



Overcoming Resistance

Expert Panel on Antimicrobial Availability



CCA | CAC

Overcoming Resistance

Expert Panel on Antimicrobial Availability



The Council of Canadian Academies 180 Elgin Street, Suite 1401, Ottawa, ON, Canada, K2P 2K3

This project was undertaken with the approval of the Board of Directors of the Council of Canadian Academies (CCA). The members of the expert panel responsible for this report were selected by CCA for their special competencies and with regard for appropriate balance.

This report responds to a request from the Public Health Agency of Canada (PHAC) for an independent assessment. PHAC was not involved in either panel selection or report development; any opinions, findings, or conclusions expressed in this publication are those of the authors, the Expert Panel on Antimicrobial Availability, and do not necessarily represent the views of their organizations of affiliation or employment.

Library and Archives Canada

ISBN: 978-1-990592-26-3 (book)
978-1-990592-27-0 (electronic book)

This report should be cited as:

CCA (Council of Canadian Academies). (2023). *Overcoming Resistance*. Ottawa (ON): Expert Panel on Antimicrobial Availability, CCA.

Disclaimer

The internet data and information referenced in this report were correct, to the best of the CCA's knowledge, at the time of publication. Due to the dynamic nature of the internet, resources that are free and publicly available may subsequently require a fee or restrict access, and the location of items may change as menus and webpages are reorganized.



© 2023 Council of Canadian Academies
Printed in Ottawa, Canada



This assessment was made possible
with the support of the Government
of Canada

The Expert Panel on Antimicrobial Availability would like to acknowledge the First Nations, Inuit, and Métis peoples who have stewarded the lands now known as Canada since time immemorial.

The Council of Canadian Academies (CCA) acknowledges that its Ottawa office is located on the unceded ancestral home of the Anishinaabe Algonquin Nation, who have cared for the environment of this territory for millennia. Though our offices are in a single location, our work to support evidence-informed decision-making has potentially broad impacts across Canada. We at the CCA recognize the importance of drawing on a wide range of knowledges and experiences to inform policies that will build a stronger, more equitable, and more just society.

The Council of Canadian Academies

The Council of Canadian Academies (CCA) is a not-for-profit organization that supports independent, science-based, authoritative expert assessments to inform public policy development in Canada. Led by a Board of Directors and advised by a Scientific Advisory Committee, the CCA's work encompasses a broad definition of science, incorporating the natural, social, and health sciences as well as engineering and the humanities. CCA assessments are conducted by independent, multidisciplinary panels of experts from across Canada and abroad. Assessments strive to identify emerging issues, gaps in knowledge, Canadian strengths, and international trends and practices. Upon completion, assessments provide government decision-makers, researchers, and stakeholders with high-quality information required to develop informed and innovative public policy.

All CCA assessments undergo a formal peer review and are published and made available to the public free of charge. Assessments can be referred to the CCA by foundations, non-governmental organizations, the private sector, and any level of government.

www.cca-reports.ca

@cca_reports

Expert Panel on Antimicrobial Availability

Under the guidance of its Scientific Advisory Committee and Board of Directors, the CCA assembled the **Expert Panel on Antimicrobial Availability** to undertake this project. Each expert was selected for their expertise, experience, and demonstrated leadership in fields relevant to this project.

Andrew M. Morris (Chair), Professor of Medicine, University of Toronto; Medical Director, Sinai Health — University Health Network Antimicrobial Stewardship Program (Toronto, ON)

Emily Black, Associate Professor, College of Pharmacy, Dalhousie University; Clinical Pharmacist, IWK Health and Nova Scotia Health (Halifax, NS)

Nick Crabb, Programme Director, Scientific Affairs, National Institute for Health and Care Excellence (Manchester, United Kingdom)

Avram Ezra Denburg, Staff Oncologist, Division of Haematology/Oncology, The Hospital for Sick Children (SickKids); Associate Professor, Institute of Health Policy, Management and Evaluation, University of Toronto (Toronto, ON)

Aidan Hollis, President and Director, Incentives for Global Health; Professor, Department of Economics, University of Calgary (Calgary, AB)

Kevin Outterson, Austin B. Fletcher Professor of Law, Boston University; Executive Director and Principal Investigator, CARB-X (Boston, MA)

John H. Rex, Chief Medical Officer and Director, F2G, Ltd; Operating Partner, Advent Life Sciences (Wellesley Hills, MA)

Jean-Éric Tarride, McMaster Chair in Health Technology Management, Professor, Department of Health Research Methods, Evidence, And Impact (HEI), Faculty of Health Sciences, McMaster University (Hamilton, ON)

Lori J. West, Scientific Director, Canadian Donation and Transplantation Research Program; Director, Alberta Transplant Institute; Professor, Department of Pediatrics, Surgery, Medical Microbiology/Immunology and Laboratory Medicine/Pathology, Division of Pediatric Cardiology, Faculty of Medicine and Dentistry, University of Alberta (Edmonton, AB)

Christine Årdal, Senior Researcher, Antimicrobial Resistance Centre, Norwegian Institute of Public Health (Oslo, Norway)

Disclosures

To maintain the integrity of the assessment process, panelists are required to disclose to the CCA and fellow panelists any conflict of interests — actual, foreseeable, or perceived — relevant to the issues being discussed to ensure they can be managed transparently. **Dr. Kevin Outterson** is Executive Director of CARB-X, a grant-funded program on antibacterial innovation at Boston University partially funded by governments, including the Government of Canada. **Dr. John Rex** is a member of the scientific advisory boards of Basilea Pharmaceutica, Novo Holdings, Roche Pharma Research & Early Development, Bugworks Research, Forge Therapeutics, Sumitovant, and the AMR Action Fund. He received consulting fees from Forge Therapeutics, Roivant Sciences, Pfizer Pharmaceuticals, GlaxoSmithKline, and Bugworks Research, owns shares in AstraZeneca Pharmaceuticals, F2G and Advent Life Sciences, and oversaw the 2023 New Drug Application submission by F2G to the U.S. FDA for olorofim.

Dr. Jean-Éric Tarride has received research funding from AssureRx/Myriad, Boehringer Ingelheim, Edwards Lifesciences, the Canadian Partnership Against Cancer and the Canadian Agency for Drugs and Technologies in Health, consultant or advisor fees from AbbVie, Amgen, Analytica Laser, Bayer, Bristol Myers Squibb, Evidera, FlatIron, Inomar, Institute of Health Economics, Janssen, Lilly, Leo Pharma, Merck, Novartis, Novo Nordisk, Roche, Shift Health, Pfizer, Takeda and Trimedica, and payments from the Canadian Agency for Drugs and Technologies in Health as a member of their Health Technology Expert Review Panel advisory committee.

Workshop Participants

As part of the evidence-gathering process, the Expert Panel convened a workshop, which brought together its own members and 11 additional experts.

Lori Burrows, Professor, Department of Biochemistry and Biomedical Sciences, McMaster University (Hamilton, ON)

Christine Donaldson, President and CEO of HealthPRO (Hamilton, ON)

Aled Edwards, Chief Executive of the Structural Genomics Consortium (SGC); Professor, Medical Biophysics, University of Toronto (Toronto, ON)

Brent Fraser, Vice-President, Pharmaceutical Reviews, Canadian Agency for Drugs and Technologies in Health (CADTH) (Ottawa, ON)

Elena Lungu, Manager of Policy Development, Patented Medicine Prices Review Board (PMPRB) (Ottawa, ON)

Wes Miyai, Associate Director of Public Health and External Affairs, Merck Canada (Montréal, QC)

Mike Paulden, Associate Professor, School of Public Health, University of Alberta (Edmonton, AB)

Jeff Round, Chief Scientific Officer, Institute of Health Economics; Professor, Health Economics, University of Alberta (Edmonton, AB)

Sameeh M. Salama, Chief Scientific Officer (CSO), Fedora Pharmaceuticals Inc. (Edmonton, AB)

Mina Tadrous, Assistant Professor, Leslie Dan Faculty of Pharmacy, University of Toronto (Toronto, ON)

Daniel Thirion, Full Clinical Professor, Faculty of Pharmacy, Université de Montréal; Pharmacist and Researcher at McGill University Health Centre (Montréal, QC)

Message from the President and CEO

Most people have benefited from antibiotics at some point in their lives and probably expect to reliably access them again if needed. But, even today, there is no assurance they will be readily available. A defining problem with antimicrobials, including antibiotics, is that their use causes the pathogens they treat to evolve resistance, resulting in drugs that are less effective at remedying infections. As of 2018, an estimated 26% of infections were resistant to first-line treatments in Canada. As these rates continue to rise, our capacity to effectively prevent and treat infections will increasingly be challenged.

Our 2019 report, *When Antibiotics Fail*, detailed the repercussions of this growing resistance. CCA determined that more than 14,000 deaths in Canada in 2018 were associated with resistant infections, which cost healthcare systems about \$1.4 billion, and the Canadian economy \$2 billion. Modelling estimated the cumulative costs to Canadian healthcare systems could reach \$120 billion by 2050 as resistance rates increase, making it increasingly difficult and expensive to address. At the same time, antimicrobial resistance will reduce the quality of life for more people in Canada, and the most vulnerable individuals will be disproportionately at risk.

Yet, the development of new antimicrobials has been sluggish. Unlike other drugs, antimicrobials are often prescribed for short courses, and stewardship limits the use of novel antimicrobials, suggesting a less desirable marketing and revenue incentive for their development. This is in addition to known challenges of drug development generally, including the upstream costs and risks of failure.

Recognizing the challenges of enhancing the availability of novel antimicrobials, the Public Health Agency of Canada asked the CCA to examine economic pull incentives for encouraging market entry and sustained market availability of high-value antimicrobials in Canada.

Overcoming Resistance outlines the unique challenges for Canada regarding availability and access to antimicrobials and describes pull incentives that could help bring existing antimicrobials to the Canadian market and broaden access to these drugs for people in Canada. The report also analyzes the role of policies to support research and development, regulatory review, surveillance, and diagnostics.

On behalf of the CCA, I extend my thanks to the Panel, adeptly chaired by Andrew Morris, for its thorough work on this report. The Panel brought a depth of expertise in health economics, antimicrobial stewardship, oncology, infectious diseases, transplantation, law, and pharmaceutical development essential to this work. Thanks also to CCA's Board of Directors and Scientific Advisory Committee for providing guidance and oversight throughout this process.

A handwritten signature in black ink, appearing to read 'Eric M. Meslin', with a stylized flourish at the end.

Eric M. Meslin, PhD, FRSC, FCAHS
President and CEO, Council of Canadian Academies

Message from the Chair

Antibiotics are essential to keeping people in Canada and around the world healthy. From treating severe infections acquired in the community, to preventing infections in newborns or those undergoing necessary surgeries like joint replacement, to supporting patients receiving chemotherapy or undergoing organ transplantation, antibiotics are an indispensable cog in the machinery of modern healthcare.

However, multiple factors — including antimicrobial overuse in humans and animals, and persistent deficiencies in public health policies and infection prevention and control practices — have led to growing antimicrobial resistance, rendering these essential medicines increasingly ineffective. We know from a 2019 CCA report (*When Antibiotics Fail*) that antimicrobial resistance ends thousands of lives in Canada each year and costs healthcare systems more than \$2 billion annually. The global impact is several orders of magnitude greater, with antimicrobial-resistant infections responsible for over 1 million deaths annually, most in low- and middle-income countries.

These numbers are large, and perhaps even beyond comprehension, but the consequences of antimicrobial resistance are experienced by people every day. I have personally treated several patients, including those previously healthy and subsequently critically ill, with infections due to extensively drug-resistant organisms. In those instances, I have been unable to access new antimicrobials proven to work against these infections because of logistical barriers in place for medications that are not approved by Health Canada. The expected loss of life in each of these cases has been up to 65 years. These medications are not only needed for my patients, but for other patients across Canada who are all unlikely to receive them when needed.

The logical response to the growing threat of antimicrobial resistance includes investment in antimicrobial access and development, antimicrobial stewardship, public health, and infection prevention and control. Indeed, these are all necessary and currently insufficient on a global level. Among the list of necessary interventions, antibiotic development is unique in that it has been historically dependent primarily on capital markets. Up-front governmental support for early-stage drug discovery is helpful and likely necessary but, for a variety of reasons outlined in this report, existing market forces are failing to adequately drive the antibiotic development cycle. The insufficient supply of antibiotics is felt even more acutely in Canada because of poor access to newly developed drugs that are available to healthcare providers and their patients in peer countries but are neither approved nor marketed in Canada.

Most people are familiar with Sir Alexander Fleming’s chance discovery of mold inhibiting the growth of bacteria upon his return from vacation, and later isolating the mold (*Penicillium*) and the active ingredient (“penicillin”). The mystique surrounding Fleming’s discovery, however, might suggest that antibiotic development is an inexpensive, random, and unintentional event. To the contrary, the availability of a new antibiotic comes at the end of a risky and laborious process that begins with lab-based scientific enquiry and culminates in expensive, challenging human trials to demonstrate the effectiveness and safety of the new medication.

This report is based upon contemplation of existing knowledge on the problem and the synthesis and analysis of possible solutions around waning antibiotic development and access. It describes a clear path to meaningfully alter the risk-reward calculus: reward drug developers who provide novel, valuable antibiotic solutions with a fair and reasonable guaranteed revenue for their drugs.

Hopefully, policy makers and government officials, drug developers and their investors, healthcare providers and their patients, and the general public will find this report thoughtful, optimistic, practical, and useful as they seek to implement life-saving policies for Canada and the world.

It was an honour to serve as Chair and work with such an incredible group of people — both the CCA staff and the Expert Panel — on this important work which I hold near and dear to my heart.

A handwritten signature in black ink, appearing to read "Andrew Morris", with a long horizontal flourish extending to the right.

Andrew M. Morris

Chair, Expert Panel on Antimicrobial Availability

CCA Project Staff

Assessment Team: **Lida Anestidou**, Project Director
Suzanne Loney, Senior Research Associate
Sandro Marcon, Research Associate
Madison Downe, Project Coordinator
Ananda Fadila, Project Coordinator
Tijs Creutzberg, Director of Assessments

With assistance from: **Kate Hemstreet**, Project Coordinator
Anita Melnyk, Project Director

And

Design gordongroup|TAAG
Editor Jody Cooper
Translator, En-Fr Dany Gagnon and Anne-Marie Mesa

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:

Sylvie Bouchard, Director, Drug Evaluation and Technology Assessment for Reimbursement, Institut national d'excellence en santé et en services sociaux (INESSS) (Québec, QC)

Todd F. Hatchette, Head, Division of Microbiology, DPLM, Nova Scotia Health (Halifax, NS)

Ayush Kumar, Professor, Department of Microbiology, University of Manitoba (Winnipeg, MB)

I fan Kuo, Director, Optimal Use and Evaluation, Ministry of Health, Government of British Columbia (New Westminster, BC)

Reshma Ramachandran, MD, MPP, MHS, Assistant Professor, Section of General Internal Medicine, Department of Internal Medicine, Yale University School of Medicine (New Haven, CT)

Susan Rogers van Katwyk, Managing Director, AMR Policy Accelerator, Global Strategy Lab, York University (Toronto, ON)

Luke Spooner, Senior Project Manager, Pharmaceutical Management, Government of the Northwest Territories (Yellowknife, NT)

Adrian Towse, Emeritus Director and Senior Research Fellow, Office of Health Economics, (London, United Kingdom)

Spencer Tuttle, Executive Director, Lower Mainland Pharmacy Services, Provincial Health Services Authority (Vancouver, BC)

The peer review process was monitored on behalf of the CCA's Board of Directors and Scientific Advisory Committee by **Maydianne Andrade**, Professor, Biological Sciences, University of Toronto Scarborough and President, Canadian Black Scientists Network. 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 report review requirements have been satisfied. The CCA thanks Dr. Andrade for her diligent contribution as peer review monitor.

Acknowledgments

The Panel and CCA staff would like to express their sincere appreciation to the following individuals: **Jenny Hellman**, Project Leader, Public Health Agency of Sweden; **Dagmar Reitenbach**, Lead, Global Health Policy, Ministry of Health, Government of Germany, and **Céline Pulcini**, Chief of Mission for the Prevention of Antimicrobial Resistance and Coordinator of the French AMR National Action Plan, Ministry of Health and Prevention, Government of France for providing information on pull incentive policies in their respective countries; **Ian MacKay** and **Vivian Chang**, Special Access Program, for information about antimicrobial access through the program; **Ralf Sudbrak**, Interim Secretariat Lead, Global AMR R&D Hub, for advice on using and interpreting the AMR dashboard; **Rob Fowler**, Professor, University of Toronto for insight on the Canadian clinical trials networks; **Dani Peters**, President, Magnet Strategy Group, for the coordination and collection of relevant information from members of the Canadian Antimicrobial Innovation Coalition; **Kristi Coldwell**, Senior Advisor, Transplant Research Foundation of British Columbia and patient, for her perspective on antibiotic dependence; and **Ilaria Mussetto** and **Andrea Paladini**, ExACT Fellows, for their research contributions at the CCA.

Executive Summary

Antimicrobial resistance (AMR) is a global problem. Infectious microorganisms resistant to antimicrobials imperil human health and impose considerable costs on society. Resistant bacterial infections kill an estimated 1.27 million people every year. In 2018, about one million bacterial infections were reported in Canada, a quarter of which were resistant to first-line treatments. Resistant infections were responsible for over 14,000 deaths at a cost to the healthcare system of over \$2 billion. The critical importance of addressing AMR has been recognized by the Prime Minister of Canada in mandate letters to the Minister of Health.

Effective antimicrobials enable much of modern healthcare, including surgeries, transplants, and cancer treatments. People with compromised immune systems are particularly dependent on a reliable supply of effective antimicrobials to manage infections. In the face of rising AMR, the need for new and accessible antimicrobial treatments is urgent to sustain the life-saving effectiveness of antimicrobials. However, few novel antimicrobials are coming to the global market, and of those that do, many do not become accessible in Canada.

Recognizing the urgency of this issue, the Public Health Agency of Canada (PHAC) asked the CCA to convene an expert panel to provide an evidence-based, authoritative assessment that answers the following question:



What economic pull incentives have the greatest potential for success in encouraging the market entry and sustained market availability of high-value antimicrobials for use in humans in Canada?

Pull incentives are policy tools developed to incentivize antimicrobial development and commercialization, and they represent one aspect of a comprehensive response to the threat of AMR. Pull incentives offer financial compensation for qualifying antimicrobials to motivate the development and commercialization of novel antimicrobials. The Expert Panel on Antimicrobial Availability (hereafter “the Panel”) examined the available evidence on pull incentives that could lead to a viable Canadian market for new antimicrobials. Drawing from both national and international contexts, the Panel’s analysis underscores the global challenge of AMR and the need for international cooperation to address the lack of new antimicrobials.

Report Findings

Weak commercialization prospects impede the development of novel antimicrobials, creating risks and harms for people in Canada and around the world

R&D for novel antimicrobials is time-consuming, costly, and prone to failure. The use of antimicrobials leads to resistance, which decreases their effectiveness, thereby degrading their monetary and healthcare system value. As such, new antimicrobials must be used sparingly to preserve their effectiveness and longevity. This results in financially unattractive business models, with low sales and negative returns on investment for pharmaceutical companies. Companies are therefore leaving this commercial space at a time when new drugs are needed. The market challenges are particularly acute for antibiotics and antifungals, and the Panel focused its analysis accordingly.

The full value of antimicrobials extends beyond the positive health impacts experienced by an individual patient, to include savings in healthcare expenditures and increased productivity of those who are no longer infected and those who provide care for them. The benefits of these drugs can also include a reduction in disease transmission and an increase in *preparedness-value*, that is, as insurance against future outbreaks. These positive attributes — often summarized as spectrum, transmission, enablement, diversity, and insurance (STEDI) values — underscore the beneficial impacts of novel, effective antimicrobials.

Consistent with worldwide trends, AMR in Canada is increasing. This is particularly relevant for populations in Canada who are disproportionately at risk of acquiring resistant infections. Immunocompromised patients are aware of the importance of a reliable arsenal of antimicrobials, as they depend on them to manage the infections to which they are particularly susceptible. Prior antimicrobial treatment is the greatest contributing factor to the overall risk of acquiring a resistant infection. Lack of access to adequate housing, clean drinking water, and timely medical care also contribute broadly to health risks.

Governments can improve the market for novel antimicrobials by offering pull incentives to manufacturers

Eighteen antibiotics have come to market since 2010, but only three are marketed in Canada. In contrast, several European and other G7 countries have much broader availability of new antibiotics. Canada's multi-actor healthcare systems and challenging geography create barriers to drug access. Important actors involved in the delivery of healthcare include provincial, territorial, local, and Indigenous governments. Their engagement would be critical to the creation and development of a pull incentive. Furthermore, manufacturers seeking entrance to the Canadian drug market face an expensive and often lengthy approval process, which is then followed by multiple health technology assessments (HTAs) and price negotiations. Public investment has the potential to improve access to antimicrobials not currently available in Canada.

A number of pull incentives have been proposed, researched, or implemented in other countries, building on over a decade of academic work. These incentives include extensions of patent protections, tradable vouchers that extend the exclusivity of a qualifying drug, high per-unit prices, subscriptions, and annual revenue guarantees. In considering different types of incentives, the Panel found some to be lacking when it came to price certainty, adequacy of the incentive, and stewardship implications. The Panel therefore concluded that a subscription pull incentive (SPI) would work best for a country like Canada. This type of pull incentive provides a fixed annual payment to manufacturers, regardless of sales. The strengths of this approach include the ability to adjust payments over time as new evidence about drug effectiveness emerges, an incentive structure that supports equitable access but does not encourage overuse of novel antimicrobials, and an ability to hold manufacturers to contractual obligations that improve drug availability.

An SPI could boost access to antimicrobials that already exist but are not currently approved or available in Canada. It could also motivate research, development, and commercialization of new drugs. An SPI's core design elements can include establishing fixed unit prices at an affordable level and a limited window of incentive eligibility for manufacturers — for example, initially offering 3-to-5-year contracts, with an option to extend to 10 years. Setting unit prices comparable to the standard of care could keep costs affordable for provinces and territories and help promote appropriate prescribing. The Panel described a scenario in which payers (including provincial and territorial governments) pay for these new drugs

the same way they currently do (on a per unit basis). The federal government then supplements sales revenues for the manufacturer to bring the full revenues up to a fixed level established by the pull incentive program. This type of approach could minimize administrative burdens and integrate with Canada's existing healthcare systems.

Eligibility would be assessed by a committee of experts convened for this purpose. Drugs eligible for an SPI would (i) address a specified unmet public health need and (ii) exhibit innovations related to their class, mechanism of action, or target microorganism. In order to be effective, these two requirements would have to be satisfied for an antimicrobial to be deemed SPI-eligible. Manufacturers could be held to standards requiring accessibility and availability of a drug within explicit timeframes stipulated in their contracts. Stipulations for manufacturers could include monitoring and reporting antimicrobial use and resistance trends stemming from a drug's sales in Canada and abroad. These requirements could function as transparency and openness guarantors, supporting appropriate oversight of public funds. The requirements could also encourage ongoing data collection to improve understanding of drug performance and allow for data-responsive adjustments of future payments. By establishing an SPI, the Government of Canada could realize a valuable opportunity to support the health of people in Canada; act on the global scientific consensus calling for enhanced access to, and development of, novel antimicrobials; and establish itself as a global leader in the fight against AMR.

Canada has the opportunity to work with a group of other high-income countries to contribute its fair share to an adequate global pull incentive

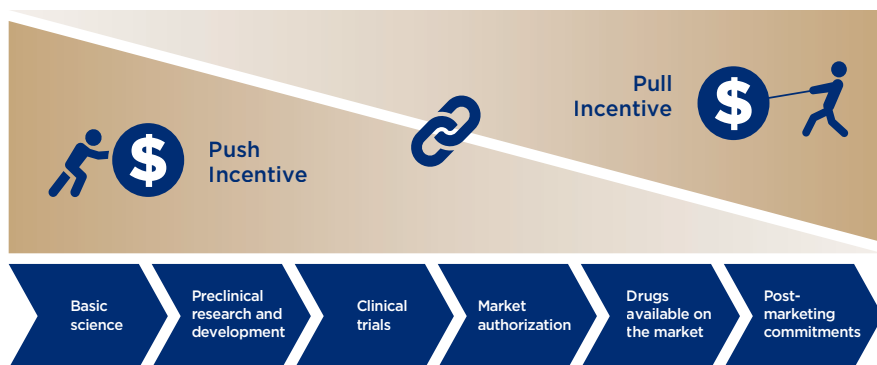
Research indicates that the global cost of incentivizing development and commercialization of novel antimicrobials exists on a range of US\$2 to US\$4 billion per drug. Adequate pull incentives may therefore be beyond economic feasibility for any one country. However, high-income countries — for example, the G7 and the 27 members of the European could act jointly to provide a global incentive. In this scenario, the Panel determined that Canada's fair incentivization share equates to an average payment of \$14.5 million per year over 10 years for each eligible drug. Were the Government of Canada to act with only G7 countries, the average payment would be \$18 million per year for each drug. While these costs are considerable, research indicates that the benefit of reliable access to effective antimicrobials is greater, offering reduced morbidity, mortality, healthcare costs, as well as STEDI benefits. Some portion of these costs would be covered by provincial and territorial governments when the drugs are used.

An SPI's effectiveness would hinge on the creation and deployment of an HTA framework capable of determining annual payment levels that would vary depending on the characteristics of each drug. Those drugs that offer the most novel mechanism of action compared to existing treatments and make the greatest contribution toward unmet public health needs would receive the greatest subscription payment. Other approved antimicrobials may not qualify for any payment, as not all new drugs will satisfy an SPI's stringent eligibility criteria.

An SPI would offer a clear price signal to manufacturers and potential investors, spurring R&D and commercialization activity in this sector. Should this approach be instituted, it could create some budgetary uncertainty for the federal government as the number of qualifying drugs and the payment level could vary over time. However, the Panel noted that, based on the current antimicrobial development pipeline, it would not anticipate more than two or three qualifying drugs per decade (though the initial uptake may be higher as some existing drugs may qualify). The Panel also emphasized that having multiple qualifying antimicrobials come to market would be a sign of program success. Furthermore, the benefits of a revitalized antimicrobial pipeline are expected to exceed the costs of such an SPI program.

Complementary policies that foster upstream R&D through push incentives, facilitate efficient regulatory review, provide necessary surveillance data, and bolster the supply of rapid diagnostics will improve the success of an SPI

An SPI would be most impactful when complemented by push incentives, so that both the R&D component and the market availability of these drugs are bolstered in tandem. Push incentives primarily encourage antimicrobial R&D rather than downstream commercialization and long-term availability of novel antimicrobials. While pull incentives are only awarded following market approval of qualifying antimicrobials, they improve commercialization prospects and thus support upstream R&D as well (Figure 1). A higher push incentive would lower the necessary pull incentive amount, and, conversely, a higher pull incentive could reduce the necessary push incentive amount.



Adapted from Årdal *et al.* (2018)

Figure 1 Funding Incentives along the Antimicrobial Innovation Continuum

Push incentives encourage antimicrobial R&D, fund clinical trials, and can improve the success of pull incentives. While pull incentives are only awarded following market approval of qualifying novel antimicrobials, they improve the commercialization prospects and thus indirectly improve support for upstream R&D.

Additional complementary interventions for an SPI may also be employed as part of a broader suite of strategies to combat AMR. These include enhanced efficiency of regulatory review, more comprehensive AMR surveillance capacity, and a broadened use of diagnostics and stewardship principles to encourage proper and effective use of antimicrobials. Enhanced surveillance of AMR and usage of antimicrobials — including novel antimicrobials that are used sparingly — would support the effective administration of an SPI. Timely diagnostics can support the appropriate use of antimicrobials, wherein novel antimicrobials are only used when needed, thereby prolonging their effectiveness and maintaining their value.

International collaborations — such as mechanisms to enable data sharing, the creation and strengthening of clinical trial networks, and the harmonization of regulatory reviews — have the potential to provide considerable value. These efforts would positively contribute to the global fight against AMR, but also to other healthcare challenges in Canada.

Securing access to existing novel antimicrobials may provide a small immediate positive health impact in Canada, but it will not contribute to international efforts to revitalize the antimicrobial pipeline and prepare for future infections. AMR is a global problem and solutions to address this challenge must be global in reach. Timely efforts to establish and support the development of a pull incentive in Canada can set an example and catalyze action abroad, which is ultimately needed to provide global funding at the necessary scale.

Abbreviations

AMR	antimicrobial resistance
AMU	antimicrobial use
ARG	annual revenue guarantee
CADTH	Canadian Agency for Drugs and Technologies in Health
GARDP	Global Antibiotic Research and Development Partnership
INESSS	Institut national d'excellence en santé et en services sociaux (Quebec)
HTA	health technology assessment
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NICE	National Institute for Health and Care Excellence (United Kingdom)
PASTEUR Act	Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act (United States)
pCPA	pan-Canadian Pharmaceutical Alliance
PMPRB	Patented Medicine Prices Review Board (Canada)
SAP	Special Access Program (Canada)
SME	small- and medium-sized enterprise
SPI	subscription pull incentive
STEDI	spectrum, transmission, enablement, diversity, and insurance

Contents

- 1 Introduction 1**
 - 1.1 The Charge to the Panel 5
 - 1.2 The Panel’s Approach 7
 - 1.3 Report Structure 9

- 2 Commercialization and Market Challenges 10**
 - 2.1 Global Antimicrobial Availability and Incentives 11
 - 2.2 Canadian Market Conditions 16

- 3 Incentivizing Enhanced Antimicrobial Development and Deployment 24**
 - 3.1 Pushing Antimicrobial R&D and Pulling Novel Antimicrobials to Market 25
 - 3.2 Pull Incentive Options 28

- 4 The Costs and Benefits of a Pull Incentive 36**
 - 4.1 Value: The True Worth of Novel Antimicrobials 37
 - 4.2 Influencing Market Entry: Scale of Incentive 44
 - 4.3 A Clear Case for Incentivizing Antimicrobials 52

- 5 A Scenario for Operationalizing a Pull Incentive for Canada 54**
 - 5.1 A Subscription Pull Incentive 55
 - 5.2 Drug Eligibility Requirements 59
 - 5.3 Establishing Eligibility and Payment Level 65
 - 5.4 Contractual Conditions 71
 - 5.5 Considerations for Implementing, Monitoring, and Evaluating an SPI 74

6 Complementary Measures to Support a Successful Pull Incentive 76

6.1 Research and Development 78

6.2 Regulatory Review 84

6.3 Surveillance 86

6.4 Diagnostics. 87

7 Final Reflections 90

References 93

Introduction

- 1.1 The Charge to the Panel
- 1.2 The Panel's Approach
- 1.3 Report Structure

Antimicrobials are an integral component of modern healthcare. If infections cannot be treated or prevented, medical procedures such as transplants, chemotherapy, and caesarian deliveries become riskier and may be less available (O'Neill, 2016; GC, 2017; OECD, 2018). However, unlike most drugs, the use of antimicrobials fosters resistance — over time, they may become less effective at preventing or treating infections (Holmes *et al.*, 2016). Antimicrobial resistance (AMR) occurs naturally. Organisms evolve the ability to survive, grow, and reproduce in the presence of the antimicrobial designed to inhibit them (Holmes *et al.*, 2016; GC, 2017; WHO, 2021c). Antimicrobial use accelerates this process and leads to increased rates of AMR.

With growing AMR, infections with few or no treatment options are increasing around the world (PHAC, 2014; OECD, 2018). In 2019, almost five million deaths were associated with drug-resistant bacterial infections globally, with 1.27 million deaths directly attributed to AMR (Murray *et al.*, 2022). A World Bank analysis estimated AMR could lead to annual reductions of global GDP between 1.1% and 3.8% by 2050, depending on trends (World Bank, 2017). An OECD analysis of Australia, Canada, Europe, and the United States (U.S.) projected 2.4 million cumulative deaths attributable to AMR, and cumulative healthcare costs of US\$134 billion by 2050 (Ouakrim *et al.*, 2018).



“However, when first-line antibiotics — that is, the most widely used, accessible, and inexpensive antibiotics — are found to be ineffective, prescribers may not have adequate access to alternative treatments.”

As of 2018, an estimated 26% of infections were resistant to first-line treatment in Canada (CCA, 2019). Modelling by the CCA's Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada estimated that resistant infections were responsible for more than 14,000 deaths in Canada in 2018, with 5,400 of those deaths directly attributable to AMR. Deaths and illnesses associated with drug-resistant infections contributed to a loss of approximately \$2 billion to the Canadian economy in 2018 (CCA, 2019). Since 2018, resistance trends continue to be concerning. Rates of AMR are increasing for most

priority pathogens, with five-year trends (2016–2020) showing increases in rates of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections, vancomycin-resistant Enterococcus bloodstream infections, carbapenemase-producing Enterobacterales infections (apart from *Clostridioides difficile*), as well as *Neisseria gonorrhoeae* and invasive *Streptococcus pneumoniae* diseases (PHAC, 2022).

The impacts of AMR in Canada are already being experienced and the incidence is growing. In the Panel's experience, the most widely used antibiotics are

inexpensive and relatively accessible. However, when first-line antibiotics — that is, the most widely used, accessible, and inexpensive antibiotics — are found to be ineffective, prescribers may not have adequate access to alternative treatments.



“Because people in Canada differ in their risk factors for health outcomes, infections, and resistant infections, the impacts of AMR are experienced unevenly across Canada.”

This is supported by Burrows (2022) who found that Canadian physicians do not have easy access to newer antibiotics. Panel members also observed that a lack of redundancy (i.e., more than one treatment option for a given infection) can mean that patients with certain co-morbidities, allergies, and intolerances, or those at risk of certain drug interactions, have limited treatment options. Sometimes the costs of alternative treatments are prohibitive (e.g., Patel *et al.*, 2022), and sometimes alternative treatments have significant adverse effects (CDC, 2022). Some last-resort antibiotics used today are harming patients, but prescribers have no better options (CDC, 2022). The long-standing availability of inexpensive antibiotics has created the false impression that they are not a

significant factor for health budgets. However, as resistance rates rise and the need for novel drugs increases, costs to confront these challenges will also increase.

Several types of health risks are important to acknowledge when considering who may acquire resistant infections. There are broad risk factors that increase the likelihood that a person in Canada will experience a negative health outcome. For example, people living in rural and remote areas face elevated health risks when their limited access to healthcare interferes with timely diagnosis and prescription of antimicrobials (Bailey *et al.*, 2021). Numerous socioeconomic factors also interact with rurality to influence health risks, including income and education levels (Probst *et al.*, 2019). Indigenous people in Canada experience significant health disparities attributable to colonialism. This has ultimately led to inadequate access to safe water and sanitation in some communities, as well as overcrowded living conditions and challenges accessing and receiving appropriate care in health systems, which in turn results in greater risks of acquiring infections (TRC, 2015a; Andermann, 2017).

Additional risk factors may increase the likelihood that a person acquires a microbial infection. King *et al.* (2022) found that those generally at risk of infectious diseases are also at risk of acquiring a resistant infection. People may have an increased probability of infection based on a number of behavioural, clinical, and socio-demographic risk factors, with prior antimicrobial treatment being the biggest contributing factor (reviewed in CCA, 2019). Because people in Canada differ in their risk factors for health outcomes, infections, and resistant

infections, the impacts of AMR are experienced unevenly across Canada. For example, MRSA disproportionately affects Indigenous people, and inadequate housing and clean drinking water contribute to its incidence (Muileboom *et al.*, 2013; Loewen *et al.*, 2017).

People in Canada have come to expect reliable access to effective antimicrobials, and they typically do not see AMR as an urgent or significant public health issue (Crago *et al.*, 2022). Whether for urinary tract infections, bacterial pneumonia, or infections at the site of injuries or surgical incisions, most people in Canada have benefited from antibiotics at some stage in their lives (GC, 2017; CDC, 2022). People with suppressed immune systems are particularly reliant on effective antimicrobials, and increasing AMR poses a distinct threat to this group (Mohammadinejad *et al.*, 2015). One patient representative relayed to the Panel her absolute reliance on antibiotics since a heart transplant two decades before:

I came to realize that I could come to the end of the line, so to speak, with available treatment options when it came to antibiotics, and for me this means a matter of life and death.

Kristi Coldwell (personal communication, 2022)

Because of the critical role antimicrobials play in delivering modern healthcare, greater rates of AMR mean that previously treatable infections could become deadly. For example, people living with cystic fibrosis (CF) rely heavily on antibiotics, and the prospect of AMR is a particular risk for this patient group. One patient reported:

Antibiotics not only became a chronic part of my routine, but the pills were no longer effective. The inhaled antibiotics were there to keep things at bay, but — once infection developed — there was nothing but IV antibiotics that would help ... I've relied on antibiotics more than I could even express with words, and I still continue every day when I inhale antibiotics. It's just such an amazing thing that science could help me in this way. We need to continue developing more antibiotics because antibiotic resistance is a huge thing in CF where we are exposed to so many antibiotics and our bugs keep getting stronger and stronger.

AMR Action Podcast (2022)

The *Pan-Canadian Action Plan on Antimicrobial Resistance* recognizes the importance of establishing targets and monitoring progress over time (PHAC, 2023). This action plan outlines five areas of focus (surveillance, infection prevention and control, stewardship, research and innovation, and leadership) as a foundation for future actions and engagement (PHAC, 2023). While some funding commitments have been made, the Government of Canada lags behind other countries in the allocation of

funding resources (Somanader *et al.*, 2022). The Panel concurred with Somanader *et al.* (2022) that the absence of a publicly available plan detailing measurable actions and outcomes to address AMR belies the urgency of the problem.

The discovery of new antimicrobials with novel mechanisms of action and targets is of great importance to addressing AMR; however, this is difficult commercially because of the high risk of R&D failure and low financial returns (HC, 2022a).



“Because of the critical role antimicrobials play in delivering modern healthcare, greater rates of AMR mean that previously treatable infections could become deadly.”

Bankruptcies and economically similar events were common among the small companies that developed antibiotics approved by the U.S. Food and Drug Administration (FDA) in the last decade (Courtemanche *et al.*, 2021). As a result, the antimicrobial clinical pipeline — drugs in clinical development — is “insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance” (WHO, 2022b). Eighteen antibiotics were launched globally in high-income countries between 2010 and 2020, while only two¹ launched commercially in Canada during that period (Outterson *et al.*, 2021). In 2022, a third antibiotic, dalbavancin, was approved and marketed in Canada (Paladin Labs, 2022). In contrast, many other high-income countries have

access to five or more of these new drugs (Outterson *et al.*, 2021). While access to all 18 drugs may not be necessary in Canada, the World Health Organization (WHO) has deemed 4 of these antimicrobial drugs “essential medicines” (WHO, 2021a). None of these four are available in Canada (HC, 2023b).

1.1 The Charge to the Panel

This report focuses on one aspect of a comprehensive solution to the growing threat of AMR — encouraging the development and commercialization of novel antimicrobials through *pull incentives* that offer enhanced financial returns to manufacturers bringing qualifying antimicrobials² to the Canadian market and, more importantly, to patients in Canada. Recognizing the need to better understand the economic pull incentives that have the greatest potential to enhance the availability of novel antimicrobials, the Public Health Agency of Canada (PHAC), with the support of Health Canada (hereafter referred to as the Sponsors), asked the CCA to answer the following question and sub-questions:

- 1 These two drugs are fidaxomicin and ceftolozane/tazobactam. An additional two drugs, lefamulin and tedizolid, received regulatory approval but have not been brought to the Canadian market (HC, 2023b).
- 2 In this report, *qualifying antimicrobials* are those that meet predetermined eligibility criteria, such as novelty, cost, efficacy, and/or unmet need within Canada.



What economic pull incentives have the greatest potential for success in encouraging the market entry and sustained market availability of high-value antimicrobials³ for use in humans in Canada?

- What are the potential costs, benefits⁴, facilitators and opportunities associated with each of the economic pull incentives?
- What are the facilitators and barriers to implementation, particularly within the context of the Canadian federation?
- What specific regulatory and/or policy measures at the federal level could complement or enhance each of the selected economic incentives?
- What evidence is there to support the application of economic incentives and/or other regulatory or policy measures to diagnostics (and other AMR-relevant products, as appropriate) to support overall efforts to encourage market entry and sustained availability of antimicrobials?

The CCA assembled a multidisciplinary panel of 10 experts to analyze the evidence and respond to the Sponsors' charge (the Expert Panel on Antimicrobial Availability, hereafter the Panel). The Panel was comprised of experts in health economics, antimicrobial stewardship, infectious diseases, pharmacy, oncology, transplantation, law, and pharmaceutical development. Members met nine times in person and via videoconference between June 2022 and June 2023 to deliberate on the question, conduct an expert workshop, refine report drafts, and respond to peer review feedback. The final report reflects the Panel's consensus based on its assessment of the evidence.

To ensure the integrity of the assessment process, panel members are required to disclose to the CCA and fellow panelists any conflicts of interest — actual, foreseeable, or perceived — relevant to the issues being discussed so that they can be managed transparently. Panelists must also abide by a confidentiality agreement and code of conduct designed to support an environment that fosters effective and respectful deliberations, is conducive to the free exchange of knowledge, and supports the assessment of evidence.

3 Like the term *qualifying antimicrobials*, *high-value antimicrobials* refers to those that treat infections for which there is a current or anticipated unmet need.

4 Assessment of benefits should include, but is not limited to, value to people in Canada in terms of cost, public health benefit, and socioeconomic impact.

To maintain the panel's independence, sponsors do not appoint panel members, nor do they engage with the expert panel during the assessment process, with the following exceptions: (i) at the panel's first meeting when the sponsors are invited to present the charge and (ii) at a sponsor briefing, where the panel chair presents the main findings to the sponsors, scheduled after the panel has formally signed off on the final report, prior to public release. For this assessment, the sponsors also attended the workshop as silent observers.

The report underwent a comprehensive peer review, whereby an additional nine experts from Canada and abroad provided further evidence, feedback, and expertise. External peer review provides feedback to inform Panel deliberations, and reviewers remain anonymous to the Panel until after the report is finalized. This process is overseen by an independent peer review monitor appointed from CCA's Scientific Advisory Committee, further supporting the integrity of the process.

1.2 The Panel's Approach

There has been significant work published on the challenge of AMR and strategies to confront it, both domestically (e.g., GC, 2017; CCA, 2019; PHAC, 2023) and abroad (e.g., O'Neill, 2016; Årdal *et al.*, 2018). Thus, this report focuses on the question of pull incentives. The Panel underscores that it was not asked to compare the potential contribution of pull incentives to addressing AMR relative to other policies and approaches, but rather to identify and assess the most promising pull incentives. These incentives allow new drugs to come to market by providing viable returns for the manufacturer despite low sales volumes and low unit prices. The Panel recognized that, in many instances, prescribers would not opt for a novel antimicrobial over a comparator and would instead reserve the novel drug for the rare instances where existing antimicrobials cannot meet patient needs. In the Panel's view, a well-resourced pull incentive program is an efficient way to motivate the development and deployment of novel antimicrobials in the Canadian market.

1.2.1 Scoping Decisions and Assumptions

The Panel's analysis was informed by both the international context and particular considerations for Canada. In June 2022, G7 leaders, including the Prime Minister of Canada, reiterated their commitment to the promotion of access to antimicrobials and to international partnerships to expand research into, and innovation of, new antibiotics, with "a particular emphasis on pull incentives" (PMO, 2022). Other jurisdictions are recognizing the need to promote antimicrobial R&D and access to new antimicrobials. Pull incentive pilot programs have already been established in Sweden and the United Kingdom (U.K.) and one is in development in Japan (Gotham *et al.*, 2021; MHLW, 2023). Germany and France account for AMR in their existing reimbursement schemes, and legislation related to pull incentives has been proposed in the U.S. (Gotham *et al.*, 2021; U.S. Congress, 2021).

The Panel emphasizes that, to succeed in Canada, any pull incentive framework needs to promote equitable access to antimicrobials, ensuring access especially for demographic groups at higher risk of resistant infections. To that end, provincial, territorial, municipal, and Indigenous governments are critical in the creation of a Canadian pull incentive program that can meet domestic needs.

This report focuses predominantly on antibiotics

The umbrella term *antimicrobial* encompasses antibiotics, antifungals, antivirals, and antiparasitics, though in practice it is often used interchangeably with *antibiotic*. The term *antimicrobial* is used throughout the report to refer collectively to antibiotics (sometimes referred to as antibacterials), antifungals, antivirals,

and antiparasitics, but the term *antibiotic* is used when that level of specificity is warranted. Resistance to all types of antimicrobials is a growing concern (WHO, 2021c).



“Among AMR trends, antibiotic resistance is particularly concerning, given the extent of mortality caused by bacterial infections, the widespread use of antibiotics, and the declining effectiveness of existing drugs (Murray *et al.*, 2022; Outterson & Rex, 2023).”

Among AMR trends, antibiotic resistance is particularly concerning, given the extent of mortality caused by bacterial infections, the widespread use of antibiotics, and the declining effectiveness of existing drugs (Murray *et al.*, 2022; Outterson & Rex, 2023). While less widely discussed, fungal infections are responsible for an estimated 1.7 million deaths per year globally, and are an emerging public health concern (Kainz *et al.*, 2020). Much of the literature cited in this report focuses on the problem of antibiotic resistance, but the nature of current market failures is similar for antibiotics and antifungals, thus the analysis presented in this report is applicable to both.

As with other types of antimicrobials, long-term exposure to antivirals is favouring the evolution of resistant strains and antiviral resistance has become common; this is a specific threat to immunocompromised patient populations (WHO, 2021c). However, the challenges and barriers to antimicrobial development and access vary by type. Antiparasitic and antiviral R&D systems are not facing the same market challenges as antibiotics and antifungals. For example, some antivirals are profitable given current market conditions, including medicines for hepatitis C and COVID-19 (Beasley, 2014; Kansteiner, 2022). Antiretroviral drugs have benefited from decades of substantial government support for R&D and funding mechanisms such as The Global Fund, PEPFAR, and UNITAID (UNITAID, 2022; hiv.gov, 2023; The Global Fund, n.d.-a). The burden of parasitic

disease is low in Canada, thus, antiparasitic resistance is of less concern. Globally, programs such as The Global Fund and organizations such as the Bill and Melinda Gates Foundation have enabled significant progress in recent decades in combatting malaria — a parasitic disease with huge impacts on human health and economies in low- and middle-income countries (PHAC, 2016; The Bill and Melinda Gates Foundation, n.d.; The Global Fund, n.d.-b).

1.2.2 Sources of Evidence

Deliberations were informed by several lines of evidence. The Panel assessed peer-reviewed literature relating to pull incentives for antimicrobials, identified through an initial semi-structured literature review and expanded on through expert-informed evidence gathering.⁵ The Panel reviewed grey literature from governments, health organizations, and others on this topic, which provided important insights into experiences to date with pull incentive programs in Sweden and the U.K. The Panel also convened a wider group of 11 additional experts for a workshop in October 2022 to better understand the Canadian context for the design and deployment of pull incentives. Participants brought expertise in pharmaceutical commercialization, economics, health technology assessments (HTAs), drug procurement, pharmacy, clinical care, and open science, all within Canada. Discussions focused on eligibility criteria, financing, and distribution within the context of the Canadian federation.

1.3 Report Structure

This report begins with a survey of the challenges of antimicrobial availability, first globally and then domestically, drawing out the particular challenges that arise in the Canadian pharmaceutical market (**Chapter 2**). In **Chapter 3**, different types of pull incentives are analyzed to review their prospects for addressing these challenges. **Chapter 4** focuses on the economics of pull incentives, specifically the value of antimicrobials to society and the scale of payment needed to incentivize industry to invest in the development and commercialization of new antimicrobials. Based on the benefits pull incentives provide to society, **Chapter 5** lays out a scenario for how a pull incentive could be effectively implemented in Canada, including appropriate eligibility criteria, payment levels, and the roles of various actors. **Chapter 6** broadens this discussion by analyzing the role of complementary policies to support the implementation of pull incentives, including R&D, efficient regulatory review, effective surveillance, and the appropriate use of diagnostics. The report concludes with reflections from the Panel (**Chapter 7**).

5 The Panel's approach followed the CCA's standard assessment methodology summarized here: <https://cca-reports.ca/process/>.

2

Commercialization and Market Challenges

- 2.1 Global Antimicrobial Availability and Incentives
- 2.2 Canadian Market Conditions

Chapter Findings

- Antimicrobials face market failures distinct from those faced by other drugs.
- There is a long-standing trend of declining activity in the field of antimicrobial development, leading to an inadequate global pipeline for novel antimicrobials for human use.
- Antimicrobial resistance is already a problem in Canada and is expected to become more problematic in the future. Compared with peer countries, Canada lags in both its access to novel antimicrobials and its efforts to establish adequate availability of antimicrobials going forward.

The challenge of increasing rates of antimicrobial resistance (AMR) is globally recognized and calls for a multifaceted set of solutions, including national and international interventions to develop a viable market for novel drugs (G7 Finance Ministers, 2021; WHO, 2022b).

As the rates of AMR increase, existing antimicrobials are becoming less effective, creating an unmet need for novel drugs (WHO, 2022b, 2022e). However, challenges in the antimicrobial business model have led to a decline in R&D, resulting in insufficient drug development to meet current and anticipated needs for the treatment of resistant infections (WHO, 2022b). Many of the market challenges are global in nature and therefore call for global cooperation, though specific features of the Canadian market can exacerbate these challenges domestically.

2.1 Global Antimicrobial Availability and Incentives

Market failures and challenges associated with development and commercialization have resulted in an innovation deficit and scarcity of novel antimicrobials.

The existing market for novel antimicrobials is not viable

Fundamentally, antimicrobials face a distinctive problem: the evolution of resistance. Antimicrobial use (AMU) hastens the evolution of resistance. This happens in individuals and at the population level, resulting in less effective treatments (WHO, 2022e). There is a need to preserve the effectiveness of new antibiotics by ensuring they are used infrequently and appropriately through antimicrobial stewardship (Morel *et al.*, 2020). Thus, government and health services promote the use of new antibiotics only as a last resort in severe cases of resistant infections. It then follows that manufacturers can reasonably

expect sales volumes for new antimicrobials to be low (Morel *et al.*, 2020). Sales volumes of antibiotics are also lower than other drugs as they tend to be prescribed for short courses; in contrast, other prescription drugs may be used indefinitely to manage chronic conditions (Outterson *et al.*, 2015). This further limits the ability of manufacturers to earn adequate returns through sales.



“Market forces therefore favour the development of other types of drugs.”

The development of any kind of new drug can take 10 to 15 years and cost over US\$1 billion (based on a 10.5% capitalization rate) (Wouters *et al.*, 2020; WHO, 2022d). While R&D costs and failure rates are broadly similar, compared to other drugs, investment in novel antimicrobials comes with a higher risk because there is only a fraction of the revenue prospects (Boluarte & Schulze, 2022).⁶ Should a manufacturer successfully

bring a novel antimicrobial to market, profitability is not guaranteed (Boluarte & Schulze, 2022). Market forces therefore favour the development of other types of drugs. For example, returns on investment for cancer drugs and rare disease drugs are among the highest, whereas returns on antibiotics are notoriously low (Projan, 2003; Placket, 2020; Boluarte & Schulze, 2022; Michaeli *et al.*, 2022).⁷

Antimicrobials are widely used across healthcare systems, enabling the primary treatment of various conditions including cancer and rare diseases. However, given that the price of most long-established antimicrobials is low (Gov. of ON, 2022), this widespread usage does not itself create a viable market.

The pricing of antimicrobials is an additional challenge that decreases market viability. Health technology assessments (HTAs) are widely used in Canada and internationally to determine the comparative value of a new drug to support funding and reimbursement decisions. The pricing of new antimicrobials may be constrained because of the presence of lower-cost antimicrobials already on the market, as the pharmacoeconomic evaluations that are conducted as part of an HTA factor in the costs of comparators (CADTH, 2020). This pricing scheme is particularly challenging in the case of antibiotic comparators that have long been genericized and are generally inexpensive (HC, 2022a). Relatively expensive new drugs may be used sparingly by price-sensitive prescribers. The Panel observed that use of linezolid — a relatively new antibiotic approved for the Canadian market in 2001 — increased substantially after it was genericized in 2014 (Walker *et al.*, 2006; HC, 2023b).

6 When the cost of developing a new drug and/or maintaining it on the market exceeds the revenues generated from its sales, it is deemed a market failure. Market failure for new antimicrobials is widespread (HC, 2022a).

7 This is reflected in the level of market activity. As of 2020, over 1,300 medicines and vaccines were currently in clinical testing for cancer (PhRMA, 2020).

In addition, many elements of the value of novel antimicrobials are not accounted for in a standard HTA (Section 4.1.2). Many have called for a new approach to providing appropriate monetary compensation for antimicrobial developers, one that encompasses non-use values above and beyond the benefits to currently treated patients, such as the “insurance” antimicrobials provide against future outbreaks (Rex & Outterson, 2016; Årdal *et al.*, 2017; Outterson, 2021a). Revised value assessments would ideally also confront another usage challenge — the treatment of



“Average share prices for antimicrobial drug companies fell by 71% between 2018 and 2020 (Placket, 2020).”

infectious disease in one patient can reduce community transmission and provide an important societal benefit. However, in this instance, it also inadvertently promotes market failure by lowering demand for that treatment among the wider population (Colson *et al.*, 2021).

Due to these realities, few large pharmaceutical companies invest in antibiotic R&D (Harbarth *et al.*, 2015). Small- and medium-sized enterprises (SMEs) are the most significant participants in discovery and pre-clinical development activities (WHO, 2021b). Of the 18 novel antimicrobials brought to market in high-income countries since 2010, 7 were sponsored by SMEs (Outterson *et al.*, 2021). However, market failures are negatively impacting SMEs in this area, as shown by recent bankruptcies and fire-sale acquisitions (Outterson *et al.*, 2021). For instance, Nabriva Therapeutics, Melinta Therapeutics, and Achaogen have all declared bankruptcy or gone into orderly liquidation (Dall, 2019; Reuters Staff, 2019; Nabriva Therapeutics, 2023). Average share prices for antimicrobial drug companies fell by 71% between 2018 and 2020 (Placket, 2020).

Scientific challenges impede the development of novel antimicrobials and limit demand from prescribers

In general, clinical trials are designed to demonstrate the *superiority* in efficacy of new drugs relative to existing comparators. Establishing superiority of novel antibiotics for drug-resistant infections via clinical trials tends not to be feasible because, for example, resistance to common antibiotics is still relatively rare (Rex *et al.*, 2017, 2019; Årdal *et al.*, 2020). Additionally, patients eligible to participate in such clinical trials may be very ill for reasons other than the microbial infection, and the associated high mortality rates can make it difficult to demonstrate significant benefits of a novel antibiotic in terms of survival, duration of hospital stay, or even quality of life (Karlsberg Schaffer *et al.*, 2017). As a result, regulatory agencies allow for clinical trials for novel antibiotics to establish *non-inferiority* of the treatment relative to existing options (Bhatti *et al.*, 2018). Non-inferiority trials seek to demonstrate that a new drug is not worse than an existing one to treat a

specified infection (Rex *et al.*, 2017; Bhatti *et al.*, 2018). As well, at least one study has shown that non-inferiority trials rely on margins of 10–20%, such that some loss of efficacy could be accepted under this method (Mitra-Majumdar *et al.*, 2022).

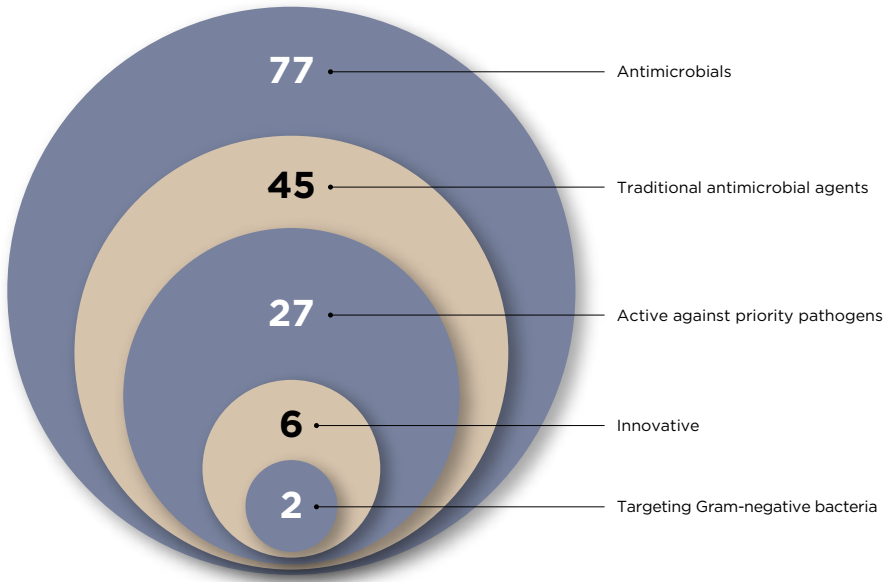
The nature of clinical trial data negatively impacts pricing. New antibiotics cannot justify high unit prices because they cannot prove their superiority to existing options (Bhatti *et al.*, 2018). Furthermore, data available to clinicians do not sufficiently differentiate one new antibiotic from another, nor do they assist with clinical decision-making for patients with no established treatment options, which limits reliance on novel antimicrobials (Ramachandran & Powers, 2022).

The clinical pipeline for novel antimicrobials is insufficient

Many of the recently approved antimicrobials have limited clinical benefits (WHO, 2022b). There are too few antimicrobials in the clinical pipeline to address current and future needs, and there are infections of concern that are not targeted by pipeline antimicrobials (WHO, 2022b). R&D challenges inherent to antimicrobial discovery and development are partially to blame for this insufficient clinical pipeline. For example, toxicity is a widespread problem in antimicrobial discovery: the high dosages required to confront microbial infections can cause unacceptable patient risks. Toxicity has led to the termination of many recent efforts to develop novel therapies (Baker *et al.*, 2018; Prasad Neha *et al.*, 2022). Research into antimicrobials with novel mechanisms of action has produced limited results to date, and the lack of rapid diagnostics has led to a need for broad spectrum antibiotics to treat all likely infections corresponding to observed symptoms (Baker *et al.*, 2018).

As of November 1, 2021, 77 antibiotics and/or combinations that include at least one new therapeutic entity were estimated to be in clinical development globally, including 45 traditional and 22 non-traditional (e.g., antibodies, phages) antibacterial agents (Figure 2.1). While many of these traditional agents have known mechanisms of action, 27 are active against WHO-designated bacterial priority pathogens — including 6 innovative agents (only 2 of which target crucial Gram-negative bacteria) (WHO, 2022b).⁸ The WHO assesses innovation of traditional small molecule antibiotics using four criteria: a new chemical class of antibiotics, a new target within the pathogen, usage of a new mechanism of action, or the absence of known cross-resistance. The preclinical pipeline is more promising than the clinical pipeline and is characterized by the WHO as “dynamic and innovative, including a wide range of drug development projects” (WHO, 2022b).

8 Bacteria with no outer membrane but thick layers of peptidoglycan are Gram-positive, while those with lipopolysaccharide-based outer membrane and a thin wall of peptidoglycan are Gram-negative (Silhavy *et al.*, 2010). Gram-negative bacterial infections include, among others, pneumonia, urinary tract infections, and wound skin infections (Bush, 2022). Gram-positive infections include anthrax, toxic shock syndrome, streptococcal infections, and those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (Bush, 2023). Gram-negative infections are generally more resistant to antimicrobial treatments (Breijyeh *et al.*, 2020).



Source: WHO (2022b)

Figure 2.1 The Antimicrobial Pipeline

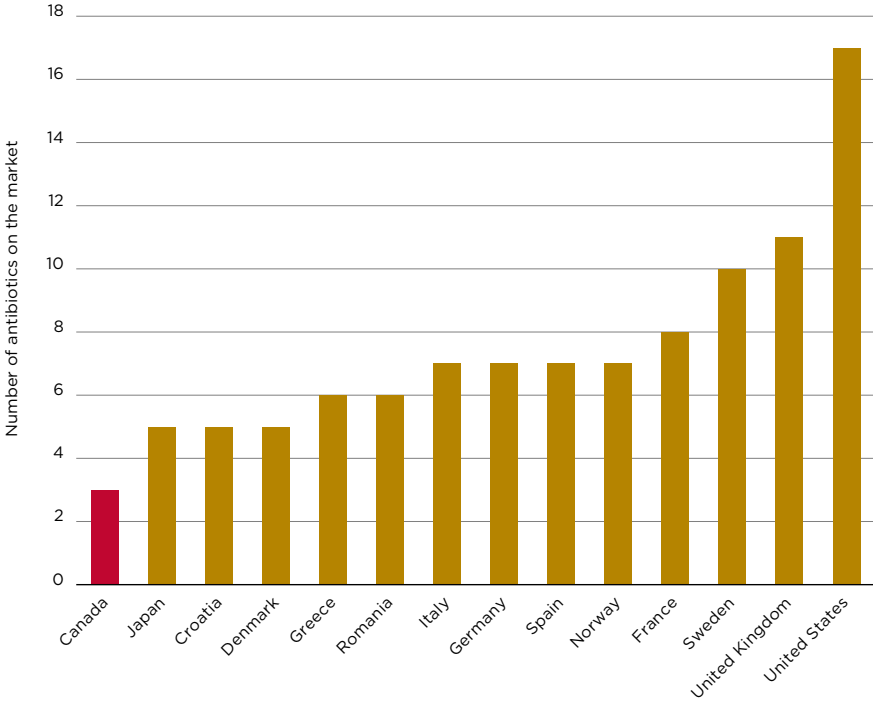
The antimicrobial pipeline contains 27 traditional agents active against priority pathogens, of which 6 are innovative and only 2 innovative agents target crucial Gram-negative bacteria.

Once new drugs enter clinical trials, the likelihood of approval remains low, since only approximately one in six new drugs successfully passes all clinical trial stages and is ultimately approved for patient use (Otterson, 2021b). Within this small set of novel antibiotics in development, only a few are likely to reach the market (WHO, 2022b). There is no consensus on the number of novel antimicrobials that are needed, and the Panel underscored that this is an important research gap. In the absence of such an estimate, various research groups have made different assumptions. For example, O'Neill (2016) posited the need for 15 new antibiotics within the decade, including at least 4 novel drugs, while Towse and Silverman Bonnifield (2022) suggested that 18 over three decades is a plausible estimate.

There are also unmet needs in the antifungals space. No new classes of antifungals have been approved in the past two decades, and only one new drug was approved at all in the past decade (Hoenigl *et al.*, 2021). The spread of a newly identified multi-drug resistant fungal pathogen, *Candida auris*, is particularly concerning given the extent of drug resistance it displays and the limited treatment options available (CDC, 2017; Forsberg *et al.*, 2019). There are several promising new antifungal classes in clinical development, some with novel mechanisms of action, but gaps remain, and further efforts and research are warranted (Hoenigl *et al.*, 2021).

2.2 Canadian Market Conditions

While global scientific and market challenges contribute to the lack of antimicrobials being developed and marketed, as noted in Chapter 1, Canada also compares unfavourably to other high-income countries when it comes to antimicrobial availability (Figure 2.2). This lack of access poses risks to people in Canada with resistant infections, as AMR is already contributing to illnesses and deaths across the country (CCA, 2019).



Source: Otterson *et al.* (2021)

Figure 2.2 Availability of Novel Antibiotics by Country

The number of novel antimicrobials that have received approval and commercially launched in 14 high-income countries between 2010 and 2019. Otterson *et al.* (2021) reported that two new drugs were launched in Canada during this period, however, a third drug (dalbavancin) was brought to the Canadian market in 2022 (Paladin Labs, 2022).

Canada lags behind other countries with respect to access to existing novel antibiotics

Canada has less access to novel antibiotics compared to similar high-income countries, including France, Germany, Sweden, and the U.K.⁹ Only 3 of the 18 new antibiotics that entered the global market between 2010 and 2019 are marketed in Canada as of May 2023 (HC, 2023b).¹⁰ A further two have received regulatory approval but have not entered the Canadian market (HC, 2023b). Thus, 15 of these 18 recent drugs are only available through specialized pathways, such as the Special Access Programme (SAP) (Box 2.2) or the urgent public health need pathway (HC, 2023a). In comparison, Sweden and the U.K. commercially launched 10 and 11 of the new antibiotics, respectively (Outterson *et al.*, 2021). While not all of the 18 antimicrobials will bring significant value to Canada, 4 are on the WHO's 2021 list of "essential" drugs (WHO, 2021a). It is important to note that Canada currently does not have access to them.

Box 2.2 Special Access Programme (SAP)

Health Canada's SAP enables access to drugs that are not available for sale in Canada via requests from healthcare professionals treating "serious or life-threatening conditions where conventional treatments have failed, are unsuitable, or unavailable" (HC, 2022c). SAP criteria limit use to patient-specific requests or potential emergencies (HC, 2022c). Requests from physicians are made to Health Canada and are reviewed within 24 hours of the request (HC, 2022b).

Novel antibiotics and their accompanying diagnostics are often not brought to the Canadian market (Burrows *et al.*, 2021). A review of SAP data between 2016 and 2021 by Burrows *et al.* (2021) found that "novel antibiotics are rarely requested compared to older drugs not approved in Canada." The Panel noted that this lack of requests may be due to the following: (i) given the urgent and life-threatening nature of some resistant bacterial infections, prescribers may choose not to submit a request because the drug would not be received quickly enough, and (ii) without Canadian approval and market launch, clinicians do not have knowledge of such drugs or experience with them.

9 Canadian access is comparable to that of other high-income countries outside of the U.S., U.K., and the E.U; for example, access in South Korea, Japan, and Australia is also quite limited (Outterson *et al.*, 2021; Lee & Lee, 2022; DHAC, 2023).

10 The three on the Canadian market are ceftolozane/tazobactam, dalbavancin, and fidaxomicin (HC, 2023b). Two new treatments — sulbactam/durolactam and Vowst — were approved in the U.S. in 2023, but these are not yet available in other countries and are excluded from this analysis (FDA, 2023b, 2023c).

Market fragmentation and the cost of doing business can discourage manufacturers from bringing novel antimicrobials to Canada

The need to apply for distinct regulatory approval for the Canadian market, compared with the consolidated marketing approval process through the European Medicines Agency (EMA), might explain some of the disparity between availability in similar-sized European countries and Canada (Outterson *et al.*,



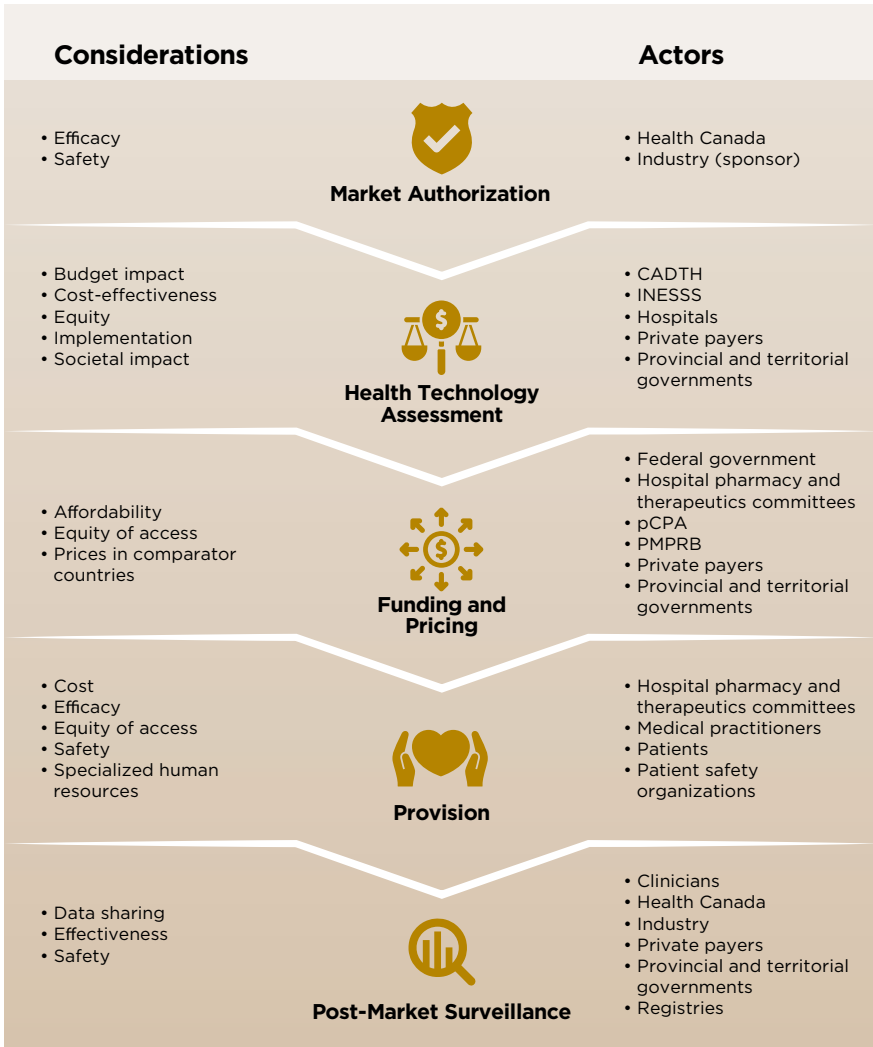
“Manufacturers may choose to prioritize larger markets, including the U.S. or the E.U., where one approval process provides a larger potential return on investment.”

2021). Manufacturers may choose to prioritize larger markets, including the U.S. or the E.U., where one approval process provides a larger potential return on investment. Submission for regulatory approval in Canada for new drugs tends to lag behind submissions to the E.U. and U.S. (Shajarizadeh & Hollis, 2015).

There are several key steps in the process of approving a new drug and then maintaining it on the Canadian market (Figure 2.3). Market authorization is the first step. The fee for submitting drugs to Health Canada for regulatory approval is approximately \$565,000,¹¹ but

applicants may incur other costs relating to legal fees and preparing the necessary documentation (HC, 2023c). Health Canada has implemented several approaches to support innovative drugs through the regulatory process including priority review (which reduces the approval process from 355 business days to a target of 180 days) and notice of compliance with conditions (that is, authorization contingent on additional clinical trials being conducted once the drug is on the market) (HC, 2007, 2009; Burrows *et al.*, 2021). In 2021, Health Canada updated their *Pathogens of Interest* list, which outlines pathogens with limited or unavailable treatment options and, therefore, areas requiring the greatest innovation in drug development (HC, 2021d). Drugs developed to treat these pathogens can be eligible for priority review.

11 On a per capita basis, this cost is high relative to those charged by the U.S. FDA and the EMA (EMA, 2023a; FDA, 2023a).



Adapted from CCA (2020)

Figure 2.3 Stages in the Approval and Use of Drugs in Canada

Each of the five stages outlined above has distinct considerations and involves different actors, including government agencies, different orders of government, industry, and healthcare providers.

CADTH – Canadian Agency for Drug and Technologies in Health

INESSS – Institut national d'excellence en santé et en services sociaux

pCPA – pan-Canadian Pharmaceutical Alliance

PMPRB – Patented Medicine Prices Review Board

Following regulatory approval, community-based and out-patient medicines undergo HTA review through the Canadian Agency for Drugs and Technologies in Health (CADTH) and, in Quebec, the Institut national d'excellence en santé et en services sociaux (INESSS) to determine whether the drug should be reimbursed by public drug plans (CADTH, 2020; INESSS, 2021b). Exclusively hospital-based medicines are reviewed by INESSS as a matter of course but not so by CADTH (Gov. of QC, 2010; CADTH, 2020). Outside of Quebec, hospital pharmacy and therapeutics committees make decisions about which drugs to include in hospital formularies, creating variability across institutions (CADTH, 2015). Hospital budgets are one factor influencing the inclusion of new drugs on hospital formularies (Burke *et al.*, 2016). A separate process exists for private drug plans, which cover many community-based medicines.

The application fee for the standard CADTH review process is roughly \$80,000, while more complex reviews or drugs with broader implications for the healthcare systems may require a higher payment (CADTH, 2022b). In Quebec, the initial evaluation of a new drug by INESSS costs roughly \$60,000 (INESSS, 2021a). Following HTA review processes, manufacturers enter collective pricing negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA), which, as an additional step in the process, can provide a further deterrent to bringing drugs to Canada (Burrows *et al.*, 2021). They must then proceed with provincial listing agreements with each province and territory separately once the negotiation with pCPA has been successfully completed (pCPA, 2019). In addition, manufacturers may have to negotiate with private drug plans for drugs prescribed in the community. Smaller drug manufacturers may not be able to invest in sales representation across the whole country (HC, 2022a). Foreign corporations can struggle to establish themselves in the Canadian market without a pre-existing presence, while SMEs struggle to establish a national workforce with the expertise to effectively operate across Canada's multijurisdictional healthcare landscape (Canadian Antimicrobial Innovation Coalition, personal communication, 2023). The prices of patented medicines are also subject to oversight by the Patented Medicine Prices Review Board (PMPRB, 2018), and price ceilings may deter prospective market entrants (Canadian Antimicrobial Innovation Coalition, personal communication, 2023).

Following approval in Canada (as with other countries), the manufacturer must promptly report serious adverse drug reactions or unusual effectiveness failures of new drugs should they occur (HC, 2019; Nicol, 2019). Furthermore, each year, manufacturers must submit to Health Canada a critical analysis of adverse reactions to each of their drugs (Nicol, 2019). Combined, the expertise and expense required to navigate the Canadian system may disincentivize smaller companies

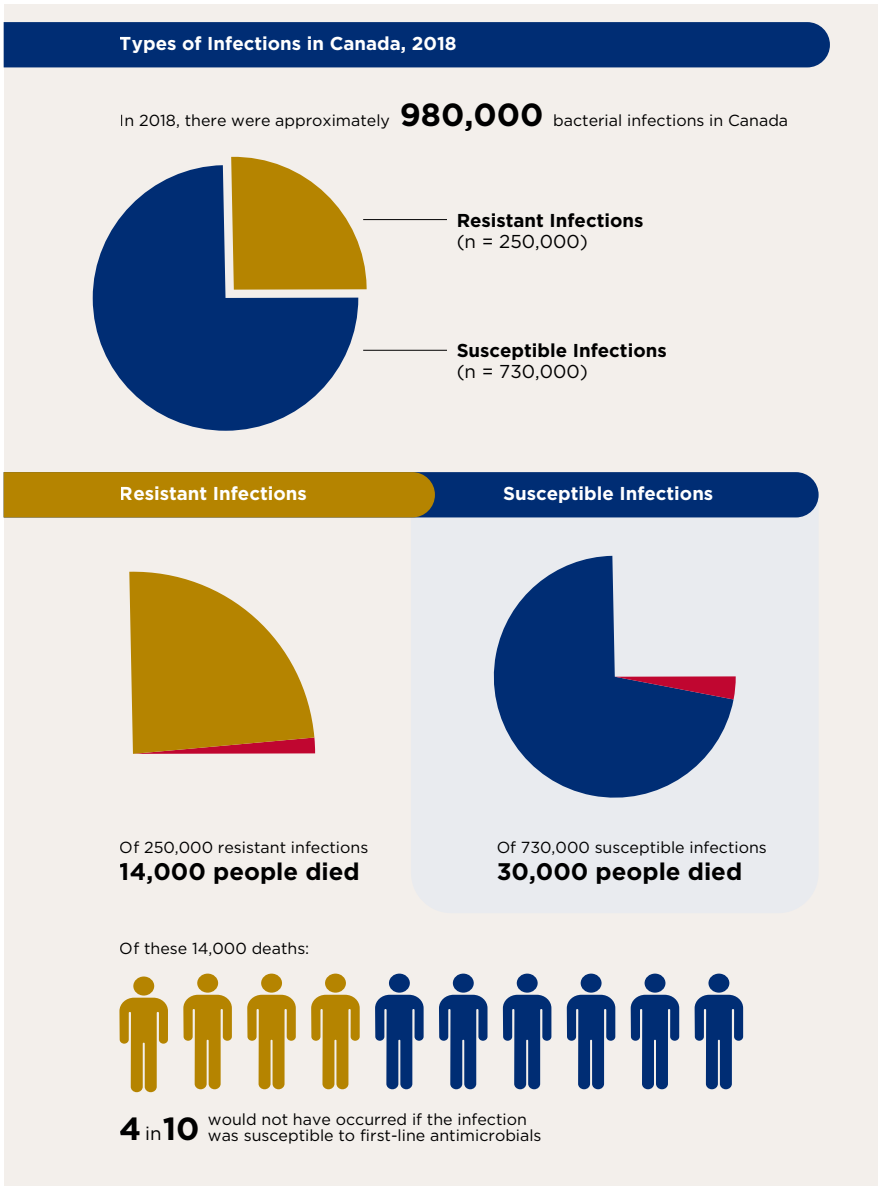
from bringing their drugs to Canada, causing them to delay or abstain from market entry (Shajarizadeh & Hollis, 2015). In some instances, the costs of market launch are expected to exceed any revenues that could be earned (Burrows *et al.*, 2021; Boluarte & Schulze, 2022; Canadian Antimicrobial Innovation Coalition, personal communication, 2023).

Global and Canadian-specific market challenges result in a lack of access to antimicrobials, which is causing harm in Canada and disproportionately impacting vulnerable groups

The CCA's Expert Panel on the Socio-Economic Impacts of Antimicrobial Resistance in Canada estimated that, in 2018, there were roughly one million bacterial infections in Canada, about one quarter of which were resistant to first-line treatments (CCA, 2019). Among the 14,000 deaths that followed a resistant infection, over 5,000 of these were directly attributable to resistance (CCA, 2019) (Figure 2.4).

While AMR is a risk for everyone in Canada, some populations — including people who are immunocompromised — are disproportionately at risk of infection (reviewed in CCA, 2019). For example, invasive fungal infections are more likely to affect patients with cancer, patients with HIV/AIDS, organ transplant recipients, and populations that are immunocompromised or severely ill (WHO, 2022c). Socioeconomic factors that are associated with increased risk of certain types of bacterial infection include living in remote or Indigenous communities, overcrowded living conditions, and incarceration (King *et al.*, 2022). A full understanding of how these risk factors translate to risk of resistant infection is lacking due to an absence of data (CCA, 2019; King *et al.*, 2022).

Some demographic groups face increased risks of specific types of resistant infections. Indigenous people face elevated risks of MRSA while also contending with persistent health disparities (Muileboom *et al.*, 2013; Loewen *et al.*, 2017). Crowded housing and a lack of clean water, which disproportionately affect Indigenous people in Canada, contribute to the spread of infectious diseases (Cecco, 2021; StatCan, 2022). Furthermore, antibiotic resistance genes have been identified in source water samples from First Nations communities in Canada (Fernando Dinesh *et al.*, 2016; Mi *et al.*, 2019).



Reproduced from CCA (2019)

Figure 2.4 Bacterial Infections and Resulting Deaths in Canada, 2018

Susceptible and resistant bacterial infections in Canada and their associated mortality estimates in 2018.

Any pull incentive that is developed for Canada should consider how populations at greater risk of infection or negative health outcomes would be served by such a policy mechanism. Ensuring access to safe and effective antimicrobials for Indigenous communities is important to factor into the implementation of a Canadian pull incentive. The *Pan-Canadian Action Plan on Antimicrobial Resistance*



“Any pull incentive that is developed for Canada should consider how populations at greater risk of infection or negative health outcomes would be served by such a policy mechanism.”

calls for “collaboration with Indigenous partners to co-develop AMR actions that recognize the unique cultures, contexts, needs and priorities of First Nations, Inuit and Métis Peoples” (PHAC, 2023). The Truth and Reconciliation Commission called on the federal government to close health gaps between Indigenous and non-Indigenous communities and consider indicators such as “chronic diseases, illness and injury incidence, and the availability of appropriate health services” (TRC, 2015b).

More generally, Canada’s large geographic area can disrupt timely access to necessary medications in rural and remote communities. Public healthcare policy, funding, and provisioning often focuses on urban centres, forcing those living in more remote areas to travel long distances to access public health services (Probst *et al.*, 2019; Bailey *et al.*, 2021). This tendency toward “structural urbanism” in healthcare results in disproportionately detrimental health outcomes in rural communities (Probst *et al.*, 2019). Rurality may impede timely diagnosis and prescription of antimicrobials. Numerous socioeconomic factors also intersect with rurality when determining health risks, including income and education levels (Probst *et al.*, 2019). Acknowledging the existence of structural urbanism within Canadian healthcare systems, and focusing on implementation policies that limit this bias to the extent possible, is an important consideration for any pull incentive that seeks to enhance access to new antimicrobials for all people in Canada.

3

Incentivizing Enhanced Antimicrobial Development and Deployment

- 3.1 Pushing Antimicrobial R&D and Pulling Novel Antimicrobials to Market
- 3.2 Pull Incentive Options

Chapter Findings

- Both push and pull incentives are needed to increase Canadian access to novel antimicrobials, but to date, more progress has been made in deploying push incentives.
- Access and stewardship requirements, payment level, and certainty for incentive providers and recipients are all important design considerations for pull incentives.
- Among pull incentives, subscriptions and annual revenue guarantees hold the most promise for revitalizing the market for antimicrobials.

There is growing international recognition that non-traditional market incentives are needed to develop and make available novel antimicrobials given the unique challenges of bringing these drugs to market. This need is greater in markets such as Canada that already experience limited access to existing antimicrobials. Internationally, both public and private interests have recognized these challenges and moved to bolster the antimicrobial pipeline. Significant efforts have been made in the last five years to study and recommend incentives suitable to stimulate antimicrobial innovation. Generally, these incentives are financial by design and target the innovation continuum as either a *push* incentive during R&D, or as a *pull* incentive during commercialization (Årdal *et al.*, 2018; Morel *et al.*, 2020).

3.1 Pushing Antimicrobial R&D and Pulling Novel Antimicrobials to Market

To support a sustained pipeline for new antimicrobials, incentives provide solutions to both scientific and market hurdles. Push incentives promote R&D in the antimicrobial space and pull incentives promote antimicrobials coming to market by providing enhanced revenue prospects, which can also support R&D. The *Pan-Canadian Action Plan on Antimicrobial Resistance* notes the importance of both push and pull incentives for antimicrobial innovation (PHAC, 2023).

Push incentives promote antimicrobial R&D, providing the building blocks for future drugs that can move through the pipeline

To date, there has been more focus on upstream measures that provide capital to support antimicrobial R&D (i.e., push incentives). For example, CARB-X is a global non-profit public-private partnership that funds the early development of antibiotics (CARB-X, 2022b). It focuses on the early stages of antibiotic development



“Pull incentives can work in tandem with push incentives to comprehensively support the development and use of novel antimicrobials.”

(from early preclinical development through to phase 1 clinical trials) when R&D projects are most promising, but drug developers are most vulnerable (CARB-X, 2022b, 2023c). In addition to grants, CARB-X also provides scientific, technical, and regulatory support (CARB-X, 2019, 2022b). So far, it has supported 92 projects with over \$400 million in grants and technical assistance, accelerating 18 of them to reach or surpass first-in-human trials (CARB-X, 2022a, 2022b).

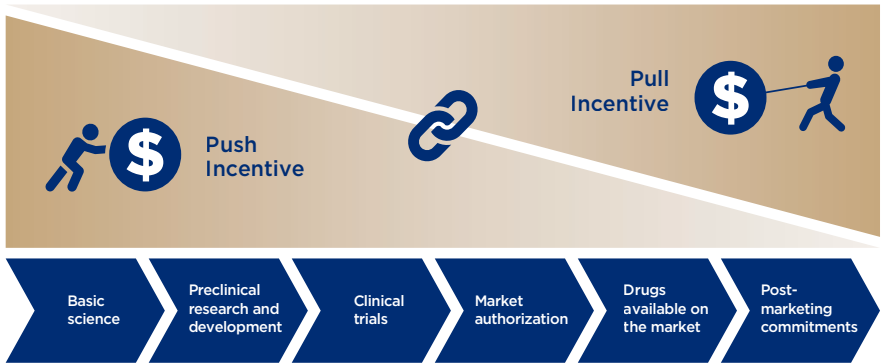
An example positioned downstream of CARB-X is the Global Antibiotic Research & Development Partnership (GARDP), developed by the Drugs for Neglected Diseases initiative and the WHO, which focuses on

development and initial deployment and access in low- and middle-income countries (GARDP, 2022b). This is achieved using a range of financial tools, including investing in, and partnering with, for-profit drug developers rather than issuing grants (GARDP, 2019, n.d.). Additional discussion of push incentives and antimicrobial resistance (AMR) research funding more broadly is provided in Section 6.1.

Pull incentives are a promising strategy to bring novel antimicrobials to the Canadian market

In the event of a widespread outbreak of an antimicrobial-resistant infection, the pharmaceutical industry would face better market prospects for developing new antimicrobials and may invest accordingly. However, the Panel underscored that the delays associated with waiting for an outbreak would impose unacceptable costs on society. Pull incentives enable the successful development of new antimicrobials by providing an improved return on investment or guaranteed revenue (Årdal *et al.*, 2017).

Chatham House (2015) notes that “the timing of the incentive in the product development cycle will influence what type of company or research institution will respond to the incentive.” Pull incentives can work in tandem with push incentives to comprehensively support the development and use of novel antimicrobials (Figure 3.1). Ultimately, push incentives are key to motivating early-stage discovery work. While pull incentives can also act in this area, they play a critical role in enabling the successful commercialization of these discoveries and allow healthcare providers and patients to gain access to these important drugs. A combination of push and pull incentives are required to increase antimicrobial R&D (DRIVE-AB, 2016; O’Neill, 2016; Outterson, 2021b). The prospects for a Canadian pull incentive are the focus of the remainder of this report.



Adapted from Årdal *et al.* (2018)

Figure 3.1 Funding Incentives along the Antimicrobial Innovation Continuum

Push incentives encourage antimicrobial R&D, fund clinical trials, and can improve the success of pull incentives. While pull incentives are only awarded following market approval of qualifying novel antimicrobials, they improve the commercialization prospects and thus indirectly improve support for upstream R&D.

3.2 Pull Incentive Options

Various pull incentives have been studied or launched over the last decade (Otterson *et al.*, 2015; Årdal *et al.*, 2017). The Panel reviewed a range of pull incentive policies, including patent protections, vouchers, higher unit prices, subscriptions, and annual revenue guarantees (ARGs), and concurred with the emerging global consensus that subscriptions and ARGs hold the most promise for appropriately incentivizing the market availability of novel antimicrobials (e.g., Årdal *et al.*, 2018; Otterson, 2021b). In the emerging field of pull incentives research, terminology has varied across projects and over time. For clarity and consistency, this report uses the terminology of Table 3.1 wherever possible.

Table 3.1 Features of Pull Incentives

Pull Incentive Type	Adequate Incentive?	Access guarantees?	Affordability for patients and hospitals?	Stewardship provisions?	Adequate certainty for manufacturer and incentive provider?
Subscription	✓	✓	✓	✓	✓
Annual revenue guarantee	✓	✓	✓	✓	✓
Patent extension	✗	✗	✗	✗	✗
Voucher	✓	✗	✗	✗	✗
Higher unit prices	✗	✗	✗	✗	✗

3.2.1 Most Promising Pull Incentive Options

Subscriptions and ARGs are two slightly different versions of *delinked incentives*, meaning they decouple reimbursement from sales volumes. Both have been piloted, as subscriptions in the U.K. and as ARGs in Sweden. While these pull incentives were developed to reflect specific national contexts with their own program objectives, in the Panel’s view, both can provide valuable insights for developing comparable proposals in Canada. The U.K. pilot was implemented solely within England (excluding Wales, Scotland, and Northern Ireland) and aimed to improve the market conditions for antibiotics by offering a relatively high payment level (via subscription). Conversely, the Swedish pilot aimed to bring existing novel antibiotics (already approved by the EMA) to its market through an ARG and offered a relatively low payment level (PHAS, 2020; NICE, 2021; Brennan *et al.*, 2022).

Subscriptions and ARGs are the most promising pull incentives because they pay for guaranteed access to important new antimicrobials

Subscriptions provide consistent annual payments to manufacturers, regardless of sales volume (Outterson, 2021b). For example, the U.K. pilot subscription paid manufacturers for access to a supply of specific high-value antimicrobials.



“The Panel underscored that subscriptions and ARGs share many characteristics and converge almost entirely when the revenue guarantee is set at a level expected to stimulate innovation.”

Two antibiotics were selected through a competitive tender — ceftazidime/avibactam and cefiderocol. The companies providing these drugs both receive a fixed annual income that is not contingent on sales (not exceeding £10 million per drug, approximately \$17 million) (Brennan *et al.*, 2022). In the U.S., the *Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act*, proposed in Congress in 2021, is also built on a subscription model (U.S. Congress, 2021).

In contrast, ARGs ensure annual income in exchange for secured supplies of a new antimicrobial, but also permit additional sales that may generate additional revenue (PHAS, 2020). In 2019, Sweden began its ARG pilot program to secure access to specific novel antibiotics in hospital settings (PHAS, 2020). The

Government of Sweden guaranteed a revenue of SEK 4 million (approximately \$600,000) for each antibiotic that met its preset criteria. Five antibiotics qualified (PHAS, 2020). Japan is also in the early stages of developing an ARG pull incentive (MHLW, 2023).

The Panel underscored that subscriptions and ARGs share many characteristics and converge almost entirely when the revenue guarantee is set at a level expected to stimulate innovation (Table 3.2). In this case, the difference between the two depends on who pays and who benefits when demand is high. In an ARG, the manufacturer is compensated for each additional unit sold, whereas in a subscription, the contract would likely need to be renegotiated. When set at a level expected to stimulate innovation, these pull incentives are anticipated to provide adequate investor certainty to bring private capital to this space, yielding a desirable multiplier effect (Brennan *et al.*, 2022).

Table 3.2 Characteristics of Subscriptions and Annual Revenue Guarantees (ARGs)

	Subscription	ARG Set to Stimulate Innovation
Total Revenues	Same anticipated total annual revenue per drug, based on value	
Pricing	Unit price set contractually between the government and the manufacturer at a level to support stewardship OR Unit prices set following normal routines (i.e., are not priced for stewardship)	
Procurement and Reimbursement	As per normal routines	
Access and Stewardship Requirements	The same conditions can be applied	
Scenarios of Extreme Consumption (i.e., when higher-than-expected demand occurs)	A contractual clause is triggered where a higher amount must be paid to the manufacturer	Revenues from unit sales exceed the revenue guarantee; the manufacturer keeps the excess

In both models, manufacturers can be held to contractual requirements that support stewardship objectives (Årdal *et al.*, 2021; NICE, 2022a, 2022e). These models can also be designed to support adequate, timely, and equitable access to novel antimicrobials, as has been done in the U.K. and Sweden (NHS, 2020b; PHAS, 2020). For example, in the Swedish program, recipients are held to the following standards:

- deliver requested drugs to hospitals within 24 hours;
- hold stock in Sweden equal to double the previous quarter’s sales, or at least two weeks’ worth of treatment (whichever is greater) for each Swedish acute hospital;
- report quarterly sales and deliveries;
- demonstrate capacities in terms of warehousing, delivery, and reporting; and
- accumulate the required stock within three months after the initiation of the contract (and demonstrate the presence of stock before receiving compensation) (PHAS, 2020).

3.2.2 Other Types of Pull Incentives

Patent extensions, vouchers, and higher unit prices were found to have weaker prospects for confronting the current market challenges.

Patent protections do not provide a sufficient incentive to motivate the private sector

Since 2017, Canada has issued patent extensions of up to two years for new drugs, as part of the Canada–European Union Comprehensive Economic and Trade Agreement (HC, 2017a). Despite this supplementary patent protection, few of the new antibiotics that entered the global market between 2010 and 2019 were marketed in Canada as noted in Chapter 2 (Outterson, 2021b). Modelling of the impact of five-year patent extensions has also found that this type of incentive is insufficient to bring novel antibiotics to the market (Towse *et al.*, 2017).

Patent protections also encourage manufacturers to promote sales, which can run counter to stewardship principles necessary to combat AMR (Schulman, 2009). When robust antimicrobial stewardship programs are in place, patent protections do little to improve market accessibility and availability, since sales for antibiotics remain low during an extended exclusivity period¹² given the slow growth in the uptake of antibiotics (Chatham House, 2015; Årdal *et al.*, 2018). Furthermore, the benefits of patent extensions accrue at the end of the standard patent period, and pharmaceutical companies discount these distant, uncertain benefits in their financial analyses (Kesselheim & Outterson, 2010; Chatham House, 2015).

Voucher models create considerable financial uncertainty and do not guarantee access

Vouchers are awards given to companies that bring an innovative antimicrobial to market (Årdal *et al.*, 2018). In contrast to the antimicrobial-specific patent protection described above, transferable exclusivity vouchers allow manufacturers to extend the exclusivity of any one of their highest-earning drugs, or to sell the voucher to another patent holder (Årdal *et al.*, 2018; Dutescu & Hillier, 2021). Transferable exclusivity vouchers can also vary significantly in the compensation they provide, as the value of a one-year extension would be based on the annual sales of the bestselling — yet soon-to-become generic — drug in a particular market (Outterson & McDonnell, 2016). Such vouchers could motivate antimicrobial

¹² Patents on new drugs provide manufacturers with an *exclusivity period* during which competitors cannot sell the same drug. After patents expire, drugs can be made generic, and competition often results in substantial decreases in drug costs (HC, 2021a).

innovation, but at an unpredictable and potentially high cost for governments and healthcare systems. As Outterson *et al.* (2007) noted, “a 2-year ... patent extension on the top ten selling drugs would protect more than \$125.3 billion in global annual sales from generic competition.” However, such vouchers have yet to be implemented, and there is ongoing debate about the true costs of such an approach (Dubois *et al.*, 2022; Gov. of the Netherlands, 2022). Analyses by Dubois *et al.* (2022) suggested that the costs of vouchers are commonly overestimated. They propose setting a fixed price for the voucher, inviting prospective buyers to bid based on the length of extension, and awarding it to the bidder demanding the fewest years of extension (Dubois *et al.*, 2022).

Vouchers have been criticized for failing to ensure access and affordability, and for the uncertain costs they would impose on healthcare systems (Anderson *et al.*, 2022; Gov. of the Netherlands, 2022; Årdal *et al.*, 2023). They have further been criticized for their inability to accurately align the size of compensation offered to the clinical value of the novel antimicrobial, though adjusting the length of the exclusivity extension provides some scope for this (Anderson *et al.*, 2022; Dubois *et al.*, 2022). Vouchers may also be unpopular with the public and could even be considered unethical, since antimicrobial drug costs are absorbed by patients who require access to whichever drug has not become generic due to the voucher (Outterson & McDonnell, 2016; Årdal *et al.*, 2018; HC, 2022a). As well, because a voucher represents a one-time payment, it would be difficult to rescind the benefit if a novel antimicrobial did not continue to comply with the expectations of the incentive program (Årdal *et al.*, 2018).

Despite these critiques, vouchers have been widely discussed in the European context as they strengthen the business case for investing in antimicrobial development, do not require upfront funding, and may be more feasible to implement across the E.U. as compared to subscription or ARG incentives (EFPIA, 2021; Dubois *et al.*, 2022; European Commission, 2023). In the E.U., vouchers are seen as complementary with other initiatives, such as country-level health technology assessments (HTAs) and reimbursement reforms (EFPIA, 2021). The pharmaceutical industry in Europe views vouchers as a viable incentive model (EFPIA, 2021). In May 2023, the European Commission recommended an antimicrobial voucher program as a part of their revised pharmaceutical legislation (European Commission, 2023).

Higher unit prices at expected sales volumes do not generate profitable markets

It is relatively simple to offer a greater per-unit payment for novel antimicrobials — an approach currently used in France and Germany (Gotham *et al.*, 2021). In Germany, the use of non-inferiority clinical trials (Section 2.1) results in an automatic reimbursement price equal to the reimbursement price of comparator



“The higher unit price model creates affordability and access issues in low- and middle-income countries and could create the same issues in Canada in outpatient settings for people lacking drug coverage (O’Neill, 2015a).”

antibiotic(s), which are generic. Recognizing that antibiotics may have greater value than clinical evidence demonstrates, France and Germany allow their manufacturers to justify higher prices. For example, in Germany an antibiotic may be classified as a “reserve” drug, meaning that its unit price is determined via negotiation (Dagmar Reitenbach, personal communication, 2022). At the end of 2022, four patented drugs had qualified as reserve antibiotics (Dagmar Reitenbach, personal communication, 2022).

In France, special provisions have been established for antibiotics comprising new active substances to ensure they are purchased at a price at or above the lowest payment level across Germany, the U.K., Italy, and Spain (CEPS & Leem, 2021). Companies can also make the case that a higher price is warranted

(CEPS & Leem, 2021). Within the hospital setting, there are special provisions for new high-cost antibiotics, which qualify these drugs for separate reimbursement (ATIH, 2023). The higher unit price model creates affordability and access issues in low- and middle-income countries and could create the same issues in Canada in outpatient settings for people lacking drug coverage (O’Neill, 2015a). This model also gives the sponsoring companies a financial incentive to increase unit sales (Chatham House, 2015).

Uncertainty around the revenues generated with high-cost antimicrobials stems from the unknown prevalence of future infections. As Towse *et al.* (2017) summarized:

High growth in pathogen prevalence and hence drug use would produce high costs for hospitals in areas where outbreaks occurred which required the use of high-cost antibiotic treatments, exposing local healthcare systems to considerable financial risk. This risk of significant financial burden could act as a barrier to use of a new antibiotic during an outbreak ... Meanwhile low growth in pathogen prevalence and low drug use would produce insufficient lifetime manufacturer revenue to drive investment in future antibiotics.

New antibiotics are subject to stringent usage restrictions to support effective stewardship, which further destabilizes this financial model and creates a need for even higher prices (Towse *et al.*, 2017).

Getting the design right is essential to the success of any pull incentive

Table 3.1 summarizes the strengths and weaknesses of the pull incentive options reviewed above, underscoring the promise of subscriptions and ARGs. Both subscriptions and ARGs can be customized to navigate the complex landscape of healthcare systems in Canada. Each can provide a sufficiently large incentive to entice novel antimicrobials to the Canadian market and even incentivize R&D and the commercialization of future novel antimicrobials. Using predetermined criteria, they can be scaled so that the most impactful novel antimicrobials receive the highest payment (outlined in Section 5.3). Both models can be fine-tuned to the needs of the country, the benefits of a specific novel antimicrobial, and the appropriate compensation level.

All of the approaches reviewed above have been criticized for transferring large sums of money to the pharmaceutical industry for drugs that have not demonstrated superiority to existing treatments, particularly for patients lacking other treatment options (Fugh-Berman *et al.*, 2022; Glover *et al.*, 2022; Ramachandran & Powers, 2022). Critics note that, for some of the novel antimicrobials that have not experienced commercial success in recent years, failure is more attributable to their lack of effectiveness in treating patients (and thus low prescribing rates), rather than the problems of the antimicrobial market (Ramachandran & Powers, 2022). The design of clinical trials may exclude important patient groups or cover few patients with resistant infections (Fugh-Berman *et al.*, 2022). Relatedly, the design of clinical trials may also fail to offer prescribers adequate assurance of the utility

(and superiority) of these drugs in meeting patient needs (Ramachandran & Powers, 2022). Pilot pull incentives have funded drugs that — while offering important utility — are arguably not as novel as the hypothetical future drugs needed to effectively confront the challenge of rising AMR (Glover *et al.*, 2022). Thus, ensuring appropriate safeguards of public funds, establishing mechanisms that continue to gather evidence over time, and adjusting payments accordingly are important design considerations for pull incentives and are discussed in subsequent chapters.

The Costs and Benefits of a Pull Incentive

- 4.1 Value: The True Worth of Novel Antimicrobials
- 4.2 Influencing Market Entry: Scale of Incentive
- 4.3 A Clear Case for Incentivizing Antimicrobials

Chapter Findings

- Antimicrobials are extremely valuable to both individual patients and healthcare systems. They provide prophylactic and active treatment options to protect society against the risks of infections.
- There is growing consensus that the value of novel antimicrobials to the public exceeds the costs of incentivizing their development.
- In order to pay its fair share of a global pull incentive, Canada would need to contribute an average of \$14.5 to \$18 million per year per novel antimicrobial for 10 years.

Research suggests that the societal value of novel antimicrobials far exceeds the costs of incentivizing their development. Calibrating the appropriate incentive level is a fundamental part of designing successful subscriptions and annual revenue guarantees (ARGs). There is a significant difference between the incentive level needed to gain access to antimicrobials that already exist but are not currently approved or available in Canada, and the level needed to motivate the research, development, and commercialization of new drugs.

4.1 Value: The True Worth of Novel Antimicrobials

Understanding the value of antimicrobials is critical when assessing the case for pull incentives. While the myriad values of antimicrobials are widely recognized, the quantification of these values is still in its infancy.

4.1.1 Use and Non-Use Values

Antimicrobials provide important benefits to patients and society. They reduce patient morbidity and mortality, which, in turn, helps the community by allowing patients to resume their work and family lives (Karlsberg Schaffer *et al.*, 2017). However, the benefits of antimicrobials extend far beyond these immediate impacts, in ways that set them apart from other drugs (Figure 4.1). These include reducing infectious disease transmission, protecting against the risk of future infection outbreaks, and making medical interventions safer.

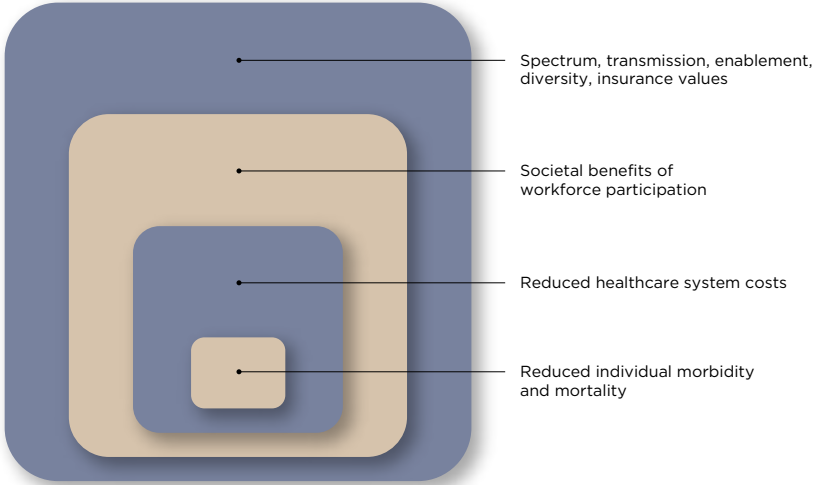


Figure 4.1 The Value of Novel Antimicrobials

Novel antimicrobials aim to provide benefits for patients by reducing morbidity and mortality. These benefits in turn reduce costs to healthcare systems. By improving health, patients and caregivers can more quickly return to the workforce, leading to economic benefits for society (Karlsberg Schaffer *et al.*, 2017). Novel antimicrobials also create a range of wider benefits referred to as STEDI values: spectrum, transmission, enablement, diversity, and insurance (Outterson & Rex, 2020).

Antimicrobials have an exceptionally high value as routine, yet life-saving therapies

As John H. Rex, a Panel member, physician, and drug developer specializing in antimicrobial resistance (AMR), has stated:

If antibiotics would be appreciated as being equivalent to anticancer drugs — but curative! — we would have no trouble ascribing a value equal to many years of life regained. However, as antibiotics have been so effective since at least the 1950s, most adults do not realize that a seemingly simple pneumonia or skin infection could be fatal.

Årdal *et al.* (2020)

Data from the U.S. show that infectious diseases caused 797 deaths per 100,000 in 1900, and that number decreased to 36 deaths per 100,000 by 1980 (Armstrong *et al.*, 1999). While the reasons for this decline are complex, the advent of antibiotics is widely agreed to have played a key role (Hinman, 1990; Armstrong *et al.*, 1999; Adedeji, 2016). The CCA (2019) found that, in 2018, first-line antibiotics saved at least 17,000 lives in Canada, while enabling \$6.1 billion in domestic economic activity. As the rate and extent of AMR increases, so too will the value of effective antimicrobials.

Antibiotics have many special values that set them apart from other drugs

The positive societal values associated with antibiotics are summarized in the acronym STEDI (spectrum, transmission, enablement, diversity, and insurance). The use of STEDI as an acronym first appears in Outterson and Rex (2020), based on the work of Karlsberg Schaffer *et al.* (2017) and Rothery *et al.* (2018). Each of these values highlight a distinct attribute associated with antibiotic drugs.

- **Spectrum:** When existing broad-spectrum antibiotics are replaced with new narrow-spectrum ones, fewer beneficial, naturally occurring bacteria in the human body are killed, and less AMR evolves across the microbiome (Karlsberg Schaffer *et al.*, 2017).
- **Transmission:** Antibiotics create value when they suppress or reduce the spread of a given pathogen (Karlsberg Schaffer *et al.*, 2017).
- **Enablement:** Antibiotics support the delivery of a wide range of treatments and procedures such as surgeries, organ transplants, and chemotherapy. In the absence of effective antibiotics, many of these interventions would be deemed too risky to pursue (CCA, 2019). Patients who undergo these interventions without antibiotics could have worse health outcomes due to increased rates of infection, which lead to increased morbidity and mortality (Teillant *et al.*, 2015).
- **Diversity:** When used in the treatment of a given pathogen, novel antibiotics that are distinct from existing antibiotics slow the evolution of resistance, thereby maintaining the value and usefulness of existing drugs (Karlsberg Schaffer *et al.*, 2017). Karlsberg Schaffer *et al.* (2017) introduced the term “novel action value” to describe a related concept — “the potential value associated with an antibiotic having a new or unique mechanism of action or representing a new chemical structure, i.e., first in class, which will provide ‘spillover benefits.’”

- **Insurance:** Novel antibiotics are valuable even when not used as stocking them in the event of an outbreak offers public health insurance (Karlsberg Schaffer *et al.*, 2017; Rothery *et al.*, 2018). Rothery *et al.* (2018) note two components of this insurance value: the conservation value of reserving drugs for future needs and the value of avoiding catastrophic outcomes in the event of an outbreak.

When it comes to novel antimicrobials, insurance is a particularly important value

The availability of antibiotics provides a general measure of protection and security for society and allows modern medical care to continue as expected (Rex & Outterson, 2016). Rex and Outterson (2016) consider the development and deployment of antibiotics to fight infections as analogous to preventing and fighting fires. In this analogy, infections act as a quickly spreading fire. The availability of a water supply (antibiotics) and firefighters (medical personnel) must be secured before the outbreak of a fire. This example illustrates the insurance value of antibiotics, akin to the value of a fire department, even if the potential epidemic (or fire) never occurs. The COVID-19 pandemic has only served

to underscore the insurance value of effective medical repositories. The negative impacts of a widespread, untreatable, transmissible illness on individuals, communities, and economies have been keenly felt since early 2020, and effective therapeutics and vaccination programs were instrumental in reducing mortality (Jabłońska *et al.*, 2021; Najjar-Debbiny *et al.*, 2023).



“In this analogy, infections act as a quickly spreading fire. The availability of a water supply (antibiotics) and firefighters (medical personnel) must be secured before the outbreak of a fire. This example illustrates the insurance value of antibiotics, akin to the value of a fire department, even if the potential epidemic (or fire) never occurs.”

4.1.2 Estimating the Value of Novel Antimicrobials

Existing approaches to drug valuation do not adequately capture the value of antimicrobials and have contributed to the market failures that characterize this sector (Section 2.1).

Many of the benefits of novel antimicrobials are under-valued in standard health technology assessments (HTAs)

When decision makers consider funding a new drug, they typically compare the costs and impacts of the new drug with those of existing drugs used for the same treatment. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends reimbursement when a new drug provides “comparable or added clinical benefit and acceptable cost/cost-effectiveness relative to one or more appropriate comparators” (CADTH, 2020). Many of the antibiotics healthcare systems routinely rely on today were discovered decades ago, are relatively cheap to produce, and are no longer under patent. As a result, their purchase cost is very low (Gov. of ON, 2022). Additionally, using an antibiotic for infections other than those for which it is indicated for use is common. This can contribute significantly to its overall value but is not recognized in standard HTAs (Karlsberg Schaffer *et al.*, 2017). This approach falls short when it comes to new antibiotics as it excludes STEDI attributes. As a result, HTAs tend to underestimate the true value of novel antibiotics.

Many have argued for an expanded approach to valuation that considers the broader societal values of novel antibiotics, including their impact on future rates of AMR at the national level (e.g., Årdal *et al.*, 2018; Colson *et al.*, 2021). However, it can be difficult to demonstrate the additional benefits and value provided by novel antimicrobials given the limitations of clinical trials in this area. The National Institutes for Health and Care Excellence (NICE), as part of the U.K. subscription pilot, is the only organization that has endeavoured to estimate the full value of antimicrobials across all STEDI attributes (Box 4.1). The estimates were calculated using economic modelling together with committee deliberations. The Institut national d'excellence en santé et en services sociaux (INESSS, 2016) evaluation of ceftolozane/tazobactam also took a wider approach to estimating value. While noting that the drug is not cost-effective when considering the clinical benefits only, they ultimately recommended using the drug in a limited set of circumstances based on the value it provides at the population level. These included the value of diversifying treatment options, as well as making available one of the few antibiotics effective in treating drug-resistant Gram-negative infections (INESSS, 2016).

Box 4.1 Estimates of the Value of Novel Antimicrobials

Quality-adjusted life years, or QALYs, are widely used to compare the cost-effectiveness of drugs, capturing both morbidity and mortality (Jaswal, 2013; NCCPH, n.d.). Cost-effectiveness analyses estimate the incremental costs of achieving one extra year of health (one QALY) using a specific drug compared to one or several alternative treatments (measured in dollars per QALY) (Jaswal, 2013). This comparison allows decision makers to determine whether the health gains from a new drug are equal to or greater than the health gains foregone by reduced spending on an existing drug (Claxton *et al.*, 2008). HTAs in Canada and elsewhere present outcomes in QALYs as a metric of comparison (CADTH, 2017; NHS, 2021a). In the U.K. subscription pilot, NICE estimated the full public health value of two antibiotics in QALYs. However, cost-effectiveness analyses (cost per QALY) were not included, as no assumptions on the price of the novel antimicrobials were made.

The table below summarizes the results of the NICE HTA for the two novel antimicrobials funded through its pull incentive subscription pilot: ceftazidime-avibactam and cefiderocol (NICE, 2022a, 2022b, 2022c, 2022e). For both drugs, estimates suggest a value to society in the hundreds of millions of pounds over the course of 20 years. The implied annual value also indicates that a maximum annual contract payment of £10,000,000 (Leonard *et al.*, 2023) provides good value for money. A breakdown of the QALYs across areas of benefit was not provided.

(Continues)

(Continued)		
	Ceftazidime-avibactam	Cefiderocol
Health opportunity cost	£20,000 per QALY	
Total QALYs per year during 10-year contract	530	970
Implied annual value (first 10 years)	£10,600,000	£19,400,000
Total QALYs over 20 years	8,880	16,200
Implied total value (over 20 years)	£177,600,000	£324,000,000
Spectrum value	None: this is a broad-spectrum antibiotic	
Transmission value	None (uncertain): impacts can run counter to one another, and while reduced length of hospital stay (and thus transmission) may result from using these novel antimicrobials, mortality could also be reduced, which could then increase the length of hospital stays (and thus the possibility of transmission)	
Enablement value	Included (partially): freed up hospital resources; enhanced treatment of post-operative infections	
Diversity value	Excluded	
Insurance value	Included (partially): explored a scenario in which a new pathogen emerges that only responds to treatment by this drug	

Estimating the value of novel antimicrobials presents a formidable methodological challenge

Use and non-use antimicrobial values are highly uncertain as they depend on the future prevalence of susceptible infections and the availability of suitable alternative treatments (Rothery *et al.*, 2018; Morton *et al.*, 2019). Furthermore, drugs that provide more successful treatments may reduce the length of hospital stays for some patients (and thus reduce transmission), but could conversely reduce mortality, thereby increasing the length of hospital stays for other patients (and thus increase the possibility of transmission) (NICE, 2022a, 2022b, 2022c, 2022e). Combining these additional elements of value is a challenge as there are overlapping attributes, so the values may not be additive (Neri *et al.*, 2019).

Additional research is needed before HTA processes can routinely quantify STEDI elements of value

Estimating the full STEDI value of specific novel antimicrobials is in its infancy, and quantification challenges are pervasive. Several early efforts have been made to attach values to specific attributes of antimicrobials. Resch *et al.* (2006) assessed the transmission values of antibiotics, Morton *et al.* (2019) assessed both transmission and diversity values, and Megiddo *et al.* (2019) estimated potential insurance values. The enablement value of antibiotics has been assessed in the context of chemotherapy prophylaxis (Teillant *et al.*, 2015). For the U.K. pilot, NICE acknowledged that some attributes of value were not adequately captured by its work, and that the estimates are subject to high uncertainty (NICE, 2022b, 2022c). In the Panel’s view, although STEDI values are considerable, more research, progress, and simplification are needed to quantitatively estimate QALYs associated with STEDI attributes before this type of analysis can be built into HTAs.

4.2 Influencing Market Entry: Scale of Incentive

The limited development and approval of novel antimicrobials suggests that these drugs remain under-incentivized in the global antimicrobial development pipeline, despite the worldwide problem of AMR. While a relatively small-scale



“While a relatively small-scale incentive could help close the access gap between Canada and similar high-income countries for existing novel antimicrobials, it would not adequately confront the challenge of creating a sustainable global market going forward (i.e., support a more active pipeline for new antimicrobials).”

incentive could help close the access gap between Canada and similar high-income countries for existing novel antimicrobials, it would not adequately confront the challenge of creating a sustainable global market going forward (i.e., support a more active pipeline for new antimicrobials). In the absence of a bigger incentive for novel antimicrobial development worldwide, it is unlikely that there will be adequate novel antimicrobials in the pipeline after existing drugs come to the Canadian market (Figure 4.2).

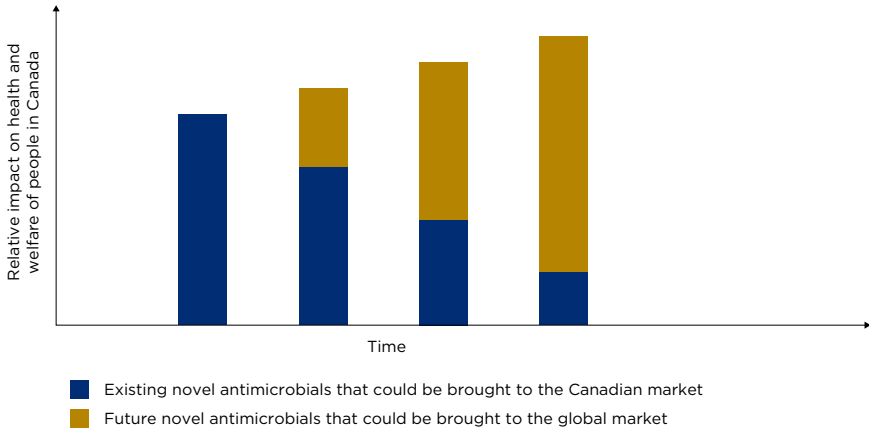


Figure 4.2 Illustration of the Potential Contribution of Existing and Future Novel Antimicrobials Over Time

This is an illustrative depiction of the future public health impact of bringing existing versus future novel antimicrobials to the Canadian market through pull incentives. Only 3 of the 18 new antibiotics that entered the global market between 2010 and 2019 are marketed in Canada as of May 2023 (Outterson *et al.*, 2021 & HC, 2023b). So, there is a small set of existing novel antimicrobials that could be drawn to the Canadian market through a pull incentive in the near term (blue area on the graph). However, this would provide only a partial and temporary solution to treating resistant infections. If high-income countries come together to provide a more compelling incentive that adequately stimulates investment in the research, development, and commercialization of novel antimicrobials, the pipeline for novel antimicrobials could be bolstered and a growing longer-term supply of future drugs could be encouraged (gold area on the graph).

Novel antimicrobials that exist in other markets may be enticed to the Canadian market with modest payment levels

A small incentive payment could offset the manufacturer costs of bringing existing drugs to the Canadian market, thereby allowing access to existing antimicrobials. This is the approach used by Sweden, which offers SEK 4 million per drug (approximately \$600,000) (PHAS, 2020). This was sufficient to incentivize four manufacturers to participate in two-year contracts that established access to five antibiotics. The minimum guaranteed revenue is provided under a partially delinked model, allowing manufacturers the possibility to generate increased revenue from additional sales (PHAS, 2020, 2023). This is an access program, only providing compensation for the costs of bringing an existing drug to a new market — it does not stimulate innovation. While such programs provide near-term access benefits, they do not address the longer-term challenge of bringing novel antimicrobials to market.

The costs of achieving the same drug access in Canada would be higher for two reasons. First, drug manufacturers did not need to obtain regulatory approvals in Sweden, as they could rely on the existing approvals issued by the EMA. In contrast, Health Canada regulatory approval would have to be sought at a cost of roughly \$565,000 per drug (HC, 2023c). Second, manufacturers would have additional costs associated with seeking regulatory approval, such as internal and legal costs, as well as the costs associated with providing a sales force, commercial distribution teams, and medical advisory services in Canada. Taken together, these add to an antimicrobial's commercialization costs.

A higher financial incentive is required to motivate novel antimicrobial R&D

The U.K.'s pull incentive pilot program was structured to provide a much higher incentive, not only to bring novel antimicrobials to market in the short-term but to also motivate the development of new antimicrobials (Section 3.2.1). Efforts to estimate the appropriate payment to manufacturers necessary to stimulate the antimicrobial pipeline have been ongoing for a decade. A payment that is too low risks failure, because a manufacturer would not be able to recover costs and earn sufficient revenues to keep the drug on the market, leading to drug unavailability and potential manufacturer bankruptcy. Conversely, one that is too high over-compensates manufacturers, wastes public resources, generates public mistrust, and would ultimately be unsustainable (Outterson, 2021a).

Analysis of the appropriate incentive level has focused on achieving the necessary expected return on investment (ROI) in antimicrobial research, development, and deployment to motivate private sector activity. When manufacturers contemplate pursuing R&D, clinical trials, or commercialization of a novel antimicrobial, they assess the expected net present value (eNPV) of undertaking this work.¹³ If the eNPV is adequate, work can proceed, but when the eNPV falls short, there is no viable business case, and the project cannot attract investment. The eNPV is a function of three elements:

- **Cost, duration, and likelihood of success at each phase of development.** For example, high rates of failure in clinical trials are the norm (Hay *et al.*, 2014; Outterson, 2021b).
- **Market revenues and expenses.** Revenues are a function of anticipated infection and resistance rates (Towse *et al.*, 2017; Outterson, 2021b).

13 The eNPV refers to calculating product value over an extended period, accounting for R&D expenditures in comparison to the time needed for return on investments based on revenue forecasts (Luepke *et al.*, 2017). The eNPV is the sum of the stream of anticipated revenues and expenditures, with future gains and losses discounted accordingly.

- **Discount rate.** Expenditures today are valued more highly than revenues anticipated in a decade due to the time value of money, which reflects costs of borrowing and the expected rates of return (TBS, 2018; Outterson, 2021b).

Figure 4.3 illustrates the directionality of impacts of each of these elements on the eNPV.

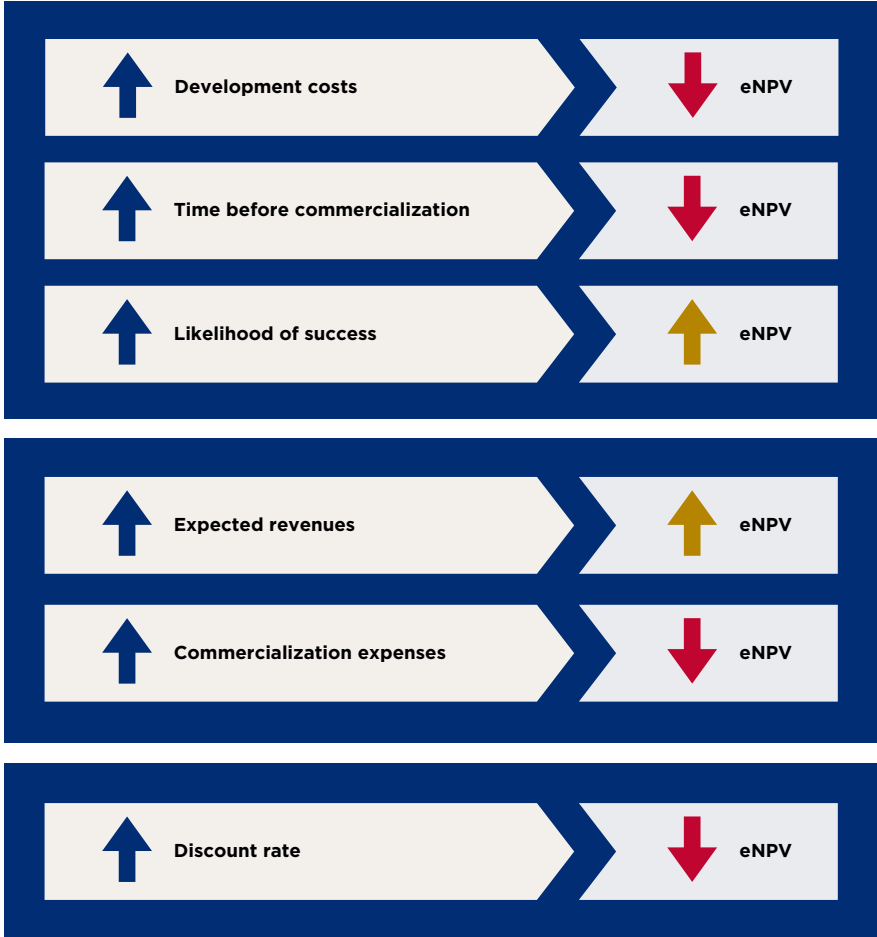


Figure 4.3 Factors Influencing the Expected Net Present Value (eNPV) of a Novel Antimicrobial

The eNPV of a new antimicrobial is higher when there is a greater likelihood of success and when expected revenues are higher. The eNPV is lower when there is a higher discount rate, higher development costs, greater amount of time preceding commercialization, and higher commercialization expenses.

Researchers have made various assumptions about the eNPV required to motivate investments in antimicrobial development. Both Towse *et al.* (2017) and Sertkaya *et al.* (2014) assume a threshold eNPV of US\$100 million. More recent analyses have relied on a higher eNPV threshold, in the range of US\$200 to US\$500 million (Årdal *et al.*, 2018). In contrast, Outterson (2021b) assumes any positive eNPV is adequate. Pull incentives are set at the level needed to improve the eNPV to the point that the project becomes viable for investors. Box 4.2 summarizes early estimates of the level of pull incentive needed to motivate adequate investment in the field, noting the corresponding push incentive scale as appropriate.

Box 4.2 Early Estimates of Requisite Global Incentives (2014–2018)

Sertkaya *et al.* (2014): This analysis looked at the overall incentives needed to motivate the development of drugs for six indications. The combined incentive level ranged from US\$900 million (in 2012 dollars) for community-acquired bacterial pneumonia to US\$1.2 billion for complicated urinary tract infections.

O’Neill (2016): This U.K. AMR Review called for pull incentives in the range of US\$800 million to US\$1.3 billion per drug coupled with a US\$400 million per year global push incentive.

BCG (2017): This report estimated that achieving sufficient eNPV required a global pull incentive of at least a US\$1 billion per drug (assuming US\$500 million in push incentives per year).

Towse *et al.* (2017): In the absence of a push incentive, this study estimated a US\$2.6 billion pull incentive, or a pull incentive of US\$1.1 billion coupled with push incentives that cover half of the R&D costs.

Årdal *et al.* (2018): This research team concluded that, without intervention, only five novel antibiotics are expected to come to market in the next 30 years. However, offering a US\$800 million partially delinked payment, or a US\$1 billion fully delinked payment, could elevate the number of new antibiotics to 16. This could rise to around 20 antibiotics at a higher incentive level (US\$1.5 billion partially delinked or US\$1.8 billion fully delinked). The authors also noted that these payment levels could be scaled back if complementary push incentives were used. They proposed a total global payment of US\$1 billion per antibiotic (partially delinked), supplemented by grant funding (a push incentive) of US\$800 million per year across all drugs.

Outterson (2021b) revises many of these earlier estimates of the value required for a successful pull incentive, landing on a considerably higher estimate of the global pull incentive needed. He argues that in past evaluations:

- chemistry, manufacturing, controls, and post-approval costs were underestimated;
- preclinical success rates were overestimated;
- global peak-year sales assumptions were overestimated; and
- prices require inflation adjustments over time.

Globally, the cost of incentivizing adequate development and deployment of novel antibiotics is estimated at US\$2 to US\$4 billion per drug

When assuming a fully delinked model, with no concomitant enhancements to existing push incentives, Outterson (2021b) finds that the costs for bringing in and sustaining a new antibiotic on the market ranges between US\$2.2 billion and US\$4.8 billion, with a preferred best estimate of US\$3.1 billion.¹⁴ In the Panel’s judgment, this analysis best reflects the current state of understanding as it is the



“Pull incentives are set at the level needed to improve the eNPV to the point that the project becomes viable for investors.”

most recent and comprehensive work and is heavily informed by earlier estimates. The Panel thus applied the Outterson (2021b) estimates to address the question of Canada’s contribution. These estimates may be further refined over time to capture the impact of public funding of clinical work, and to more accurately characterize the preclinical development phase (e.g., duration, likelihood of success, costs).

Given global coordination challenges and income disparities, it is likely that a relatively small number of high-income countries would need to agree to fund an adequate global pull incentive. The Panel

considered two scenarios for its analysis: (i) Canada unites with the other G7 members (France, Germany, Italy, Japan, the U.K., and the U.S.), and (ii) Canada acts with both the G7 and the 27 member states of the E.U. Each country in these groups would be apportioned a *fair share* based on their share of G7 (or G7 + EU27) income. This is in line with the approach taken in the proposed

¹⁴ This result assumes the acquisition of a phase 2-ready drug at a value of US\$500 million, which is considered to be a realistic estimate were such a pull incentive to be in place.

U.S. *Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR Act)* (U.S. Congress, 2021). The Panel noted that working with this subset of high-income countries represents a compromise between sharing the costs of the incentive across countries and proceeding in a timely manner with a critical



“Given global coordination challenges and income disparities, it is likely that a relatively small number of high-income countries would need to agree to fund an adequate global pull incentive.”

mass of willing participants. Coordinating this effort across the G7, and potentially the E.U., was deemed to be a plausible scenario for what could be achieved within the next few years given the G7 Health Ministers’ commitment to exploring antimicrobial pull incentives (G7 Finance Ministers, 2021).

Of note, much of the research in this field recognizes the need for a combination of push and pull incentives. There is some degree of substitutability between the two, wherein an increasingly high push incentive can reduce the magnitude of pull incentive needed, and vice versa (Outterson, 2021b). However, both are essential. Modelling in Outterson (2021b) shows that in isolation, neither push nor pull incentives are able to generate sufficient profits for long-term sustainability given the low expected revenue returns

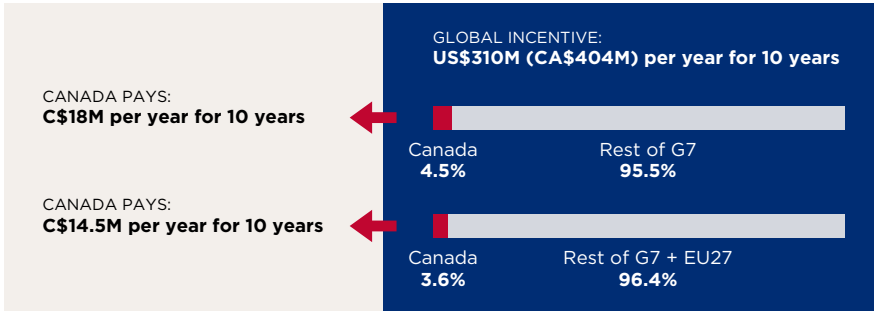
for novel antibiotics. For example, a \$2 billion global pull incentive would still require over 50% cost sharing in the preclinical stages (Outterson, 2021b). Push incentives are discussed further in Section 6.1.

Canada’s fair share of a global pull incentive is estimated at \$14.5 to \$18 million per drug per year for a decade

Were Canada to act with the G7 and the EU27, based on the analysis described above, the Government of Canada would need to offer an average of approximately \$14.5 million (US\$11 million) per drug per year for 10 years (Outterson, 2022). Were Canada to act with only the G7, the Canadian fair share would be \$18 million (US\$13.8 million) per drug per year (Outterson, 2022)¹⁵ (Figure 4.4). These results are broadly consistent with prior analyses estimating Canada’s fair share contribution at roughly US\$11 million per year per antimicrobial for G7 collaboration, and US\$9 to \$10 million for G7+EU27 collaboration (Boluarte & Schulze, 2022). In practice, there is a significant degree of uncertainty

¹⁵ These two groups of countries are selected because they are all exploring the use of pull incentives and looking into adopting them in the near term. Were a broader group of countries to deploy pull incentives, Canada’s share could fall commensurately.

surrounding these estimates, in line with the uncertainty underpinning the global estimate described above. Additionally, payment levels could vary across drugs based on their relative value (Section 5.3), and could change over time for any particular drug, for example, because of new evidence of the drug’s effectiveness (or lack thereof) published after approval.



Source: Outterson (2022)

Figure 4.4 Canada’s Fair Share of a G7 or G7+EU27 Subscription Payment for a Novel Antibiotic

Should Canada participate in a global pull incentive for antibiotics, its share would range between \$14.5 to \$18 million per year, depending on the number of participating countries.



“This level of compensation would put antimicrobials on a more equal footing with other patented medicines.”

This level of compensation would put antimicrobials on a more equal footing with other patented medicines. The Patented Medicine Prices Review Board (PMPRB) reports that annual Canadian sales of 58% of patented medicines were \$12 million or greater by their 10th year on the market — 37% had sales over \$25 million (PMPRB, 2020).

4.3 A Clear Case for Incentivizing Antimicrobials

The CCA (2019) report, *When Antibiotics Fail* found that 14,000 deaths in 2018 were from resistant infections with a corresponding cost to the Canadian healthcare system of \$2 billion. Depending on the extent of resistance to first line antimicrobials (calculated from current estimates of 26% to a possible high of 40%), Canada's GDP could fall by \$13 billion to \$21 billion per year by 2050, shrinking the economy by 0.5–0.7%. In those same scenarios, annual deaths caused by AMR were projected to range from 7,000 to 13,700 per year by 2050 (CCA, 2019). Novel antimicrobials would play an important role in reducing these costs and harms.

Estimates of the social values of novel antimicrobials are highly uncertain, but there is wide consensus these values exceed the costs of incentivizing antimicrobial development

Spellberg and Rex (2013) found that a new treatment for carbapenem-resistant *Acinetobacter baumannii* would be cost-effective in the U.S. even at US\$30,000 per treatment course. NICE found that both ceftazidime-avibactam and cefiderocol would be cost-effective for the U.K. health system at the payment levels offered through the U.K. subscription pilot (Leonard *et al.*, 2023). Sertkaya *et al.* (2014) report that, even without calculating STEDI attributes of antibiotics, the social values of novel antibiotics far outweigh the expected private returns from an incentive program.



“Ultimately, offering a subscription payment of this nature increases the likelihood that novel qualifying drugs will be developed and only pays for success.”

Towse and Silverman Bonnifield (2022) have considered the hypothetical example of a subscription payment model implemented by the G7+EU27 (as broadly laid out by Outterson (2021b)). Factoring in only the drug costs and reduction in healthcare costs, and excluding STEDI values, their analysis for Canada found a positive ROI of 5 to 1 over 10 years, or 20 to 1 over 30 years when Canada paid its “fair share” alongside the rest of the G7 and the E.U. (Silverman

Bonnifield & Towse, 2022). The U.S. shows a domestic ROI of 28 to 1 over the course of 30 years, or 6 to 1 over the first 10 years. Globally, the ROI is far higher. Even if the U.S. acts alone to offer the full necessary subscription payment (i.e., it pays 100% of the needed pull incentive instead of just its fair share), the country would still experience a positive ROI (Towse & Silverman Bonnifield, 2022). Estimates are based on the premise that 18 drugs are introduced over the course of three decades — 3 drugs to treat each of the 6 priority pathogens — and that all new drugs cause significant declines in mortality (5% reduction).

This hypothetical example is anticipated to generate US\$2.1 billion in benefits in the first decade and avoid 2,500 AMR deaths in Canada. Over the course of 30 years, these benefits rise to US\$31.5 billion and 48,000 avoided deaths, although the STEDI benefits of new antibiotics were not included in this analysis (Silverman Bonnifield & Towse, 2022). In practice, the economic benefits and avoided deaths could spread to other countries should these novel antimicrobials be brought to market elsewhere. The ROIs described above would only be achieved if these highly valuable drugs are developed, and payments would only be issued for novel antimicrobials that were judged to be of sufficiently high value. Ultimately, offering a subscription payment of this nature increases the likelihood that novel qualifying drugs will be developed and only pays for success.

A Scenario for Operationalizing a Pull Incentive for Canada

- 5.1 A Subscription Pull Incentive
- 5.2 Drug Eligibility Requirements
- 5.3 Establishing Eligibility and Payment Level
- 5.4 Contractual Conditions
- 5.5 Considerations for Implementing, Monitoring, and Evaluating an SPI

Chapter Findings

- A Canadian subscription pull incentive can strengthen the antimicrobial pipeline, addressing Canadian and global public health needs.
- An impactful subscription pull incentive requires clear and stringent drug eligibility criteria and contractual conditions that enable access and appropriate use.
- Implementation and design of a subscription pull incentive requires coordination across Canada’s multijurisdictional healthcare systems.

In the Panel’s view, a Canadian subscription pull incentive (SPI) offers the greatest potential for positive impact, given the global context of antimicrobial resistance (AMR) and the realities of Canada’s multi-actor healthcare systems (GC, 2014, 2017; Schwartz & Morris, 2018). A Canadian SPI can simultaneously address national and international needs, contributing to global antimicrobial solutions that are contingent on the involvement of many. This chapter describes a scenario for developing and implementing a pull incentive in Canada, outlining some of the key design elements and eligibility criteria that could be established, as well as some of the challenges that would need to be overcome.

5.1 A Subscription Pull Incentive

Given the growing consensus over the merits of annual revenue guarantees (ARGs) and subscriptions (Section 3.2.1), the Panel deliberated on both incentive models and concluded that an SPI could be most effective in enhancing Canadian access and furthering antimicrobial innovation. In developing this scenario, the Panel applied elements of the approaches employed in Sweden’s access-focused ARG, the U.K.’s subscription, and the proposed U.S. *Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act*.



“Both new and existing drugs could qualify for an SPI, provided they satisfy the eligibility criteria.”

Drugs qualifying for a Canadian SPI would need to meet or exceed a high eligibility threshold aligned with addressing current and future unmet public health needs. Both new and existing drugs could qualify for an SPI, provided they satisfy the eligibility criteria (described in Section 5.2). An SPI could offer

manufacturers a subscription payment determined by the value that a drug offers society. To determine the value of new drugs, an SPI could function similarly to the U.K.'s subscription and the proposed U.S. PASTEUR Act, by assessing different values for different drugs (U.S. Congress, 2021; Leonard *et al.*, 2023; Nick Crabb, personal communication, 2023).

An approximate subscription payment level of \$14.5 million per drug, paid annually over one decade, represents Canada's fair share of a global incentive offered by the G7+EU27 (Section 4.2). In practice, payment levels will vary based on drug attributes (Section 5.3). A staged or tiered reimbursement approach could be used wherein initial (and extendable) contracts could be adjusted over time, based on emerging evidence (Chatham House, 2015; Rex & Outterson, 2016). In the Panel's view, a government can insulate itself from financial risk by offering lower annual revenue in initial contracts, and greater revenue in contract extensions if a drug demonstrates increased value.

Unit prices can be set at a level that assists stewardship efforts

High unit drug prices create patient access challenges in Canada, an important consideration in the development of an SPI. High drug prices are costly for Canadian healthcare systems and have an impact on public payers as well as private payers that provide insurance coverage to many Canadians (HC, 2017b; Brandt *et al.*, 2018; GC, 2023b). Brandt (2018) approximates that out-of-pocket costs restrict 10% of Canadian patients from filling prescriptions. Furthermore, drug prices are often a consideration for listing on hospital formularies (Burke *et al.*, 2016). Controlling unit prices helps enable access by keeping drugs affordable. The Panel therefore believes that in an SPI, the unit price of drugs should be set at a level comparable to, or only slightly higher than, that of other drugs prescribed for treatment. A unit price that is too high may restrict access and deter use. A price that is too low — that is, lower than similar alternative drugs — risks being inappropriately prescribed (Chatham House, 2015). While the overuse of antimicrobials is a significant problem, underuse can also be problematic, especially in the case of innovative antimicrobials (Duke-Margolis Centre for Health Policy, 2021). As well, the Canadian unit price will impact reference pricing processes in international jurisdictions (Rand & Kesselheim, 2021), thus the Panel noted that the establishment of such prices might require consideration of the potential repercussions elsewhere in the world.

A limited period of eligibility could encourage timely Canadian access to innovative drugs

In the Panel's view, a time-limited eligibility stipulation in an SPI would help support prompt access to innovative antimicrobials approved in international jurisdictions. For example, an antimicrobial would only be eligible for an SPI in Canada so long as the application was made within a short period (e.g., one or two years) following regulatory approval in other, predetermined jurisdictions such as Japan, the E.U., the U.K, and/or the U.S. This would incentivize manufacturers with approved drugs to bring them to the Canadian market in a timely manner.

An SPI would rely on collaboration among the federal, provincial, and territorial governments, and other actors in Canadian healthcare systems

An SPI could be designed to minimize administrative burden and to integrate as seamlessly as possible with Canada's healthcare systems. In a Canadian SPI, the federal government could take on new responsibilities such as assessing drug eligibility, determining value, and securing contracts with manufacturers that establish access commitments for drug supplies in exchange for subscription payments. The Panel acknowledges that new roles, regulations, and policies may be required to support these processes within the federal government. While these changes will be integral to the implementation of an SPI, how these changes may be accomplished falls outside the Panel's expertise and was not considered in this report. Additional work is needed to assess whether the federal government has the necessary authorities in place to take on this role, or whether adjustments may be needed.

All current systems for procurement, distribution, and routine use, however, would proceed as per current practices for any newly approved drug. This highlights the integral role provincial and territorial governments will have in an SPI. In each province and territory, the sale and procurement of drugs could occur as per standard practices for hospitals as well as public and private payers, similar, for example, to the ARG in Sweden (PHAS, 2020). The Patented Medicines Prices Review Board (PMPRB) oversight of Canadian drug pricing is not anticipated to conflict with an SPI, assuming the unit prices charged for medicines are not priced excessively for Canadian consumers (PMPRB, 2018). Price negotiations typically undertaken by the pan-Canadian Pharmaceutical Alliance (pCPA) may be redundant, as the unit price would be established within the subscription contract. However, expertise from multiple organizations, including pCPA members, could be drawn upon to determine unit pricing and contract valuations in an SPI.

At the end of an annual fiscal cycle, the federal government would top-up the amount paid to the manufacturer, which would be calculated by subtracting the total revenue generated from both private and public payers at their respective prices from the annual payment (Figure 5.1). In such a structure, all actors would be required to provide accurate and transparent accounting, given its importance to determining the overall SPI payment. Provisions would need to be established for the rare scenario where revenue from sales surpasses the annual payment (Box 5.1)

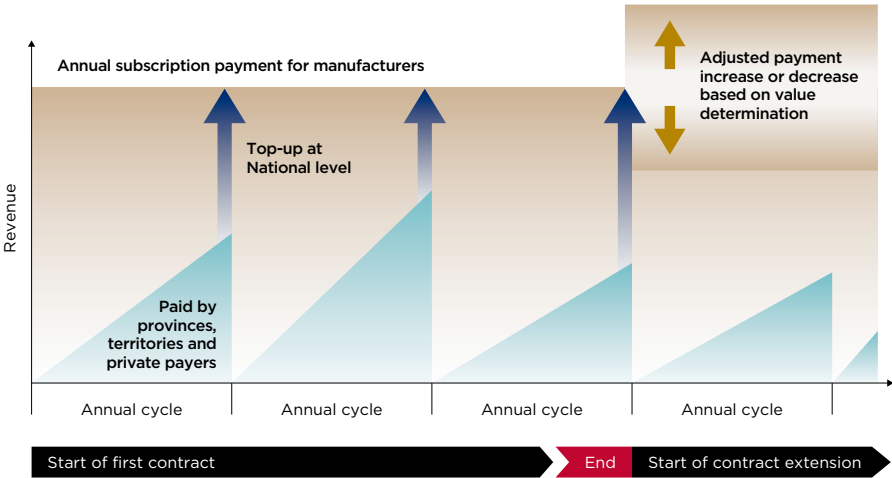


Figure 5.1 A Possible Structure of an SPI in Canada

An SPI would establish an annual payment for manufacturers. Sales revenues from public and private payers (blue shaded area) would be topped up by the federal government each year (beige shaded area). At the end of a contract cycle, the federal government could renegotiate the payment amount based on drug evaluations.

As with the U.K. subscription and the proposed U.S. PASTEUR Act, initial contracts with manufacturers could be for multiple years (e.g., 3 to 5 years), with the option to extend contracts to the end of the exclusivity period, generally up to 10 years (U.S. Congress, 2021; Leonard *et al.*, 2023). At the end of a contract cycle, the subscription payment could be renegotiated based on drug evaluation (U.S. Congress, 2021).

Box 5.1 The Unexpected SPI Scenario of High Antimicrobial Usage

In an SPI, sales revenue is not expected to surpass the annual payment. However, in a rare, unforeseen outbreak scenario, under the current structure provinces and territories would be responsible for ongoing financial costs. To ensure the longevity of a pull incentive over multiple years — and buy-in across various provincial and territorial governments — an agreement could be established wherein the federal government agrees to contribute a percentage of costs after a specified number of sales is exceeded. As well, a contractual stipulation could limit additional revenue generation more than the guaranteed payment (as was done in the Swedish approach (PHAS, 2023)). This proposed approach distributes risk among all orders of government and the manufacturer.

5.2 Drug Eligibility Requirements

Eligibility requirements are a critical tool that the federal government can use to determine which drugs are sufficiently valuable to qualify for an SPI. It has been argued, for example, that the U.S. *Generating Antibiotic Incentives Now* (GAIN) Act did not adequately target unmet needs or prioritize drugs offering new mechanisms of action, resulting in qualifying drugs with limited therapeutic benefit (Darrow & Kesselheim, 2020). In a Canadian SPI, well-designed and stringent eligibility requirements could ensure that only drugs of high value are deemed eligible, thus minimizing federal financial risk while addressing public health needs. Transparent and predictable eligibility requirements offer clear targets for manufacturers, which in turn may enhance industry uptake of an SPI. Eligibility standards need to be high but realistic, and subscription payment amounts can vary with the evidence of the benefits offered by the drug.

5.2.1 Drug Eligibility

In Canada, all marketed drugs are first approved by Health Canada, which evaluates the safety and efficacy of drugs applying to enter the Canadian market (GC, 2015). Regulatory approval by Health Canada would be an essential eligibility criterion for an SPI.

SPI-qualifying antimicrobials address unmet public health needs

An SPI would be made available to antifungal and antibacterial therapies because of the distinct needs, risks, and market challenges facing these antimicrobials (Section 1.2.1). Broadly, eligible drugs would be those that demonstrate clinically relevant antimicrobial activity against growth of dangerous, resistant bacteria or fungi (Rex *et al.*, 2017). Priority pathogen lists, which include pathogens that cause serious risk of infection and for which there are limited treatment options, have been developed, and drugs could be assessed against such lists to assess their potential to respond to unmet public health needs, as per the U.K. approach (NHS, 2020b; Nick Crabb, personal communication, 2023). Globally, the 2017 WHO *Bacterial Priority Pathogen* list identifies 12 bacteria resistant to multiple antimicrobial treatments representing significant threats to human health (WHO, 2017). In 2022, the WHO identified 19 fungal priority pathogens (WHO, 2022c). The WHO ranks these 12 bacterial and 19 fungal pathogens into categories of urgency such as *critical*, *high*, or *medium* priority, where *critical* pathogens exhibit the highest threats to human health (WHO, 2017, 2022c).

Canada and the U.S. have developed their own lists of priority pathogens (CDC, 2019; HC, 2021b). Health Canada's *Pathogens of Interest* list includes all the WHO-identified pathogens plus an additional nine (as well as three fungal pathogens), but does not prioritize their importance (HC, 2021b). In the Panel's view, the Canadian-specific priority pathogen list helps clinicians understand current domestic treatment challenges. AMR, however, is a global problem, and an effective approach for a Canadian SPI would be to contribute to collaborative global AMR solutions. The Panel observed that adhering to the most up-to-date WHO priority pathogen lists incentivizes the development of drugs that address both Canadian and global needs and improves the compatibility of an SPI with other pull incentives that may be established elsewhere. For instance, the U.K.'s subscription will also be primarily focused on the WHO list (Nick Crabb, personal communication, 2023).

Regulatory approval of antimicrobials can be issued according to syndrome indications or for specific bacterial pathogens. For instance, dalbavancin is indicated for acute bacterial skin and skin structure infections, while fidaxomicin is indicated for treatment of *Clostridioides difficile* infection (Merck Canada Inc., 2019; Endo Ventures Ltd., 2021). The drug manufacturer lists the proposed indications in its application for regulatory approval. The Panel noted that in the case of syndrome-based regulatory approval, the drug may be used off-label to treat susceptible pathogens at other infection sites. The Panel observed that pathogen-based regulatory approval offers better alignment with a pull incentive program, since it would be challenging and potentially inappropriate for a pull incentive to value and compensate off-label usage. Pathogen-based approval also offers clearer alignment with the WHO's list of priority pathogens.

SPI-qualifying antimicrobials offer novel attributes

Generally, antimicrobials are more valuable when they represent a new class, offer a novel mechanism of action, or demonstrate advancements within an antimicrobial class, such as by targeting a new pathogen or condition (Rex & Outterson, 2016). Determining antimicrobial novelty can be challenging — a dearth of clinical evidence, the dynamic nature of AMR, and diverse stakeholder interpretations of “novelty” all contribute to this challenge (Theuretzbacher, 2017). Innovation can broadly be determined when a drug avoids cross-resistance to existing drugs and demonstrates “low potential for high-frequency, high-level single-step resistance” (Theuretzbacher, 2017), or, in practical terms, when the novel drug has a low propensity for the evolution of resistance in the target pathogen. The more a drug can be used with improved efficacy, smaller doses, better safety, increased dose flexibility, and for a greater diversity of patients, the more innovative it becomes (WHO, 2020; CARB-X, 2023a, 2023b). A drug that can be taken orally, for example, increases ease of use (compared to intravenous administration and extended hospital stays) (Rex & Outterson, 2016). In the U.K.’s pilot



“Broadly, eligible drugs would be those that demonstrate clinically relevant antimicrobial activity against growth of dangerous, resistant bacteria or fungi (Rex *et al.*, 2017).”

model, novelty was determined by a points-ranking system based on the following five criteria: new chemical class or adjustment of class, new pathogen target, new mechanism of action, resistance performance, and reduced toxicity (NHS, 2020b). The U.K. plans to issue updated criteria by fall 2023, reflecting lessons learned from its pilot. Similar criteria could be considered in a Canadian SPI.

Evidentiary requirements for SPI-qualifying drugs may extend beyond clinical trial data

SPI eligibility criteria would need to reflect the likelihood that novel antimicrobials would not be accompanied with evidence from superiority trials (Section 2.1). This creates a challenge for determining SPI eligibility as, for example, most new antimicrobials approved in the U.S. through non-inferiority trials have not proven to sufficiently address public health needs (Darrow & Kesselheim, 2020; Sinha *et al.*, 2021). Concerns have been raised regarding the use of insufficient or low-quality evidence to support antimicrobial development. It has been pointed out that, when it comes to resistant infections, currently available treatments are inadequate, so establishing non-inferiority to such treatments is not meaningful (IDSA, 2012). Powers (2018) noted that “the idea that drugs that are non-inferior in today’s patients will provide superior efficacy in future patients remains conjecture.”

In contrast, it has been argued that, while superiority clinical trials generate optimal evidentiary value, they are often impractical and unethical to conduct for new antimicrobials (Boucher *et al.*, 2017; Rex *et al.*, 2017, 2019). It is unethical, for example, to wait for widespread resistance in the population so that superiority trials could then take place (Rex *et al.*, 2019). Indeed, in the context of AMR, non-inferiority trials are not necessarily inferior but “a necessary and essential part of antibiotic drug development” because they are not contingent on widespread epidemic resistance and do not jeopardize patients’ health (Rex *et al.*, 2017).

Given the lack of superiority data, other types of evidence may be needed to supplement results of non-inferiority trials. Antimicrobial evidence for an SPI may, therefore, be substantiated using robust, well-designed, non-inferiority trials, supplemented with “exhaustive *in vitro* and animal *in vivo* exposure-response relationship data” (Rex *et al.*, 2017). They may also be substantiated using pharmacokinetics/pharmacodynamics (PK/PD) data¹⁶ (Karlsberg Schaffer *et al.*, 2017), and, where possible, studies of “either open-label treatment with the novel agent or randomization versus a ‘best available therapy’ control selected on a per-patient basis” (Rex *et al.*, 2017). In addition, uncertainty can be reduced by confirming the attainability of “targeted drug exposures” in relevant patients, establishing regimen efficacy from various animal models, using “validated external controls,” and potentially by pooling data from small clinical data sets from disparate sites (Boucher *et al.*, 2017). Importantly, this body of evidence could be further substantiated by post-market observation studies from real-world use, or by additional phase 4 evidence-gathering options, such as the proposed “adaptive randomised clinical trials (aRCTs)” (Karlsberg Schaffer *et al.*, 2017; Rex *et al.*, 2017; Lanini *et al.*, 2019). In parallel, work is ongoing to establish feasible superiority trials for novel antimicrobials as a complement to non-inferiority trials (IDSA, 2012; Powers *et al.*, 2018).

Transparent and predictable eligibility requirements enable a well-functioning incentive for both manufacturers and governments

Clear eligibility criteria not only provide manufacturers with a target to direct R&D, but also guarantee fairness and transparency for all prospective manufacturing participants (Brennan *et al.*, 2022). An SPI that includes all drugs that satisfy stringent eligibility criteria establishes a clear price signal to manufacturers, which supports increased investor engagement in the

¹⁶ According to Karlsberg Schaffer *et al.*, (2017), “Pharmacokinetics describes the drug concentration-time course in body fluids resulting from administration of a certain drug dose. Pharmacodynamics describes the observed effect resulting from a certain drug concentration.”

antimicrobial R&D sector (Outterson & Rex, 2023). In the Swedish pilot, for example, where all drugs that met eligibility requirements were included, program evaluations found the model to be straightforward, quick, and effective, with manufacturers commending the program for its transparency (PHAS, 2023). While offering subscriptions to all drugs that meet a base threshold could generate budgetary uncertainty for the government, it is a risk that can be mitigated by analyzing the clinical pipeline.

An alternative method could be competition-based, whereby manufacturers compete for an established amount of SPI funding. A competition would limit financial exposure for governments while enabling payment for the drugs demonstrating the greatest value. This approach, however, would not provide



“Stringent eligibility criteria would ensure that the federal government only issues payments for novel antimicrobials that directly respond to public health needs.”

a clear development target for manufacturers and would also require extensive timeline and logistic coordination. While a competition was run in the U.K.’s pilot program, it is not the approach being used by the U.K. National Health Service going forward in its subscription (Leonard *et al.*, 2023; Nick Crabb, personal communication, 2023).

In the Panel’s view, an SPI in which all antimicrobials that satisfy eligibility criteria would qualify for an initial subscription contract could be an effective approach for a Canadian pull incentive. Stringent eligibility criteria would ensure that the federal government only issues payments for novel

antimicrobials that directly respond to public health needs. Given the current state of antimicrobial R&D (Chapter 2), it is unlikely an SPI would be flooded with new drugs, therefore the resulting financial exposure for the Government of Canada could be minimal, especially in the near- to medium-term. Among the 18 existing novel antimicrobials listed in Outterson *et al.* (2021), the Panel expects that a few may be sufficiently valuable to qualify for the pull incentive. As of 2021, 27 drugs that could be used to treat infections associated with WHO critical pathogens are being clinically developed globally, and only 6 of these are deemed innovative (WHO, 2022b). These numbers likely overestimate the number of potentially qualifying drugs, since many drugs in development do not ultimately reach the market (Hay *et al.*, 2014).

The Panel does not anticipate more than two to three additional qualifying drugs in the next decade, based on the existing phase 2 and phase 3 pipeline. However, the hope is that more innovative preclinical drugs will move into the clinical development pipeline over time. Moreover, if an SPI's objective is to generate innovative drugs that offer public health value, having multiple qualifying drugs would demonstrate a program's success. As established in Section 4.3, the benefits of these new drugs will likely exceed the costs of incentivizing them. The number of drugs funded will be a function of the stringency of the eligibility criteria, and there may be several existing qualifying drugs at the time of program inception. The implementation of multiple pull incentives in different jurisdictions may increase this forecast in the longer term, but, again, this would indicate program success at a global level.

5.2.2 Manufacturer Eligibility

The antimicrobial preclinical pipeline is currently dominated by small- and medium-sized enterprises (SMEs) (Courtemanche *et al.*, 2021). Few large pharmaceutical companies are developing antimicrobials but large companies may later acquire phase 2-ready drugs created by SMEs (Outterson & Rex, 2020; Outterson, 2021b). Different actors, therefore, might seek participation in a pull incentive, including for-profit corporations, non-profit enterprises, and public benefit corporations (Outterson & Rex, 2020). Indeed, Spellberg (2022) argued that sales revenue from new antimicrobials may be low for industry, but attractive for non-profit organizations. In the Panel's view, eligibility processes should ensure that any organization, whether they are private, non-profit, or private-public, is potentially eligible for a Canadian SPI.

SPI eligibility requirements would ensure that manufacturers demonstrate capacity and competency in delivering on contractual obligations

In the U.K.'s pilot, Sweden's access program, and the proposed U.S. PASTEUR Act, manufacturers are required to demonstrate their capacity to:

- make drugs available within a specified timeline;
- maintain supplies as per contract requirements;
- ensure drug quality;
- develop and maintain adequate communication with, and education of, healthcare practitioners regarding use and risks;
- report on use trends and relevant resistance data;

- provide a roadmap for international access (e.g., registering a drug) wherever a need is unmet; and
- assist in government evaluations when requested (NHS, 2020a, 2020b, 2021b; PHAS, 2020; U.S. Congress, 2021).

Additionally, as outlined in both the U.K.'s pilot and in the proposed U.S. PASTEUR Act, manufacturers must demonstrate adherence to environmental guidelines that avoid discharge of antimicrobials into the environment during manufacturing (NHS, 2020b; U.S. Congress, 2021). These manufacturer requirements could also be considered for a Canadian SPI.

The Panel noted that some flexibility may be necessary when assessing a manufacturer's financial stability. In the U.K.'s pilot, for example, even though manufacturers were subject to a financial stability check against multiple criteria, they did not need to achieve a perfect score, and were given opportunities to address areas of weakness (NHS, 2020a). The reality is that the financial stability of some SMEs or other companies might depend on receiving an incentive for which it has already made considerable investments. In the Panel's view, acknowledging this financial reality may help encourage greater participation from SMEs and other entities besides large pharmaceutical companies.

5.3 Establishing Eligibility and Payment Level

An SPI program would entail an iterative process of decision-making over the duration of the program (Figure 5.2). Drug marketing authorization would be required from Health Canada for a drug to be SPI eligible, but the SPI review process could be initiated three to six months before Health Canada's Notice of Compliance (NOC). This would ensure that an awarded subscription contract could be activated in a timely manner, consistent with the approach taken by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2018). Drug and manufacturer eligibility would be determined, and all qualifying antimicrobials would then go through an assessment process to determine the appropriate annual payment level. Unit price would also be established at this point, and the drugs would then be made available on the market. Manufacturers would receive sales revenues from purchasers and an annual supplemental federal payment to bring the overall revenues up to the established payment level. Evidence on drug effectiveness would be gathered and would inform periodic reassessments of SPI eligibility, as well as upward or downward adjustments in payment levels.

Overcoming Resistance

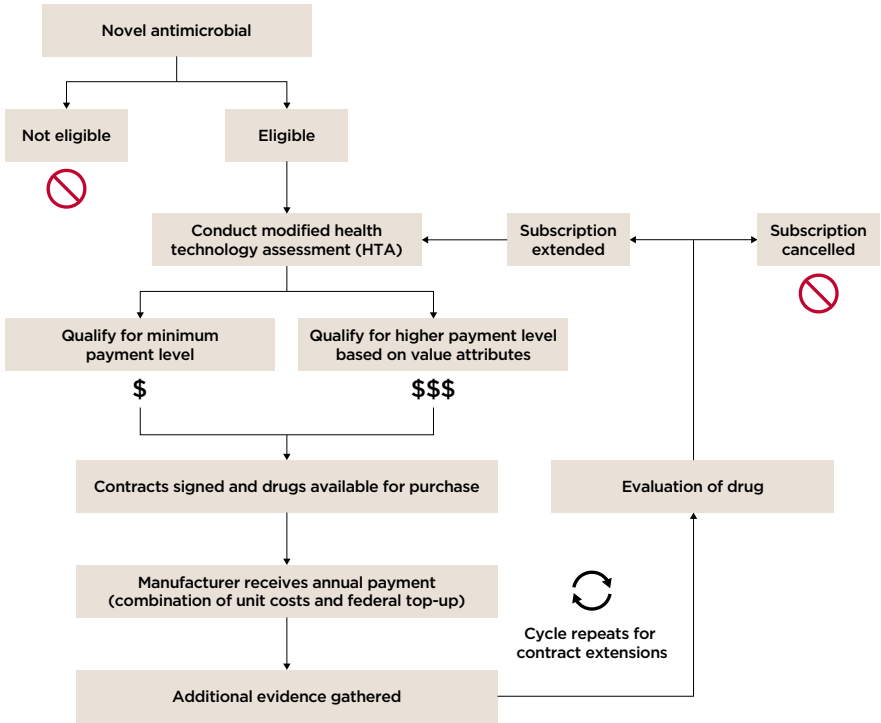


Figure 5.2 Subscription Pull Incentive (SPI) Process Flow

A novel antimicrobial must first obtain Health Canada’s regulatory approval. It is then assessed for SPI eligibility and evaluated to establish the appropriate payment level. A contract is ultimately signed, and the antimicrobial is brought to market. During the contract cycle, the manufacturer receives previously agreed-upon payments while evidence of the drug’s performance is collected. This supports a reevaluation of the drug and the determination of an appropriate incentive level for the subsequent contract cycle. Should the results of the evaluation be disappointing, the payment level could be decreased or contract terminated.

In an SPI, differential subscription payments are based on the value of each novel antimicrobial

The valuation process assesses the drug's value to patients and society (Rex & Outterson, 2016). A tiered eligibility process could be used in which a base payment is offered to all antimicrobials that meet the basic eligibility threshold, but payment levels can then be increased based on demonstrated patient and social value (Chatham House, 2015; Rex & Outterson, 2016). While a drug would, for example, need to demonstrate efficacy against a WHO pathogen, demonstrating efficacy against a *critical* WHO pathogen could have greater value within the assessment framework, as in the case of the U.K. pilot (NHS, 2020b). Drug value increases based on improved clinical efficacy, reduced toxicity, increased ease or flexibility of dosing (either broadly or for specific populations, such as children or pregnant people) (Rex & Outterson, 2016; WHO, 2020; CARB-X, 2023a, 2023b). The framework could also, wherever possible, reflect spectrum, transmission, enablement, diversity, and insurance (STEDI) values (Section 4.1.1) despite the complexities that persist around their quantification.

The Panel acknowledges the complexity of conducting value assessments that strike a balance between adequately incentivizing manufacturers while not over-paying for an antimicrobial that lacks innovation. Indeed, in the U.K.'s pilot, some concerns have been raised around payments for drugs not seen as sufficiently innovative (Glover *et al.*, 2022). The Panel believes an initial contractual payment will need to be sufficiently high to generate interest and financial feasibility among manufacturers, but not so high that it precludes the motivation to generate more substantial clinical evidence in exchange for increased financial payments. With manufacturers aware that more robust evidence can result in higher annual payments in contracts, they could be incentivized to pursue stronger preapproval evidence and/or to plan for evidence-gathering between contract cycles. Given the challenges of generating clinical superiority data, the federal government may wish to offer a much lower initial contract as a means of spurring the collection of additional evaluation data. Another option could stipulate the generation of additional evidence for contract extensions.

In the U.S. PASTEUR Act, the proposed contract values for a novel antimicrobial range from US\$75–\$300 million per year, paid over 10 years (U.S. Congress, 2021). A similar timescale could be considered for a Canadian SPI. As previously detailed, that total amount could vary over each contractual period in a Canadian SPI. Spreading payments over a decade increases budget predictability for governments, incentivizes manufacturers to demonstrate increased drug value, and protects governments from noncompliance with contractual terms (Chatham House, 2015; Rex & Outterson, 2016). However, ensuring drug availability following a funding cycle introduces additional considerations (Box 5.2).

Box 5.2 What Happens at the End of an Exclusivity Period?

Contracts are envisioned to last 10 years (roughly in line with a typical novel medicine exclusivity period). After the manufacturer loses exclusivity, if the supply of the antimicrobial is considered vulnerable and the drug still meets public health needs, a competitive tender process may be undertaken, with significantly reduced annual payments covering ongoing costs but not the original costs of R&D (Outterson *et al.*, 2011). The first SPI contract could give the Canadian government rights to exercise options to extend after the initial 10 years. These rights would mitigate the risk of a manufacturer potentially increasing prices on an in-demand drug at contract expiration, a situation exemplified in the context of COVID-19 vaccines in the U.S. (Lupkin, 2023).

It is possible that, after subscription payments have concluded, a manufacturer will no longer want to produce and stock a drug that offers public health value but is infrequently used and/or does not generate substantial sales revenue. While generic production might solve supply issues, such production may not occur if low sales revenue is expected. Revenue guarantee or subscription contracts can also stipulate that funded antimicrobials continue to exist on the market by slowly decreasing payments that would reach zero around the end of market exclusivity (Rex & Outterson, 2016). Strong stewardship practices established during the contractual period could be maintained after market exclusivity has ended (Morel *et al.*, 2020).

A multidisciplinary committee is a proven structure for assessing SPI eligibility and determining the appropriate incentive level for each antimicrobial

The Panel believes that, as with the U.K. subscription and the proposed U.S. PASTEUR Act, the most effective scenario for establishing antimicrobial eligibility and determining appropriate payment levels in Canada would rely on the creation of a special committee made up of diverse experts and relevant agencies. Committee expertise could include those with extensive knowledge and experience with health technology assessments (HTAs), price negotiations, and contract procurement processes, as well as health economists and experts in reimbursement. The committee could also include physicians, pharmacists, and epidemiologists with up-to-date knowledge of trends in resistant infections and treatment needs. With federal government involvement and oversight, this committee could create a novel modified HTA to determine drug value, from which contracts could then be negotiated with manufacturers.

Drug valuation aspects of pull incentives in the U.K. and in the proposed U.S. PASTEUR Act were addressed by committees made up of individuals with a wide range of expertise (U.S. Congress, 2021; Leonard *et al.*, 2023). The U.K.'s HTA processes for their pilot incentive were conducted by the National Institutes for Health and Care Excellence (NICE) and informed by specialists in medicine and public health (e.g., an antimicrobial pharmacist, a clinical microbiologist, and a professor of infectious diseases) (NICE, 2022d). In the proposed U.S. PASTEUR Act, the special committee establishing evaluation criteria would consist of at least one member from seven national agencies,¹⁷ with a further advisory committee that includes disciplinary experts and patients, and that is subject to strict financial conflict of interest rules (U.S. Congress, 2021). The Panel believes that much of the requisite expertise in Canada is already housed in current advisory bodies, including CADTH, INESSS, and the pCPA such that experts from these organizations could serve as valuable collaborators.

17 These seven agencies include: the National Institute of Allergy and Infectious Diseases, the Centers for Disease Control and Prevention (CDC), the Biomedical Advanced Research and Development Authority, the Food and Drug Administration, the Centers for Medicare & Medicaid Services, the Veterans Health Administration, and the Department of Defense (U.S. Congress, 2021).

Determining the appropriate value and corresponding subscription payment level for drugs will be a complex task requiring a collaborative effort from committee experts to develop and implement an effective framework. Indeed, incorporating



“Determining the appropriate value and corresponding subscription payment level for drugs will be a complex task requiring a collaborative effort from committee experts to develop and implement an effective framework.”

STEDI values was a complex endeavour in the U.K.’s pilot program (OHE, 2022). However complex, criteria do exist to conduct such evaluations. In the U.K.’s subscription program, which builds off the pilot, a points-based evaluation approach is applied to all eligible drugs, which are “scored against multiple clinical criteria that cover unmet clinical need (both globally and in the U.K.); relative effectiveness; pharmacological benefit (such as chemical novelty and absence of cross-resistance); and benefits to the health system (such as improved modes of delivery and dosing schedules, better tolerability and reduced monitoring requirements)” (Nick Crabb, personal communication, 2023). These evaluation scores will be used to inform the value of contracts offered to manufacturers (Nick Crabb, personal communication, 2023). In the Panel’s view, there is significant scope for collaboration with other countries implementing

their own pull incentives, including on the framework for determining value and payment level. Canada is well-positioned to learn from the U.K.’s valuation model and could potentially adapt this scoring system for the Canadian context (Dutescu & Hillier, 2021).

Collection of data on the use of subscription-funded antimicrobials within Canada’s healthcare systems can inform value-based pricing in contract extensions

It would be advantageous for the federal government, in collaboration with other actors in Canada’s healthcare systems, to gather real world data on its SPI-funded drugs. This would enable more accurate assessments of a drug’s clinical or STEDI values, and could play a role in supporting the collection of evidence following from approval processes (NICE, 2022a, 2022e). Real world data consist of, for example, data gathered from billing, claims, and electronic health records, and could be used to generate indicators of patient use and effectiveness (Wallach *et al.*, 2021). The development of more accurate and comprehensive data collection methods would enhance understanding of drug value and could thus inform contract renewals.

There are substantial challenges associated with collecting real world data in Canada. The existence of numerous healthcare systems across the country strains coordination efforts and data collection in this area (HealthCareCAN, 2016). Privacy laws, including those related to consent and confidentiality, complicate the collection, use, and disclosure of patient data at the provincial, territorial, and federal level (CCA, 2015).

The U.S. CDC has established mechanisms through which hospitals can report AMR trends and antimicrobial use (AMU) from acute care settings (Duke–Margolis Centre for Health Policy, 2021). Data from these mechanisms are helping build evidence on safety and effectiveness of new drugs. International clinical trial platforms, such as REMAP in the U.S. or RECOVERY in the U.K., provide examples of electronic data collection and aggregation tools that bring together disparate healthcare systems and jurisdictions (Duke–Margolis Centre for Health Policy, 2021; Seely & Fowler, 2022). In the U.S. context, questions have been asked about whether healthcare providers (i.e., clinics and hospitals) can be incentivized or compelled into reporting. For example, if access to new antimicrobials is granted (and paid for), what kinds of incentives or stipulations might generate better data-sharing participation (Duke–Margolis Centre for Health Policy, 2021)? Similar questions may be asked in relation to a Canadian SPI, especially given the challenges around collecting and sharing patient data in Canada (Pan-Canadian Health Data Strategy Expert Advisory Group, 2022). New initiatives in Canada, such as the Strategy for Patient-Oriented Research, the Health Data Research Network of Canada, and CADTH’s Post-Market Drug Evaluation Program, might play a role increasing health data collection and sharing (HDRN, 2020; CADTH, 2022a; Tricco *et al.*, 2022). Further lessons may be learned from other data collection initiatives in Canada, such as the use of oncology-focused outcomes-based agreements in Alberta, or the regulatory changes mandating the collection of socio-demographic data from COVID-19 positive people in Ontario (Abdi *et al.*, 2021; Cheung *et al.*, 2023).

5.4 Contractual Conditions

Contractual obligations for manufacturers are a critical component of SPI design. Ensuring drug availability and assisting with appropriate use practices are two important conditions that need to be established between the Government of Canada and drug manufacturers. In the U.K.’s pilot program and in the proposed U.S. PASTEUR Act, breaches of contract conditions could result in payment penalties or the termination of the contract (NHS, 2021b; U.S. Congress, 2021). Similar repercussions could be included in the Canadian SPI.

Compliance with access, stewardship, and reporting requirements can be effectively administered through clear contractual obligations

In Sweden, the U.K., and in the proposed U.S. PASTEUR Act, contractual conditions mandate that a company hold in stock a certain amount of the incentivized drug. For example, companies must accommodate a five-fold demand increase in the U.K.; ensure the supply chain will not be interrupted for more than 60 days in the U.S.; and stock supplies that are twice that of the previous quarter's sales and adequate for a minimum two week treatment course at each emergency hospital in Sweden (NHS, 2020b; PHAS, 2020; U.S. Congress, 2021).

In the proposed U.S. PASTEUR Act, an approved drug must be made available within 30 days of the first contract payment (U.S. Congress, 2021). In Sweden, manufacturers have three months to accumulate the required stock after contract initialization, and stock must be demonstrated before receiving compensation (PHAS, 2020). Program evaluations in Sweden highlighted difficulties in managing stock levels and avoiding waste (PHAS, 2023). Unused stock has been commonly observed in Sweden, but manufacturing and distribution agreements and regulations (specifically around labelling) have complicated the international distribution of these valuable drugs (PHAS, 2023). In the Panel's view, Canada's experiences with federal COVID-19 vaccine procurement could be instructional in adapting and incorporating contractual obligations into an SPI.

In the Panel's perspective, there is an ethical duty to ensure antimicrobial access for everyone in Canada. The *Pan-Canadian Action Plan on Antimicrobial Resistance* establishes equity as one of its guiding principles (PHAC, 2023). With respect to access, both in Sweden and in the U.K.'s pilot, a drug must be made available to patients within 24 hours of request (NHS, 2020b; PHAS, 2020). Given Canada's vast geography, along with current constraints within healthcare systems that prevent the timely delivery of care in remote areas, ensuring availability within such a timeframe might not be feasible. In an SPI, contracts would ideally stipulate a reasonable supply timeline calculated for the Canadian market, which could be adjusted, if necessary, over contract cycles. As outlined in the U.K.'s pilot, contracts can include consequences, such as financial penalties, if manufacturers fail to deliver drugs upon request within the agreed-upon timelines (NHS, 2021b).

Monitoring and reporting are core features of Sweden and the U.K.'s pull incentive approaches and the proposed U.S. PASTEUR Act (PHAS, 2020; NHS, 2021b; U.S. Congress, 2021). Along with monitoring and reporting on drug sales, manufacturer requirements in the U.K.'s pilot and in the proposed U.S. PASTEUR Act include identifying, tracking, and publicly reporting on resistance trends relevant to the incentivized antimicrobials (NHS, 2020b; U.S. Congress, 2021). Surveillance plays an essential role in measuring AMU and AMR, and allows for informed decision-making and policy setting (Section 6.3). Contracts offer an opportunity to stipulate manufacturer roles in these activities (Theuretzbacher *et al.*, 2017).

In an optimal SPI contract, manufacturers would be required to adhere to a set of antimicrobial stewardship guidelines to promote the appropriate use of their novel drug(s) across Canada. Promoting appropriate use helps sustain the effectiveness of novel antimicrobials (Theuretzbacher *et al.*, 2017). Appropriate use can be encouraged through enhanced diagnostics (Section 6.4), completion of use assessment reports, educational and communication strategies for relevant personnel, and by ensuring only licensed and trained healthcare professionals prescribe the drugs (Theuretzbacher *et al.*, 2017; NHS, 2021b). Prohibiting sales-based remuneration for manufacturer employees could further promote appropriate use and good stewardship practices, as salespeople would not be incentivized to promote use of a given drug (Dutescu & Hillier, 2021).

Additional considerations in contracts could pertain to manufacturers' international activities. For example, by facilitating equitable worldwide access to innovative drugs through public-private partnerships or by establishing working relationships with international and regional organizations to strengthen AMR-related stewardship and monitoring (Boluarte & Schulze, 2022). The proposed U.S. PASTEUR Act requires the submission by manufacturers of "a plan for registering their drug in additional countries where an unmet need exists" (U.S. Congress, 2021). Effective global access to innovative drugs can be enhanced by avoiding patent-based mark-ups, establishing prices comparable to similar drugs in respective markets, and strengthening supply chains to enable access (Rex & Outterson, 2016). Where excess stocks are generated, for example through stockpiling requirements of a pull incentive, manufacturers can be obligated to ensure safe disposal (Theuretzbacher *et al.*, 2017).

In the Panel’s view, enabling global access to drugs supported through a Canadian SPI is an important contractual consideration that requires collaboration from multiple actors. It may, for example, be valuable for a manufacturer to align efforts with organizations, such as GARDP or The Global Fund, the latter having highlighted fighting antimicrobial resistance as a component of its report on pandemic preparedness (The Global Fund, 2022). Contracts with manufacturers



“Indeed, implementation of an SPI will be a shared federal, provincial, and territorial responsibility, and therefore any SPI would need to be considered by all orders of government to determine responsibilities relating to specific aspects of implementation, procurement, and delivery.”

could include plans for international actions and financial penalties for a failure to adhere to such plans. The Panel notes with approval the voluntary license for cefiderocol that was granted by Shionogi to GARDP, which supports access to, and stewardship of, the drug in more than 130 low- and middle-income countries (GARDP, 2022a).

While additional clinical data post eligibility would be beneficial, in the Panel’s view, it would not be realistic or financially feasible for SPI contracts to mandate the generation of clinical data post eligibility. For example, clinical trials post eligibility are not explicitly mandated in the proposed U.S. PASTEUR Act or the U.K. pull incentive. However, the

former states that “a contract may authorize the contractor to use funds made available under the contract for completion of post marketing clinical studies, manufacturing, and other preclinical and clinical efforts” (U.S. Congress, 2021).

5.5 Considerations for Implementing, Monitoring, and Evaluating an SPI

An SPI, like any new program, will have implementation challenges. Though it could not consider an exhaustive list, the Panel discussed some salient challenges that it believes will accompany the creation and implementation of an SPI. As with the U.K.’s subscription program, an SPI would represent a somewhat uncommon contractual initiative between the Government of Canada and manufacturers, necessitating specific contractual and legislative expertise (OHE, 2022). Complex administrative and legal hurdles may emerge for both government and the manufacturers. Further, challenges among federal, provincial, and territorial governments and healthcare providers may manifest when it comes to transmitting

knowledge, for example, regarding treatment options, use guidelines, and therapeutic implementation (e.g., enabling use through formularies). Measurable SPI program goals will need to be established early in the program design to support program evaluation. Data collection capacity will be needed to accurately assess AMU and resistance in relation to the antimicrobials included in an SPI. These data could help determine the use, effectiveness, and resistance relating to the incentivized antimicrobial, and be used to monitor changes in these metrics over time.

An SPI as described in this chapter involves sharing of sales and use data across numerous payers and healthcare providers. Such a system would need to be designed, implemented, and monitored for evaluative purposes. Indeed, implementation of an SPI will be a shared federal, provincial, and territorial responsibility, and therefore any SPI would need to be considered by all orders of government to determine responsibilities relating to specific aspects of implementation, procurement, and delivery. All these considerations were judged to be of great importance by the Panel, but beyond the scope and expertise of its work.

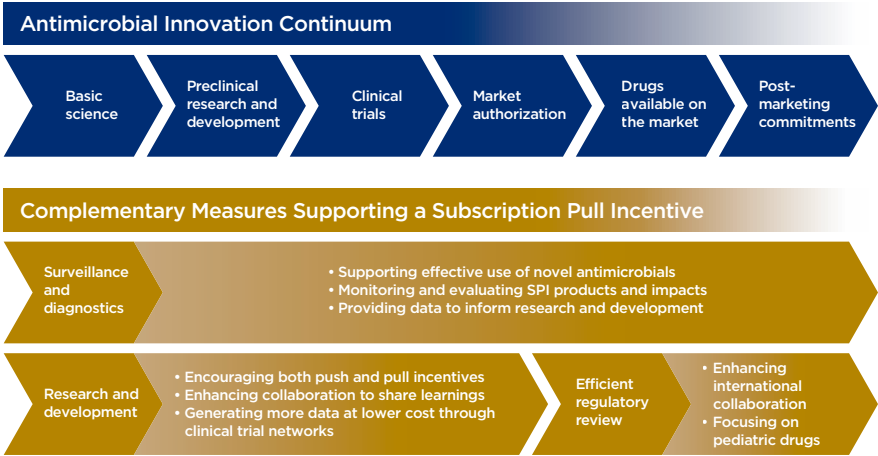
Complementary Measures to Support a Successful Pull Incentive

- 6.1 Research and Development
- 6.2 Regulatory Review
- 6.3 Surveillance
- 6.4 Diagnostics

Chapter Findings

- Sustained and directed funding for antimicrobial R&D through push incentives would support a robust pipeline of novel therapies.
- Enhanced international collaboration could improve the efficiency of regulatory review without compromising rigour.
- Improved pan-Canadian surveillance on antimicrobial resistance and use could provide valuable information for policy-makers.
- Fast and reliable diagnostic tests support the appropriate use of novel antimicrobials and can also improve the efficiency of clinical trials.

The challenge of antimicrobial resistance (AMR) requires a multifaceted response (PHAC, 2023). The Government of Canada’s 2023 *Pan-Canadian Action Plan on Antimicrobial Resistance*, which is grounded in a One Health approach, consists of five pillars: research and innovation, surveillance, stewardship, infection prevention and control, and leadership (PHAC, 2023). The Panel noted several core strategies that are particularly complementary to the establishment of pull incentives — supporting the antimicrobial R&D pipeline, facilitating efficient regulatory review of novel antimicrobials, assessing needs and trends in antimicrobial use (AMU) and resistance through surveillance, and supporting effective usage through diagnostics (Figure 6.1)



Adapted from Årdal et al. (2018)

Figure 6.1 Complementary Measures Supporting a Subscription Pull Incentive (SPI)

The success of an SPI can be enhanced through several complementary measures. The gold boxes highlight these measures, identifying key elements of each and how they relate to different stages of drug development.

6.1 Research and Development

A strong upstream R&D system is essential to the development of novel antimicrobials (PHAC, 2023). Financing upstream R&D complements the downstream funding of novel antimicrobials through a pull incentive. Strengthening clinical trial networks both in Canada and abroad could play an impactful role in generating antimicrobial evidence while reducing costs.

Push and pull incentives work in tandem to enhance the availability of novel antimicrobials

A combination of push and pull incentives is necessary to support the development of novel antimicrobials (Section 3.1). Push incentives in the form of grants are well-established and widely used. Towse and Silverman Bonnifield (2022) note that “push approaches can also be politically attractive to government funders, as the governments’ financial burden is self-limiting; research initiatives get underway with immediate effect; and funding typically offers direct support to domestic universities, non-profits, or companies.” Drawbacks of push incentives include the requirement that funders pick winners early, the potential distortions of the market, and the potential to continue investments in projects even when they show limited prospects for success (Kosiak & Silverman, 2021).

Several push incentives focused on AMR exist internationally, including CARB-X and GARDP. Canada has made financial contributions to both CARB-X and GARDP (GC, 2022a, 2023c). Canada is also a member of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), which coordinates R&D investments on behalf of its members (JPIAMR, 2022, 2023). The REPAIR Impact Fund invested in early-stage therapies with support from the Novo Nordisk Foundation, while the AMR Action Fund is a public-private partnership investing in therapeutics initiated



“Increased basic and translational research funding in Canada can build on existing and successful Canadian research and improve the quality of projects that may eventually be SPI eligible.”

by the International Federation of Pharmaceutical Manufacturers and Associations, the WHO, the European Investment Bank, and the Wellcome Trust (AMR Action Fund, 2023; REPAIR Impact Fund, 2023). In Canada, there are no targeted programs to encourage antimicrobial R&D, but researchers can access grants through a number of research programs (e.g., federal granting agencies, Fonds de recherche du Québec) (Global AMR R&D Hub, 2023). Canada’s leading centres of expertise in this area are housed at post-secondary institutions (Box 6.1).

The Global AMR R&D Hub’s Dynamic Dashboard indicates that Canadian funding is enabling over 750 AMR-related research projects, with roughly \$188 million in funds committed by various federal and provincial funding bodies (Global AMR R&D Hub, 2023).¹⁸ Seventy-six percent of the projects (and a corresponding 83% of the funds) are focused on AMR in humans. These results, however, compare unfavourably to many other high-income countries. Australia, the U.K., the U.S., and numerous European nations are

18 The Dashboard includes projects that were ongoing in 2017 or commenced since that time; its limitations include lack of information about private sector investment (Global AMR R&D Hub, 2020).

all funding AMR research at a higher level on a per capita basis. Canada is a net recipient of funding from abroad (Global AMR R&D Hub, 2023). Increased basic and translational research funding in Canada can build on existing and successful Canadian research and improve the quality of projects that may eventually be SPI eligible.

Box 6.1 Antimicrobial Development Research in Canada

Canada is among the top 10 funders of antimicrobial R&D globally (Global AMR R&D Hub, 2023). Canada is training students at all levels – undergraduate, masters, and doctoral – in antimicrobial discovery. This university-focused approach results in the development and examination of truly innovative treatments because these are the most exciting from an academic perspective. This is a global win-win situation. R&D spending has the potential to lead to tomorrow's antimicrobials (and prospective future recipients of a subscription contract). If these investments fund clinical trials, there could be a commensurate reduction in Canada's subscription costs, as clinical trial expenses can be used to lower subscription payments.

Enhanced collaboration could accelerate progress in antimicrobial R&D

Efforts are being made to encourage greater dissemination of research findings in the antimicrobial R&D space, particularly in terms of sharing experiences of failure (where there is less of a risk of losing competitive advantage) (CARB-X, 2018). The Pew Charitable Trust's Shared Platform for Antibiotic Research and Knowledge is designed to facilitate information sharing in the R&D space while safeguarding intellectual property (Prosen *et al.*, 2019). The Community for Open Antimicrobial Drug Discovery provides researchers with access to free screening for detection of antimicrobial activities in existing chemical compounds, which can support the identification and development of novel antimicrobials (CO-ADD, n.d.). The SECURE initiative, a collaborative effort from Global Antibiotic Research and Development Partnership (GARDP) and the WHO, strives to generate increased global access to essential antibiotics (SECURE, n.d.).

The Innovative Medicines Initiative established a New Drugs for Bad Bugs program to bring together private and public sector actors to make advancements in the field, while the ENABLE project established a European consortium of academics and pharmaceutical companies to collaborate on creating novel antimicrobials between 2014 and 2021 (ND4BB, 2021, 2023). GARDP’s “5 by 25” goal of bringing five novel antimicrobials to market by 2025 also recognizes the need for collaboration to bring all the pieces of the puzzle together (GARDP, 2019).

Other efforts go further, such as calling for a completely public and open approach to antimicrobial R&D. Referred to as *open science*, these strategies stress the need for openly accessible data sets, tools, and materials, and eschew the creation of intellectual property (e.g., patents) to reduce research barriers and enhance knowledge sharing (Bubela *et al.*, 2020; Gold & Edwards, 2022). Open science has the potential to play a role in public health, including AMR-related drug development, by developing antimicrobials to the end of the phase 1 clinical trial stage (Huston *et al.*, 2019; Bubela *et al.*, 2020; Gold & Edwards, 2022). Certain open science strategies could therefore act like push mechanisms, while others could co-exist alongside market systems, or even replace them (Klug *et al.*, 2021).

Glover *et al.* (2021) have argued for developing novel antimicrobials using a Networked Institute Model, a public model that could create trial facilities, offer patent buyouts, diversify manufacturing sites, and support the development of academic expertise by providing greater recognition of innovations originating in academia. Greater scientific openness could improve efficiency and cross-fertilization, and better address access inequities across countries (Singer *et al.*, 2020). Open science approaches can also create greater opportunities for participation among diverse actors, notably academics, governments, and non-profit entities, and such efforts might hasten research developments at reduced costs (Bubela *et al.*, 2020; Gold & Edwards, 2022). The notion, however, of non-profit entities replacing private actors in the antimicrobial space — and doing so at reduced costs for governments — remains speculative, especially given the ongoing financing required to achieve market stability over longer timeframes (Outtersson & Rex, 2020).

Clinical trial networks could serve both regulators and manufacturers by generating better data at lower cost

Clinical trials have been identified as a key challenge in the deployment of novel antimicrobials. O’Neill (2016) reports that over “80 percent of the costs of bringing an antibiotic to market are related to clinical trials, or 65 percent of the cost when you adjust for the risk of failure.” Reforms that improve the efficiency and practicality of clinical trials could have a meaningful impact. O’Neill (2016) also notes the challenges of enrolling sufficient patient populations with drug-resistant infections — a challenge made more difficult by a lack of suitable diagnostics. Unlike other fields, such as oncology, the concentration of expertise in a few key locations is impractical when it comes to infectious diseases.

Hospitals are highly motivated to prevent and eliminate AMR infections; as well, the timeliness of interventions is essential, thus moving patients to a centre of excellence can create significant risks (McDonnell *et al.*, 2016). Running sufficiently large trials in this context requires the participation of dozens of hospitals and takes many months to initiate (O’Neill, 2016).



“Unlike other fields, such as oncology, the concentration of expertise in a few key locations is impractical when it comes to infectious diseases.”

The creation of stable clinical trial networks has been identified as one promising innovation to address this challenge. McDonnell *et al.* (2016) suggest creating distinct networks for each of the following infections: complicated urinary tract infections, complicated intra-abdominal infections, hospital- or ventilator-associated bacterial pneumonia, community-acquired bacterial pneumonia, and acute bacterial skin or skin

structure infections. Within a stable clinical trial network, comparator drugs could remain in use. These would form a stable control arm, and trial drugs could be rotated in and out over time. Such a network would also cut the number of patients needed per clinical trial, reducing time and costs by 30–40%. In addition, the time needed to recruit hospitals and provide necessary training is significant — a pre-existing network could offer time savings of three to six months (McDonnell *et al.*, 2016). Such clinical trial networks are now operational in Asia, helping to lower costs and generate increased collaboration across multiple regions, while reducing inefficient duplicate studies (Wellcome Trust, 2020). The Panel anticipates that these trials will provide richer clinical evidence to inform clinicians as well those assessing the value of these new antimicrobials.

Canada does not currently have an effective clinical trials network, and developing one presents significant challenges given divisions among regional healthcare systems, insufficient pan-Canadian data collection and data sharing mechanisms, and a lack of stable funding (Chorhenki *et al.*, 2020; Lamontagne *et al.*, 2021; Seely & Fowler, 2022). New initiatives are being funded, however, such as the Accelerating Clinical Trials Consortium, which strives to enhance and expand upon Canada's current networks (GC, 2023a). Further initiatives undertaken by the Canadian Critical Care Trials Group have been successful in increasing capacity, and lessons could be learned from international programs, such as the U.K.'s RECOVERY program. This program was established during the COVID-19 pandemic and conducted therapeutic trials based on increased contributions of patient-level data from hospitals (Marshall & Cook, 2009; Murthy *et al.*, 2020; Seely & Fowler, 2022). Health Canada is in the process of modernizing clinical trial regulations, striving to better regulate risk, increase transparency, improve alignment with international efforts, generate increased public participation, and improve access to novel treatments (GC, 2022c).

Across numerous health fields, but especially for AMR and antimicrobial prescribing — where use will be low and geographically dispersed — unified, transparent, easily accessible pan-Canadian databases would be advantageous (Murthy *et al.*, 2020; Van Katwyk *et al.*, 2020). Database development, along with increased research collaboration and coordination, requires social and technological unification within and across jurisdictions (Chorhenki *et al.*, 2020; Lamontagne *et al.*, 2021; Seely & Fowler, 2022). Strengthening a Canadian research network would generate better evidence-informed healthcare outcomes, including for marginalized and underrepresented communities, and may also do so with greater cost-effectiveness (Lamontagne *et al.*, 2021; Sundquist *et al.*, 2021).

International clinical trial networks could enhance the participation of low- and middle-income countries, supporting the development of drugs that meet their needs, fostering domestic capacity, and lowering the costs of clinical trials (O'Neill, 2016). However, a lack of consistency in regulatory requirements across jurisdictions along with restrictions on data sharing are key limiting factors (Wellcome Trust, 2020). Enabling increased collaboration, transparency, and data-sharing among international actors through globally focused policies — for example, increased use of trial registries, transparent reporting, open-source publishing, and coordinated research directives — augments the potential to tackle AMR more effectively (Van Katwyk *et al.*, 2020).

6.2 Regulatory Review

Regulatory review requirements contribute to the costs of commercializing novel antimicrobials. When the regulatory burden is lowered, the expected net present value of investments in novel antimicrobial development increases accordingly, thereby encouraging more activity in the field (Sertkaya *et al.*, 2014). Clinical trial requirements have already been adjusted to accommodate the challenge of establishing superiority for this type of drug (Section 2.1), and further reductions in regulatory requirements could create unacceptable risks (Chatham House, 2015). However, there are other ways to assess conformity with existing regulatory requirements that may be more efficient.

Enhanced international collaboration in regulatory review could provide efficiencies without compromising on safety

Regulatory reliance processes that allow regulators to leverage the work of other regulatory agencies (rather than duplicating the work) could ease the workload for regulators and applicants while speeding up patient access to new treatments (Doerr *et al.*, 2020). Reliance processes have broad support but require trust and harmonization to succeed (Doerr *et al.*, 2020).

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), whose members include the U.S., Japan, Canada, and the European Commission, brings together regulators and pharmaceutical developers to support efficient regulatory review of new medicines to determine whether they are safe, efficacious, and high quality (ICH, n.d.-b, n.d.-c). Draft guidelines are revised based on consultation with regulatory authorities in ICH regions (ICH, n.d.-a). Implementation of these guidelines in Canada ensures regulatory requirements consistent with other ICH members. Canada is also member of the Access Consortium, along with Australia, Singapore, Switzerland, and the U.K. (GC, 2022b). The governments of these countries work together to align regulatory approaches and reduce duplication through enhanced sharing and collaboration; they also explore ways to extend this cooperation into health technology assessments (HTAs) (GC, 2022b).

Health Canada has established four Mutual Recognition Agreements to improve coordination among international regulatory authorities in Australia, Switzerland, the countries in the European Free Trade Association (Iceland, Liechtenstein, and Norway), and the E.U. member states under the Comprehensive Economic Trade Agreement (CETA) (HC, 2021c). These agreements establish the presence of equivalent drug compliance programs through reviews of legislation and guidelines. Thus, Good Manufacturing Practices certification of a manufacturer by one country is recognized by the other (HC, 2021c). Streamlining review process through enhanced cooperation with international regulatory authorities can help expedite processes and increase efficiencies, which could support the timely launch of new SPI-qualifying antimicrobials in Canada.

Enhancing pediatric focus in regulatory review processes generates increased access to and appropriate use of novel drugs in younger populations

Internationally, bacterial infections in the form of pneumonia, neonatal sepsis, and gastrointestinal infections result in substantial childhood mortality, and yet access to antimicrobials for younger populations is particularly lacking (WHO, 2022a). Indeed, regulatory processes in Canada and abroad do not adequately encompass administration for pediatric populations (Gilpin *et al.*, 2022; WHO, 2022a). As in other jurisdictions, off-label drug use is widely prescribed for Canadian children, yet Canada's support for up-to-date educational materials and pediatric formulations lags behind the U.S. and European countries (CCA, 2014; Yackey *et al.*, 2019; Gilpin *et al.*, 2022). The U.S. and E.U. have developed strategies that mandate pediatric studies by industry through the U.S. FDA's Pediatric Research Equity Act and the E.U.'s Paediatric Investigation Plans (FDA, 2019; Gilpin *et al.*, 2022; EMA, 2023b). In contrast, Canada's regulatory framework neither obligates nor incentivizes industry to update monographs with new efficacy or safety data, to market the pediatric formulations from trusted international jurisdictions, or to research pediatric indications and develop formulations where use among children is forecasted (Gilpin *et al.*, 2022). Increasing pediatric access to innovative antimicrobials strengthens an SPI's objective of ensuring universal access and addressing unmet global health needs.

6.3 Surveillance

Surveillance activities identify trends in AMR and AMU and track the emergence and spread of different infections of concern. Global surveillance efforts track international trends and offer early warning signs for future resistance trends (WHO, 2022e). The WHO's 2022 *Global Antimicrobial Resistance and Use Surveillance System (GLASS)* report detailed how antimicrobial consumption is a key AMR driver, and how challenges persist around accurately surveying AMR on a global level, particularly in low-resource settings (WHO, 2022e). The ongoing assessment of AMR and AMU in Canada can be strengthened by a comprehensive pan-Canadian surveillance system that extends beyond large hospitals to incorporate community settings, including in rural and remote areas (Somanader *et al.*, 2022).

New and strengthened initiatives could enhance Canada's AMR surveillance system

Understanding AMR in Canada requires a One Health approach, which incorporates surveillance data from humans, animals, and the environment (GC, 2017; PHAC, 2023). Canada's AMR surveillance has been described as “patchy,” carried out “at a variety of sites, under different jurisdictions, with various criteria, for different purposes, and at different levels of sophistication or development” (Haworth-Brockman *et al.*, 2021). Surveillance efforts quantify AMU in humans, but gaps remain around evaluating the appropriateness of that use (HealthCareCAN, 2016; Schwartz *et al.*, 2019). There is a need for standardized reporting metrics across all prescribing facilities, including hospitals, pharmacies, dental clinics, and long-term care facilities (HealthCareCAN, 2016).

The annual *Canadian Antimicrobial Resistance Surveillance System (CARSS)* report assesses trends in AMR and AMU by using purchases from healthcare sectors and antibiotic prescriptions dispensed in the community as proxies, compiling data from multiple surveillance initiatives and focusing on a One Health perspective (PHAC, 2022). Resistance rates are reported over time across several pathogens, supporting analysis of trends. AMU is inferred based on sales data.

Data on antimicrobial prescribing practices are essential for understanding the appropriateness of AMU in Canada. The National Antimicrobial Prescribing Survey (NAPS) was developed in Australia in 2013 as a means of collecting qualitative data about antimicrobial prescription decisions in hospitals, and of assessing the appropriateness of the prescription based on patient data (James *et al.*, 2022). Beginning in 2018, NAPS was introduced as a pilot in acute care facilities in Canada to document antimicrobial prescribing practices, quantify national AMU, and assess

the appropriateness of prescribing behaviour (BD, 2019). NAPS supplements other data sources included in CARSS by providing hospital-level insights on the appropriateness of AMU (PHAC, 2022). By the end of 2022, NAPS surveillance extended to 119 facilities from all provinces, including 12 pediatric academic hospitals. Facilities, however, included only hospital and not community settings, while data were almost exclusively based on a one-day audit performed during the calendar year (PHAC, 2022). There is scope to strengthen the NAPS to provide more detailed surveillance data, which could inform domestic policy-making in general, as well as the eligibility criteria and evaluation of an SPI in particular.

6.4 Diagnostics

Diagnostics are an essential tool for ensuring appropriate AMU. Diagnostic tests can be used broadly to determine whether an infection is bacterial or viral, or more specifically to determine whether bacteria causing an infection are susceptible to a particular drug (O'Neill, 2015a). The *Pan-Canadian Action Plan on Antimicrobial Resistance* notes the importance of incentivizing enhanced access to diagnostics (PHAC, 2023). A host of pertinent issues accompany the need for effective diagnostic tools, the vast majority of which were deemed by the Panel to be beyond the scope of this assessment. These include distinct market failures, stewardship, and other cost-related considerations that impact availability and use of diagnostics. Evidence on these issues is limited. The practice of susceptibility testing versus empirical prescribing, however, is highly relevant to an SPI and is considered below.

In the absence of rapid and reliable diagnostic testing, prescribing without confirmation of infection type is widespread

A combination of relatively expensive diagnostics, cheap antibiotics, and the time lag between submitting testing samples and receiving laboratory results encourages physicians to prescribe without diagnostics (O'Neill, 2016). The drawbacks of such empirical prescribing practices include overreliance on broad-spectrum antibiotics, failure to use the most appropriate treatment in a timely manner, unnecessary prescribing (e.g., for primary viral infections), adverse effects associated with treatment, and contributing to AMR (Outterson *et al.*, 2011; O'Neill, 2015a; Payne *et al.*, 2015). For example, gonorrhea infections illustrate the pressure an absence of diagnostics can place on reserve antibiotics. While 70% of gonorrhea cases are susceptible to older antibiotics, the lack of rapid tests to indicate drug susceptibility results in physicians in the U.K. “prescrib[ing] the last

line of defence against gonorrhoea, which is a combination of two different drugs from different antibiotic classes” (O’Neill, 2015a). This practice creates a selective pressure that can foster more drug-resistant cases of gonorrhoea (O’Neill, 2015a). An analysis of respiratory infections in the U.S. found that roughly two-thirds of patients who were prescribed antibiotics had illnesses for which those drugs were unlikely to provide any therapeutic benefit (Shapiro *et al.*, 2013). In the Panel’s experience, prescribers in Canada will often order lab cultures that test for susceptibility against a panel of potential treatment options (i.e., an antibiogram), but start treatment empirically while awaiting laboratory results. This practice may be even more common in community settings, where prescribers usually rely on slower laboratory testing services.

Effective and affordable rapid diagnostics are needed to support the appropriate use of novel antimicrobials

Improved reliance on diagnostics would enhance the impact of an SPI, as prescribers would be guided toward appropriate and timely use of novel therapies. When available, point-of-care resistance diagnosis identifies patients for whom



“When available, point-of-care resistance diagnosis identifies patients for whom a novel antibiotic would be effective, thereby increasing the value of those drugs (McAdams, 2017).”

a novel antibiotic would be effective, thereby increasing the value of those drugs (McAdams, 2017). Conversely, the absence of an appropriate diagnostic test can slow the uptake of a new antimicrobial (PACCARB, 2017).

In the U.S., the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria recommends that “development of new antibiotics should always include the development of a concomitant rapid AST [antimicrobial susceptibility test] device” (PACCARB, 2017). As O’Neill (2015a) notes, “rapid diagnostics can reduce the cost of clinical trials for narrow-spectrum drugs by making it easier to find patients who have a potentially susceptible infection of interest and therefore reducing the number of patients that need

to be screened to join a trial.” Thus, the availability of diagnostic tests in time for a phase 3 clinical trial could be valuable in reducing the enrollment numbers required to satisfy regulatory requirements (Payne *et al.*, 2015).

Rapid tests can be particularly valuable for informing time-sensitive prescribing decisions (Payne *et al.*, 2015). Timeliness of diagnostics is recognized as a key element of successful therapy as delayed tests tend not to be clinically useful. Barbut *et al.* (2014) found that faster diagnostics lead to more timely access to appropriate therapies, fewer hospitalizations, and fewer health harms. Timely treatment of serious infections is critical in minimizing morbidity and mortality, so tests that take days to complete are often not viable (Barbut *et al.*, 2014; Savage *et al.*, 2016). In the case of serious infections, Rice (2011) suggests that diagnostic tests that can rule out specific pathogens (i.e., high specificity tests)¹⁹ would provide the most value. Without full assurance that an antibiotic would not provide any benefit, physicians are inclined to prescribe on the basis that the drug is safe and *may* provide some benefit.

However, enhanced reliance on diagnostics may have the unintended consequence of driving up prescribing (Morado & Wong, 2022). Diagnostic tests — particularly rapid tests, which tend to be more sensitive — can determine whether an organism is present, but not whether it is causing disease (Curren *et al.*, 2022). Diagnostic stewardship calls for “ordering the right tests for the right patient at the right time to provide information necessary to optimize clinical care” (Curren *et al.*, 2022). The Choosing Wisely initiative was established to avoid unnecessary and unhelpful patient care (Choosing Wisely, 2023a). It has amassed a large set of recommendations designed to avoid unnecessary antibiotic usage, which could be informative in this space (Choosing Wisely, 2023b).

¹⁹ High *specificity* tests are those that accurately provide a negative result when a patient does not have the disease (i.e., they can reliably rule out specific pathogens). High *sensitivity* tests are those that accurately yield a positive test result when a patient has the disease (O’Neill, 2015b).

7

Final Reflections

Main Report Findings

- Weak commercialization prospects impede the development of novel antimicrobials, creating risks and harms for people in Canada and around the world.
- Governments can improve the market for novel antimicrobials by offering pull incentives to manufacturers.
- Canada has the opportunity to work with a group of other high-income countries to contribute its fair share to an adequate global pull incentive.
- Complementary policies that foster upstream R&D through push incentives, facilitate efficient regulatory review, provide necessary surveillance data, and bolster the supply of rapid diagnostics will improve the success of a subscription pull incentive.

Antimicrobial resistance (AMR) has been acknowledged in Canada and internationally as a serious and growing global threat to public health. Rates of resistance are increasing for most priority pathogens in Canada: there is an increasing frequency of infections that do not respond to first-line and even subsequent antimicrobial treatment options. The domestic and global health community has been encouraged to take significant action in order to avoid a future where many infections can no longer be treated and where routine health interventions are increasingly avoided. AMR puts all people in Canada at risk, particularly those who are immunocompromised and thus most susceptible to infections. The imperative for action is well recognized. Both the 2019 and 2021 mandate letters from the Prime Minister of Canada call on the Minister of Health

to respond to the threat of AMR, with the 2021 letter instructing the Minister to “work with partners to take increased and expedited action to monitor, prevent and mitigate the serious and growing threat of antimicrobial resistance and preserve the effectiveness of the antimicrobials Canadians rely upon every day” (PMO, 2019, 2021).

The current pipeline will not meet the future needs of people in Canada and around the world. The antimicrobials that have recently come to market are not filling the greatest unmet needs. However, even a highly effective novel antimicrobial would



“AMR puts all people in Canada at risk, particularly those who are immunocompromised and thus most susceptible to infections.”

struggle to maintain financial viability under current circumstances. Pull incentives are crucial policy tools for encouraging access to novel antimicrobials that can meet the needs of patients in Canada today, tomorrow, and for future generations. While their financial costs are not insignificant, such costs are smaller than the public health benefits created by novel antimicrobials. A carefully designed and diligently executed Canadian pull incentive — one that protects public value by paying only for the antimicrobials that address unmet needs — is the best way to balance the risks and rewards of supporting the antimicrobial pipeline and securing access for all people in Canada. Ensuring the effectiveness of novel antimicrobials would be a key element of the program.



“A carefully designed and diligently executed Canadian pull incentive — one that protects public value by paying only for the antimicrobials that address unmet needs — is the best way to balance the risks and rewards of supporting the antimicrobial pipeline and securing access for all people in Canada.”

Paying only for drugs that would treat infections of concern in Canada means developing eligibility criteria that demand compelling evidence of the effectiveness of new treatments while recognizing the constraints of clinical trials in this space. Canada has the opportunity to join with other G7 countries as they establish and evaluate their own pull incentives, and to provide leadership in addressing this global health challenge by stimulating the development of novel antimicrobials while securing access for patients in Canada.

AMR is a complex challenge that calls for a multifaceted response. One aspect of a comprehensive solution is the development and deployment of new drugs that can treat resistant infections. Policy makers have the means to build a future with a strong pipeline of novel antimicrobials, where enhanced diagnostic tools guide clinical decisions, high-income countries work more closely with low- and middle-income countries to improve antimicrobial stewardship and

equity in antimicrobial availability, and patients learn how to reduce infection risks and use antimicrobials appropriately. Canada has an opportunity to be a leader in addressing this global collective-action challenge. As a high-income country that has made international and domestic commitments to confront AMR, it has the means to establish a long-term pull incentive to catalyze action among antimicrobial developers and other high-income countries.

References

- Abdi, S., Bennett-AbuAyyash, C., MacDonald, L., Hohenadel, K., Johnson, K. O., & Leece, P. (2021). Provincial implementation supports for socio-demographic data collection during COVID-19 in Ontario's public health system. *Canadian Journal of Public Health*, 112(5), 853-861.
- Adedeji, W. A. (2016). The treasure called antibiotics. *Annals of Ibadan Postgraduate Medicine*, 14(2), 56-57.
- AMR Action Fund. (2023). About. Retrieved January 2023, from <https://www.amractionfund.com/about>.
- AMR Action Podcast. (2022). *Episode 5: Hailey Laxer and Kristine Russell*. n.l.: Canadian Antimicrobial Innovation Coalition.
- Andermann, A. (2017). Outbreaks in the age of syndemics: New insights for improving Indigenous health. *Canada Communicable Disease Report*, 43(6), 125-132.
- Anderson, M., Wouters, O. J., & Mossialos, E. (2022). Transferable exclusivity extensions to stimulate antibiotic research and development: What is at stake? *Lancet Microbe*, 4(3), E127-128.
- Armstrong, G. L., Conn, L. A., & Pinner, R. W. (1999). Trends in infectious disease mortality in the United States during the 20th century. *JAMA*, 281(1), 61-66.
- ATIH (Agence technique de l'information sur l'hospitalisation). (2023). Unités communes de dispensation prises en charge en sus: Mise à jour. Retrieved March 2023, from <https://www.atih.sante.fr/unites-communes-de-dispensation-prises-en-charge-en-sus>.
- Bailey, J., Morris, A., & Bean, S. (2021). Evidence-based recommendations on the use of casirivimab+ imdevimab, and sotrovimab for adults in Ontario. *Science Briefs of the Ontario COVID-19 Science Advisory Table*, 2(45), 1-20.
- Baker, S. J., Payne, D. J., Rappuoli, R., & De Gregorio, E. (2018). Technologies to address antimicrobial resistance. *PNAS*, 115(51), 12887-12895.
- Barbut, F., Surgers, L., Eckert, C., Visseaux, B., Cuingnet, M., Mesquita, C., . . . Lalande, V. (2014). Does a rapid diagnosis of *Clostridium difficile* infection impact on quality of patient management? *Infectious Diseases*, 20, 136-144.
- BCG (Boston Consulting Group). (2017). *Breaking Through the Wall: A Call for Concerted Action on Antibiotics Research and Development*. Berlin, Germany: German Federal Ministry of Health.
- BD (Becton, Dickinson and Company). (2019). Canadian National Antimicrobial Prescribing Survey: A Pilot Initiative. Retrieved November 2022, from <https://www.bd.com/en-ca/company/news-and-media/press-releases/mar-19-2019-canadian-national-antimicrobial-prescribing-survey--a-pilot-initiative>.
- Beasley, D. (2014, April 22). Gilead Profit Triples, Hepatitis C Drug Sales Beat by \$1 Billion, *Reuters*.

Overcoming Resistance

- Bhatti, T., Lum, K., Holland, S., Sassman, S., Findlay, D., & Outterson, K. (2018). A perspective on incentives for novel inpatient antibiotics: No one-size-fits-all. *Journal of Law, Medicine & Ethics*, 46(1_suppl), 59–65.
- Boluarte, T. & Schulze, U. (2022). *The Case for a Subscription Model to Tackle Antimicrobial Resistance*. Boston (MA): Boston Consulting Group.
- Boucher, H. W., Ambrose, P. G., Chambers, H. F., Ebricht, R. H., Jezek, A., Murray, B. E., . . . Rex, J. H. (2017). White paper: Developing antimicrobial drugs for resistant pathogens, narrow-spectrum indications, and unmet needs. *Journal of Infectious Diseases* 216(2), 228–236.
- Brandt, J., Shearer, B., & Morgan, S. G. (2018). Prescription drug coverage in Canada: A review of the economic, policy and political considerations for universal pharmacare. *Journal of Pharmaceutical Policy and Practice*, 11(28), 1–13.
- Breijyeh, Z., Jubeh, B., & Karaman, R. (2020). Resistance of Gram-negative bacteria to current antibacterial agents and approaches to resolve it. *Molecules*, 25(6), 1340.
- Brennan, M., Williams, M. P., & Hsu, I. (2022). *Models for Financing Antibiotic Development to Address Antimicrobial Resistance*. Santa Monica (CA): Milken Institute.
- Bubela, T., Gold, E. R., Goel, V., Morgan, M., Mossman, K., Nickerson, J., . . . Edwards, A. M. (2020). Open drug discovery of anti-virals critical for Canada's pandemic strategy. *Facets*, 5, 1019–1036.
- Burke, N., Bowen, J. M., Troyan, S., Jegathisawaran, J., Gosse, C., Tonkin, M., . . . Holbrook, A. (2016). Management of hospital formularies in Ontario: Challenges within a Local Health Integration Network. *Canadian Journal of Hospital Pharmacy*, 69(3), 187–193.
- Burrows, L., Iorio, A., Loeb, M., McCarles, J., Miyai, W., Peters, D., . . . Wright, G. D. (2021). *Antibiotic Access and Capacity*. Hamilton (ON): McMaster University, Canadian Antimicrobial Innovation Coalition.
- Burrows, L. (2022). Analysis: Why Canada Hasn't Been Getting the New Antibiotics We Need to Fight Drug-Resistant 'Superbugs'. Retrieved March 2023, from <https://brighterworld.mcmaster.ca/articles/analysis-why-canada-hasnt-been-getting-the-new-antibiotics-we-need-to-fight-drug-resistant-superbugs/>.
- Bush, L. M. (2022). Overview of Gram-Negative Bacteria. Retrieved May 2023, from <https://www.merckmanuals.com/en-ca/home/infections/bacterial-infections-gram-negative-bacteria/overview-of-gram-negative-bacteria>.
- Bush, L. M. (2023). Overview of Gram-Positive Bacteria. Retrieved May 2023, from <https://www.merckmanuals.com/en-ca/home/infections/bacterial-infections-gram-positive-bacteria/overview-of-gram-positive-bacteria?query=gram%20positive>.
- CADTH (Canadian Agency for Drugs and Technologies in Health). (2015). *Hospital Formularies Decision-making Processes*. Ottawa (ON): CADTH.
- CADTH (Canadian Agency for Drugs and Technologies in Health). (2017). *Guidelines for the Economic Evaluation of Health Technologies: Canada*. Ottawa (ON): CADTH.

- CADTH (Canadian Agency for Drugs and Technologies in Health). (2018). CADTH Common Drug Review Will Accept Submissions Up to Six Months Pre-Notice of Compliance (NOC). Retrieved June 2023, from <https://www.cadth.ca/news/cadth-common-drug-review-will-accept-submissions-six-months-pre-notice-compliance-noc>.
- CADTH (Canadian Agency for Drugs and Technologies in Health). (2020). *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review*. Ottawa (ON): CADTH.
- CADTH (Canadian Agency for Drugs and Technologies in Health). (2022a). *CADTH Post-Market Drug Evaluation Proposal: Program Overview*. Ottawa (ON): CADTH.
- CADTH (Canadian Agency for Drugs and Technologies in Health). (2022b). *Fee Schedule for CADTH Pharmaceutical Reviews*. Ottawa (ON): CADTH.
- CARB-X. (2018). CARB-X Calls for New ‘Open Science’ Era in Antimicrobial Innovation. Retrieved December 2022, from <https://carb-x.org/carb-x-news/carb-x-calls-for-new-open-science-era-in-antibacterial-innovation-sharing-scientific-data-will-help-speed-the-delivery-of-new-antibiotics-and-other-life-saving-products-to-fight-sup/>.
- CARB-X. (2019). CARB-X Expands its Global Accelerator Network to Support the Development of Antibiotics, Rapid Diagnostics, Vaccines and Other Life-Saving Products to Combat Drug-Resistant Superbugs. Retrieved May 2023, from <https://carb-x.org/carb-x-news/carb-x-expands-its-global-accelerator-network-to-support-the-development-of-antibiotics-rapid-diagnostics-vaccines-and-other-life-saving-products-to-combat-drug-resistant-superbugs/>.
- CARB-X. (2022a). *Working Together to Address the Global Threat of Antimicrobial Resistance: Annual Report 2021-2022*. Boston (MA): CARB-X.
- CARB-X. (2022b). About CARB-X. Retrieved March 2022, from <https://carb-x.org/about/overview/>.
- CARB-X. (2023a). Target Product Profile – Gram positive. Retrieved May 2023, from <https://carb-x.org/wp-content/uploads/2022/10/CARB-X-TPP-Oral-Gram-positive-Tx.pdf>.
- CARB-X. (2023b). Target Product Profiles – Gram negative. Retrieved May 2023, from <https://carb-x.org/wp-content/uploads/2022/10/CARB-X-TPP-Oral-Gram-negative-Tx.pdf>.
- CARB-X. (2023c). Our Strategy. Retrieved May 2023, from <https://carb-x.org/about/our-strategy/>.
- CCA (Council of Canadian Academies). (2014). *Improving Medicines for Children in Canada*. Ottawa (ON): The Expert Panel on Therapeutic Products for Infants, Children, and Youth, CCA.
- CCA (Council of Canadian Academies). (2015). *Accessing Health and Health-related Data in Canada*. Ottawa (ON): The Expert Panel on Timely Access to Health and Social Data for Health Research and Health System Innovation, CCA.
- CCA (Council of Canadian Academies). (2019). *When Antibiotics Fail*. Ottawa (ON): The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, CCA.

Overcoming Resistance

- CCA (Council of Canadian Academies). (2020). *From Research to Reality*. Ottawa (ON): The Expert Panel on the Approval and Use of Somatic Gene Therapies in Canada, CCA.
- CDC (Centers for Disease Control and Prevention). (2017). *Candida auris* Clinical Update – September 2017. Retrieved May 2023, from <https://www.cdc.gov/fungal/candida-auris/c-auris-alert-09-17.html>.
- CDC (Centers for Disease Control and Prevention). (2019). *Antibiotic Resistance Threats in the United States*. Atlanta (GA): CDC.
- CDC (Centers for Disease Control and Prevention). (2022). About Antimicrobial Resistance. Retrieved March 2023, from <https://www.cdc.gov/drugresistance/about.html>.
- Cecco, L. (2021, April 30). Dozens of Canada's First Nations Lack Drinking Water: 'Unacceptable in a Country so Rich', *The Guardian*.
- CEPS & Leem (Comité économique des produits de santé & Les entreprises du médicament). (2021). *Accord-cadre du 05/03/2021 entre le Comité économique des produits de santé et les entreprises du médicament (Leem)*. Paris, France: Gouvernement du France.
- Chatham House (Chatham House Working Group on New Antibiotic Business Models). (2015). *Towards a New Global Business Model for Antibiotics: Delinking Revenues From Sales*. London, United Kingdom: Chatham House.
- Cheung, W. Y., Cameron, C., Mitha, A., & Wills, A. (2023). Building infrastructure for outcomes-based agreements in Canada: Can administrative health data be used to support an outcomes-based agreement in oncology? *Supportive Care in Cancer*, 31(1), 1-6.
- Choosing Wisely. (2023a). Our Mission. Retrieved January 2023, from <https://www.choosingwisely.org/our-mission/>.
- Choosing Wisely. (2023b). Clinician Lists. Retrieved January 2023, from <https://www.choosingwisely.org/clinician-lists/#keyword=antibiotic>.
- Choronenki, N. J., Liaw, P., Bagshaw, S. M., Burns, K., Dodek, P., English, S., . . . Weiss, M. (2020). Data initiatives supporting critical care research and quality improvement in Canada: An environmental scan and narrative review. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*, 67, 475-484.
- Claxton, K., Briggs, A., Buxton, M. J., Culyer, A. J., McCabe, C., Walker, S., & Sculpher, M. J. (2008). Value based pricing for NHS drugs: An opportunity not to be missed? *BMJ*, 336(7638), 251.
- CO-ADD (Community for Open Antimicrobial Drug Discovery). (n.d.). Project. Retrieved January, 2023, from <https://www.co-add.org/?q=content/the-project>.
- Colson, A. R., Morton, A., Årdal, C., Chalkidou, K., ..., & Xiao, Y. (2021). Antimicrobial resistance: Is health technology assessment part of the solution or part of the problem? *Value Health*, 24(12), 1828-1834.

- Courtemanche, G., Wadanamby, R., Kiran, A., Toro-Alzate, L. F., Diggle, M., Chakraborty, D., . . . van Dongen, M. (2021). Looking for solutions to the pitfalls of developing novel antibacterials in an economically challenging system. *Microbiology Research*, 12(1), 173-185.
- Crago, A.-L., Alexandre, S., Abdesselam, K., Gravel Tropper, D., Hartmann, M., Smith, G., & Lary, T. (2022). Understanding Canadians' knowledge, attitudes and practices related to antimicrobial resistance and antibiotic use: Results from public opinion research. *Canada Communicable Disease Report (CCDR)*, 48(11/12), 550-558.
- Curren, E. J., Lutgring, J. D., Kabbani, S., Diekema, D. J., Gitterman, S., Lautenbach, E., . . . McDonald, L. C. (2022). Advancing diagnostic stewardship for healthcare-associated infections, antibiotic resistance, and sepsis. *Clinical Infectious Diseases*, 74(4), 723-728.
- Dall, C. (2019, April 16). Achaogen Bankruptcy Raises Worry Over Antibiotic Pipeline, *CIDRAP News*.
- Darrow, J. J. & Kesselheim, A. S. (2020). Incentivizing antibiotic development: Why isn't the Generating Antibiotic Incentives Now (GAIN) Act working? *Open Forum Infectious Diseases*, 7(1).
- DHAC (Australian Government Department of Health and Aged Care). (2023). Australian Public Assessment Reports (AusPAR). Retrieved June 2023, from <https://www.tga.gov.au/resources/auspar>.
- Doerr, P., Valentin, M., Nakashima, N., Oprhanos, N., Santos, G., Balkamos, G., & Saint-Raymond, A. (2020). Reliance: A smarter way of regulating medical products — The IPRP survey. *Expert Review of Clinical Pharmacology*, 14(2), 173-177.
- DRIVE-AB. (2016). *Incentives to stimulate antibiotic innovation: The preliminary findings of DRIVE-AB*. Geneva, Switzerland: DRIVE-AB.
- Dubois, P., Moisson, P.-H., & Tirole, J. (2022). *The Economics of Transferable Patent Extensions*. Toulouse, France: Toulouse School of Economics.
- Duke-Margolis Centre for Health Policy. (2021). Ensuring Pull Incentives for Priority Antibiotics Succeed. Retrieved November 2022, from https://www.youtube.com/watch?v=uRoNPnIYsmE&ab_channel=DukeMargolis.
- Dutescu, I. A. & Hillier, S. A. (2021). Encouraging the development of new antibiotics: Are financial incentives the right way forward? A systematic review and case study. *Infection and Drug Resistance*, 14, 415-434.
- EFPIA (European Federation of Pharmaceutical Industries and Associations). (2021). *A New EU Pull Incentive to Address Antimicrobial Resistance (AMR)*. Brussels, Belgium: EFPIA.
- EMA (European Medicines Agency). (2023a). Fees Payable to the European Medicines Agency. Retrieved May 2023, from <https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency#fees-for-marketing-authorisations-section>.

Overcoming Resistance

- EMA (European Medicines Agency). (2023b). Paediatric Investigation Plans (PIP). Retrieved February 2023, from [https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#:~:text=A%20paediatric%20investigation%20plan%20\(PIP,of%20a%20medicine%20for%20children.](https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#:~:text=A%20paediatric%20investigation%20plan%20(PIP,of%20a%20medicine%20for%20children.)
- Endo Ventures Ltd. (2021). *Product Monograph Including Patient Medication Information: Xydalba*. Dublin, Ireland: Endo Ventures Ltd.
- European Commission. (2023). *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: Reform of the Pharmaceutical Legislation and Measures Addressing Antimicrobial Resistance*. Brussels, Belgium: European Commission.
- FDA (United States Food and Drug Administration). (2019). Pediatric Research Equity Act (PREA). Retrieved February 2023, from <https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea#:~:text=PREA%20gives%20FDA%20the%20authority,pediatric%20labeling%20for%20the%20product.>
- FDA (United States Food and Drug Administration). (2023a). Prescription Drug User Fee Amendments. Retrieved May 2023, from <https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments.>
- FDA (United States Food and Drug Administration). (2023b). FDA Approves New Treatment for Pneumonia Caused by Certain Difficult-to-Treat Bacteria. Retrieved June 2023, from <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pneumonia-caused-certain-difficult-treat-bacteria.>
- FDA (United States Food and Drug Administration). (2023c). FDA Approves First Orally Administered Fecal Microbiota Product for the Prevention of Recurrence of Clostridioides difficile Infection. Retrieved June 2023, from <https://www.fda.gov/news-events/press-announcements/fda-approves-first-orally-administered-fecal-microbiota-product-prevention-recurrence-clostridioides.>
- Fernando Dinesh, M., Tun Hein, M., Poole, J., Patidar, R., Li, R., Mi, R., . . . Kumar, A. (2016). Detection of antibiotic resistance genes in source and drinking water samples from a First Nations community in Canada. *Applied and Environmental Microbiology*, 82(15), 4767-4775.
- Forsberg, K., Woodworth, K., Walters, M., Berkow, E. L., Jackson, B., Chiller, T., & Vallabhaneni, S. (2019). *Candida auris*: The recent emergence of a multidrug-resistant fungal pathogen. *Medical Mycology*, 57(1), 1-12.
- Fugh-Berman, A., Miller, M. E., Powers, J. H., Ramachandran, R., Rood, M. N., Ross, J. S., . . . Woody matters. (2022). *Letter to Chairman Reed and Ranking Member Inhofe on the Potential Inclusion of the PASTEUR Act (S.2076) in the National Defense Authorization Act (NDAA)*. n.l.: N/A.
- G7 Finance Ministers (Group of Seven Finance Ministers). (2021). *G7 Finance Ministers' Statement on Actions to Support Antibiotic Development*. London, United Kingdom: G7.

- GARDP (Global Antibiotic Research & Development Partnership). (2019). *Uniting Against Antibiotic Resistance*. Geneva, Switzerland: GARDP.
- GARDP (Global Antibiotic Research & Development Partnership). (2022a). Shionogi, GARDP and CHAI Announce Landmark License and Collaboration Agreements to Treat Bacterial Infections by Expanding Access to Cefiderocol in 135 Countries. Retrieved June 2023, from <https://gardp.org/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries/>.
- GARDP (Global Antibiotic Research & Development Partnership). (2022b). *Activity Report 2021*. Geneva, Switzerland: GARDP.
- GARDP (Global Antibiotic Research & Development Partnership). (n.d.). About GARDP. Retrieved March 2022, from <https://www.gardp.org/who-we-are/about-gardp/>.
- GC (Government of Canada). (2014). *Antimicrobial Resistance and Use in Canada*. Ottawa (ON): GC.
- GC (Government of Canada). (2015). *How Drugs are Reviewed in Canada*. Ottawa (ON): GC.
- GC (Government of Canada). (2017). *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action*. Ottawa (ON): GC.
- GC (Government of Canada). (2022a). Statement from the Minister of Health on Canada's Support for International Cooperation on Antimicrobial Resistance. Retrieved May 2023, from <https://www.canada.ca/en/public-health/news/2022/10/statement-from-the-minister-of-health-on-canadas-support-for-international-cooperation-on-antimicrobial-resistance.html>.
- GC (Government of Canada). (2022b). *Access Consortium Strategic Plan 2021-2024*. Ottawa (ON): GC.
- GC (Government of Canada). (2022c). Regulatory Innovation for Health Products: Modernizing Clinical Trial Regulations. Retrieved March 2023, from <https://www.canada.ca/en/health-canada/corporate/about-health-canada/activities-responsibilities/strategies-initiatives/health-products-food-regulatory-modernization/clinical-trial-regulations.html>.
- GC (Government of Canada). (2023a). Government of Canada Announces New Clinical Trials Consortium, Training Platforms, and Research Projects to Improve the Health of Canadians. Retrieved May 2023, from <https://www.canada.ca/en/institutes-health-research/news/2023/01/government-of-canada-announces-new-clinical-trials-consortium-training-platforms-and-research-projects-to-improve-the-health-of-canadians.html>.
- GC (Government of Canada). (2023b). *Prescription Drug Pricing and Costs*. Ottawa (ON): GC.
- GC (Government of Canada). (2023c). Government of Canada Makes Important Investment to Fight Antimicrobial Resistance (AMR). Retrieved May 2023, from <https://www.canada.ca/en/public-health/news/2023/05/government-of-canada-makes-important-investment-to-fight-antimicrobial-resistance-amr.html>.

Overcoming Resistance

- Gilpin, A. G., Bérubé, S., Moore-Hepburn, C., Lacaze-Masmonteil, T., Samiee-Zafarghandy, S., Rieder, M., . . . Litalien, C. (2022). Time for a regulatory framework for pediatric medications in Canada. *Canadian Medical Association Journal*, 16(194), 678–680.
- Global AMR R&D Hub. (2020). *Dynamic Dashboard – Data Collection, Processing, Categorization and Presentation*. Berlin, Germany: Global AMR R&D Hub.
- Global AMR R&D Hub. (2023). *Dynamic Dashboard: Incentives for Antibacterial R&D*. Berlin, Germany: Global AMR R&D Hub.
- Glover, R. E., Singer, A. C., Roberts, A. P., & Kirchhelle, C. (2021). NIMble innovation— A networked model for public antibiotic trials. *The Lancet Microbe*, 2(11), e637–e644.
- Glover, R. E., Singer, A. C., Roberts, A. P., & Kirchhelle, C. (2022). The antibiotic subscription model: Fostering innovation or repackaging old drugs? *The Lancet*, 4(1), e2 – e3.
- Gold, E. R. & Edwards, A. M. (2022). Overcoming market failures in pandemic drug discovery through open science: A Canadian solution. *Frontiers in Drug Discovery*, 2.
- Gotham, D., Moja, L., van der Heijden, M., Paulin, S., Smith, I., & Beyer, P. (2021). Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*, 125(3), 296–306.
- Gov. of ON (Government of Ontario). (2022). Formulary Search. Retrieved November 2022, from <https://www.formulary.health.gov.on.ca/formulary/>.
- Gov. of QC (Government of Quebec). (2010). *Loi sur l’Institut national d’excellence en santé et en services sociaux*. Québec (QC): Gov. of QC.
- Gov. of the Netherlands (Government of the Netherlands). (2022). *Non-paper: Novel Stimuli for the Development and Keeping on the Market of Antimicrobials*. Brussels, Belgium: Permanent Representation of the Netherlands to the European Union.
- Harbarth, S., Theuretzbacher, U., & Hackett, J. (2015). Antibiotic research and development: Business as usual? *Journal of Antimicrobial Chemotherapy*, 70(6), 1604–1607.
- Haworth-Brockman, M., Saxinger, L. M., Miazga-Rodriguez, M., Wierzbowski, A., & Otto, S. J. G. (2021). One Health evaluation of antimicrobial use and resistance surveillance: A novel tool for evaluating integrated, One Health antimicrobial resistance and antimicrobial use surveillance programs. *Frontiers in Public Health*, 9(693703).
- Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nature Biotechnology*, 32(1), 40–51.
- HC (Health Canada). (2007). *Notice of Compliance with Conditions (Therapeutic Products)*. Ottawa (ON): HC.
- HC (Health Canada). (2009). *Priority Review of Drug Submissions Policy*. Ottawa (ON): HC.
- HC (Health Canada). (2017a). *Guidance Document: Certificates of Supplementary Protection*. Ottawa (ON): HC.
- HC (Health Canada). (2017b). *Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations*. Ottawa (ON): HC.

- HC (Health Canada). (2019). *Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document*. Ottawa (ON): HC.
- HC (Health Canada). (2021a). *Guidance Document: Data Protection Under C.08.004.1 of the Food and Drug Regulations*. Retrieved March 2023, from <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html>.
- HC (Health Canada). (2021b). *Health Canada's Update to the Pathogens of Interest List*. Retrieved November 2022, from <https://www.canada.ca/en/health-canada/programs/consultation-new-addition-pathogens-interest-list/document.html>.
- HC (Health Canada). (2021c). *Mutual Recognition Agreements — Background*. Retrieved November 2022, from <https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/mutual-recognition-agreements/background.html>.
- HC (Health Canada). (2021d). *Notice — Health Canada's Update to the Pathogens of Interest List and Ongoing Efforts to Support Innovative Human Therapeutic Products to Combat Antimicrobial Resistance (AMR) – Annex A*. Retrieved November 2022, from https://www.canada.ca/en/health-canada/programs/consultation-new-addition-pathogens-interest-list/document.html#ann_a.
- HC (Health Canada). (2022a). *Challenges in the Antimicrobial Business Model and Potential Incentives to Increase Access and Promote Innovation: Best Brains Exchange Summary Report*. Ottawa (ON): HC.
- HC (Health Canada). (2022b). *Health Canada's Special Access Programs: Request a Drug*. Retrieved May 2023, from <https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html>.
- HC (Health Canada). (2022c). *Guidance Document Special Access Program for Drugs: Guidance Document for Industry and Practitioners*. Ottawa (ON): HC.
- HC (Health Canada). (2023a). *List of Drugs for an Urgent Public Health Need*. Retrieved May 2023, from <https://www.canada.ca/en/health-canada/services/drugs-health-products/access-drugs-exceptional-circumstances/list-drugs-urgent-public-health-need.html>.
- HC (Health Canada). (2023b). *Drug Product Database Online Query*. Retrieved May 2023, from <https://health-products.canada.ca/dpd-bdpp/?lang=eng>.
- HC (Health Canada). (2023c). *Fees for the Examination of a Submission: Drugs for Human Use*. Retrieved May 2023, from <https://www.canada.ca/en/health-canada/services/drugs-health-products/funding-fees/fees-respect-human-drugs-medical-devices/pharmaceutical-submission-application-review-funding-fees-drugs-health-products.html>.
- HDRN (Health Data Research Network Canada). (2020). *About HDRN*. Retrieved May 2023, from <https://www.hdrn.ca/en/about>.

Overcoming Resistance

- HealthCareCAN. (2016). *Putting the Pieces Together: A National Action Plan on Antimicrobial Stewardship*. Ottawa (ON): HealthCareCAN.
- Hinman, A. R. (1990). 1889 to 1989: A century of health and disease. *Public Health Reports*, 105(4), 374-380.
- hiv.gov. (2023). What is PEPFAR. Retrieved March 2023, from <https://www.hiv.gov/federal-response/pepfar-global-aids/pepfar/>.
- Hoenigl, M., Sprute, R., Egger, M., Arastehfar, A., Cornely, O. A., Krause, R., . . . Jenks, J. D. (2021). The antifungal pipeline: Fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs*, 81(15), 1703-1729.
- Holmes, A. H., Moore, L. S. P., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., . . . Piddock, L. J. V. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, 387(10014), 176-187.
- Huston, P., Edge, V. L., & Bernier, E. (2019). Reaping the benefits of open data in public health. *Canada Communicable Disease Report*, 45(10), 252-256.
- ICH (International Council for Harmonisation). (n.d.-a). Formal ICH Procedures. Retrieved November 2022, from <https://www.ich.org/page/formal-ich-procedure>.
- ICH (International Council for Harmonisation). (n.d.-b). Members & Observers. Retrieved May 2023, from <https://www.ich.org/page/members-observers>.
- ICH (International Council for Harmonisation). (n.d.-c). Mission: Harmonisation for Better Health. Retrieved May 2023, from <https://www.ich.org/page/mission>.
- IDSA (Infectious Diseases Society of America). (2012). White paper: Recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clinical Infectious Diseases*, 55(8), 1031-1046.
- INESSS (Institut national d'excellence en santé et en services sociaux). (2016). *ZERBAXA – Infections urinaires compliquées*. Québec (QC): INESSS.
- INESSS (Institut national d'excellence en santé et en services sociaux). (2021a). Fees. Retrieved October 2022, from <https://www.inesss.qc.ca/en/themes/medicaments/manufacturer-information-centre/fees.html>.
- INESSS (Institut national d'excellence en santé et en services sociaux). (2021b). Evaluation and Process Criteria. Retrieved March 2022, from <https://www.inesss.qc.ca/en/themes/medicaments/evaluation-process-and-criteria.html>.
- Jabłońska, K., Aballéa, S., & Toumi, M. (2021). The real-life impact of vaccination on COVID-19 mortality in Europe and Israel. *Public Health*, 198, 230-237.
- James, R., Nakamachi, Y., Morris, A., So, M., Ponnampalavanar, S. S. L. S., Chuki, P., . . . Thursky, K. (2022). The feasibility and generalizability of assessing the appropriateness of antimicrobial prescribing in hospitals: A review of the Australian National Antimicrobial Prescribing Survey. *JAC-Antimicrobial Resistance*, 4(1).

- Jaswal, A. (2013). *Valuing Health in Canada: Who, How, and How Much?* Ottawa (ON): Canada 2020.
- JPIAMR (Joint Programming Initiative on Antimicrobial Resistance). (2022). Participating Members. Retrieved November 2022, from <https://www.jpiamr.eu/about/jpiamr-members/>.
- JPIAMR (Joint Programming Initiative on Antimicrobial Resistance). (2023). About JPIAMR. Retrieved May 2023, from <https://www.jpiamr.eu/about/>.
- Kainz, K., Bauer, M. A., Madeo, F., & Carmona-Gutierrez, D. (2020). Fungal infections in humans: The silent crisis. *Microbial Cell*, 7(6), 143-145.
- Kansteiner, R. (2022, May 3). Pfizer Sticks to Guns on \$22B Paxlovid Sales Despite Reports of Lagging Demand, *Fierce Pharma*.
- Karlsberg Schaffer, S., Henshall, C., West, P., Towse, A., Mestre-Ferrandiz, J., Masterton, R., & Fischer, A. (2017). *Assessing the Value of New Antibiotics: Additional Elements of Value for Health Technology Assessment Decisions*. London, United Kingdom: The Office of Health Economics.
- Kesselheim, A. S. & Outterson, K. (2010). Fighting antibiotic resistance: Marrying new financial incentives to meeting public health goals. *Health Affairs*, 29(9), 1689-1696.
- King, T., Schindler, R., Chavda, S., & Conly, J. (2022). Dimensions of poverty as risk factors for antimicrobial resistant organisms in Canada: A structured narrative review. *Antimicrobial Resistance & Infection Control*, 11(1), 18.
- Klug, D. M., Idiris, F. I. M., Blaskovich, M. A. T., von Delft, F., Dowson, C. G., Kirchhelle, C., . . . Todd, M. H. (2021). There is no market for new antibiotics: This allows an open approach to research and development. *Wellcome Open Research*, 6, 146.
- Kosiak, S. & Silverman, R. (2021). *Participation in Pull Mechanisms for Social Impact Innovation: A Survey of Federal Authorities, Budgetary Barriers, and Potential Solutions*. Washington (DC): Center for Global Development.
- Lamontagne, F., Rowan, K. M., & Guyatt, G. (2021). Integrating research into clinical practice: Challenges and solutions for Canada. *Canadian Medical Association Journal*, 193(4), E127-131.
- Lanini, S., Ioannidis, J. P. A., Vairo, F., Pletschette, M., Portella, G., Di Bari, V., . . . Oppolito, G. (2019). Non-inferiority versus superiority trial design for new antibiotics in an era of high antimicrobial resistance: The case for post-marketing, adaptive randomised controlled trials. *Lancet Infectious Diseases*, 19(12), e444-451.
- Lee, H. J. & Lee, D. G. (2022). Urgent need for novel antibiotics in Republic of Korea to combat multidrug-resistant bacteria. *The Korean Journal of Internal Medicine*, 37(2), 271-280.
- Leonard, C., Crabb, N., Glover, D., Cooper, S., Bouvy, J., Wobbe, M., & Perkins, M. (2023). Can the UK 'Netflix' payment model boost the antibacterial pipeline? *Applied Health Economics and Health Policy*, 21(3), 365-372.

Overcoming Resistance

- Loewen, K., Schreiber, Y., Kirlew, M., Bocking, N., & Kelly, L. (2017). Community-associated methicillin-resistant *Staphylococcus aureus* infection. *Canadian Family Physician*, 63, 512–520.
- Loeplke, K. H., Suda, K. J., Boucher, H., Russo, R. L., Bonney, M. W., Hunt, T. D., & Mohr, J. F., 3rd. (2017). Past, present, and future of antibacterial economics: Increasing bacterial resistance, limited antibiotic pipeline, and societal implications. *Pharmacotherapy*, 37(1), 71–84.
- Lupkin, S. (2023). Moderna's COVID Vaccine Gambit: Hike the Price, Offer Free Doses for Uninsured. Retrieved July 2023, from <https://www.npr.org/sections/health-shots/2023/03/08/1161353892/modernas-covid-vaccine-gambit-hike-the-price-offer-free-doses-for-uninsured>.
- Marshall, J. C. & Cook, D. (2009). Investigator-led clinical research consortia: The Canadian Critical Care Trials Group. *Critical Care Medicine*, 37(1 (Suppl)), S165–172.
- McAdams, D. (2017). Resistance diagnosis and the changing epidemiology of antibiotic resistance. *Annals of the New York Academy of Sciences*, 1388, 5–17.
- McDonnell, A., Rex, J. H., Goossens, H., Bonten, M., Fowler, V. G., Jr., & Dane, A. (2016). Efficient delivery of investigational antibacterial agents via sustainable clinical trial networks. *Clinical Infectious Diseases*, 63 (2), S57–59.
- Megiddo, I., Drabik, D., Bedford, T., Morton, A., Wesseler, J., & Laxminarayan, R. (2019). Investing in antibiotics to alleviate future catastrophic outcomes: What is the value of having an effective antibiotic to mitigate pandemic influenza? *Health Economics*, 28(4), 556–571.
- Merck Canada Inc. (2019). *Product Monograph Including Patient Medication Information: Difigid. Kirkland (QC): Merck Canada Inc.*
- MHLW (Ministry of Health, Labour and Welfare). (2023). *Antimicrobial Securement Project*. Paper presented at Global Leaders Group on AMR, Barbados.
- Mi, R., Patidar, R., Farenhorst, A., Cai, Z., Sepehri, S., Khafipour, E., & Kumar, A. (2019). Detection of fecal bacteria and antibiotic resistance genes in drinking water collected from three First Nations communities in Manitoba, Canada. *FEMS Microbiology Letters*, 366(6), fnz067.
- Michaeli, D. T., Yagmur, H. B., Achmadeev, T., & Michaeli, T. (2022). Valuation and returns of drug development companies: Lessons for bioentrepreneurs and investors. *Therapeutic Innovation & Regulatory Science*, 56(2), 313–322.
- Mitra-Majumdar, M., Powers, J. H., Brown, B. L., & Kesselheim, A. S. (2022). Evidence at time of regulatory approval and cost of new antibiotics in 2016–19: Cohort study of FDA approved drugs. *BMJ Medicine*, 1(1), e000227.
- Mohammadinejad, P., Ataieinia, B., Kaynejad, K., Zeinoddini, A., Sadeghi, B., Hosseini, M., . . . Aghamohammadi, A. (2015). Antibiotic resistance in patients with primary immunodeficiency disorders versus immunocompetent patients. *Expert Review of Clinical Immunology*, 11(10), 1163–1172.

- Morado, F. & Wong, D. W. (2022). Applying diagnostic stewardship to proactively optimize the management of urinary tract infections. *Antibiotics*, *11*(308).
- Morel, C., Lindhal, O., Harbarth, S., de Kraker, M. E. A., Edwards, S., & Hollis, A. (2020). Industry incentives and antibiotic resistance: An introduction to the antibiotic susceptibility bonus. *The Journal of Antibiotics*, *73*, 421-428.
- Morton, A., Colson, A., Leporowski, A., Trett, A., Bhatti, T., & Laxminarayan, R. (2019). How should the value attributes of novel antibiotics be considered in reimbursement decision making? *MDM Policy & Practice*, *4*(2).
- Muileboom, J., Hamilton, M., Parent, K., Makahnouk, D., Kirlew, M., Saginur, R., . . . Kelly, L. (2013). Community-associated methicillin-resistant *Staphylococcus aureus* in Northwest Ontario: A five-year report of incidence and antibiotic resistance. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *24*, 1694-09.
- Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., . . . Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet*, *399*(10325), 629-655.
- Murthy, S., Fowler, R., & Laupacis, A. (2020). How Canada can better embed randomized trials into clinical care. *Canadian Medical Association Journal*, *10*(192), E928-929.
- Nabriva Therapeutics. (2023). Nabriva Therapeutics Provides Corporate Update. Retrieved January 2023, from <https://investors.nabriva.com/news-releases/news-release-details/nabriva-therapeutics-provides-corporate-update>.
- Najjar-Debbiny, R., Gronich, N., Weber, G., Khoury, J., Amar, M., Stein, N., . . . Saliba, W. (2023). Effectiveness of Paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. *Clinical Infectious Diseases*, *76*(3), e342-e349.
- NCCPH (National Collaborating Centres for Public Health). (n.d.). *Understanding Summary Measures Used to Estimate the Burden of Disease*. Ottawa (ON): NCCPH.
- ND4BB (New Drugs for Bad Bugs). (2021). Welcome to ENABLE. Retrieved December 2022, from <http://nd4bb-enable.eu/>.
- Neri, M., Hampson, G., Henshall, C., & Towse, A. (2019). *HTA and Payment Mechanisms for New Drugs to Tackle AMR*. London, United Kingdom: Office of Health Economics
- NHS (National Health Service). (2020a). *Annex 1: Selection Questionnaire*. London, United Kingdom: NHS.
- NHS (National Health Service). (2020b). *Annex 3: Award Questions Criteria*. London, United Kingdom: NHS.
- NHS (National Health Service). (2021a). *Annex 7: Health Technology Assessment Process*. London, United Kingdom: NHS.
- NHS (National Health Service). (2021b). *Annex 8 - NHS Terms and Conditions for the Supply of Goods (Contract Version)*. London, United Kingdom: NHS.

Overcoming Resistance

- NICE (National Institute for Health Care and Excellence). (2021). *Antimicrobial Resistance: Developing and Testing Innovative Models for the Evaluation and Purchase of Antimicrobials*. Paper presented at March 25, 2020 NHS AMR Market Engagement Briefing, London, United Kingdom.
- NICE (National Institute for Health and Care Excellence). (2022a). *Draft Guidance: Ceftazidime-avibactam for Treating Severe Drug-resistant Gram-negative Bacterial Infections*. London, United Kingdom: NICE.
- NICE (National Institute for Health and Care Excellence). (2022b). *Cefiderocol for Treating Severe Drug-resistant Gram-negative Bacterial Infections*. Retrieved August 2022, from <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol>.
- NICE (National Institute for Health and Care Excellence). (2022c). *Ceftazidime with Avibactam for Treating Severe Drug-resistant Gram-negative Bacterial Infections*. Retrieved August 2022, from <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam>.
- NICE (National Institute for Health and Care Excellence). (2022d). *Antimicrobials Evaluation Committee*. Retrieved August 2022, from <https://www.nice.org.uk/get-involved/meetings-in-public/antimicrobials-evaluation-committee>.
- NICE (National Institute for Health and Care Excellence). (2022e). *Draft Guidance: Cefiderocol for Treating Severe Drug-Resistant Gram-Negative Bacterial Infections*. London, United Kingdom: NICE.
- Nicol, A. M. (2019). *Commercialisation of Healthcare in Canada: Overview*. Toronto (ON): Borden Ladner Gervais LLP.
- O'Neill, J. (2015a). *Securing New Drugs for Future Generations: The Pipeline of Antibiotics*. London, United Kingdom: Review on Antimicrobial Resistance.
- O'Neill, J. (2015b). *Rapid Diagnostics: Stopping Unnecessary Use of Antibiotics*. London, United Kingdom: Review on Antimicrobial Resistance.
- O'Neill, J. (2016). *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. London, United Kingdom: Review on Antimicrobial Resistance.
- OECD (Organisation for Economic Co-operation and Development). (2018). *Stemming the Superbug Tide: Just a Few Dollars More*. Paris, France: OECD.
- OHE (Office of Health Economics). (2022). Can We “Netflix” the Broken Antibiotics Market? Retrieved December 2022, from <https://www.ohe.org/events/can-we-netflix-broken-antibiotics-market/>.
- Ouakrim, D. A., Oliveira, T. C., & Jendrossek, M. (2018). Health and Economic Burden of Antimicrobial Resistance. In M. Cecchini (Ed.), *Stemming the Superbug Tide*. Paris, France: Organisation for Economic Co-operation and Development (OECD).
- Outterson, K., Samora, J. B., & Keller-Cuda, K. (2007). Will longer antimicrobial patents improve global public health? *The Lancet Infectious Diseases*, 7(8), 559–566.

- Otterson, K., Pogge, T., & Hollis, A. (2011). *Combating Antibiotic Resistance through the Health Impact Fund. No. 11–30 Boston University School of Law, Law and Economics Research Paper* Boston (MA): Scholarly Commons at Boston University School of Law.
- Otterson, K., Powers, J. H., Daniel, G. W., & McClellan, M. B. (2015). Repairing the broken market for antibiotic innovation. *Health Affairs (Millwood)*, 34(2), 277–285.
- Otterson, K. & McDonnell, A. (2016). Funding antibiotic innovation with vouchers: Recommendations on how to strengthen a flawed incentive policy. *Health Affairs*, 35(5), 784–790.
- Otterson, K. & Rex, J. H. (2020). Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research*, 220, 182–190.
- Otterson, K. (2021a). Appropriate Pull Incentive for New Antibacterials: \$2.2–4.8b for Full Delinkage. Retrieved November 2022, from <https://amr.solutions/2021/11/01/appropriate-pull-incentive-for-new-antibacterials-2-2-4-8b-for-full-delinkage/>.
- Otterson, K. (2021b). Estimating the appropriate size of global pull incentives for antibacterial medicines. *Health Affairs*, 40(11), 1758–1765.
- Otterson, K. (2022). BU AMR Model with Dashboard. Retrieved November 2022, from <https://open.bu.edu/handle/2144/42568>.
- Otterson, K., Orubu, E. S. F., Rex, J. H., Årdal, C., & Zaman, M. H. (2021). Patient access in fourteen high-income countries to new antibacterials approved by the FDA, EMA, PMDA, or Health Canada, 2010–2020. *Clinical Infectious Diseases*, 74(7), 1183–1190.
- Otterson, K. & Rex, J. H. (2023). Global pull incentives for better antibacterials: The UK leads the way. *Applied Health Economics and Health Policy*, 21(3), 361–364.
- PACCARB (Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria). (2017). *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance*. Washington (DC): PACCARB.
- Paladin Labs. (2022). Paladin Labs Announces the Launch of Xydalba (Dalbavancin for Injection) in Canada. Retrieved June 2023, from https://paladin-labs.com/wp-content/uploads/2022/01/PR_Xydalba_EN.pdf.
- Pan-Canadian Health Data Strategy Expert Advisory Group. (2022). *Pan-Canadian Health Data Strategy: Toward a World-Class Health Data System*. Ottawa, ON: Public Health Agency of Canada.
- Patel, D., Senecal, J., Spellberg, B., Morris, A. M., Saxinger, L., Footer, B. W., . . . Lee, T. C. (2023). Fidaxomicin to prevent recurrent *Clostridioides difficile*: What will it cost in the USA and Canada? *JAC-Antimicrobial Resistance*, 5(1).
- Payne, D. J., Miller, L. F., Findlay, D., Anderson, J., & Marks, L. (2015). Time for a change: Addressing R&D and commercialization challenges for antibacterials. *Philosophical Transactions of the Royal Society B Biological Sciences*, 370(1670), 20140086.

Overcoming Resistance

- pCPA (pan-Canadian Pharmaceutical Alliance). (2019). *pCPA Brand Process Guidelines*. Toronto (ON): pCPA.
- PHAC (Public Health Agency of Canada). (2014). *Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*. Ottawa (ON): PHAC.
- PHAC (Public Health Agency of Canada). (2016). Surveillance of Malaria. Retrieved March 2023, from <https://www.canada.ca/en/public-health/services/diseases/malaria/surveillance-malaria.html>.
- PHAC (Public Health Agency of Canada). (2022). *Canadian Antimicrobial Resistance Surveillance System Report*. Ottawa (ON): PHAC.
- PHAC (Public Health Agency of Canada). (2023). *Pan-Canadian Action Plan on Antimicrobial Resistance*. Ottawa (ON): PHAC.
- PHAS (Public Health Agency of Sweden). (2020). *Questions and Answers – Agreements Signed for a Pilot Study of a New Reimbursement Model*. Solna, Sweden: PHAS.
- PHAS (Public Health Agency of Sweden). (2023). *Tillgänglighet till vissa antibiotika*. Solna, Sweden: PHAS.
- PhRMA (Pharmaceutical Research and Manufacturers of America). (2020). *Medicines in Development, 2020 Report: Cancer*. Washington (DC): PhRMA.
- Plackett, B. (2020). No Money for New Drugs. *Nature*, 586.
- PMO (Office of the Prime Minister). (2019). *Minister of Health Mandate Letter*. Ottawa (ON): PMO.
- PMO (Office of the Prime Minister). (2021). *Minister of Health Mandate Letter*. Ottawa (ON): PMO.
- PMO (Office of the Prime Minister). (2022). G7 Leaders' Communiqué. Retrieved January 2023, from <https://pm.gc.ca/en/news/statements/2022/06/28/g7-leaders-communication>.
- PMPRB (Patented Medicine Prices Review Board). (2018). About PMPRB. Retrieved March 2022, from <http://pmprb-cepmb.gc.ca/about-us>.
- PMPRB (Patented Medicine Prices Review Board). (2020). *Insight into the Spending on Expensive Drugs for Rare Diseases*. Ottawa (ON): PMPRB.
- Powers, J. H., Evans, S. R., & Kesselheim, A. S. (2018). Studying new antibiotics for multidrug resistant infections: Are today's patients paying for unproved future benefits? *BMJ*, 360.
- Prasad, N.K., Seiple, I.B., Cirz, R.T., Rosenberg, O.S. (2022). Leaks in the pipeline: A failure analysis of Gram-negative antibiotic development from 2010 to 2020. *Antimicrobial Agents and Chemotherapy*, 66(5).
- Probst, J., Eberth, J. M., & Crouch, E. (2019). Structural urbanism contributes to poorer health outcomes for rural America. *Health Affairs*, 38(12), 1976–1984.
- Projan, S. J. (2003). Why is big Pharma getting out of antibacterial drug discovery? *Current Opinion in Microbiology*, 6(5), 427–430.

- Prosen, K., Lepore, C., Kim, W., & Talkington, K. (2019). *The Shared Platform for Antibiotic Research and Knowledge*. Washington (DC): The PEW Charitable Trusts.
- Ramachandran, R. & Powers, J. H. (2022, December 13). Why the PASTEUR Act Is No Cure for Antimicrobial Resistance, *The Hill*.
- Rand, L. A. & Kesselheim, A. S. (2021). International reference pricing for prescription drugs: A landscape analysis. *Journal of Managed Care & Speciality Pharmacy*, 27(9), 1309-1313.
- REPAIR Impact Fund. (2023). REPAIR Impact Fund. Retrieved January 2023, from <https://www.repair-impact-fund.com/about/>.
- Resch, S. C., Salomon, J. A., Murray, M., & Weinstein, M. C. (2006). Cost-effectiveness of treating multidrug-resistant tuberculosis. *PLOS Medicine*, 3(7), e241.
- Reuters Staff. (2019, December 27). Antibiotics Maker Melinta Files for Chapter 11 Bankruptcy, *Reuters*.
- Rex, J. H. & Outterson, K. (2016). Antibiotic reimbursement in a model delinked from sales: A benchmark-based worldwide approach. *Lancet Infectious Diseases* 16(4), 500-505.
- Rex, J. H., Talbot, G. H., Goldberger, M., Einstein, B. I., Echols, R. M., Tomayko, J., . . . Dane, A. (2017). Progress in the fight against multi-drug resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. *Clinical Infectious Diseases*, 65, 141-146.
- Rex, J. H., Fernandez Lynch, H., Cohen, I. G., Darrow, J. J., & Outterson, K. (2019). Designing development programs for non-traditional antibacterial agents. *Nature Communications*, 10(1).
- Rice, L. B. (2011). Rapid diagnostics and appropriate antibiotic use. *Clinical Infectious Diseases*, 52(S4), S357-S360.
- Rothery, C., Woods, B., Schmitt, L., Claxton, K., Palmer, S., & Sculpher, M. (2018). *Framework for Value Assessment of New Antimicrobials*. York, United Kingdom: Policy Research Unit in Economic Evaluation of Health & Care Interventions.
- Savage, R. D., Fowler, R. A., Rishu, A. H., Bagshaw, S. M., Cook, D., Dodek, P., . . . Daneman, N. (2016). The effect of inadequate initial empiric antimicrobial treatment on mortality in critically ill patients with bloodstream infections: A multi-centre retrospective cohort study. *PLOS One*, 11(5), e0154944.
- Schulman, J. P. (2009). Patents and public health: The problems with using patent law proposals to combat antibiotic resistance. *DePaul Law Review*, 59(1).
- Schwartz, K. L. & Morris, S. K. (2018). Travel and spread of drug-resistant bacteria. *Current Infectious Disease Reports*, 20(29).
- Schwartz, K. L., Wilton, A. S., Langford, B. J., Brown, K. A., Daneman, N., Garber, G., . . . Tu, K. (2019). Comparing prescribing and dispensing databases to study antibiotic use: A validation study of the Electronic Medical Record Administrative data Linked Database (EMRALD). *Journal of Antimicrobial Chemotherapy*, 74, 2091-2097.
- SECURE. (n.d.). Homepage. Retrieved May 2023, from <https://www.secureantibiotics.org/>.

Overcoming Resistance

- Seely, A. J. E. & Fowler, R. (2022). Importance of nationally coordinated data collection and quality improvement networks. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*, 6(1), 6–8.
- Sertkaya, A., Eyraud, J., Birkenbach, A., Franz, C., Ackerley, N., & Overton, V. (2014). *Analytical Framework for Examining the Value of Antibacterial Products*. Washington (DC): United States Department of Health and Human Services.
- Shajarizadeh, M. A. & Hollis, A. (2015). Delays in the submission of new drugs in Canada. *Canadian Medical Association Journal*, 187, E47–E51.
- Shapiro, D. J., Hicks, L. A., Pavia, A. T., & Hersh, A. L. (2013). Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *Journal of Antimicrobial Chemotherapy*, 69, 234–240.
- Silhavy, T. J., Kahne, D., & Walker, S. (2010). The bacterial cell envelope. *Cold Spring Harbor Perspectives on Biology*, 2(5), a000414.
- Silverman Bonnifield, R. & Towse, A. (2022). *Estimating Canada’s Return on Investment from an Ambitious Program to Incentivize New Antibiotics*. Washington (DC): Center for Global Development.
- Singer, A. C., Kirchhelle, C., & Roberts, A. P. (2020). (Inter)nationalising the antibiotic research and development pipeline. *Lancet Infectious Diseases*, 20(2), e54–e62.
- Sinha, M. S., Powers, J. H., & Kesselheim, A. S. (2021). The wrong cure: Financial incentives for unimpressive new antibiotics. *Journal of Infectious Diseases*, 223(9), 1506–1509.
- Somanader, D. S., Brunskill, I., Perrin, M., Barkema, H. W., Hillier, S. A., Hindmarch, S., . . . Morris, A. M. (2022). Canada has an opportunity to address antimicrobial resistance through COVID–19 recovery spending. *Lancet Regional Health Americas*, 16(100393).
- Spellberg, B. & Rex, J. H. (2013). The value of single–pathogen antibacterial agents. *Nature Reviews Drug Discovery*, 12(12), 963.
- Spellberg, B. (2022). The Non-Profit Future of Antibacterial R&D. Retrieved May 2023, from <https://revive.gardp.org/the-non-profit-future-of-antibacterial-rd-by-brad-spellberg/>.
- StatCan (Statistics Canada). (2022). *Census in Brief: Housing Conditions Among First Nations People, Métis and Inuit in Canada from the 2021 Census*. Ottawa (ON): StatCan.
- Sundquist, S., Batist, G., Brodeur-Robb, K., Dyck, K., Eigl, B. J., Lee, D. K., . . . Dancy, J. E. (2021). CRAFT—A proposed framework for decentralized clinical trials participation in Canada. *Current Oncology*, 28(5), 3857–3865.
- TBS (Treasury Board of Canada Secretariat). (2018). *Review of Methodologies to Determine Discount Rates*. Ottawa (ON): TBS.
- Teillant, A., Gandra, S., Barter, D., Morgan, D. J., & Laxminarayan, R. (2015). Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: A literature review and modelling study. *Lancet Infectious Diseases*, 15(12), 1429–1437.
- The Bill and Melinda Gates Foundation. (n.d.). Malaria. Retrieved March 2023, from <https://www.gatesfoundation.org/our-work/programs/global-health/malaria>.

- The Global Fund. (2022). *Pandemic Preparedness and Response*. Geneva, Switzerland: The Global Fund.
- The Global Fund. (n.d.-a). HIV and AIDS. Retrieved March 2023, from <https://www.theglobalfund.org/en/hivaids/>.
- The Global Fund. (n.d.-b). Malaria. Retrieved March 2023, from <https://www.theglobalfund.org/en/malaria/>.
- Theuretzbacher, U. (2017). Antibiotic innovation for future public health needs. *Clinical Microbiology and Infection*, 23(10), 713–717.
- Theuretzbacher, U., Årdal, C., & Harbarth, S. (2017). Linking sustainable use policies to novel economic incentives to stimulate antibiotic research and development. *Infectious Disease Reports*, 9(1), 6836.
- Towse, A., Hoyle, C. K., Goodall, J., Hirsch, M., Mestre-Ferrandiz, J., & Rex, J. H. (2017). Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy*, 121(10), 1025–1030.
- Towse, A. & Silverman Bonfield, R. (2022). *An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment*. Washington (DC): Center for Global Development.
- TRC (Truth and Reconciliation Commission of Canada). (2015a). *Honouring the Truth, Reconciling for the Future: Summary of the Final Report of the Truth and Reconciliation Commission of Canada*. Winnipeg (MB): TRC.
- TRC (Truth and Reconciliation Commission of Canada). (2015b). *Truth and Reconciliation Commission of Canada: Calls to Action*. Winnipeg (MB): TRC.
- Tricco, A. C., Zarin, W., Clement, F., Abou-Setta, A. M., Curran, J. A., LeBlanc, A., . . . Straus, S. E. (2022). Introducing the Strategy for Patient Oriented Research (SPOR) Evidence Alliance: A partnership between researchers, patients and health system decision-makers to support rapid-learning and responsive health systems in Canada and beyond. *FACETS*, 7, 639–653.
- UNITAID. (2022). *UNITAID and HIV/AIDS*. Geneva, Switzerland: UNITAID.
- U.S. Congress (Congress of the United States). (2021). *H.R.3932 - PASTEUR Act of 2021*. Washington (DC) U.S. Congress.
- Van Katwyk, S. R., Hoffman, S. J., Mendelson, M., Taljaard, M., & Grimshaw, J. M. (2020). Strengthening the science of addressing antimicrobial resistance: A framework for planning, conducting and disseminating antimicrobial resistance intervention research. *Health Research Policy and Systems* 18(1), 1–13.
- Walker, S., Dresser, L., Becker, D., & Scalera, A. (2006). An assessment of linezolid utilization in selected Canadian provinces. *The Canadian Journal of Infectious Diseases & Medical Microbiology*, 17(3), 177–182.

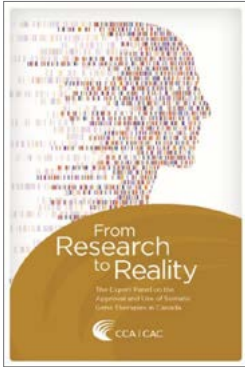
Overcoming Resistance

- Wallach, J. D., Zhang, A. D., Skydel, J. J., Bartlett, V. L., Dhruva, S. S., Shah, N. D., & Ross, J. S. (2021). Feasibility of using real-world data to emulate postapproval confirmatory clinical trials of therapeutic agents granted US Food and Drug Administration accelerated approval. *JAMA Network Open*, 4(11).
- Wellcome Trust. (2020). *Clinical Trial Networks for AMR Research*. London, United Kingdom: Wellcome Trust.
- WHO (World Health Organization). (2017). WHO Publishes List of Bacteria for Which New Antibiotics Are Urgently Needed. Retrieved November 2022, from <https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>.
- WHO (World Health Organization). (2020). *Target Product Profiles for Needed Antibacterial Agents*. Geneva, Switzerland: WHO.
- WHO (World Health Organization). (2021a). *WHO Model List of Essential Medicines – 22nd List (2021)*. Geneva, Switzerland: WHO.
- WHO (World Health Organization). (2021b). *2020 Antibacterial Agents in Clinical and Preclinical Development*. Geneva, Switzerland: WHO.
- WHO (World Health Organization). (2021c). Antimicrobial Resistance. Retrieved March 2023, from <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>.
- WHO (World Health Organization). (2022a). *Paediatric Drug Optimization for Antibiotics*. Geneva, Switzerland: WHO.
- WHO (World Health Organization). (2022b). *2021 Antibacterial Agents in Clinical and Preclinical Development: An Overview and Analysis*. Geneva, Switzerland: WHO.
- WHO (World Health Organization). (2022c). *WHO Fungal Priority Pathogens List to Guide Research, Development and Public Health Action*. Geneva, Switzerland: WHO.
- WHO (World Health Organization). (2022d). Lack of Innovation Set to Undermine Antibiotic Performance and Health Gains. Retrieved May 2023, from <https://www.who.int/news/item/22-06-2022-22-06-2022-lack-of-innovation-set-to-undermine-antibiotic-performance-and-health-gains#:~:text=It%20currently%20takes%20approximately%2010,preclinical%20development%20will%20reach%20patients>.
- WHO (World Health Organization). (2022e). *Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022*. Geneva, Switzerland: WHO.
- World Bank. (2017). *Drug-Resistant Infections: A Threat to Our Economic Future*. Washington (DC): World Bank.
- Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated research and development investment needed to bring a new medicine to market, 2009–2018. *Journal of the American Medical Association*, 323(9), 844–853.
- Yackey, K., Stukus, K., Cohen, D., Kline, D., Zhao, S., & Stanley, R. (2019). Off-label medication prescribing patterns in pediatrics: An update. *Hospital Pediatrics*, 9(3), 186–193.

- Årdal, C., Røttingen, J. A., Opalska, A., Van Hengel, A. J., & Larsen, J. (2017). Pull incentives for antibacterial drug development: An analysis by the Transatlantic Task Force on Antimicrobial Resistance. *Clinical Infectious Diseases*, *65*(8), 1378–1382.
- Årdal, C., Findaly, D., Savic, M., Carmeli, Y., Gyssens, I., Laxminarayan, R., . . . Rex, J. H. (2018). *Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access*. Geneva, Switzerland: DRIVE-AB.
- Årdal, C., Balasegaram, M., Laxminarayan, R., McAdams, D., Outtersson, K., Rex, J. H., & Sumpradit, N. (2020). Antibiotic development — Economic, regulatory and societal challenges. *Nature Reviews Microbiology*, *18*(5), 267–274.
- Årdal, C., Lacotte, Y., Edwards, S., & Ploy, M. (2021). National facilitators and barriers to the implementation of incentives for antibiotic access and innovation. *Antibiotics (Basel)*, *10*(6), 749.
- Årdal, C., Baraldi, E., Busse, R., Castro, R., Ciabuschi, F., Cisneros, J. M., . . . O'Neill, J. (2023). Transferable exclusivity voucher: A flawed incentive to stimulate antibiotic innovation. *Lancet*.

CCA Reports of Interest

The assessment reports listed below are available on the CCA's website (www.cca-reports.ca):



From Research to Reality (2020)



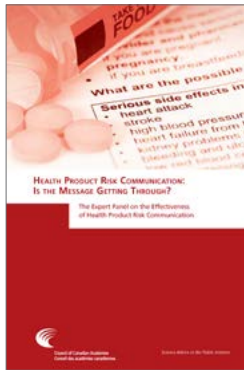
When Antibiotics Fail (2019)



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



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



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

CCA Board of Directors*

Sue Molloy, FCAE, (Chair), President, Glas Ocean Electric; Adjunct Professor, Dalhousie University (Halifax, NS)

Soheil Asgarpour, FCAE, President, Petroleum Technology Alliance Canada; President-Elect, Canadian Academy of Engineering (Calgary, AB)

Pascal Grenier, Senior Vice President, Flight Services and Global Operations, CAE (Montréal, QC)

Chantal Guay, FCAE, Chief Executive Officer, Standards Council of Canada (Ottawa, ON)

Jawahar (Jay) Kalra, MD, FCAHS, Professor, Department of Pathology and Laboratory Medicine and Member, Board of Governors, University of Saskatchewan (Saskatoon, SK)

Catherine Karakatsanis, FCAE, Chief Operating Officer, Morrison Hershfield Group Inc.; President-elect, Canadian Academy of Engineering (Toronto, ON)

Cynthia E. Milton, FRSC, Associate Vice-President Research, University of Victoria (Victoria, BC)

Donna Strickland, C.C., FRSC, FCAE, Professor, Department of Physics and Astronomy, University of Waterloo (Waterloo, ON)

Gisèle Yasmeen, Associate Vice-President, International, University of Ottawa (Ottawa, ON)

*As of July 1, 2023

CCA Scientific Advisory Committee*

David Castle (Chair), Professor, School of Public Administration and Gustavson School of Business, University of Victoria; Researcher in Residence, Office of the Chief Science Advisor to the Prime Minister of Canada (Victoria, BC)

Maydianne C. B. Andrade, Professor, Biological Sciences, University of Toronto Scarborough; President, Canadian Black Scientists Network (Toronto, ON)

Peter Backx, FRSC, Professor, Department of Biology, and Canada Research Chair in Cardiovascular Biology, York University (Toronto, ON)

Kyle Bobiwash, Assistant Professor and Indigenous Scholar, Department of Entomology, University of Manitoba (Winnipeg, MB)

Stephanie E. Chang, Professor, School of Community and Regional Planning and Institute for Resources, Environment and Sustainability, University of British Columbia (Vancouver, BC)

Jackie Dawson, Canada Research Chair in Environment, Society and Policy, and Associate Professor, Department of Geography, University of Ottawa (Ottawa, ON)

Colleen M. Flood, FRSC, FCAHS, Dean (Faculty of Law), Queen's University (Kingston, ON)

Digvir S. Jayas, O.C., FRSC, FCAE, Distinguished Professor and Vice-President (Research and International), University of Manitoba (Winnipeg, MB)

Malcolm King, FCAHS, Scientific Director, Saskatchewan Centre for Patient-Oriented Research, University of Saskatchewan (Saskatoon, SK)

Chris MacDonald, Associate Professor; Director, Ted Rogers Leadership Centre; Chair, Law and Business Department; Ted Rogers School of Management, Toronto Metropolitan University (Toronto, ON)

Nicole A. Poirier, FCAE, President, KoanTeknico Solutions Inc. (Beaconsfield, QC)

Louise Poissant, FRSC, Scientific Director of Fonds de recherche du Québec – Société et culture (Montréal, QC)

Jamie Snook, Executive Director, Torngat Wildlife Plants and Fisheries Secretariat (Happy Valley-Goose Bay, NL)

David A. Wolfe, Professor of Political Science, University of Toronto Mississauga; Co-Director, Innovation Policy Lab, Munk School of Global Affairs and Public Policy, University of Toronto (Toronto, ON)

*As of July 1, 2023



Council of
Canadian
Academies

Conseil des
académies
canadiennes

180 Elgin Street, Suite 1401
Ottawa ON K2P 2K3
Tel: 613 567-5000
www.cca-reports.ca