CNISP hospitals and by including data on on-reserve populations through Health Canada's First Nations and Inuit Health Branch. Animal use information will be enhanced through a partnership between CIPARS and FoodNet Canada to collect some regional AMU information from beef cattle, dairy cattle, layer chicken and turkey farms located within the FoodNet sentinel sites. In addition, the Agency will work with international partners such as the United States Food and Drug Administration (FDA), ESVAC and the OIE to identify and utilize the best metrics for regional, national and international reporting of AMU in animals.

The Agency will monitor the effects of regulatory and policy changes, such as Health Canada's work with CAHI to implement the removal of production claims of medically-important antimicrobials, through AMU/AMR surveillance of antimicrobials distributed for use for all animals and on sentinel broiler chicken and grower-finisher pig farms.

Together, these activities will provide a broader understanding of human and animal AMU, including reasons for use and outcomes. This will help to inform the development of stewardship programs and treatment guidelines ensuring appropriate AMU to help protect their effectiveness in treating Canadians.

[n] Data provided by Health Canada's Pest Management Regulatory Agency to CIPARS. Personal communication.

ANTIMICROBIAL RESISTANCE IN CANADA

The following section provides information on antimicrobial-resistant microbes currently under surveillance by the Agency. Information identified by the WHO[12] is denoted for each microbe under "Antimicrobials of Importance".

ORGANISMS TRANSMITTED IN HEALTH CARE SETTINGS

Organisms of importance in health care settings include those that cause infections acquired during hospitalization or as the result of health care provided in hospitals or alternate settings such as outpatient clinics, physician/dental offices and long-term care facilities. These organisms can cause severe, life-threatening infections, especially in the elderly, young infants and patients who have weakened immune systems due to other diseases, such as cancers and heart or kidney disease. AMR is particularly significant in these settings as the organisms spread easily from person-to-person within or between health care facilities and have been linked to large hospital outbreaks. In addition, patients are prescribed antimicrobial agents for other infections or for prevention of infection, which may lead to the emergence of novel AMR. Many of these organisms are now emerging in community settings as well as in individuals with no recent exposure to health care settings.

Clostridium difficile (C. difficile)

Antimicrobials of Importance: metronidazole, vancomycin, fidaxomicin

C. difficile is the most common cause of infectious diarrhea in hospitals and long-term care facilities in Canada. Symptoms of *C. difficile* infection (CDI) range from diarrhea and abdominal cramps to more serious intestinal inflammation that can cause death. While resistance in *C. difficile* is not a concern at present, the extensive use of antimicrobials in hospitals to treat patients often creates a competitive advantage for *C. difficile* (which is frequently carried in human intestines). The competing bacteria are reduced by the administered antimicrobials, resulting in the overgrowth of *C. difficile*. The disease is caused by the bacterium-releasing toxins that destroy the lining of the bowel that, in turn, causes bloating and frequent watery diarrhea. Most cases of CDI occur in patients who are elderly and who have other underlying medical conditions. *C. difficile* spreads rapidly in health care settings by direct contact because it is naturally resistant to many antimicrobials used to treat other infections and *C. difficile* spores in the environment tend to be resistant to more 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% will die from the infection.[13,14]

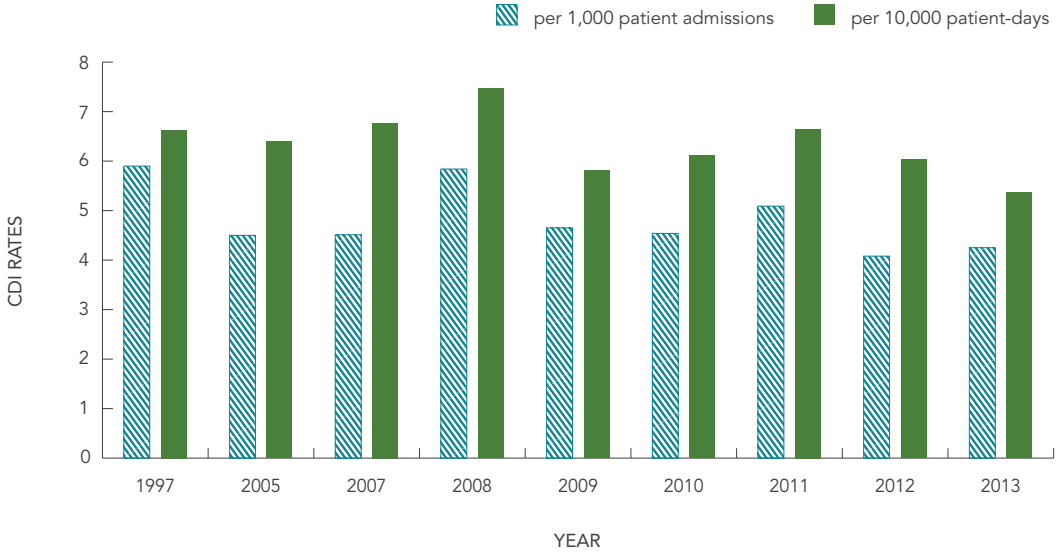
A more virulent strain of *C. difficile* emerged in 2000. This strain, characterized as the North American pulsed-field Type 1 (NAP1) was found to be resistant to fluoroquinolones, a class of antimicrobials commonly used to treat other infections in both the hospital and community setting. NAP1 has spread throughout North America and Europe and is responsible for increasing CDI rates, hospital outbreaks and more severe disease especially in the elderly.

Resistance to the first-line antimicrobials used for treatment of CDI is rare; however the rate of response to metronidazole, the first-line treatment regimen for mild-to-moderate CDI, has been decreasing. Recurrence of the disease occurs in approximately 30% of patients who initially responded to antimicrobial therapy.[15]

For initial episodes consisting of mild-to-moderate CDI, treatment with oral metronidazole is recommended, while oral vancomycin is used for treating initial episodes of severe CDI or in patients who have failed metronidazole on more than two occasions. If the infection is severe and has complications, oral vancomycin is administered with or without intravenous metronidazole. In 2012, Health Canada approved the use of fidaxomicin, a new antimicrobial used specifically for treating CDI. Fidaxomicin is currently recommended for use in patients with recurrent or non-responsive CDI that has failed both metronidazole and vancomycin. Fidaxomicin is generally considered equal to oral vancomycin in terms of cure rates.

The Agency has collected information on health care-associated (HA) CDI through CNISP since 2005. A total of 22,032 cases of HA-CDI have been reported to the Agency between 2007 and 2013 of which 3.1% (679 cases) were in children. In 2013, the overall rate of HA-CDI was 3.99 cases per 1,000 patient admissions, which is lower than the rate of 4.61 reported in 2007 (Figure 9). In 2013, 3.1% of deaths in CNISP hospitals could be attributed to CDI compared to 4.8% in 2007. In 2013, 29.6% of *C. difficile* strains submitted to the Agency were the NAP1 strain compared to 41.1% in 2007. Over the entire surveillance period, two *C. difficile* strains were resistant to metronidazole. In 2012, one *C. difficile* strain from Western Canada showed diminished susceptibility to vancomycin.

FIGURE 9: Incidence of health care-associated *Clostridium difficile* infections per 1,000 patients admissions and per 10,000 patient-days, 1997, 2005, 2007–2013



Multi-Drug-Resistant *Enterobacteriaceae*

Antimicroibals of Importance: Carbapenems (ertapenem, imipenem, meropenem, doripenem), extended-spectrum cephalosporins (ceftazidime, ceftriaxone, cefotaxime), fluoroquinolones

Enterobacteriaceae are Gram-negative bacilli (GNB) commonly encountered in health care settings and include species such as *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp. These organisms are normal flora in the gastrointestinal tract in healthy humans, but they are a cause of infections, including urinary tract infections, bloodstream infections, 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 ß-lactamases (ESBL), an enzyme class that renders it resistant to commonly-used extended-spectrum (third-generation) cephalosporins (i.e., ceftazidime, cefotaxime and ceftriaxone) as well as beta-lactam-lactamase inhibitor combinations (i.e., piperacillin tazobacatam, etc.).

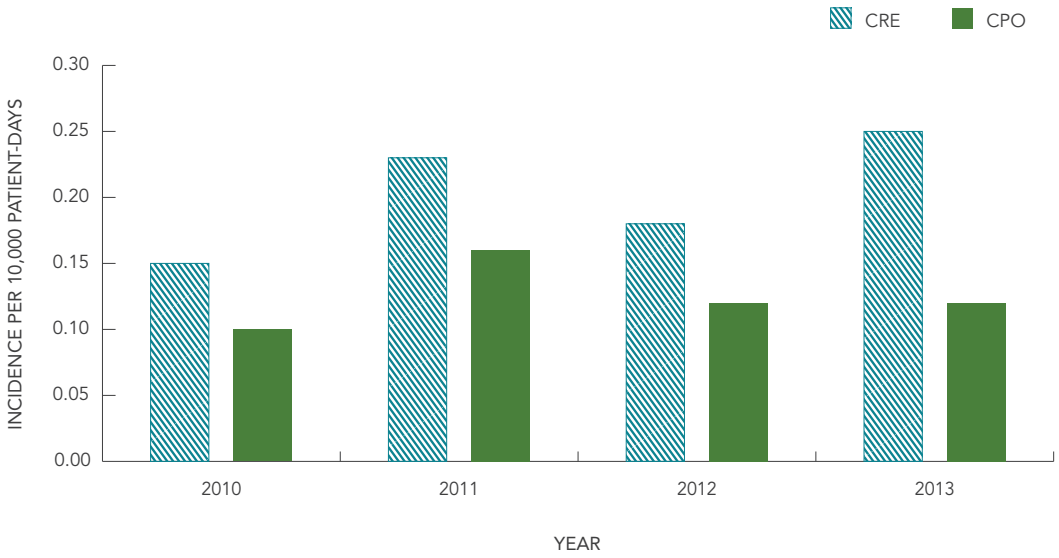
The carbapenem group of antimicrobials is a relatively safe and generally effective treatment for ESBL as well as other highly resistant Gram-negative organisms, and there are few alternative treatments available when resistance to carbapenems occurs. *Enterobacteriaceae* that have acquired resistance to carbapenems are called carbapenem-resistant *Enterobacteriaceae* (CRE). Some CRE are also carbapenamase-producing organisms (CPO) by virtue of their ability to produce enzymes, called carbapenamases, which break down carbapenems. There are other GNB outside of the Enterobacteriaceae family that have also shown to be resistant to carbapenems. These include *Acinetobacter* spp. and *Pseudomonas* spp. Both of these bacteria can be found in the hospital environment and can cause infection in vulnerable patients.

All of these bacteria cause a variety of diseases ranging from pneumonia to UTIs, as well as serious BSIs or wound infections with symptoms varying depending on the disease. Individuals can also harbour ESBL-producing bacteria and CRE without causing disease (referred to as colonization). ESBL and CRE infections and colonization typically occur in ill patients with exposure to acute and long-term care settings.

CNISP has been collecting information on CRE and CPO in patients hospitalized in sentinel CNISP hospitals since 2010.[16] Participation in surveillance has increased from 33 CNISP hospitals in 2010 to 38 CNISP hospitals in 2013. Between 2010 and 2013, CNISP hospitals have reported a total of 390 cases of CRE and 219 cases of CPO (Figure 10). Among the 219 CPO cases, 74 (33.8%) were infections, 106 (48.4%) were in patients who harboured the bacteria without showing signs of infection (colonization) and the status was unknown for 39 (17.8%) cases. The incidence of CPO has remained stable from 2010 (0.10 per 10,000 patient-days) to 2013 (0.11 per 10,000 patient-days). The incidence of CRE has nearly doubled from 0.15 per 10,000 patient-days in 2010 to 0.26 per 10,000 patient-days in 2013. However, this increase in the rate of CRE in 2013 is largely due to an ongoing outbreak at one hospital and is not reflective of a national trend. From 2010–2013, a total of three (1.6 %) deaths were attributed° to CPO; all were in patients with BSIs.

° CPO was the primary or contributing cause of death 30 days after diagnosis.

FIGURE 10: Carbapenem-resistant Enterobacteriaceae (CRE) and carbapenemase-producing organisms (CPO) infection rates per 10,000 patient-days



The NML has also been working closely with provincial public health laboratories to monitor the total number of CPO cases identified in Canada. Between January 1, 2008 and June 30, 2014, 725 CPOs were reported to the NML by provincial public health laboratories.

CIPARS routinely screens all its *Salmonella* and *E. coli* isolates for the possibility that they are carbapenem resistant. To date, no carbapenem resistance has been observed through routine screening.

Staphylococcus aureus

Antimicrobials of Importance: penicillinase-resistant penicillin (methicillin, oxacillin, nafcillin), vancomycin, cefoxitin (as a surrogate for oxacillin resistance)

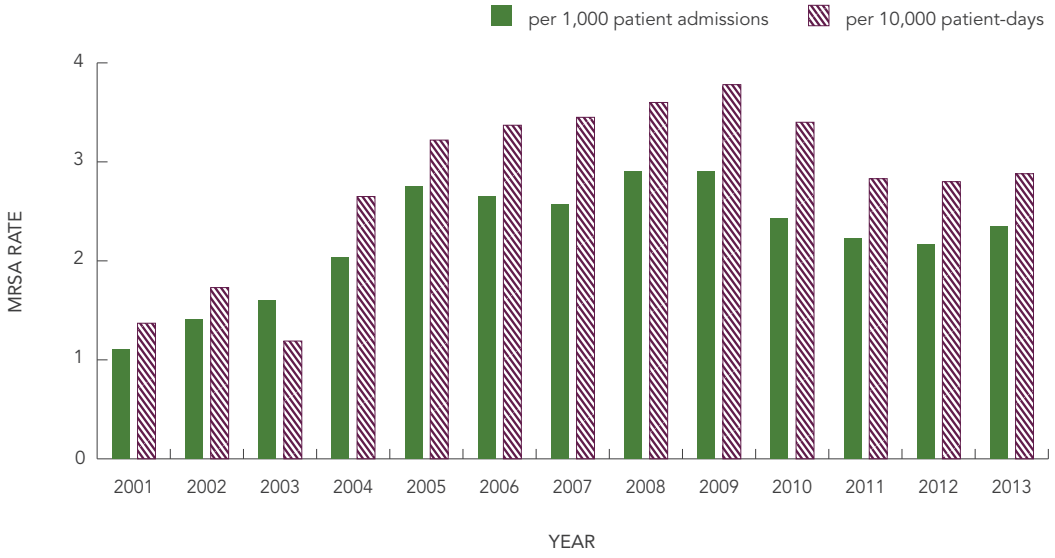
Staphylococcus aureus (*S. aureus*) is a common Gram-positive bacterium normally found on the skin of healthy individuals. The bacteria can also be found in the interior of the nose and the groin region of healthy individuals without causing disease (colonization). *S. aureus* can cause a variety of infections, most notably in the skin and soft tissue, bone and bloodstream (BSI). When penicillin was first introduced, it was an effective treatment for *S. aureus* infections, but resistance developed soon after. *S. aureus* that are resistant to ß-lactam antimicrobials (e.g., penicillins such as oxacillin, methicillin and dicloxacillin) are called methicillin-resistant *Staphylococcus aureus* (MRSA).

S. aureus, including MRSA is one of the most common causes of health care-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 health care settings but over the past decade, community-associated MRSA (CA-MRSA) has been increasing in Canada, especially in certain vulnerable populations (e.g., homeless people, 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. Canadian prevalence studies have estimated that approximately 4.2% of hospitalized patients will become infected or colonized with MRSA resulting in an annual hospital cost of about $36.3 million.[17,18]

Hospital data presented here were reported to CNISP.[19] In 2013, the rate of MRSA infection in patients was 2.18 per 1,000 patient admissions and 2.84 per 10,000 patient-days (Figure 11). Since 2009, national MRSA infection rates have decreased, with the most dramatic reduction seen in health care-associated MRSA (HA-MRSA) infection rates. However, current MRSA infection rates still exceed rates observed in the late 1990s and early 2000s, consistent with trends seen in other developed countries.

In 2013, 368 (19.9%) of MRSA infections were from blood and 1485 (80.1%) were from clinical sources other than blood. Skin and soft tissue infections (SSTI) represented the largest proportion (43%) of MRSA infections identified from clinical sources other than blood. The rate of MRSA BSI was 0.56 cases per 10,000 patient-days in 2013. The proportion of MRSA infections (all clinical sources) identified as CA-MRSA has steadily increased from 25% in 2008 to 33% of cases in 2012. In 2012, 8.6% of patients with a clinical MRSA infection died, and the following year, 25% of patients with a MRSA BSI died 30 days after the date of positive culture.[19]

FIGURE 11: Incidence of methicillin-resistant *Staphylococcus aureus* infections per 1,000 patient admissions and per 10,000 patient-days in Canada, 2001–2013

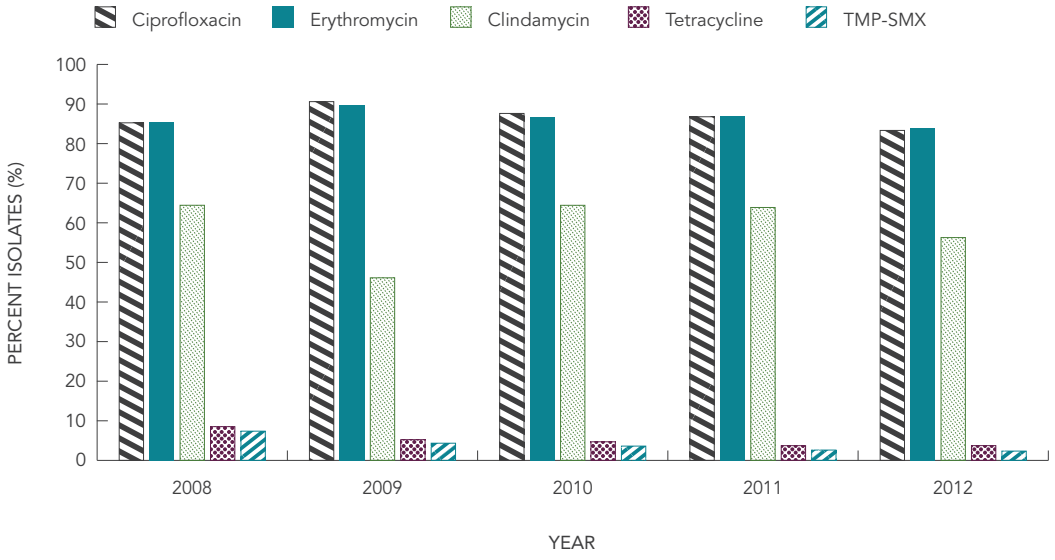


Although intravenous vancomycin is one of the primary antimicrobials recommended for treatment of MRSA, both linezolid (IV and oral) and daptomycin (IV) are used within Canadian health care settings. Other antimicrobials are treatment options for specific sites of MRSA infections including: telavancin (IV) for SSTIs, doxycycline for SSTIs, trimethoprim-sulfamethoxazole (TMP-SMX) (IV) as well as clindamycin (IV and oral) for treating SSTIs and pneumonia.[20]

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.[21] There has also been no documented resistance to tigecycline, linezolid or daptomycin in the isolates tested from 2008 to 2012. The proportion of tested MRSA isolates across Canada that were resistant to ciprofloxacin, erythromycin and clindamycin has remained relatively unchanged over this period (Figure 12). 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 region (Atlantic provinces), while resistance to tetracycline and TMP-SMX is lower in the east compared to the rest of Canada.

FIGURE 12: Antimicrobial resistance of Methicillin-resistant *Staphylococcus aureus* isolates, 2008–2012, Canada



Vancomycin-Resistant *Enterococci*

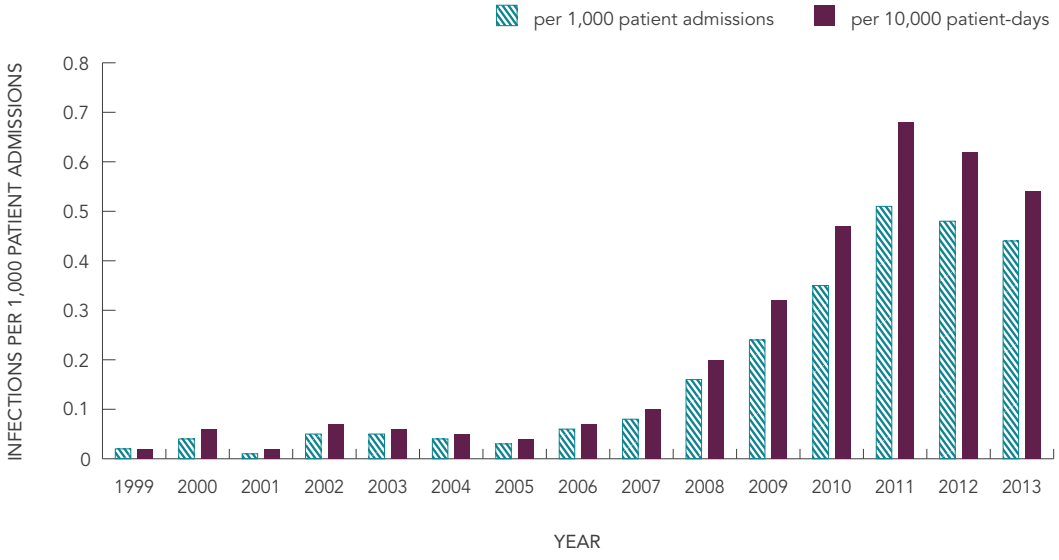
Antimicrobials of Importance: Aminopenicillin (ampicillin and amoxicillin), linezolid, lipopeptide (daptomycin)

Enterococci are part of the normal intestinal flora of both humans and animals but can also cause a range of illnesses including bloodstream, surgical site and urinary tract infections. The majority of human infections are caused by *E. faecalis* and *E. faecium*. The naturally high level of AMR found in *E. faecalis* and *E. faecium* makes infections difficult to treat.

Vancomycin-resistant Enterococci (VRE) are strains of Enterococcus that have acquired resistance to this antimicrobial of last recourse, leaving few or no treatment options. VRE infections most commonly occur in patients in hospitals who are more susceptible or who have been previously treated with vancomycin or other antimicrobials for long periods of time. Those who have undergone surgical procedures or who have medical devices such as in-dwelling urinary catheters are more at risk of infection. VRE infections are often difficult to treat. In Canada, treatment can consist of one of the following antimicrobials: linezolid, daptomycin, tigecycline, combination therapy with gentamicin, or nitrofurantoin, depending on the type of infection. Although VRE is considered a low-virulence pathogen, infection rates have been increasing in Canada and in other developed countries. There is also a concern that vancomycin-resistant genes may transfer from VRE to *Staphylococcus aureus* resulting in few alternative treatments for the more severe VRSA infections.[22]

CNISP has collected data on ongoing surveillance of VRE in patients in participating hospitals since 1999.[22] The VRE infection rate has increased since 2008 (Figure 13). In 2013, 324 VRE infections were reported to the Agency for a rate of 0.53 per 10,000 patient-days. Information on where the VRE was acquired was available for 223 patients. Of these, the majority (97%) were health care-associated with 54% of total infections affecting patients 65 years or older. Urinary tract infections (UTI) were the most commonly reported type of VRE infection (31%, n=100), followed by BSIs (29% n=95).

FIGURE 13: Incidence rates of vancomycin-resistant *Enterococcus* infections per 1,000 patient admissions and per 10,000 patient-days, 2001–2013



ORGANISMS TRANSMITTED PRIMARILY IN THE COMMUNITY SETTING

Infections that are contracted outside the hospital setting are commonly referred to as "community-acquired". The organisms cause a range of infections that, in most instances, are treatable with antimicrobials. AMR is particularly significant in this setting as organisms are more difficult to control if treated with an inappropriate antimicrobial. In addition, community-acquired infections can be severe and easily transmitted which could lead to large community outbreaks. When these infections are caused by an AMR organism there is a potential for life-threatening disease.

The end of this section deals with two organisms that are viruses (Human Immunodeficiency Virus and Influenza) both of which are treatable by antivirals. Antibiotics (that treat bacteria) are not effective against either of these pathogens.

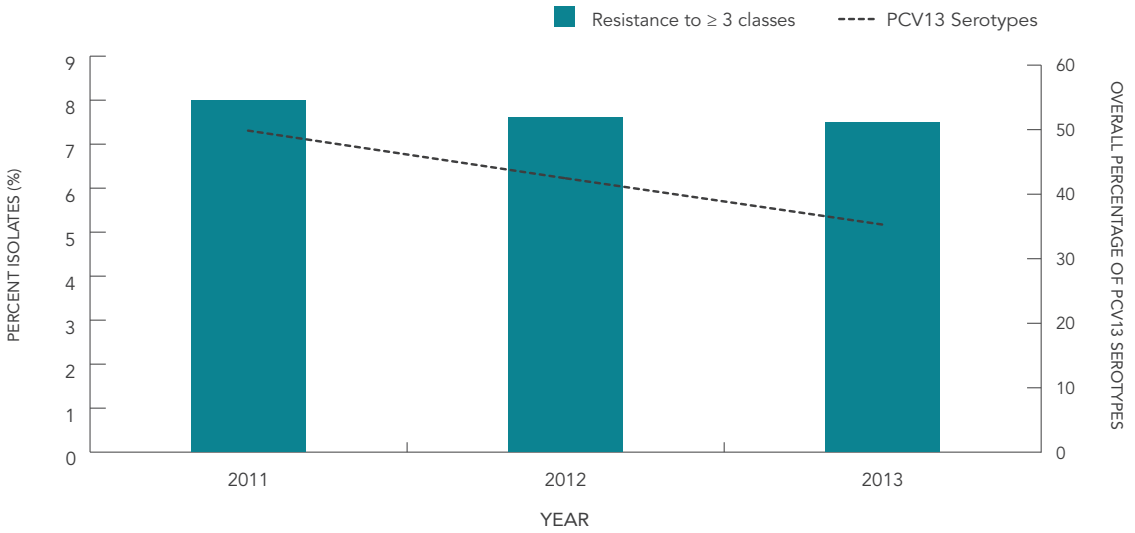
Streptococcus pneumoniae

Antimicrobials of Importance: Macrolides (erythromycin), lincosamides (clindamycin), penicillin, extended-spectrum cephalosporins (cefuroxime, cefotaxime, ceftriaxone, cefepime),trimethoprim/sulfamethoxazole

Diseases caused by *S. pneumoniae* include common, mild, self-limiting infections such as acute otitis media (middle ear infection) as well as severe invasive pneumococcal disease (IPD) with high mortality.[23] Only a few of the 93 currently recognized pneumococcal serotypes cause the majority of disease and have been incorporated into effective vaccines. Incidence of IPD in children under five years has declined in Canada since the implementation of the seven valent pneumococcal conjugate vaccine (PCV7) from 40 cases per 100,000 in 2003 to 15 cases per 100,000 in 2006. However the emergence of a multi-drug-resistant (MDR) non-PCV7 serotype soon occurred and paediatric incidence rates increased to 20 cases per 100,000 by 2009. In 2010, a 13-valent vaccine (PCV13) that included the MDR non-PCV7 serotype in its formulation was introduced. As of 2013, paediatric incidence has now declined to 17 cases per 100,000 in children less than one year and to 11 cases per 100, 000 in children two to four years. Incidence rates in older age groups remain constant with a rate of nine cases per 100,000 in 2013.

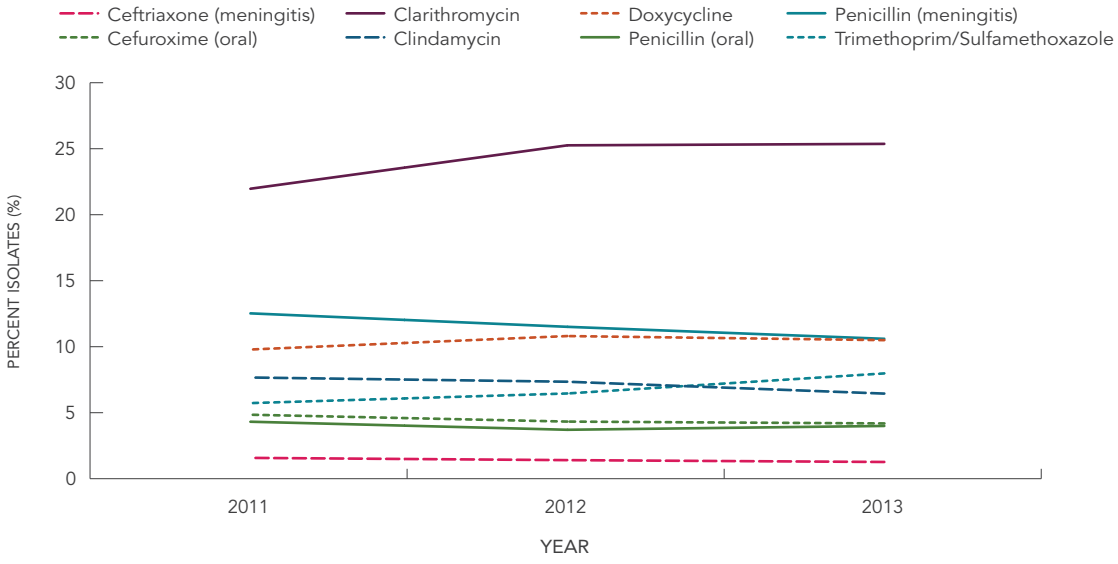
The vaccine-induced decline of PCV13 serotypes (including the MDR strain)[23] has driven a concurrent decline in overall AMR in pneumococci (Figure 14). While PCV13 serotypes have declined from 50% of the isolates in 2011 to 35% in 2013, resistance to three or more classes of antimicrobials has declined from 8.0% to 7.5%. The impact of the *S. pneumoniae* vaccine on resistant strains illustrates the importance of vaccines as part of a strategy to mitigate the impact of AMR.

FIGURE 14: Multi-drug resistance and proportion of PCV13 serotypes of pneumococci in Canada, 2001–2013



Resistance of *S. pneumoniae* to penicillin has decreased from 12% in 2011 to 10% in 2013 (Figure 15). Resistance to clindamycin (7% to 6%) and to doxycycline (10%) has remained relatively stable since 2010, both of which are common first-line treatments for pneumonia.[24] In contrast, resistance to clarithromycin, which can be used in community-acquired pneumonia, increased from 21% in 2001 to 25% in 2013 and TMP-SMX resistance has increased from 5 to 7%. To date, there has been no resistance reported to linezolid, tigecycline or vancomycin. *S. pneumoniae* has now developed resistance to less commonly used antimicrobials such as carbapenems for which resistance has been detected at levels less than 3% in 2013, with meropenem resistance increasing slightly from 2.0% in 2011 to 2.6% in 2013.

FIGURE 15: Antimicrobial resistance of *Streptococcus pneumoniae* isolates, 2011–2013



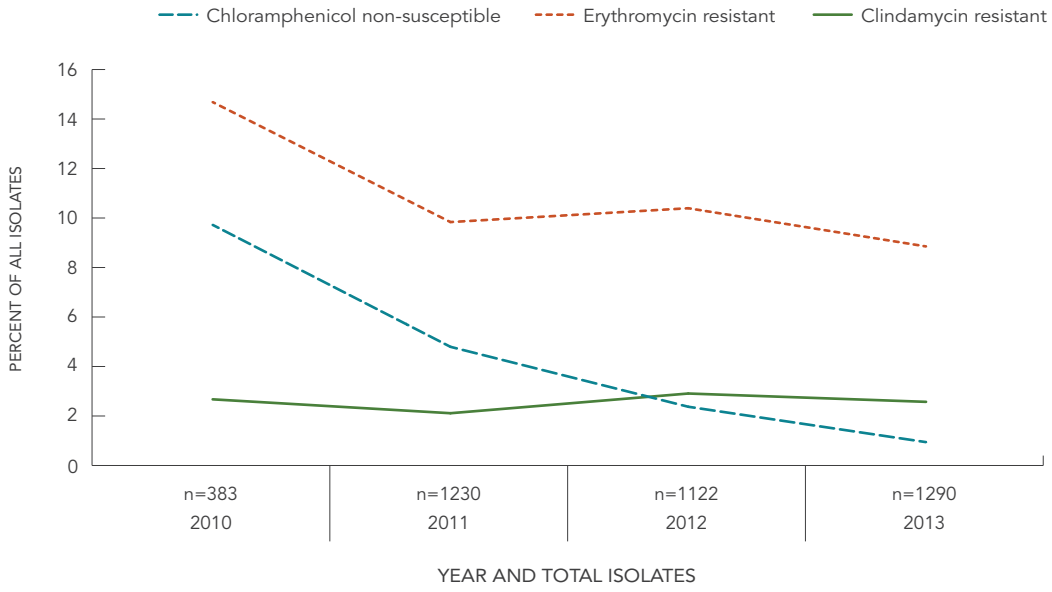
Streptococcus pyogenes (Group A Streptococcus (GAS))

Antimicrobials of importance: penicillin, macrolides (erythromycin) and Lincosmaide (clindamycin)

GAS causes many illnesses, including invasive diseases 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.

The most predominant types of invasive GAS in 2013 were *emm* types 1 and 89, accounting for 23% and 8% of the isolates tested, respectively. The majority were from blood samples (68%), followed by synovial fluid (8%). Notably, all GAS were susceptible to penicillin and vancomycin. Resistance to clindamycin, a second-line drug for treatment,[24] has remained relatively unchanged from 2010 to 2013, while resistance to erythromycin and non-susceptibility to chloramphenicol has decreased over the same time period (Figure 16).

FIGURE 16: Antimicrobial resistance of invasive *Streptococcus pyogenes*, 2010–2013



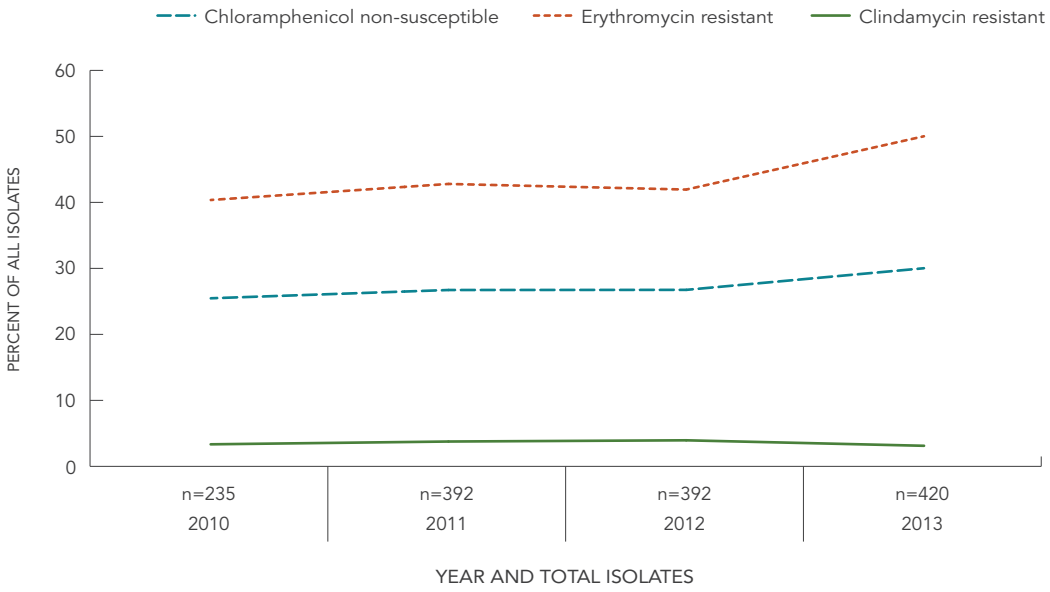
Invasive Streptococcus agalactiae (Group B Streptococcus)

Antimicrobials of importance: penicillin, macrolides (erythromycin), and lincosamides (clindamycin)

Invasive Group B Streptococcus (GBS) is commonly associated with neonatal disease where the highest infection risk is during childbirth and often treated prophylactically with antimicrobials. GBS is also an increasing health concern in adults causing septicemia, meningitis, pneumonia, and bone, joint and tissue infections. At risk adults groups include the elderly, those with underlying medical conditions, pregnant women and those residing in extended health care facilities.

Antimicrobial resistance towards macrolide drugs has increased, with erythromycin resistance rising from 41% to 49% between 2012 and 2013 (Figure 17). Clindamycin resistance has also increased from 26% to 29% while chloramphenicol non-susceptibility has remained constant since 2010.

FIGURE 17: Antimicrobial resistance of invasive *Streptococcus agalactiae* (iGBS) tested, 2010 to 2013



Neisseria gonorrhoeae

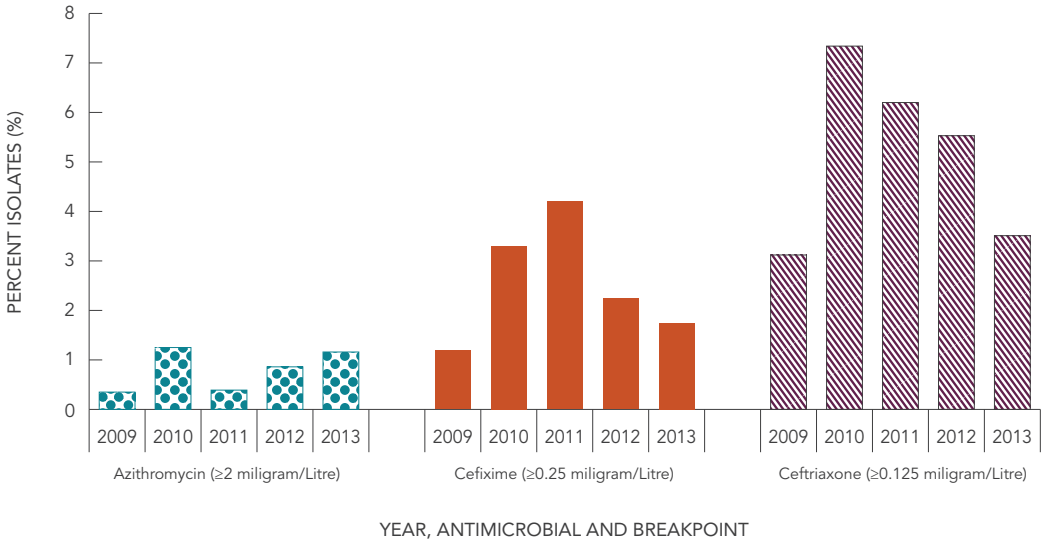
Antimicrobials of Importance: macrolide (azithromycin), cephalosporin (cefixime, ceftriaxone), aminocyclitol (spectinomycin), aminoglycoside (gentamicin), fluoroquinolone (ciprofloxacin)

Neisseria gonorrhoeae causes gonorrhoea, a highly infectious sexually transmitted disease. It results in an acute infection of the reproductive tract that may be symptomatic or asymptomatic. If untreated or inappropriately treated, it may cause genital/reproductive tract inflammation and damage as well as infertility. The treatment and control of gonorrhoea is complicated because it develops resistance to the antimicrobials used to treat it, including penicillins, tetracyclines, macrolides and quinolones. Recently, resistance to azithromycin and isolates with decreased susceptibility to the cephalosporins are emerging and threatening the last available treatment options.

Gonorrhoea is the second most commonly reported bacterial sexually transmitted infection in Canada. Rates of reported cases have more than doubled from 15 cases per 100,000 population in 1997 to 36 cases per 100,000 population in 2012. Of the 3,195 *N. gonorrhoeae* isolates cultured in public health laboratories across Canada in 2013, 1,183 were submitted to the NML for antimicrobial susceptibility testing (samples are submitted to NML when the provincial laboratories identify resistance to at least one antibiotic or if the provincial laboratories do not perform any antimicrobial susceptibility testing). A total of 1,153 of

these were found to be resistant to at least one antibiotic tested, indicating that 36.1% of all *N. gonorrhoeae* cases diagnosed by culture in 2013 were resistant to one or more antibiotics (1,153/3,195) (Figure 18). 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 seven (2012) and eight (2013) isolates observed. Despite the small numbers, this is of concern as it represents a threat to the success of currently recommended dual therapy treatment options.

FIGURE 18: Percentage of gonorrhoea isolates resistant to azithromycin, reduced susceptibility to cefixime and ceftriaxone in Canada, 2009–2013



According to the data available on indications and antimicrobial recommendations for patients seeking medical treatment from office-based physicians,[2] antimicrobials were recommended for the treatment of all cases of gonorrhoea included in the physician dataset. In 2013, the most commonly recommended treatment reported by physicians was a combination of cefixime and azithromycin (34% of cases), followed by cefixime alone (33%). A small number of cases also received treatment with azithromycin (17%) alone or the combination of ceftriaxone and doxycycline (17%).

The data demonstrates a pattern of use different from what is currently recommended by use guidelines. The departure from current guidelines advising the use of a combination of antimicrobials is concerning. These guidelines are developed with relevant knowledge of resistance and treatment effectiveness based on Canadian information. It is essential to follow Canadian-based guidelines because international guidelines may not be applicable in Canada.

Physicians are now discouraged from using tetracyclines and penicillins[16] due to high levels of resistance. In response to rates of decreasing susceptibilities to cephalosporins, the recommended treatment of gonorrhoea infection was updated to third-generation cephalosporins (ceftriaxone or cefixime) as the remaining first-line treatment regimen in

combination with the macrolide azithromycin. There is no ideal alternative to the third-generation cephalosporins and there are very few new treatment options being developed. Early identification of emerging patterns of AMR and timely public health notification of cefixime, ceftriaxone or azithromycin treatment failures will assist in identifying effective treatment regimens and preventing the emergence of untreatable gonorrhoea in Canada.

Salmonella enterica

Antimicrobials of Importance: Carbapenems (ertapenem, imipenem, meropenem, doripenem), extended-spectrum cephalosporins (ceftazidime and ceftriaxone, or cefotaxime), fluoroquinolones (ciprofloxacin, levofloxacin, pefloxacin), macrolides (azithromycin)

Salmonella gastrointestinal infections are common and often self-limiting. Because gastrointestinal salmonellosis does not generally require clinical treatment, the majority of cases are not reported. Treatment of Invasive salmonella infections are indicated as these infections can become life threatening. Recent guidelines published in the Canadian Medical Association Journal recommend treatment of salmonellosis when infection occurs in those less than six months, older than 65 years, are immunosuppressed, and suffer from other comorbidities.[26] If treatment is required, recommended antimicrobials are azithromycin in children and those with travel history and ciprofloxacin in adults for outpatients, while ceftriaxone is recommended for those patients requiring hospitalization, children under the age of 6 months, adults over 50 years of age, pregnant women or if suffering from bacteremia.[27,28]

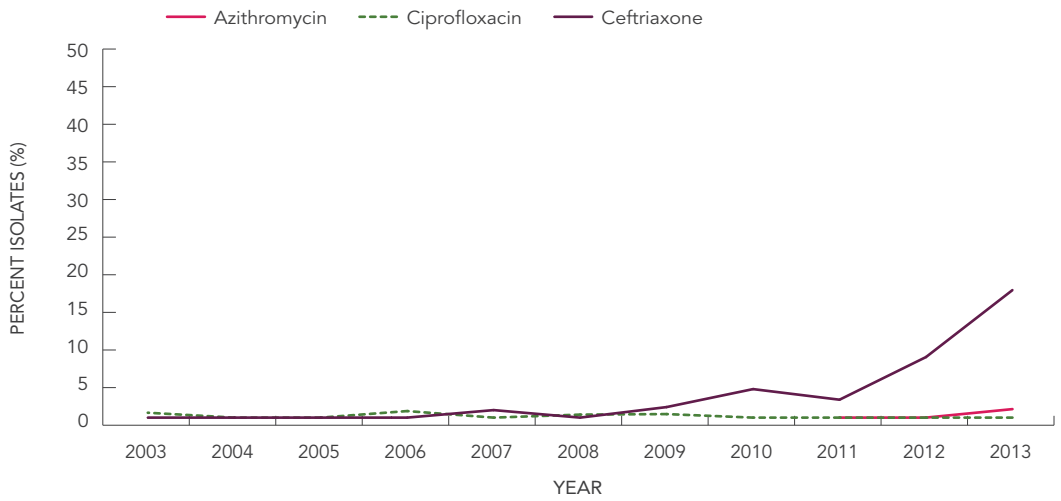
Antimicrobial resistance for *Salmonella* has been monitored through CIPARS since 2002. Current levels of ciprofloxacin resistance in non-typhoidal *Salmonella* are relatively low and are not considered a significant problem.[29] However, as with other organisms, the potential for ciprofloxacin resistance is high due to the frequency with which Canadians travel abroad.

Typhoidal *Salmonella* (*Salmonella* Typhi, Paratyphi A, Paratyphi B and Paratyphi C)

Humans are the only reservoir of typhoidal *Salmonella*. Infection (enteric fever) is caused by contact with another infected person or through contaminated water or food prepared by a person carrying this organism. In Canada, this type of infection is mainly acquired through exposure to contaminated food/water while traveling to countries where typhoidal infections are endemic. Typhoidal infections are potentially life-threatening as they are more likely to move from the intestines into the bloodstream than other enteric infections.[30,31] For Canadian travelers, the Agency recommends that those traveling to South Asia obtain the typhoid vaccine, as this is the area of greatest risk.[32]

The rate of infection observed in Canada has ranged from a low of 0.5 cases per 100,000 individuals in 2003 to a high of 0.7 cases per 100,000 individuals in 2008. A total of 177 cases of typhoidal infections were reported in 2013 and submitted to NML for AMR testing.[29] Only two and 11 isolates have been identified as resistant to azithromycin and ceftriaxone, respectively since 2003 (Figure 19). In contrast, resistance to ciprofloxacin has increased from no resistance in 2003 to 17% in 2013. In 2013, 83% of the ciprofloxacin-resistant infections were identified from blood samples, implying that these were from bloodstream infections. Thirteen percent of typhoidal isolates were resistant to two or more antimicrobial classes.

FIGURE 19: Resistance to azithromycin, ciprofloxacin and ceftriaxone in typhoidal *Salmonella* in Canada, 2003–2013



Non-typhoidal *Salmonella*

In Canada, it is estimated that non-typhoidal *Salmonella* causes 88,000 cases per year.[33] There are over 2,000 different strains of non-typhoidal *Salmonella* that cause human salmonellosis. In Canada the top three *Salmonella* strains causing human infection are *Salmonella* Enteritidis, *Salmonella* Heidelberg and *Salmonella* Typhimurium. Non-typhoidal *Salmonella* is found in the intestines of many food-producing animals such as poultry and pigs. Human infection is usually acquired by consumption of contaminated food of animal origin, mainly undercooked meat, poultry, eggs and unpasteurized milk. Fruits and vegetables can become contaminated with human or animal faeces, leading to foodborne outbreaks if not handled properly.

Salmonella Enteritidis

A total of 746 human *Salmonella* Enteritidis were received from provinces in 2013 for AMR testing out of 2,987 samples. Fifteen percent (111/746) were resistant to at least one antimicrobial. Resistance to nalidixic acid (a fluoroquinolone) was observed in 12% (91/746) of the *S.* Enteritidis human samples. In terms of antimicrobials of human clinical importance, resistance to ceftriaxone and azithromycin was present in less than 1% of samples and has remained stable over time (Figure 20). Resistance to ciprofloxacin was present in 1% of samples in 2013, a slight increase from 0.2% in 2011, the first year this resistance was observed.

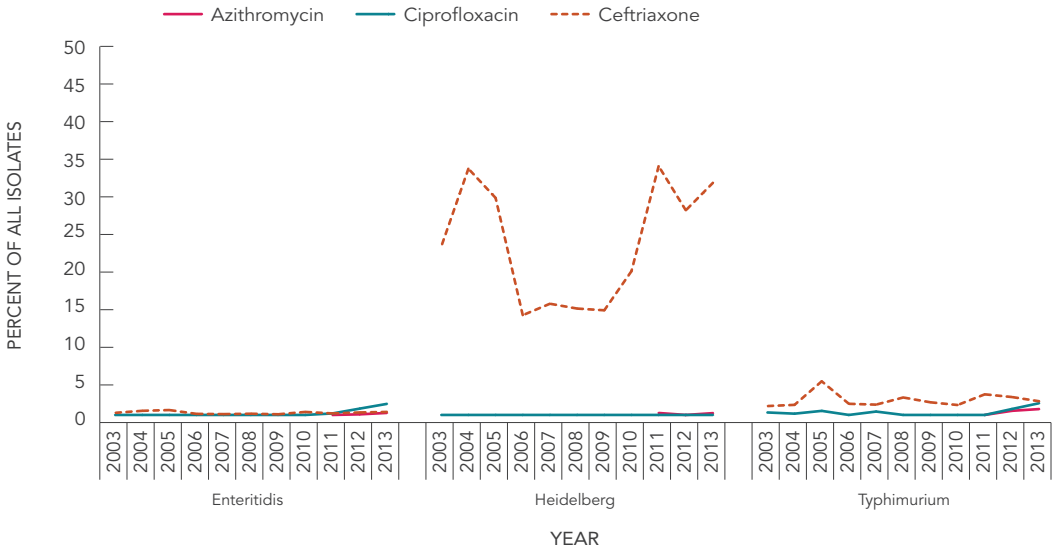
Salmonella Heidelberg

In 2013, there were 418 human *Salmonella* Heidelberg samples tested for AMR. Of the 418 cases, 41% were resistant to at least one antimicrobial. Of these resistant infections 75% were resistant to the combination of amoxicillin-clavulanic acid, ampicillin, cefoxitin and ceftriaxone. In terms of antimicrobials of human clinical importance, resistance to ceftriaxone was present in 31% (129 cases) of samples in 2013, an increase from 27% observed in 2012 (Figure 20). There was no resistance to azithromycin or ciprofloxacin in 2013.

Salmonella Typhimurium

A total of 385 human *Salmonella* Typhimurium samples were tested for AMR of which 128 (33%) were resistant to at least one antimicrobial. The majority (68/128) of these resistant samples were resistant to the combination of ampicillin, chloramphenicol, streptomycin, sulfisoxazole and tetracycline. In terms of antimicrobials of human clinical importance, resistance to ceftriaxone and ciprofloxacin was present in 2% (seven cases and six cases, respectively) of samples in 2013, while resistance to azithromycin was present in 1% of samples. Resistance to these antimicrobials has remained stable over time (Figure 20).

FIGURE 20: Resistance to azithromycin, ciprofloxacin and ceftriaxone in *Salmonella* Enteritidis, *Salmonella* Heidelberg and *Salmonella* Typhimurium in Canada, 2003–2013



Shigella

Antimicrobials of Importance: Extended-spectrum cephalosporins (ceftazidime in combination with either ceftriaxone or cefotaxime)

Shigella usually causes diarrhea (sometimes bloody), fever and abdominal pain. High-risk groups include young children, individuals with inadequate hand washing practices and hygiene and men who have sex with men. Infections resistant to traditional first-line antimicrobials can last longer than those where bacteria are susceptible. Resistant *Shigella* is a significant cause of morbidity and mortality internationally.[34] In Canada *Shigella* is reported through the Canadian Notifiable Disease Surveillance System (CNDSS). Shigellosis in Canada averaged about 813 cases per year, with an unknown level of resistance to first-line antimicrobials. A survey conducted in 2002 on *Shigella* isolates collected from 1993–2001 showed that approximately 80% were resistant to at least one of the 35 antimicrobials tested.[35] The highest rate of resistance was in folate pathway inhibitors, tetracycline and penicillin. Low levels of resistance were seen for nitrofurantoin (0.52%), quinolones (0.84%) and other beta-lactams (1.7%). In Canada, provinces are able to handle the vast majority of *Shigella* identification and characterization in their laboratories.

Tuberculosis (TB)

Antimicrobials of Importance: isoniazid, rifampin, ethambutol and pyrazinamide

TB is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. It is spread through the air when individuals who are sick with pulmonary TB expel bacteria (e.g., by coughing). One-third of the world's population is estimated to be infected with the TB bacterium and although they do not have active TB, they may develop it in the near or remote future.[36] Those with weakened immune systems are at greater risk of becoming ill[37] and those living with Human Immunodeficiency Virus are 15 times more likely to develop an active form of the disease.[38]

Antimicrobial-resistant strains represent a significant challenge in the management and control of TB.[37] In 1998, in response to a growing concern about TB drug resistance worldwide, the Agency established the *Canadian Tuberculosis Laboratory Surveillance System* in partnership with the *Canadian Tuberculosis Laboratory Technical Network* to monitor trends and patterns in anti-tuberculosis drug resistance in Canada over time.

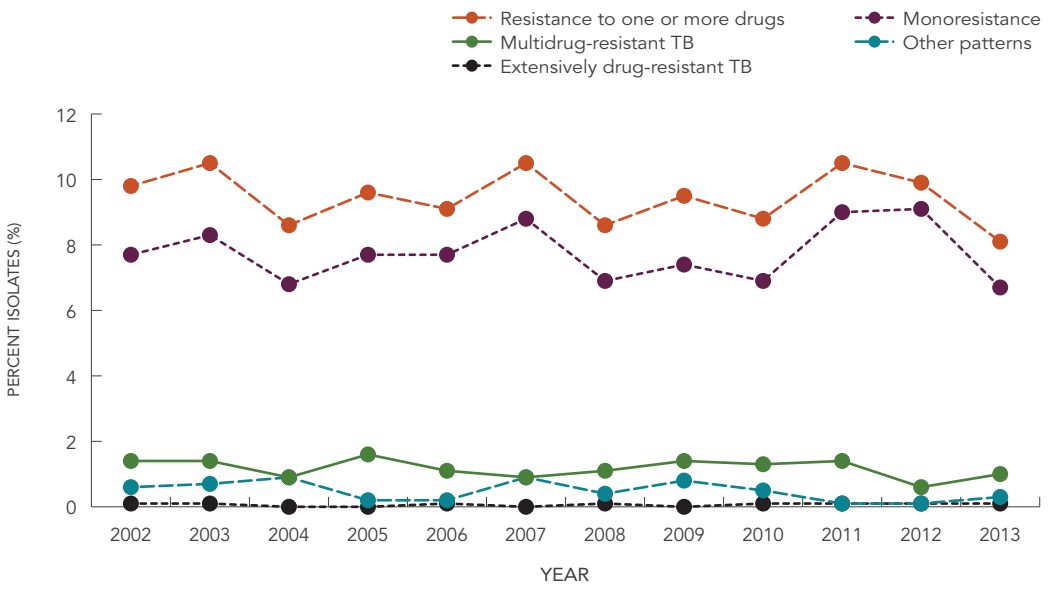
Four main antimicrobials are considered first-line drugs for treating tuberculosis: isoniazid, rifampin, ethambutol and pyrazinamide. These are used in combination to maximize their effectiveness. Once susceptibility testing identifies a susceptible infection, the use of ethambutol is not needed.[39] Ethambutol is not recommended in the treatment of children and can be replaced with streptomycin, kanamycin, or amikacin when necessary.

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).
- *Multidrug-resistant tuberculosis (MDR-TB)*—defined as resistance to isoniazid and rifampin with or without resistance to other anti-tuberculosis drugs.
- *Polyresistance (other patterns)*—defined as resistance to more than one first-line anti-TB drug, not including the isoniazid and rifampin combination of MDR-TB.
- *Extensively drug-resistant TB (XDR-TB)*—defined as resistance to isoniazid, rifampin, any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin).

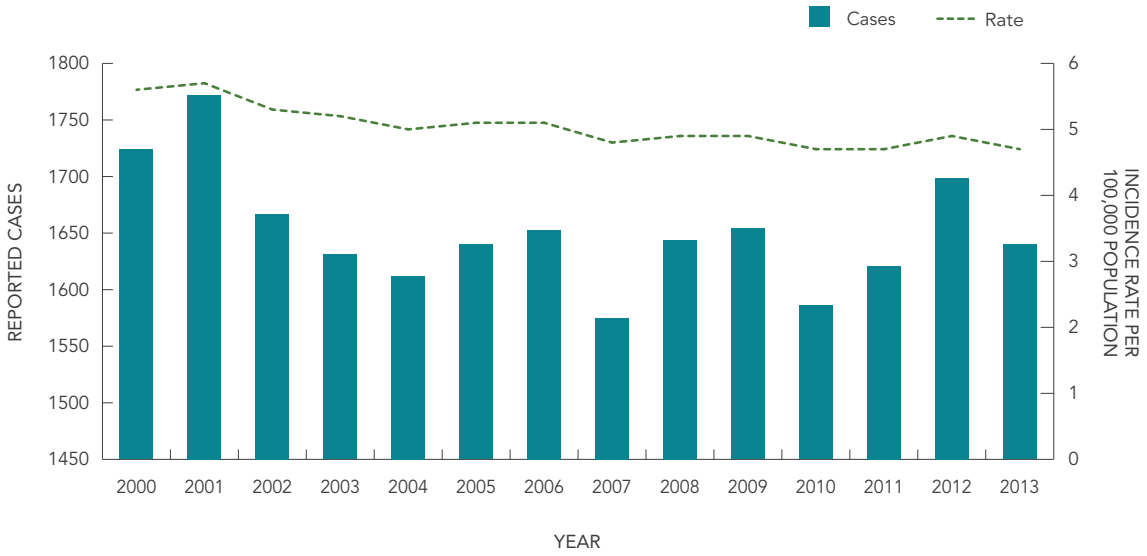
Surveillance data indicate that TB drug resistance in Canada has remained relatively stable since reporting began (Figure 21). In 2013, a total of 1,380 TB isolates were tested for AMR. Of these, 7% were classified as mono-resistant, 1% multidrug-resistant and 0.1% extensively drug-resistant.[40] Prince Edward Island did not report any cases of TB in 2013 and all the isolates from Northwest Territories, Nunavut, Yukon and Newfoundland and Labrador were fully sensitive to all TB drugs. The majority of isolates showing any resistance (56%) or resistance to both isoniazid and rifampin (67%) were in females. All of the MDR-TB isolates were from individuals between the ages of 15 and 64 years and there were no MDR-TB cases reported for ages less than 15 years of age or over 65 years of age.

FIGURE 21: Tuberculosis drug resistance patterns as percentage of isolates tested, 2002–2013



The incidence of new and re-treated TB disease has decreased since 2002, with the lowest rates observed in 2010 (Figure 22).[41] Since then, rates have remained relatively stable over time and the Agency will continue to monitor this trend.

FIGURE 22: Reported number of tuberculosis cases and incidence rate per 100,000 population, Canada, 2000–2013



Human Immunodeficiency Virus (HIV)

Drugs of Importance: Nucleoside Reverse Transcriptase Inhibitors, Non-nucleoside Reverse Transcriptase Inhibitors, Protease inhibitors, Integrase inhibitor, Fusion Inhibitors, Co-receptor inhibitors

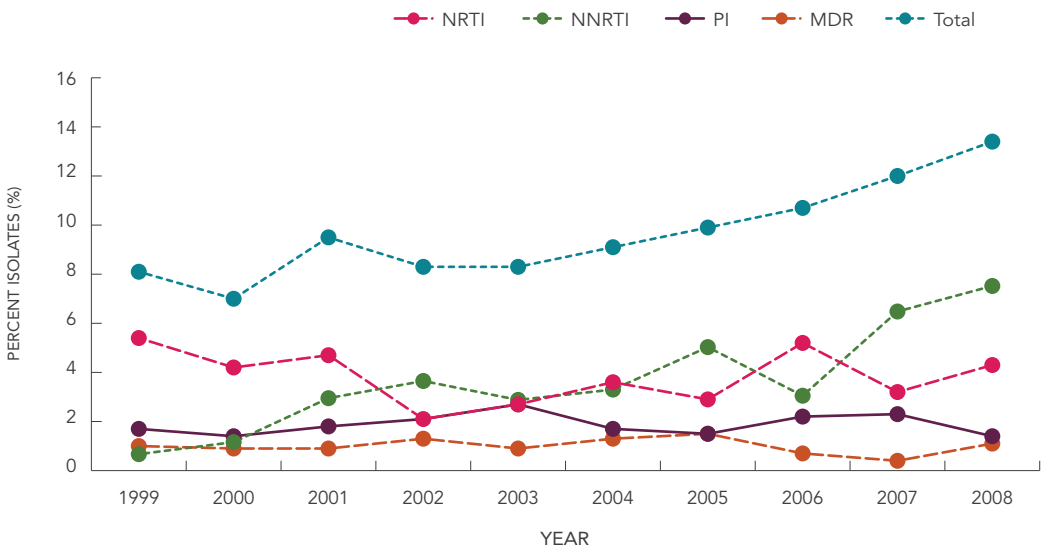
Since it was first identified in the early 1980s, HIV has emerged as a significant public health challenge. The WHO estimates that 35.0 million people worldwide are living with HIV. Of these, 2.1 million were newly infected with HIV in 2013 and 1.5 million died that same year.[42] Despite significant advances in the understanding of the virus, control of this infection remains a challenge in many parts of the world. By the end of 2013, a cumulative total of 78,511 HIV cases had been reported to the Agency since HIV reporting began in Canada in 1985. In 2013 alone, 2,090 newly diagnosed HIV cases were reported. This represents a small decrease (0.4%) from the 2,099 newly diagnosed cases reported in 2012 and is the lowest number of annual HIV cases since reporting began in 1985.[43]

There are over twenty antiretroviral drugs available in Canada to treat HIV infection. Each is assigned to one of six different drug classes. Treatment regimens are composed of a variety of possible drug combinations, usually consisting of three antiretroviral drugs from at least two different classes. The Canadian HIV Strain and Drug Resistance Surveillance Program monitors genetic mutations in HIV that confer resistance to three major drug classes: Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI), and Protease inhibitors (PI).

Among 4,521 newly diagnosed, treatment-naïve individuals from 1999 to 2008,[44] an overall proportion of 9.8% had resistance to at least one antiretroviral drug class. Of those with drug resistance (n=442), the majority were mono-resistant to NRTI (38.2%) or NNRTI (32.4%) drug classes, while approximately 10.2% had resistance to two or more drug classes (MDR).

Resistance varied over time, as shown in Figure 23. Overall drug resistance increased from 8.1% in 1999 to 13.4% in 2008, largely attributed to an increase in NNRTI resistance over time (up to 6.6% in 2008).[44] The proportion resistant to NRTI or PI was relatively stable over time; NRTI mono-resistance varied from 2.1% (2002) to 5.4% (1999), and PI mono-resistance was below 3% annually from 1999 through 2008. Multi-drug resistance was consistently below 2% (range: 0.4% in 2007 to 1.5% in 2005).

FIGURE 23: Prevalence of transmitted HIV drug resistance, by drug class and year of diagnosis, 1999–2008



Preliminary data for 196 persons newly diagnosed with HIV in 2013 within two participating provinces found 12% resistant to at least one drug class. Of all specimens tested, 6% were mono-resistant to NRTI while 5% were mono-resistant to NNRTI. Two isolates (1%) exhibited PI resistance while one isolate exhibited multi-drug resistance (unpublished data). Caution must be taken in applying these results widely as they are not representative of all participating provinces.

Transmission of antiretroviral resistant HIV is concerning from a clinical point of view because it may be associated with reduced treatment options for patients. Transmission of drug resistant strains also complicates the selection of appropriate medication for post exposure prophylaxis. HIV drug resistance among newly diagnosed, treatment-naïve persons may be associated with ongoing HIV transmission by persons who are on treatment, and, therefore, indicates suboptimal HIV prevention and control from a public health perspective. Continued surveillance of transmitted drug resistance is needed to inform antiretroviral treatment guidelines and interventions aimed at reducing the spread of drug resistant HIV.

Influenza

Drugs of Importance*:* Oseltamivir (Tamiflu); Zanamivir; Amantadine

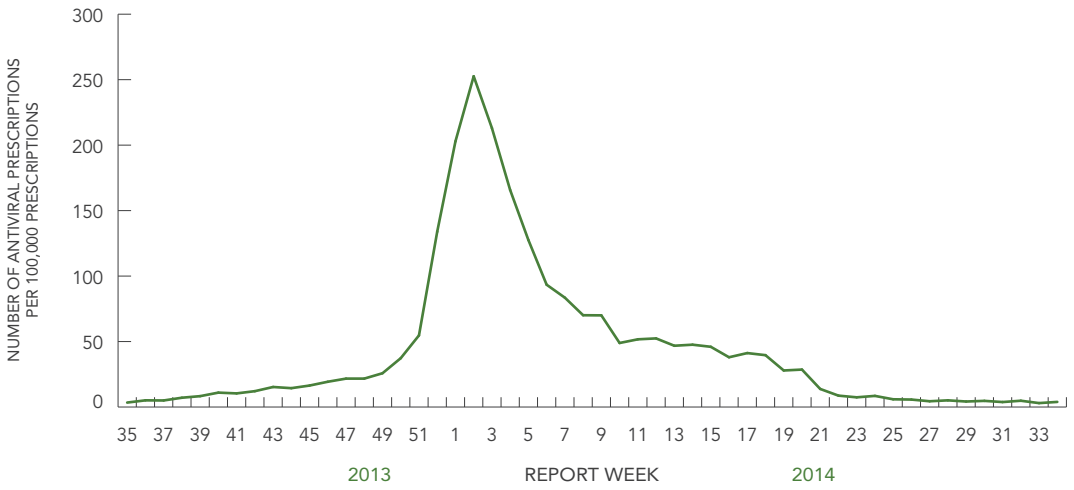
Influenza is a viral respiratory infection that usually causes some or all of the following symptoms: fever, cough, sore throat, muscle aches and fatigue, loss of appetite, runny or stuffy nose. Some individuals (especially children) may also have stomach upset and pain, vomiting and diarrhea. Influenza is highly contagious and spreads easily from person to person by coughing and sneezing or through contact with objects in the environmental that are contaminated by the virus.

Influenza is caused primarily by the influenza A and B viruses and can be prevented by annual immunization with the influenza vaccine. Most individuals with influenza become only mildly ill and do not need medical care or antivirals. Some are more likely to suffer influenza-related complications or to be hospitalized because of these complications, including the elderly, young children, pregnant women, Aboriginal people and those with an underlying medical condition such as cancer, diabetes, heart disease or lung disease, obesity.

During the 2013–2014 influenza season, 5,457 hospitalizations and 344 deaths were reported to FluWatch from participating regions. During the 2013–14 flu season NML tested 2,496 influenza viruses for resistance to oseltamivir and all but five were sensitive (0.2% resistant). All 2,493 viruses tested for resistance to zanamivir were sensitive. All 1,699 influenza A viruses tested for amantadine were resistant.

During the 2013–2014 influenza season the largest proportion of prescriptions for antivirals were in children two to 18 years of age and adults 19–64 years of age. The rates observed in the 2013–2014 season were lower overall than those observed during the 2012–2013 season (Figure 24).

FIGURE 24: Prescription sales for influenza antivirals by week, Canada 2013–14[P]



FOOD AND ANIMALS

The WHO *Global Strategy for Containment of Antimicrobial Resistance* was developed in 2012 to limit the impact of AMR on human health. This document includes a chapter on the use of antimicrobials in food-producing animals, with associated recommendations arising not from the perspective of animal health, but because of the impact that drug use in animals and developing resistance has on human health.

[P] Pharmacy sales data are provided to the Public Health Agency of Canada by Rx Canada Inc. and sourced from major retail drug chains representing over 2,500 stores nationwide (excluding Nunavut) in 85% of health regions. Data provided include the number of new antiviral prescriptions (for Tamiflu and Relenza) and the total number of new prescriptions dispensed by province/territory and age group.

Organisms that move between humans and food producing animals through contact or from exposure to contaminated food or environments are known as foodborne organisms. *Escherichia coli, Salmonella* and *Campylobacter* are foodborne organisms of particular interest as they represent a means to measure the movement of antimicrobial resistant organisms from animals to humans. Because the same or similar antimicrobials are used in humans and animals, AMU in both sectors contributes to the emergence and spread of resistance along the food chain. These enteric organisms of interest may cause a diarrheal illness, or go un-noticed and share their AMR genes freely among other bacteria residing in the human gut. The bacteria picking up the resistant genes may go on to cause other potentially more untreatable infections as skin, urinary tract or surgical site infections.

Generic *Escherichia coli*

Antimicrobials of Importance: Carbapenems, extended-spectrum cephalosporins, fluoroquinolones (e.g., ciprofloxacin)

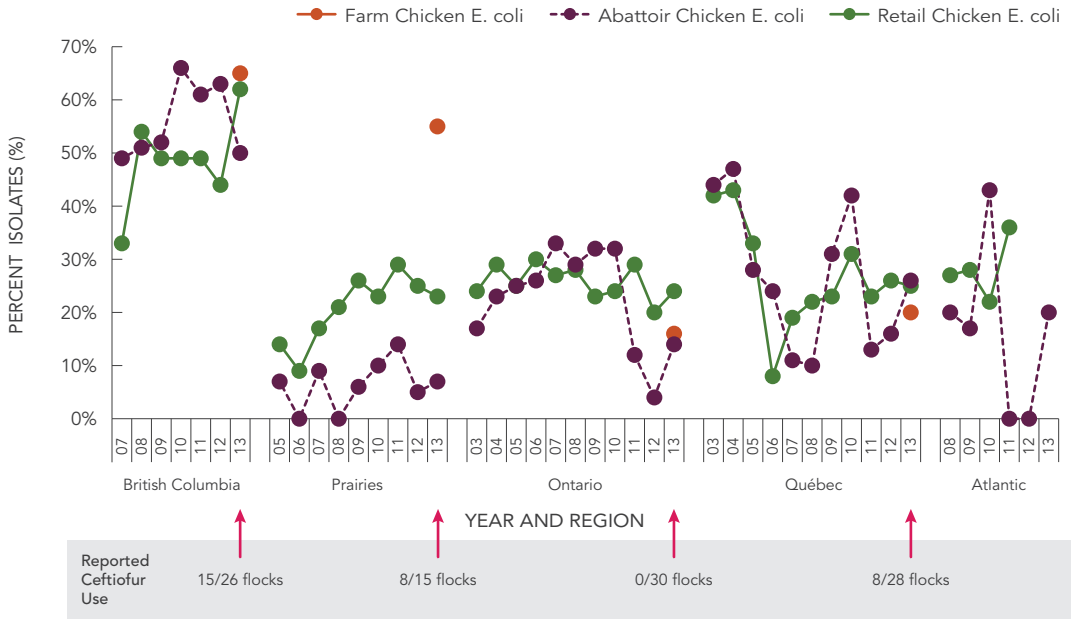
Surveillance of generic *Escherichia coli* is considered a good measure of how resistance develops after antimicrobial exposure because they are so widespread in the intestines of animals and people. Generic *E. coli* is tested for among samples collected from farm animals, slaughtered animals, and from retail meat. *E. coli* are found everywhere and it is estimated that for every *Salmonella* that may inhabit the gastrointestinal tract, there are potentially thousands of *E. coli* that are capable of carrying resistance genes that are available to swap with other organisms.[6] Additionally, monitoring AMR in generic *E. coli* in the food chain can help us understand potential risk factors for resistance in pathogenic *E. coli* human infections, such as urinary tract infections[45,46] (that may be considered in part of zoonotic origin) and *E. coli* infections in sites other than the gastrointestinal tract.

The Agency does not currently monitor resistance in generic or pathogenic *E. coli* in humans in the community (see Next Steps, below). In 2013, *E. coli* was isolated from retail meat with recovery rates of 93% for chickens and turkeys, 50% for ground beef and 29% for pork. Of the *E. coli* isolates recovered from chickens, 81% were resistant to at least one antimicrobial. For other commodities, the percentages of isolates resistant to at least one antimicrobial were 68% in turkeys, 65% in pigs/pork and 25% in cattle/beef. Resistance to carbapenems has not been detected in any *E. coli* isolates.

In 2013, the prevalence of resistance to ceftriaxone in *E. coli* isolates from cattle/beef, pigs/pork and turkeys was less than 4% across all surveillance components.[29] In contrast, for chickens, the prevalence of ceftriaxone resistance was 34% for farm samples, 21% for slaughter chickens and 30% for retail chickens. Fluoroquinolone resistance was detected in three *E. coli* isolates in 2013: two chicken isolates and one beef isolate. Resistance to nalidixic acid was found in *E. coli* from all commodities, but always less than 5%. For multi-class resistance, 50 *E. coli* isolates resistant to six to seven antimicrobial classes have been detected since 2002. While the total number of isolates remains low year-to-year (e.g., nine isolates in 2013), retail beef, pork, chickens and turkeys have all been contaminated with these highly multiclass-resistant *E. coli*.

Regarding the integration of data on animal AMU and AMR in agri-food *E. coli*, for ceftriaxone resistance, the prevalence of resistance in *E. coli* from chickens appears to correlate better with reported AMU on chicken farms (i.e., provinces with more farms that reported using these drugs had higher resistance rates (Figure 25) in comparison to the situation with all *Salmonella* (data not shown). The correlation between resistance in *E. coli* and reported use supports maintaining surveillance of this organism as an indicator of overall selective pressure. Furthermore it provides an opportunity to examine the genetic relatedness between animal and human E. coli if surveillance of resistant commensal or pathogenic *E. coli* in humans is undertaken.

FIGURE 25: Category I ß-lactam resistance in generic *E. coli* from chickens on farm, at slaughter and at retail along with reported ceftiofur use in participating broiler flocks (2003–2013)



Campylobacter

Antimicrobials of Importance: fluoroquinolones and macrolides

In chickens and cattle, the predominant *Campylobacter* species is *C. jejuni*, whereas in pigs the predominant species is *C. coli*. Among retail meat samples, *Campylobacter* in 2013 was isolated at rates of 30% for chickens and 12% for turkeys. CIPARS does not test retail pork or beef for *Campylobacter* due to very low recovery rates from previous testing.

In 2013, at the farm-level, 20% of pre-harvest chicken *Campylobacter* isolates were resistant to fluoroquinolones.[28] At slaughter, 5% of cattle isolates, 13% of pig isolates and 14% of chicken *Campylobacter* isolates were resistant to fluoroquinolones. At retail, 11% of chicken and 16% of turkey *Campylobacter* isolates were resistant to fluoroquinolones. There are provincial differences in the prevalence trends of ciprofloxacin-resistant *Campylobacter* from

poultry. Most notably in 2013, ciprofloxacin resistance in isolates from retail and slaughter chickens and retail turkeys increased in British Columbia. Conversely, in Ontario in 2013, there was a decrease in the proportion of ciprofloxacin-resistant retail chicken isolates.

Macrolide resistance was high in *Campylobacter* isolates from pigs at slaughter, with 48% of the isolates resistant to either azithromycin or erythromycin. For *Campylobacter* isolates from chickens, 0%, 5% and 7% of the isolates from farm (at slaughter and from retail meat respectively) were resistant to either erythromycin or azithromycin. For turkeys at retail, resistance rates were 1% for azithromycin and 9% for erythromycin. There was no macrolide resistance detected in the cattle isolates at slaughter.

In terms of integration of AMR and AMU data, British Columbia was the only region that reported any fluoroquinolone use in poultry farms in 2013 and also had the highest level of resistance in *Campylobacter* farm, slaughter and retail meat isolates. One year of data is not sufficient to draw conclusions about the association between fluoroquinolone use and resistance in broiler chickens. Monitoring use and resistance data from the broiler chicken sector will continue to be monitored.

Non-typhoidal *Salmonella*

Antimicrobials of Importance: Carbapenems (ertapenem, imipenem, meropenem, doripenem), extended-spectrum cephalosporins (ceftazidime and ceftriaxone, or cefotaxime), fluoroquinolones (ciprofloxacin, levofloxacin, pefloxacin)

In 2013, 34% of chicken and 22% of turkey store samples purchased by CIPARS were found to be contaminated with *Salmonella*. The top three *Salmonella* strains causing human salmonellosis can be found in the top five serovars isolated from agri-food sources. In Canada, the prevalence of *Salmonella* for pork or beef/cattle at slaughter is too low for ongoing reportable surveillance.

In terms of the drugs of importance to human medicine, no resistance to carbapenems has ever been detected in agri-food *Salmonella* isolates in Canada and in 2013, there were no *Salmonella* agri-food isolates resistant to ciprofloxacin. Resistance to ceftriaxone has been found in *Salmonella* from all animal species under surveillance, but is most common in chickens (overall 24% in 2013) and clinical isolates from cattle (44%). It is important to recognize that for many drugs (ceftriaxone in particular) resistance in *Salmonella* is very serovar specific.

Salmonella Enteritidis

All *S.* Enteritidis recovered from retail meat, slaughtered animals, animals on farm or from veterinary diagnostic isolates were not resistant to any of the antimicrobials tested.

Salmonella Heidelberg

No isolates were resistant to azithromycin or ciprofloxacin. Resistance to ceftriaxone has demonstrated both temporal changes and regional differences. In 2013, ceftriaxone resistance from retail chickens ranged from 26% to 80% by region, while temporal resistance trends in poultry isolates mirrored changing AMU practices. For example, in 2003 the prevalence of ceftriaxone resistance in S. Heidelberg from retail chickens in Quebec was 65% (during high

levels of ceftiofur[q] use in chicken hatcheries). This figure dropped significantly during a period of little use in 2006 (to 7%) and rose again during a period of rotational use (43% in 2013).

Salmonella Typhimurium

Salmonella Typhimurium is most commonly isolated from healthy pigs and pork meat, with *S.* Typhimurium representing 31% of all *Salmonella* isolates.[29] The relative proportion of *S.* Typhimurium recovered from other animal species (healthy animals or meat) was much lower (<2%). In 2013, 90% of isolates overall from healthy animals/meat were resistant to one or more antimicrobials. No isolates were resistant to ciprofloxacin or azithromycin. Three percent were resistant to ceftriaxone. These prevalences of resistance have remained stable over time.

Among *Salmonella* isolates submitted from sick livestock, *S.* Typhimurium was the most common serovar recovered from cattle (45%) and pigs (41%). Eleven of the cattle isolates (10%) were resistant to six antimicrobial classes. It should be noticed that sick animals do not enter the food chain for human consumption.

AMR CONCLUSION

The emergence of antimicrobial-resistant organisms is a major public health concern in Canada, particularly in health care settings and in vulnerable populations. Agency surveillance programs have identified that these organisms appear to be thriving in both health care and community settings and are capable of causing severe, life-threatening infections that may be more difficult to manage because of limited treatment options. This leads to the use of more expensive, last-recourse antimicrobials. Because AMR may emerge in bacteria as a response to selective antimicrobial pressure, there is a potential risk that fewer and fewer antimicrobials will remain effective in the future. The use of last-recourse antimicrobials to treat serious infections (after all other treatment options have failed) is becoming more common in both health care and community settings.

Clostridium difficile, multi-drug-resistant Enterobacteriaceae (including ESBL and CRE), MRSA, and VRE are organisms of clinical significance in Canadian hospitals. The prevalence of many of these organisms continues to increase and they are causing more illness and death. These organisms are also responsible for multiple hospital outbreaks and contribute to the overall burden in Canada's publically-funded health care system.

Antimicrobial-resistant organisms are also becoming more prevalent in community settings. For example, of the *Neisseria gonorrhoeae* isolates submitted to the Agency for susceptibility testing, almost 4% are resistant to antibiotics according to current treatment guidelines, and over 10% of *Streptococcus pneumoniae* isolates are resistant to the most commonly prescribed antibiotics. MDR-TB is of significant concern because susceptible TB is difficult to treat. The prevalence of TB in vulnerable populations is high and the introduction of MDR-TB in community groups such as those living on First Nation reserves and incarcerated individuals can be devastating. Viral infections are also a growing concern. Overall drug resistance in HIV strains tested in Canada has increased since surveillance began in 1999. Preliminary 2013 data

[q] Resistance to ceftiofur confers resistance to ceftriaxone. Ceftiofur is the product used in animals whereas ceftriaxone is the product used in humans.

from two participating sentinel sites showed an overall resistance of 12%. For the *Salmonella* strains identified in this report, it does not appear that ciprofloxacin or azithromycin resistance from the Canadian agri-food sources under surveillance is contributing to the resistance observed in *Salmonella*-causing human illness. However, changing rates of ceftriaxone resistance for one *Salmonella* strain (S. Heidelberg) do appear to correlate.

Treatment of these resistant infections is associated with substantial morbidity and mortality and utilizes considerable health care resources. Antimicrobial prescriptions have also increased significantly. Unfortunately, the increase in the incidence of antimicrobial-resistant organisms and the use of antimicrobials in both the human and animal sectors is occurring at a time when the development of new drugs is decreasing. The collection of new information must be a priority in order to better understand the burden of disease caused by AMR and the impact of prescribing practices on the emergence of resistance.

Next Steps

The Agency has a strong foundation for AMR and AMU surveillance and generates robust data on AMR in a specific number of settings. However, there is a need to expand the scope of surveillance in order to provide more representative and comprehensive data for public health action. In collaboration with stakeholders, the Agency is currently developing a list of priority pathogens for AMR surveillance in Canada. Although the Agency is already monitoring many of the highest-ranked organisms of interest, there are some organisms not currently under surveillance. Moving forward, the Agency will regularly review and revise priority organisms of interest and target surveillance accordingly. As a first step, the Agency will conduct surveillance of resistance on an additional priority foodborne bacterial organism causing human illness.

The Government of Canada is working with provincial partners and academia in the animal sector to improve knowledge about additional veterinary pathogens that are currently submitted to diagnostic laboratories for antimicrobial susceptibility testing. This information will better inform veterinary prescribing behaviours, identify potential resistance determinants that could be transmitted to human pathogens, and provide an indicator of potential treatment failures due to resistance in animals.

To increase our understanding of community-associated AMR infections and how these spread beyond hospitals, the Agency will implement a community-level surveillance pilot to gather and analyze existing susceptibility data generated by front-line diagnostic laboratories. This will include information for all organisms identified in the priority exercise and will position the Agency to provide additional information about organisms that cause blood and urinary tract infections.

These new and enhanced initiatives will improve the Agency's understanding of how AMR is spread in the community and how it travels between the community and hospitals and along the food chain. New and emerging public health threats may be identified earlier which will direct new activities and enable the development of new policies and guidelines to reduce the burden and impact of AMR on the health of Canadians.

CONCLUSION

This report has illustrated that AMR is a serious and potentially growing threat to the health of Canadians. Increased national and international surveillance will be essential to inform targeted effective actions that will prevent the worst-case scenario, where infections are no longer treatable with antimicrobials.

The good news is that continued progress towards mitigating the impact of AMR and enhancing the stewardship of antimicrobials across sectors is well within the influence of actors in Canada. The Agency has established robust surveillance programs for AMR/AMU and the implementation of CARSS will be an important step towards providing decision-makers with the integrated information they need to make further progress in reducing the threat of AMR and preserving the efficacy of today's antimicrobials.

The Agency will continue to monitor its enhanced efforts to mitigate AMR and improve AMU, and will report on its progress in future reports.

ANNEX 1 PUBLIC HEALTH AGENCY OF CANADA'S ANTIMICROBIAL RESISTANCE AND USE SURVEILLANCE SYSTEMS

SYSTEM NAME	PATHOGENS	SCOPE	MOVING FORWARD
Canadian Nosocomial Infection Surveillance Program (CNISP)	Methicillin-resistant *S.aureus, Clostridium difficile,* Vancomycin-resistant Enterococci, Carbapenem-resistant Enterobacteriaceae and Carbapenemase producing organisms	Monitors health care- and community-associated infections in patients admitted to select acute-care hospitals.	Expansion of coverage to include other resistance mechanisms, e.g., Antibiogram in hospitals.
Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)	*Campylobacter* *Salmonella* *E. coli*	*Salmonella* from cases reported in the community and hospital, as well as that isolated from retail food and animals. *Campylobacter* and *E. coli* isolated from retail food and animals. CIPARS collects AMU information from sentinel grower-finisher pig and broiler chicken farms. Antimicrobial quantities distributed for sale for use in animals is provided to CIPARS from the Canadian Animal Health Institute.	Human *Campylobacter*, E. coli and Enterococcus data will be obtained through the Antibiogram Project. In addition, human *Campylobacter* samples will be obtained from FoodNet Canada sites for AMR testing and will be linked to outcome information.
FluWatch	Influenza A and B (of human, avian or other lineages, isolated from human cases)	Monitors circulating strains of the flu virus and assesses their sensitivity to antiviral medications.	Ongoing
Canadian Tuberculosis Laboratory Surveillance System (CTBLSS)	Multi-drug-resistant Tuberculosis	Sentinel laboratories report their results on anti-tuberculous drug susceptibility testing for every patient for whom a specimen or an isolate has been received for each calendar year.	Ongoing
Antimicrobial-Resistant Neisseria gonorrhoeae Surveillance System	*Neisseria gonorrhoeae*	Monitors antimicrobial susceptibility of *Neisseria gonorrhoeae* in Canada. Passive, voluntary submission by provinces and territories.	Ongoing
Invasive Streptococcal Disease Surveillance	*Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae*	Voluntary passive system. In 2013, isolates include 82% of *S. pneumoniae*, and 78% of *S. pyogenes*, cases reported to Canadian Notifiable Diseases Surveillance System.	Ongoing
HIV Strain and Drug Resistance Surveillance System	*Human Immunodeficiency Virus*	Monitors drug resistance in HIV isolates from patients with newly diagnosed infections. Five provinces currently participate.	Ongoing
Antimicrobial usage (AMU)	N/A	National and provincial information on antimicrobials dispensed through community pharmacies, purchased by hospitals and clinical indication for which they were recommended by physicians.	Integrate data from the Non-Insurable Health Benefits program from FNIHB and from hospital pharmacies within the CNISP network

ANNEX 2 INFECTIONS AND PATHOGENS FOR INITIAL GLOBAL SURVEILLANCE COMPARED TO THE AGENCY'S CURRENT SURVEILLANCE DATA

INFECTION	PROPOSED METRIC	PATHOGEN	CANADA BASELINE*	SOURCE
Bloodstream infections	Number of resistant infections per 10,000 patient-days	*Acinetobacter* spp.	Carbapenem resistance: 0.005/10,000 patient-days	CNISP
		Escherichia coli	Carbapenem resistance: 0.007/10,000 patient-days	CNISP
		Klebsiella pneumonia	Carbapenem resistance: 0/10,000 patient-days	CNISP
		Pseudomonas aeruginosa		
		Salmonella spp.		
		Staphylococcus aureus	MRSA: 0.56/ 10,000 patient-days	CNISP
		Streptococcus pneumoniae		
	Percentage resistance infections/total infections	*Acinetobacter* spp.		
		Escherichia coli		
		Klebsiella pneumonia		
		Pseudomonas aeruginosa		
		Salmonella spp.	Ceftriaxone: 11% Ciprofloxacin: 1%	CIPARS
		Staphylococcus aureus		
		Streptococcus pneumoniae	Clindamycin: 6% Penicillin: 10% Ceftriaxone: 0.7% Cefuroxime: 4% Sulfamethoxazole trimethoprim: 7%	NML
Urinary tract infections	Percentage resistance infections/total infections	*Escherichia coli*		
		Klebsiella pneumonia		
Diarrhea	Percentage resistance infections/total infections	*Salmonella* spp. (Non-typhoidal)	Ceftriaxone: 6% Ciprofloxacin: 1%	CIPARS
		Shigella spp.	Ceftriaxone: < 0.17% Ciprofloxacin: < 0.10%	CIPARS (2002)
Gonorrhoea	Percentage resistance infections/total infections	*Neisseria gonorrhoeae*	Azithromycin: 1.2% Ceftriaxone and/or Cefixime: 3.9%	NML
Tuberculosis	Percentage resistant isolate/total isolates tested	Multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB)	0.6%	CTBLSS
		Extensively drug-resistant *Mycobacterium tuberculosis* (XDR-TB)	0.1%	CTBLSS

* Most recent available data, 2013 unless otherwise indicated, shaded areas represent data that is not available.

The purpose of collecting data for global surveillance of human pathogens resistant to antimicrobial agents is to assess those infections and antimicrobial-resistant organisms that are the greatest global threat. For this reason, the WHO has selected, for initial surveillance, those organisms that are resistant to several drugs, thus limiting treatment options; and that are spreading across the globe. The WHO acknowledges that not all organisms included in the first phase of surveillance priorities are representative of the population being monitored. As a next step, the Agency will review the WHO priority infections and pathogens to determine which additional infection or pathogen is of concern in Canada.

REFERENCES

(1) Public Health Agency of Canada. *The Chief Public Health Officer's report on the state of public health in Canada 2013: Infectious diseases – The never-ending threat*. Ottawa ON: Public Health Agency of Canada; September 2013. www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/assets/pdf/2013-eng.pdf

(2) Government of Canada. Human antimicrobial use report, 2012/2013. Guelph ON: Public Health Agency of Canada; 2014.

(3) Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012; 54: e72–e112. Doi: 10.1093/cid/cir1043.

(4) Centers for Disease Control and Prevention [Internet]. Acute cough illness (Acute Bronchitis). www.cdc.gov/getsmart/campaign-materials/info-sheets/adult-acute-cough-illness.pdf

(5) Personal communication, Dr. Fawzia Marra, Clinical Pharmacotherapeutic specialist, Infectious Diseases, lower mainland pharmacy, Fraser Health and University of British Columbia .

(6) O'Brien TF. Emergence, spread and environmental effect of antimicrobial resistance: How use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. Clin Infect Dis. 2002; 34(Suppl 3): S78–S84.

(7) Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance 2012 Chapter 1: Design and methods. Guelph ON: Public Health Agency of Canada; 2014.

(8) European Medicines Agency. European surveillance of veterinary antimicrobial consumption, 2014. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012. (EMA/333921/2014). www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500175671.pdf

(9) European Medicines Agency. European surveillance of veterinary antimicrobial consumption (ESVAC). Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011. (EMA/236501/2013). www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf

(10) European Medicines Agency [Internet]. European surveillance of antimicrobial consumption network (ESAC-Net) information. www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx

(11) European Medicines Agency [Internet]. European surveillance of veterinary antimicrobial consumption, 2011. Trends in the sales of veterinary antimicrobial agents in nine European countries (2005–2009). www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

(12) World Health Organization. Global surveillance of human pathogens resistant to antimicrobial agents: Initial implementation. Unpublished report. November 24, 2014.

(13) Miller M, Gravel D, Mulvey M,et al. Hospital-acquired *Clostridium difficile* Infection in Canada: Patient age and infecting strain type are highly predictive of severe outcome and mortality. Clin Infect Dis. 2010;50: 194–201.

(14) Mulvey M, Boyd D, Gravel D, et al. Hypervirulent *Clostridium difficile* strains in hospitalised patients, Canada. Emerg Infect Dis. 2010; 16: 678–681.

(15) Dubberke ER, Carlin G, Carrico G, et al. Strategies to prevent *Clostridium difficile* infections in acute care hospitals: 2014 update. Infect Contr Hosp Epidemiol. 2014; 35: 628–45.

(16) Public Health Agency of Canada. Carbapenem-resistant Gram-Negative Bacilli in Canadian acute-care hospitals: Surveillance report January 1, 2010 to December 31, 2012. Ottawa ON: Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada; 2014.

(17) Etchells E, Mittmann N, Koo M, et al. The economics of patient safety in acute care: Technical report. Toronto ON: Canadian Patient Safety Institute; 2009. www.patientsafetyinstitute.ca/English/research/commissionedResearch/EconomicsofPatientSafety/Documents/Economics%20of%20Patient%20Safety%20-%20Acute%20Care%20-%20Final%20Report.pdf

(18) Simor AE, William V, McGeer A, Raboud J, et al. Prevalence of colonization and infection with Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus* and of *Clostridium difficile* Infection in Canadian hospitals. Infect Control Hosp Epidemiol. 2013;34:687–93.

(19) Public Health Agency of Canada. Methicillin-resistant *Staphylococcus aureus* in Canadian acute-care hospitals: surveillance report January 1, 2008 to December 31, 2012. Ottawa ON: Public Health Agency of Canada; 2014.

(20) Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in adults and children. Clin Infect Dis. 2011; 52: e18–e55.

(21) Shoyinka A, Moreno D, Arshad S, et al. Evaluation of *in vitro* susceptibility trends by strain type to Vancomycin and Daptomycin of *Staphylococcus aureus* causing gloodstream infections. *J Glob Antimicrob Resist*. 2014; 2: 280–85.

(22) Ofner-Agostini M, Johnston L, Simor AE, et al. Vancomycin-resistant Enterococci in Canada: Results from the Canadian Nosocomial Infection Surveillance Program, 1999–2005. Infect Control Hosp Epidemiol. 2008; 29: 271–274.

(23) Demczuk WHB, Martin I, Griffith A, et al. Serotype distribution of invasive *Streptococcus pneumoniae* in Canada after the introduction of the 13-valent pneumococcal conjugate vaccine, 2010–2012. Can J Microbiol. 2013; 59: 778–88.

(24) Blondell-Hill E, Fryters S. Bugs and drugs antimicrobial reference. Calgary AB: Capital Health; 2006.

(25) Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections. Ottawa ON: Public Health Agency of Canada; 2013.

(26) Hatchette TF, Farina D. Infectious diarrhea: When to test and when to treat. Can Med Assoc J. 2011; 183: 339–344.

(27) John Hopkins Medicine. Treatment recommendations for adult inpatients – Antibiotic guidelines 2014/15. Line Drawing, Illinois; 2014. www.hopkinsmedicine.org/amp/guidelines/Antibiotic_guidelines.pdf.

(28) Bugs and Drugs Antimicrobial Reference 2012. [Internet]. [updated 2012 Available at: www.dobugsneeddrugs.org/health-care-professionals/bugs-drugs-antimicrobial-reference

(29) Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2012 Chapter 2: Antimicrobial resistance. Guelph ON: Public Health Agency of Canada; 2014.

(30) Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Athens, Georgia: CDC; 2013. www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

(31) World Health Organization [Internet]. Water sanitation health: Water-related diseases: Typhoid and Paratyphoid enteric fevers. www.who.int/water_sanitation_health/diseases/typhoid/en

(32) Greenway C, Schofield S, Henteleff A, et al. Summary of the Statement on International Travellers and Typhoid by the Committee to Advise on Tropical Medicine and Travel (CATMAT). Can Comm Dis Rep. 2014;40–4. www.phac-aspc.gc.ca/publicat/ccdr-rmtc/14vol40/dr-rm40-04/dr-rm40-04-tropmed-eng.php

(33) Thomas MK, Murray R, Flockhart L, et al. Estimates of the burden of foodborne illness in Canada for 30 specified pathogens and unspecified agents, circa 2006. Foodborne Pathog Dis. 2013; 10: 639–48.

(34) World Health Organization [Internet]. Health Topics: Shigella. www.who.int/topics/shigella/en

(35) Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2002 annual report. Guelph ON: Health Canada; 2004.

(36) World Health Organization [Internet]. Latent Tuberculosis infection (LTBI). www.who.int/tb/challenges/ltbi/en

(37) Glaziou P, Falzon D, Floyd K, Raviglione M. Global epidemiology of tuberculosis. Semin Respir Crit Care Med. 2013; 34: 1–14.

(38) World Health Organization [Internet]. Tuberculosis fact sheet No 104. Geneva, Switzerland: WHO; 2014. www.who.int/mediacentre/factsheets/fs104/en

(39) Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis. Am J Respir Crit Care Med. 2003; 167: 603–62.

(40) Public Health Agency of Canada. Tuberculosis: Drug Resistance in Canada 2013. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2015.

(41) Public Health Agency of Canada. Tuberculosis in Canada 2013 – *Pre-release*. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2015

(42) World Health Organization [Internet]. HIV/AIDS data and statistics. www.who.int/hiv/data/epi_core_dec2014.png?ua=1

(43) Public Health Agency of Canada. HIV and AIDS in Canada: Surveillance Report to December 31, 2013. Minister of Public Works and Government Services Canada; 2014.

(44) Public Health Agency of Canada. HIV Strain and Transmitted Drug Resistance in Canada: Surveillance Report to December 31, 2008. Minister of Public Works and Government Services Canada; 2012.

(45) Manges AR, Smith SP, Lau BJ, et al. Retail meat consumption and the acquisition of antimicrobial-resistant *Escherichia coli* causing urinary tract infections: a case-control study. Foodborne Pathog Dis. 2007; 4(4): 419–31.

(46) Jakobsen L, Garneau P, Bruant G, et al. Is *Escherichia coli* urinary tract infection a zoonosis? Proof of direct link with production animals and meat. Eur J Clin Microbiol Infect Dis. 2012 Jun;31(6):1121–9.