When Antibiotics Fail

The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada

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WHEN ANTIBIOTICS FAIL

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THE COUNCIL OF CANADIAN ACADEMIES
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The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada

Under the guidance of its Scientific Advisory Committee, Board of Directors, and founding Academies, the CCA assembled the Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada to undertake this project. Each expert was selected for their expertise, experience, and demonstrated leadership in fields relevant to this project.

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Message from the Chair

The ability of microbes to resist antimicrobials (antimicrobial resistance, AMR) is a serious existential threat to millions, and is potentially responsible for the loss of hundreds of millions of lives globally over the next few decades. As antimicrobial use continues, resistance levels continue to rise (currently about 26% to first line antimicrobials in Canada and potentially increasing significantly). Resistant organisms cause a major problem to the healthcare system, and also agriculture and other activities such as tourism. One problem is that AMR does not respect borders — antimicrobial use in one country today leads to AMR in another country tomorrow. Increasing AMR is predicted to cause significant disruptions to society, although determining the extent of these problems is difficult.

If actions are not taken to combat the increase of AMR, Canada will be greatly changed within a few decades. The economy will shrink, the healthcare system will be less sustainable, and social inequality will further increase. It is clear that AMR needs not only to be seen as a scientific and healthcare issue, but also as an economic and security threat. It is an insidious problem that increasingly permeates all aspects of our society.

For a country like Canada, there have been few studies that measure and predict future economic and social impacts related to AMR. This report directly addresses this, and provides important evidence on how AMR not only has tragic human costs, but also real and tangible economic costs to Canada. Members of the Expert Panel have diverse expertise, and are engaged at the cutting edge of infectious diseases, healthcare delivery, agriculture, research and innovation, and economic modelling. Their collective wisdom was immensely useful in addressing this significant and wide-ranging problem in our society. I would like to express my sincere gratitude to all the members of the Panel for their incredibly hard and focussed work and strong commitment to this project. Their wisdom, guidance, questioning, challenging, and congenial yet constructive discussions were invaluable.

On behalf of the Panel, I would like to give thanks to the reviewers whose thoughtful critiques led to an improved report. Finally, I would like to express my sincere appreciation to the staff members of the Council of Canadian Academies, for their hard work, major effort in helping draft and edit the report, and congeniality throughout the process, making meetings and discussions both constructive yet also enjoyable. We are confident this report helps define the potential social and economic impacts of AMR in Canada, and can guide decisions and policies in the future to help combat this significant threat to our society.

B. Brett Finlay, PhD, O.C., O.B.C., FRSC, FCAHS, Chair
Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada

Message from the CCA President and CEO

Antimicrobial resistance (AMR) is now recognized as a global threat that if not addressed will have a devastating impact on the health and welfare of the planet that may be difficult to reverse.

AMR is an example of the "tragedy of the commons:" the very benefits enjoyed by the public from the availability and use of antimicrobials can lead to the overuse, limited effectiveness, and eventual reduction in benefit. The impact of AMR will not be limited to the immediate effect on human and animal health — broader impacts are also expected.

Recognizing this, the Minister of Science, requested that CCA undertake an assessment on behalf of the Public Health Agency of Canada to better understand the socio-economic impacts of AMR in Canada. This acknowledges the potential impact of AMR for all of Canada and the broad types of policy decisions that may be required to address this problem.

The CCA brought together a multidisciplinary panel of 13 experts in biology, microbiology, epidemiology, infectious diseases, veterinary medicine, public health, medicine, sociology, economics, public policy, and industrial practices. The final report, *When Antibiotics Fail*, presents novel analyses that quantify current and future economic impacts of AMR, while also exploring the social impacts in a future with limited antimicrobials.

The magnitude of the economic estimates in this report are alarming, and provide evidence to support decision-making about this topic. The Panel's report couldn't be more timely as the Public Health Agency of Canada is set to release an Action Plan on AMR in 2020.

I would like to thank Dr. B. Brett Finlay, and his fellow expert panellists, for contributing their time and expertise to produce this report. The CCA Board of Directors, Scientific Advisory Committee, and the CCA's three founding Academies — the Royal Society of Canada, the Canadian Academy of Engineering, and the Canadian Academy of Health Sciences — all provided guidance and input. Particular appreciation is extended to our colleagues at the CAHS, who convened an influential forum on AMR in 2017 that provided valuable leadership and insight on this topic from some of the world's foremost experts.

Eric M. Meslin, PhD, FCAHS
President and CEO

Acknowledgements

The Panel and CCA staff would like to express their gratitude for the exceptional work undertaken by Marco Hafner, Jirka Taylor, and Erez Yerushalmi, who developed and simulated the Panel's computation general equilibrium model. Their insights, flexibility, and good humour throughout the assessment process were deeply appreciated. The Panel and CCA staff would also like to thank Jenine Leal for helpful discussions about micro-costing approaches and challenges.

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Peer Review

This report was reviewed in draft form by reviewers selected by the CCA for their diverse perspectives and areas of expertise. The reviewers assessed the objectivity and quality of the report. Their confidential submissions were considered in full by the Panel, and many of their suggestions were incorporated into the report. They were not asked to endorse the conclusions, nor did they see the final draft of the report before its release. Responsibility for the final content of this report rests entirely with the authoring Panel and the CCA.

The CCA wishes to thank the following individuals for their review of this report:

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The peer review process was monitored on behalf of the CCA's Board of Directors and Scientific Advisory Committee by **Jean Gray, MD, C.M., FCAHS,** Professor Emeritus, Medical Education, Medicine, Pharmacology, Dalhousie University. The role of the peer review monitor is to ensure that the Panel gives full and fair consideration to the submissions of the peer reviewers. The Board of the CCA authorizes public release of an expert panel report only after the peer review monitor confirms that the CCA's peer review requirements have been satisfied. The CCA thanks Dr. Gray for her diligent contribution as peer review monitor.

Executive Summary

Effective antimicrobials are extremely valuable. Medical, veterinary, and agricultural practices depend extensively on the widespread availability of antimicrobials to prevent and treat bacterial infections in humans, animals, and crops. But with their use, disease-causing bacteria have increasingly evolved to become resistant to these antimicrobials, resulting in drugs that are no longer effective at treating infections. Antimicrobial resistance (AMR) is increasing worldwide, and with widespread trade and travel, resistance can spread globally within a short time, posing a serious threat to all countries. While AMR predates the use of antimicrobials, it drastically increased after the introduction of antimicrobial therapy in the last century. For a country such as Canada, the implications of AMR are stark. AMR is already having negative health, economic, and social impacts, and these will only worsen if actions are not taken to combat it.

Recognizing how little is known about potential AMR impacts on the Canadian public and healthcare system, the Minister of Science, on behalf of the Public Health Agency of Canada, asked the Council of Canadian Academies (CCA) to convene an expert panel to provide an evidence-based, authoritative assessment that answers the following question:

> *What is the socio-economic impact of antimicrobial resistance (AMR) for Canadians and the Canadian healthcare system?*

In order to address this charge, the CCA's Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada looked at AMR impacts today and how these could change in the future if resistance grows. There is no doubt that antimicrobials are an essential part of Canada's economy. According to the Panel's economic model, first-line antimicrobials contributed to saving at least 17,000 lives and preventing 2.6 million hospital days in 2018 while generating $6.1 billion in economic activity in Canada. This contribution is at risk because the number of effective antimicrobials are running out. The consequences of a future with limited or no antimicrobials are alarming.

AMR Negatively Impacts the Canadian Economy

The Canadian economy has already begun to shrink as a result of AMR, as the number of deaths have increased and fewer people are able to work due to illness. Based on the Panel's economic model that uses current estimates of resistance, AMR's impact on labour productivity reduced Canada's GDP by $2.0 billion in 2018, with much of this effect concentrated in industries such as hospitality, transportation, and education, where human interaction is central to the services provided. Agriculture is also experiencing the effects of AMR, with the health of animals and current industrial practices under threat.

By 2050, if resistance to first-line antimicrobials (i.e., those generally first prescribed to treat an infection) remains constant at today's rate of 26%, or reaches 40%, the Panel estimates that AMR would reduce Canada's GDP by $13 to $21 billion per year, respectively (Table 1). The Canadian economy would be up to 0.7% smaller in 2050 if resistance remained constant at today's rates, a significant decline about equal to one-third of the GDP of Manitoba or the oil sands extraction industry. If resistance were to reach 40% by 2050, a scenario the Panel deems likely, Canada's cumulative GDP would decline by about $388 billion.

AMR Negatively Impacts the Healthcare System

The ubiquity of antimicrobials in modern medicine means that declining effectiveness will place an increasing pressure on an already strained healthcare system. Antimicrobials are used for the treatment, but also prevention, of infections. For example, many surgeries and other medical procedures, including chemotherapy, are dependent on prophylactic treatment with antimicrobials. Ineffective antimicrobials will ultimately change the way that most people access and plan the care of their health. This lack of prophylactic treatment will become especially problematic for hospitalized patients who require invasive care.

The Panel found that, in 2018, lengthier hospital stays, longer courses of treatment, and other expenses attributable to AMR cost the Canadian healthcare system about $1.4 billion. Eventually, if resistance rates continue to rise, they will lead to substantial financial implications for Canada's healthcare system, fundamentally changing the delivery of most services and eroding public trust. By 2050, Canada's healthcare costs as a result of increasing AMR would grow to about $6 to $8 billion per year, were resistance to first-line antimicrobials to remain constant or reach 40%. The latter amount is roughly equal to about 1% of Canada's healthcare spending or about the total expenditure on all hospitals in Atlantic Canada or all physicians in Quebec. In the unlikely scenario that resistance to first-line antimicrobials reaches 100% AMR may cost the equivalent of 1.6% of Canadian healthcare spending, equal to the current total expenditure for all physicians in Quebec and Ontario.

Table 1

Impact of Antimicrobial Resistance on Canadian Population and GDP, 2018–2050

Resistance Rate	Population Decline			Preventable Deaths	GDP Decline			Potential GDP Loss
	2018	2050	Cumulative		2018	2050	Cumulative	
Status Quo (26%)	5,400	7,000	256,000		$2.0 billion	$13 billion	$268 billion	
40%		13,700	396,000	140,000		$20.8 billion	$388 billion	$120 billion
100%		39,600	808,000	620,000		$44 billion	$747 billion	$479 billion

This table presents estimates from the Panel's model for three resistance scenarios: (i) resistance to first-line antimicrobials remains constant at 26%, (ii) reaches 40% resistance by 2050, and (iii) reaches 100% resistance by 2050. The Panel considers the 40% resistance scenario highly plausible, while the 100% resistance rate by 2050 represents the worst-case scenario. The estimates for 2050 are average annual declines in population and GDP, and the cumulative estimate is for the period 2018 to 2050. *Preventable deaths* represents the number of lives that could be saved if resistance does not grow to 40% or 100%. Similarly, *potential GDP loss* is the amount of GDP that could be saved if resistance does not increase.

AMR Negatively Impacts Health

Numerous bacterial infections are becoming more difficult, and sometimes impossible, to treat as antimicrobials become less effective. Because an average of about 26% of bacterial infections are currently resistant to first-line antimicrobials, the Panel estimates that resistant bacterial infections were responsible for the deaths of over 14,000 people in Canada in 2018 (about 1 in 19 deaths) (Figure 1). Of these deaths, 5,400 (or almost 15 a day) could be considered directly attributable to AMR itself. In other words, these 5,400 deaths would not have occurred if these patients' infections had been susceptible to first-line antimicrobials. In 2018, AMR was therefore the attributable cause of only slightly fewer deaths in Canada than from Alzheimer's disease in 2016.

The risk of acquiring a resistant infection is not uniform across Canada. Groups that have a higher likelihood of consuming antimicrobials, or being exposed to AMR in healthcare settings, are often at greater risk. For example, those with compromised or weaker immune systems (including the very young and older adults), as well as those with other medical conditions, are most at risk. Marginalized groups, including people living in poverty, homeless people, and people with substance use disorder, are at higher risk of acquiring some types of resistant infections. The greatest risk factor for acquiring a resistant infection is previous antimicrobial treatment.

AMR Negatively Impacts Society

The social impacts of AMR may far outweigh the economic costs. If antimicrobials are limited in the future, everyone will be at risk and more people in Canada will see their quality of life decline as a result of the morbidity and mortality associated with resistant infections. By 2050, if resistance to all first-line antimicrobials reaches 40%, a scenario the Panel deems highly plausible, 13,700 people in Canada would die each year from resistant bacterial infections, and cumulatively Canada's population decline would reach almost 400,000 by 2050. In the unlikely scenario that resistance to first-line antimicrobials reaches 100% by 2050, 39,600 people would die each year from resistant bacterial infections, and cumulatively Canada's population decline would reach 800,000. Notably, this impact will be unequally distributed, as some socio-demographic groups will be more at risk of infection.

Broader social impacts, beyond those related to healthcare, include the potential for decreases in social trust, social capital, quality of life, and equality among different socio-demographic groups. Social connectivity may weaken, and discrimination may be targeted at those with resistant infections or deemed to be at risk of infection. Canadian society may become less open and trusting, with people less likely to travel and more supportive of closing Canada's borders to migration and tourists.

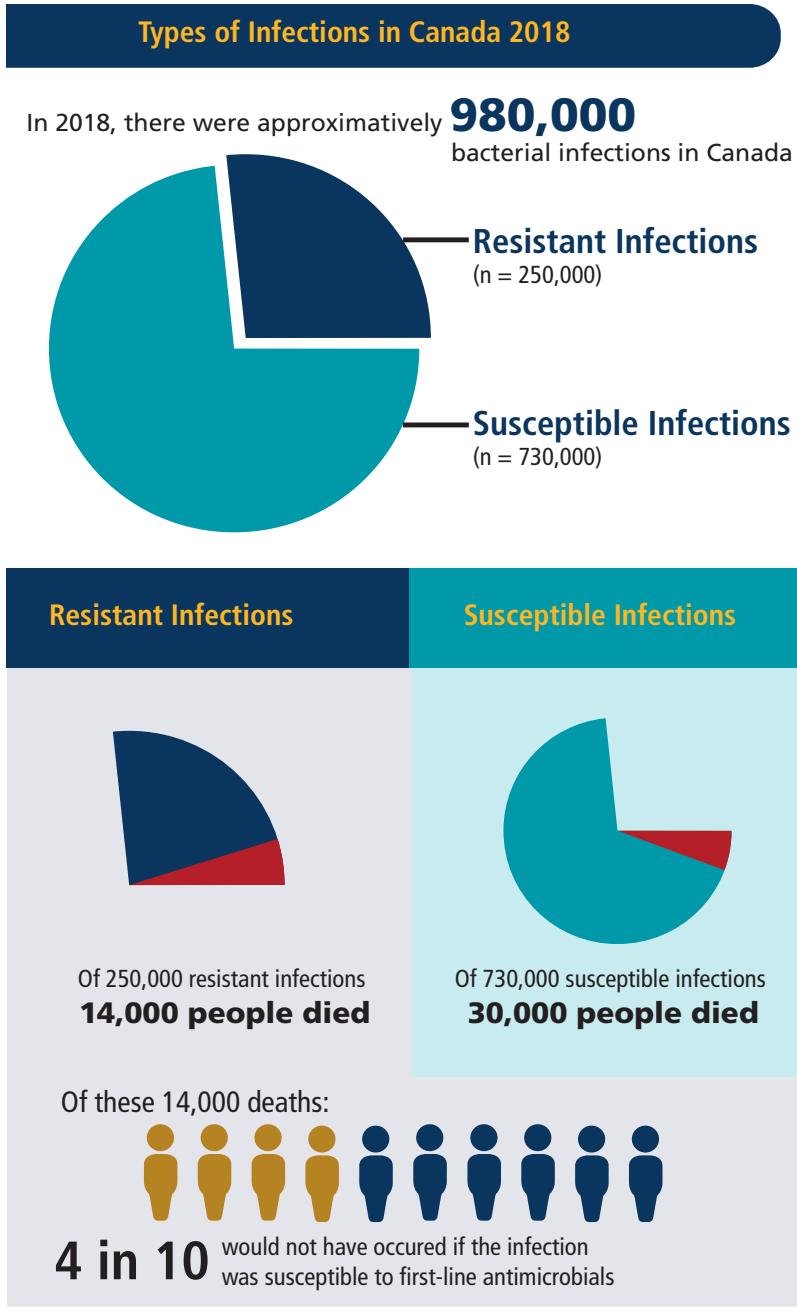

Figure 1
Bacterial Infections and Resulting Deaths in Canada, 2018

Multi-Faceted Mitigation Strategies Can Limit the Impact of AMR

Limiting AMR impacts requires a complete re-evaluation of healthcare, centred on reducing the rate of infections so that the use of antimicrobials is less necessary. Since healthcare is a complex system, it is nearly impossible to predict any given intervention's impact on the behaviour of patients, healthcare providers, hospitals, governments, communities, and companies. The effect of each intervention is subject to significant uncertainty, since feedback loops among behaviour, infection rates, resistance rates, and costs per patient are interconnected. As such, the Panel concluded that the most effective approach to addressing AMR is globally coordinated, multifaceted, and combines elements of four mitigation strategies — surveillance, infection prevention and control, stewardship, and research and innovation — that have been shown to be effective.

Surveillance underpins successful mitigation efforts, as it allows for targeted use of resources by providing an up-to-date and accurate portrayal of the current state of resistance and use of antimicrobials. Surveillance programs monitor antimicrobial use and AMR, thereby providing governments, hospitals, prescribers, and other stakeholders involved in mitigation a sense of where and how to best target interventions. Surveillance can also be used for monitoring and feedback, such as providing prescribers with anonymous benchmarking data. Weaknesses in current Canadian surveillance include limited data on infections attributable to priority pathogens (especially in community settings), on antimicrobial use in many regions of Canada, on AMR in domestic animals and wildlife, as well as the lack of an effective federal/provincial/territorial surveillance system. Additionally, the data that are collected are not easily accessed. One of the Panel's major findings is that there is a lack of comprehensive surveillance data describing the number of resistant infections across Canada, and their characteristics.

Infection prevention and control measures are wide-ranging, and have the ultimate goal of decreasing infection, and therefore the use of antimicrobials. To reduce infections, including those due to resistant microbes, hospitals and other settings where healthcare is delivered must, for example, meet current standards of handwashing, hand hygiene, environment and equipment cleaning, and adhere to patient treatment protocols. This will require that all healthcare providers are adequately trained, and that hospitals and other healthcare settings have adequately resourced teams to optimize both patient care and institution-wide infection prevention and control, not to mention other relevant programs. When healthcare is provided outside of institutions, appropriate methods for infection prevention and control must also be followed. Similar improvements are possible in the agricultural sector, with major opportunities

for infection prevention and control (biosecurity) through increased vaccination and improved hygiene standards, for example, as antimicrobial use decreases in this sector.

Stewardship initiatives, which promote the judicious use of antimicrobials, represent another major opportunity to limit the impact of AMR. The Panel concluded that stewardship requires a One Health approach, which includes all sectors collaborating to address AMR and incorporating leading practices, while stakeholders from both the human and animal health sectors coordinate actions. The Canadian agriculture industry has already made strides in decreasing antimicrobial use. Although the industry accounted for about 78% of antimicrobial use in Canada in 2016, the federal government halted the use of antimicrobials for growth promotion in 2018 and, for the first time (among other regulatory changes), mandated that all antimicrobial use in food animals be under veterinary prescription. From the human health perspective, antimicrobial use as measured through prescriptions dispensed remains stable in Canada, but there may be an opportunity for targeted interventions that reduce unnecessary use.

Research and innovation is a fundamental mitigation strategy, complementing known interventions that already have an immediate impact in reducing the effects of AMR. Given current trends, it seems unlikely that novel, broad-spectrum antimicrobials will be discovered. But, by using innovative methods, such as focusing on unconventional targets, new narrow-spectrum antimicrobials that treat infections caused by specific bacteria may be discovered. Making such discoveries will require more fundamental research, more flexible regulations, and new economic incentives to address a challenging commercial model, thereby reconciling public health needs with return on investment for the pharmaceutical industry. Alternative therapies are also being developed to treat or prevent resistant infections, including vaccines, phage therapy, lysins, and antimicrobial adjuvants, and the potential of the microbiome is being explored. Research and innovation can also offer ways of measuring the effectiveness of interventions, provide new technology (such as rapid diagnostics that allow for more accurate and systematic measures of antimicrobial use and for tracking AMR), update methods for data sharing and analysis, and provide evidence on which interventions are likely to be most effective.

There are also opportunities to limit the impact of AMR that extend beyond the health sector, animal industry, and government. Informed and encouraged by public health campaigns, everyone in Canada can improve their handwashing and food-handling, obtain recommended vaccinations, engage in safer sexual

practices, and change their behaviour in other ways that help to prevent the spread of infections. They can also engage in their own personal stewardship, asking their doctors, dentists, veterinarians, and other healthcare providers to prescribe antimicrobials only when necessary. Canada is in the middle of the pack among OECD countries when it comes to antimicrobial use, rates of AMR, and mitigation efforts. While there is much room for improvement, Canada can build on its existing strengths with key investments in infrastructure, innovation, and education.

The Need for Action is Urgent

AMR is a threat to millions, potentially responsible for the loss of some 300 million lives globally over the next 30 years. There is both a disconnect and time lag between the cause and effect of AMR: antimicrobial use in one country today leads to AMR in another country tomorrow. Antimicrobial stewardship, antimicrobial use and AMR surveillance, and innovation all require a coordinated global effort, with countries such as Canada leading the way. There is an opportunity for coordinated action and change across Canada through the development and use of the national action plan on AMR.

AMR is a looming public health threat and potential economic disaster in Canada. The implications of inaction are significant for Canadian society and the economy; AMR will unequally impact different socio-demographic groups as well as food security. Few health and economic crises have had the potential for such a prolonged impact in post-war Canadian history. If actions are not taken to combat the increase of AMR, Canada will be greatly changed within a few decades. The economy will shrink, the healthcare system will be less sustainable, and social inequality will further increase. Even more serious will be the hundreds of thousands of deaths caused by infections that have been treatable for the last century. In order to change course, action is required now.

Glossary

Antibiotic	"A type of antimicrobial used to treat infections caused by bacteria" (GC, 2017).
Antimicrobial	"A natural, semisynthetic or synthetic substance that is capable of killing or inhibiting the growth of microbes." They can include antibiotics, antivirals, antifungals, and antiparasitics (PHAC, 2014b).
Antimicrobial resistance (AMR)	A phenomenon whereby antimicrobials no longer inhibit or kill microbes because the microbes' biological makeup has changed (PHAC, 2014b).
Antimicrobial stewardship (AMS)	"A system-wide approach that includes coordinated interventions designed to promote, improve, monitor, and evaluate the judicious use of antimicrobials to preserve their future effectiveness and promote and protect human and animal health" (AMR Stewardship Task Group, 2017).
Antimicrobial use (AMU)	The use of antimicrobials in humans, animals, and agriculture.
One Health	An assessment that considers "wider societal costs of lost labour, changes in health seeking behavior, impacts on animal health and welfare, higher costs of animal-origin food production, and reduced consumer confidence in safety and international trade of such food" (Queenan *et al.*, 2016).
Socio-demographic group	A group defined by its sociological and demographic characteristics, such as homeless people, racialized people, people with substance use disorder, or people with lower incomes.
Syndrome	An infection characterized by a group of associated symptoms that typically occur within a common location in the body. For example, bacterial gastro-intestinal infections are infections caused by pathogenic bacteria in the gut, leading to symptoms that may include vomiting, severe abdominal cramps, fever, and diarrhea.

List of Acronyms and Abbreviations Used in the Report

AGP antimicrobial growth promoter
AMR antimicrobial resistance
AMS antimicrobial stewardship
AMU antimicrobial use
API active pharmaceutical ingredient
BGI bacterial gastro-intestinal infection
BSI bloodstream infection
CARSS Canadian Antimicrobial Resistance Surveillance System
CDI *Clostridioides difficile* infection
CIPARS Canadian Integrated Program for Antimicrobial Resistance Surveillance
CNISP Canadian Nosocomial Infection Surveillance Program
CRE carbapenem-resistant Enterobacteriaceae
DCGE dynamic computable general equilibrium
DDD defined daily dose
ESBL extended-spectrum beta-lactamase
FAO Food and Agriculture Organization of the United Nations
GDP gross domestic product
GLASS Global Antimicrobial Resistance Surveillance System
HAI healthcare-associated infection
IAI intra-abdominal infection
IPC infection prevention and control
LOS length of stay (in hospital)
MDR multi-drug-resistant
MIA medically important antimicrobial
MRSA methicillin-resistant *Staphylococcus aureus*
MSI musculoskeletal infection
MSSA methicillin-susceptible *Staphylococcus aureus*
OECD Organisation for Economic Co-operation and Development
OIE World Organisation for Animal Health
PHAC Public Health Agency of Canada

SSI	surgical site infection
SSTI	skin and soft tissue infection
STI	sexually transmitted infection
TB	tuberculosis
UTI	urinary tract infection
VRE	vancomycin-resistant *Enterococcus*
WHO	World Health Organization

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1 Introduction

With antimicrobial use (AMU) underpinning much of modern medicine and agriculture, the prospect of a world where antimicrobials no longer work is alarming. In such a world, infections that are now treatable would be more difficult, or, in extreme cases, impossible to treat. Illnesses would be longer and more severe, treatments more expensive, and the risk of death higher. If infections could not be treated or prevented, many standard medical interventions that rely on prophylactic antimicrobials, such as organ transplants, chemotherapy, surgery for joint replacements, or caesarean deliveries, would be deemed too risky to be made widely available (GC, 2017). Furthermore, the food we eat may be more expensive or limited in quantity.

The risk of a post-antimicrobial era in the 21st century is no longer remote. Indeed, antimicrobial treatments no longer work for some infections, and these treatment-resistant infections are on the rise globally (PHAC, 2014b; OECD, 2018a). Currently 700,000 people worldwide are estimated to die each year from treatment-resistant infections, with the potential cumulative loss of 300 million lives by 2050 (O'Neill, 2016a). A projected increase in the consumption of antimicrobials, coupled with a lack of new antimicrobials (Klein *et al.*, 2018), means that antimicrobial resistance (AMR) is expected to increase in the future. AMR has the potential to impact everyone — it is a global problem that ignores wealth or status.

The rise in AMR has prompted many warnings. The United Nations, for example, has acknowledged AMR as "a fundamental, long-term threat to human health [and] sustainable food production and development," adding that "it is a very present reality — in all parts of the world, in developing and developed countries; in rural and urban areas; in hospitals; on farms and in communities" (UN, 2016). The World Economic Forum (2013) has recognized antibiotic-resistant bacteria as arguably the greatest risk to human health.

Bacterial infections causing pneumonia, gonorrhea, urinary tract infections, and gastroenteritis are becoming more difficult, and sometimes impossible, to treat as antimicrobials become less effective. Canada for its part is already experiencing the impacts of treatment-resistant infections. This report estimates that about 1 in 19 deaths in Canada are attributable to bacterial infections that are resistant.

Medical, veterinary, and agricultural practices depend extensively on the widespread availability of antimicrobials to prevent and treat bacterial infections in humans, animals, and crops (PHAC, 2014b); AMR therefore has the potential to impact many facets of contemporary social and economic life in Canada. This interconnectedness of AMU in humans and animals, and the presence of antimicrobials and resistant bacteria within the environment, have led to widespread support internationally for taking a One Health approach to responding to AMR, whereby programs, policies, legislation, and research are developed with communication across multiple sectors (WHO, 2017a).

1.1 THE CHARGE

Recognizing how little is known about potential AMR impacts on the Canadian public and healthcare system, the Minister of Science, on behalf of the Public Health Agency of Canada (PHAC, the Sponsor), asked the Council of Canadian Academies (CCA) to convene an expert panel to provide an evidence-informed, authoritative assessment. Specifically, the CCA was asked to answer the following question and sub-questions:

> ***What is the socio-economic impact of antimicrobial resistance (AMR) for Canadians and the Canadian healthcare system?***
>
> *What data are available to determine the state of antimicrobial usage (AMU) in human and non-human environments in Canada, and what can these data reveal about the contribution of AMU in different environments to AMR problems in humans in Canada?*
>
> *What data are available to determine the state of and socio-economic impact of AMR in general, and particularly in hospitals and community-based settings and across particular populations in Canada? If not, what information is needed, and how can the data gap be closed?*
>
> *How is the state and impact of AMR assessed in other OECD countries, and are these data and lessons learned comparable to Canada?*
>
> *What are the policy implications of the impact of AMR? (i.e., how can this evidence inform policy and investment)?*
>
> *What are the science and technology gaps in the understanding of these impacts?*
>
> *What lessons from other OECD countries could assist in improving AMR surveillance and stewardship in Canada?*

1.2 THE PANEL'S APPROACH

To address the charge, the CCA assembled a multidisciplinary panel of 13 experts (the Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, hereafter the Panel) from Canada and abroad. Panel members brought knowledge from biology, microbiology, epidemiology, infectious diseases, veterinary medicine, public health, medicine, sociology, economics, public policy, and industrial practices. Each member served on the Panel as an informed individual rather than as a representative of a specific discipline, organization, region, or set of values.

Over the course of a year, the Panel met in person five times to refine its assessment of the issues at hand. At the beginning of the assessment process, the Panel met with the Sponsor to acquire a full understanding of the charge. At this meeting, the Panel confirmed with the Sponsor that the primary focus of the assessment was quantifying socio-economic impact. The Panel confirmed the use of a One Health approach (Section 1.2.3) to better understand the problem of AMR, which meant that AMU and AMR within healthcare, agriculture, and the broader environment were all within scope. The Panel also confirmed that the focus of this assessment was on bacterial pathogens, not all microbes.

1.2.1 Evidence

The Panel's assessment is based on a review of various sources of health, social, and economic evidence, drawn from peer-reviewed publications, publicly available government information and statistics, and other grey literature[1] related to AMR impacts, both within Canada and internationally. To find the best available evidence, the Panel conducted keyword-based searches of published literature and explored the websites of PHAC, Health Canada, Statistics Canada, the Organisation for Economic Co-operation and Development (OECD), the World Health Organization (WHO), and other relevant government agencies in Canada and abroad. This report is not based on a systematic review, but rather a detailed analysis of the key references as identified by the Panel.

To estimate the economic impact of AMR, the Panel also commissioned a quantitative economic model to explore the complex relationship among AMR, health, labour productivity, agriculture, and trade (Section 4.1 and Appendix C). The model considers production and trading patterns among industries and countries, assuming that if AMR affects labour productivity in one country, global production and trade adjust throughout the world. This

1 *Grey literature* refers to various types of documents produced by government, academia, industry, and other organizations that are not published commercially/formally.

method is similar to those used in reports estimating AMR's economic impact published by other groups (e.g., KPMG, 2014; RAND Europe, 2014; OECD, 2015; World Bank, 2017).

The Panel's model differs from those used in other reports. It includes more comprehensive epidemiological data on resistant infections germane to a Canadian perspective, in order to strengthen the linkage between economic projections and existing data. Specifically, the Panel examined the impacts of resistant infections through the lens of a syndrome (a group of associated symptoms that may involve multiple causal bacterial pathogens, such as bloodstream infections). Estimates from this model — which are based on scenarios of resistance rates to first-line antimicrobials staying at today's rate (26%) or increasing gradually to 40% by 2050 — also consider the impact of AMR on Canada's industries. These projections are the first of their kind in Canada, and provide policy-makers and other stakeholders with credible estimates of the potential magnitude of AMR impacts over the next three decades.

1.2.2 Limitations

Any socio-economic analysis is limited by available data as well as methodology. Three types of inherent limitations constrain this report's socio-economic analysis of AMR: (i) data limitations relating to the current epidemiological measures of resistant infections in Canada (i.e., limitations in quality, availability, and quantity of data); (ii) limitations based on the methodology of the Panel's economic model, which estimates AMR's impact on Canada's gross domestic product (GDP); and (iii) limitations based on the methodology used to approximate healthcare costs, which estimates increased costs associated with treating resistant infections. Where assumptions were necessary, the Panel took a conservative approach.

Data limitations in particular hampered the Panel's ability to accurately characterize the current state of AMR in Canada. To the extent possible, the Panel sought to ensure Canadian data on resistant bacterial infections informed both current and future estimates of impact. However, in some cases, these data were not available, so data from comparable countries were used. Furthermore, the current Canadian evidence on the amount of resistance, and its variation geographically and among bacterial species, is inconsistent. Indeed, one of the Panel's major findings is the lack of comprehensive surveillance data describing the number of resistant infections across Canada and their characteristics (e.g., morbidity, mortality, and associated costs); these are needed for informed

decision-making (Section 6.1). Because of this knowledge gap, the Panel chose to focus on 10 important clinical syndromes that, in their expertise, encompass the majority of resistant infections in Canada:

- bacterial gastro-intestinal infection (BGI)
- bloodstream infection (BSI)
- *Clostridioides difficile* infection (CDI)
- intra-abdominal infection (IAI)
- musculoskeletal infection (MSI)
- pneumonia
- sexually transmitted infection (STI)
- skin and soft tissue infection (SSTI)
- tuberculosis (TB)
- urinary tract infection (UTI)

While encompassing most resistant infections, these syndromes do not capture all resistant infections in their entirety. All estimates deriving from these data therefore underestimate the actual magnitude of resistant infections in Canada.

Assessing the relative significance of the economic and social impacts of AMR is also made difficult by the fact that the economic dimension of impact can be quantified with simulations based on current data, while the social dimensions of impact are often qualitative. Ultimately, however, economic impacts are embedded within a social system, and the social impacts of AMR in the future may outweigh the economic costs.

1.2.3 Key Concepts

What Are Antimicrobials?

Antimicrobials are drugs that kill or inhibit the growth of disease-causing microbes, such as certain bacteria, viruses, parasites, and fungi (PHAC, 2014b). Since antimicrobials began to be used widely about 70 years ago, they have saved hundreds of millions of lives (World Bank, 2017). The most common and familiar antimicrobials are antibiotics, which treat infections caused by bacteria. This report focuses on resistant bacteria, but the broader term *antimicrobial* is generally used because surveillance data tend to be collected under this heading.

How Are Antimicrobials Used?

Globally, antimicrobials are used for prevention and treatment of infections in humans, animals, and plants. In Canada in 2016, 78% of antimicrobials used were in the production of food animals, 20% were for human use, 1% for crops, and 1% for companion animals (measured by kilograms of active ingredient) (PHAC, 2017a). While the presence of antimicrobials in healthcare and agricultural settings is easily explained based on AMU, it is less clear why

antimicrobials are also found in other environments. Some antimicrobials may be naturally occurring, but others may reach environments through various pathways including sewage systems (e.g., from hospitals) and run-off from farms (PHAC, 2017a). Any AMU creates opportunities for the evolution and spread of resistance.

What Is Antimicrobial Resistance?

AMR is a phenomenon whereby antimicrobials no longer kill or inhibit the growth of microbes because the biological makeup of the microbe has evolved (PHAC, 2014b). As a result, antimicrobials are ineffective in stopping infections in humans, animals, and plants. While much research focuses on resistant bacteria, there are four groups of pathogenic microbes that evolve AMR and may be important to human health and agriculture: bacteria (e.g., *Escherichia coli*), viruses (e.g., HIV), fungi (e.g., *Candida* species), and parasites (e.g., *Plasmodium falciparum*, which causes malaria). When antimicrobials are present within the environment of a population of microbes, the microbes with genetic traits that allow them to grow in the presence of the antimicrobial will survive and multiply, while those that are susceptible to antimicrobials will die (Andersson & Hughes, 2010). Over time, as populations of microbes are repeatedly exposed to various antimicrobials, the surviving microbes become increasingly resistant to a wider range of drugs. This report focuses on resistant bacteria.

AMR has been observed since the first antimicrobials were discovered. In fact, genes conferring resistance predate the use of antimicrobials by many years (Hughes & Datta, 1983; Wright, 2007; D'Costa *et al.*, 2011; Perry *et al.*, 2014; Perron *et al.*, 2015). For example, resistance genes have been identified in permafrost sediments in Yukon (D'Costa *et al.*, 2011). AMR has become increasingly problematic because of "a unique convergence of overuse and misuse of antibiotics, the remarkable genetic plasticity of bacteria, the acquisition of resistant bacterial infections in both community and hospital settings, and a market failure of antibiotic development [that] has created an enormous public health concern" (IDSA, 2011).

A One Health Approach to AMR

One Health is defined as "the collaborative effort of multiple health science professions, together with their related disciplines and institutions — working locally, nationally, and globally — to attain optimal health for people, domestic animals, wildlife, plants, and our environment" (One Health Commission, 2018). Many believe that taking action to mitigate AMR exemplifies the principles of this approach (e.g., Queenan *et al.*, 2016; Robinson *et al.*, 2016; Kahn, 2017; WHO, 2017a; McEwen & Collignon, 2018). In an AMR context, One Health recognizes that resistant organisms exist in humans, animals, food, and the

environment, and that the major driver of resistance is AMU (Queenan *et al.*, 2016). It also acknowledges that tackling AMR requires a global approach and therefore advocates for coordinated actions across domestic and international borders, sharing solutions for a comprehensive, effective response (GC, 2017). This requires that human and animal health, agriculture, and food production sectors all work together to contain the emergence and spread of AMR (WHO, 2016b).

One of the challenges of addressing AMR "has been the blame game going on between medicine and agriculture as to who is most at fault for causing the crisis" (Kahn, 2017). While many current estimates of AMR impact focus on the costs and benefits to human health, a One Health assessment looks at "wider societal costs of lost labour, changes in health seeking behavior, impacts on animal health and welfare, higher costs of animal-origin food production, and reduced consumer confidence in safety and international trade of such food" (Queenan *et al.*, 2016). The Panel agrees and has explored these wider societal costs to the extent possible given the current evidence, which are examined in Chapters 3 through 5.

In Canada, federal, provincial, and territorial governments are using a One Health approach to combat AMR. This approach is outlined in a 2017 report entitled *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action* (hereafter Pan-Canadian Framework) (GC, 2017). Although the focus of the Panel's report is primarily focused on AMR's impacts on human health, examining the problem through a One Health lens means looking also at AMU in animals and the environment, and how this contributes to AMR in humans and impacts the Canadian healthcare system and economy. The *Pan-Canadian Action Plan*, a follow-up report that will identify deliverables, measurable outcomes, and timeframes to support the implementation of the Pan-Canadian Framework (PHAC, 2017b), is currently being developed, and is expected to be released in 2020.

1.3 A FRAMEWORK FOR UNDERSTANDING AMR IMPACT AND STRUCTURING OF THE REPORT

The Panel developed a framework showing the main groups of economic and social impacts that may result from AMR (Figure 1.1). The framework is reflected in the structure of this report, with the exception of direct AMR impacts on animals and farmers in the agricultural sector, which are outside the remit of this assessment. However, the Panel did choose to model agricultural scenarios that briefly examine how changes to productivity and trade that may occur as a result of AMR and related issues would impact the food animal agriculture sector.

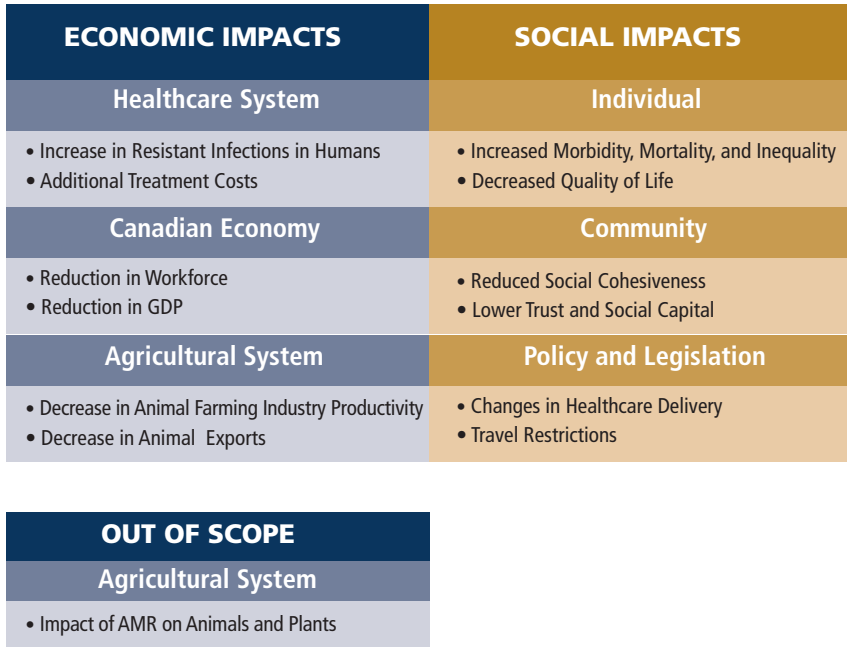


Figure 1.1

A Framework for the Socio-Economic Impacts of Antimicrobial Resistance in Canada

This report examines the economic and social impacts of antimicrobial resistance (AMR) in Canada. The economic impact of AMR is examined through the impact of resistant infections on hospital costs (Chapter 3), through changes to Canada's economy based on simulated changes to labour productivity and through impacts to the agricultural system through decreases in productivity and animal exports (Chapter 4). Possible future social impacts of AMR on the Canadian public are examined at the individual and community level (Chapter 5).

Chapter 2 provides context necessary to understand the charge by outlining current AMU and AMR in Canada.

Chapter 3 focuses on the economic impacts of AMR on healthcare systems due to the increased hospital costs associated with treating more patients for longer periods of time, and in some cases with more expensive antimicrobials (Gandra *et al.*, 2014; Valiquette *et al.*, 2014; NAS, 2018). Using measurements of the costs associated with treating resistant bacterial infections, the Panel estimates the Canadian hospital costs associated with resistant infections for specific bacterial pathogens. These costs are expected to increase as the number of resistant infections increase. A number of studies have estimated the costs of a specific type of resistant bacteria in a given hospital, region, or country, but only one has extrapolated measures across bacteria to estimate the healthcare costs of resistance as a whole for an entire country (OECD, 2018a).

The Panel's report differs from a recent OECD report that provides healthcare costing and economic projections of AMR impacts in Canada but does so using contrasting methods in order to present a high-level cross-country analysis (OECD, 2018a). The OECD report was informed by limited Canadian epidemiological data; only one bacterial species was used (*E. coli*) over a three-year period. The epidemiological data underlying the Panel's report, however, stem from a variety of sources (e.g., from both hospital and community settings where available), and encompass 10 different syndromes accounting for many species of bacteria. The OECD report estimates that, currently, about 400 people in Canada die annually from resistant infections, whereas — based on more comprehensive data and members' clinical experience — the Panel estimates more than 5,000 deaths in 2018 could be attributed to AMR. The OECD report provides a high-level analysis; the Panel's report focuses on Canadian-specific data and projections, using Canadian experts to validate the results. For these reasons, the OECD report does not reflect the Canadian reality.

Chapter 4 projects the future impact of AMR on Canada's GDP stemming mainly from decreased labour productivity due to increased morbidity and mortality associated with resistant infections. A number of studies have estimated GDP impacts resulting from potential decreases in labour market productivity and a shrinkage of the workforce (e.g., O'Neill, 2014; OECD, 2015; World Bank, 2017). A recent study by the World Bank, for example, estimates that by 2050 AMR impacts could decrease global GDP by 3.8% and cause 28.3 million additional people to become impoverished (World Bank, 2017). Similarly, the OECD estimates that the economic impact associated with current rates of AMR will reach 0.78% of GDP in OECD countries by 2050, resulting in cumulative losses of approximately US$2.9 trillion (OECD, 2015). By employing an economic model similar to those used in these studies, the Panel estimates the potential future AMR impacts on Canadian GDP.

The potential social impacts arising from widespread AMR are discussed in **Chapter 5**, with a focus on those affecting individuals and communities, and those that come about through changes in policy and legislation. To aid in the identification of impacts, the Panel uses a future scenario in which AMR has continued to increase such that many antimicrobials are ineffective. In this scenario, everyone in Canada will be impacted by AMR — quality of life will decrease while morbidity and mortality will increase. Less trust in institutions such as the healthcare system will lead to changes in care-seeking behaviour. A more pervasive lack of trust will fundamentally alter society such that people will also become less trusting of others, growing more insular, travelling less, and being less willing to open the nation's borders to immigrants and visitors.

Chapter 6 looks at the policy implications of the impact of AMR and four mitigation strategies — surveillance, stewardship, infection prevention and control, and research and innovation — and investigates how each strategy might contribute to slowing the spread of AMR.

The report concludes by stating that now is the time to act, encouraging Canada to take immediate action to address the problem of AMR using a One Health approach.

1.4 REPORT RELEVANCE

This report is unique because of both its comprehensive approach and Canadian point of view, making it different from previous reports that also examined AMR impacts on GDP (e.g., KPMG, 2014; RAND Europe, 2014; OECD, 2015; O'Neill, 2016a; World Bank, 2017). First, it is more comprehensive than previous reports that measured the global economic impact of AMR because it (i) uses epidemiological measures of current resistant infections within Canada to inform the economic model, (ii) investigates how several mitigation strategies might reduce the future impacts of AMR using the economic model, and (iii) includes impacts on the agricultural sector through changes to the labour force as a result of AMR within the economic model, to better reflect a One Health approach.[2]

Second, this report examines AMR impacts from a distinctly Canadian perspective. It looks at impacts on both the Canadian healthcare and agricultural sectors through effects on human health, which is crucial for a One Health approach. It also considers social impacts using past Canadian experiences, examining socio-demographic groups and data relevant within a Canadian context.

2 The Panel notes that the direct impact of AMR on animals and farmers is not modelled or included in this report, as it was out of scope.

2

Antimicrobial Use and Resistance in Canada Today

- The Relationship Between Antimicrobial Use and Antimicrobial Resistance
- Antimicrobial Use in Canada
- Resistant Infections in Canada
- Conclusion

2 Antimicrobial Use and Resistance in Canada Today

Key Findings

The main cause of AMR is antimicrobial use, with misuse acting as a key driver.

Based on the Panel's research, one in every four bacterial infections in Canada is resistant to a first-line antimicrobial treatment.

Resistant infections already result in a substantial burden of disease among people in Canada.

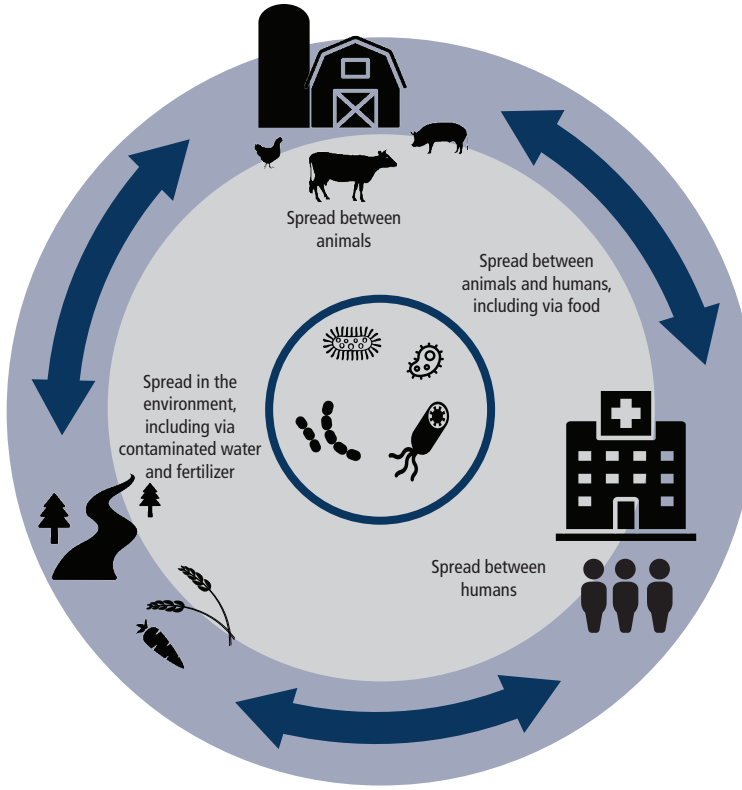
The Panel estimates that 14,000 deaths in Canada in 2018 were associated with resistant infections. Of these, 5,400 deaths (almost 15 a day) were directly attributable to AMR. In 2018, AMR was therefore the attributable cause of only slightly fewer deaths in Canada than Alzheimer disease in 2016.

Antimicrobial use (AMU) in humans and agriculture contributes to increased AMR (Section 2.1). A One Health approach to AMR — which considers AMU in all sectors, as well as antimicrobials found in the environment — removes the blame from any one sector since all stakeholders must work together to find a solution (Figure 2.1). AMR is not just a One Health issue but a "One World" issue as the global mobility of people and food facilitates the spread of AMR genes (Robinson *et al.*, 2016).

This chapter examines AMR in Canada through a One Health lens. The Panel presents evidence on current AMU in Canada, in both the healthcare system and in food animals and other food sources. This is followed by a discussion of the relationship between AMU in people and animals, and AMR. Finally, the chapter surveys AMR in Canada today, as represented by mortality and morbidity associated with resistant infections linked to 10 important clinical syndromes identified by the Panel.

2.1 THE RELATIONSHIP BETWEEN ANTIMICROBIAL USE AND ANTIMICROBIAL RESISTANCE

The most important driver for the emergence and increase in AMR is AMU (Aarestrup, 2015). Therefore AMU, even if appropriate or conservative, leads to the development of AMR (Cars *et al.*, 2008; Ventola, 2015; Roope *et al.*, 2019). As explained by Laxminarayan *et al.* (2013), "antibiotic use is a main driver of selection pressure that contributes to resistance." However, misuse,



Adapted with permission from GC (2017)

Figure 2.1

A One Health Approach to Antimicrobial Resistance

The movement of resistant bacteria among and between humans, animals, and the environment underscores the importance of taking a One Health approach to the problem of antimicrobial resistance.

including overuse, plays a significant role in the emergence of AMR in both humans and agriculture (WHO, 2012b; Laxminarayan *et al.*, 2013; Holmes *et al.*, 2016). There are many factors that impact the acquisition, persistence, and transmission of antimicrobial-resistant microbes among people, animals, and the environment, including a lack of access to clean water, open (as opposed to closed) sewage systems, suboptimal healthcare infection-control practices, insufficient provision of antimicrobials and diagnostics, and high population density (Holmes *et al.*, 2016).

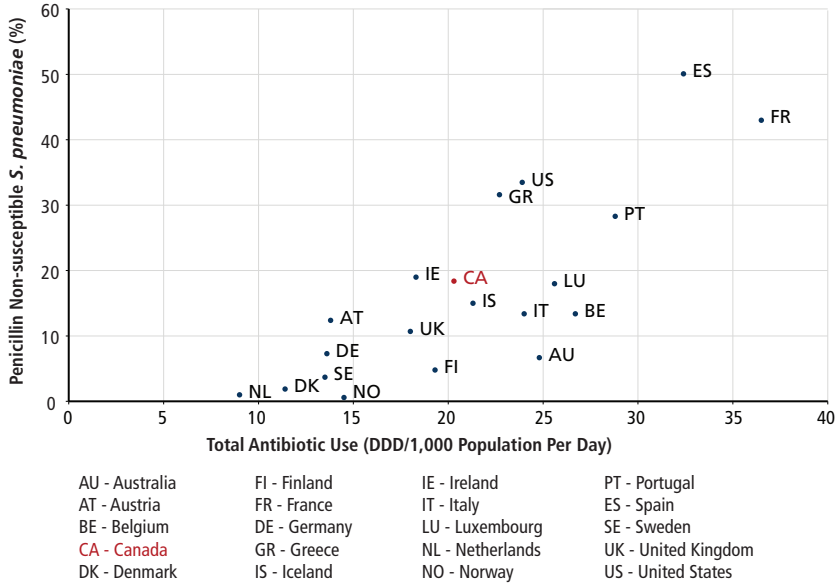
2.1.1 AMU in Humans Leads to AMR in Humans

There is clear evidence that AMU in humans leads to the evolution of resistance in microbes that affect humans. For example, Goosens *et al.* (2005) examined AMU and AMR in Europe and found that countries with higher use of a class of antibiotic (as measured by out-patient defined daily dose, DDD,[3] per 1,000 inhabitants) also had higher rates of resistance to a particular antibiotic within that class. Significant correlations were identified for all four organisms studied, with the greatest observed between *Streptococcus pneumoniae* non-susceptibility (which includes intermediate and high-level resistance) to penicillins and use of penicillins. Albrich *et al.* (2004) observed similar results when examining the outpatient use of antibiotics and the rate of pencillin-non-susceptibility in *S. pneumoniae* in 20 countries (Figure 2.2). More recently, the Joint Interagency Antimicrobial Consumption and Resistance Analysis also looked at associations between AMU and AMR in Europe (JIACRA, 2017). Significant positive associations were found between AMU and AMR for some combinations of antimicrobials and bacteria, including fluoroquinolones and *Escherichia coli*, and carbapenems and polymyxins in *Klebsiella pneumoniae*. On a smaller scale, within hospitals, there is evidence of a relationship between AMU and AMR for some bacterial species and antimicrobials (e.g., ceftazidime and Gram-negative bacilli) (Lopez-Lozano *et al.*, 2000).

In some instances, reducing the use of a particular antibiotic has led to declines in resistance rates, but not always (Enne, 2009). In Finland, a decrease in macrolide (a class of antibiotic) prescribing led to a significant decrease in the frequency of erythromycin resistance among *S. pneumoniae* (Seppälä *et al.*, 1997). Similarly, in Iceland, a decrease in the use of penicillin led to a decrease in penicillin resistance among pneumococci (Austin *et al.*, 1999), and in Israel a decrease in quinolone prescribing was associated with a decrease in quinolone resistance in *E. coli* (Gottesman *et al.*, 2009). However, in Sweden, a decrease in trimethoprim prescriptions was not associated with any effect on trimethoprim resistance levels in *E. coli* (Sundqvist *et al.*, 2009); and, in the United Kingdom, as sulfamethoxazole prescriptions decreased by 97%, the prevalence of sulphonamide resistance increased in *E. coli* (Enne *et al.*, 2001).

While AMU is linked to AMR, establishing a causal relationship between the frequency of resistance and AMU in humans is not straightforward. Some have modelled the relationship using population genetic models and epidemiological data (Austin *et al.*, 1999), while others have investigated the relationship between AMR and AMU for a specific organism and antimicrobial (Seppälä

3 Defined daily dose is "a standardized metric for human drug use, allowing for comparisons to be made between populations" PHAC (2017a). Refer to the same reference for more information on how this term is defined.



Adapted with permission from Albrich *et al.* (2004)

Figure 2.2

Correlation Between Penicillin Use and Prevalence of Penicillin Non-Susceptible *S. pneumoniae*

There is a positive correlation between the total outpatient use of penicillin in a country, as measured by the defined daily dose (DDD) per 1,000 inhabitants per day, and the proportion of *S. pneumoniae* isolates that are non-susceptible (i.e., with intermediate or high-level resistance) to penicillin.

et al., 1997; Monnet *et al.*, 1998; Bronzwaer *et al.*, 2002; JIACRA, 2017), but no clear relationship exists for all bacteria and all antimicrobials. The lack of a universal relationship between AMU and AMR is not surprising given the complexity of factors affecting the activity of different antimicrobials against different bacterial pathogens, as well as the development and spread of resistance. Additionally, JIACRA (2017) notes a complex epidemiological relationship between resistance and many other factors in addition to AMU; this may account for whether a certain drug and resistance in a certain species of bacteria are significantly associated or not. Other factors may include resistance to other antimicrobials (co-resistance), travel by humans, patient transfers between different healthcare settings, importation and trade of food and live animals (both within and between countries), and the exposure of animals and humans to antimicrobials via the environment (JIACRA, 2017).

2.1.2 AMU in Animals Leads to AMR in Humans

AMU in food and companion animals may lead to the development of AMR that affects humans through a variety of direct or indirect routes. Webb *et al.* (2017) offer multiple examples of how AMU in food-animal production contributes to the selection and dissemination of resistance determinants reaching human populations. Importantly, one of the studies reviewed by Webb *et al.* (2017) showed how AMU in animals contributed to resistance to the third-line antibiotic colistin, which is now classified as a critically important antimicrobial (WHO, 2016a). In countries like Canada, where there are generally drinking-water treatment and sewage systems, and where most people have little or no direct contact with food-producing animals, the transmission of resistant bacteria from agricultural sources is primarily foodborne through the contamination of meat during slaughter and processing (McEwen & Collignon, 2018). There may also be indirect transmission of resistant bacteria to humans from fruits and vegetables contaminated by manure or irrigation water (McEwen & Collignon, 2018).

Using the same antimicrobials in farm animals that are used to treat human infections increases the likelihood that human pathogens will develop resistance or cross-resistance (Shea, 2003; Tang *et al.*, 2017). Complex host-pathogen-environmental factors determine whether infection occurs after exposure to resistant bacteria which limits the understanding of the extent to which AMU in animals (and the resultant AMR) impacts humans. However, there is good evidence illustrating the contribution of animal AMU to human-pathogen AMR in studies of human gut bacteria with a food-animal origin (e.g., *Campylobacter jejuni*, *Enterococcus faecium*, *E. coli*, non-typhoidal *Salmonella enterica*), as well as livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) (Cameron & McAllister, 2016). A study commissioned by the WHO also shows how AMU in animals "contributed to the selection — and subsequent transfer — of resistance determinants from food animals to humans" for streptothricins, glycopeptides, and colistin (Webb *et al.*, 2017).

The data on ceftiofur-resistant *Salmonella* Heidelberg (*S.* Heidelberg) in chickens and humans present the clearest direct evidence of the impact of AMU in food animals on AMR in humans (Dutil *et al.*, 2010; Seiffert *et al.*, 2013; McEwen & Collignon, 2018). Third-generation cephalosporins are broad-spectrum beta-lactam antimicrobials used widely in both humans and animals (e.g., cefotaxime or ceftriaxone in human medicine, ceftiofur in food animals) (McEwen & Collignon, 2018), and are classified as critically important antimicrobials by the WHO (WHO, 2016a). Ceftiofur is used at times for mass therapy in food-producing animals (McEwen & Collignon, 2018), and ceftiofur resistance gives cross-resistance to ceftriaxone, a first-line antimicrobial used to treat serious

salmonellosis in people (Dutil *et al.*, 2010). The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) (Deckert *et al.*, 2015) showed a high correlation between ceftiofur resistance in both *S.* Heidelberg and *E. coli* indicator bacterial contaminants in chicken products collected at retail stores and ceftiofur-resistant *S.* Heidelberg in humans (Dutil *et al.*, 2010). Voluntary reduction of ceftiofur use in hatcheries was followed by a decline in ceftiofur resistance in *E. coli* in retail chicken, and in *S.* Heidelberg in retail chicken and humans (Dutil *et al.*, 2010; McEwen & Collignon, 2018). As a result of these findings, in 2014, the Chicken Farmers of Canada banned the preventative use of ceftiofur and other critically important antimicrobials against bacterial diseases in chickens (McEwen & Collignon, 2018), and in 2018 extended this ban on preventative use to antimicrobials of high importance (Health Canada's Category II ranking system) (CFC, 2019).

AMU in companion animals may also contribute to AMR in humans, but few studies have explored this relationship. In general, AMR in companion animal pathogens is increasing and is problematic due to close contact between pets and people (Wieler *et al.*, 2011). Since about 2000, there has been a rapid emergence and global spread of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) — a common pathogen in dogs — that is difficult to treat because of multi-drug resistance (Perreten *et al.*, 2010; McCarthy *et al.*, 2014). The increasing prevalence of MRSP was identified as a wake-up call for veterinarians, demonstrating the need for more focus on AMR and improved infection control in companion animals (Lloyd, 2012). There is also evidence that *S. pseudintermedius* impacts human health. There were 24 cases in humans over a two-year period in the Calgary Health Region, 3 of which were methicillin-resistant (Somayaji *et al.*, 2016).

While the contribution of AMU in animals to AMR in humans has not been precisely quantified, recent research has focused on how restricting AMU impacts AMR rates. Two systematic reviews, commissioned by the WHO, assessed whether a restriction of AMU in food-producing animals reduces the presence of resistant bacteria in these animals, and in humans (Tang *et al.*, 2017; Scott *et al.*, 2018). Tang *et al.* (2017) analyzed 13 studies that examined AMR outcomes in human populations following an intervention that restricted AMU in animals; they found AMR decreased by 24% compared to control groups. The authors note that the overall effect of reducing AMU in food animals on the resistomes (antibiotic-resistant genes) of both animals and humans remains unknown (Tang *et al.*, 2017). The second systematic review was narrative, and not a meta-analysis. It concludes that limiting AMU in food animals reduces AMR in food animals and probably reduces AMR in humans, but that the magnitude of the effect could not be quantified (Scott *et al.*, 2018).

Attributing the source of resistant pathogens that affect humans to AMU in food animals should be done with some caution. For example, it was assumed that vancomycin-resistant *Enterococcus faecium* (a type of VRE) emerged in European hospitals because of the use of a glycopeptide, avoparcin, as a growth promoter in European livestock (Kahn, 2017). A European ban on avoparcin in 1997 dramatically reduced VRE in pigs and chickens, but hospital VRE rates varied dramatically across the continent. In some countries (the Netherlands, Sweden), these rates were consistently low, while they fluctuated and increased in others (Belgium, Cyprus, Germany, Greece). Whole genome sequencing has shown that VRE strains in European farm animals are distinct from those in hospitalized human patients (Kahn, 2017).

2.1.3 Antimicrobials Present in the Environment May Lead to AMR in Humans

Many pathogens, as well as the antimicrobials used to treat them, have environmental origins as soil and other environments are sources of highly diverse populations of bacteria (McEwen & Collignon, 2018). There are examples of resistance to a number of antimicrobials in environmental bacteria isolated from pre-antimicrobial-era soil, as well as from areas that have not been exposed to modern antimicrobials (Holmes *et al.*, 2016). The natural environment may therefore play an important role as both a reservoir and source of resistance (Martinez, 2009; Berendonk *et al.*, 2015). There is concern that resistance genes and antimicrobial residues in the environment may impact human health, but more definitive evidence is needed to understand whether there is a link and its relative contribution to AMR that impacts humans.

Specific concerns exist over antibiotics found in natural environments close to areas of agriculture (You & Silbergeld, 2014). Sources of environmental contamination with antimicrobials include AMU in crops. Although the amount of AMU in crops is very small, their application may increase the risk of environmental contamination. Typically, antimicrobials are applied to crops in a fine mist, part of which may settle into the soil or drift off-site (McManus, 2014). However, a number of studies that examined the use of aerosolized streptomycin on fruit orchards found that streptomycin application did not change bacterial community structure, or increase the abundance of resistance genes in orchards (McManus, 2014). The use of manure on croplands also adds antimicrobials to the environment (Levy & Marshall, 2004).

Antimicrobials are also used in fish farming (aquaculture). They are primarily present in food given to fish, which results in their consumption by both healthy and diseased fish; by some estimates, up to 30% of unconsumed medicated food

is deposited in sediments under and around aquaculture sites (Sapkota *et al.*, 2008; Pelletier *et al.*, 2009; Rodgers & Furones, 2009). Of the antimicrobials that are ingested, approximately 80% move "into the environment in unabsorbed form in faeces, or after absorption [through] urine and other secretions" (Armstrong *et al.*, 2005; Cabello *et al.*, 2013). Both unabsorbed and absorbed antimicrobials in the environment can remain in sediment and the surrounding waters for long periods. Many studies show increases in the frequency of resistant bacteria found near aquaculture farms that use antimicrobials, suggesting a causal relationship (e.g., Dang *et al.*, 2007; Gordon *et al.*, 2007; Suzuki, 2010).

Some genetic elements and resistance determinants are shared among "aquatic bacteria, fish pathogens, and human pathogens, and [seem] to have originated in aquatic bacteria" (Cabello *et al.*, 2013). Therefore, there is some evidence that AMU in aquaculture can lead to AMR in humans through several pathways. For example, laboratory and field evidence show that there is transfer of genetic material between bacteria in the aquatic environment and human pathogens, thereby linking the aquatic and terrestrial reservoirs of resistance. Alongside selection and dissemination of resistant bacteria, "excessive [AMU] in aquaculture can have other detrimental impacts on human health" (Cabello *et al.*, 2013). For example, fish products consumed by humans can have higher than allowed residues of antimicrobials, thereby potentially altering human intestinal flora. Additionally, workers in aquaculture sites and food mills may become exposed to antimicrobials and resistant bacteria (Burridge *et al.*, 2010; Castillo Neyra *et al.*, 2012).

Evidence shows that antimicrobial-resistant genes are present in urban sewage. Hendriksen *et al.* (2019) found that, while AMR genes are present in sewage around the world, the abundance and diversity varied by region. Overall, the predicted abundance of AMR in urban sewage in Canada was low (Hendriksen *et al.*, 2019). Concerns exist over whether the release of active pharmaceutical ingredients into the environment during the manufacturing process leads to AMR. Contamination of water, for example, as a result of manufacturing can lead to "elevated concentrations of resistant bacteria" (Wellcome Trust, 2018). There is also evidence that people are at higher risk of infection if they are exposed to water with high levels of resistant bacteria versus if they are not. It is not clear, however, exactly what the significance of manufacturing waste is to environmental contamination (Wellcome Trust, 2018).

2.2 ANTIMICROBIAL USE IN CANADA

In Canada, antimicrobials are primarily used in humans and animals. Adjusting for population size and average mass (i.e., mg drug/kg animal or mg drug/kg human), approximately 1.5 times more antimicrobials were used in animals than humans in Canada in 2016[4] (PHAC, 2017a). New regulations implemented in 2018, however, are expected to significantly reduce AMU in animal agriculture (Section 2.2.2). This section briefly outlines current AMU in humans (within the healthcare system), animals, and other food sources.

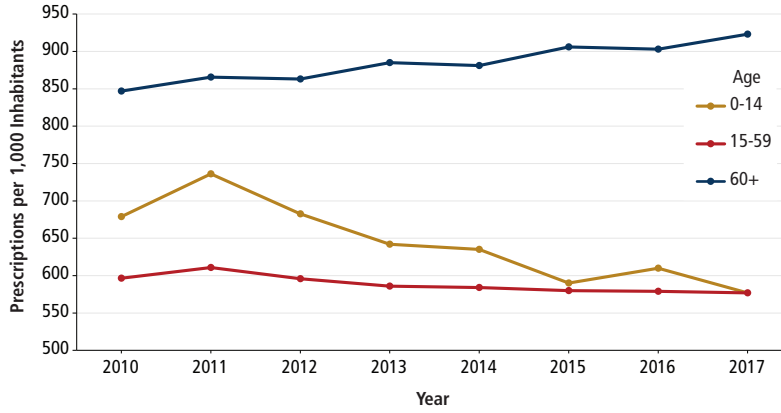
2.2.1 Antimicrobials Form the Basis of Canadian Healthcare

Antimicrobials are an essential part of healthcare systems around the world. They have reduced the economic, medical, and social burden of infectious diseases and are part of many commonplace medical interventions (Davies & Davies, 2010; Smith & Coast, 2012; Laxminarayan *et al.*, 2013). In Canada, the majority of antimicrobials used in humans are available by prescription only (PHAC, 2017a). The majority of AMU in humans occurs in communities (i.e., prescribed by a general practitioner, dentist, or other healthcare provider through a pharmacy); 92% of DDD in 2016 were dispensed through pharmacies, compared to 8% purchased by hospitals (PHAC, 2017a).

In 2015, people in Canada filled more than 25 million prescriptions for antibiotics through a pharmacy (CIHI, 2018c). Overall prescription rates have been lowest among adults aged 15 to 59, followed by children (0 to 14 years). Older adults (60+) have the highest rates by far, which have risen slightly from 2010 to 2017. The prescription rates for children have decreased significantly since 2010, and were approximately equal to the rates for adults in 2017 (PHAC, 2017a). Figure 2.3 illustrates these rates, as measured by antimicrobials dispensed by Canadian pharmacies between 2010 and 2017.

In 2015, Canadian antibiotic prescription volumes, as measured by DDDs, per 1,000 population per day, were approximately equal to the average for OECD countries (CIHI, 2019a). Canada's rate is more than twice that of the Netherlands, the OECD country with the lowest prescribed DDDs, per 1,000 population per day. However, Canada is a heterogeneous federation of provinces and territories, and AMU varies across the country. For example, the DDDs per inhabitant dispensed in community pharmacies in Quebec and the territories is approximately half of what is dispensed in Newfoundland and Labrador, the province with the highest rate of AMU (PHAC, 2016a).

4 This estimate does not include the amount of antimicrobials used in aquaculture (Section 2.1.3) and therefore is an underestimate of the total AMU in animal farming.



Data Source: PHAC, 2017a, 2018a

Figure 2.3

Patterns of Antimicrobial Use by Age Group, 2010–2017

Antimicrobials dispensed by Canadian pharmacies in community settings, as measured by prescriptions per 1,000 inhabitants. Since 2010, the prescription rate has risen slightly for older adults (60+), decreased slightly for adults (15-59), and dropped significantly for children (0-14).

2.2.2 Antimicrobials Are Used in Food Animals and Other Food Sources

AMU is not restricted to human populations. As noted in Section 2.1.2, numerous antimicrobials are used in food-producing animals, many of which are closely related, or identical, to those used to treat human infections (WHO, 2017c; McEwen & Collignon, 2018). Canada is a major food-producing country for both domestic and international markets, and has roughly 19 times more food-producing animals than inhabitants (PHAC, 2016a). Historically, in food-producing animals, antimicrobials were used to prevent disease, promote growth (even in the absence of disease), and treat bacterial infections (Page & Gautier, 2012; PHAC, 2014b, 2017a). In 2014, Canada ranked seventh highest (out of 27 countries) for antimicrobial sales for animals, adjusted by populations and weights, compared to countries in the European Surveillance of Veterinary Antimicrobial Consumption Network (PHAC, 2016a).

In 2016, approximately one million kg of medically important antimicrobials (MIAs) were distributed for sale by Canadian Animal Health Institute member companies. Since 2010, there has been an 11% decrease in the quantity of MIAs per kilogram of animal (PHAC, 2017a). Of the total distribution amount, 99% of AMU was intended for food-producing animals, and 1% for companion animals. Many commonly used antibiotics, including tetracyclines, penicillin, macrolides, and sulphonamides, are used in both human and veterinary medicine in Canada (Page & Gautier, 2012; PHAC, 2017a).

A paradigm shift on the use of antimicrobials in food animals led to changes in federal regulations. These changes, implemented in 2018, should reduce the quantity of AMU in food animals in Canada for three reasons. First, MIAs can no longer be used as growth promoters in food animals, only for either treatment or prevention of disease (GC, 2018). Second, these regulations expand manufacturing requirements according to Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients (APIs) to all veterinary APIs. Pharmacists or veterinarians compounding drugs must hold a Drug Establishment Licence when importing MIAs. The "Own Use Importation" loophole of earlier regulations has also been closed. Third, all MIAs used in food animals now require a veterinary prescription in Canada (GC, 2018). The mechanisms and approaches that will be used for AMU surveillance and benchmarking under the new regulations are under discussion. Regulations in the European Union go further, limiting prophylactic use to single animals (as opposed to groups) (EP, 2018).

Antimicrobials are also used in plant agriculture, although less commonly than in food animals (Williams-Nguyen *et al.*, 2016); Canadian data are scarce, however. Estimates of the total amount of antimicrobials used on crops indicate they are not a major source of AMU (e.g., in the United States in 2011, 13,542 metric tons of antimicrobials were used in food animals, while 36 metric tons were used on crops, or 0.3% of total agriculture use) (FDA, 2014).

As noted in Section 2.1.3, antimicrobials are also used therapeutically and prophylactically in aquaculture (Cabello *et al.*, 2013). There is, however, limited information on both AMU and AMR in this sector (Tusevljak *et al.*, 2013). Aquacultural AMU in Canada and peer countries is generally restricted to avoid use of antimicrobials that are also medically important to humans (Cabello *et al.*, 2013). However, several authors note that data on classes of antimicrobials used in aquaculture in these countries are lacking, because most regulatory agencies do not collect this information (Sapkota *et al.*, 2008; Burridge *et al.*, 2010). Only Denmark and Norway have AMU surveillance programs that monitor aquaculture (DANMAP and NORM-VET, respectively) (DANMAP, 2017; NORM/NORM-VET, 2017), although British Columbia reports total grams of AMU in aquaculture, irrespective of drug class (e.g., DFO, 2017). There are additional difficulties quantifying the amount of AMU in aquaculture: the "large size and geographical extent of the industry," the various methods used, and the large numbers of species of fish and shellfish involved (Cabello *et al.*, 2013). Collecting AMU data is also complicated by types of ownership (family units, village ownership, small businesses, international conglomerates) (Cabello *et al.*, 2013), and by different national, provincial or territorial regulations that do not enable data sharing (Burridge *et al.*, 2010).

2.3 RESISTANT INFECTIONS IN CANADA

Bacterial infections contribute substantially to the burden of disease in Canada. Infections can be acquired in healthcare settings (healthcare-associated infection, HAI), with Gravel *et al.* (2007b) finding that patients acquire a HAI at a rate of 1 per 10 hospital discharges. Bacterial infections can also be acquired in the community (community-acquired infection).

2.3.1 Using a Clinical Syndrome Approach

One of the Panel's first tasks was to estimate Canada's burden of resistant infections. To do this, a method was needed for classifying infections. While studies and reports on AMR often focus on causal pathogens (e.g., PHAC's priority organisms), such an approach puts the focus on biology rather than the people infected. As the Panel was charged with examining the socio-economic impacts of AMR, they sought an approach that would be relatable to both the healthcare providers seeking to identify, treat, and prevent microbial infections, as well as the people who bear the burden of disease caused by the infection. For this reason, the Panel chose to examine AMR through the symptoms of infection and therefore chose a syndrome approach. This approach allowed the Panel to take full advantage of the expertise around the table, as it relates to the presentation, diagnosis, and treatment of disease in Canada.

Syndromes are used to describe a group of associated symptoms that typically occur within a common location in the body. They can be caused by a single pathogen, but more frequently involve multiple pathogens. In short, it is a syndrome that presents at a practitioner's office or hospital, not a particular pathogen. Having said this, the syndrome approach does not discount the importance of pathogens and the drugs used to treat them; rather, it simply examines them through the lens of an individual (i.e., the symptoms they experience). This approach recognizes that not every person with a given syndrome will have the same causal pathogen(s), but also that a single pathogen can cause a variety of different syndromes. Syndromes may also have variable impacts depending on patient characteristics, including age, prior treatment with antimicrobials, and overall health.

The Panel chose to examine syndromes that can be caused by bacteria and that have the greatest impact on mortality and morbidity in Canada. While this approach is not based directly on causal pathogens, by examining syndromes with the greatest impact in Canada, the most relevant pathogens are included. Using these criteria, the Panel first identified nine important clinical syndromes in Canada: bacterial gastro-intestinal infections (BGIs), bloodstream infections (BSIs), intra-abdominal infections (IAIs), musculoskeletal infections (MSIs),

pneumonia, sexually transmitted infections (STIs), skin and soft tissue infections (SSTIs), tuberculosis (TB), and urinary tract infections (UTIs). The Panel then identified a tenth important syndrome, *Clostridioides difficile* infections (CDIs). While CDIs could be considered BGIs, they are distinct from all of the other clinical syndromes. *C. difficile* is naturally resistant to many antimicrobials (Bloomfield & Riley, 2016), and are almost always contracted either during or following antimicrobial treatment (Barbut & Petit, 2001). During treatment, antimicrobials disrupt the normal gut flora, which allows *C. difficile* to both establish itself and proliferate in the colon (Barbut & Petit, 2001). Because people with a resistant infection are more likely to require longer or multiple courses of antimicrobials (as compared to susceptible infections), AMR therefore increases the risk a person will acquire a CDI. Like all bacteria, *C. difficile* can also evolve to have AMU-related resistance, which may contribute to infection.

While these 10 syndromes do not represent all resistant microbes that infect people in Canada, in the Panel's experience, they do represent the majority of cases. Each of these syndromes may be acquired in healthcare settings or in the community. There is overlap between the 10 clinical syndromes and the syndromes caused by the priority AMR organisms identified by both PHAC and the WHO (Table 2.1). The third column in Table 2.1 demonstrates that the same organism may cause different syndromes and that a given syndrome may be caused by different organisms. More details on some of the specific organisms that may lead to the 10 important clinical syndromes are provided below.

Table 2.1

PHAC and WHO Global Antimicrobial Resistance Surveillance System (GLASS) Priority Organisms

PHAC First-Tier Organisms	WHO GLASS Priority Organisms	Panel's Important Clinical Syndromes
Clostridioides difficile		*Clostridioides difficile* infection (CDI)
Extended-spectrum beta-lactamase (ESBL)-producing organisms	*Escherichia coli* *Klebsiella pneumoniae*	Bacterial gastro-intestinal infection (BGI) Pneumonia Intra-abdominal infection (IAI) Urinary tract infection (UTI) Skin and soft tissue infection (SSTI)

continued on next page

PHAC First-Tier Organisms	WHO GLASS Priority Organisms	Panel's Important Clinical Syndromes
Carbapenem-resistant organisms (*Acinetobacter* spp. & Enterobacteriaceae spp.)	*Acinetobacter baumannii* *Escherichia coli* *Klebsiella pneumoniae*	Bacterial gastro-intestinal infection (BGI) Pneumonia Bloodstream infection (BSI) Intra-abdominal infection (IAI) Urinary tract infection (UTI) Skin and soft tissue infection (SSTI)
Enterococcus spp.		Bloodstream infection (BSI) Intra-abdominal infection (IAI) Musculoskeletal infection (MSI) Urinary tract infection (UTI)
Neisseria gonorrhoeae	*Neisseria gonorrhoeae*	Sexually transmitted infection (STI)
Streptococcus pyogenes (Group A Streptococcus) and *pneumoniae*	*Streptococcus pneumoniae*	Pneumonia Skin and soft tissue infection (SSTI) Musculoskeletal infection (MSI)
Salmonella spp.	*Salmonella* spp.	Bacterial gastro-intestinal infection (BGI)
Staphylococcus aureus	*Staphylococcus aureus*	Bloodstream infection (BSI) Intra-abdominal infection (IAI) Musculoskeletal infection (MSI) Skin and soft tissue infection (SSTI)
Mycobacterium tuberculosis		Tuberculosis (TB)
Campylobacter spp.		Bacterial gastro-intestinal infection (BGI)
	Shigella spp.	Bacterial gastro-intestinal infection (BGI)

Data Source: PHAC (2017a) and WHO (2017a)

There is significant overlap between the organisms identified by PHAC and the WHO as particularly relevant for antimicrobial resistance. Furthermore, the organisms identified by PHAC and the WHO are often the cause of the Panel's 10 important clinical syndromes.

Below are brief descriptions of the 10 important clinical syndromes; their incidence, resistance, mortality, and morbidity are discussed in Section 2.3.2.

Bacterial Gastro-Intestinal Infections (BGIs)

BGIs are caused by pathogenic bacteria in the gut, which cause gastroenteritis, the inflammation of the gastrointestinal tract, possibly involving both the stomach and the intestine. Symptoms include vomiting, severe abdominal cramps, fever, and diarrhea. These infections are most often caused by ingesting contaminated food or water. Common causes of infection include *Shigella* species (sources include contaminated water), *Salmonella enterica* (sources include contaminated beef, poultry, dairy, and eggs), *Campylobacter jejuni* (sources include contaminated beef, pork, and poultry), and *E. coli* (sources include contaminated beef and vegetables) (Heredia & García, 2018).

Bloodstream Infections (BSIs)

BSIs occur when bacteria are present in the blood (bacteremia), which frequently invokes an immune response (sepsis) consisting of symptoms such as fevers, chills, and hypotension. Septic shock is a subset of sepsis involving persistent hypotension, which is associated with a high mortality rate (Singer *et al.*, 2016). Bacteria can infect the bloodstream because of complications from other infections (such as pneumonia), during surgery, or due to catheters or other foreign bodies entering veins or arteries. BSIs are a major cause of "infectious disease morbidity and mortality worldwide" (Laupland & Church, 2014).

Clostridioides difficile Infections (CDIs)

As discussed above, all CDIs are caused by the same bacteria (*C. difficile*) and often occur following antimicrobial treatment. *C. difficile* is naturally resistant to many antimicrobials. The symptoms of CDIs can range from mild diarrhea to more serious complications, such as colitis (Barbut & Petit, 2001). While traditionally CDIs were largely acquired in healthcare settings, in the last 20 years, community-associated cases have become increasingly common (Bloomfield & Riley, 2016).

Intra-Abdominal Infections (IAIs)

IAIs are infections of the abdominal cavity by pathogenic bacteria. These types of infections are either uncomplicated, where they involve one organ, or complicated, where the infection spreads beyond the initial organ, into the peritoneal space, resulting in inflammation of the peritoneum or abscess (Walkty & Karlowsky, 2012).

Musculoskeletal Infections (MSIs)

MSIs are infections of muscle and bones by pathogenic bacteria. These can include osteomyelitis (bacterial infection of the bone), myositis (bacterial infection of the muscle), and septic arthritis (bacterial infection of the joint). Complications from these types of infections may result in long-term morbidity (Fayad *et al.*, 2007).

Pneumonia

Pneumonia is an infection in one or both lungs stemming from bacteria, viruses, or fungi. While there are other important respiratory diseases in Canada, pneumonia is responsible for the vast majority of incidence of respiratory disease that are microbial in origin. This report focuses on bacterial pneumonia, which is the most common type of pneumonia in adults. Most pneumonia in Canada is treated with antimicrobials. In 2016, about 80% of pneumonia diagnoses were given an antimicrobial recommendation (PHAC, 2017a).

Sexually Transmitted Infections (STIs)

STIs are spread by sexual activity. In some cases, STIs do not initially cause symptoms, which can result in greater risk of transmission. Over 30 different bacteria, viruses, and parasites can be transmitted through sexual activity (WHO, 2019b). Symptoms may include genital discharge, ulcers, and pelvic pain. The negative impacts of STIs are often predominately felt by women and the very young. For example, gonococcal infections in women that are untreated or inadequately treated may cause serious complications like pelvic inflammatory disease, infertility, ectopic pregnancy, premature birth, low birth weight, or neonatal gonococcal conjunctivitis (eye infection due to passage of gonorrhea from a mother to a child during pregnancy, delivery, or immediately after birth) (Eschenbach *et al.*, 1975; Donders *et al.*, 1993; Skerlev & Čulav-Košćak, 2014; Heumann *et al.*, 2017). Bacterial STIs include chlamydia, gonorrhea, mycoplasma, and syphilis (and does not include HIV). The Panel uses gonorrhea as a representative STI throughout this report.

Skin and Soft Tissue Infections (SSTIs)

SSTIs result from microbial infection of the skin and supporting structures. They include infections of the skin and underlying soft tissue, and have a wide variety of presentations, from cellulitis (red, swollen areas of infected skin) to necrotizing fasciitis (infection where skin and underlying muscle are destroyed) (Ki & Rotstein, 2007). SSTIs can be simple — resulting from a single bacterium and infecting a localized area — or they can be complicated, with multiple bacteria present within the infected area, leading to systemic inflammation. Between 7 and 10% of hospitalized patients are affected by SSTIs, and they are especially common in emergency care settings (Ki & Rotstein, 2007).

Tuberculosis (TB)

Like CDIs, TB is caused by a single bacterium (*Mycobacterium tuberculosis*). While TB can affect any part of the body, it usually affects the lungs, presenting as a respiratory infection (PHAC, 2017a). TB can be divided into latent TB (where a person is infected with TB but the bacteria are in an inactive state and a person shows no symptoms and is not contagious) and active TB (where the TB can be transmitted to others and the person exhibits symptoms). Symptoms of active TB include coughing, coughing up blood, chest pain, weight loss, fatigue, fever, and night sweats and chills (CDC, 2019). While TB is not prevalent across Canada, it is a serious problem in certain communities (e.g., among Inuit in the North (ITK, 2018)).

Urinary Tract Infections (UTIs)

UTIs can affect any part of the urinary system (kidneys, ureters, bladder, and urethra). A UTI is classified as either lower (confined to bladder) or upper (pyelonephritis — infection of the kidney), and as either complicated or uncomplicated (Foxman, 2010). Symptoms of UTIs include a burning feeling when urinating, frequent and intense urges to urinate, pain and pressure in the lower back or abdomen, discoloured and strange-smelling urine, and fever or chills. UTI diagnosis is made using a combination of urinary symptoms together with a urine culture growing a uropathogen above a given concentration (Foxman, 2010). In aging populations, the most frequent bacterial infections are UTIs (Nicolle, 2013).

2.3.2 AMR Leads to a Significant Number of Infections and Deaths in Canada

For each important clinical syndrome, the Panel used published data to estimate how frequently these infections occur (incidence), the percentage of infections resistant to one or more first-line antimicrobials (resistance) (Table 2.2), the percentage of infections that lead to death (mortality), and the length of stay in hospital (morbidity) (Table 2.3). The derivations for these estimates are described in Appendix A. The expertise of Panel members was essential for both identification of the relevant literature, and for ensuring these values were consistent with Canadian clinical experience.

First-line antimicrobials are defined as those being prescribed first for a particular syndrome. The Panel notes that what is considered a first-line antimicrobial for a given syndrome will vary by location, patient history, and time. For instance, if resistance to a particular antimicrobial becomes relatively ubiquitous, physicians will cease to prescribe that antimicrobial (Section 2.3.3), and a patient with a history of infection may be prescribed a different treatment than someone with their first infection. The Panel notes that adaptive

prescribing makes identifying what is considered a first-line antimicrobial challenging, and therefore has clearly identified the antimicrobials considered in Appendix A. Where possible, Canadian data were used to establish these estimates; however, international data were used to fill in gaps in Canadian data. The Panel's expertise was critical for evaluating the international data selected to ensure they were approximately consistent with the Canadian context. That international data needed to be used highlights the important data gaps in Canadian surveillance of the important clinical syndromes. Filling these gaps would be beneficial for targeting efforts related to AMR in Canada, and would allow the measurement of the effectiveness of any interventions meant to reduce incidence or resistance of infections.

Incidence, resistance, and mortality rates were used to estimate the number of infections, resistant infections, and deaths in 2018, based on the total population of Canada (StatCan, 2018d) (Tables 2.2 and 2.3). These estimates are unique in that they are specifically focused on Canada, have a strong evidentiary base, and have benefited from the vast clinical expertise provided by the Panel. They offer a snapshot of the current health impacts of AMR in Canada, and inform the hospital costs of AMR (Chapter 3) and the costs to the economy (Chapter 4). Of the 10 important clinical syndromes, SSTIs were by far the most common infection type in 2018, followed by UTIs, IAIs, and pneumonia. The most resistant infections are MSIs and SSTIs.

The Panel notes that, because of the lack of high-quality data for all of the syndrome parameters, these values should not be considered precise, but rather approximations. For one, the incidence rates used are based on formal diagnoses, which means only confirmed infections are used to produce the estimates listed in Table 2.2.[5] In some cases (IAIs, pneumonia, UTIs), only infections associated with hospitalization are included in the estimates. This means many infections are not included. For example, many people who experience BGIs in the community do not seek medical attention and/or are therefore never formally diagnosed. The mortality rates for some conditions in Table 2.3 are likely higher than they would be if all infections were considered. This is because infections that do not lead to hospitalization often go unreported, while patients with severe infections will generally end up in hospital, as will those who have other serious concurrent medical conditions. The metric used for morbidity and additional length of stay in hospital does not take into account factors such as lost days of work due to an infection that does not require hospitalization.[6]

5 The incidence estimates may be more accurate for STIs (modelled by gonorrhea), TB, and CDIs, as these three infections are nationally notifiable (GC, n.d.).

6 Additional length of stay in hospital was used to measure morbidity for all infections except STIs, which used estimates of Disability-Adjusted Life Year (DALY). The rationale for using this different metric is provided in Appendix A.

Table 2.2

Estimates of the Number of Infections and Resistant Infections Associated with the 10 Important Clinical Syndromes in Canada in 2018

Syndrome	Incidence*		Resistance‡		Source(s)
	Rate (per 100,000)	Cases†	Rate (%)	Cases	
Bacterial gastrointestinal infection (BGI)	55	20,382	15	3,057	Vrbova *et al.*, 2012; PHAC, 2017a
Bloodstream infection (BSI)	91.4	33,872	9.3	3,150	Laupland *et al.*, 2007a; Laupland *et al.*, 2008b; Laupland *et al.*, 2008c; Laupland *et al.*, 2013
C. difficile infection (CDI)	109.2	40,468	11.58	4,686	Levy *et al.*, 2015; CNISP, 2018
Intra-abdominal infection (IAI)	287.3	106,470	22.4	23,849	Edelsberg *et al.*, 2008; CIHI, 2013; Sartelli *et al.*, 2013
Musculoskeletal infection (MSI)	104	38,541	34.8	13,412	Sarkissian *et al.*, 2016; Miller & Polgreen, 2019
Pneumonia	248	91,906	22.1	20,311	Ye *et al.*, 2008; Jain *et al.*, 2015
Sexually transmitted infection (STI)	55	20,382	3.40	693	PHAC, 2017a
Skin and soft tissue infection (SSTI)	1073	397,642	32.0	127,245	Borgundvaag *et al.*, 2013; Miller & Polgreen, 2019
Tuberculosis (TB)	4.9	1,816	8.1	147	LaFreniere *et al.*, 2019a; LaFreniere *et al.*, 2019b
Urinary tract infection (UTI)	613	227,171	23.9	54,294	Zilberberg & Shorr, 2013; Koningstein *et al.*, 2014; CIHI, 2018a
Canadian Totals¶	**2,641**	**980,000**	**25.6**	**250,000**	

Summary of the number of bacterial infections and resistant infections associated with the 10 important clinical syndromes in Canada in 2018. The infection and resistance rates used for these calculations are also provided. Details for how these rates were determined can be found in Appendix A.

*Incidence rates are based on literature values for confirmed infections and are therefore likely to be underestimated. In three cases (IAIs, pneumonia, UTIs), only infections associated with hospitalization are included in the estimate — see Appendix A for further details. †Calculated using the estimated Canadian population in Q3 in 2018 (StatCan, 2018d). ‡Resistance rates are estimated based on available data and Panel expertise — see Appendix A for more details. ¶The Canadian totals for cases are rounded due to the uncertainty in the estimates.

Table 2.3

Estimates of the Number of Deaths and the Morbidity Associated with Resistant Infections for the 10 Important Clinical Syndromes in Canada in 2018*

Syndrome	Total Mortality†		Additional Mortality‡		Additional Morbidity§		Source(s)
	Rate (%)	Deaths	Rate (%)	Deaths	LOS (Days per Infection)	Total LOS (Days)	
Bacterial gastrointestinal infection (BGI)	0.1	3	0.04	1	2.33	7,124	Marano *et al.*, 2000 as cited in Travers & Barza, 2002; Smith *et al.*, 1999; Nelson *et al.*, 2004; Varma et al., 2005
Bloodstream infection (BSI)	20.0	630	7	221	10.6	33,391	Laupland *et al.*, 2007a; Laupland *et al.*, 2013; Kim *et al.*, 2014; Thampi *et al.*, 2015; PHAC, 2017a
C. difficile infection (CDI)	4.5	211	2.45	115	13.6	63,733	Levy *et al.*, 2015; Leal, 2019
Intra-abdominal infection (IAI)	9.5	2,266	8.2	1,956	4.6	109,707	Edelsberg *et al.*, 2008
Musculoskeletal infection (MSI)	2.8	376	1.72	231	5	67,062	Al-Nammari *et al.*, 2007; Sarkissian *et al.*, 2016; Miller & Polgreen, 2019
Pneumonia	10.2	2,072	1.8	366	1.33	27,014	Lambert *et al.*, 2011; Zilberberg *et al.*, 2017
Sexually transmitted infection (STI)	0.1	1	0.1	1	1.5	1,040	Ebrahim *et al.*, 2005
Skin and soft tissue infection (SSTI)	1.4	1,781	0.5	636	2	1.4	Weigelt *et al.*, 2010
Tuberculosis (TB)	4.6	7	0	0	76.5	11,252	Marks *et al.*, 2016; Ronald *et al.*, 2016
Urinary tract infection (UTI)	12.4	6,732	3.5	1,900	5.6	304,045	Zilberberg & Shorr, 2013
Canadian Totals¶	**5.6**	**14,000**	**2.2**	**5,400**	**3.5**	**880,000**	

Summary of the mortality and morbidity associated with resistant infections for the 10 important clinical syndromes in Canada in 2018. The total mortality, additional mortality (relative to susceptible infections), and morbidity rates used for these calculations are also provided. Details for how these rates were determined can be found in Appendix A. *Calculated using number of resistant infections in Table 2.2. †*Total mortality rate* refers to the mortality due to resistant infections. Mortality rates are likely overestimated, as infections that are not formally diagnosed and/or do not lead to hospitalization are less likely to lead to death. ‡*Additional mortality rate* refers to additional deaths that occur because an infection is resistant (i.e., the difference in rate as compared to susceptible infections). §*Additional morbidity* was calculated using length of hospital stay (LOS) for all syndromes except STIs, which used Disability-Adjusted Life Years (DALYs), and non-CDI BGIs, which used days with diarrhea. ¶The Canadian totals for deaths and LOS are rounded due to the uncertainty in the estimates.

The Panel also notes that the estimated rates in Tables 2.2 and 2.3 are drawn from diverse populations, geographies, years, and sample sizes (Appendix A). The Panel's expertise was therefore critical for ensuring the validity of these approximate estimates in the contemporary Canadian context, and for filling in gaps when no literature values were available.

The estimates in Table 2.3 demonstrate that AMR is already a serious problem in Canada and responsible for significant negative health outcomes. Based on the 10 important clinical syndromes, people in Canada acquired at least 250,000 resistant infections in 2018;[7] over 14,000 deaths were caused by infections that were resistant to first-line treatment (Figure 2.4). Furthermore, 5,400 of these deaths, or almost 15 a day, could be considered to be directly attributable to AMR itself. In other words, these 5,400 deaths would not have occurred had the people had a susceptible infection. These results suggest that 4 out of every 10 deaths from a resistant infection would not have occurred if the infection were not resistant (Figure 2.4). In 2018, AMR was therefore the attributable cause of only slightly fewer deaths in Canada than Alzheimer disease in 2016 (StatCan, 2019).

Based on the Panel's estimates, the average mortality rate of resistant infections is 5.6%, compared to 4.1% for susceptible infections. In 2018, there were almost 730,000 total bacterial infections related to the 10 important syndromes in Canada that were susceptible to first-line antimicrobials. These infections were the attributable cause of death of just under 30,000 people. If all of these infections were resistant to first-line antimicrobials, however, more than 10,000 *additional* people would have died in Canada.

Importantly, an infection that is resistant to first-line antimicrobials does not mean that there is no available treatment. In most cases, antimicrobials are available to treat resistant infections (e.g., second-line therapies) if the first course of treatment fails. Despite this, as discussed, resistant infections have a higher mortality rate as compared to susceptible infections. This is likely due to complications centred on delays in acquiring effective treatment. This can include an increased need for other procedures (e.g., surgery) as a result of an infection not responding to treatment (Cosgrove, 2006). Delays in effective treatment may be especially problematic in the context of patients who have other medical conditions that made them more susceptible to infections in the first place (Section 5.1).

7 The numbers for infections and resistant infections in Canada are likely underestimated, as some syndrome estimates only include cases that result in visits to a hospital.

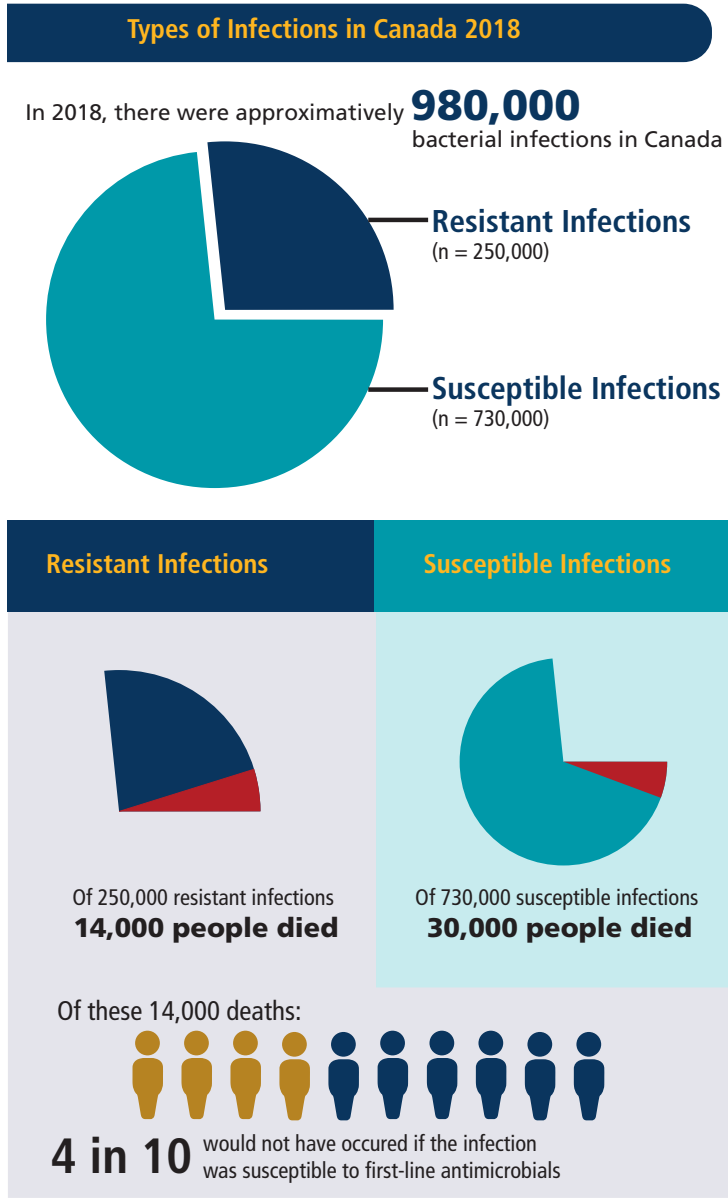


Figure 2.4

Resistance and Mortality of Bacterial Infections in Canada for the 10 Important Clinical Syndromes

The Panel estimates that there were just under one million bacterial infections in Canada in 2018 leading to one of the 10 important syndromes. Approximately a quarter of these infections were resistant to first-line antimicrobials. In that same year, it is estimated that approximately 4 in 10 of those who died from resistant infections would have survived were their infection susceptible to first-line antimicrobials.

The current morbidity of resistant infections is also high, with an estimate of 880,000 lost days (or over 2,400 years) in 2018. Discussion of current and potential future impacts of AMR on healthcare costs and the economy can be found in Chapters 3 and 4, respectively.

2.3.3 Resistance Rates Are on the Rise

Based on the Panel's research, the average resistance rate to first-line antimicrobials in Canada was 26% in 2018. This means that one in every four bacterial infections is already resistant to a first antimicrobial treatment choice. This level of resistance is not unique to Canada, with the OECD (2018a) finding that average resistance in G20 countries was about 30% in 2015.

The *average* resistance rate is only part of the story since infection resistance rates are lower for some bacteria, while for others the rates are significantly higher. For example, a study of patients with acute purulent SSTIs presenting at Canadian hospital emergency departments and health centres found that 32% of the infections were due to MRSA[8] (versus methicillin-susceptible *Staphylococcus aureus*, or MSSA) (Borgundvaag *et al.*, 2013). Additionally, there are infections, such as multi-drug-resistant (MDR) gonorrhea (the second most common STI in Canada), for which the Canadian healthcare system is already using antibiotic treatments of last resort (WHO, 2017d; Smyczek *et al.*, 2019). For example, in the absence of new effective agents to treat resistant gonorrhea, growing resistance may "lead to a situation reminiscent of the pre-antibiotic era where there were no effective treatments for gonorrhea" (Dillon *et al.*, 2015).

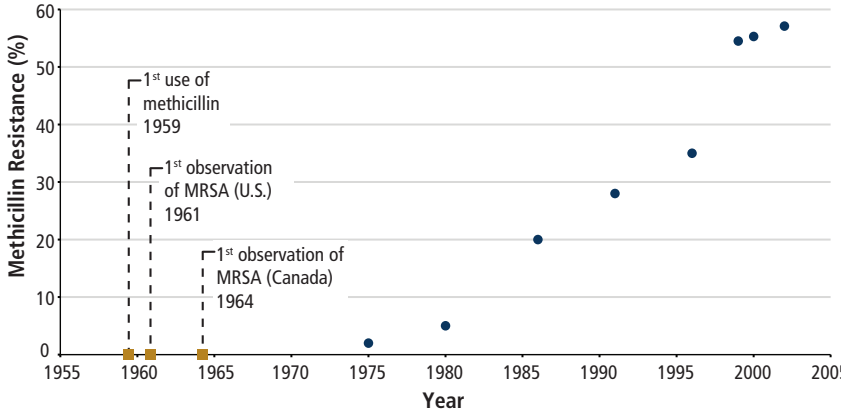
The first-line resistance rates listed in Table 2.2 are the best estimates of current rates of resistance based on the Panel's research and assessment, but these rates will undoubtedly change in the future. If treatment recommendations do not change (i.e., if the same antimicrobial continues to be prescribed as the first-line treatment), it can be expected that resistance rates will rise over time. There is evidence that when an antimicrobial is in frequent use, resistance arises and can spread quickly. For example, it was observed that the rate of resistance of *S. aureus* to penicillin (which used to be the first-line treatment for infections caused by that bacterium) reached 25% for HAIs only six years after the drug was introduced during the Second World War. While it took longer for penicillin resistance to spread to community-acquired *S. aureus* infections (15 to 20 years to reach 25% resistance), within 30 years the overall resistance rate had dramatically climbed to 80% (Chambers, 2001).

8 *S. aureus* that is resistant to anti-staphylococcal beta-lactam antibiotics (e.g., methicillin, oxacillin, and cefazolin) (PHAC, 2017a).

In response to these rising penicillin resistance rates, new antibiotics were deployed more widely. MRSA was observed within two years following the introduction of methicillin in the United States, became more prevalent within just a few years (Ventola, 2015), and over time continued to rise (Figure 2.5). It was estimated that the prevalence of MRSA (relative to MSSA) in the United States in the mid-1980s was 5 to 10% in large urban medical centres and less than 5% in other settings (Chambers, 2001). By the 1990s, the MRSA rate in smaller U.S. hospitals had reached 20%, and by 1998 it was approaching 50% in some intensive care units. In 2001, it was estimated that MRSA rates in U.S. hospitals had reached 50% and similar rates in U.S. communities were expected (Chambers, 2001). Data on resistance rates of *S. aureus* in Canada follow a similar trend. While the overall rate of MRSA infections and colonizations of *S. aureus* in Canadian hospitals was just under 1% in 1995, by 2003 it had grown to almost 10.5% (PHAC, 2005), mirroring the rate of rise observed in the United States. The Panel was unable to identify more recent Canadian data specific to resistance rates of *S. aureus* isolates, illustrating an important research gap in Canada.

Resistance to the next line of treatment for *S. aureus* is also a concern. The first isolates of *S. aureus* that were completely resistant to vancomycin — the antibiotic generally used to treat MRSA — were detected in the United States in 2002 (CDC, 2002). There are also cases of *S. aureus* with reduced susceptibility to vancomycin, and these remain more frequently observed than those with complete resistance (McGuinness *et al.*, 2017). While increasing resistance rates over multiple decades is generally clear, on more short-term and recent time-scales, there are also multiple examples where the resistance rate of bacteria to certain antimicrobials has increased in Canada. Examples include tetracycline-, ciprofloxacin-, and erythromycin-resistant *N. gonorrhoeae*, and streptomycin- and trimethoprim/sulfamethoxazole-resistant *E. coli* (PHAC, 2017a).

These examples demonstrate how resistance rates to antimicrobials increase over time. It is therefore highly likely that the resistance rate to first-line antimicrobials, as it relates to the 10 important clinical syndromes, will increase from where it is today. For this reason, in later chapters where the Panel presents a model that quantifies future economic impacts of AMR, simulations are done assuming both a status quo resistance rate (i.e., using the values in Table 2.2) and an increase to 40% by 2050. Given past trajectories of resistance rates, the Panel is confident that 40% resistance to first-line antimicrobials by 2050 is reasonable and, potentially, even an under-estimate of AMR rates in the future.



Data Source: Farkas-Himsley *et al.* (1964); CDC (1997); NNIS System (1999); Chambers (2001); NNIS System, (2001, 2003); and Cimolai (2010)

Figure 2.5

Methicillin Resistance Rates of *S. aureus* in U.S. Hospitals Over Time

Methicillin was first used as a treatment for *S. aureus* in 1959; hospital-acquired methicillin-resistant *S. aureus* (MRSA) isolates were first observed only two years later in the United States, and in Canada in 1964. Starting in the late 1970s, resistance rates began to climb steadily in the United States.

2.4 CONCLUSION

The growing problem of AMR must be examined holistically in order to gain a full picture of its causes and impacts. AMU in Canada is a ubiquitous and valuable part of healthcare and agriculture. But eventually AMU leads to resistance with misuse, including overuse, acting as an important driver. The effects of AMR are already significant in Canada, with people dying as a result of resistant infections. Using data related to resistance and 10 important clinical syndromes in Canada, the Panel estimates 5,400 deaths in Canada in 2018 could be attributed to AMR, and led to almost 900,000 extra days spent in hospital. In addition to these significant health impacts, the monetary costs of resistant infections are also very high. In the following chapter, the Panel estimates AMR's current and future costs to the Canadian healthcare system.

3

Hospital Costs of Antimicrobial Resistance in Canada

3 Hospital Costs of Antimicrobial Resistance in Canada

Key Findings

Antimicrobial-resistant infections cost approximately $18,000 per patient in 2018.

The most common treatment-resistant infections, skin and soft tissue infections, urinary tract infections, pneumonia, and intra-abdominal infections, account for about 91% of the hospital costs associated with AMR.

AMR's additional cost to the Canadian healthcare system is estimated to have been $1.4 billion in 2018, or about 0.6% of national healthcare spending. This amount is roughly equal to the total expenditure on all hospitals in Newfoundland and Labrador or all physicians in Manitoba.

Based on the Panel's economic model, if resistance to first-line antimicrobials remains at today's rate of 26% or reaches 40% by 2050, Canada's additional hospital costs would increase to $6 to $8 billion per year, respectively.

In 2050, AMR may comprise almost 1% of Canadian healthcare spending if resistance reaches 40%. This amount is roughly equal to the total expenditure on all hospitals in Atlantic Canada or all physicians in Quebec.

Antimicrobials saved the Canadian healthcare system $4.1 billion in 2018. If resistance to first-line antimicrobials reaches 40% by 2050, their failure could cumulatively cost the healthcare system nearly $120 billion.

People in Canada were hospitalized more than three million times in 2018, and about 1 in 10 patients acquired infections (Gravel *et al.*, 2007a; Gravel *et al.*, 2007b; CIHI, 2019b). Antimicrobials are integral to healthcare. For instance, they are given to women delivering by caesarean section, to patients before knee or hip surgery, and to those undergoing chemotherapy for cancer treatment. According to the Panel's estimates, in 2018 there were almost one million bacterial infections that resulted in the clinical presentation of 10 important clinical syndromes (Table 2.2). About 26% of these infections — about 250,000 — were resistant to first-line antimicrobials. Resistant infections are already a problem in Canada, and if rates of resistant pathogens continue to rise, the financial sustainability of the healthcare system will be increasingly under threat. This chapter examines the costs of healthcare-associated infections (HAIs) — an estimated 80,000 in 2018 — drawing on estimates from a range of studies. Using the Panel's economic model, the future hospital costs of AMR are projected to 2050 in three resistance scenarios.

3.1 ESTIMATING THE HOSPITAL COSTS OF ANTIMICROBIAL-RESISTANT INFECTIONS

Resistant infections are more difficult to treat, requiring lengthier hospital stays and longer courses of antibiotics and other therapies (Gandra *et al.*, 2014), and as a result more care by hospital personnel. As Valiquette *et al.* (2014) note, "although it is difficult to estimate...[the] spending attributed to the management of nosocomial [healthcare-acquired] infections, overuse and/or misuse of antimicrobials, and [community-acquired] infections due to multi-drug-resistant bacteria is significant." Yet despite this known healthcare burden and the growing need for cost containment, relatively few studies have examined the costs of AMR in Canada. In order for the Panel to do so, it examined six Canadian studies and a dozen international studies that estimate the hospital costs of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL) gram-negative bacteria, and *Clostridioides difficile* infections (CDI). These studies were identified by an iterative search process and vetted by Panel expertise. Collectively, they reveal a range of cost estimates (using various methods) across patient populations and locations.

Given this range, the Panel did not simply use the average of different studies to establish estimates for the costs of resistant infections in Canada. Rather, it considered all of these studies and then used members' expert judgment to establish which values best represented the average costs of resistant bacterial HAIs in Canada. These bacterial estimates were then converted into cost estimates for the 10 important syndromes the Panel identified in Section 2.3. The estimates that follow are based on hospital costs (Section 3.1.2)[9] and do not reflect non-hospital costs, for which there are limited data.

3.1.1 The Average Cost of a Resistant Bacterial Infection in Hospital Is Estimated to Be $18,000

The three most common antimicrobial-resistant bacteria found in Canadian hospitals are MRSA, VRE, and ESBL gram-negative bacteria (Valiquette *et al.*, 2014; PHAC, 2017a). Despite decreasing incidence, CDI (which can be susceptible or resistant) causes more infections in people in Canada than MRSA, VRE, or ESBL gram-negative bacteria (PHAC, 2017a). Most estimates of healthcare costs are undertaken for a specific bacterium, and in the context of hospitals. This is because data about in-hospital morbidity, mortality, and costs associated with treatment are relatively easy to retrieve, and hospitals

9 All values reported in this chapter have been converted into 2018 Canadian dollars using the Bank of Canada yearly exchange rates and inflation calculator, unless otherwise noted.

are most likely to implement changes in response to information assessed at the hospital level. However, there is variation within hospital cost estimates because of the variability in morbidity and mortality associated with different pathogens and the syndromes they cause. For example, the mortality and morbidity burden for a patient with a BSI may be different depending on the causative pathogen (e.g., MRSA, VRE). All else being equal, a patient with a BSI caused by MRSA may spend a different amount of time in the hospital, receive different antimicrobial therapy, and experience different complications than if their BSI were caused by VRE. Furthermore, as Gandra *et al.* (2014) point out, current estimates of the disease burden of antimicrobial-resistant bacteria vary widely because of heterogeneity in study populations, control groups, bacteria with different virulence and pathogenicity, infection location, definitions of resistance, and other factors. These limitations render it difficult to accurately estimate the cost of resistant bacterial infections, which in turn adds further uncertainty to estimates of hospital costs of syndromes (Section 3.1.2).

The majority of studies to date have compared outcomes among patients infected with a resistant bacterium with outcomes among uninfected control subjects selected on the basis of health or other demographic criteria. Such a comparison measures the cost of having a resistant infection rather than no infection, resulting in a much higher estimate of cost than is directly attributable to the resistant bacteria. The calculations carried out by the Panel in Section 3.2 reflect the cost of resistant infections relative to no infection, because for some bacteria these are the only data available.

Other studies, by contrast, compare outcomes in patients infected with a resistant strain of bacteria to patients infected with a susceptible strain of the same bacteria. This provides a measure of the *attributable* cost of resistance by comparing, for example, infections caused by MRSA to those caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). In some cases, such studies demonstrate that there can be a significant additional cost associated with resistant infections. It is also important to adjust for differences in hospital length of stay (LOS) before the onset of infection in patients with resistant infections and in the comparison group. There is a direct correlation among hospital LOS before infection with its cost, future LOS, and mortality (Gandra *et al.*, 2014). In addition, care must be taken to control for pre-infection illness severity and co-morbidities. Appendix B describes these and other methodological challenges.

MRSA Infection

S. aureus is a bacterium that can cause infections in different parts of the body — symptoms are dependent on the site of infection. Most often, it causes mild infections on the skin, such as sores or boils. However, it may also cause more serious SSTIs, BSIs, pneumonia, or MSIs. MRSA infections are associated with a number of different syndromes, and the costs associated with these types of infections are dependent on both the location of the infection and patients themselves. For example, Box 3.1 describes a fatal case of MRSA pneumonia, but also shows how the same bacterial strain can cause different types of infections in different people.

Box 3.1
Pneumonia in an Ontario Teen After He Acquired a MRSA Infection in Texas

In 2006, a 17-year-old Ontario high school student (Patient A) and his family stayed with relatives in Houston, Texas. One of these relatives had recently suffered from an MRSA infection. A few weeks later, the teenager presented to a Scarborough emergency department with fever, shortness of breath, and a dry cough that started two days earlier. He quickly developed respiratory distress and hypotension, and was moved to the ICU to be intubated and ventilated. Patient A was diagnosed with severe community-acquired necrotizing pneumonia with septic shock and was treated with six antimicrobials. Despite aggressive supportive care, he died five days after admission. A fluid sample from his lungs grew a common North American community-associated MRSA strain (CMRSA-10) and influenza A virus. Months after Patient A's death, his father and 19-year-old sister developed MRSA SSTIs. The authors hypothesized that the family members were colonized with MRSA either during the Texas visit or Patient A's illness.

(Adam *et al.*, 2007)

The hospital costs of MRSA have been widely estimated in the academic literature. There is large variation in these estimates, however, for the reasons outlined above (e.g., heterogeneity in study populations, control groups, bacteria with different virulence) as well as because of variation in healthcare spending by country (OECD, 2017) and degree of infection resistance. For example, in South Korea, Joo *et al.* (2013) and Kim *et al.* (2014) estimate the cost per patient infected with MRSA to be $5,809 (total cost) and $13,603 (relative to susceptible

infection) for BSI patients and hospital-acquired BSI patients, respectively. Some of this variation is likely because the estimates are from different populations and locations. Nelson *et al.* (2015a) estimate the in-patient cost of MRSA infections among approximately 400,000 U.S. veterans to be about $15,309 per patient (relative to patients with no infection), whereas Shorr (2010) found that the median cost for 87 patients with MRSA pneumonia was only slightly more ($1,489) than those with MSSA in a Detroit hospital. In a North Carolina hospital, Engemann *et al.* (2003) found that the median hospital cost for MRSA surgical site infections (SSIs, a type of SSTI) ($188,396) is significantly higher than the median cost for MSSA SSIs ($107,680), and patients with either type of infection cost significantly more than patients without infection ($60,081). As mentioned above, the variation in estimates may be attributable to the methods used to estimate cost (e.g., multivariate regression, propensity score matching, conventional costing) (Nelson *et al.*, 2015b).

Table 3.1 summarizes four Canadian studies of MRSA infections, which report median hospital costs per patient. Thampi *et al.* (2015) compare 58 MRSA patients to 377 MSSA patients in four Ontario hospitals, finding that MRSA BSIs cost $21,511 per patient, an increase of $8,223 over patients with MSSA BSIs. When combined with similar findings in Kim *et al.* (2001) ($21,158), Goetghebeur (2007) ($12,371), and Rosner *et al.* (2004) ($10,080), the average cost per MRSA patient is $16,280, which the Panel takes to be an estimate of the hospital cost of MRSA in Canada.

Table 3.1

Estimates of the Hospital Costs of MRSA, Summary of Four Canadian Studies

Syndrome	Region or City	Hospitals	Sample Size	Methods	Year	Cost	Reference
BSI	Toronto	4	58 MRSA 377 MSSA	Propensity score matching; costs from Ontario Case Costing Initiative	2007–2010	$21,511 (total cost) $8,223 (compared to susceptible infection)	Thampi *et al.*, 2015
All infections	Toronto	1	20 MRSA	Administrative data	1996–1998	$21,158	Kim *et al.*, 2001
All infections	All			Literature review	Pre-2007	$12,371	Goetghebeur *et al.*, 2007
SSTI	Vancouver, Toronto, Montréal	3	89 MRSA	Administrative data, simulations	1997–2000	$10,080	Rosner *et al.*, 2004

This table compares four Canadian studies of the hospital costs associated with methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Costs are presented in 2018 Canadian dollars.

Table 3.2

Estimates of the Hospital Costs of VRE, Summary of Five Studies

Definition	Country	Hospitals	Sample Size	Methods	Year	Cost	Reference
All infections	Canada (Vancouver)	1	217 VRE cases, 1,075 non-VRE control	Logistic regression	2008–2009	$21,185 (compared to hospitalized patients without VRE)	Lloyd-Smith *et al.*, 2013
BSI - Acute leukemia	United States	1	15 VRE cases, 45 controls	Matched regression	2006–2012	$114,492 (compared to leukemia patients without VRE)	Ford *et al.*, 2015
BSI	Australia	2	116 VRE cases, 116 controls	GLS regression, propensity scores	2010–2011	$31,434 (compared to susceptible infection)	Cheah *et al.*, 2013
BSI - Autologous hematopoietic stem cell transplant (HSCT)	United States	1	Out of 300 total; no VRE colonization or BSI = 191, VRE colonization without BSI = 100, VRE colonization with BSI = 9, VRE BSI without colonization = 0	Matching and Cox proportional hazards models	2006–2014	$7,293 (compared to autologous HSCT patients without VRE)	Ford *et al.*, 2015
BSI	United States	1	94 VRE cases, 182 controls	GLS regression; patient costs were provided by the finance records	2002–2003	$12,791 (total cost) $6,000 (compared to susceptible infection)	Butler *et al.*, 2010

This table compares five studies of the costs associated with vancomycin-resistant Enterococci (VRE) infections. Costs have been converted into 2018 Canadian dollars.

VRE Infection

VRE infections can occur anywhere in the body, but common sites include the urinary tract, abdomen, bloodstream, and surgical sites. While they are more difficult to treat than susceptible enterococcal infections, they are somewhat less common than other bacterial infections (HealthLink BC, 2017). VRE infections are associated with higher levels of mortality and morbidity for patients who receive bone marrow, liver, kidney, and other transplants (Freitas *et al.*, 2006; Rolston *et al.*, 2007; Linfield *et al.*, 2018).

Only one study has estimated the cost of VRE in Canada. Lloyd-Smith *et al.* (2013) compared 217 VRE patients to a random sample of 1,075 other patients in a Vancouver hospital. They found that VRE increased the mean additional hospitalization cost per patient by $21,185, relative to hospitalized patients who did not have VRE. As this was the only Canadian study, the Panel used this value as their estimate for the hospital cost of VRE in Canada.

Table 3.2 summarizes the study by Lloyd-Smith *et al.* (2013), along with four other studies from Australia and the United States. As with MRSA, however, it is difficult to compare the cost of VRE across studies; the five studies summarized in Table 3.2 cover different medical conditions (e.g., leukemia, transplants) and countries (Australia, Canada, United States), and use different methods. While not directly comparable, these studies suggest that VRE infections are, on average, costlier than MRSA infections. This difference may be due to the fact that the studies mostly focus on BSIs, or may show that the actual costs associated with treating patients with VRE infections are greater.

Table 3.3

Estimates of the Hospital Costs of ESBL Infections, Summary of Four Studies

Definition	Location	Hospitals	Sample Size	Methods	Year	Cost	Reference
Various infections (high-risk patients in ICU)	South Korea	1	49 resistant cases, 49 controls	Propensity matching	2007–2011	$2,556 (total cost) $719 (compared to susceptible infection)	Vasudevan *et al.*, 2015
Various non-UTI	United States	1	21 resistant cases, 21 controls	Propensity matching	2001–2004	$68,844 (total cost) $27,387 (compared to susceptible infection)	Lee *et al.*, 2006
UTI	8 European countries	20	643 cases (166 resistant)	Multivariate regression	2013–2014	$7,104 (total cost) $955 (compared to susceptible infection)	Vallejo-Torres *et al.*, 2018
UTI	Spain	1	60 resistant cases; 60 susceptible cases	Multivariate regression, propensity matching	2011–2012	$5,067 (total cost) $1,556 (compared to susceptible infection)	Esteve-Palau *et al.*, 2015

This table compares four studies of the costs associated with extended-spectrum beta-lactamase (ESBL) infections. Costs have been converted into 2018 Canadian dollars.

ESBL Infection

ESBL gram-negative bacteria produce an enzyme, beta-lactamase, that has the ability to break down commonly used antimicrobials, rendering them ineffective for treatment (i.e., the bacteria are resistant). Syndromes that can be caused by ESBL-producing bacteria include UTIs, IAIs, pneumonia, and BGIs.

The one Canadian study of ESBL infections (Chaulk *et al.*, 2014) did not measure costs of infection but instead estimated 30-day mortality associated with third-generation cephalosporin-resistant spontaneous bacterial peritonitis (SBP, a type of IAI) in an Edmonton hospital. It found that cirrhosis patients who develop resistant infections are approximately five times more likely to die within 30 days as a control group of cirrhosis patients. The high mortality rate for SBP may help explain the relatively low additional mean cost per patient ($719 relative to patients with susceptible infections) in a study from a Singapore hospital (Vasudevan *et al.*, 2015). This study and three others are summarized in Table 3.3, providing international cost estimates for UTIs and other infections caused by ESBL. The Panel used the average hospital cost per patient with ESBL infections (relative to no infection) from these studies — $20,893 per patient — as their estimate for the cost of ESBL infections. This estimate is similar to the estimated cost of VRE infections.

Table 3.4

Estimates of the Hospital Costs of CDI, Summary of Five Studies

Definition	Location	Hospitals	Sample Size	Methods	Year	Cost	Reference
Hospital Associated-and Community Acquired-CDI	Canada	All		Generalized linear regression	2012	$13,028 (total cost)	Levy *et al.*, 2015
Hospital Associated-CDI	United States (Pennsylvania)	6	255 CDI vs. 765 non-CDI	Propensity score matching, random-effects model	2007–2008	$25,822 (total cost) $5,361 (compared to hospital patient with no CDI)	Tabak *et al.*, 2013
Hospital Associated-CDI	United States		1,000 adults through the simulation model 1,000 times	Computation simulation model	2010	$10,869 (total cost)	McGlone *et al.*, 2012
Hospital Associated-CDI	United States (New York)	All	3,826 CDI vs. 4,849,917 controls	Generalized linear regression	2007–2008	$37,285 (compared to hospital patients with no CDI)	Lipp *et al.*, 2012
Hospital Associated-CDI in patients with renal disease, cancer, inflammatory bowel disease	United States (Missouri)	74	4,521 CDI, no controls specified	Propensity score matching	2005–2011	$6,383 (compared to similar patients without CDI)	Campbell *et al.*, 2013

This table compares five studies of the costs associated with *Clostridioides difficile* infections (CDIs). Costs have been converted into 2018 Canadian dollars.

CDI

CDIs are the most frequent cause of infectious diarrhea in hospitals and long-term care facilities in Canada and peer countries (PHAC, 2018b). CDIs frequently occur alongside other resistant infections and the use of antimicrobials, which alter patients' internal gut flora. Because of this relationship to other resistant infections (as discussed in Section 2.3.1 in reference to CDI morbidity), the total cost estimates discussed here refer to all types of CDI, both susceptible and resistant.

A recent study has estimated the cost of CDI in Canada. Levy *et al.* (2015) developed an economic model to estimate the costs of managing both hospital- and community-acquired CDI. In 2012, across an estimated 37,900 cases, they found that CDIs increased the mean hospitalization cost by greater than $13,000 for an initial episode (the cost was even greater for a recurrent episode). The authors found that the cost of CDIs to Canada in 2012 was $281 million dollars (in 2012 dollars); 92% ($260 million) of this was for in-hospital costs, 4% ($12 million) was due to direct medical costs in the community, and 3.5% ($10 million) was linked to lost productivity. This study also highlights differences across provinces and territories; the estimated rate of CDI in Quebec (17 cases per 10,000 bed days) is nearly twice the estimated rate in British Columbia (8.3), and six times that in Atlantic Canada (2.8). The four additional U.S. studies summarized in Table 3.4 provide cost estimates of CDI that are slightly higher, on average, than the Canadian values estimated by Levy *et al.* (2015). The differences in the values in Table 3.4 likely reflect differences between the healthcare systems in the two countries as well as other differences related to patient populations and methods of estimating costs. The Panel chose to use the value reported in the Canadian study as their estimate of the cost of CDI ($13,028), which is less expensive than the estimates of ESBL, VRE, and MRSA infections.

In summary, while not always directly comparable, and while based on different syndromes, populations, locations, and methods, 18 studies (summarized in Tables 3.1 through 3.4) were considered by the Panel in the development of its estimate of the average Canadian hospital costs of MRSA, VRE, ESBL infections, and CDI. These results indicate that patient costs associated with resistant bacteria are sizeable. It costs about $18,000 more to treat a patient with a resistant bacterial infection than a patient without an infection. The bacterial estimates in Figure 3.1 are used to construct hospital costs for each of the Panel's 10 important syndromes in the next sub-section.

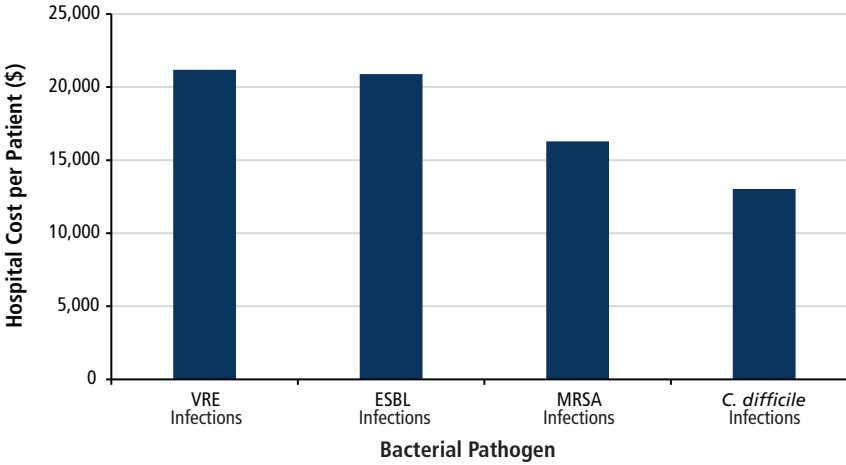


Figure 3.1

Hospital Costs per Patient by Bacterial Pathogen, Selected Studies, 1996–2015

This figure plots the hospital costs per patient with a resistant infection in 2018 Canadian dollars, averaged across selected studies. VRE, vancomycin-resistant Enterococci; ESBL, extended-spectrum beta-lactamase gram-negative bacteria; MRSA, methicillin-resistant *S. aureus*.

3.1.2 TB, BGIs, IAIs, and UTIs Are the Most Expensive Resistant Syndromes to Treat

In Chapter 2, the Panel examined 10 important clinical syndromes for which AMR is prevalent and leads to high levels of mortality and morbidity in Canada. For each syndrome, Table 3.5 presents the Panel's estimates of the hospital costs per resistant infection.

Table 3.5

Estimated Hospital Costs of Antimicrobial Resistance by Syndrome in Canada, 2018

Syndrome	Hospital Costs per Resistant Infection
BGI	$20,893
BSI	$18,733
CDI	$13,028
IAI	$20,893
MSI	$16,280
Pneumonia	$18,587
SSTI	$16,280
STI (gonorrhea)	$247
TB	$38,466
UTI	$20,893
Average	**$17,900**

This table presents the estimated hospital costs by syndrome weighted by the cost of causal bacteria identified in Section 3.1.1 (further described in Appendix B). Cost per infection for STIs and TB are based on estimates in Chesson (2018) and Diel (2014), respectively. The Panel recognizes many other pathogens can cause these syndromes, but were unable to obtain costing estimates for these pathogens. The Panel also recognizes that the method used to estimate costs does not take into account the likelihood of a syndrome being acquired in a hospital-setting. BGI, bacterial gastrointestinal infection; BSI, bloodstream infection; CDI, *C. difficile* infection; IAI, intra-abdominal infection; MSI, musculoskeletal infection; SSTI, skin and soft tissue infection; STI, sexually transmitted infection; TB, tuberculosis; UTI, urinary tract infection. The syndrome totals for cases are rounded due to the uncertainty in the estimates.

Since about 1 in 10 patients acquires an infection while in hospital (Gravel *et al.*, 2007a; Gravel *et al.*, 2007b), about 300,000 infections were acquired in Canadian hospitals in 2018.[10] Based on the assumption that the infection and resistance rates presented in Chapter 2 can be applied to hospital settings, the Panel used its own estimates of resistant HAIs for each syndrome to calculate hospital costs (Table 3.5). The Panel recognizes that the method used to estimate costs does not take into account the likelihood of a syndrome being acquired in a hospital-setting. The Panel chose to calculate the hospital costs of AMR using HAIs for two reasons. First, most of the studies outlined above relate to the cost of bacterial HAIs; the Panel was unable to find reliable estimates of the costs of community-acquired infections. Second, by estimating the costs of HAIs only, the Panel is providing a conservative estimate of the impact of AMR on the Canadian healthcare system.

10 This calculation is based on the 2018 total number of hospital discharges (3,074,965) (CIHI, 2018a).

To calculate hospital costs per resistant infection, the Panel converted the hospital costs of resistant bacteria (Figure 3.1) into costs for resistant syndromes. This conversion was based on the Panel's expert judgment on the causative relationship between bacteria and syndromes, calculating the cost of a syndrome as the average cost of the causative bacteria. For example, since SSTIs are predominantly caused by MRSA bacteria (along with other bacteria, for which there is no attributable cost estimate), the Panel based the cost of resistant SSTIs on the average cost of MRSA infections ($16,280).[11] By contrast, since pneumonia can be caused by MRSA and ESBL bacteria, the Panel estimated the cost of resistant pneumonia as the average hospital cost of these two bacteria ($18,587). Using this bacterial weighting method, the four most expensive resistant syndromes to treat per patient are TB, UTIs, IAIs, and BGIs. The Panel recognizes that this weighting is imperfect, as syndromes are also caused by other bacteria.[12] Data were not available to allow the Panel to directly estimate the cost of resistant syndromes. This highlights an important area of future research.

3.2 THE COST OF AMR TO THE CANADIAN HEALTHCARE SYSTEM

Healthcare spending in Canada is forecast to have reached $254 billion in 2018 (CIHI, 2018b). Equal to $6,839 per person annually, this spending represents more than 11% of Canada's GDP. While trending upward since 1975, healthcare spending has more than doubled over the last decade. This section outlines current and future AMR costs to the Canadian healthcare system based on the estimates discussed in Section 3.1.

3.2.1 AMR Cost the Canadian Healthcare System an Estimated $1.4 Billion in 2018

Based on resistant HAIs, the Panel estimates that AMR cost Canadian hospitals about $1.4 billion in 2018. While only about 0.6% of national healthcare spending, this amount is roughly equal to total expenditure on all hospitals in Newfoundland and Labrador or all physicians in Manitoba (CIHI, 2018b).

11 While VRE infections sometimes cause UTIs, IAIs, and BGIs, especially among vulnerable populations, ESBL bacteria more frequently cause these three resistant syndromes. Therefore, the Panel based its attributable cost estimate on ESBL bacteria only. Since VRE infections are costlier to treat than ESBL infections, this leads to an underestimate of the cost per resistant UTI, IAI, and BGI.

12 For example, IAIs can also be caused by *Bacteroides fragilis* and *Bacteroides distasonis* (in addition to ESBL bacteria).

As depicted in Figure 3.2, SSTIs were the most costly resistant syndrome in 2018. Along with UTIs, IAIs, and pneumonia, these four syndromes accounted for 91% of the hospital costs associated with AMR. This is because they had the highest infection rates and among the highest resistance rates as shown in Figure 3.3. Comprising about 90% of resistant HAIs, these four syndromes were only slightly more expensive to treat than other syndromes (except for TB) (recall Table 3.5). Despite a similar number of resistant cases, IAIs cost the Canadian healthcare system almost $40 million more than pneumonia because of a higher incidence of infection and the higher costs associated with its treatment ($20,893 vs. $18,587). MSIs were the fifth costliest syndrome in 2018, responsible for about 5% of hospital costs, which is partially the result of having the highest resistance rate. Figure 3.3 shows the relationship between hospital-associated resistant infections, resistance rate, and total hospital costs for the 10 important clinical syndromes.

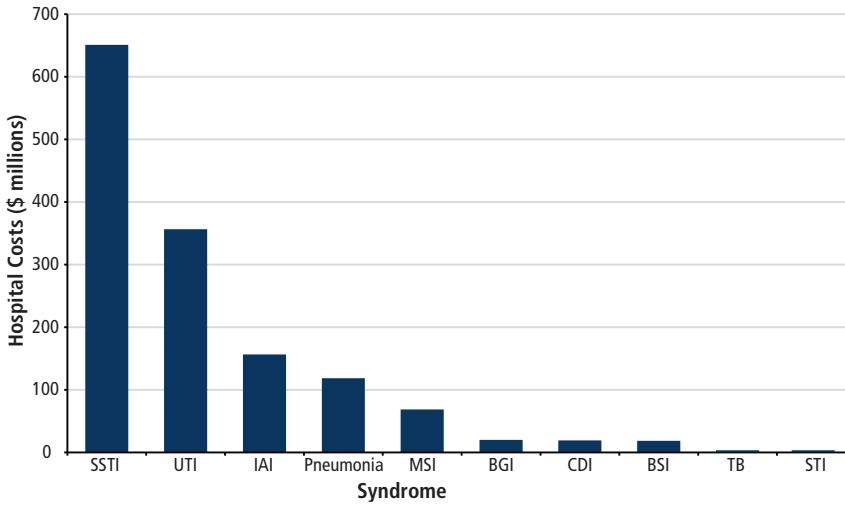


Figure 3.2

Canadian Hospital Costs Associated with Antimicrobial Resistance, 2018

This figure plots the estimated 2018 hospital costs associated with 10 important syndromes in Canada. BGI, bacterial gastrointestinal infection; BSI, bloodstream infection; CDI, *C. difficile* infection; IAI, intra-abdominal infection; MSI, musculoskeletal infection; SSTI, skin and soft tissue infection; STI, sexually transmitted infection; TB, tuberculosis; UTI, urinary tract infection.

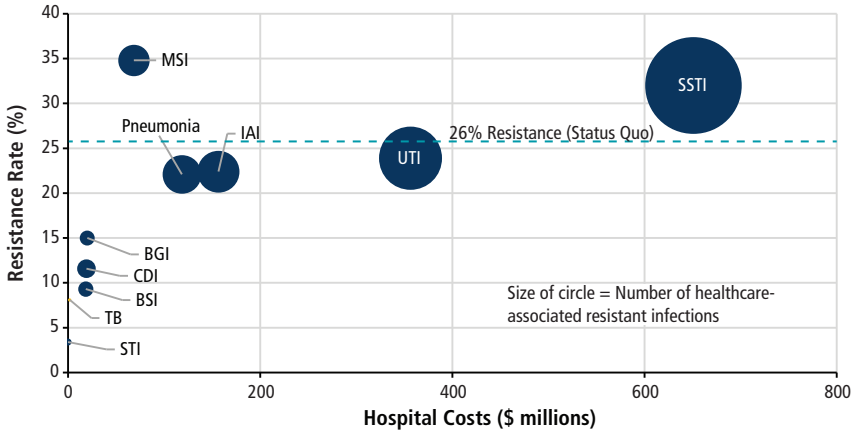


Figure 3.3

Healthcare-Associated Resistant Infections, Resistance Rates, and Hospital Costs, 2018

This figure plots estimated resistance rates, hospital costs, and number of healthcare-associated resistant infections (size of circle areas) for 10 important syndromes in Canada. BGI, bacterial gastrointestinal infection; BSI, bloodstream infection; CDI, *C. difficile* infection; IAI, intra-abdominal infection; MSI, musculoskeletal infection; SSTI, skin and soft tissue infection; STI, sexually transmitted infection; TB, tuberculosis; UTI, urinary tract infection.

The Panel recommends exercising caution in interpreting these calculations. The costs of resistant HAIs are heterogeneous, varying by hospital, geographic location, and patient group. As will be described in Chapter 6, AMU, surgical procedures, handwashing, and other practices differ across hospitals. Similarly, infection rates can vary across provinces and territories, reflecting differences in socio-demographics, public health policies, and other factors. For older adults, for example, costs can be significant after they are discharged from the hospital as these may include home care, long-term care, or other types of healthcare services. Therefore, using estimates from a single study or even the average from academic literature could be misleading if applied to all hospitals, provinces/territories, or patients.

As in Chapter 2, the Panel used its clinical expertise and expert judgment to select the studies highlighted in Figure 3.1 and used in this chapter. Where possible, it examined Canadian studies to avoid assigning variation in hospital costs to what are actually differences in healthcare systems. While somewhat imprecise, the Panel considers $1.4 billion to be a conservative approximation of the healthcare costs of AMR for three reasons. First, this estimate does not include community-acquired resistant infections, which account for upwards of 70% of total infections (CIHI, 2018a). There are healthcare costs associated

with these infections, such as physician visits and prescription drugs, which the Panel's estimate does not include. Second, if infection and resistance rates are under-reported (which might be expected for some syndromes, such as BGIs), hospital costs would be proportionally higher. Third, to the extent that susceptible infections increase the likelihood of acquiring resistant infections (Chapter 5), the Panel's estimate does not include the future costs associated with the present use of antimicrobials.

3.2.2 AMR May Comprise About 1 to 2% of Future Canadian Healthcare Spending

As mentioned in Chapter 1, the Panel commissioned a quantitative economic model to help estimate the future impact of AMR (discussed in more detail in Chapter 4). According to this model, by 2050, if resistance to first-line antimicrobials remains constant at approximately 26%, or reaches 40%, Canada's additional hospital costs would increase to about $5.5 to $7.6 billion per year, respectively (Figure 3.4). The latter amount is roughly equal to total expenditure on all hospitals in Atlantic Canada or all physicians in Quebec (CIHI, 2018b). It is likely an under-estimate of the future healthcare costs of AMR because it assumes that Canadian healthcare spending growth remains constant (Figure 3.2), that immigration remains constant (Bohnert & Dion, 2013), and that new health technology does not alter costs (Chandra & Skinner, 2012).

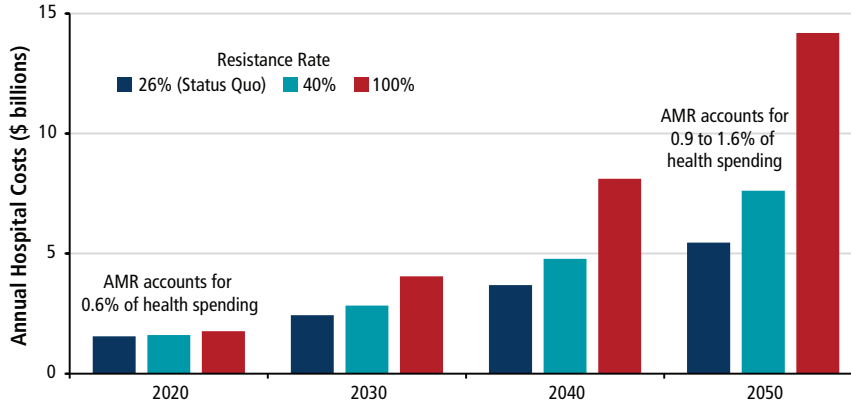


Figure 3.4

Projected Canadian Annual Hospital Costs Associated with Antimicrobial Resistance, 2020–2050

This figure plots the estimated total Canadian annual hospital costs based on three resistance scenarios in the Panel's model: status quo (26%), 40%, and 100%. It assumes that hospital costs grow at 4.2% per year from 2020 to 2050.

The Panel's estimate of Canadian healthcare costs differs significantly from a recent estimate provided by the OECD (2018a) for two main reasons. First, the OECD uses a pathogen approach, basing their estimates of resistance, mortality, and morbidity on data from the Center for Disease Dynamics, Economics & Policy and the European Antimicrobial Resistance Surveillance Network, which allow for international comparisons. However, as noted in Chapter 1, Canadian data from these sources were limited to *E. coli* resistance between 2012 and 2014. As a result, the OECD estimates of annual deaths and LOS (approximately 400 deaths, 28,000 hospital days) due to AMR in Canada is an order of magnitude lower than the Panel's estimates (approximately 5,400 deaths, 880,000 hospital days). Second, the 2018 OECD report combines several models (mixed-effects linear regression, exponential smoothing with an additive trend, and random forecast) to forecast future resistance levels and thereby estimate future mortality, LOS, and healthcare costs. By contrast, and as described in more detail in Chapter 4, the Panel estimated future deaths, LOS, and hospital costs based on three resistance scenarios (i.e., 26% (status quo), 40%, and 100%), focusing on collecting comprehensive Canadian data on 10 syndromes. The Panel adopted this approach because the focus of its modelling was the impact of AMR on labour productivity. As a result of these differences in approach, the Panel's estimate of current and future healthcare costs is based on hospital costs for resistant syndromes (e.g., $16,280 per SSTI) under three resistance scenarios, whereas the OECD's estimate is based on LOS for a single resistant bacterium under forecasted resistance rates. When combined with very limited Canadian data, the OECD's healthcare cost estimates ($380 million by 2050 at 14% resistance) are much lower than the Panel's ($7.6 billion by 2050 at 40% resistance). Ultimately, the Panel's approach is more accurate for the Canadian context.

Figure 3.4 underscores why it is imperative to slow the increase in resistance rates. It highlights the sizeable gap in 2050 healthcare spending between a scenario in which there is complete resistance (100%) to all first-line antimicrobials and more conservative projections of 40% or status quo first-line resistance. In 2050, AMR may comprise between 0.9 to 1.6% of Canadian healthcare spending, up from 0.6% today, if resistance to first-line antimicrobials reaches 40% or 100%, respectively. Such a major increase in one dimension of healthcare would put significant financial strain on the rest of the system, perhaps resulting in spending cuts elsewhere in the health system or in government services. The annual growth in healthcare costs attributable to AMR between 2020 and 2050 — about 6 to 8% — would comprise the largest single growth factor for Canadian health expenditures, dwarfing the impact of the Canadian population's changing age structure on health expenditures. AMR is a problem for the Canadian healthcare system that may get much worse in the future.

3.3 CONCLUSION

Left unaddressed, AMR has the potential to debilitate the Canadian healthcare system. While the current cost of resistant infections represents a relatively small share of healthcare spending, if resistance to first-line antimicrobials rises to 40% by 2050, the healthcare system will be less sustainable — the gradual failure of antimicrobials could cost almost $120 billion over the next 30 years. This unsustainability is driven by the healthcare system's dependence on antimicrobials. As Smith and Coast (2012) argue, ineffective antimicrobials would be a "catastrophic blow to health system development . . . requiring [the] redesign of many facilities, the reintroduction of sanatoria and so forth." It is difficult to imagine the broad impacts of such a shock to the Canadian healthcare system.

Effective antimicrobials are extremely valuable to medicine and modern healthcare. While first-line antimicrobials were unable to treat about 26% of bacterial infections in 2018, they were able to treat almost 230,000 susceptible HAIs. Antimicrobials thus saved the Canadian healthcare system at least $4.1 billion in 2018. This value is at risk. The world is running out of effective antimicrobials and Canada cannot ignore the urgency and gravity of this issue.

4

The Impact of Antimicrobial Resistance on the Canadian Economy

- Modelling the Economic Impact of AMR
- Economic Impact of AMR
- The Impact of AMR on the Animal Farming Industry
- Conclusion

4 The Impact of Antimicrobial Resistance on the Canadian Economy

Key Findings

Current

In 2018, AMR reduced the Canadian effective-labour supply by an estimated 9,000 person years of employment.

Based on the Panel's economic model, AMR reduced Canada's GDP by an estimated $2 billion in 2018, or about 0.13% of the economy. This amount is about equal to one-third of the size of the economy of Prince Edward Island or the Canadian motor vehicle manufacturing industry.

About 50% of this decline in economic activity occurred in the most labour-intensive industries: recreation and culture, transportation, and public services.

According to simulations of the Panel's model, first-line antimicrobials contributed $6.1 billion to the Canadian economy in 2018 by saving some 17,000 lives and 2.6 million hospital days.

Future

In 2050, AMR will reduce Canada's GDP by an estimated $13 to $21 billion per year if resistance to first-line antimicrobials remains constant at today's rate of 26% or continues to rise to 40%, respectively.

If resistance to first-line antimicrobials remains constant at 26% or rises to 40%, the Canadian economy will be 0.5 to 0.7% smaller in 2050 than it is today, the latter about equal to the one-third the size of the GDP of Manitoba or the oil sands extraction industry.

Canada's economy could lose an estimated $268 to $388 billion in GDP between 2016 and 2050 if resistance rates remain constant at 26% or reach 40%.

AMR could lead to a prolonged economic contraction that is rare in Canada's post-war history, about equal to losing more than the combined GDPs of Prince Edward Island and Nova Scotia or one-quarter the GDP of the manufacturing sector each year if resistance were to reach 100% by 2050.

Based on simulations of the Panel's model, the Canadian animal farming industry may lose an estimated $26 to $37 billion if resistance rates remain constant at 26% or reach 40% by 2050.

If AMR were also to reduce animal farming productivity and animal product exports by up to 10%, the industry could lose an additional $190 billion over the next 30 years.

This chapter examines the impact of AMR on the Canadian economy. It describes the Panel's model and how it was applied to estimate the current and future economic impacts of AMR, including the data and assumptions underlying them. Chapter 4 also presents the Panel's findings on the current and future impacts of AMR on the Canadian labour force, GDP, and industries, including the animal farming industry. The final section considers the global economic impact of AMR.

4.1 MODELLING THE ECONOMIC IMPACT OF AMR

To better understand the impact of AMR on the Canadian economy, the Panel commissioned a quantitative economic model to estimate the effects of mortality and morbidity on the labour force and GDP. Estimates from this dynamic computational general equilibrium (DCGE) model — which considers scenarios wherein future resistance to first-line antimicrobials remains constant at today's rate (26%) or grows to either 40% or 100% by 2050 — also weigh the impact of AMR on international trade, as well as on Canada's industries.

4.1.1 AMR Could Cost the World Economy Up to an Estimated 3% of GDP by 2050

DCGE models can illustrate production and trading patterns among industries, regions, and countries. If AMR or other economic and social factors affect labour productivity in one country, global production and trading patterns adjust (within a model). This captures the dynamic, interconnected nature of global markets. As discussed by Dervis (1982), Shoven (1992), Lofgren (2002), and many others, DCGE models view the many markets of goods and inputs as an interrelated system, whereby values at equilibrium for all variables are simultaneously determined. Applied general equilibrium modelling is now a standard tool for empirical analysis, predominantly used for analyzing policy issues such as income distribution, trade policy, environment, structural adjustments to external shocks, growth and structural changes, government tax (subsidy) policy, and others. It has also gained ground recently in health economics through its application to estimating the impacts of AMR, HIV/AIDS, malaria, pandemic influenza, and certain non-communicable diseases (Dixon *et al.*, 2004; Smith *et al.*, 2005; Smith *et al.*, 2006; Keogh-Brown *et al.*, 2010; RAND Europe, 2014; Keogh-Brown *et al.*, 2015). As summarized in Table 4.1, several reports have used similar models to simulate the effect of AMR on the global economy.

Based on these models, AMR could reduce annual global GDP by up to 3% by 2050 as morbidity and mortality increase (KPMG, 2014; RAND Europe, 2014; World Bank, 2017). In these models, as AMR rises, fewer people are able to work

because they are sick or have died. These models consistently show major variation across countries (e.g., greater than 10% decline in GDP in some countries for the most extreme scenarios) and industries (e.g., agriculture, healthcare). The impact to Canada is on the low end of these models' estimates — around 2% reduction in annual GDP — reflecting the fact that it uses more capital (e.g., machinery, infrastructure) in production than the world average and has less population density.

Table 4.1

International Estimates of the Potential Economic Impact of Antimicrobial Resistance on the Global Economy

Report	Model & Assumptions	Data	Selected Key Findings
Drug-Resistant Infections: A Threat to Our Economic Future (World Bank, 2017)	• DCGE (multi-country, multi-industry) with neoclassical growth • If resistance rate = 100%, with number of cases of infection constant • Other scenarios	• Industry and regional data • World Bank • WHO	**2050** • 3.8% reduction in world GDP • US$30–110 trillion loss • US$6.1 trillion world GDP loss per year • Low-income countries: >5% GDP • 28.3 million people in extreme poverty • Healthcare costs $1.2 trillion per year
Estimating the Economic Costs of Antimicrobial Resistance (RAND Europe, 2014)	• DCGE (multi-region); reduction in effective labour • AMR rates = 100% in 2025, with number of cases of infection constant • Other scenarios	• Regional data • Expert opinion • WHO • UN	**2050** • 0.83% reduction in world GDP • US$2.7 trillion world GDP loss per year • US$37.5 trillion cumulative world GDP loss • Significant differences by region
The Global Impact of Antimicrobial Resistance (KPMG, 2014)	• DCGE (multi-region) with neoclassical growth; reduction in labour stock • If AMR rates increased by 40% and number of infections doubled • Other scenarios	• Regional data • Expert opinion • WHO • UN	**2050** • 3.44% reduction in world GDP • Significant differences by region

This table summarizes three key reports that estimate the global cost of AMR.

4.1.2 The Panel's Model Accounts for Global Production and Trade Patterns

For the purpose of estimating AMR's economic impact, the Panel used a DCGE model in which Canada is viewed as an open economy, connected to the rest of the world through trade and investment. Like other DCGE models, the Panel's model links production and trading patterns among industries and countries such that, if AMR (or other economic factors) affects labour productivity in one country, global production and trade adjust throughout the world (and within the model).

Figure 4.1 depicts the linkages in the Panel's DCGE model as it relates to AMR. It also highlights the main effects that AMR could have on the economy. Production sectors, which include different agricultural, manufacturing, and service industries, require labour and capital inputs accessed through the labour and capital markets. Firms hire labour and rent capital from households (i.e., consumers/workers), enabling firms to produce goods and providing households with income. Through product markets, the economy also trades with the rest of the world via a complex set of international linkages. In this way, Canadian firms, households, and governments are connected to each other and the rest of the world through production and trading patterns. Further technical details of the model can be found in Appendix C.

The Panel's quantitative economic model is just that — a model. It is intended to be a helpful simplification of the complex relationship among AMR, human health, labour productivity, and trade. Like all analytical models, it relies on a set of assumptions, modelling choices, and uncertainties, which are often driven by data availability (Appendix C). The purpose of the model is to impose a logic on the above relationships in order to study how they interact and evolve; this allows for estimates of the future economic impact of AMR.

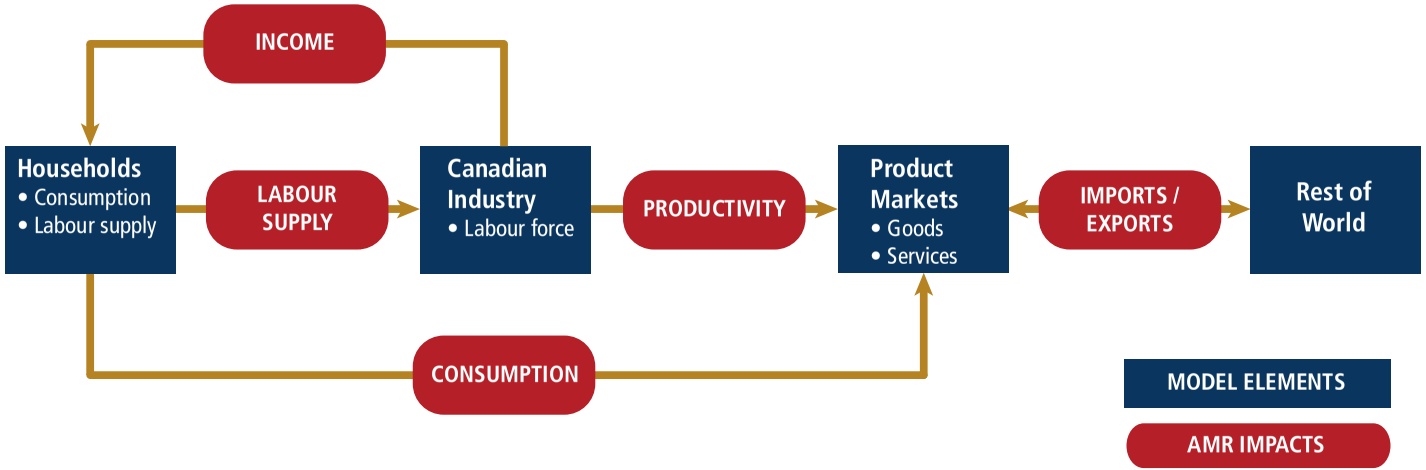


Figure 4.1

The Panel's Dynamic Computational General Equilibrium (DCGE) Model

This figure summarizes the Panel's DCGE model. Households supply labour to Canadian industries (e.g., animal farming, transportation), enabling firms to produce goods and services and providing households with income to consume these products. AMR increases mortality and morbidity among workers, thereby reducing labour productivity. Firms will therefore produce less, and households will consume less, reducing Canadian GDP overall. Through product markets, the economy also trades with the rest of the world via a complex set of international linkages.

Mortality, Morbidity, and Demographics

In the Panel's model, the impact of AMR is captured through two direct effects that reduce the supply of effective labour, a crucial economic resource. The *effective-labour supply* is defined as the productivity level of the working age population (GDP per hour worked) as opposed to simply the number of workers (i.e., the labour supply). Based on different infections and resistance scenarios, the reduction in effective-labour supply is measured by two health outcomes:

- **Increased Mortality:** Deaths attributable to AMR permanently reduce the population size; the effect of increased mortality on economic production is channelled through decreases in the growth rate of the working-age population, lowering the supply of available labour and increasing the dependency ratio (the ratio of the labour force to the dependent population, i.e., ages 0 to 14, 65+).
- **Increased Morbidity:** Prolonged periods of sickness attributable to AMR temporarily reduce the country's workforce and may in severe cases lead to permanent reductions in labour productivity. Furthermore, children affected by resistant infections might lose schooldays or have permanent physical disabilities that could lower productivity when they reach adulthood. In addition, increased morbidity of non-working people may also affect the labour supply if their condition requires the attention of a carer who would otherwise be economically productive.

The logic linking health outcomes to economic impact is straightforward: as AMR increases, fewer people are able to work, either because they are sick or have died. Using the best available Canadian data (Table 2.3), the Panel estimated the reduction in effective labour supply as the number of deaths and days in hospitals attributable to AMR. Taking 2016 as the baseline, the Panel then simulated the growth rate of employment up to 2050, using population projections and resistance scenarios described below (Section 4.2).

This approach rests on two assumptions. First, the model assumes that the likelihood of acquiring a resistant infection, and then either becoming sick or dying, is uniformly distributed across the population by age. Since susceptibility to infection is generally greater in children (0 to 14 years) and older adults (65+) (Section 5.1.1) who are not generally part of the labour force, this assumption likely leads to an over-estimate of economic impact. Second, the model considers morbidity measured by LOS, which only accounts for infections that require hospitalization. Since some resistant infections may entail time off work but not hospitalization, this assumption likely leads to an under-estimate of economic impact (Section 4.2.1).

The population projections in the Panel's model are based on data from the United Nations Population Database (UNPD) (UN, 2018). They are divided into four geographic regions in the model (see below). Also used in O'Neill *et al.* (2016a), the UNPD's large set of population and demographic data contains information on virtually every country in the world. Since these data are drawn from national statistics offices (e.g., census data), they are comparable to Canadian data in terms of coverage and collection methodology. The advantage of using UNPD data, instead of country-specific population forecasts, is that they allow population forecasts for the countries included in the *rest of the world* region (see below) and contain information needed to project population changes across various cohorts such as fertility by age, mortality by age and gender, gender birth ratios, and net migration. This cohort component of the model assumes exogenous fertility and migration rates, which are not affected by resistance levels. The demographic and population data used in the Panel's model are listed in Appendix C.

Countries, Economies, and Industries

The Panel's model includes four different regions: (i) Canada, (ii) the United States, (iii) other OECD countries, and (iv) the rest of the world. The United States is modelled separately as it is a direct neighbouring country to Canada, with a large shared border and very close trade linkages across many industries. All other OECD countries are included as one region, as they characterize other high-income countries that are likely to be affected in similar ways by AMR. The fourth region is the rest of the world in order to incorporate all global trade flows into the model.

The Panel's model is calibrated to the macroeconomic and microeconomic features of Canada and other countries using the Global Trade Analysis Project (GTAP) database (Aguiar *et al.*, 2016). GTAP covers 140 regions, 57 commodities, and includes all bilateral trade patterns, production, consumption, and intermediate inputs for the reference year 2011. Using this database, the model is based on a Social Accounting Matrix (SAM), a complex table expressed in terms of incomes and expenditures (i.e., double entry accounting) developed from national accounts data (e.g., use-supply tables, input-output tables) and information from household survey and trade data. GTAP collects, cleans, and standardizes the economic data required to produce SAMs that are comparable across countries. The use of GTAP is an improvement over other reports (e.g., O'Neill, 2014), which was calibrated to five aggregated world regions with limited specificity in terms of production, consumption, and trade.

As is standard in DCGE models, production is a function of labour, capital, and multi-factor productivity (MFP), a measure of the overall efficiency with which labour and capital inputs are used together in the production process. Over the long run, economic growth is primarily driven by the rate of innovation, which is often proxied by MFP growth. For simplicity, the Panel's model assumes constant MFP growth across all years and industries. As shown in Table 4.2, Canadian MFP growth is relatively slow, reflecting Canada's poor innovation performance (Nicholson, 2018).

Table 4.2
MFP Growth Rates, 2016

5-Year Average MFP Growth Rates	
Canada	2.64%
United States	4.58%
OECD	6.12%
Rest of world	2.80%

Panel calculations based on Feenstra *et al.*, 2015

The 57 industries in the GTAP database are aggregated into 8 industries in the Panel's model. Production in these industries is characterized by different capital-labour ratios, with industries such as transportation and recreation requiring relatively more labour than industries such as farming or manufacturing. All else being equal, industries with higher capital-labour ratios will be impacted less than industries that use labour more heavily in production. The eight aggregated industries that the Panel included in the model are:

- Crop Farming
- Animal Farming
- Animal Product Manufacturing
- Manufacturing, Construction, Retail Trade
- Transportation
- ICT, Finance, Real Estate, Business
- Recreation and Culture
- Health, Education, Defence, Other Public Services (Public Services)

Scenarios

The Panel's model simulates the economic impact of AMR in three future scenarios with respect to rates of resistance to first-line antimicrobials, always in relation to the 10 important clinical syndromes discussed in Section 2.3. Under each resistance scenario, the infection rate is held constant so that the number of infections increases only with population growth.

- **Status Quo —** The resistance rate for each syndrome remains constant at current levels (26%) until 2050 (Tables 2.2 and 3.5).
- **40% —** Based on observed and projected future resistance rates in some countries, a second scenario is considered in which resistance gradually increases to 40% between 2020 and 2050. The Panel considers this scenario to be realistic of what may happen in 2050 (Section 2.3.3).
- **100% —** The worst-case scenario in the Panel's model, in which there is complete resistance to all first-line antimicrobials by 2050.

The Panel's model also simulates today's world without first-line antimicrobials where the resistance rate is 100% into the future (2020-2050). The Panel interprets the difference between this hypothetical world and the status quo as the *value* of first-line antimicrobials. Since first-line antimicrobials *are* effective (about 75% of the time), their value can be thought of in terms of the lives or GDP they save (as opposed to the deaths or GDP declines their resistance causes).

4.2 ECONOMIC IMPACT OF AMR

This section summarizes the Panel's findings in terms of the current and future impact of AMR on the Canadian economy.

4.2.1 AMR Reduced Canada's GDP by an Estimated $2 Billion in 2018

The Canadian economy has already begun to shrink as a result of AMR, as the number of deaths increase and fewer people are able to work due to resistant infections. In 2018, AMR was responsible for 5,400 deaths and 880,000 additional days (3,500 work years) in hospital (Table 4.3). If these people were in the labour force, it would correspond to an economy-wide loss of approximately 9,000 person years of employment. As shown in Figure 4.2, UTIs were responsible for the greatest decrease in the effective-labour supply in 2018. Along with IAIs and SSTIs, these three syndromes accounted for about 75% of the reduction in person years of employment.[13]

13 To test the sensitivity of the model estimates to changes in clinical inputs, the Panel ran the model with a 10% increase and decrease in input parameters. This led to an approximate 10% change in population and GDP across all resistance (status quo, 40%, 100%) and clinical scenarios.

As described in Chapter 5, older adults and children, who are not in the labour force, account for some of the estimated deaths and hospitalizations that comprise effective labour supply. However, the Panel believes that this is likely still a *conservative* estimate of the negative impact of AMR on the labour force. The estimates in Table 4.3 do not include the work days lost due to infections that do not require hospitalization. For the working-age population, syndromes such as BGIs, pneumonia, STIs, and UTIs may result in staying home from work rather than going to the hospital. In addition to lost work days, resistant syndromes may also diminish the physical and mental capabilities of workers, and these types of health effects are likely to lead to lower labour productivity (Sharpe & Murray, 2011). Moreover, if AMR affects older adults who help with childcare, working parents may work fewer days or exit the labour force. A lack of Canadian data prevented the Panel from including sick leave and worker performance as dimensions of morbidity.

Table 4.3

Canadian Estimates of Lost Years of Employment, 2018

Syndrome	Total Deaths	Attributable		
		Deaths	LOS (Work Years)	Lost Employment (Work Years)
BGI	3	1	28	29
BSI	630	221	134	355
CDI	211	115	255	370
IAI	2,266	1,956	439	2,395
MSI	376	231	268	499
Pneumonia	2,072	366	108	474
SSTI	1,781	636	1,018	1,654
STI (gonorrhea)	1	1	4	5
TB	7	0	45	45
UTI	6,732	1,900	1,216	3,116
Total	**14,000**	**5,400**	**3,500**	**8,900**

This table presents total deaths, attributable deaths, and attributable length of stay (LOS) in hospital for resistant infections (in work years), as estimated in Table 2.2. Lost years of employment are calculated as the number of attributable deaths plus LOS. For example, resistant UTIs are estimated to have caused 1,900 deaths and 1,216 years (304,045 days) in hospital in 2018, which translates to 3,116 lost years of employment (where one year equals 250 days in LOS). See Table 2.3 for references. BGI, bacterial gastrointestinal infection; BSI, bloodstream infection; CDI, *C. difficile* infection; IAI, intra-abdominal infection; MSI, musculoskeletal infection; SSTI, skin and soft tissue infection; STI, sexually transmitted infection; TB, tuberculosis; UTI, urinary tract infection. The totals for deaths and LOS are rounded due to the uncertainty in the estimates.

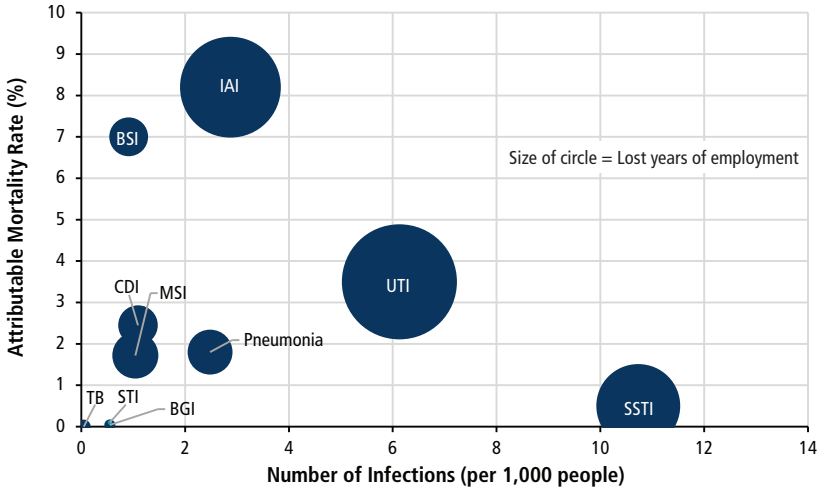


Figure 4.2

Infection Rate, Mortality Rate, and Lost Years of Employment, by Syndrome, 2018

This figure plots infection rate, mortality rate, and lost years of employment (size of circle) for 10 important clinical syndromes in Canada in 2018. BGI, bacterial gastrointestinal infection; BSI, bloodstream infection; CDI, *C. difficile* infection; IAI, intra-abdominal infection; MSI, musculoskeletal infection; SSTI, skin and soft tissue infection; STI, sexually transmitted infection; TB, tuberculosis; UTI, urinary tract infection.

Based on the Panel's economic model, mortality and morbidity due to resistant infections reduced Canada's GDP by $2.0 billion in 2018. For comparison, this decline in economic activity — about 0.13% of real (inflation-adjusted) GDP — is about 6% of the average growth (2.1%) of real Canadian GDP over the last five years (between 2013 and 2018). This is a significant decline, more than one-third the size of the economy of Prince Edward Island or the Canadian motor vehicle manufacturing industry (StatCan, 2018c).

In the Panel's model, production is a combination of labour, capital, and MFP. As noted above, industries that use relatively more labour will be relatively harder hit by AMR. Figure 4.3 breaks down the percentage point change in real GDP by industry, highlighting that about 50% of this decline in economic activity occurred in the most labour-intensive industries: recreation and culture (-0.19%), transportation (-0.18%), and public services (-0.18%). These are industries where human interaction is central to the services provided such as at sporting/music venues, museums/galleries, airports/train stations, and educational institutions. As will be discussed in Chapter 5, these reductions in economic activity are consistent with declining tourism and business travel resulting from AMR.

By contrast, more capital-intensive industries such as crop farming (-0.05%), animal farming (-0.10%), and ICT, real estate and finance (-0.10%) saw smaller declines in economic activity. Because the Panel's model does not consider the effect of AMR on animal health, animal industrial practices, or trade in animal products, the impact on animal farming estimated by the model is an under-estimate. The Panel addresses this issue in more detail in Section 4.3.

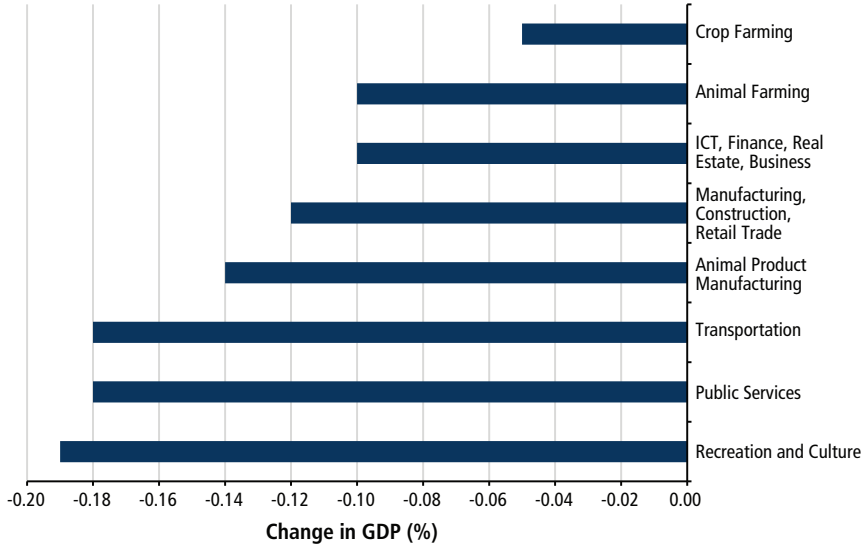


Figure 4.3

Reduction in GDP by Industry, 2018

This figure plots the percentage point decline in GDP for eight Canadian industry sectors. In 2018, the Canadian economy was about 0.2 percentage points smaller as a result of antimicrobial resistance.

Canada spent over $800 million on antimicrobials for human health in 2017 (PHAC, 2018a). Based on simulations of the Panel's model, if first-line antimicrobials were completely ineffective, resistant infections would have caused an additional 17,300 deaths and 2.7 million days in hospital in 2018.[14] All else being equal, by saving lives and preventing hospitalizations, antimicrobials contributed $6.1 billion to the Canadian economy in 2018. The Panel interprets this as an estimate of the *current economic value* of first-line antimicrobials. When viewed this way, effective antimicrobials are an important input into economic activity, generating a significant rate of return.

14 In the Panel's model, 17,300 equals the difference between current resistance (26%) and a simulated world where resistance is 100% to first-line antimicrobials.

4.2.2 Canada's Economy May Lose an Estimated $268 to $388 Billion in GDP by 2050 if Resistance Rates Remain Constant or Continue to Rise to 40%

According to simulations of the Panel's model, if resistance to first-line antimicrobials were to reach 40% or 100% by 2050, about 1 in 26 to 1 in 9 deaths in Canada will be attributable to AMR, respectively. This is a sharp increase from the status quo as shown in Figure 4.4. If resistance rates were to rise to 40% or 100%, AMR would be responsible for about 13,700 to 39,600 deaths in 2050. When combined with higher levels of hospitalization, this reduction in the effective labour supply would reduce Canada's GDP by $21 to $44 billion per year in 2050 (Figure 4.5). Even if resistance rates were to remain constant with today's levels (26%), AMR would reduce Canada's GDP by an estimated $13 billion by 2050.The Canadian economy, on average, would be about 0.5 to 0.7% smaller in 2050 if resistance remains at today's rates or rises to 40%, the latter about equal to the one-third the size of the GDP of Manitoba or the oil sands extraction industry (StatCan, 2018c).

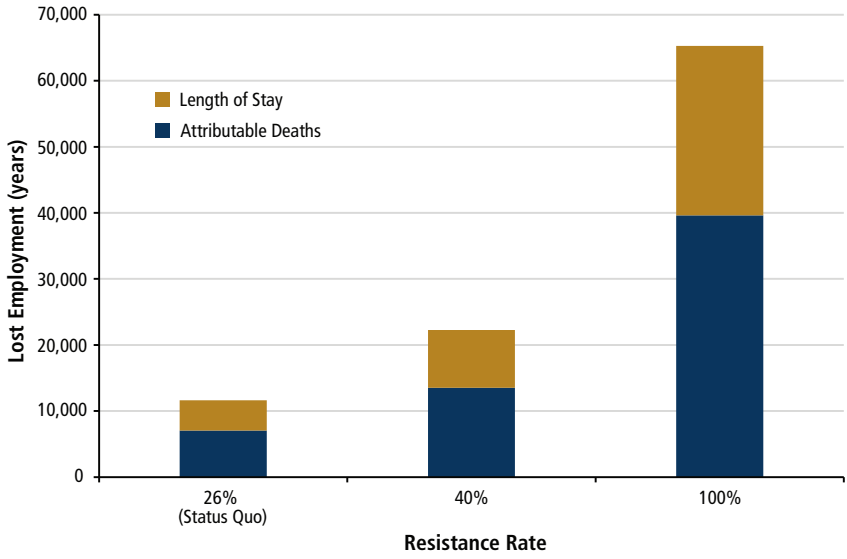


Figure 4.4

Lost Years of Employment in Three Resistance Scenarios in 2050

This figure compares lost years of employment — deaths plus length of stay (LOS) in hospital — in 2050 using three resistance scenarios: resistance to first-line antimicrobials remains constant at 26%, resistance reaches 40%, and resistance reaches 100%.

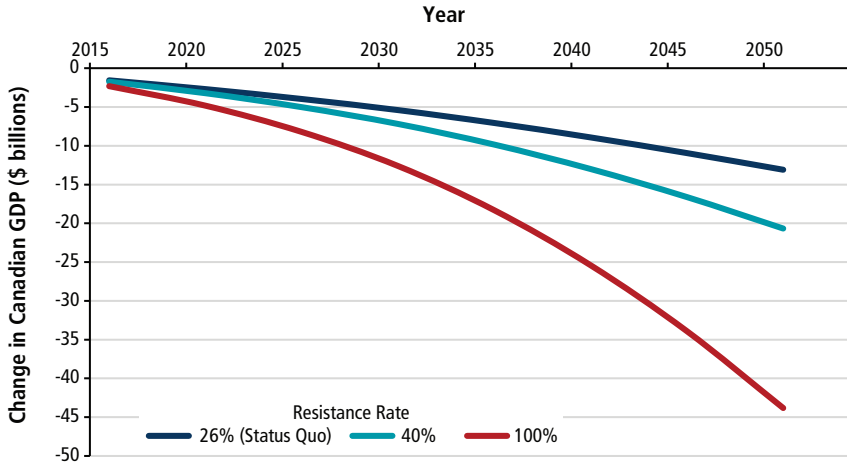


Figure 4.5

Annual Change in Canadian GDP, 2016–2050

This figure plots the annual decline in Canadian GDP for the three resistance scenarios: resistance to first-line antimicrobials remains constant at 26% (status quo, navy blue), reaches 40% resistance (teal), and reaches 100% resistance (red) by 2050.

As shown in Figure 4.6, in a worst-case scenario where resistance to first-line antimicrobials reaches 100% by 2050, the largest reduction in GDP would be in the most labour-intensive industries, recreation and culture (-3.2%), transportation (-3.0%), and public services (-2.5%). Such an economy-wide contraction is rare in Canada's post-war history, with a loss close to this magnitude experienced only during the height of the 1980s and 2008–2009 recessions. In a world where there was 100% resistance to first-line antimicrobials, by 2050 Canada would lose more than the equivalent of the combined GDPs of Prince Edward Island and Nova Scotia, or one-quarter of the manufacturing sector GDP each and every year (StatCan, 2018c).

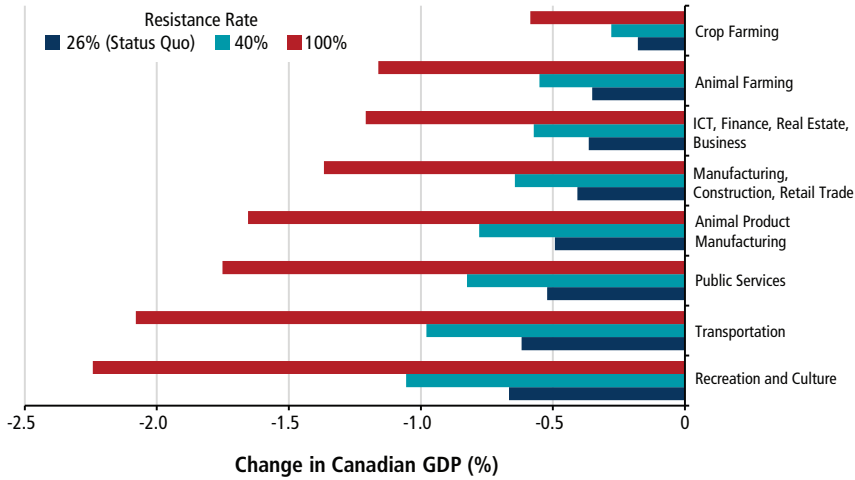


Figure 4.6

Change in Canadian GDP by Industry, 2050

This figure plots the percentage point decline in GDP for eight Canadian industry sectors in 2050 based on the three resistance scenarios: resistance to first-line antimicrobials remains constant at 26% (navy blue), reaches 40% resistance (teal), and reaches 100% resistance (red) by 2050.

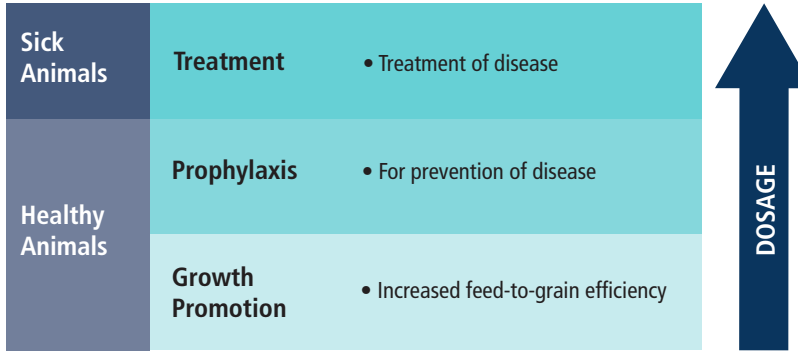
Since the deaths attributable to AMR permanently reduce the size of the labour force, the effect of AMR accumulates through time. As depicted in Figure 4.5, even if resistance were to remain constant at its 2018 level, the Canadian economy will still cumulatively lose about $268 billion in GDP between 2018 and 2050. If resistance reaches 40% or 100%, the impacts of AMR could result in an estimated $388 billion or $750 billion loss in GDP during this period, respectively. In a sense, the future value of antimicrobials is the difference between the status quo and a hypothetical world in which antimicrobials no longer work at all. The Panel interprets this difference — $800 billion — as the *future economic value* of antimicrobials. This value is under increasing risk as the world runs out of effective antimicrobials.

4.3 THE IMPACT OF AMR ON THE ANIMAL FARMING INDUSTRY

In 2018, the animal farming industry directly contributed about $5.6 billion to the Canadian economy (StatCan, 2018c). Like other similarly sized agricultural industries such as crop farming, fishing, and forestry, animal farming is a small share of the economy, accounting for less than 1% of GDP in 2016. While animal farming has grown at similar rates as the Canadian economy, employment has declined significantly over the last two decades (StatCan, 2018a, 2018c). Spread

across the country, Canadian animal farmers are part of a global supply chain, which has replaced labour with capital, investing more in automatic feeders than farmhands.

The animal farming industry accounted for 78% of the total AMU (as measured by kilograms of active ingredient) in Canada in 2016 (PHAC, 2017a). As illustrated in Figure 4.7, antimicrobials are used for three main purposes in animal farming. First, as in humans, they are used to treat infections. The therapeutic use of antimicrobials in clinically sick animals is central to animal welfare and food production (Aarestrup, 2015; O'Neill, 2015). Especially on farms with poor conditions, antimicrobials are an effective animal health tool. A significant volume of antimicrobials has historically been used prophylactically in animals to prevent the development of infections within healthy herds or flocks, and to promote growth (weight gain). AMU for prevention and growth promotion is particularly widespread in intensive animal food production, where animals are often stocked at high densities and kept in confined conditions (Aarestrup, 2015; O'Neill, 2015). As Aarestrup (2015) points out, "[a]ntimicrobials are an integrated and routinely used management tool, and in many cases, farmers might not even be aware that they are using them or for what purpose."



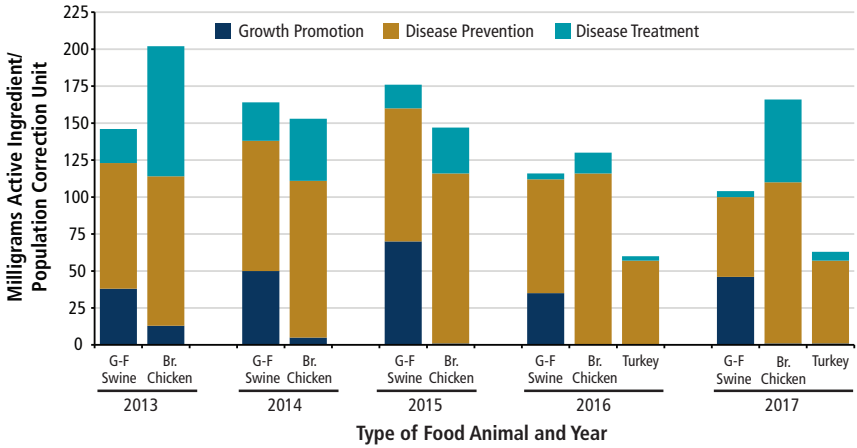
Reproduced with permission from O'Neill (2015)

Figure 4.7

Three Uses of Antimicrobials in Food Animals

This figure compares three uses and relative dosage of antimicrobials in food animals.

As shown in Figure 4.8, the majority of antimicrobials consumed by Canadian farm animals from 2013 to 2016 were used for preventative purposes. Since 2006 in the European Union, and since 2018 in Canada, using antimicrobials for growth promotion has been banned (EC, 2005; GC, 2018). Recent regulatory changes in Canada that require veterinary prescription to use medically important antimicrobials in food animals, combined with voluntary actions of producers, market requirements, and other influences, are anticipated to markedly reduce prophylactic AMU in food animals in Canada. It is expected that these regulatory changes will drastically decrease AMU in animal agriculture.



Data Source: PHAC, 2017a

Figure 4.8

Uses of Antimicrobials in Canadian Food Animals, 2013–2016

This figure shows trends in the proportion of antimicrobials by purpose, used on grower-finisher pigs (G-F swine), broiler chickens (Br. Chicken), and turkey sentinel farms based on estimates of mg of use per kg of animal. Grower-finisher pigs and broiler chickens are animals in which there is high AMU in conventional intensive farming. There is a trend of reduced AMU in these animals.

4.3.1 The Benefits of AMU to Promote Farm Animal Growth Has Declined Over Time

In principle, antimicrobial growth promoters (AGPs) can have a positive influence on farm productivity through at least two mechanisms — by "enhancing the growth rate and feed efficiency of animals and by potentially increasing labour or capital productivity by substituting AMU for hygiene-management practices in animal housing or transportation" (Laxminarayan *et al.*, 2015). There is considerable variability in growth response to growth promotional and preventive (or sub-therapeutic) doses of antimicrobials according to animal species, age, and genetic makeup, and to specific hygiene and management conditions

(Laxminarayan *et al.*, 2015). The terminology around growth promotional and sub-therapeutic use is confusing and confused, but it describes specific regulated quantities of antimicrobials, often dating to regulatory approval in the 1950s (Prescott, 2006). Despite 50 years of AGP use, recent, reliable data on its effect on productivity are lacking; however, there is growing evidence that suggests it does not have as much economic benefit as previously thought, particularly in countries with advanced farming techniques (Aarestrup, 2015; O'Neill, 2015). Studies conducted before the 1980s reported an improvement as high as 5 to 15% in the growth rate and feed efficiency of pig, poultry, and cattle fed sub-therapeutic antimicrobials (Cromwell, 2002). More recently, studies conducted in Denmark, Sweden, and the United States point to more limited effects of using AGPs: statistically insignificant or between 1 and 3% improvement in production. Seven such studies are summarized in Table 4.4.

Table 4.4

Productivity Change from the Withdrawal of Antimicrobial Growth Promoters

Country	Farm Animal	Year	Effects	Source
Denmark	Broiler chickens	1995–1999	No effect on productivity Minor increase (<1%) in feed conversion ratio	Emborg *et al.*, 2001
Sweden	Dairy calves	2007	Cost saving of US$10 per calf	Berge *et al.*, 2009
United States	Broiler chickens	1998–2001	Cost saving of 0.45% per broiler chicken	Graham *et al.*, 2007
United States	Broiler chickens	1998–2001	1% decrease in feed conversion ratio	Engster *et al.*, 2002
United States	Grower-finisher pigs	1990 and 1995	0.5% decrease in daily average weight gain 1.1% decrease in feed conversion ratio	Miller *et al.*, 2003
United States	Broiler chickens	2009	No effect on production	MacDonald & Wang, 2011
United States	Feeder to finish pigs	2011	1% reduction in production	Key & McBride, 2014

This table compares the effects of antimicrobial growth promoters on animal productivity in three countries and across seven studies.

Drawing from this literature, Sneeringer *et al.* (2015) simulated the removal of antimicrobials used for production purposes generally, showing that AGPs have limited effects on the productivity of raising livestock at the farm level, around 1 to 3%. Laxminarayan *et al.* (2015) used a CGE model to estimate the potential loss to global meat production if AGPs were banned worldwide. They compared a high-growth impact scenario (based on 1980s data) to a low-growth impact scenario (based on 2000s data), projecting that a ban on AGPs would decrease global annual meat production by between US$14 and US$44 billion. For Canada, they estimated an AGP ban would decrease production between 1.1% (2000s data) and 5.6% (1980s data), leading to a loss of between $180 and $880 million in meat value each year (Laxminarayan *et al.*, 2015).

One explanation as to why the growth response of farm animals to antimicrobials has declined over time is that animal health and herd management practices have improved during the same period. The gradual decline in efficacy of AGPs in animal farming has been coupled with significant improvements in nutrition, hygiene, animal husbandry, infection control, vaccination, biosecurity, waste management, diagnostics, benchmarking, and other practices[15] (Aarestrup, 2015; Laxminarayan *et al.*, 2015; O'Neill, 2015). As Laxminarayan *et al.* (2015) noted, with "drastic changes in the animal industry over the last 30 years in the OECD countries, all [nutrition, hygiene practices, genetic potential of animals, health status] of these key parameters have changed, potentially explaining the decrease in the efficacy of AGP." An additional explanation might be the development of resistance in the largely unknown microbial targets of AGPs.

The experiences of Denmark and the Netherlands demonstrate that reducing AMU at farm levels does not have major effects on productivity when coupled with good herd management practices. Beginning in 1995, Denmark began banning certain antimicrobials, eventually phasing out all AGPs by 2000. It also established DANMAP, a surveillance system to monitor AMR in farm animals and humans (Cogliani *et al.*, 2011; O'Neill, 2015). Between 1992 and 2008, AMU in pigs declined by 51% while production increased by 47%, highlighting that AGPs are not necessary for competitiveness (Cogliani *et al.*, 2011). However, during this period, the number of pig farms declined, suggesting that "only the farms with good farm management techniques in place were able to remain profitable" and that there were "up-front costs to Danish farmers as they moved to new farming practices less reliant on antimicrobials" (O'Neill, 2015). This

15 These practices may include "fully enclosed and more tightly constructed housing, improved in-house climate control, expanded biosecurity protocols aimed at wildlife and rodent access, changing clothes and washing for workers, and limited access for outsiders, all-in, all-out production, and feed formulations targeted at stage of production" (Laxminarayan *et al.*, 2015).

example underscores the point that, while reducing AMU may not hurt the animal farming industry as a whole, farms that cannot afford or choose not to invest in herd management may become unprofitable.

While the Netherlands established its surveillance system to monitor AMR — MARAN — in 1999, it did not ban AGPs until the E.U.-wide ban came into effect in 2006 (O'Neill, 2015). Between 2007 and 2012, Dutch animal farming production remained constant despite a decline in AMU of 56% (McKenna, 2014). By adopting good herd management practices, the "Dutch experience shows that it is possible to reduce antibiotic use in a short time period and still maintain production" (O'Neill, 2015).

Significant data gaps prevent a more comprehensive estimate of the impact of AMR on animal farming productivity. Canada does not have a national system for reporting resistance in important endemic animal pathogens in different branches of animal agriculture; national data are difficult to obtain. The Panel is not aware of published estimates related to the cost of responding to current and anticipated increased AMR, which may include:

- the possible costs of requiring veterinary prescriptions for antimicrobials in food animals;
- adjustments in production costs as a result of changes in production methods;
- the impact of any future benchmarking practices (e.g., development of a "Yellow Card" system) on requirements for improved production buildings (e.g., improved ventilation systems, improved biosecurity systems); or,
- the costs of increased vaccination and improved nutrition.

4.3.2 AMR May Affect Animal Farming Productivity

The Panel recognizes resistance as an increasing and serious problem in some important endemic food animal pathogens. To explore the magnitude of the effect of AMR on animal farming, the Panel estimates increased resistance could reduce animal farming MFP (Section 4.1) by up to 10% by 2050 as a result of declining animal productivity, increasing animal death and disease, and the cost of investing in changed herd or flock management practices or new production facilities. In the Panel's model, a reduction in animal farming *productivity* (i.e., the MFP) of 10% translates into about a 3% reduction in animal farming *production* (Laxminarayan *et al.*, 2015; Nicholson, 2018).

- **Animal Productivity —** The literature does not support a significant decline in animal productivity as a result of removing medically important antimicrobials in countries with well-developed intensive animal agriculture. Estimates suggest a productivity decline of between 0 to 3% as a result of reduced AMU for growth promotion, provided farms adopt good herd management practices (Sneeringer *et al.*, 2015).

- **Animal Health —** Most notably, the Panel is not aware of estimates of the negative effects on animal health resulting from increasing levels of AMR, which would limit the effectiveness of antimicrobials for therapeutic or preventative use. If AMR were to increase morbidity and mortality rates among farm animals, the decline in animal farming productivity could be far greater than any decline due to removing antimicrobials for growth promotion or disease prevention.

- **Herd Management Practices —** If, as the Panel believes, AMR is a problem that is only going to get worse, the animal farming industry will be forced to adopt better herd management practices or face productivity declines. Since the Panel's model assumes no adaptation or changes to herd management practices, simulating an up-to-10% decline in productivity may capture some of the adaptation costs of improving nutrition, hygiene, animal husbandry, infection control, vaccination, biosecurity, waste management, diagnostics, and benchmarking.

It is exceedingly difficult, in part because national data do not exist, to definitively predict AMR's impact on the animal farming industry. The estimates in the Panel's model are based on what might happen under current herd management practices and on a trajectory of increasing resistance in some important food animal pathogens. However, if herd management practices improve, AMR may have a relatively small effect on the animal farming industry, whereas if herd management practices remain constant, and bacterial pathogens continue to develop or acquire resistance and continue to spread, AMR may have a sizeable impact on both the Canadian and international markets. AMR is a current risk and future threat to animal farming. As will be discussed in Chapter 6, this suggests there is a need for a multifaceted approach to addressing AMR in animal farming, including more and better surveillance, biosecurity (i.e., infection prevention and control), stewardship, and research and innovation.

4.3.3 AMR May Affect Animal Product Trade

Although diversifying through trade with China, Japan, and other countries, over half of Canadian trade in animal products is with the United States (StatCan, 2018b). Since Canadian and U.S. farms have similar practices and use similar quantities of antimicrobials (Sneeringer *et al.*, 2015), and since recent regulatory changes in food animal AMU are generally in lock-step, it is unlikely that rising AMR would have a major impact on North American trade in animal products. However, the situation in relation to trade in animal products with other countries may become quite different as global efforts to curtail AMR increase.

As noted in Section 2.2.2, changes made in 2018 to Canadian federal regulations that banned AGPs in food animals should decrease AMU in food animal production, and the forthcoming *Pan-Canadian Action Plan* may lead to further decreases (GC, 2018). Similarly, AMR and its influence on global trade in animal products have been the subject of intense discussions at the Codex Alimentarius Commission, the international body that sets standards for food safety in global trade (FAO *et al.*, 2015; George, 2019). Currently, these guidelines provide countries with the option to limit the import of food products with antimicrobial-resistant bacteria, although progress on developing international standards related to AMU has been slow, owing to technical and scientific complexity, political and legal obligations, and the "huge number" of Codex standards and guidelines (George, 2019).

As food animals and food animal products are "traded worldwide... the selection of AMR in one country is today a problem for all countries" (Aarestrup, 2015). As global concern about AMR increases, it is possible that, like other countries, Canada will restrict the import of animal products from countries where AMU in food animals is inappropriate and/or AMR in imported foods are identified as problematic. Yet, few "if any countries currently systematically test food imports for the presence of AMR microorganisms (whether immediately harmful or not)" (George, 2019). The reasons given for inaction are often centred on claims there is not enough scientific evidence and/or the necessity of first complying with the World Trade Organization (George, 2017, 2019). The Canadian Food Inspection Agency (CFIA) does not monitor any imported animal products for resistant bacteria (PHAC, 2015) and Codex standards remain complex and politically charged (George, 2019).

Having already banned AGPs in 2006, the European Parliament recently voted to limit the preventative use of antimicrobials and ban the use of unprescribed antimicrobials and human-reserve antimicrobials in food animals (EP, 2018). This legislation will also restrict the import of animal products from countries using MIAs for growth promotion or disease prevention. The Canadian animal farming industry uses more antimicrobials than most European countries, ranking 8th among 31 OECD countries in mg for drug/kg of animal in 2016 (when using Canadian average weights at treatment) (Figure 4.9), and therefore may be a possible target for European trade restrictions. Even in the absence of formal trade restrictions, Canadian animal products could become less attractive as customers in other countries grow more concerned about global AMR. If Canada restricts imports from countries where resistant bacteria in animal products have been identified, these countries might retaliate by stopping importation of Canadian animal products rather than alter AMU in animal production.

In sum, if Canada does not decrease AMU in the long run, other countries will begin to apply pressure, perhaps by restricting Canadian imports. The Panel modelled such a scenario — where Canadian exporters of animal products face trade restrictions from import markets — as a 10% reduction in food animal exports. The Panel notes that AMU in animal agriculture is expected to decrease significantly as a result of the recent regulatory changes discussed above.

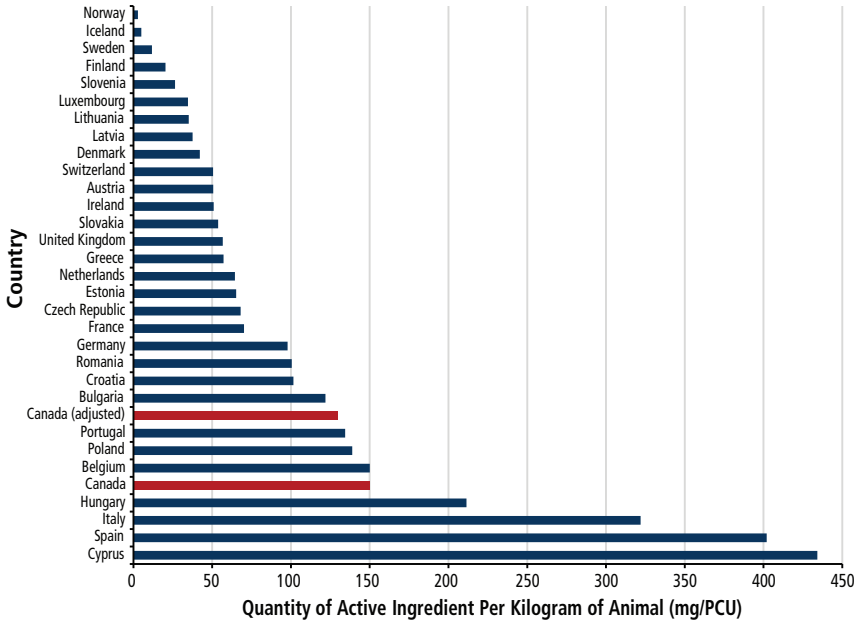


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Figure 4.9

Sales of Antimicrobials for Use in Animal Farming, 2016

This figure compares the sales of antimicrobials for use in animal farming between Canada and 30 European countries. The *adjusted* Canadian bar is based on the weight of the average Canadian animal at treatment, as opposed to the European average animal weight.

4.3.4 The Canadian Animal Farming Industry May Lose Between $26 to $235 Billion by 2050 as a Result of AMR

AMR cost the Canadian animal farming industry an estimated $200 million in 2018 through its impact on labour productivity. Current resistance (26% resistance to first-line antimicrobials) reduced the number and productivity of agricultural workers, leading to about a 0.2% decline in animal farming GDP. If AMR remains at its current level, it will cumulatively cost the animal farming industry $26 billion by 2050 in lost worker productivity. As illustrated

in Figure 4.10, if resistance to first-line antimicrobials were to grow to 40%, the animal farming industry could lose about an additional $11 billion due to lost worker productivity. Even under this conservative assumption, the declining health of the labour force in the animal farming industry could reduce animal farming GDP by 0.5% per year by 2050.

However, as noted in Section 4.1.2, the reduction in economic activity in animal farming is likely underestimated by the Panel's model since it does not account for changes in animal productivity or animal product trade. To account for some of these additional effects on animal farming, the Panel simulated two additional scenarios:

- **Up to 10% Productivity Decline —** Primarily as a result of growing resistance in food animal pathogens, and to a lesser extent reducing AMU for growth promotion and prevention, the productivity (MFP) of the Canadian animal industry declines by up to 10% by 2050. This effect is large, potentially costing up to $185 billion between 2020 and 2050.

- **Up to 10% Export Restriction —** As a result of concerns over AMU in animals and the spread of related AMR, Canada faces export restrictions from import markets in other countries. Canadian animal food product exports decline by up to 10%. This effect is much smaller than the effect of a productivity decline, potentially costing up to $4 billion in exports over the 30-year period.

The individual and combined effects of reductions in labour productivity, as well as 10% reductions in animal productivity and exports, are illustrated in Figure 4.10. Based on simulations of the Panel's model, AMR could cost the animal farming industry upwards of $225 billion over the next 30 years, if resistance to first-line antimicrobials reaches 40% and if animal productivity is 10% lower than today.

As AMR increases in food animal pathogens — jeopardizing the health of farm animals — and as decreased AMU leads to changing animal farming practices, the industry will continue to adjust, finding new ways to use fewer antimicrobials by innovating in animal husbandry and housing, herd management, vaccination, and disease eradication. What are not clear are the longer-term implications of those strategies for animal health, farm profitability, and food prices. The Panel believes that a first step towards more clarity around these potential impacts is to develop a national system for reporting AMU and AMR in food animal agriculture (especially related to medically important antimicrobials and endemic animal pathogens), as well as better reporting on production and productivity in food animal agriculture.

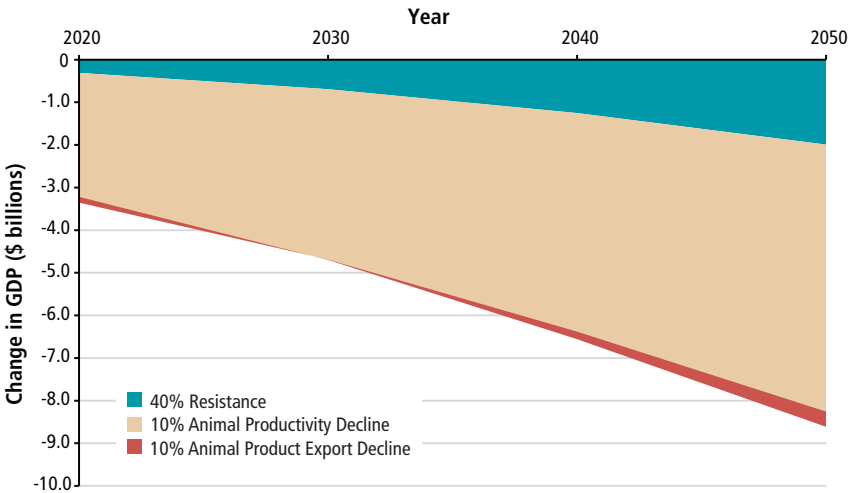


Figure 4.10

Possible Impacts of Antimicrobial Resistance on Canada's Animal Farming Industry, 2020–2050

This figure combines the cumulative annual decline in animal farming GDP resulting from three sources: (i) resistance to first-line antimicrobials reaches 40% by 2050 (teal area); (ii) a 10% decline in food animal productivity by 2050 (beige area), and (iii) animal product export trade restrictions (orange area). By 2050, the cumulative effect of antimicrobial resistance (AMR) could cost almost $9 billion per year.

4.4 CONCLUSION

The Panel estimates that about 1 in 50 deaths in Canada were attributable to resistant bacterial infections in the 10 important clinical syndromes in 2018. Should the rate of resistance to first-line antimicrobials increase to 40% by 2050, 1 in 26 deaths will be caused by resistant bacterial infections, eliminating almost $400 billion of GDP along the way. This underscores the substantial time lag between the cause and effect of AMR, requiring action today for a problem that gets much worse in the future. It is difficult to estimate the future costs and impacts of AMR based on current data given the intrinsically uncertain pace of AMR emergence and spread; in addition, the estimates presented in this chapter are based on several judgments and modelling assumptions that can be challenged. On balance, these assumptions result in more conservative estimates of future impacts. The magnitude of these estimates is alarming, sending a strong signal for global investment and cooperation.

5

The Social Impacts of Antimicrobial Resistance Today and in a Future with Limited Antimicrobials

- Risk Factors Associated with Resistant Infections in Humans
- The Potential Severity of Infections in a Future with Limited Antimicrobials
- Potential Social Impacts of AMR in a Future with Limited Antimicrobials
- Conclusion

5 The Social Impacts of Antimicrobial Resistance Today and in a Future with Limited Antimicrobials

Key Findings

Contact with the healthcare system is an overarching risk factor for acquiring a resistant infection. This is in part because those seeking healthcare may have a history of antimicrobial treatment, or prior conditions that predispose them to resistant infections (e.g., people with compromised or weaker immune systems, including the very young and older adults).

The greatest risk factor for acquiring a resistant infection is previous antimicrobial treatment.

If there are limited antimicrobials in the future, more people in Canada will see their quality of life decline as a result of the morbidity and mortality associated with resistant infections. This impact will be unequally distributed, as some socio-demographic groups will be more at risk of infection.

Increasing rates of AMR will directly impact healthcare delivery, restrict travel, and increase surveillance, isolation, and quarantine.

Responses to increased AMR will likely impact society through decreased trust, social capital, and well-being, and increased social inequality in Canadian society.

This chapter summarizes key clinical, behavioural, and socio-demographic risk factors that increase the likelihood of developing a resistant infection, and how these cluster among certain social groups. The Panel drew on summaries of published clinical case studies to provide a tangible illustration of the social impacts of AMR today in Canada. Next, drawing on epidemiological and clinical evidence, and supported by social science research, the Panel reflected on how Canadian society might be impacted in a future with limited antimicrobials. In this hypothetical future, impacts are explored as they relate to individuals, communities, and social behaviours, and to policies and legislation likely to be instituted to limit the spread of AMR. Impacts are described through changes to a set of metrics: changes to inequality,[16] social capital, trust, and well-being.

16 The Panel elected to use the term *inequality* over *inequity*. The latter indeed refers specifically to inequalities that are preventable, modifiable, and deemed unfair, notably because they disproportionately affect certain groups because of structural constraints. However, a number of the key risk factors discussed in this chapter (e.g., age) do not fall into this category, and thus the term *inequality* was deemed more inclusive in this context. Nevertheless, the Panel agreed that a future with limited antimicrobials would most likely pose singular threats to equity in Canadian society, and that this question deserves specific consideration in future AMR assessments.

Based on its research and expertise, the Panel developed vignettes to describe plausible social scenarios, offering a more personal view of the social impacts of a future with limited antimicrobials.

5.1 RISK FACTORS ASSOCIATED WITH RESISTANT INFECTIONS IN HUMANS

In this section, the Panel explores four categories of risk factors — socio-demographic, clinical, behavioural, and travel — that increase the risk of acquiring a resistant infection. However, the Panel emphasizes that no one is immune to bacterial infection. For instance, a healthy adult who is at low risk for infection based on all of the risk factors described in this section may become infected from eating contaminated meat or produce, such as chicken contaminated with *Salmonella* or lettuce contaminated with *Escherichia coli*. How risk factors for bacterial infections translate to risk factors for *resistant* bacterial infections is not always clear due to a lack of data. However, where possible, the Panel presents risk factors specific to resistant infections. While this section aims to highlight areas requiring the most attention, it is important to remember that AMR is a population-wide issue.

5.1.1 Socio-Demographic Factors Increasing the Risk of Resistant Infection

Age

Resistant infections disproportionately affect certain age groups. Older adults are at greatest risk, followed by infants (particularly neonatal patients) and children. These higher risks arise out of a combination of immune system characteristics (underdeveloped or depressed in neonatal patients and older adults, respectively) and higher exposure to infections. Young adults also feature in this section as they are disproportionately exposed to certain infections.

As the immune systems of neonatal patients, especially those born premature, are underdeveloped, such patients are particularly at risk of infection (Simon *et al.*, 2015). Some of the most fragile pediatric patients are those who spend time in neonatal intensive care units, where outbreaks of resistant organisms can occur (Lukac *et al.*, 2015). Mortality rates in neonates infected with ESBL-producing Enterobacteriaceae have been estimated at greater than 30% (Stapleton *et al.*, 2016; Flokas *et al.*, 2017b). Box 5.1 describes the case of an infant with a resistant infection in Winnipeg, Manitoba.

Box 5.1
Osteomyelitis in a Manitoba Infant Caused by Resistant Bacteria Acquired in Pakistan

While visiting relatives in Pakistan, a four-month-old female infant sustained burns on the front of her lower legs from an electric steamer. She was treated locally with a standard antibiotic and daily dressing changes, but her wounds became infected within a week. Her family flew home to Winnipeg for further treatment, where examination revealed full-thickness burns on both legs and feet, three gangrenous toes on the right foot, and ear discharge. The infant underwent surgery for wound debridement and toe amputation, and began treatment with vancomycin and meropenem (a carbapenem antibiotic). Samples from the patient's ears and nostrils grew two strains of methicillin-resistant *Staphylococcus aureus* (MRSA) (one Canadian). Swabs from the left leg and right foot grew MRSA as well as multi-drug resistant (MDR) strains of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Both types of Gram-negative bacteria were later confirmed to be carbapenemase producers; the *K. pneumoniae* isolate was also an ESBL producer. One week after admission, a possible bone infection on the patient's right foot was investigated; samples produced MDR *Providencia stuartii* and another strain of *P. aeruginosa* with a different susceptibility pattern. Based on the varied susceptibilities of all isolates, the patient was given six weeks of therapy with vancomycin, meropenem (initially intermittent but switched to continuous infusion), ciprofloxacin (a fluoroquinolone), and amikacin (an aminoglycoside). After the addition of amikacin, the patient improved rapidly and did not experience any other complications. This case highlights the extensive testing that must be performed when multiple types of bacteria with suspected resistance are present, as well as the complex and potentially toxic antimicrobial combinations that may be required for treatment. It also highlights how a Canadian hospital can be exposed to resistant pathogens from a high AMR country (Section 5.1.4).

(Sepehri *et al.*, 2014)

Aside from neonatal patients, infants and children do not represent the most affected populations for many resistant infections from a prevalence standpoint; however, recent increases in infection rates among pediatric patients have generated concern (Lukac *et al.*, 2015). From 2011 to 2016, the rate of healthcare-associated MRSA BSIs remained stable in adult hospitals in Canada, but increased more than five-fold in pediatric hospitals (PHAC, 2017a). One study in northern Saskatchewan showed that almost half of all community-associated MRSA cases occurred in children ages 0 to 10 years (Golding *et al.*, 2010). Furthermore, PHAC (2017a) notes that "the rate of community-associated MRSA infection in pediatric hospitals from 2011 to 2016

was consistently higher than the rate in adult and mixed-patient hospitals." These trends in rising infection rates may signal an increasing impact of AMR in this population.

While older adults and the very young are usually more at risk of acquiring infections generally, greater exposure to some infections disproportionately impacts younger adults. Gonorrhea is most common in those aged 20 to 24 in Canada, but resistant gonorrhea occurs more frequently in adults aged 25 or older (PHAC, 2014a). In an Ontario study that compared the characteristics of patients who acquired quinolone-susceptible and quinolone-resistant gonorrhea, the resistant group had a higher proportion of patients aged 30 and over (Ota *et al.*, 2009).

Older adults are particularly at risk for a variety of infections, in part due to normal aging processes, such as impaired immunity and changes in the composition of gut microbiota (Berg & Cassells, 1990). The risks introduced by these underlying factors may be further compounded by co-morbidities and the clustering of other risk factors such as living in long-term care facilities, more frequent hospital contacts, and taking more antimicrobials (Cimolai, 2010; Kline & Bowdish, 2016; Shin *et al.*, 2016; Marshall *et al.*, 2017). Older age is a key risk factor for CDI, for example, with 70 to 80% of infections occurring among those 65 years or older (Shin *et al.*, 2016; Asempa & Nicolau, 2017). Furthermore, a study of CDI in over 4,000 patients in six Ontario and Quebec hospitals shows an age-graded association for the risk of healthcare-associated CDI (Loo *et al.*, 2011).

Sex

According to Canadian AMR surveillance data from 2015 and 2016, most resistant pathogens affect men and women at similar rates (PHAC, 2017a), but men are more likely to be affected by carbapenemase-producing organisms and gonorrhea. However, in the case of gonorrhea, these epidemiologic data may be affected by underreporting of asymptomatic infections, and certainly underestimate the social impacts of these infections, which are largely experienced by women.

The largest reported difference in infection rates between sexes involved carbapenemase-producing organisms (70% of patients were male) (PHAC, 2017a). In a cohort of 458 BSIs caused by beta-lactamase-producing Enterobacteriaceae between 2000 and 2008, 283 (62%) occurred in males (Chaubey *et al.*, 2014). However, of 247 people with community-onset ESBL-producing *E. coli* infections from 2004 to 2006, 81% were female (Laupland *et al.*, 2008a). This increased risk was likely due, in part, to the fact that *E. coli* was isolated from the urine in almost all patients and females have a much higher risk of experiencing

community-onset UTIs than males (Laupland *et al.*, 2007b). Therefore while males may be at greater risk of infection with carbapenemase-producing organisms overall, females may be at greater risk of acquiring certain syndromes.

Reported cases of gonorrhea are also higher among men across Europe and North America, (Abraha *et al.*, 2018), as well as in Canada, where 63% of infections occur in males (PHAC, 2017a). The Canadian Antimicrobial Resistance Surveillance System (CARSS) report does not provide a sex breakdown for *resistant* gonorrhea infections in Canada, but studies from other countries have indicated that men also have a greater risk of acquiring resistant gonorrhea (Abraha *et al.*, 2018). However, an important caveat is that the lower reporting rates among women may be affected by the high proportion of asymptomatic infections in this population: up to 80% of females with gonorrhea can be asymptomatic, whereas only 10 to 20% of males have no symptoms (Wong *et al.*, 2004). Furthermore, as mentioned in Section 2.3, the negative impacts of gonorrhea (and some other STIs) are disproportionally experienced by women.

Living Conditions

Living conditions that involve overcrowding and/or poor housing conditions — including homeless shelters, military barracks, prisons, and subsidized housing — pose risk factors for community-associated MRSA SSTIs (Gorwitz, 2008; Loewen *et al.*, 2017). Staphylococci establish reservoirs in households or at community sites, either by colonizing individuals or contaminating the environment, which leads to further spread and recurrent infections (Knox *et al.*, 2012; Knox *et al.*, 2015). Several Canadian studies have identified incarceration and homelessness as risk factors for MRSA infection (Gilbert *et al.*, 2006; Achiam *et al.*, 2011; Vayalumkal *et al.*, 2012). Similarly, homeless and disadvantaged urban populations in Canada experience a higher prevalence of invasive pneumococcal disease, although it has not been demonstrated that this risk extends to resistant infections (Plevneshi *et al.*, 2009; Vanderkooi *et al.*, 2011; Marrie *et al.*, 2017).

In contrast, while imprisonment and homelessness have also been associated with MDR TB in other countries (Faustini *et al.*, 2006; Story *et al.*, 2007; Biadglegne *et al.*, 2015; Pradipta *et al.*, 2018), they do not appear to be risk factors in Canada. Indeed, while homeless people in Canada experience higher rates of TB, drug resistance is rare in this population (Khan *et al.*, 2011).

Indigenous Populations

As a result of a legacy of colonialism and the associated intergenerational trauma (TRC, 2015), Indigenous people in Canada experience a number of structural inequities that put them at higher risk of acquiring infections

relative to the rest of the population (Andermann, 2017). TB (PHAC, 2017a), pneumococcal disease (Kovesi, 2012; Das & Kovesi, 2015; Marrie *et al.*, 2017), and gastrointestinal infections (Bradford *et al.*, 2016) disproportionately impact Indigenous people in Canada. They are also disproportionately affected by STIs relative to non-Indigenous people in Canada: the rate of chlamydia is approximately seven times higher among First Nations adults than the overall population (PHAC, 2013). However, in Canada, none of these conditions are associated with a higher risk of resistant infections among Indigenous people relative to non-Indigenous people. In fact, TB surveillance data indicate that, while Indigenous people have higher rates of TB, they also experience much lower rates of resistant TB than Canadian-born non-Indigenous people (PHAC, 2017d; LaFreniere *et al.*, 2019a).

As such, MRSA is the main resistant infection disproportionately affecting Indigenous people. MRSA surveillance data from 1995 to 2002 indicated that, compared to non-Indigenous people, hospitalized Indigenous people were more likely to have a community-associated strain (Ofner-Agostini *et al.*, 2006). Furthermore, there is evidence that rates in northern communities have been increasing since the early 2000s (Larcombe *et al.*, 2007; Dalloo *et al.*, 2008; Golding *et al.*, 2011; Muileboom *et al.*, 2013). Inadequate housing and a lack of running water have been suggested as important modifiable risk factors for the high MRSA rates in Indigenous communities (Hennessy *et al.*, 2008; Muileboom *et al.*, 2013; Loewen *et al.*, 2017).

Occupation

Work that involves contact with agricultural animals is a risk factor for resistant infections. In a meta-analysis, Tang *et al.* (2017) found that the association between an intervention to reduce AMU in food-producing animals and a decrease in AMR was stronger for humans in direct contact with food-producing animals (e.g., farmers). In Ontario, high rates of MRSA colonization have been observed in pigs and pig farmers (Khanna *et al.*, 2008), a finding confirmed by a systematic review indicating that MRSA carriage is indeed higher in this population, particularly among those who directly and frequently contact animals such as pigs and cattle (Liu *et al.*, 2015). Compared to veterinarians and slaughterhouse workers, farmers have higher rates of MRSA carriage, likely due to the intensity of their contact with live animals (Liu *et al.*, 2015), though MRSA colonization rates are still higher than expected among non-farmers who frequently contact animals, such as horse owners, veterinarians, and veterinary personnel (Weese, 2010). Box 5.2 presents an example of animal-to-human transmission in Guelph, Ontario.

Box 5.2
Horse-to-Human MRSA Transmission at a Veterinary Hospital in Ontario

In February 2004, a one-day-old foal was brought to a veterinary teaching hospital associated with the University of Guelph. It was admitted to the equine neonatal intensive care unit, diagnosed with acute renal failure and septicemia. It was cared for by university students involved in the Foal Watch program, which provides 24-hour nursing care to foals using 4-hour shifts. For most of their shift, students were in direct contact with the foal, which may have sat partially on their laps. Gloves were the only protective gear typically worn. By day 6 post-admission, MRSA nasal swabs from the foal came back positive and the foal had developed MRSA arthritis and omphalophlebitis (infection of the umbilical vein). Following these results, additional protective gear was worn during contact with the foal. Three female Foal Watch students were diagnosed with MRSA skin infections — two had contact with the foal on day 2 and one on day 4. Two had lesions on their hands, one on her lower arms and left leg, and one also had a facial rash resembling impetigo. In all cases, MRSA was isolated from the infected area. One patient was also colonized in two uninfected areas (nasal passages and groin). Of 103 additional Foal Watch students and veterinary personnel who were screened, 10 were colonized with MRSA, and all reported contact with the affected foal; however, personnel had also contacted other animals at the hospital, including other horses.

(Weese *et al.*, 2006)

Nativity Status

The greatest risk factor for MDR TB in Canada is being born outside of the country (Moniruzzaman *et al.*, 2006; Minion *et al.*, 2013; PHAC, 2017a). From 2005 to 2015, 83% of the Canadian TB cases that involved resistance to at least one first-line drug occurred in people born outside of Canada. Among more severe drug-resistant infections (MDR TB and extensively drug-resistant TB), 96% of cases involved foreign-born patients (PHAC, 2017a).

5.1.2 Contact with the Healthcare System Is the Greatest Risk Factor for Acquiring Resistant Infections

Many resistant pathogens share a similar set of clinical risk factors that often act jointly to increase a person's chances of developing a resistant infection (Guillamet & Kollef, 2016). Generally, people at risk of developing a resistant infection already have a disease or condition that compromises their health (Safdar & Maki, 2002; Trecarichi *et al.*, 2012; Guillamet & Kollef, 2016; Bassetti *et al.*, 2017; Tian *et al.*, 2018). In addition, the treatment process itself — which

may involve an in-patient stay, invasive devices (e.g., catheters), surgery, chemotherapy or radiation, or treatment with antimicrobials, biologics, or other drugs — further compounds the risk that these patients will acquire a resistant pathogen (Safdar & Maki, 2002; Ofner-Agostini *et al.*, 2009; Trecarichi *et al.*, 2012; Boyle & Zembower, 2015; Gerding & Lessa, 2015; Biehl *et al.*, 2016; Guillamet & Kollef, 2016; Bassetti *et al.*, 2017; Tian *et al.*, 2018).

Previous Treatment with Antimicrobials

The strongest, most consistent, and commonly agreed-upon risk factor for acquiring a resistant infection is previous antimicrobial treatment (Safdar & Maki, 2002; Ofner-Agostini *et al.*, 2009; Trecarichi *et al.*, 2012; Boyle & Zembower, 2015; Gerding & Lessa, 2015; Biehl *et al.*, 2016; Guillamet & Kollef, 2016; Bassetti *et al.*, 2017; Tian *et al.*, 2018). The mechanisms by which antimicrobial treatment leads to resistant infections are not fully established. In some cases, exposure to a particular antibiotic results in resistance to the same antibiotic class (Guillamet & Kollef, 2016). For example, treatment with cephalosporins (a class of beta-lactam antibiotics) is a risk factor for developing a beta-lactam-resistant bacterial infection (Ofner-Agostini *et al.*, 2009). Additionally, use of one type of antibiotic can also promote resistance to other types (Guillamet & Kollef, 2016). *P. aeruginosa* can develop cross-resistance when treatment with one antibiotic activates a membrane efflux pump system that allows it to expel multiple classes of antibiotics (Lopez-Dupla *et al.*, 2009). In one study, *P. aeruginosa* isolated from the blood of patients treated with ciprofloxacin (a fluoroquinolone antibiotic) prior to developing bacteremia was more likely to be resistant not only to ciprofloxacin, but also to several drugs in other classes, including cephalosporins and beta-lactams (Lopez-Dupla *et al.*, 2009).

The most important risk factor for MDR TB is previous treatment for TB (Jimma *et al.*, 2017; Asgedom *et al.*, 2018; Pradipta *et al.*, 2018). Using data from 1997 to 2008, Minion *et al.* (2013) reported that 1.1% of all culture-confirmed cases of TB in Canada were MDR, and most occurred in patients who acquired TB outside of Canada. This is lower than the global rate of MDR TB (3.6%); almost 50% of all cases of MDR TB worldwide occur in India and China (WHO, 2010).

One hypothesis is that treatment with antibiotics may lead to overgrowth of other types of pathogenic bacteria in the gut (Cascals-Pascual *et al.*, 2018). For example, exposure to antibiotics is the most important risk factor for CDI (both healthcare- and community-associated) (Schäffler & Breitrück, 2018). Disrupting the complex ecosystem of commensal gut bacteria with antibiotics leaves patients vulnerable to CDI (Schäffler & Breitrück, 2018). Historically, CDI was considered "a complication of broad-spectrum antimicrobial therapy in hospitalized patients" (Bloomfield & Riley, 2016; Eze *et al.*, 2017). However,

according to a 2018 review, cases of community-associated CDI have almost doubled in the past decade, and approximately half of CDI cases are now community-associated (Ofori *et al.*, 2018). Furthermore, depending on the country, approximately one-third to two-thirds of community-associated CDI cases do not involve patients who were previously treated with antibiotics (Bloomfield & Riley, 2016; Ofori *et al.*, 2018); the Panel notes, however, that some of these studies did not have complete data regarding antimicrobial exposure, and therefore the range may be an over-estimate. Other factors are, however, clearly playing a role.

Hospitalization and Long-Term Care

Although some resistant organisms (e.g., MRSA) have emerged as major community-based pathogens (Knox *et al.*, 2015), others are primarily found in healthcare facilities and hospitalized patients (e.g., carbapenem-resistant Enterobacteriaceae) (Bassetti *et al.*, 2017). Thus, contact with a healthcare facility, particularly if it is prolonged, represents an important risk factor for developing a resistant infection (Safdar & Maki, 2002; Boyle & Zembower, 2015; Bassetti *et al.*, 2017). By comparing patients with resistant infections to patients infected with susceptible strains of the same species, studies in Canadian hospitals have identified an association between prolonged hospitalization and infection with resistant *Klebsiella* species, *E. coli*, and *P. aeruginosa* (Ofner-Agostini *et al.*, 2009; Parkins *et al.*, 2010). Using the same case-control approach at an Ottawa-area hospital, Allen *et al.* (1999) found that, compared to children who had not visited the hospital, children with one or more hospital admissions in the past year were more likely to have UTIs caused by resistant *E. coli*.

Hospitals are also a key *Clostridioides difficile* reservoir. Rooms occupied by patients with CDI are contaminated with *C. difficile* 9 to 50% of time, and recent hospitalization is a risk factor for CDI acquisition (Crobach *et al.*, 2018). Some studies have suggested an association between a longer hospital stay and CDI, but results have been inconsistent; however, LOS is strongly associated with *C. difficile* colonization[17] (reviewed in Eze *et al.*, 2017). For all infections, it is difficult to disentangle the influence of LOS from other risk factors for acquiring a resistant infection, such as severity of underlying illness and exposure to antimicrobials, since these factors may also be associated with longer hospitalization (Safdar & Maki, 2002).

17 Colonization with a pathogen may occur without causing any symptoms. This differs from an infection, whereby the pathogen causes an illness and there are symptoms of a syndrome.

Like hospitals, long-term care facilities are reservoirs for resistant pathogens. Residence in a long-term care facility is a risk factor for infection with ESBL-producing organisms and MRSA (Cimolai, 2010; Boyle & Zembower, 2015). For example, in North America the colonization rate for ESBL-producing Enterobacteriaceae among residents in long-term care facilities was estimated at 13% (Flokas *et al.*, 2017a).

Invasive Devices

Patients who require invasive devices such as catheters, feeding tubes, and ventilators face an increased risk of developing a resistant infection (Safdar & Maki, 2002; Ofner-Agostini *et al.*, 2009; Trecarichi *et al.*, 2012; Boyle & Zembower, 2015; Bassetti *et al.*, 2017; Tian *et al.*, 2018). This risk results from the potential for pathogens to contaminate the outer or inner surface of the tubing that these devices use to deliver or remove substances to and from the body (Gominet *et al.*, 2017). The tubing may develop a biofilm (an aggregate of microorganisms attached to its surface and within in an extracellular matrix), which is much more resistant to antimicrobials than planktonic (single, free-floating) cells (O'Flaherty & Crowley, 2014; Gominet *et al.*, 2017).

One Canadian study identified haemodialysis as one of the most important risk factors for developing a BSI caused by *S. aureus* (Laupland *et al.*, 2008c). In this study, the relative risks of acquiring methicillin-sensitive and -resistant *S. aureus* bacteremia were similar for heamodialysis patients (Laupland *et al.*, 2008c). Additionally, in intensive care units, a main risk factor for pneumonia caused by resistant bacteria is mechanical ventilation (Parker *et al.*, 2008; Bassetti *et al.*, 2018). Of note, patients who require invasive devices and procedures are likely to have other risk factors that increase their chances of acquiring a resistant infection, including having a serious illness or undergoing surgery (Safdar & Maki, 2002).

Surgery

As with invasive devices, surgery presents an opportunity for pathogens to breach the protective barriers of the body; thus, recent surgery is a risk factor for developing a resistant infection (Safdar & Maki, 2002; Boyle & Zembower, 2015). The most prevalent post-operative complications are surgical site infections (SSIs), which may be superficial (involving skin and subcutaneous tissue) or deep (involving soft tissue, organs, or body spaces) (Young & Khadaroo, 2014; GlobalSurg, 2018). In a systematic review of studies from across the globe, the median incidence of SSIs was 3.7%, and incidence was highest in tumour-related surgeries and transplants (Korol *et al.*, 2013). These two surgery types were also associated with the highest incidence of MRSA (Korol *et al.*, 2013).

According to a report on 29 Ontario hospitals participating in the Ontario Surgical Quality Improvement Network, the surgical outcome with the greatest need for improvement in 2017 was SSIs (HQO, 2017). Of particular concern is the frequency of SSIs caused by MRSA: the most recent data indicate that, in the United States, almost 43% of *S. aureus* SSIs were caused by MRSA in 2014 (Weiner *et al.*, 2016).

In patients undergoing solid organ transplantation, BSIs are the leading cause of mortality and morbidity (Berenger *et al.*, 2016). Kidney transplants are associated with UTIs, liver transplants with IAIs, and heart and lung transplants with chest infections such as pneumonia; these site-specific infections may progress to BSIs, or primary BSIs may develop due to catheterization or other factors (Berenger *et al.*, 2016; Kritikos & Manuel, 2016). Risk factors for infection may be present before the transplant (e.g., underlying diseases such as cystic fibrosis), may arise as a result of the transplant operation (e.g., tissue damage and other complications that could prolong surgery), or may develop after the transplant (e.g., reduced immune function caused by immunosuppressive drugs) (Fishman, 2011; Kritikos & Manuel, 2016). In a 10-year Canadian study (2003 to 2012) on risk factors for nosocomial BSIs following solid organ transplantation, VRE emerged as a key causal pathogen (Berenger *et al.*, 2016). No BSIs were due to VRE until 2010, and, by 2012, it was responsible for five of the eight BSIs caused by enterococcal pathogens (Berenger *et al.*, 2016).

Compromised Immune System or Disruptions to Gut Bacteria

Patients with existing diseases or conditions may be particularly vulnerable to developing resistant infections due to underlying aspects of their condition or because of effects of the medications needed to treat it (Safdar & Maki, 2002; Trecarichi *et al.*, 2012; Guillamet & Kollef, 2016; Bassetti *et al.*, 2017; Tian *et al.*, 2018). For example, those undergoing stem cell transplants have increased risk of infection because the procedure itself severely compromises the patient's immune system (Magauran & Salgado, 2011). CDI is particularly common in these patients, with studies indicating an occurrence rate ranging from 4 to 25% (reviewed in Lavallée *et al.*, 2017; Neemann & Freifeld, 2017). At a hospital in Quebec — a province that has been dealing with a CDI outbreak since 2003 — the incidence of CDI in patients undergoing certain types of stem cell transplants between 2002 and 2011 was 8.6% (65 of 760 patients) (Lavallée *et al.*, 2017). There are many other immunocompromised populations at a greater risk of resistant infection, including the very young or very old (Section 5.1.1), patients with HIV (Sabbagh *et al.*, 2019), and patients with cancer (particularly those receiving chemotherapy) (Bello-Chavolla *et al.*, 2018). Box 5.3 presents an example of a fatal resistant infection in a patient who was immunocompromised.

Box 5.3

Fatal Necrotizing Fasciitis in an Immunocompromised Patient at a Canadian Hospital

A 37-year-old man presented to a rural hospital in Canada with relapsed aplastic anemia (where the body does not produce enough blood cells due to damage to bone marrow) that had been diagnosed 10 months earlier. His condition had improved following immunosuppressive therapy, but his treatment compliance had gradually decreased. Immunosuppressive therapy was re-initiated, and on day 10 post-admission, he developed a fever with abdominal pain, followed by watery diarrhea. He was diagnosed with *E. coli* bacteremia and treated with a beta-lactam antibiotic, which dramatically improved his condition. On day 19, he developed a high-grade fever, severe rectal and leg pain, and his blood cultures grew *Aeromonas hydrophila*, an opportunistic, water-dwelling pathogen that primarily causes severe infections in immunocompromised people. His leg pain worsened, and an MRI on day 24 showed extensive necrotizing fasciitis in both legs. Testing of *A. hydrophila* isolates from the patient's blood and muscle tissue revealed multi-drug resistance. Despite multiple surgical procedures to remove damaged tissue, eventual above-knee amputations, and broad-spectrum antibiotics, the patient developed septic shock and died from cardiac arrest two hours after the final surgery. Given the gastrointestinal symptoms and *E. coli* bacteremia that preceded the *A. hydrophila* infection, the authors hypothesized that the patient's immunosuppressed state led to intestinal colonization with *Aeromonas*, followed by bacterial translocation through the wall of the gut, entry into the bloodstream, and seeding of soft tissue and muscle in the legs.

(Ugarte-Torres *et al.*, 2018)

Medications that damage the gut (e.g., chemotherapy) or disrupt the composition of commensal gut bacteria (e.g., antibiotics) result in susceptibility to CDI (Furuya-Kanamori *et al.*, 2015; Neemann & Freifeld, 2017; Schäffler & Breitrück, 2018) and colonization with antibiotic-resistant microbes (Cascals-Pascual *et al.*, 2018). Inflammatory bowel disease (IBD) has been associated with CDI (Nguyen, 2012; Furuya-Kanamori *et al.*, 2015; D'Aoust *et al.*, 2017), and it has been hypothesized that disruption of the gut microbiota that occurs in IBD patients might underlie this association (Rao & Higgins, 2016). Hospitalized IBD patients are more likely than non-IBD gastroenterology patients and general in-patients to become infected with MRSA and VRE, but the mechanisms for this increased risk are unknown (Nguyen *et al.*, 2011; Nguyen, 2012).

5.1.3 Certain Behaviours Can Increase the Risk of Acquiring a Resistant Infection

Behaviours that increase the risk of acquiring a resistant infection include certain sexual practices, substance use disorder, participating in certain sports, and having pets.

Sexual Practices

A person's sexual practices may elevate their risk of acquiring a resistant STI (Abraha *et al.*, 2018). In Canada, the three main STIs that are reported to public health agencies are chlamydia, gonorrhea, and syphilis[18] (PHAC, 2014a). Resistance is extremely rare in *Chlamydia trachomatis* (Mestrovic & Ljubin-Sternak, 2018). Although the syphilis rate has recently risen dramatically in Canada — increasing by 232% between 2002 and 2011 (PHAC, 2014a) — very limited data on the prevalence of resistant syphilis are available; however, a few resistant cases have been reported (Morshed & Jones, 2006; Martin *et al.*, 2009).

Due to increasing rates of infections and resistant *Neisseria gonorrhoeae*, gonorrhea is a concern in Canada and around the world (Dillon *et al.*, 2015; Alirol *et al.*, 2017; PHAC, 2017c; Abraha *et al.*, 2018; Blank & Daskalakis, 2018). An estimated 78 million people contract the disease each year and resistance, including to the last-resort treatment (extended-spectrum cephalosporins), has been reported in more than 50 countries (WHO, 2017d). The first case of ceftriaxone-resistant gonorrhea in Canada was observed in a woman in Quebec in 2017 (Lefebvre *et al.*, 2018). The patient acquired gonorrhea through a sexual relationship with a man who reported having unprotected sex in China and Thailand in 2016 (Lefebvre *et al.*, 2018). Similarly, a male patient acquired the second case of ceftriaxone-resistant gonorrhea following intercourse with two women, one from Taiwan and one visiting from China (Smyczek *et al.*, 2019).

Several sexual practices have been investigated as potential risk factors for acquiring resistant gonorrhea. A high number of sexual partners was identified by univariate analysis in several studies but only remained a statistically significant risk factor following multivariate analysis in one of these studies (Abraha *et al.*, 2018). Sex with partners abroad and commercial sex work have also been associated with a higher risk of resistant gonorrhea (Abraha *et al.*, 2018). There is potentially a correlation between men who have sex with men and resistant gonorrhea, but studies in several countries have had conflicting results (Abraha *et al.*, 2018). Results from a study looking at MRSA SSTIs in people with HIV also indicate that sexual contact may transfer MRSA and that high-risk sexual behaviours may increase the risk of acquiring this type of infection (Crum-Cianflone *et al.*, 2011).

18 Estimates of syphilis provided by PHAC relate to cases of infectious syphilis only, as the number of cases of non-infectious syphilis are unknown.

Substance Use Disorder

Use of injection drugs has been identified in Canada as a risk factor for MRSA SSTIs (Stenstrom *et al.*, 2009; Vayalumkal *et al.*, 2012). Two studies in Vancouver's downtown east side, which has a large population of people with substance use disorder, showed that the MRSA colonization rate in those who use injection drugs more than doubled in a six-year period, increasing from 7.4% in 2000 to 18.6% in 2006 (Daly *et al.*, 2002; Al-Rawahi *et al.*, 2008). In 218 patients who used Vancouver's supervised injection facility in 2008, 59 patients had at least one wound and of these, 16 wounds (27%) tested positive for community-associated MRSA (Lloyd-Smith *et al.*, 2010). Similarly, a Calgary study found that illicit drug use was one of the factors that put people at highest risk of acquiring a community-acquired MRSA SSTI (Gilbert *et al.*, 2006). In addition to SSTIs, which include abscesses and cellulitis, *S. aureus* can cause other severe infections in people who use injection drugs, including bacteremia and endocarditis (infection of a heart valve or the endocardial surface of the heart) (Bassetti & Battegay, 2004; Cahill & Prendergast, 2016).

AMR associated with substance use disorder is particularly relevant given the Canada-wide opioid crisis. Opioids, including fentanyl, can be injected and therefore put users at increased risks of certain types of infection. Another narcotic of concern is methamphetamine (i.e., crystal meth) whose popularity has surged in recent years in the Prairies, and Manitoba in particular (Froese, 2018; The Canadian Press, 2018). It is suspected that the increase in injection methamphetamine use is linked to a significant increase in syphilis, as well as other more common blood-borne illnesses (e.g., hepatitis, HIV) in Manitoba (Froese, 2018; Malone, 2019). A 2018 retrospective cohort study of emergency department and in-patient visits in California, Florida, and New York found that, since 2008, there has been a steady rise in the percentage of infections related to injection drug use (Miller & Polgreen, 2019). While use of narcotics is a risk factor for bacterial infection generally, there are no data relating directly to resistant infections.

Participation in Sports

MRSA infections have become increasingly common in people who participate in sports, particularly those that involve physical contact (Kirkland & Adams, 2008; Redziniak *et al.*, 2009; Braun & Kahanov, 2018). MRSA SSTIs usually occur in athletes when open abrasions (e.g., turf burns, irritations from abrasive equipment, other skin traumas) become infected after close contact with a person who is infected or colonized with MRSA. Indirect infection can occur due to shared environments (e.g., locker rooms, whirlpools), shared equipment, and shared personal items (e.g., towels, balms) (Kirkland & Adams, 2008; Redziniak *et al.*, 2009; Braun & Kahanov, 2018).

A meta-analysis by Karanika *et al.* (2016) of 15 studies from around the world (though none from Canada) estimated that 6% of asymptomatic athletes are colonized with MRSA. The authors noted that this prevalence was at least three times higher than that of the general community and comparable to the prevalence in other high-risk populations, such as people receiving dialysis. Colonization rates were highest among those participating in wrestling (22%), American football (8%), and basketball (8%) (Karanika *et al.*, 2016). In a study of patients presenting to three emergency departments at academic healthcare centres in London, Ontario, competitive sports participation was a significant predictor of MRSA SSTIs (Achiam *et al.*, 2011).

Pet Ownership

Several studies have shown that identical MRSA strains can be isolated from people and their pets (mainly dogs and cats), either in the context of a colonized pet and infected human or vice versa (reviewed in Weese, 2010). These studies could not confirm the direction of transmission or the possibility of a common infection source (Weese, 2010). Many of the MRSA strains found in pets are widespread among humans, suggesting that transmission between humans and pets can occur, but pets may harbour these strains and re-infect or re-colonize people (Damborg *et al.*, 2016). Dog owners have been found to carry bacteria that are not commensal in humans (e.g., methicillin-resistant *Staphylococcus pseudintermedius* or MRSP, which has a canine origin), providing indirect evidence that pet-to-human transmission of resistant pathogens indeed occurs (Ishihara *et al.*, 2010; Walther *et al.*, 2012). In a study of hospital personnel in Austria and Germany, contact with pets was identified by multivariate analysis as a risk factor for colonization with ESBL-producing *E. coli* (Meyer *et al.*, 2012). Thus, although the evidence is not strong enough to suggest that owning a pet is a risk factor for acquiring a resistant infection, it is clear that resistant pathogens may be shared between pets and people (Weese, 2010).

5.1.4 Travel Is a Key Risk Factor for Contracting a Resistant Infection

Population mobility is one of the main reasons why AMR has become a global problem (MacPherson *et al.*, 2009; Schwartz & Morris, 2018). Worldwide, international tourist arrivals increased from 528 million in 2005 to 1.2 billion in 2015 (Statista, n.d.). This potential for increased spread of AMR due to global mobility is compounded by the fact that asymptomatic travellers may unknowingly bring resistant bacteria to Canada.

The spread of AMR from low- and middle-income countries to high-income countries is particularly apparent for organisms that spread via the fecal-oral route, and ESBL-producing Enterobacteriaceae have emerged as, by far, the most common resistant pathogens acquired during travel (Woerther *et al.*, 2017; Schwartz & Morris, 2018). Nonetheless, international travel has played

a role in spreading other resistant organisms, such as carbapenem-resistant Enterobacteriaceae (CRE), MRSA, and several enteric pathogens (e.g., species of *Salmonella*, *Campylobacter*, *Shigella*) (Schwartz & Morris, 2018), as well as resistant STIs (Lefebvre *et al.*, 2018; Smyczek *et al.*, 2019), although the risk of these infections is much smaller compared with ESBL.

International travellers are much more likely to acquire ESBL-producing Enterobacteriaceae compared to CRE and MRSA, particularly after visiting India (Ruppé *et al.*, 2018; Schwartz & Morris, 2018). The estimated ESBL colonization rates for travellers to various regions are: the Indian subcontinent (64%), other parts of Asia (50%), the Middle East (36%), Africa (34%), and South and Central America (19%) (Schwartz & Morris, 2018). In a study of patients in the Calgary Health Region from 2004 to 2006, 247 patients acquired ESBL-producing *E. coli* (Laupland *et al.*, 2008a). More detailed information was available for 163 patients, and of these, 71 (44%) reported travel to an area other than the United States. Travellers to India had a significantly increased risk of acquiring ESBL than travellers to other countries (Laupland *et al.*, 2008a).

It should be noted that, although ESBL colonization is associated with a greater risk of ESBL infection (Ruppé *et al.*, 2018), in most cases, those who are colonized do not develop an infection (Woerther *et al.*, 2017). However, they can still spread the bacteria to others. The median duration of colonization with MDR Enterobacteriaceae after travelling is less than 30 days, and by 3 months, fewer than 10% of people remain colonized (Ruppé *et al.*, 2018).

Based on surveillance data from 58 hospitals across Canada collected between 2010 and 2014, the five-year incidence rate of CRE was 0.07 per 1,000 admissions, and 24% of cases involved people who reported international travel within the past 12 months (Mataseje *et al.*, 2016). Of these cases, 86% indicated that they sought medical care while travelling and 31% travelled to India (Mataseje *et al.*, 2016). By calculating the weighted average of several published studies, Schwartz and Morris (2018) estimate the CRE colonization rate for healthy people visiting the Indian subcontinent and other parts of Asia to be 0.4%, whereas it was zero for visiting any other region.

Medical treatment obtained in other countries, including medical tourism, combines two risk factors, namely contact with a healthcare system and travel. In 2019, PHAC announced that at least 30 people in Canada who underwent weight-loss surgery at a hospital in Tijuana, Mexico may have been exposed to a resistant strain of *P. aeruginosa* (Cook, 2019). A detailed example of a patient acquiring a resistant infection in a healthcare setting in India before returning to Canada is provided in Box 5.4.

Box 5.4
Transmission of Resistant Bacteria from India to Alberta

A 62-year-old female who lived in Canada (Patient A) had surgery for a fractured femur in India, which then developed an infection that did not respond to treatment. She flew back to Canada and was admitted to a surgical ward in an Edmonton hospital on March 31, 2012. Two types of MDR Gram-negative bacteria (*K. pneumoniae* and *Acinetobacter baumannii*) were cultured from the patient's thigh tissue and a separate rectal swab cultured *K. pneumoniae*. All strains produced carbapenemases. Both *K. pneumoniae* strains produced the carbapenemase NDM-1, which is widespread in the Indian subcontinent and confers broad resistance to various drug classes. Five other patients in the same hospital acquired either the *A. baumannii* strain or the rectal *K. pneumoniae* strain, likely from Patient A. Collectively, these patients spread the pathogens across three different surgical units. On May 8, blood and an endotracheal specimen cultured *A. baumannii* from a 74-year-old male who had undergone surgery to remove a lung nodule. He developed organ failure and septic shock, was transferred to intensive care, and died several hours later. During the outbreak, which was declared over on May 25, transmission occurred even after the implementation of active surveillance and infection control precautions.

(Ahmed-Bentley *et al.*, 2013)

Given the social and economic importance of travel for Canada, it is probable that international travel will continue to provide a mechanism for resistant human pathogens to move quickly from other countries into Canada. Therefore, AMR in all regions of the world will continue to have direct impacts in Canada. This emphasizes the global nature of AMR and the opportunity for Canada to participate in global actions to combat its spread.

5.2 THE POTENTIAL SEVERITY OF INFECTIONS IN A FUTURE WITH LIMITED ANTIMICROBIALS

Increasing rates of AMR, combined with a lack of new antimicrobials, have led some to suggest that a return to the pre-antibiotic era is possible (Cars *et al.*, 2008). Although the sharp decline in mortality due to infectious diseases — which began at the start of the 20th century — has been largely attributed to improvements in public health (e.g., sewage disposal, drinking water treatment, better housing) (Armstrong *et al.*, 1999; CDC, 1999), the introduction of antibiotics was still associated with a further decline (Armstrong *et al.*, 1999; IDSA, 2011). During

the first 15 years after antibiotics were introduced in the 1940s, the overall infectious disease mortality rate in the United States fell by approximately 75% (Armstrong *et al.*, 1999). Estimates of changes in mortality rates from the pre-antibiotic to the antibiotic era indicate that the most serious infections experienced the greatest reductions. For example, IDSA (2011) summarized several studies and found that mortality from bacterial endocarditis fell from approximately 100 to 25%, and bacterial meningitis from greater than 80% to less than 20%.

Based on the Panel's model (Section 4.1), the cumulative number of deaths in Canada between 2020 and 2050 that will be attributable to AMR would range between just under 256,000 if resistance stayed at today's rates to just over 396,000 if there is a gradual increase to 40% resistance to first-line antimicrobials (Figure 5.1).

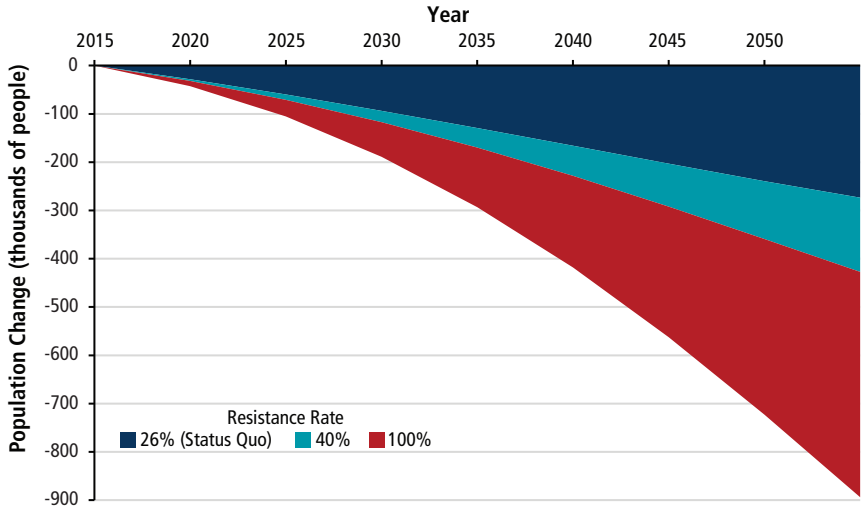


Figure 5.1

Cumulative Population Change in Canada Due to Antimicrobial Resistance, Projected Through 2050

The figure illustrates cumulative population decline due to antimicrobial resistance, as projected by the Panel's model through 2050, if resistance rates to first-line antimicrobials remain at 26% (navy blue), or reach 40% (teal) or 100% (red) by 2050. Canada's population will decline an estimated 250,000 by 2050 if resistance rates remain constant. If resistance rates reach 100% by 2050, Canada's population decline may reach approximately 800,000.

In 2012, then Director-General of the WHO Margaret Chan stated that a "post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill" (WHO, 2012a). Whether or not such a sombre portrayal of the post-antimicrobial era is likely, there is no doubt that, as the number of effective antimicrobials decreases, morbidity and mortality from previously treatable diseases will drastically increase. As resistance increases, it will become more challenging to achieve a balance between conserving the remaining effective antimicrobials while still providing optimal care for patients.

5.3 POTENTIAL SOCIAL IMPACTS OF AMR IN A FUTURE WITH LIMITED ANTIMICROBIALS

It is impossible to determine unequivocally the nature and magnitude of all future social impacts of increased AMR in Canada, due to the absence of a counterfactual (i.e., modern societies without AMU). Accordingly, this section presents plausible hypothetical future scenarios informed by the Panel's expert knowledge. Evidence is drawn from the data and projections presented thus far, as well as from other infectious disease outbreaks, such as severe acute respiratory syndrome (SARS). The Panel judged that the SARS example provides a pertinent evidence base — as Canada was the country most affected outside of the Asian region — and its social impacts have been well documented, including the restructuring of health agencies at both the provincial/territorial and federal levels (National Advisory Committee on SARS and Public Health, 2003; Expert Panel on SARS and Infectious Disease Control, 2004).

It may be argued that disease outbreaks such as SARS are rapid disruptions from the norm associated with major uncertainties, whereas AMR is an endemic problem, growing slowly through time. Thus, one might assume systemic adjustments will be made progressively as resistance increases, and may never lead to a crisis situation such as SARS. However, there are already examples of resistant strains spreading rapidly, and exhibiting outbreak patterns resembling those of SARS. For example, recall Box 5.4, which describes a patient who was infected with resistant bacteria while in India and brought the strains back to a Edmonton hospital, where they spread across three surgical units. Furthermore, there are already examples of bacterial outbreaks impacting communities in Canada. The Walkerton *E. coli* outbreak in May 2000 had devastating impact. Briefly, the water system in Walkerton, Ontario (population 4,800) became contaminated with *E. coli*, eventually causing 2,300 people to become sick and leading to 7 deaths (O'Connor, 2002; Vicente & Christoffersen, 2006). A judicial inquiry was formed by the Ontario government (Kondro, 2000), and Justice Dennis O'Connor found that the outbreak could have been prevented

by the Ontario government (which cut Ministry of Environment funding) and Walkerton's water supply managers (O'Connor, 2002). In the aftermath of the outbreak, "citizens were terrified of using tap water to satisfy basic human needs" (Vicente & Christoffersen, 2006). Those who were infected or lost loved ones suffered psychological trauma, the larger community suffered anxiety, and people across Ontario and Canada worried about whether similar fatal events could occur elsewhere (Vicente & Christoffersen, 2006). While not caused by a resistant organism, the Walkerton outbreak provides a compelling illustration of how the potential social impacts of a bacterial outbreak can resemble those of a viral one. Therefore, the Panel believes there is utility in examining societal responses to past viral outbreaks in order to inform our understanding of what a future with limited antimicrobials might be like.

While this section primarily uses a human-centred approach to identify impacts, "the consequences of the spread of resistant bacteria could also include shortages of food due to untreatable infections in livestock and, as leaders seek to slow the spread of pathogens, restrictions on trade in foodstuffs, and even on travel and migration" (World Economic Forum, 2013). Because of the dearth of direct evidence on the impacts that may occur if AMR spreads, Panel members also drew on their expertise to hypothesize how AMR may affect the day-to-day lives of people in Canada. These ideas are presented through *fictional* vignettes of people living in a future Canada (contained within teal boxes) to illustrate some of the scenarios that might arise if effective antimicrobials were to become limited.

5.3.1 AMR Impacts on Individuals

As noted in Section 5.1, certain socio-demographic risk factors put segments of the Canadian public at greater risk of developing a resistant infection. As the general population level of risk increases, these groups will likely experience compounded risks. The well-being of those with resistant infections will undoubtedly decrease due to decreased life expectancy and increased morbidity. Additionally, protocols put in place to prevent the spread of resistant pathogens, such as isolation of infected individuals, may adversely impact their health. It has been shown that isolated patients are twice as likely as patients who are not isolated to experience adverse health effects during their hospitalization (Stelfox *et al.*, 2003).

AMR Will Lead to Increased Inequality

The impacts of rising resistance would be unequally distributed among people in Canada. It would be reasonable to assume that those currently among at-risk groups (Section 5.1) would continue to be at greater risk; as the number of resistant infections increases, people in these groups would experience a

disproportionate burden, leading to increases in social inequality. The Panel notes that, while such inequalities could be made avoidable, doing so would require the implementation of very strong monitoring and equity policies.

AMR Will Decrease Well-Being

While it is clear that AMR is detrimental to health, it will also negatively affect quality of life through decreased well-being, for example. As Sachs (2018) explains, the United Nations Sustainable Development Solutions Network examines six variables to determine well-being: income, healthy life expectancy, social support, freedom, trust, and generosity. Happiness similarly correlates with these variables (Helliwell *et al.*, 2018). AMR directly impacts life expectancy through increased morbidity and mortality associated with infections (Section 5.1). Resistant STIs may impact female fecundity, impacting well-being (Section 2.3). AMR will also decrease well-being indirectly through changing trust and social capital, as outlined later in this chapter.

5.3.2 AMR Impacts on Community and Social Behaviours

If AMR were to increase, the consequences would spread beyond patients, directly affecting many facets of society. Behavioural adaptations that result from a lack of access to antimicrobials, are likely to be substantial, and yet these ramifications are often overlooked in reports that examine this topic (NAS, 2018). Because of this lack of evidence related specifically to AMR and behavioural changes, this sections draws from studies examining behaviours during infectious disease outbreaks to suggest plausible impacts of rising AMR.

AMR May Decrease Social Capital and Public Trust

Social capital can be thought of as "the resources available to individuals and groups through membership in social networks" (Alvarez & Romani, 2017). These resources can be emotional, social, and economic, and confer tangible benefits to both individuals and communities. Through social bonds (i.e., people linked by a sense of common identity), "social capital provides the glue which facilitates co-operation, exchange and innovation" (OECD, 2001). Thus, social groups characterized by higher levels of social capital perform better on a range of outcomes; in healthcare settings, for instance, social capital has been found to be as important as financial capital in promoting coordination, increasing job satisfaction, and resulting in better patient outcomes (Norrish *et al.*, 2013).

With a rise in AMR, the increased incidence and prevalence of people with resistant infections would lead to a greater number of social groups with affected individuals. However, as noted above, some groups will be at greater risk, and will count a much larger number of affected individuals, while other

groups could have very few. Social awareness of these risk factors will also likely grow, and with it, the risk of stigma associated with the condition and with belonging to a group with greater risk of resistant infection (Box 5.5). This poses a risk for social trust and social capital, as less affected groups may increasingly view themselves as dissimilar from those who have contracted resistant infections. During the SARS outbreak, people also attempted to limit contact with those assumed to be potential carriers of the virus, such as people displaying symptoms of the common cold, healthcare workers, and people of certain races or nationalities (Lee-Baggley *et al.*, 2004). In contrast to adaptive health behaviours (e.g., handwashing), avoidance of certain populations is unlikely to be effective and can lead to racism and ostracism (Lee-Baggley *et al.*, 2004). Similar avoidant behaviours were observed during avian and swine flu outbreaks, both in affected and unaffected areas (e.g., avoiding public transport, hospitals, and large gatherings; cancelling travel; eating less poultry or pork) (Bish & Michie, 2010).

Box 5.5
Stigma and Infectious Disease

Stigma is a social process that people (in groups, communities, etc.) use to label and stereotype individuals or other groups (e.g., as dangerous or as a threat), thereby distinguishing themselves from such labelled individuals or groups. Ultimately, it allows the group to exert power over others through acts of exclusion (Link & Phelan, 2001). Dimensions of stigma can include exclusion, fear, intolerance, and mistrust of people (Pescosolido, 2015).

Stigma is associated with anger, disgust, contempt, and other negative feelings. It prevents full social acceptance (Vega, 2016), and can include acts of discrimination, labelling, status loss, and stereotyping (Davtyan *et al.*, 2014). One of the most common conditions associated with stigma is infectious disease (Williams *et al.*, 2011); it has been directly associated with HIV/AIDS, TB, SARS, and other diseases (Davtyan *et al.*, 2014; Vega, 2016). Stigma has broad negative consequences not only on personal and interpersonal levels, but also on social levels, impacting quality of life (Davtyan *et al.*, 2014). Because stigma has potential effects on social trust and social capital, it may also interfere with public health prevention efforts, which aim to reduce population risks (Valdiserri, 2014). As certain sub-groups perceive themselves to be increasingly dissimilar from the general population or from other sub-groups, they tend to be less supportive of population interventions, which require a perception of the "common good."

In addition to increasing fear of infection and stigma, AMR could undermine interactions within network ties and/or limit the extent to which people (whether sick themselves or having ties to sick people) can rely on others in their own families, communities, and other networks. The potential impacts on the extent and quality of community relations and interactions, on living arrangements or preferences (especially for the elderly and youth in schools), and on general interaction and behaviour in public spaces stand to be significant.

AMR Could Affect Consumer Behaviour

If past behaviour during outbreaks can inform future reactions to increased AMR, consumer behaviour is expected to change, as consumers tend to decrease their consumption of certain services (e.g., restaurants) and in some locations (e.g., shopping malls) during serious infectious disease outbreaks.

In Hong Kong (an area affected by SARS in 2003), for instance, people avoided activities outside their homes because of fears of SARS in the community; this reduced sales at restaurants and retail outlets by 10 to 50% and increased unemployment (Siu & Wong, 2004; Beutels *et al.*, 2009). Canada's accommodation and food services sectors were also impacted; the estimated effect of SARS was US$4.3 billion on these sectors (Keogh-Brown & Smith, 2008). The future impact of AMR on the food services sector is illustrated in Robert's vignette. It is not known when the endemic and more gradual nature of AMR will allow for adaptation of consumer behaviour. For instance, current trends in online shopping and meal delivery could expand further to substitute for in-person experiences, while technological innovations in self-driving vehicles or drone deliveries could altogether eliminate human contact from these commercial interactions.

AMR Could Lead to Changes in Travel Behaviour

It is anticipated there will be an aversion to travel in a world with large, widespread AMR (O'Neill, 2014; NAS, 2018). During the SARS outbreak, air travel to and from Hong Kong, and general tourism, were affected (Keogh-Brown & Smith, 2008). From March to April 2003, the number of airline passengers and land travellers decreased by 77% and 52%, respectively, and visitors to Hong Kong decreased by 63% (Siu & Wong, 2004). Whether this was because of personal choice, the result of travel advisories (Section 5.3.3), or both, is unknown. Therefore, in a future with limited or no antimicrobials, global travel is likely to decrease as people isolate themselves or heed advisories that warn against travel to certain high-AMR areas. Both local and international transport and tourism may be impacted as a result. Similarly, travel restrictions would also impact business travel, which may endanger the interconnectedness of the Canadian economy with the rest of the world.

Vignette: Robert

Stock photo. Posed by model.

Robert is a 26-year-old living in Halifax. He originally moved to the city for university, and stayed after he graduated. Unable to find employment in his field, he is currently working as a barista in an independent coffee shop.

Robert has five shifts a week. This allows him to pay his portion of the rent for his shared apartment and have money left over for an active social life. Additional shifts are often available, making Robert secure in knowing he has enough money to live on. Robert enjoys working for an independent shop because it has regular clientele and often has outreach activities within the broader community.

Two years later, there is an outbreak of a particularly resistant and highly transmissible pathogenic bacterium in Halifax. Both the news and social media report that it came off a ship transporting food goods, although the exact source is unknown. In the month since the outbreak started, everyday life has changed in the city. Although Robert does not know anyone who has been infected, business at the coffee shop has significantly decreased. While apologetic, the owners have had to cut staff hours and, for the first time, Robert is unable to pay his rent. He is stressed and anxious, and does not know how he can make up the difference in salary, as many other local businesses are also cutting staff hours.

AMR Could Affect Public Trust in Government and Other Institutions

Finally, these social processes could also affect public trust in government and other institutions (e.g., medicine, science, public health). Should AMR become an increasing problem that proves, or is perceived, to be intractable by governmental and scientific interventions, it could affect public trust and undermine government credibility and public health responses, likely causing further health, social, and economic impacts. For example, vaccination, despite being a scientifically demonstrated successful public health measure, is increasingly "perceived as unsafe and unnecessary by a growing number of individuals" (Dubé *et al.*, 2013). It has been found that perceptions about risk (Brewer *et al.*, 2007), as well as ideas of trust in health professionals, public health institutions, and the government (Streefland *et al.*, 1999; Hobson-West, 2007), are strong predictors of vaccination behaviour.

5.3.3 Policies and Legislation to Limit the Spread of AMR

Limited effective antimicrobials will lead to national and international public health emergencies, having profound impacts on society. In an attempt to curb the spread of resistance, the delivery of healthcare will change, and other infection prevention and control (IPC) measures will be adopted that will impact society. Based on evidence from previous infectious disease outbreaks, there are several likely types of IPC-related responses should effective antimicrobials become limited. The responses can be broadly categorized as healthcare delivery changes; surveillance; isolation and quarantine; and travel restrictions (Gostin *et al.*, 2003), either on human travel or trade of foodstuffs.

AMR Will Change Healthcare Delivery

It is simplistic to believe that social impacts would be confined to infected individuals if antimicrobials were to become ineffective, or resistance were to increase dramatically. Rather, our entire healthcare system, which is now heavily reliant on antimicrobials, would be disrupted (Smith & Coast, 2013). Thus, as stated by Smith and Coast (2013), "resistance is not just an infectious disease issue; it is a surgical issue, a cancer issue, a health system issue."

Antibiotics transformed the practice of medicine from a profession of "diagnostic, non-interventional field, to a therapeutic, interventional profession" enabling "complicated and deeply invasive surgery, aggressive chemotherapy for treatment of cancer, fundamental elements of critical care such as central venous catheter placement and mechanical ventilation, supportive care for premature infants, and solid and liquid organ transplantation" (IDSA, 2011). Modern health systems and treatments that rely heavily on antimicrobials could be significantly destabilized if antimicrobials were to become ineffective. If society were to experience a true return to the pre-antibiotic era, treatments used during that time may be used again. For example, treatment might be reduced to reliance on toxic drugs (Erdem *et al.*, 2011) or, if possible, removal of the source of infection (e.g., through amputation) (Friedman *et al.*, 2016). Removing compromised tissue might not be possible for infections in certain areas (e.g., lungs), likely leading to worse outcomes for patients, including death (Harris *et al.*, 1999). Further, the actual delivery of care itself may change, as increasing AMR may bring about conversations about the duty to care versus risk to those providing care (Reid, 2005; Ruderman *et al.*, 2006).

Some of the changes to healthcare delivery enacted during the SARS outbreak in Toronto may be put in place again in the future, including:

- closures of entire hospitals;
- severe restricting of hospital services (e.g., no elective surgeries);
- screening of people entering hospitals;
- limited access to healthcare facilities;
- screening of healthcare workers going to community care centres; and,
- widespread quarantine of people who had casual contact with infected individuals.

(Gov. of ON, 2003 in Conly & Johnston, 2003)

Similar changes may be enacted in response to AMR, either periodically or put into place as a permanent IPC measures. In particular, it is likely that widespread AMR would lead to fewer elective surgeries, as the risk of infection would be too great without the use of prophylactic antimicrobials. It is unclear how many people would get infections if prophylactic antimicrobials were not available to them prior to surgery, nor is it clear how many would opt to not have surgery. However, it has been estimated that a reduction in efficacy of antibiotic prophylaxis of 30% would result in 120,000 additional infections and 63,000 infection-related deaths per year in the United States (Teillant *et al.*, 2015). If certain elective surgeries were deemed too risky to perform (by patients, healthcare providers, or both) some chronic diseases may become untreatable, leading to decreased well-being. This would have a large impact on the Canadian public as a whole, where aging populations, as well as demographic trends such as decreased rates of physical activity, mean that rates of chronic diseases are expected to increase (World Economic Forum, 2013). An example of how healthcare delivery may change is illustrated in Renée's vignette.

Vignette: Renée

Stock photo. Posed by model.

Renée is a 52-year-old from Winnipeg who has been suffering from osteoarthritis for many years. She was forced to retire early from her job as a nurse when her symptoms became too debilitating. Due to decreased mobility, Renée developed obesity and type 2 diabetes. Her left hip is the most severely affected joint and her doctor says that, in the past, a total hip replacement would have been the recommended course of action. However, the doctor is reluctant to suggest surgery as resistance

continued on next page

to first-line antimicrobials has reached 65% in Canada, several MDR strains with few treatment options have emerged, and local hospitals have been experiencing major outbreaks of two different MDR pathogens. Because of these factors, as well as the extra risk of infection caused by Renée's diabetes, both she and her doctor feel that, although the infection risk would be low, a resistant infection after surgery would be untreatable, leading to very negative health outcomes. For now, Renée and her doctor decide to manage her pain and hope that surgery might be a less risky option in the future.

Three years later, Renée's physical and mental health have deteriorated markedly. She now depends on a motorized scooter and has become increasingly isolated and withdrawn. She is receiving medication and counselling for depression and anxiety. Her son, who lives in Calgary, had a baby six months ago, and Renée is considering whether she can make the trip to meet her new granddaughter. However, she has been struggling with diabetic foot ulcers and recently required a prolonged hospital stay to treat a foot infection caused by *S. aureus*, which was resistant not only to methicillin, but also vancomycin (the drug of choice for MRSA infections). Given her issues with wound healing and the fact that her son lives at the epicentre of a large community-associated MRSA outbreak, Renée is advised by her doctors not to travel.

A year later, Renée and her doctor again discuss the possibility of a hip replacement. Her left hip is causing her constant pain that is increasingly difficult to control. Renée has made some dietary changes to address her obesity and diabetes, and is now a better candidate for surgery. Given her severely reduced quality of life, she feels that a hip replacement is worth the risk and her doctor agrees. A new hospital designed specifically to reduce the spread of AMR has been overwhelmed with surgical patients; it is currently only performing essential and emergency surgeries and placing all other patients on a waiting list. While Renée is waiting for surgery, she develops another MDR *S. aureus* infection on her foot that spreads to her bloodstream. It fails to respond to the drug combination of last resort, prompting Renée's healthcare team to treat her with an experimental drug that is known to be toxic to the kidneys. Renée dies from a combination of drug- and sepsis-induced acute kidney injury at the age of 56.

Healthcare infrastructure would also have to change in efforts to increase infection prevention and control measures (further discussed in Chapter 6). More single-occupancy hospital rooms, many with additional sterilization measures, would increase healthcare costs overall. The Panel believes there may also be a shift away from hospital care, with greater treatment occurring within the community. Additionally, there may also be a shortage of healthcare providers and other healthcare workers (e.g., cleaning staff in hospitals), as people may deem the field to be too risky to work in.

Changes to Healthcare in Response to AMR May Result in Increased Health Inequality

The impacts of rising resistance would be unequally distributed among people in Canada. Some patient groups would be impacted indirectly because of the nature of their treatment. For example, most cancer treatment suppresses patients' immune systems, and without effective antimicrobials to prevent and treat infections, chemotherapy and other treatments would be much riskier (O'Neill, 2014). Increasing resistance would also have worrying impacts on the safety of childbirth, including caesarean sections, with a significant rise in infant and maternal mortality (O'Neill, 2014). The 20th century saw a 50-fold reduction in maternal deaths in developed countries with the use of prophylactic antimicrobials (O'Neill, 2014).

Changes to Healthcare in Response to AMR May Result in Decreased Trust Leading to Changes in Care-Seeking Behaviour

AMR "deeply affects care-seeking behaviors" (NAS, 2018). If resistance is associated with healthcare settings, people may avoid seeking care (NAS, 2018). In the Panel's view, they may instead turn to less effective alternative therapies, or live with medical issues that decrease their well-being and quality of life. Someone who thinks they might have an infection may also not seek care for fear of being isolated, quarantined, or stigmatized based on their perceived association with resistance. This in turn could lead to a worsening of the infection and a spread of the bacteria. As discussed before, public trust may be eroded to the point where public health institutions are no longer perceived as effective.

Surveillance Will Continue to Feature Prominently as Part of a Response to Increased AMR

The identification and reporting of resistant infections are likely to continue to be central features of the response to AMR, as they have been in past outbreaks (Gostin *et al.*, 2003). However, if AMR were to become a larger public health crisis, surveillance may advance concerns about the limits of privacy should there be a need to breach doctor-patient confidentiality, or report details identifying specific patients (Gostin *et al.*, 2003).

Surveillance May Lead to Decreased Trust and Increased Inequality

Surveillance data may inadvertently impact certain geographic or ethnic communities, as they did in Toronto during the SARS outbreak (Gostin *et al.*, 2003). When it became known that the disease originated in China, there was evidence of overt discrimination and racism (Cheng, 2003; Rider, 2003 in Gostin *et al.*, 2003; Smith, 2006). Similar responses may occur if a highly resistant pathogen were to spread globally from a single area. An example of this scenario is illustrated in Rahul's vignette, wherein Rahul experiences stigmatization based on preconceived ideas that he may have a resistant infection.

Vignette: Rahul

Stock photo. Posed by model.

Rahul is an 18-year-old who moved from India to Vancouver at the age of nine. He and his family travel to India at least once a year to visit relatives, and this summer, before Rahul begins university, they plan a month-long trip. In an effort to control the global AMR crisis, Canada has introduced mandatory screening protocols for those who travel to certain areas. Upon their return to Canada, travellers must report to a designated healthcare facility where they are tested for colonization or infection with resistant organisms. Infections are treated promptly and patients who are colonized are counselled on the risks of spreading bacteria to others, particularly those who reside in their household.

Rahul's family is well aware of the screening procedures. His mother is a surgeon and his father is a medical laboratory technician at a major hospital. They are also aware of the precautions to take while travelling to reduce the risk of infection. Rahul is particularly careful since he lives with atopic dermatitis, a condition that causes periodic flares of eczema on his hands and face. Though the condition is not infectious, it makes him vulnerable to skin infection and colonization, particularly with *S. aureus*. When Rahul and his family arrive back in Canada, their tests come back negative for infection, but as is the case for almost all travellers to India, they have all become colonized with ESBL- and carbapenamase-producing *E. coli*, which is highly ubiquitous in the Indian subcontinent.

Rahul moves out of the family home to attend university. Due to the stress of moving away from his family, his eczema worsens and he is very unhappy to be starting his university experience with a flare-up on his face. He is finding it difficult to form any connections with new people. His roommate is particularly unfriendly, and a few weeks after the term begins, Rahul is notified that his roommate will be moving elsewhere.

Rahul continues to struggle socially and mentally, which affects his academic performance. He later discovers that, after hearing about a recent AMR crisis in India — which involved the outbreak of an extensively resistant strain of *S. aureus* causing death in many cases — his roommate requested to move because of Rahul's ethnicity and the appearance of his skin. His roommate was aware of his visits to India and assumed that Rahul was suffering from an infection acquired during his travels. Even after the situation was explained, his roommate was still uncomfortable living with someone who "might spread germs around." Rahul is devastated and decides not to go back to university after he finishes his first term.

Increased AMR Will Lead to Increased Isolation and Quarantine

If antimicrobials were to become increasingly ineffective, infected people may be isolated to prevent or limit transmission. This is already standard practice in hospitals for cases of resistant infections (PHAC, 2016b). However, a second group — those who are healthy but who have been exposed to a resistant infection — may be quarantined with the hopes of limiting transmission during the incubation period (Gostin *et al.*, 2003; National Advisory Committee on SARS and Public Health, 2003; Smith, 2006). There is precedent for quarantine responses to a public health emergency in Canada, such as school and hospital closures in response to SARS in Toronto (National Advisory Committee on SARS and Public Health, 2003). At one such school, 1,500 students were quarantined at home after a single student exhibited symptoms of SARS (Brown, 2003); elsewhere, continuing medical education courses were cancelled or postponed (Davis *et al.*, 2005).

As the number of isolated people (those who are infected), and the number in quarantine (those who were exposed and may be infected) would likely increase if AMR were to rise, broader social impacts would subsequently occur. The fear created by AMR may make it more challenging to balance among risk of infection, personal liberty, and social and economic harms, as has occurred in other infectious disease outbreaks (Bradsher & Altman, 2003).

Isolation and Quarantine May Increase Inequality

Those quarantined are likely to also suffer from lost income, loneliness, and fear of developing an infection. Such outcomes were observed in Toronto by those quarantined during the SARS outbreak (National Advisory Committee on SARS and Public Health, 2003).

Isolation and Quarantine May Decrease Social Capital

The segregation of isolated and quarantined people would greatly impact their social connectedness and well-being. Public health measures designed to control the spread of resistant infections may also, unintentionally, lead to decreased connectedness: for example, measures designed to minimize contact between susceptible and infectious individuals, such as travel restrictions, quarantine, and isolation, will result in more segregation within the population as a whole. AMR's isolating impact is illustrated in Raymond's vignette, while his daughter Rochelle's farm shows how adapting to AMR may be profitable in some sectors (innovations that may allow various industries to adapt to AMR are discussed in Chapter 6).

Vignette: Rochelle and Raymond

Stock photo. Posed by model.

Rochelle is a 44-year-old in rural Quebec. She is a married mother of two who has taken over running the family farm from her father, Raymond, who is 66 years old. Rochelle recently followed the lead of the cattle industry and virtually eliminated the use of antimicrobials while adopting the use of alternative therapies. Although initially concerned this would cut into her bottom line, Rochelle now sees that the changes, once implemented, are yielding good return — consumer demand for meat products that are certified from antimicrobial-free farms has grown exponentially in recent years.

Five years later, Rochelle's farm continues to be successful, and the profits have allowed her to build an apartment onto the homestead for her aging father. While volunteering at the local community centre, Raymond catches pneumonia and, because of a combination of co-morbid conditions and a lack of response to first-line antimicrobials, he requires hospitalization. The closest hospital is several hours away, and due to commitments on the farm, family are unable to visit Raymond every day. Raymond becomes lethargic, suffering from depressive symptoms while becoming increasingly isolated within the confines of the hospital. He also contracts *C. difficile* while in hospital, which prolongs his stay as the first-line treatment does not work. Rochelle, anxious about her father's recovery, hires help at the farm and travels to be closer to Raymond.

After several months, Raymond is able to move back to the farm. He is weaker physically, and also less willing to volunteer because he is fearful he will catch another infection. Rochelle is spending more time caring for Raymond, and has had to continue to use hired help, which is decreasing the farm's profits.

Travel Restrictions May Become More Common in Response to Increasing AMR

The SARS outbreak demonstrated how international travel could spread disease, as a physician from China infected people in a hotel in Hong Kong, who then carried the disease to Toronto, Singapore, and Vietnam (National Advisory Committee on SARS and Public Health, 2003). As discussed in Section 5.1.4, Canadian travellers can become infected with resistant strains of bacteria abroad; these can be brought back to Canada and spread through healthcare

facilities (Box 5.4). If antimicrobials were to become increasingly ineffective, travel to areas associated with outbreaks or specific resistant bacterial strains may be limited or cease, may be advised against by the WHO or national governments, and may be accompanied by unpleasant public health procedures (e.g., mandatory isolation on return).

Travel advisories associated with health outcomes, such as those that warned against travel to Toronto during the SARS outbreak (National Advisory Committee on SARS and Public Health, 2003), have significant economic and social impacts (Keogh-Brown & Smith, 2008). Travel behaviours were significantly impacted by SARS (Keogh-Brown & Smith, 2008; Beutels *et al.*, 2009), and this was supported by travel advisories to areas deemed to be significantly impacted (National Advisory Committee on SARS and Public Health, 2003).

Travel restrictions may also be instituted by other stakeholders. For example, institutions imposed their own restrictions during SARS, with universities cancelling summer programs for students from China (Murphy & Arenson, 2003), and discouraging travel to China, Taiwan, and Singapore (Harvard University Health Services, 2003 in Gostin *et al.*, 2003). Another potential national response to AMR could be detaining travellers returning from certain regions or who exhibit certain symptoms. This occurred in the United States during the SARS outbreak, where officials authorized immigration and customs agents to detain travellers who appeared to have SARS-associated symptoms (Sheldon, 2003).

Travel Restrictions May Decrease Social Capital and Well-Being

Were AMR to trigger these types of responses, well-being and social connectedness would decrease. Travel allows people to conduct business, see family and friends, and pursue goals (Gostin *et al.*, 2003). Indeed, travel is important to people living in Canada, and in 2018 Canada ranked seventh in spending on outbound international tourism, spending US$31.8 billion (UNWTO, 2018). While international law allows people to travel within one's country and abroad, this can be restricted on public health grounds (UN, 1999). Further, travel may be restricted in Canada, such that travel to certain regions may be discouraged. This would further decrease social connectedness within the nation, and decrease individual well-being.

Determining what public health measures are appropriate may also be problematic, as "there is no international consensus on travel screening and border controls" (Naylor *et al.*, 2004). This could lead to confusion, as there may be different rules and procedures in different cases. Further, in some cases, the fear associated with a certain resistant strain or infection could lead to the implementation of protection measures that are ineffective or unnecessary.

For example, a large Canadian pilot project in Toronto and Vancouver used thermal scanners to screen millions of travellers, with thousands being referred for further assessment; however, not a single case of SARS was identified (Naylor *et al.*, 2004; St. John *et al.*, 2009).

5.4 CONCLUSION

The burden of disease associated with AMR is not shared uniformly among people in Canada. The risk of acquiring a resistant infection is higher for those in certain demographic groups, such as the very young and those who live in crowded housing; those who engage in certain sexual practices or certain sports; and, most significantly, those who already have contact with the healthcare system. Of note, the greatest risk factor for acquiring a resistant infection is previous antimicrobial treatment.

Yet, everyone is likely to be affected by AMR in the future, either by becoming infected themselves, by living a more isolated, restricted existence, or by losing loved ones to previously treatable infections. AMR will have broad negative social impacts on people in Canada, decreasing well-being, social capital, and trust, and increasing inequality. As demonstrated by the journeys of Robert, Renée, Rahul, and Rochelle and Raymond, the general health and well-being of people will be negatively affected if treatments were delayed or avoided altogether, if travel within and outside the country were considered dangerous, and if certain populations were discriminated against due to their ethnicity or health status.

6

Policy Options and Lessons Learned: Reducing Infections, Slowing Resistance

- Surveillance
- Infection Prevention and Control
- Stewardship
- Research and Innovation
- Conclusion

6 Policy Options and Lessons Learned: Reducing Infections, Slowing Resistance

Key Findings

Effective approaches to addressing AMR will require evidence-based, multifaceted, and coordinated initiatives that use elements from four mitigation strategies — surveillance, infection prevention and control (IPC), stewardship, and research and innovation.

Surveillance underpins successful mitigation efforts because it can provide an up-to-date and accurate portrayal of the current state of resistance and use of antimicrobials, deliver feedback to healthcare providers, and allow for targeted use of resources.

IPC measures that result in fewer infections include adequately resourced and trained IPC teams in hospitals and other healthcare settings that enforce, for example, hand hygiene and cleaning protocols. Widespread adoption of immunization by the Canadian public, along with other practices such as respiratory hygiene, proper food handling, and clean water, would reduce community-acquired infections.

Based on the Panel's model, a multifaceted approach to IPC that reduced the infection rate by 33% would save 120,000 to 200,000 lives and $117 to $177 billion in GDP between 2020 and 2050, if resistance to first-line antimicrobials remains constant at 26% or rises to 40%, respectively.

Antimicrobial stewardship promotes judicious use of antimicrobials, and the best initiatives coordinate approaches and stakeholders from both the human and animal health sector; however, it is unclear how long lasting their effects might be using measures such as changes in prescribing practices and AMR awareness.

Research and innovation are fundamental to tackling AMR, whether directly through the development of new therapies to treat resistant infections, or by supporting surveillance, IPC, and stewardship strategies.

Potential benefits may stem from research and innovation related to, for example, new antimicrobials, therapies, vaccines, rapid diagnostics, the microbiome, hospital practices, data analytics, medical technologies, nanotechnologies, and cellular agriculture.

In Canada, the federal, provincial, and territorial governments, along with other stakeholders, have programs that aim to address the problem of AMR in some way. These work to prevent infections, to quantify AMR, to prevent and control its spread, and to support research and innovation for new therapies and a greater understanding of how AMR evolves. *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action* (hereafter Pan-Canadian Framework) (GC, 2017), a federal government report, describes how various orders of government, the private sector, and the general public must collaborate to address AMR in Canada. Actors include officials from all orders of government, healthcare providers, business leaders, researchers, and members of the public.

The Pan-Canadian Framework identified four core strategies to tackle AMR: surveillance, IPC, stewardship, and research and innovation (GC, 2017). This chapter reviews these four strategies in order to identify opportunities that, if put in place, could reduce infection and slow resistance. For an overview of current Canadian surveillance, stewardship, and IPC strategies, the Panel refers readers to task force reports on each of the four mitigation components used to inform the Pan-Canadian Framework (F/P/T AMR Surveillance Task Group, 2016; AMR Research and Innovation Task Group, 2017; AMR Stewardship Task Group, 2017; IPC TG, 2017). The Panel takes a forward-thinking approach to explore how these four mitigation strategies can be used to combat AMR. The potential implications of various mitigation strategies are also explored based on different scenarios in the Panel's model. The Panel notes that tackling AMR will require coordinated action across multiple fronts through various mitigation strategies (Figure 6.1).

6.1 SURVEILLANCE

Surveillance strengthens the AMR evidence base, allowing assessment of the spread of AMR, the identification of emerging problems, and the effectiveness of various interventions (Queenan *et al.*, 2016; WHO, 2017e). Without surveillance, the impact of local, national, and global strategies cannot be assessed. Surveillance of *both* AMR and AMU is therefore needed to inform stewardship activities to reduce unnecessary AMU, and interventions and policy decisions to help combat AMR (F/P/T AMR Surveillance Task Group, 2016). Existing provincial/territorial and federal surveillance resources could be combined to form a cohesive, integrated national surveillance system (F/P/T AMR Surveillance Task Group, 2016). Surveillance can also inform treatment guidelines and patient care. For example, the WHO's Gonococcal Antimicrobial Surveillance Program (GASP) uses surveillance data to inform practice, and Canadian gonococcal treatment guidelines are updated based on these data (WHO, 2018b).

Adapted with permission from O'Neill (2016a)

Figure 6.1

Tackling Antimicrobial Resistance Requires Coordinated Global Action on Many Fronts
Strategies to mitigate antimicrobial resistance will require coordinated action across multiple fronts, involving numerous stakeholders locally, nationally, and worldwide.

In Canada, PHAC has led AMR surveillance initiatives, and established the Canadian Antimicrobial Resistance Surveillance System (CARSS) in 2015 as the overarching coordinating program for all AMU and AMR surveillance systems and programs in Canada (PHAC, 2015). CARSS collects AMU and AMR data from:

- The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). CIPARS monitors AMU and AMR trends for select bacteria in humans, animals, and retail meat in Canada. The collected data are analyzed by drug and by province/territory.
- The Canadian Nosocomial Infection Surveillance Program (CNISP). CNISP collects data from more than 50 hospitals from 10 provinces to calculate trends in healthcare-associated infections at healthcare facilities across Canada.
- Surveillance programs for specific diseases, such as the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea program (ESAG) and the Canadian Tuberculosis Laboratory Surveillance System (CTLSS)

(GC, 2016)

There is an opportunity to further enhance Canadian AMU and AMR surveillance using existing strengths. For example, CIPARS notably takes a One Health approach to surveillance through a system that "meets stakeholder needs while providing a holistic understanding of AMR in Canada" (Deckert *et al.*, 2015).

The provincial/territorial systems work with federal systems, for instance, by providing up-to-date AMU and AMR data to CARSS and CIPARS (PHAC, 2014b). Not all provinces and territories participate equally, and there are regional disparities in the reporting of data. Further, some areas of Canada lack any surveillance. Weaknesses in current Canadian surveillance include:

- limited AMR data focused on priority pathogens, especially data from animals (both domestic and wild);
- a lack of AMU data, especially in rural, northern, and First Nations communities, in both healthcare and community settings, and for veterinary prescriptions; and,
- a lack of national AMR data from animals (with the exception of data collected by CIPARS) and the environment.

(Canadian Committee on Antibiotic Resistance, 2009; Grant *et al.*, 2014; F/P/T AMR Surveillance Task Group, 2016)

6.1.1 One Health Approach to AMR Surveillance

A One Health approach to surveillance includes AMU and AMR data from humans, animals, and the environment. This would help combat AMR because it necessitates a broad, systems-based approach to a complex problem (Zinsstag *et al.*, 2011). Queenan *et al.* (2016) propose a framework for a One Health AMR surveillance system with the key facet being the integration of AMU and AMR surveillance data for humans, animals, food, and the environment.

To enable integrated analysis, data from various sectors would need to be collected in similar ways, facilitated by a centralized program led by experts with inter-sectoral knowledge (Queenan *et al.*, 2016). Centralized leadership and funding would be required in order to build a functional One Health surveillance system in Canada. Impediments to achieving this type of centralized, integrated surveillance include traditionally siloed institutions, variation in definitions and data collected, cost, and complexity, and jurisdictional challenges. Increased cooperation and integration would facilitate the analysis and interpretation of results and the evolution of joint recommendations should these be required (Queenan *et al.*, 2016).

6.1.2 International AMU and AMR Surveillance

International surveillance programs have addressed some of the gaps and impediments identified by previous reports. Globally, the WHO is taking a leadership role in standardizing AMR surveillance through various programs, such as the Global Antimicrobial Surveillance System (GLASS) and the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) (F/P/T AMR Surveillance Task Group, 2016). GLASS fosters a standardized global AMR surveillance system, and AGISAR supports the WHO's effort to minimize the public health impact of AMR associated with AMU in food animals (F/P/T AMR Surveillance Task Group, 2016).

A 2014 program evaluation of AMR surveillance initiatives compared major Canadian AMR surveillance programs to select programs from other countries (Grant *et al.*, 2014). Programs were evaluated based on criteria such as data quality, sensitivity in detecting trends, organism samples, stability and timeliness of reporting, and availability of data. The evaluation found that all national Canadian AMU and AMR surveillance programs were limited in scope in one of two ways: by the patient population from which the resistance organism is collected, or by the pathogens under surveillance. The majority of surveillance in Canada involves a limited number of hospital patients and specific antimicrobial-resistant organisms under public health surveillance, or focuses on *Salmonella* surveillance in food animal production (Grant *et al.*, 2014). Previous evaluations had similar findings (Canadian Committee on Antibiotic Resistance, 2009).

This evaluation also found that highly ranked international public health surveillance programs feature integrated oversight of national and regional surveillance, across veterinary, food animal, and human medicine (Grant *et al.*, 2014) — these are crucial for a One Health approach to surveillance. Specifically, the Danish DANMAP program, the Dutch NethMap program, and the European Antimicrobial Resistance Surveillance Network (EARS-Net) stood out as exemplary programs (Grant *et al.*, 2014; Queenan *et al.*, 2016). DANMAP and NethMap had the strongest community AMR surveillance, whereas EARS-Net surveyed fewer pathogens but was notable for its coordination across multiple jurisdictions, and its provision of current, accessible, and useful data (Grant *et al.*, 2014). Components of these programs could be used to improve Canadian surveillance: DANMAP and NethMap provide examples of how to survey across the entire food chain, while EARS-Net models how to incorporate data in different forms from several member states. The Panel also identified two programs in the United States with components that might inform future Canadian surveillance initiatives: the Antimicrobial Resistance Monitoring and Research (AMRoR) program (Lesho *et al.*, 2014) and the Active Bacterial Core Surveillance System (ABCs) (CDC, 2018).

With respect to AMU surveillance in the veterinary sector, DANMAP and NethMap use benchmarking systems that could be emulated (Mills *et al.*, 2018), as these have been highly effective in reducing food animal AMU in these countries (Speksnijder *et al.*, 2015). Benchmarking — that is, evaluating AMU by a given industry, company, veterinarian, etc., using a common set of guidelines — need not be punitive, but instead can be informative and provide a standardized means of measurement for a given sector. In the future, one possible surveillance strategy could be having regulators monitor and evaluate AMU by veterinarians and farms against agreed-upon benchmarks (Prescott, 2017). In Canada, the Food Safety Recognition Program (FSRP) provides government recognition to on-farm and post-farm food safety systems developed and implemented by national industry organizations (CFIA, 2018). If this type of program were to include AMU benchmarking as part of its recognition criteria, it may be feasible and fairly inexpensive to implement.

6.2 INFECTION PREVENTION AND CONTROL

IPC is relevant for all types of infections, and plays an important role in limiting the acquisition and transmission of AMR organisms (Kiernan, 2017; Price *et al.*, 2017). IPC programs were introduced in healthcare facilities in the 1950s as a response to *Staphylococcus aureus* outbreaks that were associated with substantial mortality (Scheckler *et al.*, 1998; Forder, 2007). Progressing over decades, they have become comprehensive, evidence-based programs, integral to the delivery of safe healthcare (Scheckler *et al.*, 1998; Price *et al.*, 2017). In healthcare settings, IPC practices include appropriate hand hygiene, environmental cleaning, facility construction, occupational health, and best practices for management of invasive procedures and devices. These are now considered routine practices (PHAC, 2016b). For suspected or confirmed infections caused by selected pathogens that bring an increased risk of severe infection, additional precautions are required. These may include gowning and gloving for patient contact, engineering controls requiring specific air handling characteristics for airborne pathogens, and the use of enhanced employee barrier protection (PHAC, 2016b).

IPC programs have been expanded to include long-term care facilities, outpatient healthcare facilities, and home healthcare. Community measures, such as immunization, community hygiene, and appropriate follow-up of those who have come into contact with infectious pathogens, are also important IPC measures. For example, flu vaccinations can prevent the unnecessary use of antimicrobials in the treatment of viral infections. In some cases, IPC recommendations for specific organisms, such as community MRSA, have also been developed (Henderson & Nimmo, 2017).

Animal health and welfare depend on the effectiveness, availability, and appropriate use of antimicrobials (OIE, 2016), but IPC is also integral. Routine IPC practices discussed above, including handwashing and waste management, are also used. In the agricultural sector more broadly, IPC practices are important for biosecurity (Higgins *et al.*, 2016), food safety, and maintaining exports of food animals (Ministry of Environment and Food of Denmark, n.d.). The World Organisation for Animal Health (OIE) has encouraged the implementation of international standards related to AMU in animals, the production of food products, and the circulation of these products worldwide (OIE, 2016). The Food and Agriculture Organization of the United Nations (FAO) also recognizes the importance of prevention; it is working on promoting improved hygiene and biosafety, with global and local campaigns "to prevent disease outbreaks through flock and herd health schemes," including improved nutrition and vaccination (FAO, 2018).

IPC activities limit the emergence and dissemination of AMR organisms in several ways:

- By decreasing the overall burden of infection in healthcare, the community, and animal husbandry, thereby limiting the overall need for antimicrobials (Swaminathan *et al.*, 2017; FAO, 2018).
- By preventing transmission of resistant organisms from colonized or infected individuals or animals to other individuals in healthcare facilities or the community (Swaminathan *et al.*, 2017; FAO, 2018).
- By controlling outbreaks attributed to antimicrobial resistant organisms in healthcare facilities. This may include additional precautions implemented for management of selected resistant organisms such as MRSA or carbapenemase-producing organisms (Price *et al.*, 2017).

6.2.1 One Health Approach to IPC

From a One Health perspective, human, animal, and plant sectors all have a shared responsibility and role in preventing and minimizing AMR selection pressures through both human and non-human AMU. One of the ways to decrease AMU in every sector is through preventing and controlling infections. As noted above, not only are IPC measures important in human health settings, but the WHO, OIE, and FAO have stated that "through stringent implementation of good agricultural practices, including good animal husbandry and good veterinary practices, it is possible to reduce the necessity for antimicrobials" (FAO *et al.*, 2004). Biosecurity measures that help prevent and control infections are likely part of the "good practices" in both animal husbandry and veterinary methods that reduce AMU. The WHO has principles for the containment of AMR in animals intended for food, supported by the FAO and OIE (FAO *et al.*, 2004).

6.2.2 Pan-Canadian Framework and the IPC Task Group for AMR

PHAC's Infection Prevention and Control Task Group developed a report to inform the Pan-Canadian Framework (IPC TG, 2017). It identified issues that may compromise the optimal practice of IPC in Canada, and potentially limit the effectiveness of these programs in addressing AMR. Specific gaps include:

- Variability in the accessibility, competence, and practice of IPC programs.
  - Some rural and remote communities, where access to clean water and sanitation is limited, have particular challenges in implementing IPC strategies.
  - Some IPC guidelines are not adapted into practice for non-traditional settings, such as long-term care facilities or out-patient clinics.
- Limitations in consistency and timelines of data collected, so evidence is not optimally used to promote action.
- Inconsistent application of core IPC practices across jurisdictions and facilities (e.g., hand hygiene, additional precautions).
- Inadequate monitoring of compliance with IPC standards and practices.
- Limitations of IPC resources in some settings.
- Healthcare workers receiving inadequate or inconsistent IPC training, which compromises their ability to provide optimal practice.
- A failure of coordination and cooperation among relevant IPC stakeholders.
- A lack of research identifying the most effective IPC strategies in community settings.

(IPC TG, 2017)

In Canadian food animals, biosecurity measures have been put forward for various types of livestock, but there is a lack of practical tools (e.g., templates, checklists) and insufficient sharing of best practices among veterinarians and farmers (IPC TG, 2017). There are also few economic drivers to facilitate the implementation of on-farm food safety certification systems. One such possible driver would be requiring IPC programs to be put in place as a pre-requisite for access to antimicrobials through a farm's veterinarian. Existing production and marketing systems, such as auction markets, community pastures, and assembly yards, may allow pathogens to spread among many animals from various sources, thereby imposing a risk for the spread of infection (IPC TG, 2017). As AMU decreases in animal agriculture, there are major opportunities for IPC improvements (i.e., biosecurity) through, for example, increased vaccination and better hygiene standards.

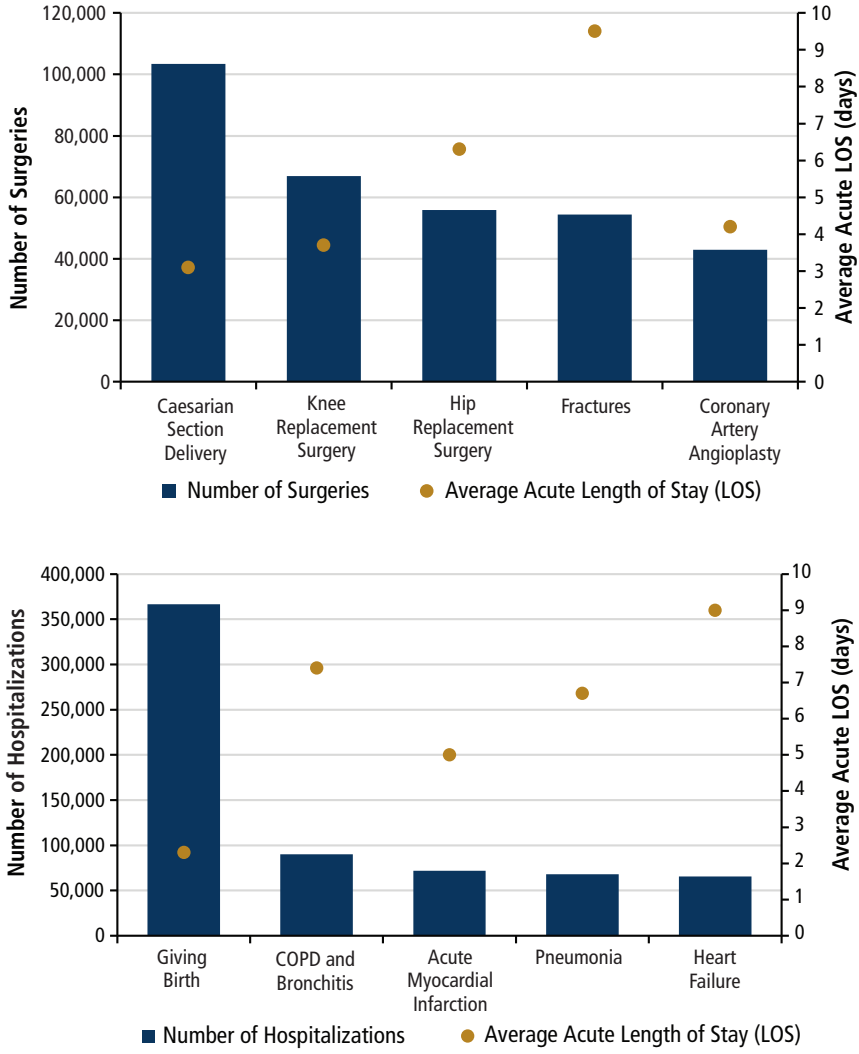
Moving forward, a One Health approach requires that human, animal, and plant sectors all have a shared role in efforts to prevent and control infections, thereby reducing the need for AMU. There may be challenges in coordinating actions and sharing knowledge among different sectors. Additionally, without clear economic incentives in all sectors, IPC practices may not be implemented in the same way, or at all, across Canada.

6.2.3 Reducing the Impact of AMR with Better IPC in Hospitals and Communities

Hospitals

It has been estimated that approximately 1 in 10 adults contract an infection while in hospital (Gravel *et al.*, 2007a; Gravel *et al.*, 2007b). Although surveillance data on the exact number of resistant infections in all hospitals do not exist, the Panel estimates that 80,000 resistant infections were acquired in hospitals in 2018, costing the Canadian healthcare system around $1.4 billion. As noted in Section 5.1.2, patients with weakened immune systems or chronic disease are particularly susceptible to resistant infections; however, as the rate of resistance rises, it is likely that resistant infections will be an increasingly common occurrence among *all* patients admitted to hospitals. AMR will disproportionately affect women giving birth as well as children, older adults, and others who are frequently admitted to hospitals (Figure 6.2).

One of the top patient safety priorities in Canadian healthcare has been reducing the rate of healthcare-associated infections (HAIs) (CIHI, 2008). In 2018, the public sector spent about $72 billion on hospitals, the largest share of healthcare spending (CIHI, 2018b). As shown in Chapter 3, resistant HAIs result in extra costs for hospitals compared to other HAIs. If resistance to first-line antimicrobials continues to increase, these costs may jeopardize the financial sustainability of hospitals; reducing HAIs will therefore become a growing priority. A variety of IPC policies and practices can help provide better care to patients and reduce the number of infections, as well as decrease costs (OECD, 2018a). Following the WHO core components of IPC (Figure 6.3), the Panel briefly discusses hospital IPC programs, guidelines, and training; surveillance and monitoring; and patient care activities and bed occupancy (WHO, 2018a).

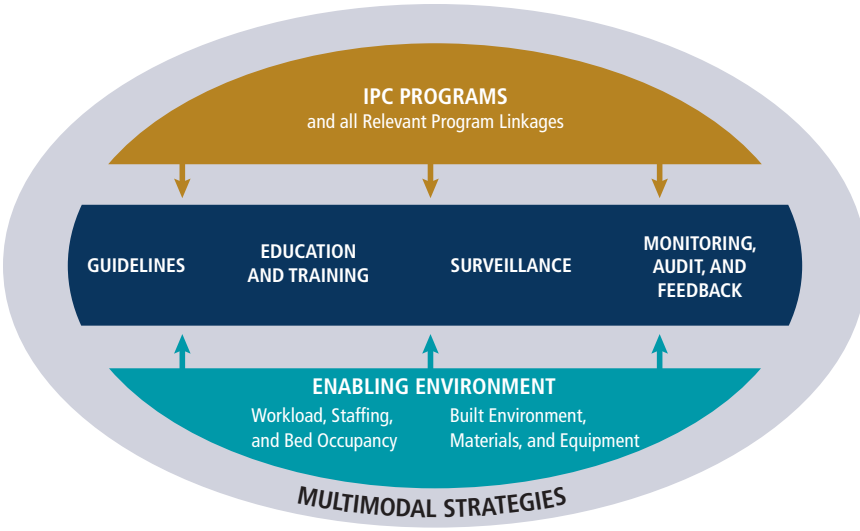


Data Source: CIHI, 2018a

Figure 6.2

Top Five Reasons for In-Patient Hospitalizations and Surgeries, 2017

This figure shows the top five reasons for in-patient surgeries (top) and hospitalizations (bottom) in Canada in 2017. It also plots the average length of stay (LOS) associated with surgeries (top) and hospitalizations (bottom).



Adapted with permission from WHO (2018a)

Figure 6.3

WHO Core Components of Hospital Infection Prevention and Control

This figure shows the relationship among the eight components of the WHO's Infection Prevention and Control (IPC) model.

Hospital IPC Programs, Guidelines, and Training

IPC plays a key role in patient safety, reducing risks and significantly decreasing rates of infection, potentially by more than 30% (PHAC, 2010). As the WHO (2018a) points out, the "development and maintenance of an IPC programme is the foundation for the implementation of all other core components" since it "ensures that facility leadership and the right technical expertise [are] in place." This requires evidence-based guidelines about reducing infections and AMR,[19] dedicated and trained IPC teams, clearly defined objectives based on local epidemiology and risk assessments, and measurable indicators and targets (WHO, 2018a).

19 The WHO (2018) lists the following standard precautions: hand hygiene; transmission-based precautions; prevention of surgical site infection; prevention of vascular catheter-associated BSI; prevention of hospital-acquired pneumonia; prevention of catheter-associated urinary tract infections; prevention of transmission of multidrug-resistant organisms (MDRO); disinfection and sterilization; healthcare worker protection and safety; injection safety; waste management; antibiotic stewardship; and outbreak preparedness and management.

The Canadian Institute for Health Information (2008) notes than "[a]n infection control practitioner (ICP) and a physician trained in infection control are key requirements for a hospital's infection control program." ICPs are healthcare providers with IPC expertise and training who work with entire organizations to prevent infection. They do this by educating staff, planning and implementing infection control practices, and evaluating existing healthcare practice (CIHI, 2008). Many Canadian healthcare institutions have IPC programs, but previous expert groups have found that these practices need to be fully resourced (Buick *et al.*, 2015; IPC TG, 2017). The need for adequate resources to implement effective IPC programs has been identified within hospitals (Zoutman *et al.*, 2003; Zoutman & Ford, 2008) and other healthcare institutions, such as long-term care facilities (Zoutman *et al.*, 2008). The Panel supports these findings, and believes that IPC programs need to be enhanced and adequately resourced in order to be fully effective.

Surveillance and Monitoring

The WHO (2018a) notes that hospital surveillance "should be performed to identify the most frequent HAIs and detect HAI outbreaks, including AMR surveillance." Monitoring and reporting on HAIs, in coordination with prevention activities, can decrease their rate (CIHI, 2008). Surveillance within hospitals varies such that it can be institutional-wide, targeted to specific departments (such as intensive care), or to specific priority infections. In a 2008 survey of Ontario hospitals, "hospital-wide surveillance was reported as the most commonly used approach to routinely track and monitor nosocomial infections (74%), whereas one-quarter (26%) of hospitals reported that targeted surveillance was their most commonly used method" (CIHI, 2008). Strategies depended on the type of hospital: "most small (84%) and community hospitals (78%) reported hospital-wide surveillance as their most common surveillance method, while teaching hospitals reported an even split between hospital-wide (47%) and targeted surveillance (53%)" (CIHI, 2008).

The low rate of MRSA infections in Dutch hospitals (approximately 1%) is attributed to their search and destroy strategy (CUPE, 2009; Souverein *et al.*, 2016). The *search and destroy* approach, as outlined by CUPE (2009), includes "screening, isolation cohorting, decolonization of MRSA infected patients, education of healthcare workers, and daily disinfection of rooms and the healthcare environment;" this approach is further detailed by Vos (2007). The labour-intensive nature of search and destroy makes it costly (CUPE, 2009); however, analysis by Souverein *et al.* (2016) demonstrates that this approach is less expensive than the treatment costs associated with MRSA infections. It is not clear whether such an approach could be used in a Canadian context. Monitoring of changes in AMR within hospital settings after an IPC policy is

enacted allows for impact monitoring that can help to ensure that IPC policies lead to lower infection rates while improving transparency and accountability (CUPE, 2009).

Patient Care Activities and Bed Occupancy

According to the WHO (2018a), patient care activities "should be undertaken in a clean and/or hygienic environment that facilitates practices related to the prevention and control of HAI, as well as AMR." Indeed, for more than 150 years, proper handwashing has been acknowledged as a critical step in preventing the spread of infection (CIHI, 2008; Pittet *et al.*, 2009; WHO, 2009). While new concerns related to IPC have emerged, proper handwashing — which includes using antiseptic hand wash, hand rub, or surgical hand antisepsis — "is considered the single most important practice for preventing the transmission of hospital-acquired infections" (CIHI, 2008). Rates of HAIs have been shown, in some cases, to fall between approximately 15 to 50% when hospital staff adhere to handwashing and other infection control programs (Luangasanatip *et al.*, 2015). Australia launched its National Hand Hygiene Initiative, and there is evidence that improved hand hygiene compliance is associated with declines in the incidence of *S. aureus* bacteremia in that country's major hospitals (Grayson *et al.*, 2018). The OECD (2018a) recently ranked hand hygiene as the best and most cost-effective approach to reduce infections: a 70% compliance rate in healthcare facilities was estimated to cost between US$0.90 and US$2.50 per capita, and resulted in fewer HAIs.

Given that guidelines and practices for hand hygiene are already in place (PHAC, 2012; IPAC, 2017), the potential to reduce HAIs through improved practices may be somewhat limited in Canadian hospitals. In Ontario, where hospitals are required to publicly report how often staff wash their hands, the average compliance rate is approximately 88%, although there is a large variation among hospitals (32 to 100%) (Health Quality Ontario, 2019). Similarly, Bernard *et al.* (2018) found that handwashing compliance ranged from 53 to 77% in two Quebec healthcare centres. The Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control recommends that a "multifaceted, multidisciplinary hand hygiene program must be implemented in all healthcare settings" (PIDAC, 2014) This means that effective hand hygiene requires a collaborative approach that involves everyone — physicians, nurses, attendants, housekeeping, visitors, and even patients — and is supported by administrative leadership and incentives. Handwashing compliance may be improved by health education, on-the-job training, employee monitoring, and behavioural nudges (Blackwell *et al.*, 2018).

IPC experts also put in place proper cleaning protocols in hospital healthcare settings (IPC TG, 2017). Without thorough cleaning, some procedures may spread bacteria. Without adequate disinfection, some detergent-based cleaning procedures could increase contamination in the environment (PHAC, 2010; Han, 2015). For example, Ontario's Provincial Infectious Diseases Advisory Committee (PIDAC) recommends that, if a patient has or is suspected of having *Clostroides difficile*, hospitals should clean "[a]ll horizontal surfaces in the patient's room and all items within reach of patients twice daily with a hospital-grade disinfectant. Particular attention should be paid to the cleaning of patient-specific items and 'high touch' surfaces including bed side-rails, telephone, call bells, light switches, door handles, faucets, commodes, and toilets" (PIDAC, 2004). As with handwashing, clear cleaning guidelines and practices are already in place in Canadian healthcare settings (e.g., PIDAC, 2004; CHICA, 2012). Cleaning compliance can be improved, however, by on-the-job training and employee monitoring in addition to adopting evidence-based cleaning protocols (IPC TG, 2017).

Nurses in both hospitals and long-term care facilities play a central role in patient care activities, assessing and diagnosing infections, administering antimicrobials, and monitoring outcomes (CNA, 2017). There is a strong link between infection rates and numbers of registered nursing staff. Using administrative data from 799 U.S. hospitals in 11 states and employing several regression models, Needleman *et al.* (2002) found that UTIs and pneumonia rates were 9% and 6% lower, respectively, in hospitals with a higher proportion of registered nurses. Numerous other studies have shown that understaffing, overstaffing, and other imbalances between nursing skills and patient needs are correlated with increasing infection rates (Shang *et al.*, 2015). PHAC (2010) recommends that hospitals should "ensure that there is adequate nurse staffing with the appropriate skills to apply infection prevention and control measures when providing patient care." Since 2008, however, the growth in the supply of nurses has slowed to less than 1% per year while spending on healthcare has increased approximately 4% per year (CBOC, 2017; CIHI, 2018b). This decrease in the supply of nurses, coupled with increasing rates of resistance, may be problematic in future Canadian healthcare settings.

High patient turnover and high bed occupancy rates are contributors to breakdowns in IPC practices (CUPE, 2009). For example, "overcrowding and rapid turnover between patients seriously hamper infection control procedures and are a major factor in infection outbreaks" (CUPE, 2009). As explained by CUPE (2009), "[c]urrent policies promoting higher patient turnover have

resulted in many hospitals working at near or full capacity," as demonstrated in a study by Clemens *et al.* (2008). This is a particular problem in Canadian hospital emergency departments (Drummond, 2002; Affleck *et al.*, 2013), and is associated with adverse patient outcomes and inferior levels of service (Affleck *et al.*, 2013). The most significant factor contributing to overcrowding in emergency departments is a lack of in-patient beds in other hospital departments (Affleck *et al.*, 2013). In acute care hospital settings across Canada, overcapacity is increasingly the norm. A survey of 235 IPC professionals working in acute care hospital settings showed that a quarter of sites (26%) had to continuously (i.e., every one to seven days) use overcapacity/full capacity protocols (Ocampo *et al.*, 2017). Canada has fewer acute care beds per capita than the OECD average and the third highest occupancy rate, at 92% (the OECD average in 2005 was 75%) (CUPE, 2009; OECD, 2017). By contrast, the Netherlands had the lowest bed-occupancy rate at 64% in 2005, as well as a low rate of hospital-acquired MRSA (CUPE, 2009). Decreases in the number of hospital beds continue to contribute to overcrowding — nationwide, hospital beds decreased from 3 per 1,000 populations in 2006 to 2.5 in 2017 in Canadian hospitals (OECD, 2018b).

Communities

Although the majority (70%) of infections are community-acquired, as the IPC Task Group's report points out, there is limited evidence on which community-based IPC interventions are most effective (IPC TG, 2017). The IPC Task Group nonetheless highlights five areas:

- immunization against vaccine-preventable diseases (e.g., *Streptococcus pneumoniae, Bordetella pertussis*);
- effective hand and respiratory hygiene in daycares and schools;
- safe food handling practices and proper environmental cleaning in all community and institutional settings;
- clean water, sanitation, and adequate housing in rural and remote communities; and
- staying home from work and avoiding community settings (e.g., public transportation, sporting/music venues) when ill.

The Panel stresses that the widespread adoption of immunization by the Canadian public may be a particularly effective community IPC intervention. Vaccines can reduce the number of bacterial infections that require antimicrobial treatment, but they can also help prevent viral infections such as the flu for which antibiotics are incorrectly prescribed (Lipsitch & Siber, 2016; O'Neill, 2016b). As such, immunization can reduce infections, AMU, and potentially AMR.

Simulating an Improvement in IPC

As summarized above, effective IPC is multifaceted, requiring the adoption of best practices and adherence to guidelines in both hospital and community settings. Reducing the rate of infections requires buy-in from hospital management, doctors, nurses, pharmacists, hospital staff, and the general public. The Panel used its model (Section 4.1) to simulate the effect of a multifaceted approach to IPC, which reduced the spread of infection by 33%. According to those simulations, such an IPC program would save 120,000 to 200,000 lives and $117 to $177 billion in GDP between 2020 and 2050, if resistance remains constant or gradually reaches 40%, respectively (Figure 6.4). The low cost of some IPC interventions, such as hand hygiene and safe food handling, makes them particularly attractive from a policy perspective.

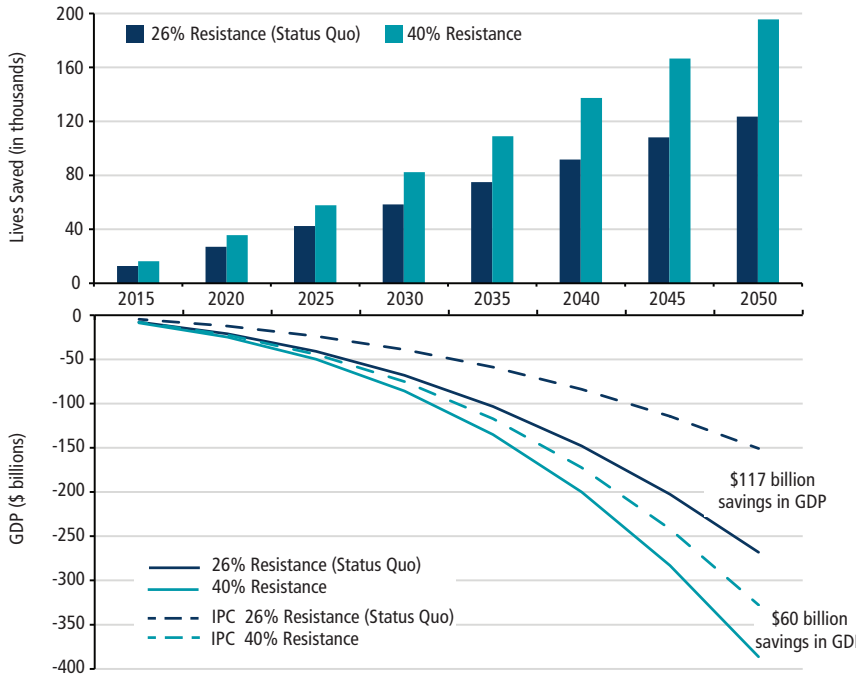


Figure 6.4

The Effect of an IPC Program on Mortality and GDP in Canada

This figure plots the cumulative number of lives saved by the introduction of a nationwide, coordinated infection prevention and control (IPC) effort. By 2050, based on simulations from the Panel's model, the IPC program saves between 120,000 if resistance remains at 26% in 2050 (navy blue bar) and 200,000 (teal bar) lives, if resistance reaches 40% by 2050. By saving these lives (as well as the associated morbidity), an IPC program would contribute between $117 billion and $177 billion to Canadian GDP between 2020 and 2050, if resistance remains constant at 26% (status quo – navy blue line) or grows to 40% (teal line).

6.3 STEWARDSHIP

Antimicrobial stewardship (AMS) is "a system-wide approach that includes coordinated interventions designed to promote, improve, monitor, and evaluate the judicious use of antimicrobials to preserve their future effectiveness and promote and protect human and animal health" (AMR Stewardship Task Group, 2017). AMS stakeholders are everyone who prescribes, dispenses, uses, sells, or influences AMU for human or animal health (AMR Stewardship Task Group, 2017). While AMS measures have had success in promoting AMR awareness, a key to further advancement will be transitioning from awareness to engagement. The gap between raising knowledge and awareness about AMR, and changing public and prescriber behaviour around the use of antimicrobials, remains a challenge. In order for AMS initiatives to be successful in the long term, engagement from all stakeholders — ranging from healthcare providers and veterinarians to all who consume antimicrobials — will be necessary and the effort will have to be sustained.

6.3.1 One Health Approach to AMS

Effective AMS must include both human health and animal/agricultural sectors; the Panel believes a One Health approach is warranted. Importantly, this approach emphasizes that human and animal sectors need to be aligned and work towards the same outcomes, though it does not mean equality of actions. This type of approach was also endorsed by the AMR Stewardship Task Group's report, which informed the Pan-Canadian Framework (AMR Stewardship Task Group, 2017). One example of a principle that looks at AMS from a One Health perspective is the Good Stewardship Practice (GSP), which takes "a continuous improvement and dynamic approach to addressing resistance and sustaining the future of antimicrobial therapy" (Weese *et al.*, 2013) and allows for multiple interventions with cumulative impact (Prescott, 2014). While practitioners, whether it be doctors or veterinarians, are at the front line of stewardship, a GSP approach also involves many other elements and actors, and requires ways of measuring outcomes of various AMS initiatives (Weese *et al.*, 2013).

The *Global Framework for Development & Stewardship to Combat Antimicrobial Resistance* also takes a One Health approach, stating that AMS includes practices that promote appropriate AMU in human, animal, and plant health across different societal levels (i.e., from the individual to the hospital/community level to the

national level) (WHO *et al.*, 2017). The Framework notes that AMS programs depend on the capacity and context of national regulatory authorities, and suggests programs could, for example, include:

- regulation of labelling, pricing, and distribution of new antimicrobials (global level);
- regulation, legislation, and national treatment guidelines (national level);
- optimizing AMU for patients (hospital level)[20]; and
- promoting access and appropriate AMU in primary healthcare settings and in animal health by raising awareness and targeted interventions for the public and prescribers (community level).

(WHO *et al.*, 2017)

6.3.2 Canadian AMS Responsibilities

In Canada, human health AMS is generally concentrated on prescriber education, health promotion directed at consumers of antimicrobials, and hospital-based oversight programs, while AMS in the animal health sector has centred on promoting regulatory changes and is expanding to include AMS campaigns within industry groups (AMR Stewardship Task Group, 2017). To date there have been no joint initiatives across sectors. Various stakeholders have responsibilities to promote AMS, and many stakeholders have introduced one or more initiatives (AMR Stewardship Task Group, 2017). From the human health perspective, AMU as measured through prescriptions dispensed remains stable in Canada; an opportunity for increased judiciousness may therefore be present in this area (PHAC, 2017a).

Accreditation Canada is a key component of stewardship in healthcare facilities in Canada (HealthCareCAN & NCCID, 2016). It provides AMS requirements for organizations delivering in-patient rehabilitation, in-patient cancer care, in-patient acute care, and continuing care, and it offers incentives for investment in AMS (HealthCareCAN & NCCID, 2016).

Successful AMS extends far beyond the hospital and other healthcare facilities to include community-based measures and veterinary practice. Within the community, AMS will primarily be undertaken by independent clinicians, including physicians, dentists, and nurses (HealthCareCAN & NCCID, 2016). In these settings, AMU is guided by consumer demand and prescriber tendencies (HealthCareCAN & NCCID, 2016), and is therefore a primary focus of AMS measures. Some provinces assist their community prescribers by operating sustained programs of prescriber and public education (Carson & Patrick,

20 The Panel notes that AMS programs included at the hospital level could also apply to long-term care facilities.

2015). Such programs provide up-to-date, readily accessible guidelines on the appropriate treatment of infections and include targeted efforts to decrease the public's demand for antimicrobial therapy (Carson & Patrick, 2015).

Veterinary practice in Canada also has important stewardship components. Veterinary oversight can provide guidance and direction for appropriate AMU in animals (CVMA, n.d.). For example, the College of Veterinarians of Ontario includes guidelines for veterinary stewardship of antimicrobials (CVO, 2017). As discussed in Section 2.2, an increase in veterinary oversight was instituted by Health Canada over the use of medically important antimicrobials (GC, 2018). Important stakeholders who continue to work with Health Canada include the Canadian Food Inspection Agency, Canadian Veterinary Medical Association, Animal Nutrition Association of Canada, Canadian Animal Health Institute, and national produce associations (e.g., Canadian Cattlemen's Association, Canadian Pork Council, Chicken Farmers of Canada, Dairy Farmers of Canada, and Equestrian Canada) (GC, 2018).

6.3.3 International Examples of Successful AMS

A recent review of interventions to improve prescribing practices in hospital settings (n=221 studies) found strong evidence that interventions are effective and can lead to patients receiving appropriate treatments according to prescribing policies; it also found moderate evidence that interventions reduced hospital length of stay without increasing patient mortality, and that both restrictive and enabling techniques could be effective interventions (Davey *et al.*, 2017).

Several systematic reviews have tried to identify the characteristics of successful AMS initiatives in out-patient settings. A 2005 review examined the effectiveness of professional interventions (e.g., printed education materials for doctors, educational outreach visits, healthcare and financial system changes, patient-based interventions) in reducing the unnecessary prescription of antimicrobials for viral infections in out-patient settings (Arnold & Straus, 2005). Based on 39 studies, the authors found that intervention effectiveness in prescribing was largely dependent on particular prescribing behaviours and the barriers to change in a particular community: "[m]ulti-faceted interventions combining physician, patient, and public education in a variety of venues and formats were most successful in [decreasing antimicrobial] prescribing for [viral infections]" (Arnold & Straus, 2005). Another systematic review examined various quality improvement strategies that were implemented to decrease prescribing for out-patient illnesses for which antimicrobials are inappropriate (Ranji *et al.*, 2008). Among the 30 trials included in the quantitative analysis of prescribing practices, the median reduction in the proportion of patients

receiving antimicrobials was 9.7%. No single strategy was superior to others, but active clinician education strategies trended towards greater effectiveness than passive strategies (Ranji *et al.*, 2008).

Targeting patients as well as clinicians in stewardship initiatives is important, as patient expectations and demands for antimicrobials are often put forward as key reasons why clinicians inappropriately prescribe antimicrobials (Hamm *et al.*, 1996; Coenen *et al.*, 2006). Interventions have been used to target unnecessary use of antimicrobials by the public. A systematic review of both qualitative and quantitative studies (n=54) that examined the public's beliefs and knowledge about AMU and AMR found that the public has an incomplete understanding and misconceptions about the causes of AMR, and do not believe the use of antimicrobials would contribute to the development of AMR (McCullough *et al.*, 2016). Therefore, raising public awareness and understanding before people become patients could play a role in combatting AMR.

A recent systematic review sought to examine a broad range of interventions that spanned hospital and community settings, including community-led campaigns, randomized clinical trials, and studies from low- and middle-income countries, in order to determine what parts of an intervention make it successful (Cross *et al.*, 2017). The authors found that communication interventions that were multifaceted and target both the general public and clinicians can decrease antimicrobial prescriptions in high-income countries, but it was unclear whether the reduction would last through time, based on 14 studies with an estimated 74 to 75 million total participants (Cross *et al.*, 2017). One might conclude that sustained programs will be more valuable than one-time campaigns as an approach at all levels. Within hospitals, a systematic review of 221 studies found that interventions designed to improve prescribing practices to in-patients can lead to increased compliance with antimicrobial hospital policy, and decreased length of antimicrobial treatment (Davey *et al.*, 2017).

Successful National AMS Initiatives in Comparator High-Income Countries

Huttner *et al.* (2010) reviewed 22 public stewardship campaigns targeted at improved AMU in out-patients; these were performed between 1990 and 2007 in high-income countries at the national or regional level. Campaigns varied from low-cost, simple internet campaigns to more expensive, mass media campaigns. The evaluated campaigns indicated they had the intended effect of decreasing AMU (Table 6.1), with multifaceted campaigns repeated over several years being the most effective (Huttner *et al.*, 2010).

Table 6.1

National Antimicrobial Stewardship Interventions and Their Associated Outcomes

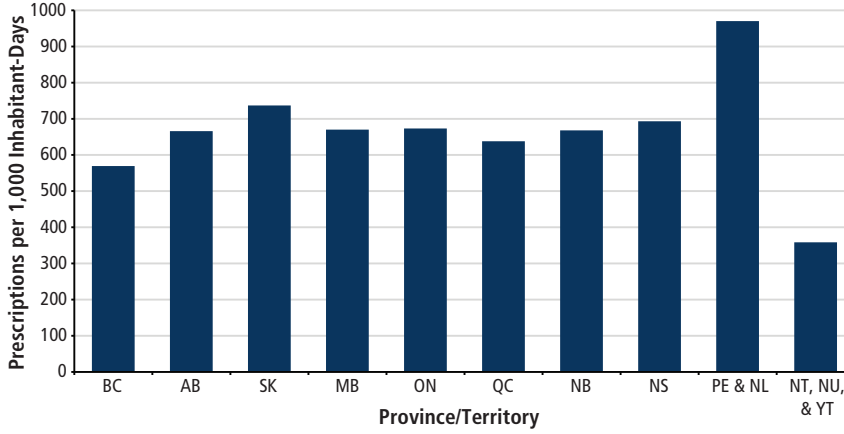
Country	Interventions	Outcome	Source
Australia	Restriction of fluoroquinolone use	Low fluoroquinolone use and low proportion of fluoroquinolone-resistant *E. coli* (but high overall AMU)	Cheng *et al.*, 2012
Chile	Enforcement of a sales restriction for antimicrobials (i.e., prescription only) in 1999, in combination with a public campaign	Decrease in antibiotic consumption from 1999 to 2000 (but overall AMU has increased since 2000)	Bavestrello *et al.*, 2002; Bavestrello & Cabello, 2011; Wirtz *et al.*, 2013
France	Yearly national antimicrobial campaign since 2001	Overall out-patient prescriptions decreased for the first few years, but has increased more recently (and overall AMU remains high relative to other E.U. countries)	Sabuncu *et al.*, 2009
South Korea	National policy change in 2000; separation of prescribing and dispensing of antimicrobials	Net decrease in antimicrobial prescribing for patients with presumed viral illness between 2000 and 2001	Park *et al.*, 2005
Sweden	National program to contain AMR involving all stakeholders	Low overall AMU and low AMR (but increase in hospital AMU)	Molstad *et al.*, 2008a; Molstad *et al.*, 2008b; Hanberger *et al.*, 2014
United States	Ongoing public campaign since 1995	Decrease in out-patient AMU (but overall AMU remains high)	Fridkin & Srinivasan, 2014

Source: Huttner *et al.*, 2014

6.3.4 Antimicrobial Consumption in Canada

As discussed in Section 2.1, an important driver in the emergence and increase in AMR is AMU. Therefore, the impacts of AMR can be reduced through better stewardship of antimicrobials. In comparison with eight peer OECD countries, people in Canada consumed an average amount of antimicrobials in 2015 (defined daily dose, DDD, of 21 per 1,000 population) (CIHI, 2018c). This consumption is considerably greater than the Netherlands, Sweden, Germany, and Norway (10, 12, 14, and 16 DDD per 1,000 population, respectively), though it should be noted that use in some provinces (e.g., British Columbia, Quebec) is considerably lower than the Canadian average and compares favourably with lower-use OECD countries (CIHI, 2018c).

In Canada in 2016, an estimated 22.6 million prescriptions were filled, at a cost of almost $700 million. As shown Figure 6.5, drug prescriptions vary significantly across provinces and territories (PHAC, 2017a). This may reflect variation in climate, age, population, and income, among many other factors.



Data Source: PHAC, 2018a

Figure 6.5

Variation in Prescription Rates Per Capita Among Provinces and Territories, 2017

This figure plots antimicrobial prescriptions per 1,000 inhabitants across Canadian provinces and territories in 2017. PHAC reported prescription data from PE & NL together for 2017.

Prescribing Practices

Many studies have demonstrated a relationship between inappropriate AMU and the development of AMR. Prescribing practices govern inappropriate AMU, which can refer to prescribing the wrong antimicrobials for a given affliction, prescribing antimicrobials when none are necessary, or prescribing the wrong amount of antimicrobials. While physician prescribing practices are important to AMS, it is also important to recognize other practitioners who can prescribe antimicrobials in Canada, including dentists, veterinarians, pharmacists, and nurse practitioners (e.g., Gov. of ON, 1991; CVMA, n.d.).

For example, a multi-site, multi-study investigation of prescribing patterns among American physicians in out-patient settings revealed wide-scale overuse and misuse of antimicrobials (Fleming-Dutra *et al.*, 2016). Half the prescriptions for acute respiratory conditions — 110 per 1,000 population — were deemed to be appropriate for the diagnosed condition (Fleming-Dutra *et al.*, 2016). A follow-on study from the workgroup concluded that, in 2010 and 2011, recommended first-line antimicrobials were correctly prescribed by physicians only about 50% for otitis media, sinusitis, and pharyngitis, leading to around 40 million incorrect prescriptions (Hersh *et al.*, 2016). As Zhuo *et al.* (2018) describe, complex factors influence physician prescribing behaviour, including the "availability and acceptance of guidelines and other information sources; level of knowledge and training; perceptions about the causes, impacts and risks of AMR; availability of diagnostic facilities and diagnostic uncertainty; pressure from patients/clients; fear of clinical failure; [and] time pressures and social and organisational contexts." Prescribing may be improved by behavioural nudges (Meeker *et al.*, 2016).

A recent low-cost intervention used social norm feedback to general practitioners as a way to reduce antimicrobial prescriptions (Hallsworth *et al.*, 2016). It was performed using a national randomized controlled trial targeting 1,581 general practitioners in the United Kingdom with the highest antimicrobial prescribing rates in their areas. First, letters were sent to general practitioners (the intervention group) from the United Kingdom's Chief Medical Officer stating their prescribing rates were higher than 80% of neighbouring practices. Those in the control group did not receive a letter. These letters also included resources to help physicians decrease their prescribing rates, including ways to offer a delayed prescription and support self-care among their patients. Over a six-month period, the rate of antimicrobials dispensed per 1,000 weighted population was approximately 127 in the intervention group and 131 in the control group. This translated into 73,406 fewer antimicrobial prescriptions (Hallsworth *et al.*, 2016).

Changing prescribing practices is not limited to human health: the use of antimicrobials in food animals now requires a veterinary prescription in Canada (GC, 2018). Therefore, there is an important role for provincial/territorial veterinary regulators to promote and require stewardship programs and standards of practice.

6.4 RESEARCH AND INNOVATION

Research and innovation are fundamental to the other three mitigation avenues (surveillance, IPC, and stewardship) discussed in Sections 6.1 to 6.3. As the AMR Research and Innovation Task Group (2017) notes, addressing the challenge of AMR requires "research that supports the epidemiology and understanding of the emergence and transmission of AMR and/or relates to the development of solutions to AMR." Developing solutions to the problem of AMR requires both fundamental research as well as innovation, whereby research ideas are translated into new therapies, technologies, and practices that benefit their users. Innovation puts research into practice, whether in hospitals or on farms, in ways that help treat infections, reduce AMU, or better target interventions.

The AMR Research and Innovation Task Group (2017) found that Canada's research and industry sectors involved in AMR are small, but that there are pockets of expertise, centred in a few research and innovation hubs across the country. Specific areas of expertise include pre-clinical drug discovery, microbiology, epidemiology, AMU, herd management, and housing. Canadian researchers also pursue collaborative research opportunities, which have been identified as particularly important for combatting AMR, as it requires initiatives across disciplines, sectors, and international borders. For example, there is strong collaboration between PHAC's National Microbiology Laboratory and the academic research community with respect to their facilitation of access to information and strains of pathogens. The Task Group concluded that Canada should focus on its strengths in the areas of alternatives to antimicrobials, adjuvants, vaccines, diagnostics, livestock management practices, and supporting clinical (i.e., human) and field (i.e., livestock) trials to identify the most cost-effective practices to minimize risks from AMR (AMR Research and Innovation Task Group, 2017).

This section discusses 10 areas of research and innovation that the Panel deems important in the struggle against AMR. The list is neither comprehensive nor exhaustive, but represents areas and examples that the Panel considers particularly promising. In Figure 6.6, these 10 areas are grouped according to the general timeframe in which innovations might be widely adopted, reflecting

the level of technological maturity and regulation in each area (e.g., vaccines vs. nanotechnology). Given data limitations and the inherent uncertainty of innovation, the Panel did not attempt to forecast future developments in these areas. Moreover, the Panel did not prioritize these areas of research and innovation, in order to emphasize the need for sufficient investment and effective cooperation to help diversify the response to AMR.

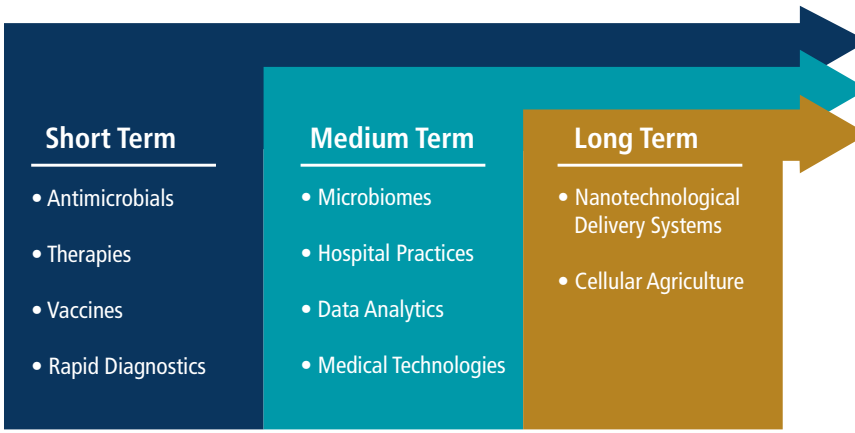


Figure 6.6

Ten Important Areas of Research and Innovation

The Panel identified 10 promising areas of research and innovation that it deems important in the struggle against antimicrobial resistance. These areas are grouped by the timeframe in which innovations might be widely adopted.

6.4.1 Short-Term Innovations

Antimicrobials

The discovery of penicillin in 1929 (Fleming, 1929) and the isolation of streptomycin in 1943 (Comroe, 1978) ushered in a golden era of antimicrobials (Brown & Wright, 2016). By exploiting the specialized metabolism of fungi and bacteria to uncover new antimicrobial scaffolds or by chemically modifying previously identified scaffolds, researchers discovered many new and highly effective antimicrobials (Brown & Wright, 2016). With subsequent use of these antimicrobials, resistance became a problem, which sparked a new model of drug discovery — rational drug design — that primarily created synthetic, broad-spectrum versions of the naturally occurring scaffolds discovered in the golden era (Brown & Wright, 2016). However, even with significant drug discovery efforts, no new classes of antibiotics have been developed for decades (Tyers & Wright, 2019). The "crisis of the deteriorating antibiotic pipeline for resistant bacteria is well known" (Rex *et al.*, 2013), with the number of

approved novel antimicrobials falling from 19 between 1980 and 1984, to 6 between 2010 and 2014 (Ventola, 2015). A 2017 report by the WHO focusing on the antibacterial pipeline confirms that there are few novel antimicrobials in development, with "a lack of potential treatment options for priority resistant bacteria" (WHO, 2017b).

Nonetheless, antimicrobials remain essential to treating infection. While it is unlikely given current trends that broad-spectrum drugs will be discovered (Brown & Wright, 2016), using innovative methods, such as treatment with combinations of drugs (Tyers & Wright, 2019), or focusing on unconventional targets, should help to create new narrow-spectrum drugs that target specific causative pathogens (Brown & Wright, 2016). For example, over the past decade, antimicrobials that specifically target *Acinetobacter* or *Neisseria gonorrhoeae*, as well as two new classes of anti-TB drugs, have been approved (Brown & Wright, 2016). Indeed, the Pew Charitable Trusts estimates that, as of December 2017, there are 42 antimicrobials in Phases I to III clinical trials (PEW, 2019). The Panel believes that the narrow-spectrum approach to antimicrobial discovery will require more fundamental research, more flexible regulations, and new economic models to overcome three major challenges:

Scientific Challenges: Relative to other therapeutic fields, "[s]cientific and clinical advancements in antibiotic development are inherently challenging" (Simpkin *et al.*, 2017). While narrow-spectrum antibiotic discovery is considered to be the most likely field to yield results, it will yield only a narrow selection of chemical compounds, with a limited range of mechanisms (Brown & Wright, 2016; Tyers & Wright, 2019). The chemical properties and complex mechanisms of existing antibiotics are incompatible with and elusive to medicinal-chemistry approaches and modern drug-discovery platforms, respectively. As "new targets and approaches to antibiotic drug discovery are fraught with risk, there is a substantial need for fundamental research" on the biological action of antimicrobials as well as on unconventional targets and discovery platforms (Brown & Wright, 2016).

Regulatory Challenges: Traditionally regulations require the completion of two large clinical trials before a new antimicrobial can be approved (Rex *et al.*, 2013). In the case of "narrow-spectrum agents, or those focused on emerging forms of resistance, it might be possible to generate only limited clinical data... Because the clinical applicability of preclinical data for antibiotics is unusually high relative to other drug classes, initiatives such as learn and confirm models and single clinical trials with causal evidence seem to be especially applicable to new antibiotics" (Rex *et al.*, 2013). Ultimately, balancing data needed for registration with medical need would boost research in this area (Rex *et al.*, 2013).

Market Challenges: The challenge of developing a new antimicrobial relates as much to the structure of pharmaceutical markets as to the scientific and regulatory challenges (Renwick *et al.*, 2015). Large pharmaceutical companies invest less in antimicrobial research and innovation than in other areas, with 15 of the 18 largest global pharmaceutical companies abandoning the antimicrobial field over the last two decades (Bartlett *et al.*, 2013). Developing new antimicrobials to treat resistant infections lacks a sufficient return on investment for three reasons (Rex & Outterson, 2016). First, infections generally occur over a short time-scale, unlike other therapies for chronic conditions that may bring in revenue for the remainder of a patient's lifetime. Second, the costs of clinical trials are high and the prices for antimicrobials comparatively low, contributing to a lack of revenue. Third, since clinicians are unwilling to use new antibiotics as they did in the past, the volume sales model is smaller, making these drugs a poor investment (Renwick *et al.*, 2015). Addressing this challenge may require "delinking reward from antibiotic sales through prizes, milestone payments, or insurance-like models in which innovation is rewarded with a fixed series of payments of a predictable size" (Rex & Outterson, 2016).

While Canada has a history of discovering antimicrobials such as Tazobactam (NAEJA-RGM, n.d.), in general, the national research and innovation system struggles to support the commercialization of research in the pharmaceutical industry (CCA, 2018). The AMR Research and Innovation Task Group (2017) identified three barriers specific to Canada in commercializing antimicrobials: regulations, jurisdictions, and resources. The relatively small Canadian market (for both the testing of therapies and also for number of customers), coupled with the length of time and costs relative to potential profit associated with obtaining approvals for new products, may present a regulatory barrier that results in industry not seeking Canadian approval, especially smaller companies. Similarly, the Canadian-specific regulatory and approval issues for new drugs and products — a jurisdictional barrier — may lead to less international collaboration on alternative solutions to antimicrobials. Finally, additional funds are needed to overcome resource barriers, and to continue to work on the challenge of AMR (AMR Research and Innovation Task Group, 2017). Currently, the federal government provides about $10 million per year to support AMS and AMR research, with very little of this directed to help researchers transform their lab discoveries into commercial treatments (HESA, 2018).

Globally, research and innovation into novel antimicrobial therapies "needs to address the issue of the challenging commercial model, and come up with strategies to reconcile public health needs with an attractive economic model for the pharmaceutical industry" (Roca *et al.*, 2015). The WHO has taken a leading

role in efforts to incentivize research and innovation into novel therapies through its Global Action Plan on Antimicrobial Resistance, which identifies partnerships as a key way forward to develop and conserve antimicrobials (WHO, 2019a). For example, the WHO participates in many partnerships to foster research and innovation (e.g., the Global Antibiotic Research and Development Partnership, or GARDP) (WHO, 2019a). Internationally, governments have used various initiatives to increase investment in antimicrobial research and development, primarily targeted at industry. Generally, incentives can be grouped as *push* incentives, targeted at pre-clinical and clinical trial phase development, including grants and pipeline coordination to bring down research and development costs, and *pull* incentives, targeted at therapies that have made it to market, including market entry rewards and long-term incentives to increase return on investment (Shlaes & Bradford, 2018; Roope *et al.*, 2019).

There are several examples of push incentives such as CARB-X, funded by BARDA (the U.S. Biomedical Advanced Research and Development Authority) and the Wellcome Trust. This non-profit public–private partnership is "dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria" by providing research support through the early stages of product development and Phase I testing (CARB-X, 2018). A European example is the Innovative Medicines Initiative, which supports collaborative research projects across sectors, including academia and the pharmaceutical industry, and combines public and private funding to advance the development of, and patient access to, the next generation of vaccines, medicines, and treatments such as new antibiotics (Innovative Medicines Initiative, n.d.).

There are fewer examples of pull incentives, however. In the United States, the *Generating Antibiotic Incentives Now (GAIN) Act* of 2012, and the more recent *Re-Valuing Antimicrobial Products* (REVAMP) Bill, were implemented to incentivize the development of new antimicrobials through longer market exclusivity. The GAIN Act incentivized research by extending the years of market exclusivity for new antibiotics (Shales, 2018). This approach did not have the anticipated results, as it did not make the non-profitable product (the new antibiotic) profitable. The newer REVAMP Bill also centres on longer periods of exclusivity, but it is transferrable such that the company that develops a new antibiotic could transfer the exclusivity period to another (more profitable) therapeutic product (Shales, 2018).

There remain great hopes for new antimicrobial discoveries, especially those with narrow-spectrum, but scientific, regulatory, and market challenges need to be addressed. The Panel supports a wide-ranging approach to antimicrobial

development, not picking any winners, but making sure that sufficient resources and incentives are available to encourage the development of antimicrobials with the greatest social value. Without Canadian-based incentive programs encouraging research into novel antimicrobials, the solutions will be found in other jurisdictions, and a potentially fruitful avenue of exploration will be lost. Without these incentives, Canada will continue to lag behind other countries in this important field.

Therapies

Given the challenges associated with developing new antimicrobials, researchers and companies have turned to developing alternative therapies (also called *non-traditional products*) to treat or prevent AMR infections, including phage therapy, lysins, adjuvants, and probiotics (PEW, 2018). Alternative therapies, such as phage, lysins, and adjuvants, may hold promise to treat infections once they are acquired. An American study of the drug development pipeline for non-traditional products found that the majority were vaccines (12/32) and antibodies (10/32), and few had reached advanced phases of clinical testing (PEW, 2018).

Therapies that could help to treat resistant infections include antibiotic adjuvants, phage, and lysins. Antibiotic adjuvants are compounds with "little or no antibiotic activity themselves, but act to block resistance or otherwise enhance antibiotic action" (Wright, 2016). They are delivered in combination with antibiotics, thereby providing a way to slow resistance and salvage the activity of existing antibiotics, acting as a complementary strategy to the discovery of new antibiotics. There are several examples already in clinical trial (Wright, 2016); therefore, this class of therapy is likely a low-risk area of research.

Phage therapy uses bacterial viruses (phage) to treat infections, and has been used in some parts of the world for almost a century (Lin *et al.*, 2017). Traditionally, this type of therapy relies on naturally occurring phages to infect and lyse bacteria at the infection site. More recently, biotechnological innovations have expanded phage therapy to include new strategies that use bioengineered phages or purified phage lytic proteins. Ongoing research suggests that phage therapy has the potential to be used as either a supplement, or an alternative, to traditional antibiotic treatment. Phage therapy has been explored for use in both humans and animals (Lin *et al.*, 2017).

Some therapies used to treat non-bacterial infections have been repurposed to treat bacterial infections. For example niclosamide — originally used to treat human tapeworm infections — has now been shown to protect human colon cells from CDI, and may be repurposed to help prevent infections (Tam *et al.*, 2018; Hospital News, n.d.-a). Therapy breakthroughs such as this one may help to minimize drug discovery costs.

Vaccines

The successful introduction of immunization programs to prevent and control vaccine-preventable diseases has reduced dependence on antimicrobials, in turn reducing risks associated with AMR. While the developmental pathway for vaccines is clear, the research into developing safe, effective vaccines has proven difficult.

Large pharmaceuticals are eyeing this market: Sanofi Pasteur, Merck, Pfizer, and others have all been involved in developing MRSA vaccines (Schneewind & Block, n.d.), and three candidate vaccines for CDI are in clinical trial (Kociolek & Shulman, 2017). Merck was leading the race towards an *S. aureus* vaccine but ended a clinical trial over safety concerns (Reid, 2011). In Canada, the *Canadian Action Plan on Vaccine Research, Innovation and Development* is guiding prioritization of innovative vaccines that may help to prevent resistant infections (PHAC, 2015). PHAC and the Canadian Institutes of Health Research (CIHR) have established the Canadian Immunization Research Network (CIRN), which is composed of researchers studying vaccine safety and efficacy, as well as the development of interventions aimed at improving immunization levels (PHAC, 2015). For example, researchers at The Ottawa Hospital and the Children's Hospital of Eastern Ontario developed a smartphone app called CANImmunize (formerly ImmunizeCA) that allows the public to track their immunization history and schedule (Hospital News, n.d.-b). The app includes customizable schedules, catch-up schedules for recent immigrants to Canada, and information for patients about their health conditions (CANImmunize, 2019; Hospital News, n.d.-b).

To better understand how a vaccine might reduce the impact of AMR, the Panel simulated the effect of a CDI vaccine in its model (Section 4.1); resistant CDIs were responsible for 115 deaths and 64,000 extra days in hospital. In the Panel's model, eradicating CDI would save 6,000 to 46,000 lives and $7 to $44 billion in GDP between 2020 and 2050 (Figure 6.7).

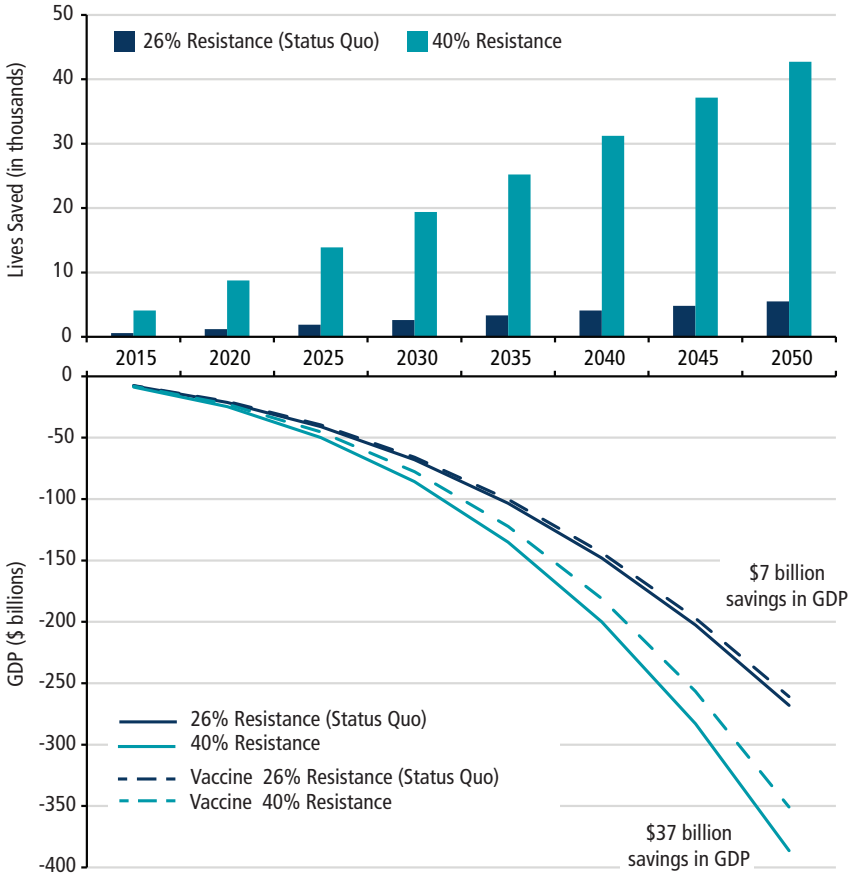


Figure 6.7

The Effect of a CDI Vaccine on Mortality and GDP

This figure plots the cumulative number of lives saved by the introduction of a hypothetical *Clostridioides difficile* vaccine in 2020. By 2050, the *C. difficile* infection (CDI) vaccine saves between 6,000 (navy blue bar) and 46,000 (teal bar) lives. By saving these lives (as well as the associated morbidity), the vaccine would contribute between $7 billion and $37 billion to Canadian GDP between 2020 and 2050, if resistance remained constant at 26% (status quo – navy blue line) or grows to 40% (teal line).

Rapid Diagnostics

Faster and more effective detection and diagnosis of resistant infections are important because giving a patient or animal the correct treatment earlier can improve clinical outcomes and decrease transmission. Until recently, identifying the most appropriate treatment was done via an *empirical* diagnosis — physicians or veterinarians using their expertise, professional judgment, and intuition to determine the cause of an infection, thereby identifying the most appropriate treatment; in some cases, diagnostic tools, typically lab-based, are later used to confirm or change the diagnosis and prescription (O'Neill, 2016c). With advances in genomics, researchers can now look for genes that indicate resistance to specific antimicrobials, thus making it possible to detect and describe resistant bacteria rapidly, reducing the time to get test results to healthcare providers so that patients can be treated with effective drugs in a timely manner. This also improves the capacity of national laboratories and other public health facilities to prevent outbreaks (Burnham *et al.*, 2017).

Researchers in Canada were early leaders in using rapid molecular diagnosis, developing various assays that can detect antibiotic resistance genes directly from clinical samples including MRSA (Turner *et al.*, 2017), CDI (Longtin *et al.*, 2016), and other organisms (Bergeron *et al.*, 2000; Vidovic *et al.*, 2014; Perera *et al.*, 2018; Rumore *et al.*, 2018). PHAC's National Microbiology Laboratory, along with collaborators, have developed technology for diagnosing AMR gonorrhea using bioinformatics: *Neisseria gonorrhoeae* Sequence Typing for Antimicrobial Resistance, or NG-STAR (Demczuk *et al.*, 2017). NG-STAR includes the DNA sequences of seven genes associated with resistance for hundreds of isolates of drug-resistant strains of gonorrhea. Making their data publicly available in Canada and internationally enables researchers and public health officials to compare a given strain of gonorrhea to the sequences in the NG-STAR database, allowing them to determine whether that strain is likely to be resistant to a given antimicrobial (Demczuk *et al.*, 2017). Many countries, including Canada, are already performing whole-genome sequencing of pathogens to rapidly detect drug-resistant bacteria to inform outbreak analysis (Quainoo *et al.*, 2017).

6.4.2 Medium-Term Innovations

Microbiome

The human microbiota consists of all invisible microbes, including bacteria, fungi, viruses, and protozoa, that live symbiotically in and on the human body, primarily in the gut; the microbiome consists of the collection of genes these cells harbour (Turnbaugh *et al.*, 2007). The "human gut microbiota is a complex microbial community and implicated in a large number of beneficial host functions," involved in both health and disease (MacPherson *et al.*, 2018). Gut

microbiota have a vital role in human well-being, and changes in gut microbiota composition can impact on health, including both acute or chronic disease states (MacPherson *et al.*, 2018). Prior exposure to antimicrobials, the environment (such as diet), and host immune system activity shape microbiome structure and function (Relman & Lipsitch, 2018). The microbiome relates to AMR because of the impact of antimicrobials on its general composition. Antibiotics do not target specific microbes, but instead affect many diverse microbes in addition to those specifically causing infections. Normal microbiota can harbour AMR genes, which can serve as a genetic reservoir for AMR that can be passed on to pathogens. Additionally, modifying the microbiome can be used to alter disease outcomes, as witnessed by the effective therapeutic use of fecal transfers to treat certain infections.

The negative impact of antimicrobials on microbiota composition and the damaging consequences of AMU on human health through resultant changes to the microbiome have been illustrated in multiple studies (Perez-Cobas *et al.*, 2013; Gillies *et al.*, 2015; Raymond *et al.*, 2016). For example, changes to the microbiome, which can be brought about by AMU, may lead to obesity, diabetes, asthma, allergies, and depression (Tilg & Kaser, 2011; Foster & McVey Neufeld, 2013; Ohland & Jobin, 2014; Arrieta *et al.*, 2015; Kostic *et al.*, 2015). CDIs can be an unintended consequence of AMU. *C. difficile* primarily causes infections after the use of broad-spectrum antimicrobials, often in hospitalized patients or residents of long-term healthcare facilities (Cascals-Pascual *et al.*, 2018). Ironically, fecal transfers are an effective therapy for this disease, while antibiotics (which triggered the disease) have limited utility in treatment. Because antimicrobials have severe negative impacts on the microbiome, any new antimicrobials may be harder to approve.

However, the microbiome itself has great potential for therapy. The use of fecal transplants to displace resistant or pathogenic bacteria and to restore colonization and gut microbiome function is now a CDI treatment (Cascals-Pascual *et al.*, 2018), and shows promising results in treating inflammatory bowel disease (Anderson *et al.*, 2012). Despite the success of stool transplants in treating CDIs, many patients find the idea of receiving someone else's stool unappealing. In the future, it is hoped that defined mixtures of key microbes can be used to replace fecal transfers. Other research has shown how changes that decreased the diversity of a baby's microbiome affected their risk of childhood asthma (Arrieta *et al.*, 2015); there is hope that repairing the microbiome could potentially decrease asthma rates, which are partly caused by AMU. The microbiome is also being applied to displace resistant organisms, although not yet clinically.

Overall, maintaining a healthy microbiome can be viewed as a method of preventing infection, whereby healthy microbes already present in the body displace incoming pathogens via competitive exclusion (Ohland & Jobin, 2014). These healthy microbiomes in turn help prevent infections, thereby decreasing AMU.

Hospital Practices

Hospitals are frequently associated with the transmission of resistant infections. Poor hand hygiene is likely responsible for thousands of HAIs every year in Canada (Section 6.2.3). To help address this problem, researchers at University Health Network's Toronto Rehabilitation Institute have developed a badge that uses sensors in patient areas to determine if hospital staff have washed their hands: if a staff member fails to do so, the badge buzzes as a reminder (Pong *et al.*, 2018; Hospital News, n.d.-b). This intervention increased overall hand hygiene performance (Pong *et al.*, 2018). Similar technology could be used to prevent infections in other settings where healthcare is delivered.

Technologies that sterilize large areas reduce the transmission of infections. Vancouver General Hospital has become the first hospital in Canada to test a germ-killing robot, Trudi, that uses ultraviolet light to kill viruses and bacteria in hospital rooms (Hospital News, n.d.-b; Tru-D SmartUVC, 2019). Two U.S. companies, AltaPure and Medizone, already sell machines that can help sanitize hospitals. AltaPure sells a technology that sanitizes a room using a disinfectant fog, and Medizone's AscepticSure technology uses ozone-based gas (Altapure, 2019; AsepticSystems, 2019). As with all new medical technologies, patient safety must be paramount when considering sterilization technologies.

Data Analytics

Research and innovation can also support better data collection, improving surveillance and informing stewardship and IPC. Gathering more infection data from healthcare facilities allows for better measurement of the challenges facing healthcare quality and patient safety. This includes determining the effectiveness of interventions and their potential economic impacts on healthcare systems and the agricultural sector (AMR Research and Innovation Task Group, 2017). In order to respond to the threat of AMR, potential solutions should be evidence-based, and will require research and innovation that allows for the advancement of medical knowledge and practices (e.g., rapid diagnostic tests) as well as new therapies.

There are numerous gaps in understanding the dimensions and scale of the contribution of AMU in food and companion animals to AMR problems in humans. Attribution of the animal contribution to AMR in humans is a complex and multi-dimensional problem (Section 2.1); not all AMR contributors are clear, and obtaining an integrated and balanced perspective is challenging and can readily revert to a blame game. Whole-genome sequencing offers considerable promise in source attribution but is best when supported by well-designed surveillance systems. The international dimension of the problem is important, including the role of imported foods from countries with poor use of antimicrobials in food animals. The relative importance of AMU in food versus companion animals needs to be investigated as part of the prioritization process in addressing AMR.

Medical Technologies

Catheter-related infections are common when using catheters for extended periods. In a systematic review of the effectiveness of antimicrobial-coated central venous catheters, 23 of 33 trials found significant differences in rates of catheter-related BSIs (Wang *et al.*, 2018). Compared with standard catheters, those made of chlorhexidine/silver sulfadiazine and antibiotic-coated catheters were associated with decreased rates of infection (Wang *et al.*, 2018). Many medical technology companies are developing this type of device: Cook Medical has developed a central venous catheter that contains the antimicrobials minocycline and rifampin, meeting the CDC's highest recommendation for reducing catheter-related infections (Cook Medical, 2019).

Surgical site infections (SSIs) are another common source of healthcare-associated resistant infections. Teillant *et al.* (2015) estimate that between 39 and 51% of pathogens causing SSIs are resistant to antimicrobials in the United States. One technique that reduces the likelihood of infection is minimally invasive surgery because it minimizes or even eliminates surgical incisions as well as reduces the trauma to a patient's body (Tonutti *et al.*, 2017). Minimally invasive surgeries have surged in popularity over the past few decades because of rapid technological advances. Tonutti *et al.* (2017) provide several examples: high-resolution miniaturized cameras, stereovision, and optimal lighting "provide a detailed view of targets inside the body;" and precision of surgery by providing "planning and real-time navigation during surgery." Finally, virtual and augmented reality systems offer new opportunities for training and guidance, using realistic simulations and anatomical renderings.

6.4.3 Long-Term Innovations

Nanotechnological Delivery Systems

Nanotechnology can preserve and extend the effectiveness of existing antimicrobials by acting as an enhanced drug delivery system, providing more selective delivery (Baptista *et al.*, 2018; Muzammil *et al.*, 2018). It has been used in targeted cancer treatments for about a decade, but its application for antimicrobial delivery is more recent (Pharmaceutical Technology, 2014). Currently nanotechnology is used synergistically to enhance antimicrobial delivery and treatment, alone as treatment, or to detect infection (Pharmaceutical Technology, 2014; Baptista *et al.*, 2018; Muzammil *et al.*, 2018).

Researchers at the Methodist Hospital Research Institute have used a nanotechnology approach to detect multi-drug-resistant tuberculosis (MDR-TB); using wafers filled with TB cells, diagnosis and susceptibility testing can be assessed simultaneously, thereby streamlining diagnosis (Pharmaceutical Technology, 2014). At the Massachusetts Institute of Technology (MIT) and Brigham and Women's Hospital, researchers have developed nanoparticles that can deliver antibiotics directly to the site of an infection, where they release a high and prolonged dose in order to maximize effectiveness (Pharmaceutical Technology, 2014).

Beyond extending the effectiveness of existing antimicrobials, nanotechnological innovations offer a number of possible alternative therapies. Nanoparticles that can be used as replacement therapies include metal and metallic oxide nanoparticles, especially silver nanoparticles, which have been shown in studies to be effective against MRSA and *Escherichia coli* (Pharmaceutical Technology, 2014; Baptista *et al.*, 2018; Muzammil *et al.*, 2018). IBM Research and Singapore's Institute of Bioengineering and Nanotechnology (IBM, 2013) have created "novel nanostructures that are effective at targeting and destroying bacteria [that] unlike [antimicrobials]... attack the bacterial cells physically rather than chemically, ripping open the cell wall and membrane so the cell breaks down" (Pharmaceutical Technology, 2014).

Cellular Agriculture

In 2016, about 78% of antimicrobials were used in industrial agriculture (PHAC, 2017a). In the same way that alternative forms of energy have been developed to reduce fossil fuel dependence, cellular agriculture may enable diversification of animal agriculture. Cultured meat, part of cellular agriculture, generates animal products from cells and not from whole animals (Datar, 2018; Stephens *et al.*, 2018). Instead of raising an animal from birth to slaughter — requiring antimicrobials as well as feed, water, and land — animal protein can be created without farms (Mattick, 2018; Stephens *et al.*, 2018).

The central challenge to cellular agriculture is scaling up the technology; currently, most cellular agriculture is experimental and small scale (Cosgrove, 2017; Datar, 2018). In 2013, Mark Post, the co-founder of Mosa Meats, was the first to make a cell-cultured beef burger (Cosgrove, 2017). The process took three lab technicians about three months to culture the 20,000 fibres of the burger, costing about $1.2 million per pound. However, progress has been made that decreases the price of cultured meat. Currently, Memphis Meats is developing lab-made chicken meat, which would sell at about $6,000 per pound — about a 99% reduction in price (Cosgrove, 2017). Ultimately, cellular agriculture is an entirely new industry — a new field of science and new set of products that may change the entire structure of the animal food industry. How this technology will be adopted is unclear, especially with the recent increase in vegetable-based meat alternatives that are currently more economically feasible.

6.5 CONCLUSION

Since healthcare is a complex system, it is virtually impossible to predict the impact of a given intervention on the behaviour of patients, healthcare providers, hospitals, governments, communities, and companies. The effect of each intervention is subject to significant uncertainty, since the feedback loops among human behaviour, infection rates, resistance rates, and costs per patient are interconnected. As such, the Panel stresses that the most effective approach to addressing AMR is multifaceted, combining elements of all four mitigation strategies that have been shown to be effective. This includes greater immunization of people living in Canada and adequate training and resourcing of hospital IPC programs, which would prevent infections and thereby decrease AMU. Physicians and veterinarians can also play a central role in decreasing AMU through changes in prescribing practices; however, a multifaceted approach would also involve other stakeholders through the use of regulations, organizational accreditation requirements, as well as consistent standards for prescribing and dispensing antimicrobials. Whether interventions target decreased AMU or AMR, both IPC and stewardship require a robust system for collecting data, assessing the impact of the problem, and supporting the measurement of the success of each intervention. Therefore, both surveillance and research and innovation are integral to any multifaceted mitigation strategy.

There are also opportunities to limit the impact of AMR beyond the health sector, animal industry, and government. Informed and encouraged by public health campaigns, all people in Canada can improve their handwashing and food-preparation practices, get vaccinations, engage in safer sexual practices, and change their behaviour in other ways to prevent the spread of infections. They can also engage in their own personal stewardship, asking their doctors or vets to prescribe antimicrobials only when necessary.

AMR is a global tragedy of the commons. Each individual country uses antimicrobials to improve human and animal health, but this use contributes to the spread of resistant bacteria and declining antimicrobial effectiveness around the world (McLean & Dye, 2018). This dichotomy between individual benefit and global cost can lead to overuse of antimicrobials, sacrificing global human and animal health as individual countries prioritize their own economy and the health of their citizens. This is more challenging for countries with broad scale AMU combined with high population density, and low levels of economic and social development (Laxminarayan *et al.*, 2013). Indeed, the increase in healthcare expenditures resulting from AMR are expected to be the most severe in low- and middle-income countries (Ahmed *et al.*, 2018).

Since no single country can manage AMR alone, this challenge calls for coordinated global action. In its 2015 *Global Action Plan* on AMR, the WHO specifically calls for international collaboration to establish surveillance networks, enforce medical and veterinary codes of practice, develop inspection teams to monitor drug quality, and encourage research and innovation into new drugs, technologies, and medical and industrial practices (WHO, 2015). Like other OECD countries, Canada has approved the WHO plan and developed its own Pan-Canadian Framework (PHAC, 2017d). But Canada is in the middle of the pack among OECD countries when it comes to AMU, AMR, and mitigation efforts (OECD, 2018a). As a scientifically and economically advanced country, Canada has an opportunity — and obligation — to play a significant role in this coordinated global effort, helping to reduce AMU, improve surveillance, and foster innovation.

7

Conclusion

- Key Findings
- A Time for Action

7 Conclusion

This report reflects the findings of an interdisciplinary expert panel assembled to answer the timely and important question: *What is the socio-economic impact of antimicrobial resistance (AMR) for Canadians and the Canadian healthcare system?* The Panel used multiple approaches to examine its charge. These included consideration of evidence in the literature on antimicrobial use (AMU), AMR, and the costs associated with infections; a detailed estimation of the current morbidity and mortality impacts of resistant infections in Canada today; and the commission of an economic model to estimate the future economic impacts of AMR. In this chapter, the Panel summarizes its key findings and concludes by emphasizing the importance of taking steps to tackle AMR immediately.

7.1 KEY FINDINGS

Antimicrobials are an essential part of contemporary life in Canada, forming the basis for modern healthcare and playing a central role in agriculture. Antimicrobials have reduced the burden of infectious diseases; enabled commonplace medical interventions, such as caesarean sections, joint replacements, and tonsillectomies; and improved agricultural productivity. While their full economic value is difficult to quantify, according to simulations of the Panel's model, antimicrobials saved at least 17,000 lives and 2.6 million hospital days in 2018, thereby contributing $6.1 billion to the Canadian economy.

Antimicrobials are indispensable, but those used in healthcare and agriculture, as well as those found in the environment through processes such as run-off from farms and sewage treatment, all contribute to AMR. While all AMU contributes to resistance, the misuse and overuse of antimicrobials in all sectors have further compounded the problem. The Panel therefore chose to examine the issue of AMR through a One Health lens that recognizes the interconnected nature of AMR; that there is no benefit in apportioning blame for AMR between medicine and agriculture; and that a holistic approach is needed to address the problem now and in the future.

The Panel further chose to examine the health and economic impacts of AMR based on important clinical syndromes. Using this approach, it estimated epidemiological measures (incidence, rate of resistance, morbidity, and mortality) of resistant infections associated with 10 syndromes that encompass the majority of resistant infections in Canada. The 10 syndromes examined in this report are: bacterial gastro-intestinal infections (BGIs), bloodstream infections (BSIs), *Clostridioides difficile* infections (CDIs), intra-abdominal infections (IAIs),

musculoskeletal infections (MSIs), pneumonia, sexually transmitted infections (STIs), skin and soft tissue infections (SSTIs), tuberculosis (TB), and urinary tract infections (UTIs).

AMR already leads to substantial negative health impacts in Canada, which are unequally distributed among socio-demographic groups.

AMR is not only an issue for future generations. It already impacts people across Canada. Using epidemiological estimates of the 10 important clinical syndromes, the Panel estimates that resistance to first-line antimicrobials is already about 26% and that there were over 250,000 resistant infections in 2018. Perhaps most significantly, the Panel estimates that, in 2018, over 14,000 deaths in Canada were caused by resistant infections. Furthermore, about 5,400 of these deaths, or almost 15 a day, were directly attributable to AMR (i.e., would not have occurred had people contracted an infection susceptible to first-line antimicrobial treatment).

The negative health impacts of AMR are substantial, but the burden of resistance is not shared equally across the Canadian population. This is because some groups are more at risk of acquiring resistant infections. In many cases, the acquisition of a resistant infection stems from contact with the healthcare system, so those who have cancer or other medical conditions are at greater risk. Additionally, the risk of infection is higher for those with compromised or weaker immune systems, including the very young and older adults.

Other demographic groups are also at higher risk of getting a resistant infection. For instance, some of the conditions that contribute to the risk of acquiring a resistant infection, such as crowded living conditions and inadequate access to clean water, are known to be more prevalent in Indigenous communities. Others who live in crowded conditions, such as people in homeless shelters or on very low incomes, are also at higher risk compared to the general population. Additionally, certain behaviours increase the risk of AMR, including risky sexual practices, substance use disorder, participation in certain sports, and pet ownership.

Global travel and trade make AMR a worldwide problem. People who travel internationally can bring resistant microbes back to Canada, whether they exhibit symptoms of infection or not. Travel to regions where resistant microbes are more common is therefore an important risk factor for acquiring a resistant infection.

AMR places a significant financial burden on the Canadian healthcare system, costing about $1.4 billion in 2018. If resistance rates increase to 40% by 2050, it is estimated that the cumulative costs of AMR to the healthcare system will be $120 billion.

Resistant infections are associated with additional costs to the Canadian healthcare system. Each resistant infection related to the 10 important clinical syndromes that results in hospitalization has an average inpatient cost of about $18,000. The most common resistant infections — those that lead to SSTIs, UTIs, and IAIs — place the greatest financial burden on the healthcare system.

The healthcare costs of resistant infections are already substantial, representing about 0.6% of all national healthcare spending, equal to the entire budget for all hospital expenditures in Newfoundland and Labrador. The cost of AMR is expected to increase even further as it becomes more prevalent. If resistance to first-line antimicrobials were to slowly rise to 40% by 2050, AMR would cost the healthcare system $8 billion per year, roughly equal to the current total expenditure on all hospitals in Atlantic Canada. Even if resistance rates stayed at the current levels, AMR would still cost $6 billion per year by 2050. The Panel notes that such an increase in costs associated with only a single dimension of healthcare would create financial strain and may lead to spending cuts in other healthcare or government services.

AMR has a sizable negative impact on the economy, having reduced Canada's GDP by an estimated $2 billion in 2018. By 2050, rising resistance rates could lead to the economy losing between $13 and $21 billion per year.

The Canadian economy is already negatively impacted by AMR, beyond costs directly attributable to healthcare. The Panel estimated the impact of AMR on the Canadian economy using a quantitative economic model that considered the effects of mortality and morbidity on the labour force and GDP. The model found that the industries most negatively affected by AMR are those that are labour-intensive, including recreation and culture, transportation, and public services. As with healthcare costs, the magnitude of these economic impacts is only going to grow as rates of AMR increase.

The reduction in Canada's GDP as a result of AMR was 0.13% in 2018, equal to one-third the value of the Canadian motor vehicle manufacturing industry. If resistance rates were to rise to 40% by 2050, Canada's GDP would decrease by $21 billion that year. Overall, the yearly economic reductions due to AMR

would mean that Canada's economy would lose more than $388 billion over the next 30 years. Even if resistance rates were to remain constant, the economy would still be losing $13 billion per year by 2050.

These estimated projections of AMR's economic and healthcare costs underscore a time lag between the cause and effects of resistance. AMR is a growing problem, and inaction today will only lead to impacts that are much greater in the future.

Increased AMR will lead to direct and indirect social impacts that may include a reduction in social capital, quality of life and trust, and greater inequality.

AMR is unlike any other healthcare crisis Canada has ever faced. It is therefore impossible to fully predict the nature and magnitude of all of the social impacts that will result from increased AMR. Despite this, it is clear that these impacts will be both significant and far-reaching.

A range of social impacts will stem directly and indirectly from measures put in place because of increased AMR. One important class of measures may be changes to healthcare delivery, including fewer elective surgeries due to the increased risk of infection resulting from an inability to use prophylactic antimicrobials. Fewer surgeries would lead to decreased quality of life for people with certain chronic diseases or conditions, such as joint pain, which can only be alleviated by replacement.

The implementation of national and international public health measures to contain the effects of AMR may also lead to negative social impacts. These measures could include additional surveillance; isolation and quarantine of people infected with, or exposed to, resistant microbes; and travel restrictions. While these measures could have merit, it may be challenging to find a balance between mitigating AMR and the loss of liberty, increased fear, and reduced quality of life caused by such measures. Enhanced surveillance may impinge on people's right to privacy, and may inadvertently create stigma against certain geographic or ethnic communities. Those in isolation and quarantine may be stigmatized in addition to potentially losing income and experiencing loneliness while dealing with the fears associated with developing an infection. Lastly, travel restrictions may decrease the quality of life and social connectedness of those wishing to visit restricted regions, while travel advisories against Canada would have significant social and economic impacts due to reduced tourism and participation in the economy (e.g., eating in restaurants).

The most effective way to address AMR is to take a multifaceted approach that coordinates initiatives related to four key mitigation strategies: surveillance; infection prevention and control (IPC); stewardship; and research and innovation.

The health and economic costs of AMR are large, but so too are the potential benefits of measures to reduce resistant infections. Based on the Panel's model, an intervention that reduces the infection rate by 33% would save 120,000 to 200,000 lives and $117 to $177 billion in GDP between 2020 and 2050, if resistance remains constant at 26% or rises to 40%.

A key element that supports mitigation is surveillance, as a clear picture of the current state of AMU and AMR in Canada would enable targeted use of resources. Limited data on priority pathogens, AMU in northern Canada, and AMR in animals, along with the absence of an effective federal/provincial/territorial framework for coordination of data collection and sharing, are hindering current surveillance efforts in Canada.

By reducing the rate of infections, IPC practices can have a significant effect on the transmission and spread of resistant infections, provided they are adequately resourced and fully implemented. Beneficial IPC practices that have a large impact include hand hygiene, appropriate environmental and device cleaning, hospital IPC, monitoring processes and outcomes, hiring healthcare staff, and reducing occupancy rates. Ensuring that good IPC practices are followed in healthcare settings (e.g., cleaning protocols, best-practice hand hygiene) limits the occurrence and spread of infections.

Stewardship initiatives that promote the judicious use of antimicrobials in both healthcare and agriculture provide opportunities to slow the increase in rates of resistance and therefore limit the spread of AMR. This includes ensuring, for example, that best practices in medicine are followed — particularly in hospitals — and that consistent messaging and education reach the public. Progress in the agricultural sector has been made, demonstrating that change is possible. While agriculture accounted for over three-quarters of AMU in Canada in 2016, the federal government eliminated medically important AMU for growth promotion in 2018 and, for the first time, mandated that all AMU in food animals be under veterinary prescription.

While known interventions can have a great and immediate impact in reducing the effects of AMR, research and innovation are also fundamental. This includes directly through the development of new therapies to treat resistant infections,

but also through innovations that decrease infection rates, such as vaccines and improvements in IPC, stewardship, and surveillance. Potential benefits may result from research and innovation related to, for example, new antimicrobial therapies and vaccines, the microbiome, hospital practices, rapid diagnostics, data analytics, medical technologies, nanotechnologies, and cellular agriculture.

7.2 A TIME FOR ACTION

AMR is both a One Health and One World problem. There is no single sector at fault, no part of the world immune, and no one solution to solve the challenges brought on by resistant microbes. There is also a time lag between the cause and effect of AMR: AMU in one place today may lead to resistant infections in another place tomorrow. The negative impacts of AMR are already experienced in Canada and around the world; inaction today ensures that, as resistance grows, these impacts will only worsen with time. The importance of AMR as a world issue has been recognized by the United Nations, which has stated that AMR is a fundamental and long-term threat throughout the world (UN, 2016). There is an opportunity for Canada to build on its history in global health innovation by becoming a driving force in addressing the challenge of AMR, benefiting both this country and the world.

The economic and health estimates calculated by the Panel should not be taken as exact. Gaps in the available data and the need to make certain assumptions limited the level of precision possible. Having said this, the methodologies behind the Panel's calculations and model are strong, and the resulting estimates should be considered representative of the types of impacts Canada could face as a result of increasing AMR. A lack of precision should not prevent action. The magnitude of these estimates is alarming, sending a strong signal for global investment and cooperation.

There have been few health crises on this scale in Canadian history. If AMR is not slowed and measures to limit its effects not taken, Canada will be a different country within a few decades. More and more lives will be lost from infections that used to be treatable. The economy will suffer because of illness and loss of life. And there may be broad social impacts, such as increased inequality and stigma against those most at risk of infection. The time to act is now.

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Appendices

- **Appendix A — Epidemiological Estimates of Important Clinical Syndromes**
- **Appendix B — Hospital Costs and Bacterial Weighting**
- **Appendix C — Technical Details of the Panel's DCGE Model**

Appendix A — Epidemiological Estimates of Important Clinical Syndromes

The Panel chose to examine syndromes for which AMR is prevalent and has the greatest impact. The syndromes included in this report are bacterial gastro-intestinal infections (BGIs), bloodstream infections (BSIs), *Clostridioides difficile* infections (CDIs), intra-abdominal infections (IAIs), musculoskeletal infections (MSIs), pneumonia, sexually transmitted infections (STIs), skin and soft tissue infections (SSTIs), tuberculosis (TB), and urinary tract infections (UTIs). The epidemiological measures of incidence, resistance (to first-line antimicrobials), mortality, and morbidity (additional length of stay in hospital, or LOS) were estimated for each syndrome, details of which are described below (and summarized in Table 2.2). In order to consider effects for all people in Canada (as opposed to only those who have had recent contact with the healthcare system), the Panel used estimates that related to both healthcare- and community-associated infections, where possible. The estimated rates were established through the Panel's expert appraisal of the literature, but it did not carry out a systematic review. The Panel notes that its challenges in developing these estimates illustrate the important data gaps related to AMR in Canada.

A.1 BACTERIAL GASTRO-INTESTINAL INFECTIONS (BGIs)

Incidence

A descriptive study of reportable gastrointestinal infections in Ontario from 2007 to 2009 found that the average incidence of all reportable BGIs, excluding *C. difficile*, was 55 per 100,000 (Vrbova *et al.*, 2012). The Panel notes that this is an under-estimate of all BGIs in Canada as it only includes those that are reported to a public health agency in Ontario.

Resistance

PHAC reports resistance associated with *Salmonella* (PHAC, 2017a). The rate of multi-class-resistance in *S. typhi* and *S. paratyphi* was 19%, and non-typhoidal *Salmonella* was 11%. The average of these two values was 15%, and was used by the Panel as an approximation of the rate of resistance in BGIs.

Mortality

A review of outbreaks involving non-typhoidal *Salmonella* in the United States found that the mortality rate of infections caused by resistant bacteria was 0.04% higher than that of infections caused by susceptible strains (0.1% versus 0.06%) (Varma *et al.*, 2005).[21] The Panel used these numbers as a proxy for the mortality rate, and increased mortality rate for all BGIs.

21 The authors note the difference in these rates is not significant ($p = 0.57$).

Morbidity

Contrary to the measures of morbidity for all other syndromes (other than STIs), the Panel here decided to use additional days with diarrhea, not additional days in hospital, for the morbidity of BGIs. The average of three studies reporting these data was 2.33 days (Marano *et al.*, 2000 as cited in Smith *et al.*, 1999; Travers & Barza, 2002; Nelson *et al.*, 2004).

A.2 BLOODSTREAM INFECTIONS (BSIs)

Incidence

In the Calgary area between 2000 and 2004, the annual incidence of community-onset BSIs was 81.6 per 100,000 (Laupland *et al.*, 2007a). In the Victoria area, between 1998 and 2005, the annual incidence of community-onset BSIs was 101.2 per 100,000 (Laupland *et al.*, 2013). The average incidence from these two studies is 91.4 per 100,000.

Resistance

In the Calgary area between 2000 and 2006, there were 1,373 MSSA and 169 MRSA cases of bacteremia (a BSI) (Laupland *et al.*, 2008c), therefore 11% of cases involved resistant *S. aureus*. In the Calgary area between 2000 and 2006, among *E. coli* BSI isolates tested, reduced susceptibility to amoxicillin-clavulanate was observed in 19% of cases, to ciprofloxacin in 12%, to ceftriaxone in 4%, to piperacillin-tazobactam in 3%, and to imipenem in no cases (Laupland *et al.*, 2008b). The average resistance for *E. coli* BSIs was therefore 7.6%. The average resistance of *S. aureus* and *E. coli* BSI isolates was 9.3%.

Mortality

In the studies of both Calgary and Victoria area BSIs, the in-hospital case-fatality rate for all infections was 13% (Laupland *et al.*, 2007a; Laupland *et al.*, 2013); this rate was used as a proxy for the mortality rate of susceptible infections. According to the PHAC CARSS report, the mortality rate of MRSA bloodstream infections across Canada in 2015 was 20%; this was used as a proxy for the mortality rate for resistant BSIs (PHAC, 2017a). The difference between these rates, 7%, was used as the estimate for additional mortality due to AMR.

Morbidity

Additional LOS for resistant *S. aureus* BSIs was 8.5 days in a study of adult patients from four hospitals in Toronto (Thampi *et al.*, 2015) and 12.7 days in a study of 22 South Korean hospitals (Kim *et al.*, 2014). The average of these two studies is 10.6 days.

A.3 CLOSTRIDIOIDES DIFFICILE INFECTIONS (CDIs)

CDIs are different from the other important syndromes as they often occur following previous antimicrobial therapy. This means CDIs are doubly affected by AMR as they can be resistant infections themselves, but also may be more likely to occur in people who have had other resistant infections. This is because people who have a resistant infection are more likely to require longer or multiple courses of antimicrobials (as compared to susceptible infections). As CDI is impacted by AMR in general, the morbidity rate used is for all CDIs, as opposed to those related specifically to resistant infections.

Incidence

Based on data from Manitoba and information from other sources, Levy *et al.* (2015) estimate that the rate of CDIs in Canada was 109.2 cases per 100,000 people in 2012. This value was selected over other estimates as it includes both healthcare-acquired and community-acquired infections.

Resistance

CNISP reports CDI resistance to three antimicrobials — clindamycin, moxifloxacin, and rifampin. The average resistance of CDI to one or more of these antimicrobials in 2017 was 11.58% (CNISP, 2018).

Mortality

Leal (2019) found that the attributable mortality rate of hospital-acquired CDIs in Alberta hospitals between April 2011 and April 2016 was 4.5%. Labbé *et al.* (2008) examined the mortality rates associated with different strains of CDI in a hospital in Montréal. The authors found that the adjusted odds mortality ratio for a strain of CDI that was less susceptible to metronidazole (which was almost always the antibiotic first provided for treatment), relative to all other strains, was 2:2. Using this odds ratio and assuming a mortality rate of 4.5% for all resistant infections, the additional mortality rate of resistance for CDI is 2.45% (Labbé *et al.*, 2008; CNISP, 2018).

Morbidity

A study on CDI in Canada found CDIs (both healthcare- and community-associated infections) were associated with an additional LOS of 13.6 days in 2012 (Levy *et al.*, 2015). The Panel used this as a proxy for LOS as a result of CDI while noting it is related to all CDIs, and that LOS is relative to no infection. No specific data related to the attributable morbidity due to resistance were identified by the Panel.

A.4 INTRA-ABDOMINAL INFECTIONS (IAIs)

Incidence

Data from a multicentre observational study underway at 57 medical institutions worldwide were used to estimate the proportion of different types of complicated IAIs (Sartelli *et al.*, 2013). The proportion of appendicitis relative to other complicated IAI was then used in combination with data on incidence of appendicitis in Canada (CIHI, 2013) to calculate an incidence rate of 287.3 per 100,000 people.

Resistance

Resistance was estimated from an American study of hospitalized adults with complicated IAIs (Edelsberg *et al.*, 2008). This study was based on a large U.S. multi-institutional database that included 6,056 patients who were adults with any complicated IAI. Of 6,056 U.S. patients, 22.4% of complicated IAIs failed initial antibiotic therapy (Edelsberg *et al.*, 2008).

Mortality

In the study by Edelsberg *et al.* (2008), patients who failed initial antibiotic therapy were more likely to die in hospital (9.5% vs. 1.3%). Therefore, the mortality associated with resistant infections increased an additional 8.2%.

The Panel chose to use measures of mortality associated with all complicated IAIs and, based on members' expertise, recognizes that bacterial peritonitis would be associated with higher rates of mortality (which are not captured in the Panel's estimates).

Morbidity

In the study by Edelsberg *et al.* (2008), patients who failed initial antibiotic therapy stayed in hospital an additional 4.6 days on average.

A.5 MUSCULOSKELETAL INFECTIONS (MSIs)

Incidence

Incidence was estimated using an American retrospective cohort study of in-patient and emergency visits in California, Florida, and New York, which found the yearly incidence of osteomyelitis and septic arthritis was 104 per 100,000 (Miller & Polgreen, 2019). The Panel used these two conditions as a proxy for all MSIs.

Resistance

A retrospective review of U.S. pediatric patients who had a diagnosis of osteomyelitis, septic arthritis, or both found that the prevalence of *S. aureus* MSIs caused by MRSA in 2009-2010 was 34.8% (Sarkissian *et al.*, 2016). The study included only those who had community-acquired MRSA. This was used as a proxy of resistance of MSIs.

Mortality

In the study by Miller and Polgreen (2019), the in-hospital mortality rate for all cases of osteomyelitis and septic arthritis was 2.8%. Al-Nammari *et al.* (2007) carried out a retrospective review of the differences in the clinical features and outcomes of adult patients with septic arthritis caused by MRSA versus susceptible *S. aureus*. The authors found that the average sepsis-related mortality rate of patients with an MRSA infection was 13%, versus 5% for a susceptible infection (Al-Nammari *et al.*, 2007).[22] Converting the additional mortality to a crude odds ratio for all MSIs, and assuming an overall mortality rate of 2.8% for resistant infections, the additional mortality due to resistance in MSIs is 1.72%.

Morbidity

In the study by Sarkissian *et al.* (2016), pediatric MRSA infections resulted in five additional days in hospital compared to MSSA infections. This estimate was used as a proxy to represent morbidity in the model for all MSIs.

A.6 PNEUMONIA

Incidence

A U.S. study of community-acquired pneumonia (CAP) found that the average yearly incidence rate of CAP requiring hospitalization was 248 per 100,000 in 2010-2012 (Jain *et al.*, 2015).

Resistance

A U.S. retrospective analysis of adult patients diagnosed with CAP in out-patient settings treated with levofloxacin or macrolides found an average treatment failure rate of 22.1% (Ye *et al.*, 2008).

Mortality

Zilberberg *et al.* (2017) conducted a retrospective cohort study of data from 175 U.S. hospitals examining the impact of carbapenem-resistant Enterobacteriaceae (CRE) on the outcomes of patients with Enterobacteriaceae

22 The authors note this difference is not significant ($p > 0.2$).

infections. The mortality rate for CRE pneumonia was 10.2%, whereas it was 8.4% for carbapenem-susceptible infections. Therefore, the additional mortality due to resistance was 1.8% (Zilberberg *et al.*, 2017).

Morbidity

A European cohort study of patients admitted to intensive care units found that patients with pneumonia with resistant strains caused by *E. coli*, *P. aeruginosa*, or *S. aureus* stayed on average 1.33 days longer than patients with pneumonia with susceptible strains (Lambert *et al.*, 2011). Strains of *E. coli* (tested with third-generation cephalosporins), *P. aeruginosa* (tested with ceftazidime), and *S. aureus* (tested with oxacillin) were included in the analysis.

A.7 SEXUALLY TRANSMITTED INFECTIONS (STIs)

For the measures of incidence, resistance, morbidity, and mortality associated with resistant STIs, the Panel chose to use estimates associated with *N. gonorrhoeae* infections, as there are no good estimates related to the epidemiology of Canadian *Mycoplasma genitalium* infections, and there is no considerable resistance in Canadian chlamydia infections.

Incidence

National surveillance data on *N. gonorrhoeae* are "passively collected by PHAC through collaboration with provincial public health laboratories" (PHAC, 2017a). The submissions are voluntary and there are no standardized methods for submission across Canada. The incidence of gonorrhea has increased in Canada, from 22 cases per 100,000 in 2001, to 55 per 100,000 in 2015 (PHAC, 2017a). The 2015 data were used as an input for the Panel's model. The Panel notes, however, that a number of provinces and territories appreciably exceed this rate.

Resistance

The average resistance of gonococcal isolates to azithromycin, cefixime, or ceftriaxone in 2015 was 3.4%; this was used as input for the Panel's model (PHAC, 2017a). The Panel notes that, for some strains of resistant gonorrhea, the antimicrobials listed above are the last effective antimicrobials.

Mortality

There are no specific data on deaths from gonococcal infections; therefore the Panel used members' expert knowledge to estimate a mortality rate of 0.1% for its model, and assumes this is entirely due to resistant infections.

However, fetal or maternal deaths due to ectopic pregnancies can occur due to *N. gonorrhoeae* infections, so this input may be an under-estimate of impact. Generally, complications of gonococcal infections are not fatal but have devastating long-term consequences on female health (e.g., infertility).

Morbidity

Morbidity as measured by increased LOS likely will not capture the long-term impacts of gonococcal infections. Therefore, for STIs, disability adjusted life years (DALYs) were used and translated into additional days lost due to morbidity. The use of DALYs for gonorrhea for morbidity was possible because the mortality rate was approximately zero. A study that included an analysis of morbidity due to gonorrhea in the United States found that there were 2,678 DALYs per 650,300 infections. This translates to 1.5 additional days per infection (Ebrahim *et al.*, 2005).

A.8 SKIN AND SOFT TISSUE INFECTIONS (SSTIs)

Incidence

An American retrospective cohort study of in-patient and emergency visits in California, Florida, and New York found an incidence rate of 1,073 per 100,000 (Miller & Polgreen, 2019).

Resistance

Borgundvaag *et al.* (2013) studied patients with acute purulent SSTIs presenting at 17 Canadian hospital emergency departments and 2 health centres between July 1, 2008 and April 30, 2009. To be included in the study, the SSTI wound culture had to grow *S. aureus*. The authors found that 32% of the SSTIs were due to MRSA (versus MSSA).

Mortality

Weigelt *et al.* (2010) studied 8,302 patients who were readmitted to 97 U.S. hospitals from 2003 to 2007 because of a surgical site infection (SSI, a type of SSTI). The mortality rate associated with MSSA (monomicrobial) infections was 0.9% versus 1.4% for MRSA (mono- or polymicrobial) infections. The Panel used the MRSA increased mortality rate for surgical site infections (0.5%) as a proxy for all SSTIs.

Morbidity

Weigelt *et al.* (2010) studied 8,302 patients who were readmitted to 97 U.S. hospitals from 2003 to 2007 because of a SSI. The raw LOS associated with MRSA infections (mono- or polymicrobial) was, on average, two days longer than infections caused by MSSA (monomicrobial). The Panel used the MRSA increased LOS for surgical site infections as a proxy for increased LOS for all SSTIs.

A.9 TUBERCULOSIS (TB)

Incidence

PHAC monitors active TB infections through a national surveillance system, the Canadian Tuberculosis Reporting System (CTBRS) (Vachon *et al.*, 2018). CTBRS is a case-based surveillance system that collects data from provinces and territories about individuals infected with active cases of TB. The incidence rate of TB reported in Canada in 2017 was 4.9 per 100,000 (LaFreniere *et al.*, 2019a).

Resistance

In 2017, a study from PHAC found that 8.1% of TB isolates were resistant to first-line antimicrobials (LaFreniere *et al.*, 2019b).

Mortality

In a study by Ronald *et al.* (2016) of all cases of TB in Montréal between 1996 and 2007, the mortality rate was found to be 6.9%. Very few of these cases were considered drug-resistant. Marks *et al.* (2016) found the mortality rate of 135 patients with MDR TB in California, New York City, and Texas was 9.6%. The difference in mortality due to resistance was therefore estimated to be 2.7%.

Morbidity

The study by Ronald *et al.* (2016) found that those patients who were hospitalized initially because of TB (where the majority of cases were susceptible) had a median LOS of 17.5 days. In the study by Marks *et al.* (2016), however, patients with MDR TB were hospitalized an average of 94 days. The difference in LOS due to resistance was therefore 76.5 days. This estimate of morbidity is low, as patients with resistant TB are more likely to be hospitalized (Marks *et al.*, 2016; Ronald *et al.*, 2016).

A.10 URINARY TRACT INFECTIONS (UTIs)

For the measures of incidence, resistance, morbidity, and mortality associated with resistant UTIs, the Panel chose to consider only UTIs that lead to hospitalization (e.g., complicated UTIs, pyelonephritis). Complicated UTIs impose a high burden on healthcare systems and are frequent causes of hospitalization, whereas hospitalization and mortality are not expected with uncomplicated UTIs. Additionally, resistance is not typically associated with uncomplicated UTIs. A caveat of this approach is that, as the Panel only considered hospitalized patients, all community-based infections are not included. Most people who are treated for complicated UTIs are treated in the community, and failure of antimicrobials for this population is likely to substantially increase the need for parenteral therapy and hospital admission for some patients.

Incidence

Zilberberg and Shorr (2013) found there were 76.76 UTIs per 1,000 hospitalizations in the United States in 2009. Using the Canadian hospitalization rate from 2016 to 2017, as reported by CIHI (7,980 per 100,000), the Canadian estimate of UTIs used for the Panel's model is 613 per 100,000 (CIHI, 2018a).

Resistance

Koningstein *et al.* (2014) used 2012 data from the Dutch Infectious Diseases Surveillance Information System for Antibiotic Resistance to calculate the resistance of complicated UTIs to cefotaxime and ceftriaxone of 23.9%.

Mortality

Zilberberg *et al.* (2017) conducted a retrospective cohort study of data from 175 U.S. hospitals examining the impact of CRE on the outcomes of patients with Enterobacteriaceae infections. The mortality rate for CRE UTIs was 12.4%, whereas it was 8.9% for carbapenem-susceptible infections. Therefore, the additional mortality due to resistance was 3.5% (Zilberberg *et al.*, 2017).

Morbidity

Zilberberg *et al.* (2017) conducted a retrospective cohort study of data from 175 U.S. hospitals examining the impact of CRE on the outcomes of patients with Enterobacteriaceae infections. The study included adult patients with community-onset culture-positive UTIs. The difference in mean LOS for resistant UTIs was 14.6 days, whereas with susceptible infections it was 9.0 days. Therefore, morbidity associated with UTIs was approximated as 5.6 days (Zilberberg *et al.*, 2017).

Appendix B — Hospital Costs and Bacterial Weighting

Cost of illness studies are often used to measure the economic burden of disease on patients, hospitals, and governments (Shrive *et al.*, 2009; Roberts *et al.*, 2010; Nelson *et al.*, 2015b; Shrestha *et al.*, 2017). The most common method measures the gross costs of infections based on the average cost of hospitalization per day. For example, if a patient stays in hospital for two weeks recovering from both a knee surgery and an MRSA infection, the gross cost would be calculated as the length of stay or LOS (14 days) x average cost of hospitalization (say $2,000 per day). This gross-costing approach would produce a biased estimate of the cost of MRSA for three reasons:

- LOS is determined by both post-operative recovery and infection treatment;
- cost of hospitalization varies by procedure and course of treatment; and
- both LOS and cost of hospitalization vary by patient, hospital, regional health authority, and province/territory.

Micro-costing addresses these measurement challenges. It separates the incremental (or marginal) costs that result directly from the infection itself, involving the "direct enumeration and costing out of every input consumed in the treatment of a particular patient" (Frick, 2009). This is a bottom-up approach where each component of resource use is estimated, and a unit cost is applied to each specific patient. If, in the above example, the MRSA infection increases the LOS by a week and requires an additional course of antimicrobials, micro-costing would include only these costs (i.e., 7 extra days x $2,000 plus the cost of the antimicrobials). This approach requires financial and administrative data from hospitals, as well as observational data on patients.

However, studies using observational data are prone to selection bias, with results confounded by individual, hospital, or other characteristics (Rovithis, 2013). Avoiding selection bias requires determining the incremental effect of resistant infections by accounting for systematic differences between patients with and without an infection. In patient groups with similar baseline characteristics (e.g., age, gender, health status, social determinants of health), the likelihood of acquiring the resistant infection is as good as random. It follows that cost differences between these two groups are a statistically unbiased estimate of the average cost of resistance for that bacterium. The precision of this approach can inform strategic planning in hospitals and regional health authorities as well as provide a key input to determine the cost-effectiveness of national health policies related to AMR (Rennert-May *et al.*, 2018).

To convert hospital costs of resistant bacteria into costs for resistant syndromes, the Panel used the weighting in Table B.1, which was based on members' expert judgment on the causative relationship between bacteria and syndromes. The Panel recognizes that this weighting is imperfect, as syndromes are caused by bacteria that are not included but for which no cost estimates were available. Moreover, while BGIs, IAIs, and UTIs are sometimes caused by VRE infections, since these cases are often vulnerable patients, the bacteria weighting is based on ESBL bacteria, which is the more common cause.

Table B.1

Bacterial Weighting

Syndrome	Bacteria Weighting
BGI	ESBL bacteria
BSI	MRSA, VRE
CDI	*C. difficile*
IAI	ESBL bacteria
MSI	MRSA
Pneumonia	MRSA, ESBL bacteria
SSTI	MRSA
STI	*N. gonorrhoea*
TB	*M. tuberculosis*
UTI	ESBL bacteria

Appendix C — Technical Details of the Panel's DCGE Model

To estimate the impact of AMR on the Canadian economy, the Panel developed a dynamic computation general equilibrium model (DCGE), where Canada is connected to the rest of the world through production, investment, and trade patterns. This appendix provides technical details of the Panel's DCGE model.

Consider country r (such as Canada) where output in sector i consists of goods and services $Y_{ir,}$ that are produced by capital $K_{ir,}$ other inputs N_{ijr} (e.g., intermediate inputs from sector j), and effective labour L_{ir} (i.e., a labour input adjusted for efficiency units) (RAND Europe, 2014). Thus, production is modelled as a function of $Y = F(K,N,L)$, where subscripts i and r are omitted for simplicity.

Similar to the method used by Yerushalmi *et al.* (2016) in a different context for the study of malaria, for each time period t, the model assumes that effective labour supply is adjusted for efficiency units by $L_{r,t} = \overline{L}_{r,t} \cdot E_{r,t,}$ with the physical supply of labour input $\overline{L}_{r,t,}$ and efficiency of labour $E_{r,t}$ growing at a rate of $g_{r,t}$ and $e_{r,t,}$ respectively, based on the model's AMR scenarios.

The effective labour for country r therefore progresses over time by:

$$L_{r,t+1} = \overline{L}_{r,0}(1 + g_{r,t}) \cdot E_{r,0}(1 + e_{r,t}) \qquad (1)$$

Equation (1) breaks down effective labour supply into two components: demographic factors (on the left) and labour efficiency (on the right). The first component (demographic factors) was addressed by using a cohort-component model to estimate the size of both the working-age population and the overall population. An increase in AMR will reduce the size of the workforce and the population, leading to a smaller supply of workers (RAND Europe, 2014).

The cohort-component model is estimated from base population, which is categorized by age, skill, and gender, and which evolves based on assumptions of mortality, fertility, and migration rates. The model then projects annual population change, broken down by age, skill, and gender. The cohort-component model estimates population change based on a "natural" increase (births minus deaths) and net-migration (in-migration less out-migration) (RAND Europe, 2014). Formally, the population by age cohort a, skill s, and gender g at time t is written as:

$$P(a,s,g,t_1) = P(a,s,g,t_0) + B(a,s,g) - D(a,s,g) + IM(a,s,g) - OM(a,s,g) \qquad (2)$$

where $B(a,s,g)$ is total births, $D(a,s,g)$ total deaths, and $IM(a,s,g)$ and $OM(a,s,g)$ inward and outward migration, respectively. The total number of births in a given period depends on age structure, age-specific fertility, and population sizes. The cohort-component model applied in the modelling exercise projects the population of Canada and other countries or regions (e.g., United States, OECD countries, the rest of the world) (RAND Europe, 2014).

The second component of the model (labour efficiency) is developed to link adult and child health to the number of days lost (or gained) by the workers. The idea is that an increase in AMR leads to a greater number of lost working days because adult workers are unable to work due to (i) their own illness, and (ii) caring for their ill children. In addition, lost days are also affected by adults who were ill as children. It follows that, in the model, labour efficiency is based on the number of lost days of work (normalized to a year) relative to the baseline yearly efficiency level with these AMR-attributable lost days a combination of the adult workers and children (RAND Europe, 2014). The yearly efficiency of a worker is thus:

$$E = 1 - \textit{Number of lost days normalized to a year}$$

where an increase in AMR resistance rates raises the number of lost working days due to illness. Increasing rates of resistance will have a productivity-reducing effect. Formally, let x be the frequency of infections per year at time t, with i being the syndromes incorporated in this model, and $A = \{a,c\}$ for adult workers or children of adult workers, respectively. Furthermore, $p(x_i^A)$ is the probability of acquiring an infection, $f_{sc,t}(x_i^A)$ the probability that infection is drug-resistant for scenario sc at time t, and $z(x_i^A)$ a loss function of the number of working days lost per infection of type i (RAND Europe, 2014). $\phi_{sc,t}$ is the ratio of children to working-age adults for each scenario sc and time t. Efficiency can be expressed as:

$$E_t = 1 - \sum_i p\left(x_i^a\right) \cdot f\left(x_i^a\right) \cdot z\left(x_i^a\right) - \phi_{sc,t} \sum_i p\left(x_i^c\right) \cdot f_{sc,t}\left(x_i^c\right) \cdot z\left(x_i^c\right) \qquad (3)$$

In this setting, the efficiency parameter is affected by two components: (i) change in resistance rate $f_{sc,t}\left(x_i^A\right)$, and (ii) endogenous changes in the ratio of children to adult working population, driven by the demographics cohort-component model that depends on each future AMR scenario.

Key inputs into the demographics model are taken from the United Nations Population Database (UN, 2018). Tables C1 to C3 below provide information regarding the age-specific survival rates, the age-specific fertility rates, as well as the net migration rates and the sex ratio at birth (based on 2016 data).

Table C.1

Age-Specific Rates of Survival

Age group	Female	Male
0–4	0.996	0.995
5–10	1.000	1.000
11–14	1.000	0.999
15–19	0.999	0.998
20–24	0.999	0.996
25–29	0.998	0.997
30–34	0.998	0.996
35–39	0.997	0.995
40–44	0.995	0.993
45–49	0.992	0.989
50–54	0.988	0.982
55–59	0.982	0.972
60–64	0.972	0.956
65–69	0.955	0.932
70–74	0.928	0.892
75–79	0.881	0.825
80–84	0.797	0.714
85+	0.718	0.643

Table C.2

Age-Specific Fertility Rates (Births per 1,000 Women)

Age group	Births per 1,000 women	Average five-year change since 1985
15–19	13.9	-10.89%
20–24	51.7	-9.52%
25–29	99.4	-4.21%
30–34	104.7	8.68%
35–39	48.9	19.61%
40–44	8.2	24.63%
45–49	0.4	45.83%

Table C.3

Sex Birth Ratio and Overall Net Migration Rate

Sex birth ratio	1.06
Net migration rate (per 1,000 population)	6.5
Net migration rate growth (5-year average since 1985)	0.16

The Panel's theoretical model is calibrated to the macroeconomic and microeconomic features of Canada and other countries using the Global Trade Analysis Project (GTAP) database (Aguiar *et al.*, 2016). GTAP covers 140 countries, 57 commodities, and includes all bilateral trade patterns, production, consumption, and intermediate inputs for the reference year 2011. Table C.4 shows the 57 commodities included in the GTAP database.

Table C.4

GTAP Sector Aggregation

Sector No.	Description	Aggregation No.	Description
1	Paddy rice	1	Crop Farming
2	Wheat	1	Crop Farming
3	Cereal grains	1	Crop Farming
4	Vegetables, fruit, nuts	1	Crop Farming
5	Oil seeds	1	Crop Farming
6	Sugar cane, sugar beet	1	Crop Farming
7	Plant-based fibres	1	Crop Farming
8	Crops	1	Crop Farming
9	Cattle, sheep, goats, horses	2	Animal Farming
10	Animal products	2	Animal Farming
11	Raw milk	2	Animal Farming
12	Wool, silkworm cocoons	2	Animal Farming
13	Forestry	2	Animal Farming
14	Fishing	2	Animal Farming
15	Coal	3	Manufacturing, Construction, Retail Trade
16	Oil	3	Manufacturing, Construction, Retail Trade
17	Gas	3	Manufacturing, Construction, Retail Trade
18	Minerals	3	Manufacturing, Construction, Retail Trade

continued on next page

Sector No.	Description	Aggregation No.	Description
19	Meat: cattle, sheep, goats, horses	4	Animal Product Manufacturing
20	Meat products	4	Animal Product Manufacturing
21	Vegetable oils and fats	3	Manufacturing, Construction, Retail Trade
22	Dairy products	4	Animal Industry
23	Processed rice	3	Manufacturing, Construction, Retail Trade
24	Sugar	3	Manufacturing, Construction, Retail Trade
25	Food products	3	Manufacturing, Construction, Retail Trade
26	Beverages and tobacco products	3	Manufacturing, Construction, Retail Trade
27	Textiles	3	Manufacturing, Construction, Retail Trade
28	Wearing apparel	3	Manufacturing, Construction, Retail Trade
29	Leather products	3	Manufacturing, Construction, Retail Trade
30	Wood products	3	Manufacturing, Construction, Retail Trade
31	Paper products, publishing	3	Manufacturing, Construction, Retail Trade
32	Petroleum, coal products	3	Manufacturing, Construction, Retail Trade
33	Chemical, rubber, plastic products	3	Manufacturing, Construction, Retail Trade
34	Mineral products	3	Manufacturing, Construction, Retail Trade
35	Ferrous metals	3	Manufacturing, Construction, Retail Trade
36	Metals	3	Manufacturing, Construction, Retail Trade
37	Metal products	3	Manufacturing, Construction, Retail Trade
38	Motor vehicles and parts	3	Manufacturing, Construction, Retail Trade
39	Transport equipment	3	Manufacturing, Construction, Retail Trade
40	Electronic equipment	3	Manufacturing, Construction, Retail Trade
41	Machinery and equipment	3	Manufacturing, Construction, Retail Trade
42	Manufactures	3	Manufacturing, Construction, Retail Trade
43	Electricity	3	Manufacturing, Construction, Retail Trade
44	Gas manufacture, distribution	3	Manufacturing, Construction, Retail Trade
45	Water	3	Manufacturing, Construction, Retail Trade
46	Construction	3	Manufacturing, Construction, Retail Trade
47	Trade	3	Manufacturing, Construction, Retail Trade
48	Transport	5	Transportation

continued on next page

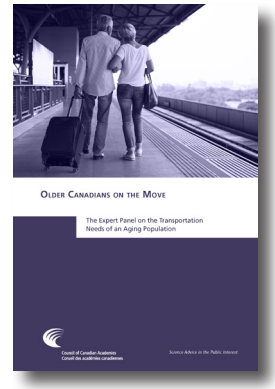
Sector No.	Description	Aggregation No.	Description
49	Sea transport	5	Transportation
50	Air transport	5	Transportation
51	Communication	7	ICT, Finance, Real Estate, Business
52	Financial services	7	ICT, Finance, Real Estate, Business
53	Insurance	7	ICT, Finance, Real Estate, Business
54	Business services	7	ICT, Finance, Real Estate, Business
55	Recreation and other services	6	Recreating and Culture
56	PubAdmin/Defence/ Health/Education	8	Public Services
57	Dwellings	7	ICT, Finance, Real Estate, Business

Council of Canadian Academies' Reports of Interest

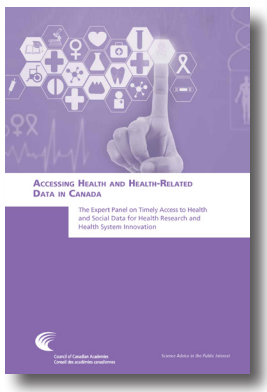
The assessment reports listed below are accessible through the CCA's website (**www.cca-reports.ca**):

Medical Assistance in Dying
(2018)

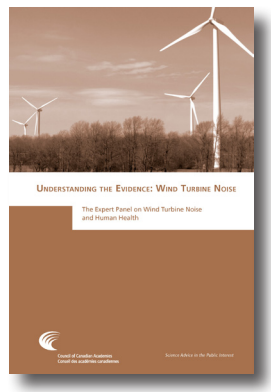
Building on Canada's Strengths in Regenerative Medicine
(2017)



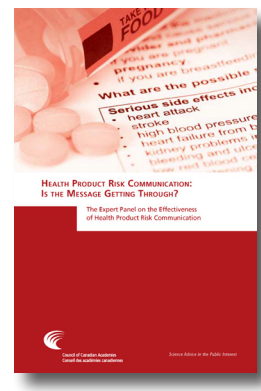
Older Canadians on the Move
(2017)



Accessing Health and Health-Related Data in Canada
(2015)



Understanding the Evidence: Wind Turbine Noise
(2015)



Health Product Risk Communication: Is the Message Getting Through?
(2015)

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