McMaster University

CAIC
CANADIAN ANTIMICROBIAL INNOVATION COALITION

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ANTIBIOTIC ACCESS AND CAPACITY

A grassroots solution to improving patient access to novel antibiotics in Canada

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This work is a collaboration between the Canadian Antimicrobial Innovation Coalition (CAIC) and McMaster University that seeks to improve the health of Canadians by increasing options and optimizing the use of appropriate antibiotics via an integrated model that follows the principles of accessibility, stewardship, and reasonable costs and provides incentives for manufacturers to produce, seek approvals for, and supply new antibiotics to the Canadian market.

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EXECUTIVE SUMMARY

About this report

This proposal is the result of a grassroots endeavour to explore and present solutions to extensive issues with new antibiotic access and capacity in Canada. Jointly led by McMaster University and the Canadian Antimicrobial Innovation Coalition (CAIC), this project was catalyzed by the urgent need to slow the spread of antimicrobial resistance (AMR).

Background

AMR occurs when pathogenic bacteria develop the ability to resist the drugs designed to kill them. These resistant infections come with considerable economic downside, and, more importantly, are costing Canadian patients their lives. AMR was declared by the World Health Organization as one of the top-10 Global Public Health Treats facing humanity. While COVID-19 caught the world by surprise, AMR is a predictable and preventable crisis, but we need to get ahead of it today before it becomes the next pandemic.

Today, a number of novel antibiotics — drugs with efficacy against otherwise resistant bacteria — have been approved for use in other jurisdictions but are unavailable to Canadian patients. For example, of 18 novel antibiotics approved and commercially launched in 14 high-income countries between 2010-2019, only two had been introduced in Canada — the fewest number on the entire list — while the U.S. introduced as many as 17. Similarly, several new antibiotics already approved in Canada are rarely used due to costs and administrative barriers. The result is the overuse of first-line drugs in Canada, which ultimately has implications for resistance rates and health outcomes.

Under the leadership of a steering committee comprised of experts from industry, academia, economics, microbiology, policy, medicine, and beyond, we sought to develop ways in which newer antibiotics could be better accessed by Canadian prescribers — and thereby Canadian patients. Consulting broadly with a range of stakeholders from across Canada and across sectors, we took a two-pronged approach to address the problem:

1. We considered ways to improve appropriate, stewarded access to essential, new, and newer antibiotics that are already approved but underutilized in hospitals due to administrative or cost barriers.
2. On a broader scale, we explored ways to improve market access for manufacturers of novel, essential, and new antibiotics currently in the R&D pipeline or newer antibiotics approved in other jurisdictions.

> “While COVID-19 caught the world by surprise, AMR is a predictable and preventable crisis, but we need to get ahead of it today before it becomes **the next pandemic**.

Solution

This work resulted in a set of 30 concise recommendations designed to not only improve antibiotic access and capacity, but also to protect these vital medications through stewardship efforts and improved surveillance of resistance rates in Canada.

These recommendations feed into a proposed integrated solution — a patient-centered model designed to bring more novel antibiotics to Canada through incentivization and regulatory improvements, and to expand front-line access through measures related to data, costs, distribution, and supply and demand. Our integrated solution proposes to establish:

- Guaranteed minimum revenue agreements for manufacturers of novel antibiotics
- Antibiotic- and diagnostic-specific funding envelopes for hospitals
- Data collection and reporting processes, leveraging new and existing information systems
- Infrastructure to improve antimicrobial stewardship at a pan-Canadian level

The integrated solution is suited to Canada's health delivery model, where the federal government provides health care funding to Canada's provinces and territories. This particular model envisions the federal government will lead efforts to establish pricing/procurement mechanisms for essential/priority antibiotics and related diagnostics. Provinces could contribute funding to support the model's implementation and ensure optimal use of essential/priority antibiotics (for example, data generation, care delivery, stewardship, and surveillance). Canada's response to the COVID-19 pandemic demonstrated the federal government, through the Public Health Agency of Canada and Public Services and Procurement Canada, can play a critical role in securing access to public health products, in partnership with Canada's provinces to facilitate product distribution and delivery.

> Although our focus is currently on applying the integrated solution to the hospital setting, the combined models are **adaptable** and **highly relevant** to community settings as well.

Although our focus is currently on applying the integrated solution to the hospital setting, **the combined models are adaptable and highly relevant to community settings** as well.

With respect to economic incentives, our recommendations are in line with the work undertaken at the international level to determine the public funding required to address market challenges. This proposal introduces a funding range for economic incentives in Canada, through the application of

models prepared for other jurisdictions, such as Sweden, the UK, and the US.

We understand that this solution is ambitious — that is why we are proposing that it is initially piloted in a select region using a limited number of antibiotics. We recommend the Hamilton-Niagara-Haldimand-Brant region as a candidate location and suggest starting with two novel antibiotics that have already been approved for use in Canada to demonstrate the contractual, distributional and federal-provincial coordination elements that will be relevant to a made-in Canada antibiotics incentive model..

The 12-18 month pilot will expose strengths and weaknesses in the proposed model, which can then be enhanced or rectified before the solution is subsequently scaled to meet pan-Canadian needs.

Costs

After a thorough and collaborative costing exercise, we estimate that such a pilot would require an investment in the range of $4.2-7.8 million (in 'new money') to support, in short, the streamlining and integration of processes related to data collection and reporting, the implementation of a stewardship application and antibiotics guidelines, and strengthening of the distribution systems for a timelier access to novel antibiotics by hospitals.

In parallel, work will be undertaken to validate and operationalize the incentives policies and funding estimated to range from $1.7-17.7 million per year over 10 years, depending on where the antibiotic is in its lifecycle, including whether or not it has already been approved in Canada.

This funding would be provided collaboratively between Health Canada and the Public Health Agency of Canada.

Impact

Investing in this AMR pilot project and subsequently expanding to all provinces and territories in Canada brings along a substantial number of benefits:

- a more effective and safe use of antibiotics and antimicrobials
- a more effective use of diagnostics, informing treatment decisions
- improved treatment outcomes
- reduced complications and more severe infections
- an incentive for the pharmaceutical industry to continue investing in the Canadian market to keep Canadians healthy
- direct and indirect financial savings for the system as a whole
- a clear message to international partners that Canada is doing its share to combat the AMR crisis

Most importantly, however, are the lives of Canadians that will be improved and even saved as a result of having access to treatments that are more responsive to their needs and condition.

Enclosed, you will find our methodology and approach, findings from our environmental scan, our recommendations and detailed solutions, including a pathway leading to implementation and operationalization. While we consider this proposal to be comprehensive, we are available to answer any questions.

With your support, Canada can take meaningful action against AMR and join a growing number of countries implementing new antibiotic access programs to allow the best possible patient care while helping to maintain a pipeline for essential medicines.

—1—

INTRODUCTION

This project, an industry-academia collaboration, was a partnership between McMaster University and the Canadian Antimicrobial Innovation Coalition (CAIC), together seeking to improve the health of Canadians by increasing access to novel antibiotics in Canada. Alongside a long list of stakeholders from across the country and relevant sectors, we worked toward developing innovative solutions that will ensure Canadian patients have access to the right medications at the right time.

The outcome of a variety of stakeholder inputs and specialized guidance from a diverse committee of experts, this document formally proposes a number of concise recommendations and an integrated solution that, together, can set Canada on a path to improving health outcomes and reducing antimicrobial resistance (AMR). To set the stage, this section details the impetus for this important work, charts strategic alignment with ongoing government initiatives, outlines our objectives and scope, and presents our methodology and approach.

1.1 BACKGROUND

Antibiotic resistance has become highly prevalent and problematic in treating common illnesses. As defined by Health Canada,[1] resistance occurs when pathogenic bacteria develop the ability to resist the drugs designed to kill them. Currently, 26% of infections[2] in Canada fail to resolve when treated with first-line antibiotics. The 2019 *When Antibiotics Fail* report also surmised that resistance to all first-line antimicrobials is likely to reach 40% by 2050, with 13,700 Canadians dying from resistant bacterial infections. More worrisome is that these forecasts were made prior to the arrival of COVID-19, and research[3-6] already shows that the ongoing pandemic is exacerbating resistance considerably.

A proven way[7] to minimize resistance is to reduce the repeated use of broad-spectrum antibiotics. However, despite the development of newer, narrow-spectrum alternatives indicated to treat specific infections, the often ineffective first-line drugs continue to be widely used, largely because they are less costly and more accessible than their novel counterparts. One of the key reasons novel antibiotics are not more accessible is because so few of them are coming to market. Indeed, given the cost of developing these drugs and their limited return on investment, many pharmaceutical companies have abandoned or neglected this market. Meanwhile, for a number of business and administrative reasons, the few companies that have continued to develop novel antibiotics are not consistently bringing their products to the Canadian market.

In fact, a recent study[8] showed that, of 18 novel antibiotics approved and commercially launched in 14 high-income countries between 2010-2020, only two had been introduced in Canada — the fewest number on the entire list. For comparison, the same study showed that the US brought 17 new antibiotics to market during the same timeframe, and the EU, the UK, and Sweden trailed not far behind with 14, 11, and 10 respectively.

Patient access to 18 novel antibiotics in 14 high-income countries[8]

Although infectious disease physicians and pharmacists in Canada can request special access to drugs approved in other jurisdictions for patients infected with multidrug-resistant organisms, the length of time and complex processes required to do so are considered an impediment to timely patient care. The time to correct this situation is now. Not only are patients bearing the burden of this problem, but antibiotic resistance is considered by the World Health Organization (WHO) to be one of the "top 10 global public health threats facing humanity."[9] The good news is we don't have to start from scratch. Many countries around the world are already responding to the WHO's global call-to-action on resistance. Several G7 and G20 countries — including Canada — are responding to the growing problem with formal action plans and considerable financial commitments. As well, many grassroots and government initiatives related to antimicrobial resistance (AMR) are sprouting up across

the planet, including Canada's own PHAC-funded project: AMR Network, which examined the issue of governance for AMR across One Health. That said, there is still much room for improvement — especially regarding access to new and newer antibiotics. Having examined innovative access strategies and international best practices, we concluded that access to novel antibiotics can be improved considerably in Canada, and that doing so will invigorate an inadequate market, foster antibiotic research and development, reduce stress on the Canadian healthcare system, and — most importantly — save lives.

This document proposes a holistic, integrated solution to the barriers that prevent novel, priority antibiotics — those essential to treating complex, life-threatening infections caused by priority pathogens — from entering the Canadian market and provides a series of recommendations to improve the situation in the short term. This important work has been conducted by the McMaster Antibiotic Access & Capacity (MAAC) Project, a grassroots endeavour that builds upon previous and continuing efforts of key stakeholders in Canada's AMR space.

The MAAC Project is a collaboration between the Canadian Antimicrobial Innovation Coalition (CAIC) and McMaster University. Steered by a committee whose members represent the many facets of the antibiotic space in Canada — industry, academia, economics, microbiology, policy, knowledge translation, and medicine — we developed this proposal by critically examining antibiotic access issues from two key perspectives.

Starting with the micro level, we considered ways to improve patient access to essential, new, and newer antibiotics that are already approved and marketed in Canada. Then, on a macro level, we explored ways to increase market access to novel antibiotics that have been approved in other jurisdictions but are not yet available in Canada.

Alignment with the Federal Government

The *Pan-Canadian Framework for Action*,[10] a 2017 roadmap for action against AMR published by the Public Health Agency of Canada, consists of four key components: surveillance, infection prevention and control, stewardship, and research and innovation. This project is well-aligned with each of these pillars. Implementing our proposed solutions to address the current lack of access to novel antibiotics will:

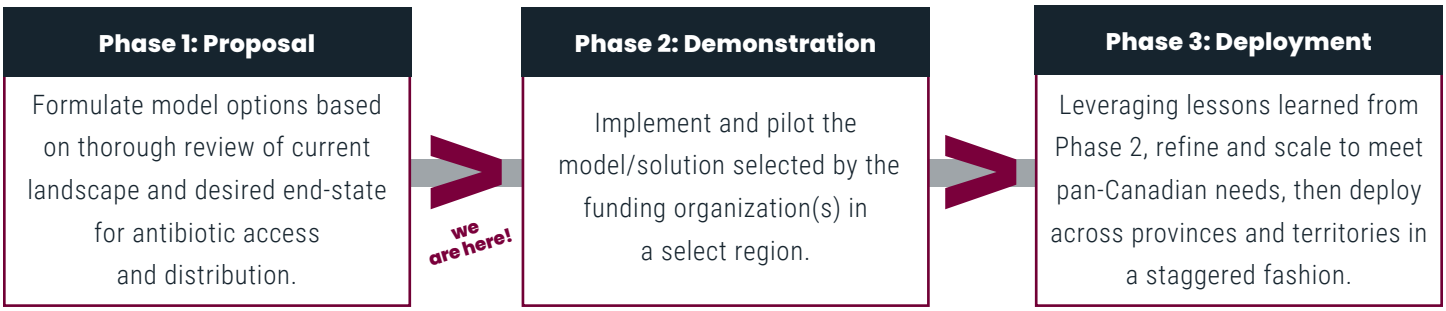
- Streamline data collection and dissemination, thereby enhancing **surveillance** of emerging or worsening resistance
- Minimize and shorten hospital stays, which reduces exposure to nosocomial **infections**
- Introduce more improved options for prescribers, thereby reducing use and improving **stewardship** of existing antibiotics
- Incentivize manufacturers to bring new antibiotics to market, thereby fostering **R&D**

Similarly, our proposal maps well onto the current draft of the forthcoming Pan-Canadian Action Plan on AMU/AMR. Not only do our recommendations and solution contribute to more than 20 objectives outlined in the document, but they align perfectly with several, including:

- **Establish and implement** common case definitions and minimum data sets for collection of data, and identify new sources of data.
- **Implement antimicrobial stewardship programs** in all hospitals according to accreditation standards
- **Develop and implement regulatory incentives** to encourage the submission for authorization in Canada of new antimicrobials for human use.
- **Explore the need for alternative payment models** to ensure sustained marketing of new antimicrobials, alternatives to antimicrobials, and diagnostic devices for human use in Canada.

Indeed, improving access to antibiotics would expedite progress in key issue areas determined by the federal government and provincial/territorial authorities.

1.2 PROJECT OBJECTIVES & SCOPE



The MAAC Project was established to improve the health of Canadians by increasing prescribing options and optimizing the use of appropriate antibiotics via an integrated model that follows the principles of accessibility, stewardship, and reasonable costs. As well, we set out to recommend ways in which Canada could incentivize manufacturers to supply new antibiotics and accompanying diagnostics to the Canadian market. At its outset, the project was divided into three distinct phases. While this document represents Phase 1, it was designed with demonstration, implementation, and optimization in mind. Our specific project goals are outlined in the chart below:

Design solutions that...

- Optimize the utilization of novel antibiotics, in conjunction with stewardship principles, to increase downstream investments in novel drug discovery and improved access to new antimicrobials for critically-ill patients with drug-resistant infections
- Alleviate the burden of cost for novel antibiotics faced by hospitals
- Realize economies of scale for the overall system
- Expand access and reduce barriers to novel antibiotics
- Improve prescribing-related transparency, data collection, and knowledge sharing across Canada

Provide recommendations to...

- Expedite approval of high-demand novel antibiotics
- Streamline availability of novel antibiotics at reduced costs to hospitals
- Revitalize the antibiotic market in Canada by attributing a more appropriate value to antibiotics and working with manufacturers that wish to ensure a healthy ecosystem of pharmaceutical innovation, discovery, and supply for Canadians

Secure funding to...

- Demonstrate contract structure, access, distribution, oversight and information systems for available newer drugs through a pilot.
- Scale findings from the pilot to implement and operationalize a pan-Canadian solution to antibiotic access and capacity issues, which are discussed further in Section 2 ("Analysis of the Current State").

1.3 APPROACH & METHODOLOGY

Over the course of this project, we examined a variety of models and pathways to improve access and capacity, including what has (and hasn't) worked in other jurisdictions, what has worked in Canada in other contexts, and what is not working with the status quo. This research was undertaken using a variety of methodologies.

First, we conducted a thorough review of relevant literature, including foundational reports published by the Council of Canadian Academies,[2] Project: AMR Network,[11] and others. We also examined work published in a number of high-impact journals, including Clinical Infectious Diseases, Health Policy, and BMJ Open, and reviewed over five years' worth of Special Access Program (SAP) antibiotic requests. The full list of resources consulted has been appended to the end of this document.

This information was strengthened by stakeholder inputs, including multiple surveys, more than 20 one-on-one interviews, and a series of broad consultations. These inputs offered both qualitative and quantitative data that informed our design process. Since June 2021, we have consulted with Canadian pharmacists, physicians, and microbiologists, distribution and supply chain experts, and various international leaders, among others (See Appendix 5 for complete list). While the literature review and jurisdictional scan formed the bedrock of our project, it was these stakeholder inputs that shaped the credibility and feasibility of our solutioning process.

Finally, at various touchpoints throughout the course of this project, we engaged different areas of government. We held a preliminary meeting with representatives of Health Canada (HC) and the Public Health Agency of Canada (PHAC) to apprise them of our project goals. As well, we invited observers from HC and PHAC to listen in on our stakeholder consultation sessions — and several did so.

Meanwhile, during our model design stage, we consulted with provincial government representatives to ensure that our vision was in alignment with their own mandates. We worked closely with stakeholders to understand how to improve the situation holistically. Then, leveraging stakeholder inputs as the bedrock of our plan, we formed a working group to conceive model options that are not only appropriate for the Canadian context, but also position Canada to uphold its international commitments around combatting AMR as a whole. Our working group was composed of representatives from our steering committee and project team, and, through a thorough workshopping process, arrived at the recommendations, proposed measures, and integrated solution outlined in this document.

We also attended a government-run 'Best Brains Exchange' in October 2021, at which we presented drafts of our proposed solutions to senior policymakers, researchers, and implementation experts. This engagement helped us refine our work so that our solutions could both meet the needs of stakeholders and satisfy the mandates of government.

High-Level Project Timeline

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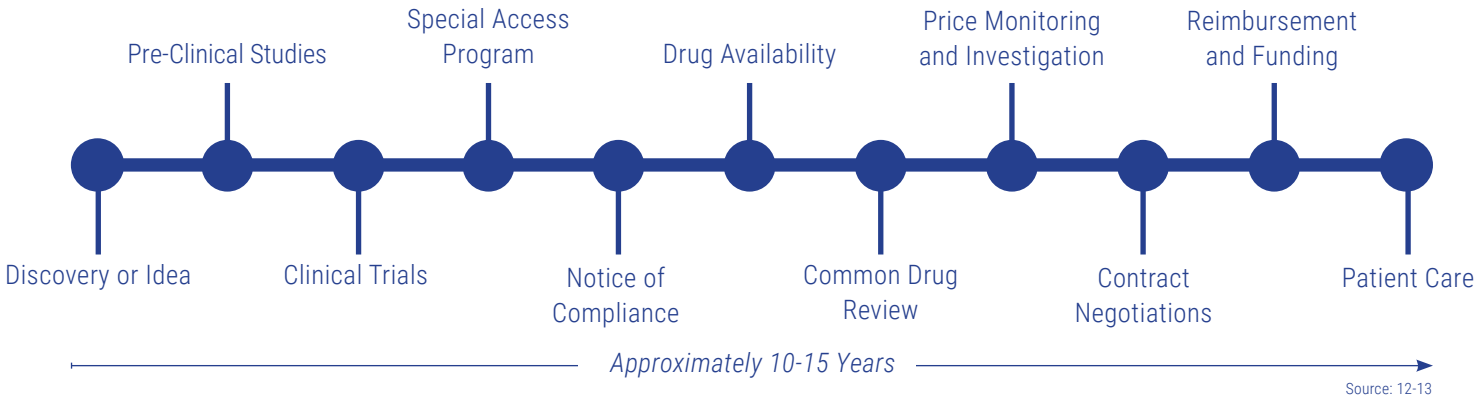
ANALYSIS OF THE CURRENT STATE



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With antibiotic-resistant infections becoming more frequent, patients are facing a reduced chance of successfully clearing their infection upon treatment with a first-line antibiotic. Given this problem, novel antibiotics are becoming more important than ever before — where infecting pathogens are resistant to all available antibiotics, they become the only treatment option. Ensuring that healthcare teams readily have access to existing novel antibiotics to give patients a fighting chance against their infections; however, ensuring access is much easier said than done.

Right now, a lack of assured revenue is keeping manufacturers from bringing their products to Canada. Couple that with a rigorous regulatory process, a time-consuming special access program, a general lack of important data, and a litany of other hurdles, and you can see why access to these novel drugs is not seamless. This section navigates the current antibiotic landscape in Canada and explores a series of case studies that, together, serve as a conceptual framework for how change could be implemented.

2.1 INCENTIVES

Because the global antibiotics pipeline is drying, we engaged in discussions around what could be done to invigorate the Canadian and international markets. These broad conversations explored push and pull incentives that could help in both the short- and long-terms — the former to elicit immediate results and the latter to ensure sustenance.

Because this project intended to focus on pull incentives, they comprise the majority of findings enclosed herein; however, as both types of incentives are needed for a healthy antibiotic ecosystem, we have also included some information on push incentives for future consideration.

In Canada, pull incentives are few and far between, and not necessarily meant to attract manufacturers to this market. For instance, Canada invested heavily in the Gavi Pneumococcal vaccine Advance Market Commitment (AMC) pilot[14] as an AMR-specific pull incentive; however, it was designed to benefit low-income countries — not Canada. Patent protection (including extended patent protection) is another type of pull incentive in which Canada has invested significantly over the years, but it has been around so long that it has become the norm rather than a true form of incentive.

Push incentives are slightly more common across the country, as Canada routinely subsidizes pharmaceutical companies. While there is currently no public information regarding the total value of direct subsidies nationally for antibiotic development, one study[15] estimated that Quebec's private pharmaceutical subsidies ranged from $688M to $1,936M in 2010. Regarding public funding specific to antibiotics, a 2016 study[16] ranked Canada third amongst 19 Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) countries for total number of AMR-related projects and associated funding. However, much of this funding flows through academia; not industry. Federal granting agencies like the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institutes of Health Research (CIHR) fund academic research to generate subsidized capital, labour, and knowledge. The motivation for this is clear and as stated in a 1985 federal government policy shift to provide R&D for industry through academia: "Industry can no longer afford to do all of the long term-research it needs to survive; thus, it is no longer looking at universities simply as an inexpensive source of trained people, but also as a vast reservoir of expertise which can perform that urgently-needed long-term effort." [17]

It should be noted, though, that this investment in research and training of highly qualified personnel has not been enough to sustain the antibiotic ecosystem due to the unique nature of these medicines.

Push & Pull Incentives [18]

There are many ways in which governments can incentivize activity across industry. These incentives are often classified as belonging to one of two categories — either 'push' or 'pull.' Push incentives are mechanisms that drive inputs, while pull incentives are mechanisms that reward outputs. Examples of push incentives include tax credits, grants, and public-private partnerships. Pull incentives, meanwhile, could include advanced market commitments or patent extensions.

2.2 THE REGULATORY ENVIRONMENT

The antibiotic regulatory environment in Canada includes four key steps and involves a number of disparate stakeholder groups. While products to be administered in hospitals are often only subject to the first step in most provinces and territories, the outcomes of those steps regularly impact the hospitals' ability or decision to add a product to their formulary, as well as the price hospitals will ultimately pay for those products.

First, companies must seek **marketing authorization** from Health Canada.[19] During this process, the federal government assesses the safety, efficacy, and manufacturing quality of the drug in question. If it meets Health Canada standards, the manufacturer is given a Notice of Compliance (NoC) or a Notice of Compliance with Conditions (NoC/c). At this point, a monograph outlining indications and clinical claims can be made. Once the NoC or NoC/c is granted, a unique Drug Identification Number (DIN)[20] is also issued to enable the identification, sales, and tracking of that drug throughout its lifecycle as it is sold, distributed, dispensed, and administered.

Next is **pricing review** — the Patented Medicines Prices Review Board (PMPRB) is called upon to review the product and determine a maximum average potential price (MAPP).

From there, the product undergoes **reimbursement review.** This involves a common drug review, where experts consider comparative clinical and cost-effectiveness for new medicines. This process results in a formulary recommendation — list, do not list, or list with conditions.

The final step in the regulatory pathway is jurisdictional **formulary decision-making**. At this point, the drug is subjected to a Public Drug Benefit Plan review. This process results in recommendations for inclusion on more localized formularies.

Throughout these four steps, a number of stakeholder organizations play key roles. Health Canada's approval role during the marketing authorization phase is obvious, as is PMPRB's role in pricing. However, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institut national d'excellence en santé et en services sociaux (INESSS) in Quebec play the pivotal role of price monitoring and investigation during the patent period. Private drug plans, meanwhile, handle reimbursements during and after the patent period, and, at the provincial/territorial level, the pan-Canadian Pharmaceutical Alliance begins negotiations after the CADTH or INESSS review concludes, and handles reimbursement after this point.

It's clearly a complex landscape that comes with unique challenges. Acknowledging this, Health Canada has created two processes to expedite the regulatory pathway for certain drugs meeting the innovation criteria:

- priority review (a review period reduced from 355 business days to approximately seven months), and
- notice of compliance with conditions (approval on Phase-II data, with the condition that Phase-III data is later required to support efficacy)

Although approval of innovative medicines has become more efficient due to these processes, the average approval time for Health Canada still remains well above the average time for FDA approval. But while the regulatory pathway is slow-

moving, an analysis of post-approval time to marketing for antibiotics across different countries showed that the delay in marketing is highly variable and that "regulatory approval is clearly not the only barrier."[8] Additional delays to market occur as manufacturers reassess whether to move forward with the launch of their product in this country. This decision is typically based on a number of factors, but often ultimately comes down to whether or not market launch in Canada will yield a reasonable return and thus justify the investment — and without enhanced pull incentives, it often does not.

Key Players on Canada's Regulatory Pathway

Health Canada	PMPRB	CADTH & INESSS	pCPA	Drug Plans
Health Canada plays a vital role as the Canadian public safeguard for ensuring only safe and effective medicines are used in Canada. In order for an antibiotic to be approved for use in Canada, manufacturers must submit data from clinical trials to prove safety and efficacy.	PMPRB provides stakeholders with price, cost, and utilization information to help them make pricing, purchasing, and reimbursement decisions. It also acts as a check on the prices of patented medicines. The price is set by comparing clinical data between new drugs and existing standards of care, as well as prices in countries with similar economic metrics.	CADTH is a national-level organization that provides recommendations on drug usage and prices. Like CADTH, INESSS is a Québec-based organization that recommends whether a drug should be reimbursed with public funding. While INESSS's jurisdiction extends to hospitals, CADTH's does not.[21]	The pan-Canadian Pharmaceutical Alliance conducts joint price negotiations for brand name and generic drugs for the P/T public drug plans and/or cancer agencies, and federally for Non-Insured Health Benefits (NIHB), Correctional Services of Canada (CSC), and Veterans Affairs Canada (VAC). Their jurisdiction excludes hospitals.[22]	The P/Ts' public drug plans under the respective departments or ministries of health determine which drugs will be covered under public drug plans. In most provinces, this process excludes hospitals.[23]

2.3 PRICING, CONTRACTING, AND PROCUREMENT

Since manufacturers may choose to sell a new product to hospitals as soon as a DIN is provided, they may approach hospitals directly about their product or enter an agreement for a large procurement contract through a Shared Services Organization (SSO) or a Group Purchase Organization (GPO), depending on how the province/territory, regional health authority, or hospital network is set up for procurement.

In parallel — or immediately after — price negotiations between the pCPA and manufacturers begin. The pCPA uses the price ceiling provided by the PMPRB and the recommendations made by CADTH/INESSS to establish a Product Listing Agreement (PLA) that sets the price at which a manufacturer agrees to sell its product to the different provinces and territories.

As the pCPA's objective is to reduce costs for Canadians, the price is typically a reduction from what CADTH recommended — or at least from what PMPRB set as the ceiling. If the PLA is completed after a contract was established between the SSO/GPO and the manufacturer, the contract will be adjusted to reflect any further rebates obtained by pCPA that exceed those secured by the SSO/GPO to provide hospitals with the same prices as public payers would be granted for purchases made for the community settings. Once the pCPA has set a price, P/Ts must determine whether or not to include the product on their provincial formulary for reimbursement by the public drug plans. While for most provinces this step excludes hospitals, and hospitals have the discretion to add any approved product onto their respective formularies, the P/T-level decisions often influence whether hospitals will purchase and administer a particular drug.

As these processes take time and usually result in deductions for purchasers and therefore a reduction in profit margin for the manufacturer, manufacturers must perform careful calculations and assess business risks before entering the small Canadian market.

While Canada pays, on average, close to the reference list price for a drug, this is much less than what the US pays. In fact, Americans pay approximately 2.56 times more[24] for medications than citizens in other countries.

Hospitals may choose to order through or outside the contracts established by the GPO/SSO; however, doing so subjects them to higher prices.

SSOs & GPOs

Shared services organizations (SSOs) are medical or administrative services for which two or more hospitals or health care organizations agree to share responsibility. Examples include Health Shared Services BC (HSSBC), HSS Ontario, And Service New Brunswick. **Group purchasing organizations (GPOs)** are companies that negotiate prices for drugs, devices, and other medical products and services on behalf of healthcare providers, including hospitals, ambulatory care facilities, physician practices, nursing homes, and home health agencies. Examples include HealthPRO and Mohawk Medbuy.

2.4 MANUFACTURING AND DISTRIBUTION

Manufacturers are responsible for large-scale production and packaging of antibiotics, which can be divided into Active Pharmaceutical Ingredient (API) and Finished Dosage Form (FDF). An API is the component of a drug with biological activity that is not yet prepared in a form suitable for administration to patients, while an FDF is the final state of a drug that is ready for consumption. These two stages of manufacturing often occur at separate facilities. Distributors are responsible for moving the FDF from the manufacturers to hospital pharmacies. Once the products are ready for distribution, manufacturers may choose to list their product for distribution by the distributor of their choice. Serving Canadian hospitals are the Canadian Pharmaceutical Distribution Network (CPDN) and McKesson. The two organizations have implemented information systems to allow the online ordering and tracking of inventory at the hospital level.

Hospital pharmacies are the endpoint for the manufacturing and distribution process, and they are responsible for purchasing and receiving the drugs from the distributors. Pharmacies typically order and hold stock for what they foresee needing in the short-term amongst the drugs on their hospital formularies; however, shortages occur frequently enough, leaving pharmacies on backorder for key medications.

2.5 DISPENSING NOVEL ANTIBIOTICS ALREADY APPROVED IN CANADA

Although new antibiotics are not necessarily superior to existing treatments, increased usage of old/older and broad-spectrum antibiotics drives resistance and thus jeopardizes their efficacy. Unfortunately, the list of antibiotics new to the Canadian market is relatively short.

It is also worth noting that for many of these newer drugs, marketability does not necessarily equate to availability. For instance, despite being approved for use in Canada since 2015, ceftolozane-tazobactam is currently not available in the country due to supply chain issues.

And while Canada's list of approved novel antibiotics is growing, it is doing so at a glacial pace — at least compared to our international counterparts. In a survey of 18 new antibiotics that entered the global market from 2010-2019,[8] fidaxomicin and ceftalozane-tazobactam were the only two to gain market access in Canada. It should be noted that this survey did not include all new antibiotics — as evidenced by the exclusion of ozafloxacin — and, in some cases, such as with tedizolid, a notice of compliance *was* issued, but the manufacturer did not subsequently proceed to market. In any case, this study shows that many novel drugs available to global patients have not yet received approval from Health Canada.

Some newer antibiotics recently approved in Canada

Novel Antibiotic	Use
Fidaxomicin	*Clostridium difficile*
Ceftolozane-tazobactam	Complicated intra-abdominal infections and complicated urinary tract infections
Ozafloxacin	Impetigo
Dalbavancin	Acute bacterial skin and skin structure infections
Telavancin	Methicillin-resistant *Staphylococcus aureus* infections

Meanwhile, Lefamulin, used to treat community-acquired pneumonia, is the latest novel antibiotic to receive marketing approval from Health Canada in 2020.

2.6 DISPENSING NOVEL ANTIBIOTICS *NOT* APPROVED IN CANADA

Clinicians trying to treat Canadian patients with multi-drug-resistant infections encounter a significant barrier in that many novel antibiotics are not yet available in Canada.[25] While clinicians can request these drugs through Health Canada's Special Access Program (SAP), and – pending approval of the request – have these drugs shipped directly to their hospital, this step adds yet another administrative and time-consuming layer to the care process when time is of the essence for the treatment of rapidly progressing infections, leading to poor health outcomes for these patients.

In addition to the time delay for SAP requests, hospitals are usually required to purchase these antibiotics at the manufacturer's price, which is typically based on the US-market's unit cost and therefore far beyond the cost of common/generic antibiotics. In some cases, the manufacturer declines the request due to the costs and time associated with filling out the paperwork and supplying the drug. Others — like the manufacturers of meropenem-varbobactam and ceftazidime-avibactam, for example — are choosing not to make their product available via the SAP program altogether.

Further, when novel antibiotics are not marketed in Canada, their accompanying diagnostics are also unavailable. This situation, combined with the dearth of practical information and hands-on experience with novel antibiotics, causes uncertainty for providers about their efficacy against specific pathogens, as well as hesitancy around requesting them through the SAP. Supporting this, our analysis of the last five years of SAP data showed that despite their potential availability from international suppliers, novel antibiotics are rarely requested compared to older drugs that are not approved in Canada.

The SAP data also revealed a significant proportion of requests for alternative formulations of antibiotics that are already marketed in Canada. This points to fragile supply chains as another barrier to clinician access. While supplying antibiotics based on anticipated yet highly variable demand can cut costs for manufacturers, it often results in shortages and delays during demand surges, which ultimately manifest as added public healthcare costs linked to longer hospital stays and less effective treatment for patients. Indeed, our discussions with experts in the field verified that providers typically turn to the SAP during shortages[26] until a resolution is found with the manufacturer, with support from all stakeholders involved in the supply chain.

> Despite their potential availability from international suppliers, **novel antibiotics are rarely requested** compared to older drugs that are not approved in Canada.

Canada's Priority Pathogens vs. Antibiotics Not Approved in Canada

Canada's federal health agencies have identified pathogens that may cause serious and life-threatening infections in Canadian patients, and for which "there are no or limited treatment options available."[27] However, our research shows that there *are* in fact relevant treatments available for patients in other countries — just not for those here in Canada. This chart shows how novel antibiotics approved elsewhere could help treat infections caused by the pathogens Canada has deemed a priority.

Priority Pathogen / Corresponding Antibiotic	Bezlotoxumab	Cefiderocol	Ceftaroline	Ceftazidime/avibactam	Delafloxacin	Eravacycline	Imipenem-cilastatin/relebactam	Lascufloxacin	Meropenem/vaborbactam	Omadacycline	Oritavancin	Plazomicin	Sarecycline	Tedizolid
Methicillin-Resistant *Staphylococcus aureus*			✓		✓	✓				✓	✓			✓
Vancomycin-Resistant *Enterococcus*					✓	✓				✓				✓
Carbapenemase-producing *Enterobacteriaceae*		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		
Clostridium difficile	✓*													
Neisseria gonorrhoeae														
Mycobacterium tuberculosis														
Streptococcus pneumoniae			✓					✓		✓				
Streptococcus pyogenes			✓			✓		✓		✓	✓			✓
Typhoidal and non-typhoidal *Salmonella enterica*														
Acinetobacter spp.		✓												
Campylobacter spp.														
Escherichia coli		✓	✓	✓	✓	✓	✓		✓			✓		

✓ indicates some degree of efficacy on combatting infections caused by the corresponding priority pathogen.

✓* indicates efficacy when used in combination with another drug.

2.7 DATA, CLINICAL EVIDENCE, & INFORMATION MANAGEMENT SYSTEMS

Currently, there is a lack of relevant data captured — or at least shared publicly — in this space. Stakeholders from across the country and across sectors are desperately seeking more information related to usage, inventory, and costs. This includes data on antibiotic prescriptions, utilisation metrics, and resistance trends.

This data chasm has left experts from diverse backgrounds appealing for access to an integrated information hub that could harmonize the relationship between government and hospital administrators, clinicians, distributors, and manufacturers, keeping all relevant parties at the cutting edge. Such a system has been central to Canada's coordinated response to COVID-19.

And while data is crucial to improving decision-making in the care, pricing, and provisioning processes, stakeholder inputs revealed that it could also create a more equitable landscape for Canadian patients. Right now, smaller hospitals are at a disadvantage when it comes to establishment of formal stewardship infrastructure, and enhancing access to pertinent antimicrobial information is considered a cost-effective way to rectify that.

2.8 STEWARDSHIP & DIAGNOSTICS

Data on antibiotic resistance and usage is collected and compiled by the Public Health Agency of Canada (PHAC) and published in the Canadian Antibiotic Resistance and Surveillance System (CARSS) Report. The data from CARSS informs a list of priority pathogens in Canada. Antibiotic usage is divided between animal and human use, and quantified by drug class. The CARSS data for humans documents the infection rates and types for different common pathogens, as well as the antibiotic resistance profiles and trends for each pathogen, informing stewardship.

Antibiotic-resistant pathogens emerge remarkably quickly — typically within five years[28] after a new antibiotic is introduced to the clinic. In contrast, the delay between discovering a new antibiotic in the lab and its launch as a commercial product is between 10 and 15 years. This situation has been compounded by the fact that the rate of discovery and development for new antibiotics is slowing over time. Larger pharmaceutical companies have been divesting from antibiotic research. Considering this, preserving the efficacy of existing antibiotics through stewardship is one of the most efficient ways to combat AMR.

What is Stewardship?

Stewardship is the preservation of antibiotic efficacy through critical management of antibiotics. There are many different aspects of stewardship, such as infection prevention through overall health improvements or controlling major sources of infections, developing policies that reduce unnecessary antibiotic usage in humans and agriculture, using the proper test rather than empirical evidence to diagnose, and adhering to stricter antibiotic administration by prescribing only the most appropriate antibiotic and dosage. For new antibiotics, the latter example is the most critical form of stewardship, since new antibiotics are not approved for use in agriculture and are typically tightly controlled for prescription in human use.

There are multiple stewardship mechanisms in effect in health care in Canada. In 2013, antimicrobial stewardship became required by Accreditation Canada for many facilities, including hospitals.[29]

Stewardship in hospitals is also monitored at the provincial level; for example, Public Health Ontario conducts surveys to track implementation of different stewardship methods. Despite this however, stewardship programs are still lacking and are not fully effective at providing prescribers and dispensers with the appropriate information and tools required to make routine clinical decisions about certain cases. Depending on hospital capacity, stewardship programs may be reliant on a single individual — and thus on their presence on site and ability to support several cases and providers at once.

Although much headway has been made in this regard in Canada, we can also look abroad for inspiration on further improvements. For instance, Sweden has become a world leader in stewardship. In 1986, the country implemented a ban on antibiotics as growth promoters. In 1995, they created a national strategy (called Strama) to apply comprehensive stewardship strategies. The net result[30] was a decrease in, or maintenance of low levels of antibiotic resistance in many priority pathogens, and the lowest usage and resistance levels in the EU.

In Canada, stewardship is informed by the growth and subsequent identification of specific pathogens from patient samples. This process may require a toolset unrelated to antibiotics. Microbial identification takes place in a hospital lab and takes 24-48 hours — or up to eight weeks for fungi and slow growing organisms such as those causing tuberculosis. If a pathogen (or pathogens) is identified, additional tests to determine which antibiotic kills the pathogen are performed. These tests result in resistance profiles called antibiograms. Hospital labs perform the antibiogram, which takes 18-24 hours. Public Health Ontario[31] has a database of hospital antibiogram information. Determination of susceptibility to new antibiotics requires that a testing method for the antibiotic be made available to labs. BioMerieux makes many of the tests and offers susceptibility testing through their Vitek instrument, or traditional E-Test strips. For outpatients and long-term care residents in Ontario, LifeLabs typically performs the antibiogram and posts the corresponding data online.

Because this process is so slow-moving, physicians tend to empirically prescribe first-line antibiotics to a patient. Then, depending on the results of microbial culture and antibiogram data, they will either stop antibiotics due to a negative culture, change antibiotics due to resistant bacteria or level of appropriateness, or continue current antibiotics if the bacteria appear susceptible. In the event of the former two scenarios, that initial administration of antibiotics contributes to resistance.

Selection and dosing of antibiotics are typically informed by an antimicrobial stewardship pharmacist or physician and/or relevant informational resources. While this specialized personnel and infrastructure is commonplace in some hospitals, stewardship programs are lacking in others. Only 15 of 84 Canadian hospitals surveyed in 2018 noted that they use computerized decision-making assistance programs.[32]

2.9 CASE STUDIES: INTERNATIONAL ANTIBIOTIC ACCESS MODELS

Canada is not the only country facing barriers to bringing novel antibiotics to its market. In fact, this problem is challenging countries all over the world, and each is responding in its own distinct way. Five countries in particular — France, Germany, Sweden, the UK, and the US — are pioneering innovative market access models that could bring more new antibiotics to those countries. Understanding these models and how they might be applicable to the Canadian context were foundational to our solutioning process.

France

The French model involves changes to the regulatory/pricing process for antibiotics. Prices for antibiotics with a 'minor' added therapeutic benefit are not allowed to drop below the lowest price of four reference countries. Antibiotics are also exempt from the claw-back program, which requires repayment of some sales revenue beyond the set cap. Finally, in this model, if a company finds conditions no longer favourable to produce an antibiotic, they are allowed to apply for price increases to avoid drug shortages.

Germany

The German model is similar to the French model in that it also relies on changes to the regulatory/pricing process. In the price-setting process, new antibiotics are selected ad hoc to bypass internal price references, while 'reserve' antibiotics automatically qualify for price reference bypass. These 'reserve' antibiotics undergo an accelerated reimbursement review process.

Sweden

The Swedish model is a mixed guaranteed sales/revenue model, where specific antibiotics have a fixed revenue floor to ensure a base drug supply. As sales revenue increases below the fixed floor, it replaces the guaranteed revenue. If the annual sales revenue rises above the fixed floor, 100% of revenue comes from sales. If the annual sales revenue is below the floor, the difference is calculated, and the revenue is topped up to ensure the manufacturers receive requisite funding regardless of sales volume. The Public Health Agency of Sweden (PHAS) sets the minimum revenue value, and the agreed-upon price is set through a national-level contract. The lowest guaranteed annual revenue is calculated[33] as follows: price per package (estimated average price) multiplied by the number of packages (based on medical need) multiplied by 150% to cover administrative overhead and logistical costs. In this model, estimated average price is determined by the average European list price.

United Kingdom

While the UK model is similar to the Swedish model, it differs slightly in that it is driven purely by a fixed annual subscription payment, making it fully delinked from sales volume. The amount of the fixed annual payment is determined by an antibiotic-specific health technology assessment (HTA) that takes into consideration the societal value of new antibiotics and the funding necessary to incentivize manufacturers to continue research and development of these drugs.

United States

In the US,[34-35] the Generating Antibiotic Incentives Now (GAIN) Act of 2012 grants certain antimicrobials five additional years of market exclusivity, independent of any patent protection. This access model is designed to allow higher prices to be charged for a longer period, thereby generating greater revenues for manufacturers. Stewardship was made central to this model — if bacteria develop resistance to a novel antibiotic, then the additional years of market exclusivity would be rendered unimportant. Please refer to Appendix 9 for additional measures proposed by the US.

Comparing Key International Access Models

Model Name	Country of Origin	Year Established	Primary Mechanism
PHAS Pilot Study	Sweden	2020	Guaranteed minimum revenue in exchange for guaranteed volume of supply.
Innovative Models for the Evaluation and Purchase of Antimicrobials	UK	2020	Annual fee based on AMR-specific HTA, delinked from volume supplied.
Changes in 35 SGB V	Germany	2017	Ad hoc exception of antimicrobials from internal price reference group.
Exceptions for antibacterials with ASMR level-IV	France	2015	Antibiotics with moderate added therapeutic benefit are guaranteed a price not lower than the lowest price of four reference countries.
Generating Antibiotic Incentives Now (GAIN) Act	US	2012	Additional market exclusivity leading to additional revenues.

These models all have elements that are compatible with the Canadian landscape, including the fixed annual revenue and the antibiotic-specific HTA. That said, there are risks that should be acknowledged. Indeed, lessons can be gleaned from instances in which advanced market commitment models have been used in other contexts, such as for pneumococcal vaccines. One particular pneumococcal vaccine pilot, which ran from 2005 to 2020, was administered by a global alliance called Gavi and offered $1.5B in potential AMCs for any company worldwide with a priority objective of stimulating R&D. However, while vaccine supply, availability, and uptake improved, there was only a miniscule effect on stimulating R&D.

2.9 CASE STUDIES: CANADIAN MODELS (NON-ANTIBIOTIC)

In addition to international models, we also examined a series of established Canadian models for the provision of non-antibiotic drugs and biologics. Among them, the Canadian Association of Poison Control Centres, the Canadian Malaria Network, and Canadian Blood Services served as excellent case studies for what may — and may not — work for novel antibiotics.

Canadian Association of Poison Control Centres (CAPCC) and Canadian Poison Centres

CAPCC is a national entity providing a centralized forum for communication, information, and idea exchange in support of the eight[36] provincial/territorial Canadian Poison Centres (e.g., Ontario Poison Control). This model implies:

- The establishment of multiple new organizations — one at the pan-Canadian level and several more across the country to support the different provinces and territories
- Unified messaging and communication, and knowledge-sharing about best practices across centres
- Localised establishment and management of dispensing guidelines and drug inventories by the respective jurisdictions, as required for their own unique context
- Additional effort for the coordination of data for decision-making and investments at a national level

Canadian Malaria Network (CMN)

The CMN oversees access to two critical antimalarial drugs — Artesunate and Quinine.[37] Through this network, the two drugs are distributed via a hub-and-spoke model that branches out from a central stockpile at The Ottawa Hospital to 13 major regional centres (e.g., large hospital pharmacies) across Canada, which then distribute further to smaller, local hospital pharmacies as needed. Resources are also provided to specific labs to perform diagnostic testing under this network's program. The network collects usage data and reports back to stakeholders. This model implies:

- If applicable, an agreement with Health Canada to allow the distribution and dispensing of drugs that have not yet been approved in Canada
- Consistent coordination among coordinating centres and satellite hospitals for the purchasing, tracking, and distribution of the drugs across sites
- Continuous stocking, thus space planning to store additional quantities that were not initially held on-site at hospitals
- Potential for product expiry where/when not used
- Use of existing infrastructure, so lower set-up and operating costs
- Localised stewardship programs

Canadian Blood Services (CBS)

CBS is a pan-Canadian not-for-profit organization[38] that operates at arms-length from government and manages its own pipeline of blood and blood products. This model leverages existing healthcare infrastructure as appropriate — such as Transfusion services — and provides stewardship guidelines to providers, both of which make sense in the antibiotic context. This model implies:

- The establishment of a national organization that functions independently from existing bodies but has relationships with all involved in the provisioning process
- The establishment of a national formulary for the products in scope
- The development and operationalization of central, comprehensive stewardship programs
- The development and implementation of an information management system to track all products through the lifecycle and several related indicators, including medical errors linked to the administration of products to patients

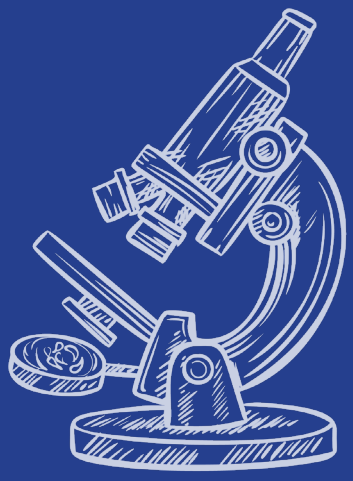
All three of these models have positive aspects and elements that are worth considering for an antibiotic access and capacity initiative:

- From a **funding and governance** perspective, all models obtain funding from the Federal and Provincial governments to support all or part of their operating budgets. The idea of one large organization that, to various degrees, oversees or liaises with sub-organizations or entities delivering products and services to the front lines is also appealing.
- From a **distribution** perspective, the CMN has the advantage of using existing infrastructure and ensuring that the required drug is readily available to the patient when needed. It appears more relevant at this point than establishing a separate large, national organization and/or multiple provincial/territorial centres dealing exclusively with a select few antibiotics.
- From a drug **stewardship** perspective, the CBS model is the strongest and can provide many lessons-learned to shape the antibiotic access and capacity initiative — including the implementation and use of a system to strengthen stewardship and ease the burden on the front-line while providing care to patients. One of the CMN's strong points is also in stewardship – as each regional medical centre benefits from an Infectious Disease physician's oversight of drug dispensing for that region.
- From a **data access, collection, and dissemination** perspective, the CBS model provides inspiration via its dedicated system; however, there is also room for improvement here as there is currently no mechanism in place to collate and share that data with all relevant stakeholders.
- From an **overall resourcing** perspective, none of the models quite seemed right for our purposes. It is obvious that, based on what was heard during consultations, this context requires a dedicated team to oversee and deliver activities to support the front-line and liaise with the many stakeholders involved.

Comparing the Canadian Access Models

Model Organization	Model Type	Strengths
Canadian Association of Poison Control Centres	Umbrella entity with affiliated regional centres	Establishes centralized messaging and knowledge-sharing while still embracing regional autonomy.
Canadian Malaria Network	Hub-and-spoke	Direct governance of specific medications with a central stockpile and satellite-style distribution.
Canadian Blood Services	Independent pan-Canadian entity	Manages its own pipeline of relevant products and leverages existing infrastructure.

The State of Antibiotic R&D in Canada



While R&D falls outside the scope of this project's mandate, we did explore its current state at a surface level.

It turns out that Canada has been pulling its weight in recent years in the international push to invigorate the global antibiotic pipeline. In fact, a 2019 WHO survey[39] of the antibacterial clinical development pipeline shows that two of the 32 clinical pipeline antibiotics under development globally — Nacubactam+Meropenem and BCM-0184 — are from Canadian companies.

Tax subsidies for Canadian R&D undoubtedly factor into this, as foreign companies are more likely to contract R&D efforts to a Canadian company eligible for subsidies than they would be to establish their own Canadian entities. An example is the novel FabI inhibitors from Debiopharm, where Toronto-based Nobolex was contracted to help with preclinical development.

A Patient's Perspective

J.Z. is a healthy middle-aged woman from the Greater Toronto and Hamilton Area (GTHA). But in October 2021, a nasal infection prompted her to seek medical treatment. She was prescribed 500mg of cephalexin by her doctor and was instructed to take it four times daily. Despite following these guidelines, her infection quickly spread to her face and eyes, worsening considerably in just three days.

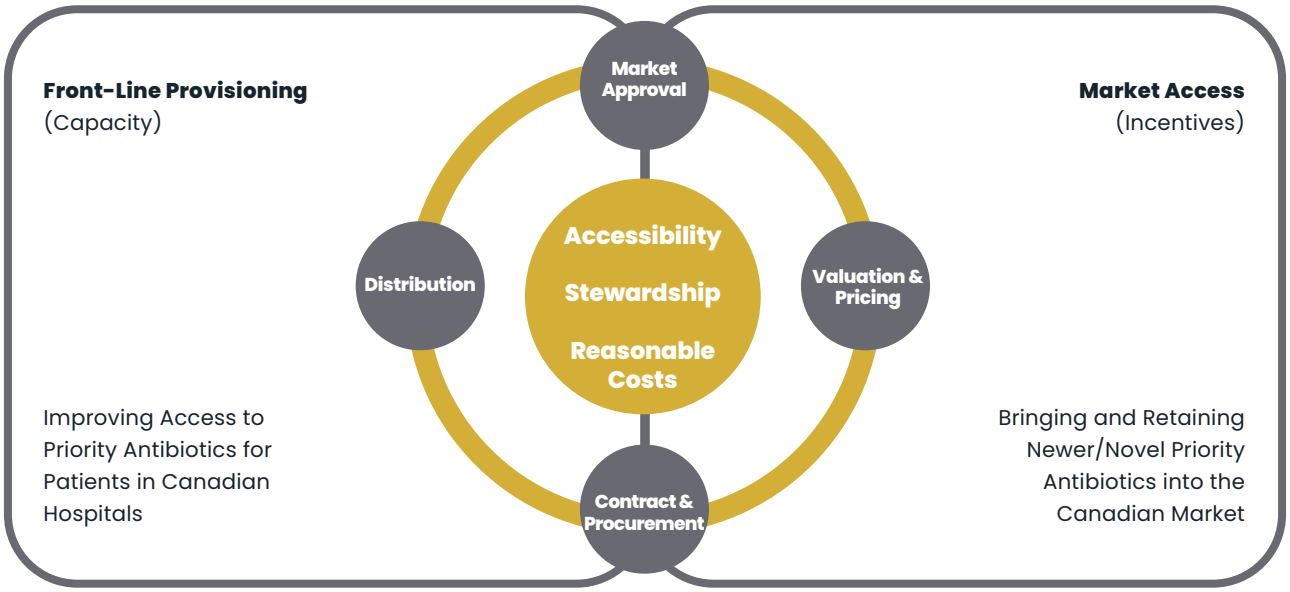
At this point, J.Z. was sent to a nearby hospital for further treatment. Here, they doubled the dosage of antibiotics — and, still, the infection worsened. To make matters worse, J.Z. acquired a secondary infection somewhere along the way. To combat her worsening condition, hospital prescribers changed her treatment to 14 days of IV ceftriaxone. Four days into this treatment, the infection again worsened.

Following that, J.Z. was admitted as an inpatient at the hospital, where she was treated with a third antibiotic and monitored overnight. Except one night turned into two, which turned into three, which turned into four. Finally, when doctors prescribed piperacillin/tazobactam — her fourth antibiotic regimen in under two weeks — her condition began to improve. In total, J.Z. spent five full days in hospital, not counting two separate 24-hour stays in emergency.

In the end, J.Z. was sent home on oral amoxicillin/clavulanic acid — a fifth antibiotic — and, as of publication, doctors are monitoring her for *C. diff* due to her intensive antibiotic treatment, which carries its own risk.

Throughout this process, J.Z. noticed that her doctors expressed concern about her infection's resistance to antibiotics. She suggests that the trial-and-error prescription process was frustrating, and feels that having a more appropriate prescription at the outset could have swiftly freed up the hospital beds she occupied for so long. She also believes the right treatment at the right time could have prevented her condition from worsening in the first place. Despite all of this, J.Z. is one of the lucky ones who emerged on the other side of a drug-resistant infection — which is not a guarantee for Canadian patients.

— 3 —
THE FUTURE STATE



Designing and implementing a solution to antibiotic access issues in Canada is a complex challenge. With stakeholders embedded in industry, academia, policy, logistics, healthcare, and beyond, it is important to recognize the key roles that existing infrastructure can play in shaping a future in which Canadian patients have greater access to appropriate treatments.

As such, the ideas that formed the basis of our recommendations and integrated solution were developed in consultation with experts from across sectors and across Canada. Throughout this process, we sought different perspectives and accounted for different — and sometimes competing — interests, all while maintaining a patient-centered focus.

3.1 RECOMMENDATIONS & PROPOSED MEASURES

Project findings were refined into 30 concise recommendations and proposed measures. In many cases, these items align well with the forthcoming pan-Canadian Action Plan on AMU/AMR. Many of these items could be swiftly executed during the demonstration phase of our project — henceforth referred to as "the antibiotic access and capacity (AAC) initiative" — but others are broader in scope and could be addressed and implemented independently of this proposal, or at least beyond the pilot.

These measures are designed to streamline processes, simplify requirements, improve knowledge-sharing and reporting, minimize administrative burden, and invigorate the Canadian antibiotic marketplace. They were grouped into themes that would serve to edify the overall model and make their implementation tangible. **In sequential order of precedence**, they are:

Legend

These recommendations are designed to make improvements in three key areas:

- Access
- Stewardship
- Surveillance

Phase 1

1. Form an 'antibiotic resistance task force' (or action group) to establish partnerships and foster engagement, participation, and input from members of key organizations, both nationally and internationally.

2. Establish the task force as the lead entity and coordinating body for the AAC initiative and all related implementation activities, including piloting the new integrated solution.

3. Working closely with government, health, industry and research sector partners, establish a process to proactively identify priority antibiotics to meet current and future needs in order to inform licensing approval and enable product listing.

4. Establish pricing and procurement mechanisms for essential and priority antibiotics administered in hospitals that could be managed through a federal, provincial/territorial, or F/P/T program.

5. Expedite and streamline the marketing approval of select priority antibiotics that qualify for Health Canada's Accelerated Review and have already been approved by EMA in the EU or FDA in the US for the purpose of the AAC initiative.

6. Create/enable a special funding envelope outside of hospital budgets for access to priority antibiotics.

7. Create/enable a special funding envelope outside of the hospital budget for up-to-date diagnostic testing that supports antimicrobial stewardship.

8. Gather data from health centres where antibiotics of interest are already in use — both in Canada and internationally — to inform inclusion decisions for the AAC initiative and to inform providers of indication, efficacy, and usage specifications of newer drugs.

9. Establish national requirements for annual reporting of relevant data, including but not limited to common pathogens, infections, corresponding indicated antibiotics, adverse events, efficacy, and resistance.

10. Establish a systematic process at the national and provincial/territorial levels to assess, package, and disseminate evidence and recommendations related to antibiotics that were recently approved for sale in Canada to inform formulary decisions by relevant entities (including hospitals).

11. Establish data collection and information management systems (IMS) for reporting and improving accessibility to data, enabling routine clinical decisions and enhancing overall programs.

12. Leveraging the aforementioned IMS tool, establish a mechanism to:
    - ensure up-to-date information about antibiotics and diagnostic tests for rare infections is available to providers, including location of accredited testing facilities
    - share summaries of evidence for recently approved and unapproved novel antibiotics[40]
    - support clinical practice and stewardship, allowing providers to access updated hospital formularies, guidelines, antibiogram data, and more, while alerting stewardship teams when a patient is prescribed antibiotic
    - provide user-defined reports with relevant data and statistics.

13. Streamline distribution by leveraging and/or implementing a central information system to, in real-time, track and manage antibiotics orders, inventories, and backlogs, and collect/view usage-related data across regions, provinces and territories, and the country.

14. Establish 'Canada-centric' banks of AMR isolates for susceptibility testing and diagnostic validation.

15. Develop a communications plan and target messaging to specific audiences — ID specialists, pharmacists, administrators, etc. — to improve awareness and know-how amongst those who may interact with the AAC initiative and peripheral programs (e.g., SAP).

16. Support the SAP request process by enabling the electronic submission, prioritisation, and tracking of requests for unapproved antibiotics via the AAC initiative, and by guiding providers with filling out submissions and liaising with manufacturers as necessary.[41-42]

17. Establish measures to reduce time lags associated with access to essential antibiotics that are not marketed in Canada. For example, stocking quantities of those most requested on Canadian soil, digitizing the process to obtain manufacturer approval (or removing the requirement altogether), and ordering once approved by Health Canada and/or the manufacturer.

18. Develop and operationalize hospital antibiotic stocking guidelines for priority antibiotics.

19. Review existing tools and establish or strengthen stewardship programs as applicable.

Phase 2

20. Assess opportunities to expand capacity by adding new distribution centres or leveraging existing depots for the antibiotics most needed in Canada.

21. Establish 'Just in Time' (JIT) delivery and replenishment processes using newly established forecasts for priority antibiotics.

22. Work with hospitals to ensure all priority antibiotics are included on their respective formularies.

23. Increase the availability of rapid diagnostics (e.g., susceptibility tests) at point-of-care, and appropriately pair them with antibiotics where feasible.[43]

24. Collaborate with international entities to define solutions for establishing demand, value, and procurement standards related to novel antibiotics.

25. Establish national forecasts of antibiotics required by Canadian patients (including for those approved/not approved, older/newer, and not yet in the pipeline).

26. Develop and publish comprehensive reports related to antibiotic resistance, susceptibility, usage, and demand for certain antibiotics to enable market access and other operational and provisioning decisions by manufacturers.

27. Invest in Canadian research and development efforts supporting:
    - efficient and cost-effective strategies, such as partnerships with accelerators or incubators like CARB-X
    - the development of antibiotics that will treat infections caused by priority pathogens as identified by Health Canada and partners based on current and emerging evidence
    - the development and procurement of innovative solutions and technologies that may be used as an alternative to antibiotics
    - local production of API/compounds required for essential antibiotics[44]
    - the use of diagnostic technologies for/with priority antibiotics to optimize appropriate use.

28. Work with hospital administrators and providers to further identify and define access barriers and determine whether systematic solutions may be applied by the AAC initiative.

Phase 3

29. Collaborate with partners to harmonize marketing approval and HTA processes to:
    - include the systematic consideration of programmatic factors such as economics, ethics, equity, feasibility, and antibiotic acceptability when developing evidence-based recommendations
    - reduce the costs and overall length of the market entry process.

30. Develop and establish an antibiotic valuation model that reflects public health and stewardship benefits.

3.1 CURRENT & FUTURE STATES COLLIDE

The recommendations and proposed measures outlined in the previous subsection are far-reaching and will thus require the cooperation and participation of Canada's existing infrastructure. At a high level, the following chart demonstrates some of the roles that key stakeholders could play in the implementation of these recommendations.

ISED/Other Agencies*	PHAC	Health Canada	PMPRB	CADTH & INESSS	pCPA	Prov MoH/HAs	GPOs	Select Manufacturers	Distributors	Hospitals	Labs	AAC Initiative
	1-2: Approve/fund AAC task force and initiative				5: Exclude priority antibiotics from List Price negotiations	2: Partially fund and fully support the implementation of the model together with PHAC	5: Exclude priority antibiotics from List Price negotiations	4: Commit agreed-upon quantities of antibiotics	13: Streamline distribution through integration of a central system	12: Support adoption of new stewardship tools/ app	7/14: Establish new diagnostic tools/ systems for novel antibiotics	15: Develop a communications plan and engage with local and international stakeholders
	4: Establish pricing/ procurement mechanisms for essential/ priority antibiotics and related diagnostics					10: Support the development of a review process for priority antibiotics			20: Assess opportunities to expand distribution capacity	18: Establish 'Antibiotic Stocking Guidelines'		9-10: Establish a process to identify antibiotic and diagnostic requirements and availability and review evidence
	6-7: Enable dedicated funding envelopes for priority antibiotics and diagnostics	5: Streamline the Marketing Approval of select priority antibiotics							21: Establish 'Just In Time' (JIT) process based on new guidelines	19: Establish more ubiquitous use of stewardship tools/ programs		
	9: Establish national requirements for data** submission	16: Seek to harmonize and digitize SAP processes								22: Expand hospital formulary to include essential/ priority antibiotics		8/11/12: Establish data collection and reporting processes, systems, and tools
	10: Support establishment of antibiotic and tests review process	15. Raise Market Access process awareness										
										28. Work with administrators, providers, and labs to further identify and define access barriers and corresponding solutions		
27: Invest in Canadian R&D efforts supporting: 1) efficient/cost-effective strategies; 2) antibiotics targeting priority pathogens; 3) alternate solutions to antibiotics; 4) local production of APIs required for essential antibiotics; 5) point-of-care, rapid diagnostic technologies												
	29: Harmonize the Marketing Approval, valuation, and HTA processes for novel antibiotics to include public health benefits and programmatic factors such as economics, ethics, equity, feasibility and antibiotic acceptability											

Legend

Timeline for initiation and operationalization of proposed measures following funding approval

Short Term (<1 Year)	Medium Term (1-2 Years)	Long Term (2-3 Years)

* Other funding/granting agencies and organizations
** Data to include: Bacterial pathogens, infections, lab results, diagnoses, prescribed antibiotic(s), adverse events, efficacy, resistance, utilisation, and all related costs

The Future State

As this blueprint began to take shape, our working group developed an integrated solution that would support the operationalization of the key recommendations. As patients are on the receiving end of the entire supply chain and provisioning process, they remained central to the design of this solution.

Although ensuring greater capacity and security of supply for certain priority antibiotics and diagnostics was, and remains, a principal objective for this project, we recognize that this cannot be adequately accomplished without appropriate standards, protocols, and infrastructure in place. Indeed, without shifting from the status quo, any upfront investments are set up to fail.

So, on the premise that **financial (pull) incentives alone will not fully address the antimicrobial resistance and antibiotic access conundrums**, we ensured our solution would also support the principles that we had embedded into our project goal at the onset:

- **Accessibility**
- **Stewardship**
- **Reasonable Costs**

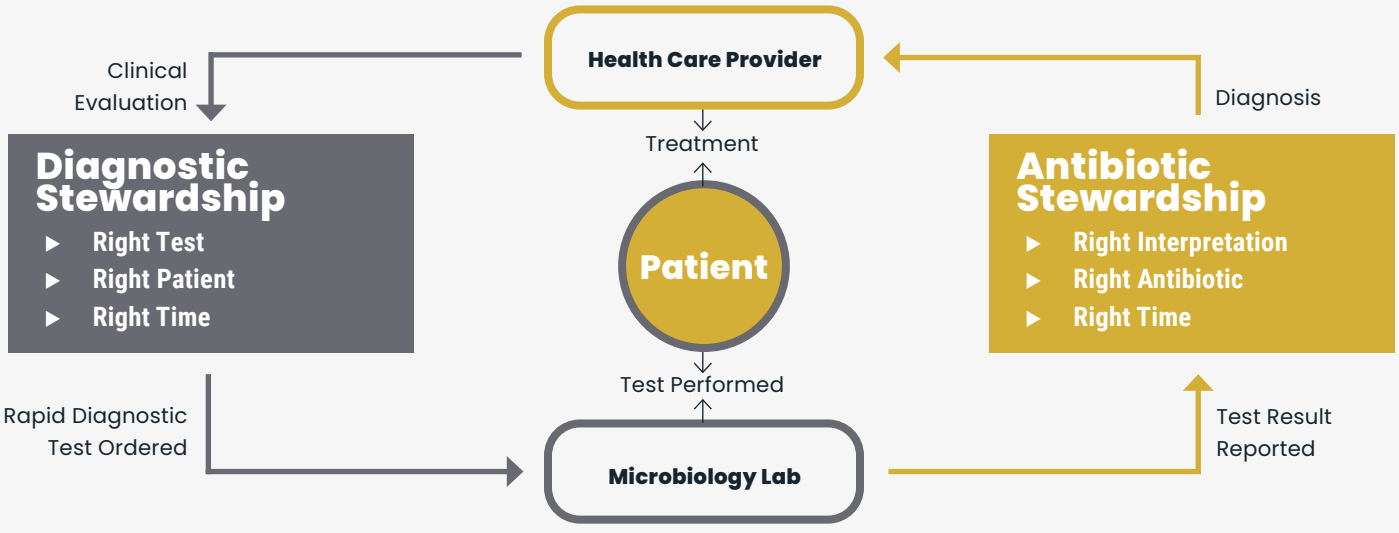
Our working group ensured all proposed measures were in line with these principles and that, collectively, they would coherently and effectively work together to achieve desired results.

For **Accessibility**, it was deemed critical to make select antibiotics available to all patients being treated in hospitals across the country and reduce the wait time for access to and delivery of those drugs. Considerations in solutioning included costs (whether on or off formulary), approvals or lack thereof, hospital location, and on-site storage capacity.

Recommendations 4, 5, 6, 10, 13, 16, 17, 18, 20, 21, 22, 27, and 28 were especially incorporated into our solution to improve access to antibiotics in Canada.

For **Stewardship**, it was deemed essential to use current evidence to select the products to include in the AAC initiative. We also determined that providing better diagnostic tools would enable providers to make efficient and appropriate prescribing decisions. Similarly, bolstering Canada's clinically reliable information about all new antibiotics will inform both

The roles of diagnostics and stewardship in care delivery and antibiotic resistance management



administrative and point-of-care decision making. Finally, we believe that collecting data on clinical and overall program outcomes is essential to guide future stewardship programming.

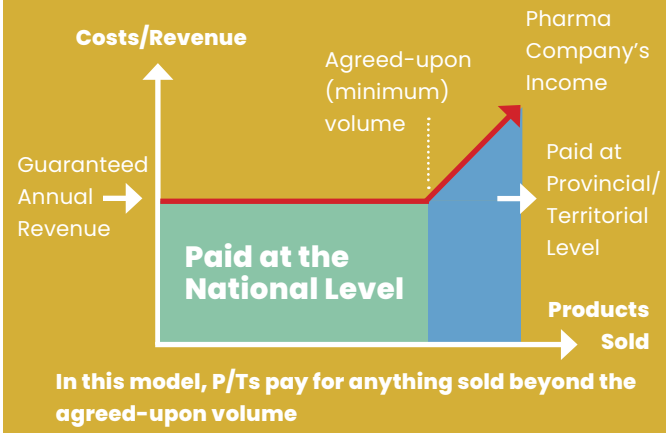
Recommendations 7, 8, 9, 11, 12, 14, 19, 23, and 25 were included into our solution to improve stewardship in Canada.

For **Reasonable Costs**, it was deemed important to not directly pass the costs associated with implementing and running the AAC initiative down to hospitals and patients, especially where the costs of the selected antibiotics and diagnostic tests are concerned. By all accounts, we determined that these costs should be absorbed at the federal level and that drug budgets should remain unaffected (as per figure in sidebar). It will also be important to find common ground with manufacturers on the prices of these products. Knowing that current valuation for antibiotics is too low but that Canada's health-care system cannot sustain the costs that countries like the US pay, a compromise must be reached to ensure security of supply for these products.

Our working group also considered leveraging existing infrastructure as much as possible to prevent unnecessary expenditures and duplication of effort. We also invested time into determining how savings could be achieved by implementing certain measures — for instance, enabling more efficient/accurate diagnoses reduces hospital costs associated with adverse events and longer patient stays.

Recommendations 4, 6, 7, 8, 24, 29, and 30 were designed with the these aspects in mind and are core to our integrated solution.

Potential F/P/T Contributions toward the Cost of Antibiotics



In this model, P/Ts pay for anything sold beyond the agreed-upon volume

This model implies that 'Paid at National Level' will bolster what is already assigned to the P/Ts for drugs, and that P/Ts will pay for volumes that are consumed above and beyond their yearly allocation.

The agreement underlying the 'Guaranteed Annual Revenue' would not preclude manufacturers from earning additional revenues if usage by P/Ts exceeded the agreed-upon yearly volumes — for example, in the event of a pandemic or outbreak.

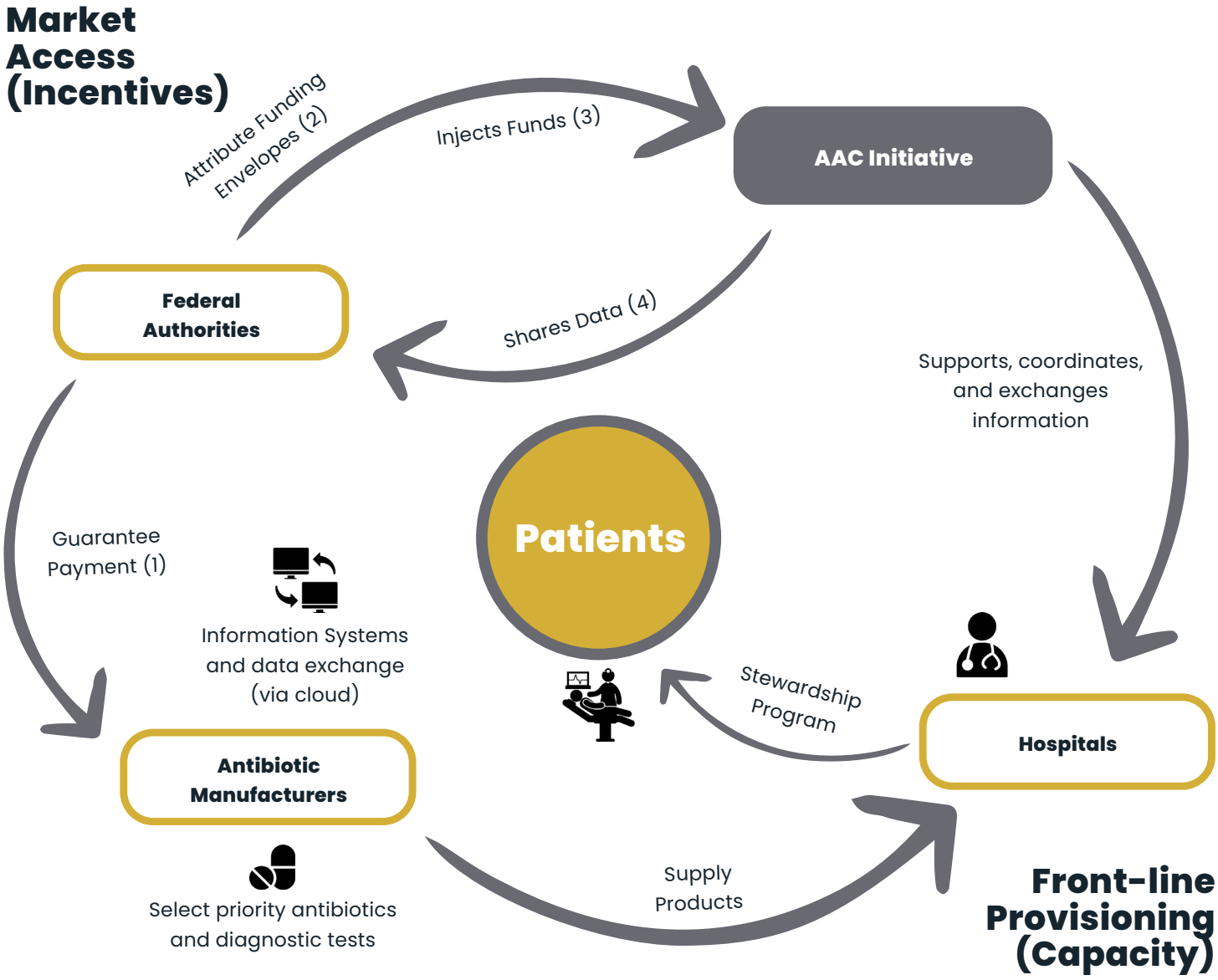
The point here is to increase capacity, not to equalize or reorganize it. See Appendix 11 for other options that were considered but ultimately discarded.

This is a high-level explanation of costs. The forthcoming sections describe our proposed solution, explain its components in more detail, and introduce the plan to implement and operationalize it across Canada.

This includes coming to an agreement on the true value of these priority antibiotics with manufacturers and not passing the incremental costs down to the hospitals nor to patients, as illustrated in the figure above.[45]

3.3 OVERVIEW OF OUR INTEGRATED SOLUTION

At the outset of this project, we endeavoured to combine two distinct but inherently connected models – 'Market Access' (via incentives) and 'Front-Line Provisioning' (via capacity) – into one end-to-end integrated solution. To achieve this, we focused on the components we deemed integral to facilitating stakeholder buy-in. The following diagram is a simplified version of the integrated solution, which we would propose to test with select antibiotics in a select region as a first phase of deployment.



(1) Pays difference between contract amount and actual sales.

(2) For select priority antibiotics and diagnostics.

(3) To support implementation costs, in addition to regular operational budgets.

(4) Data elements include pathogens/infections, corresponding antibiotics, adverse events, efficacy, resistance, utilisation, and costs.

This model is designed with patients at the centre. The idea here is that federal buy-in will translate to new antibiotics entering the market, improved hospital procurement, strong issue area governance, new data sources and infrastructure, enhanced stewardship programming, and, most importantly, better patient outcomes.

As with the market access model currently being piloted in Sweden, "federal buy-in" can be taken quite literally in this context. Indeed, our proposed solution is sustained by investment from federal authorities (i.e., Health Canada and PHAC) that will inject funds into the marketplace in three distinct ways:

1. **Guaranteed payment to manufacturers**. This funding mechanism is designed to incentivize drug companies to develop new antibiotics and to bring them to the Canadian market. Guaranteed revenue for manufacturers eliminates the financial risks associated with launching a new product in the small Canadian market.

2. **New funding envelopes**. Costs of select novel antibiotics and their corresponding diagnostics are absorbed by a federal funding envelope — not by individual hospital budgets. This funding mechanism is designed to encourage physicians and pharmacists to confidently purchase and prescribe appropriate medications without facing the administrative barrier of cost to hospital budgets. This will improve not only patient outcomes, but antimicrobial stewardship too.

3. **AAC pilot funding**. This funding will be used to establish governance, implementation, and operation of our proposed pilot model. Funding invested into this project will translate to data collection, information sharing, and stakeholder coordination, all of which have implications on the ability to scale this initiative — or similar endeavours — nationally in the future. An option is also to include the testing of contractual and legal terms as part of the pilot.

Having more appropriate treatment options available to prescribers, improved antimicrobial stewardship, and up-to-date evidence will only serve to improve patient outcomes in Canada. The integrated solution and its inherent models lend well to the community setting, which, as we heard throughout our consultation sessions, requires adequate attention for successful implementation. Thus, both the Market Access Model and the pharmaceutical distribution aspect of the Provisioning Model should eventually be adapted to address the needs of the community setting. Meanwhile, the concurrent and phased deployment of the aforementioned measures recommendations will create a landscape upon which this model can thrive. See Appendix 12 for a roadmap detailing deployment recommendations.

3.4 DETAILED INTEGRATED SOLUTION

Our integrated solution is composed of two models — a market access model and a front-line provisioning model. While inherently connected, these components function in very different ways. The market access model is designed to bring more novel antibiotics to Canada, which can be achieved through incentivization and regulatory measures. The front-line provisioning model is designed to make it easier for patients to be treated with the antibiotic(s) appropriate for their infection, which can be achieved through measures related to data, costs, distribution, and supply/demand.

The Market Access Model

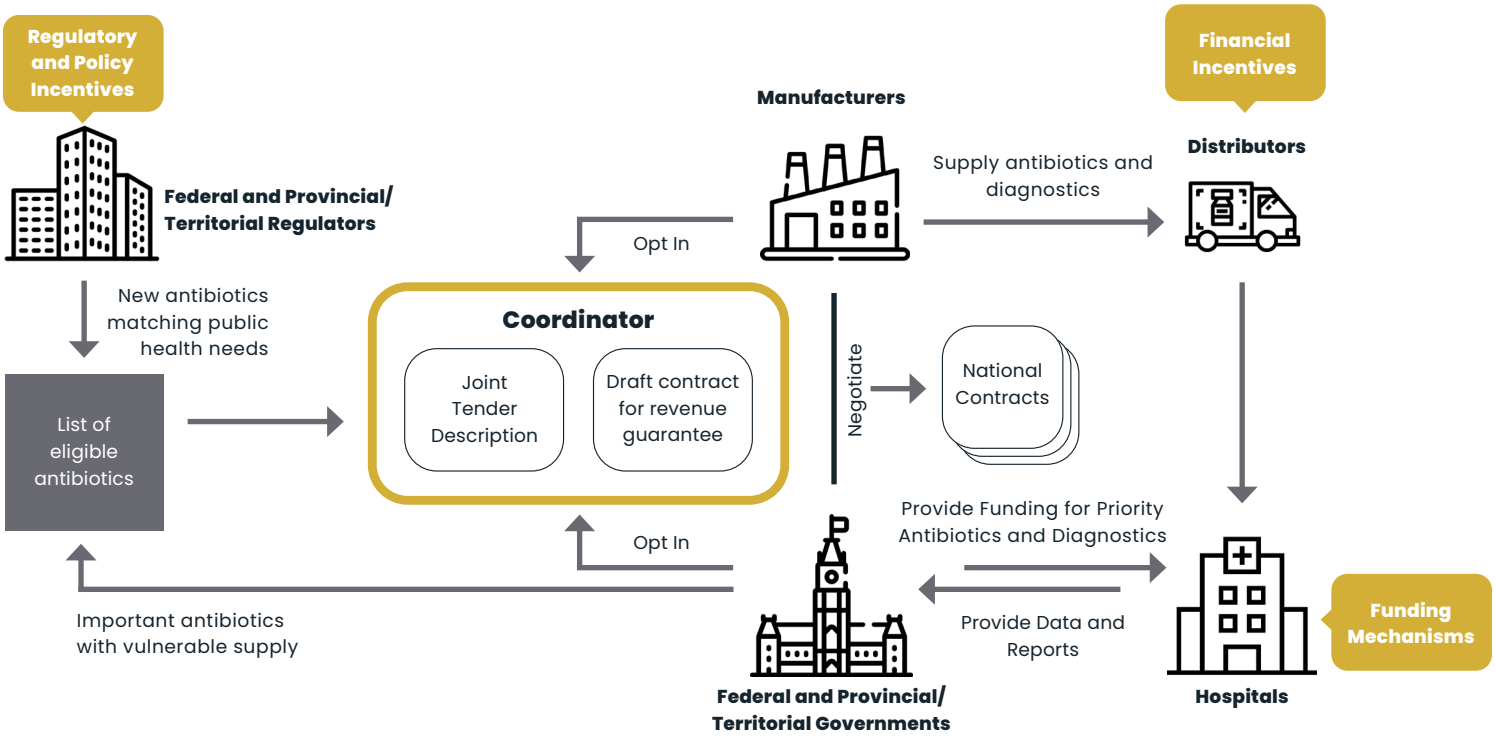
In the context of this proposal, market access refers to a manufacturer's ability to successfully and efficiently bring products to the Canadian market. While many barriers exist today, we believe they can be reduced or removed altogether via certain measures and certain stakeholders. The government — PHAC and HC in particular — showed exceptional regulatory agility in approving COVID-19 vaccines during the pandemic. We encourage the government to leverage this agility to prepare for the looming AMR crisis by implementing measures, such as exclusions to the HTA and marketing approvals for priority antibiotics. The following chart outlines **why** we're proposing each measure, and **who** we believe can play a role in executing them.

Type of Measure →	Regulatory/Policy Incentives	Financial Incentives	Funding Mechanisms
Purpose	Meant to remove regulatory and/or policy barriers to enable manufacturers of select priority antibiotics/diagnostics to market in Canada under agreed-upon conditions.	Meant to compensate manufacturers for the 'true' value of products to the Canadian market and patients; something that current valuation models do not do.	Meant to remove financial barriers for hospitals so that providers may prescribe based on need (while preventing resistance growth) instead of cost.
Stakeholders and Responsibilities	**HC:** Marketing Approval exclusions; reform directives **CADTH/INESSS:** Temporary HTA exclusions; eventual reform of model for priority antibiotics and diagnostics **PMPRB/pCPA:** Valuation/price negotiation exclusions for priority antibiotics and diagnostics	**PHAC:** Incremental funding; manufacturer agreements **HC:** Programs/processes adaptation **CADTH/ INESSS:** New model for priority antibiotics and diagnostics **PMPRB:** Application of new model for priority antibiotics and diagnostics; or full process exclusion	**PHAC:** Incremental funding assignment **HC:** Programs/processes adaptation **P/Ts:** Programs/processes adaptation **AAC Initiative:** Utilisation management; Data tracking and reporting **Hospitals:** Utilisation and other data tracking and reporting

More specifically, **the measures** proposed for each category are:

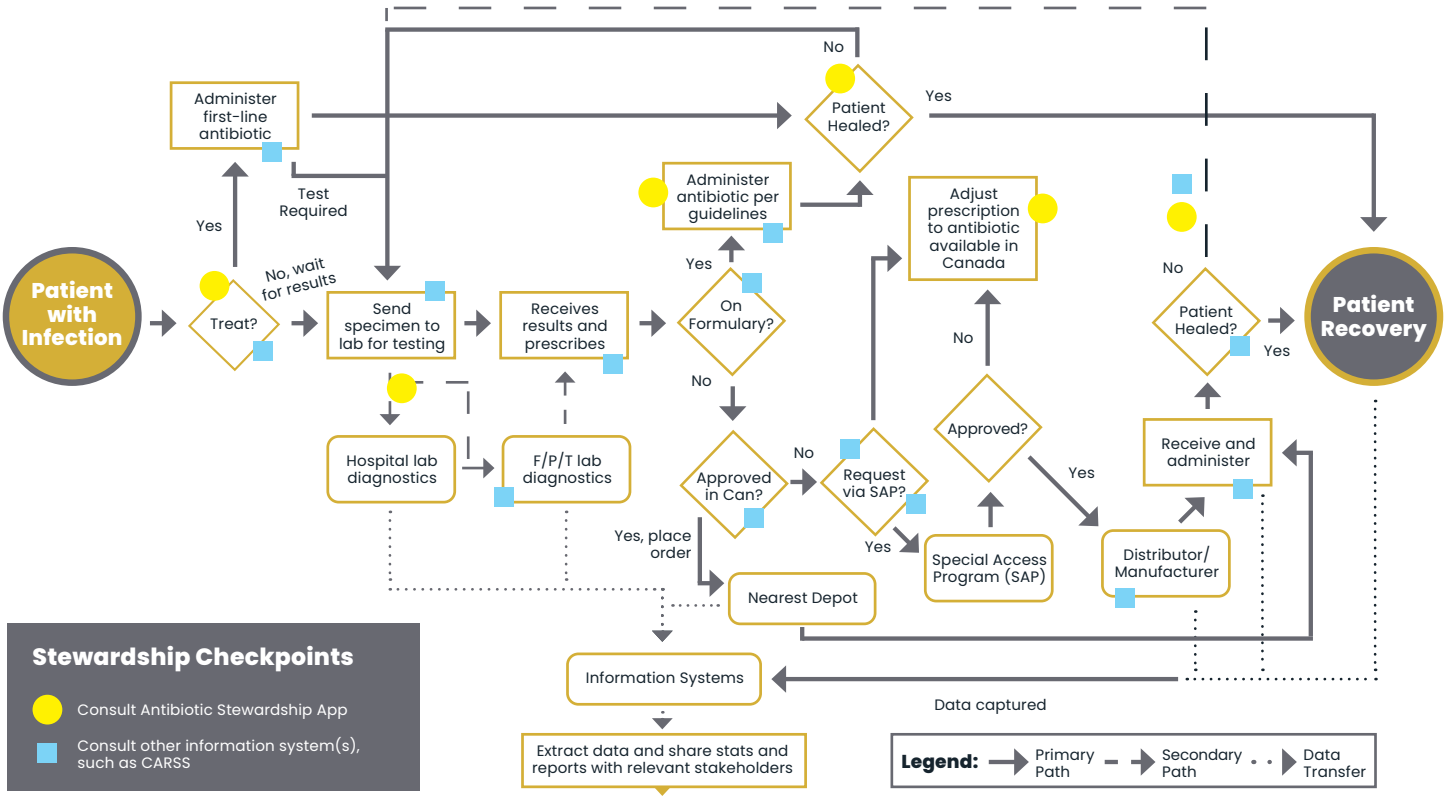
Scenario	Regulatory/Policy Incentives	Financial Incentives	Funding Mechanisms
	Short Term (<1 Year)		
Select Priority Antibiotics already approved/marketed in Canada.[46]		Guarantee manufacturers a lump-sum payment for agreed-upon quantity[47] of select products.	Establish separate funding envelope[48] for select/priority antibiotics and innovative/required diagnostics[49]
		Long Term (1–4 years)	
Select Priority Antibiotics NOT yet approved in Canada[50]	Reduce or waive Marketing Approval costs/requirements under certain conditions[50] Sign off on certain exclusions to the applicability of the existing HTA/ Valuation/Product Listing Agreement processes[51] Issue directive for streamlining of HTA/ Valuation/Pricing processes, including redesign of HTA and Valuation models (considering public health value & other factors such as positive externalities)[52]	Revisit measures already in place for applicability (See 'Short-Term'), incl. establishment of annual contracts with delinked payment[53] based on new AMR-specific HTA and valuation processes and of add-on payments for New Select Products.[54]	Revisit and expand funding envelope for additional select/priority antibiotics and innovative/required diagnostics[55]
	When manufacturer does not wish to market in Canada: Support licensing of patent rights to a local company under mutually-agreeable conditions		
Priority Antibiotics yet to be approved in any jurisdiction	Sponsor/support exploration of R&D innovations, such as local/academic-based production of API & manufacturing of antibiotics, and public clinical trials (e.g., NIM Model)		

The following diagram illustrates **how** these measures could manifest across the current landscape:



The Front-Line Provisioning Model

Front-line provisioning refers to a prescriber's ability to get patients the antibiotics they need in a timely manner. As described in our 'Analysis of the Current State,' this is a major challenge today. The following diagram illustrates the complexity of the prescribing pathway in Canada.



We believe that funding, data, and infrastructure are core to breaking down the barriers to front-line access. Foremost, new envelopes of funding that enable clinicians to make prescribing decisions independent of cost will be paramount. As well, expanding hospital formularies to include all priority antibiotics will reduce the frequency and burden of submitting special requests. In parallel, improved data collection and diagnostic tools will allow quicker action at the outset of an infection.

Embedded within this model is a plan to improve antibiotic – and overall antimicrobial – stewardship across Canada. Specifically, we are proposing the establishment of the AAC initiative team as a 'second-level' stewardship team that could act as a complement to existing programs and/or a reinforcement for hospitals with limited capacity to establish their own stewardship team. The AAC stewardship team would support to hospitals across the country in their use of novel antibiotics. This team would also be responsible for generating intelligence reports and other data to inform future decision-making.

The core stewardship team would be made up of:

- **Director**

Role: Ensure consistent coverage, liaise with external stakeholders and funders, provide reports, and support program planning.

- **Data Librarians/Analysts**

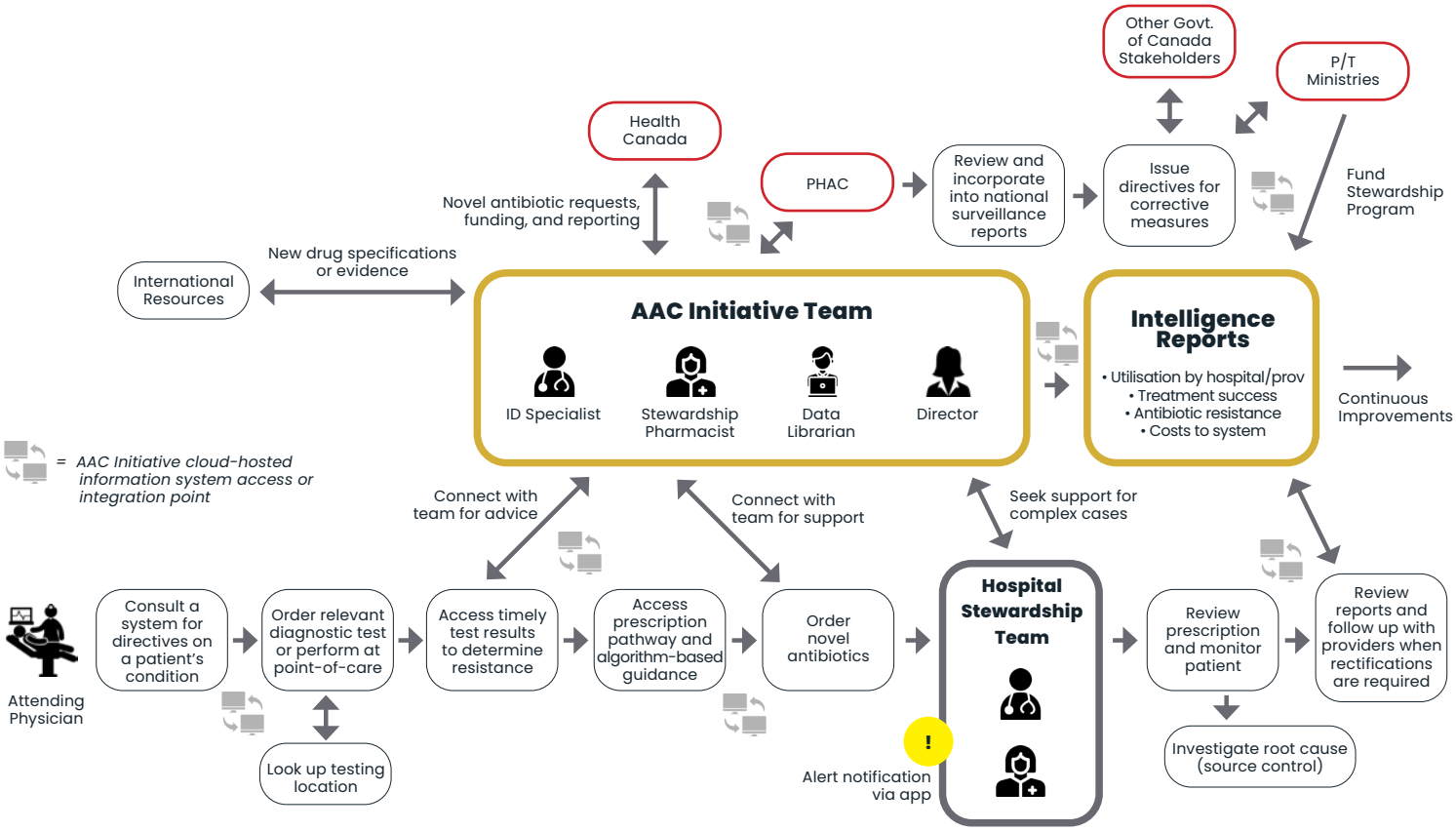
Role: Research and compile evidence on novel antibiotics, produce guidelines for stewardship app, collate the data collected, and produce reports as required.

- **Infectious Disease Specialists**

Role: Support diagnosis and provide recommendations on treating specific, rare and complex types of infections.

- **Stewardship Pharmacists**

Role: Provide recommendations on treatment options, including antibiotic indication, dosage, frequency, administration route, length of treatment.



The latter two would coordinate to ensure consistent coverage across the week between the hours of 7:00 a.m. and midnight.

All members would be hired under the AAC initiative, acting independently from government, hospitals, and other stakeholders, but accountable to those organizations.

A few information systems would be made available to them to support their role and program activities. This would include a Stewardship Application ('App') that would also be deployed to the frontlines (See Appendix 13 for an example). The AAC team would develop and publish antibiotic guidelines via this App that front-line providers would consult prior to making a treatment decision.

Further questions — regarding rare or unique cases — would be addressed by email or phone to the AAC team.

The proposed plan also involves leveraging and enhancing existing ordering/inventory management information systems to improve processes related to ordering, special access requests, and overall data collection. Eventually this will lead to integrations with additional systems to enable the flow of data and information crucial to obtaining a comprehensive view of the antibiotic landscape in Canada.

The complement of (integrated) information management systems will facilitate action on several fronts. For instance, this would:

Allow AAC Initiative Team and Distributors to...

- Obtain information regarding priority antibiotics suited for incentive program
- View and manage select priority antibiotic and diagnostic orders/requests
- Track utilisation and replenish stocks
- Forecast future demand for certain drugs based on historical use and resistance patterns
- Track costs/utilisation at varying levels

Hospital administrators, physicians, and pharmacists to...

- Access updated formularies, guidelines, and antibiogram data
- Be alerted when a patient is prescribed antimicrobials
- Support prescribing decisions by providing clinical evidence regarding various antibiotics
- Place regular orders
- Track and manage inventories and backlogs
- Fill out an SAP request when stewardship procedures establish the need for an antibiotic that is not approved in Canada
- Perform quality assurance checks

Policymakers and funders to...

- Review a wider array of data, including that related to surveillance and susceptibility at regional, provincial, and national levels
- Evaluate the benefits of investments and make decisions on future investments

The Integrated Solution

Together, the market access and front-line provisioning models shape our proposed integrated solution. If implemented in concurrence, this two-pronged approach will transform the antibiotic access and capacity landscape in Canada. Working closely with F/P/T authorities and other key stakeholders, we propose that our integrated solution be piloted by the AAC Initiative Team, with support from a project team for the implementation and deployment stages. The AAC team could exist as a subset (and initially as an 'action group') of the AMR governance entity already proposed to PHAC in July of 2020.[11]

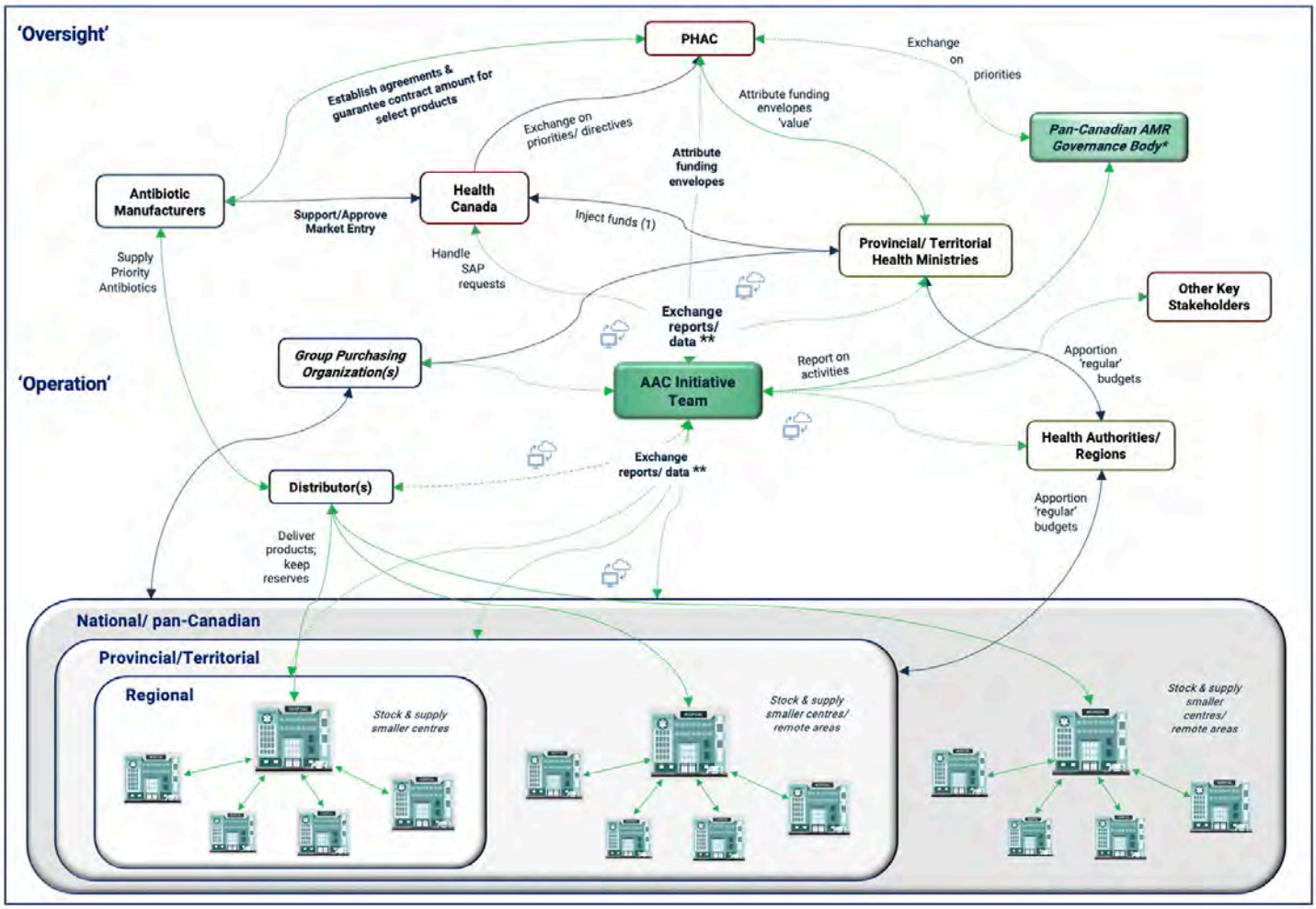
This body would be tasked with establishing a data collection/quality assurance framework and supporting and conducting relevant data collection and analysis efforts across Canada. Likewise, this body would be responsible for strengthening antimicrobial stewardship programming in Canada. Other key tasks for this group should include:

- Supporting the enhancement of the order/distribution/inventory tracking management system
- Establishing the requirements for and configuration of the inventory management and stewardship information management systems
- Work with hospitals to establish antibiotic guidelines and the 'hub-and-spoke' distribution model
- Support the deployment of the Stewardship application
- Develop guidelines for the stocking, prescribing, and dispensing of antibiotics
- Work with F/P/T governments and manufacturers to establish agreements on volume and pricing with manufacturers for select antibiotics and diagnostics
- Supporting the implementation of other recommendations put forward in this proposal
- Reviewing and forecasting future demand for certain drugs based on historical use and resistance patterns
- Tracking cost and utilisation data at hospital, regional, provincial/territorial, and national levels
- Evaluating opportunities to improve and innovate in other relevant areas
- Liaising with all relevant stakeholders to make this possible

Either by way of the proposed AMR governance body or through more direct means, the AAC Initiative Team will plug into the Public Health Agency of Canada. This connection will facilitate the allocation of funds and the dissemination of data. This group will also serve as a hub for Health Canada, P/T ministries, health authorities and LHINs, GPOs, hospitals, distributors, and other key stakeholders. But while this team is positioned at the heart of the solution, the solution itself remains traditional in structure in that the priorities of Health Canada and PHAC will trickle down from the top.

“ The solution itself remains **traditional in structure** in that the priorities of Health Canada and PHAC will trickle down from the top.

The following illustration depicts both the fluidity of the proposed landscape and also a basic hierarchy.



LEGEND

- Arrows and the corresponding text boxes between entities are meant to illustrate relationships in the context of the *AAC initiative* only.
  - indicates a relationship that already exists and that may/may not remain the same per the proposed model.
  - indicates a new relationship or a new activity within an existing relationship.
  - indicates a relationship that is more 'informational' than 'transactional'.
- Text boxes highlight the key function of the entity or relationship between organizations and are not meant to identify all functions.

Refers to an information system being used to support processes and information/data* transfer between stakeholders

- Green and grey boxes, such as those below, indicate a new entity, process or measure to be established under this initiative.
- The grey boxes also correspond to these deployment timelines/geographical areas:

Phase 2 (Pilot) – **HNHB** | Phase 3 – **Rest of Ontario** | Phase 4 – **Rest of Canada**

* If/when the proposed AMR Governance Centre or Network is implemented.

** *Data to include:* Bacterial pathogens / infections, lab results/diagnosis, corresponding indicated antibiotic(s), adverse events, efficacy, resistance, utilisation, and costs

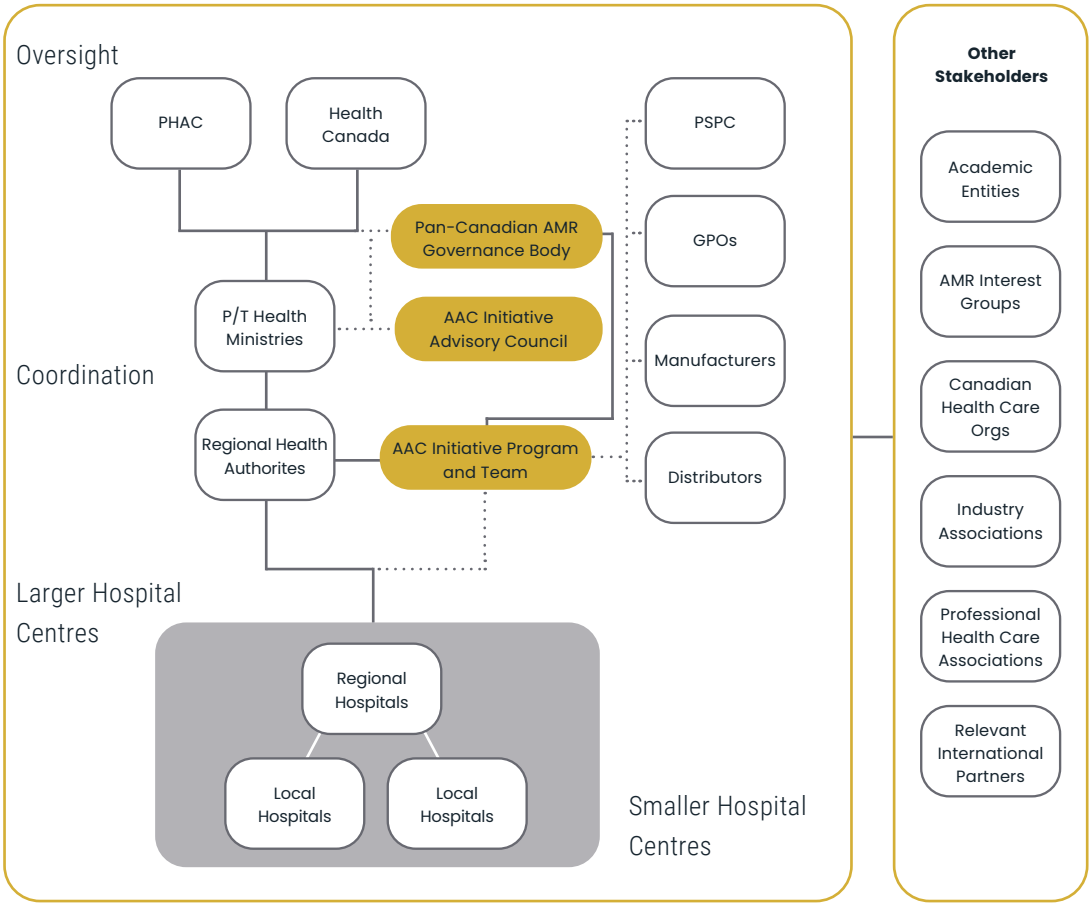
While we seriously considered another similar model option, we ultimately chose to recommend this one for the following reasons:

- It streamlines the agreement process at a national level, allowing the Federal government to negotiate pricing, establish the agreement, funding allocations and utilisation for payment purposes for the country
- It allows the AAC Initiative program team to manage the funds utilisation
- It retains a certain role for the Group Purchasing Organizations, which have established relationships with the P/T governments and hospitals and experience in navigating agreements with those entities

The other option has been included in Appendix 14 for review.

3.5 PROGRAM GOVERNANCE

In this integrated solution, different stakeholders will be counted on to assume certain responsibilities and to coordinate under a broader shared mandate. Strong relationships will be fostered through regular collaboration, touchpoints, webinars, and symposiums, all of which will facilitate knowledge-sharing and ideation. Governance, in this context, can be divided into four key domains: oversight, coordination, larger hospital centres, and smaller hospital centres. A number of key stakeholders will play vital roles on the periphery of these four categories.This structure has been designed in such a way that it will work whether or not any form of pan-Canadian AMR governance is implemented in the future. Indeed, while it would be strengthened by broader governance, this pilot has a clear focus and can therefore operate independent of other relevant initiatives.



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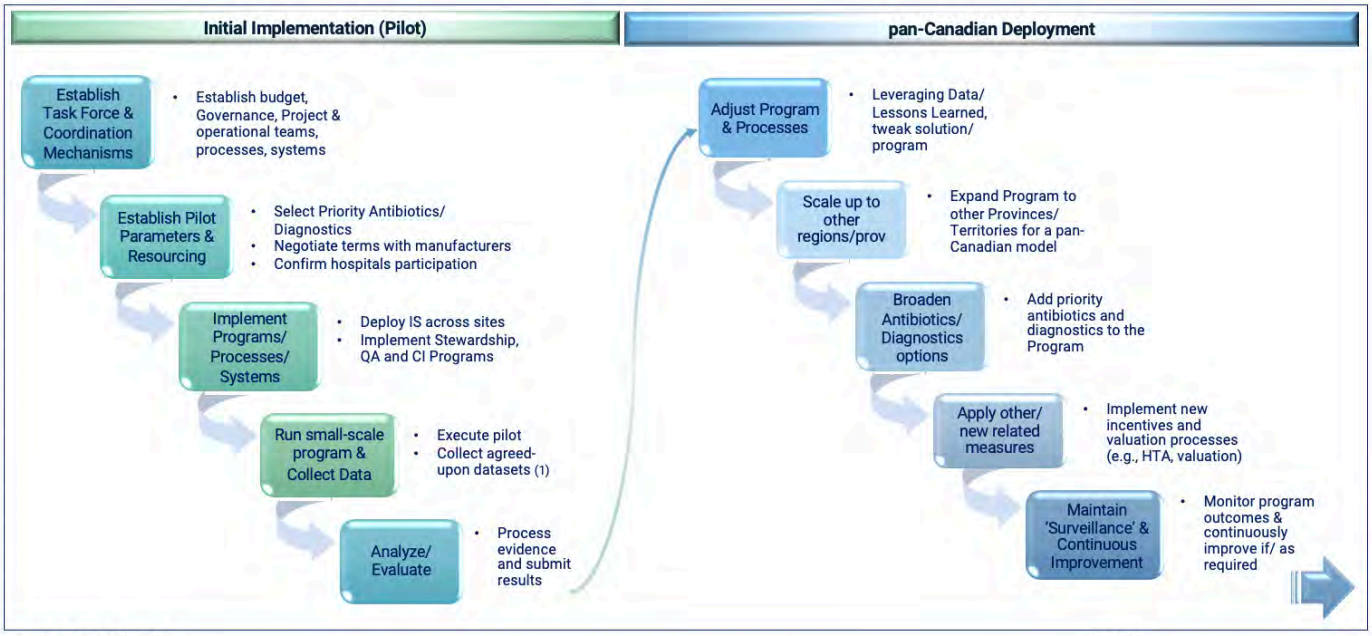
IMPLEMENTATION AND COSTING



The implementation of the overall initiative will follow a structured approach. A high-level framework is provided below as a guideline to enable the pilot. This framework will also facilitate any necessary refinement of the components pertaining to the solution, both individually and as an integrated and coherent whole.

4.1 INITIAL IMPLEMENTATION – AKA 'THE PILOT'

Following funding approval, the integrated solution should be implemented in a small area, such as the **Hamilton-Niagara-Haldimand-Brant** region (formerly Local Integration Health Network, or HNHB LIHN), which serves 1.4 million residents (and 'potential patients'), in Ontario. This will serve as a pilot project — an opportunity for the solution to show its efficacy and effectiveness.

We have recommended the pilot take place in the Hamilton-Niagara-Haldimand-Brant region because we believe that it can serve as a great example of how the integrated solution can apply in a mixed setting with single and multiple-hospital organizations. While this region is primarily located in a high-density area near Toronto, both Haldimand and Brant are considered rural areas and will therefore test the solution in both high-traffic and remote areas. This will inform scaling options, as Canada's hospitals serve a variety of urban, rural, and remote populations.

As the pilot takes root, broadening the solution across Ontario should be considered. This would provide an opportunity to test all hospital settings and a more comprehensive infrastructure; however, doing so will require the full buy-in of all hospitals and would take considerably longer to implement. In any case, the initial pilot will enable the testing and refinement of all base components and measures inherent to the overall solution. It will serve as a base model for an incremental expansion of scope as medium- and long-term recommendations are ready for integration. It will also inform best practices for when larger-scale deployment occurs. Until then, the AAC Initiative Team should focus on the following parameters and scope:

Stream	Area	Parameters & Scope	
		At Minimum	**For Consideration**
Project Governance and Management	Governance	Project Governance: Exec. Sponsor, Steering Committee, and Advisory Committee	AMR governance entity (centre or network)
	Scope (Geography/Scale/Users)	HNHB LIHN, which covers Hamilton, Niagara, Haldimand, Brant, Burlington and most of Norfolk. Includes nine hospital corporations with a total of 22 hospital sites.[56] To include at minimum: ▶ Hamilton Health Sciences (6 hospitals) ▶ Joseph Brant, Burlington ▶ St-Joseph's Healthcare, Hamilton	▶ All 22 hospitals in HNHB ▶ All of Ontario ▶ One other province
	Budget Required	Range: $4.2 to $7 million	Range: $7.8 to $12 million
	Timeline	Mid FY 2022-23 to mid FY 2023-24	Early FY 2022-23 to mid/late FY 2023-24

Stream	Area	Parameters & Scope	
		At Minimum	For Consideration
Data, Data Collection, and Analytics	Data sets	Data for the region related to: ▶ **Antibiotics**: Prescriptions, SAP requests/units approved, utilization, efficacy (incl., adverse events), resistance rates, and costs linked to use and effective/ineffective treatment ▶ **Diagnostics**: Tests requests, bacterial pathogens/infections lab results/ diagnosis, resistant isolates	Data for Ontario & as much of the other provinces as possible related to: ▶ **Antibiotics**: Prescriptions, SAP requests, utilization, efficacy (incl., adverse events, morbidity), resistance rates, and costs linked to use and effective/ineffective treatment ▶ **Diagnostics**: Tests requests, bacterial pathogens/infections lab results/ diagnosis, resistant isolates
	Processes and tools	Processes/systems/tools to collect data in geographical area of deployment and to report to AAC initiative coordination team and designated stakeholders	Processes/systems/tools to collect data across Canada to establish forecasts for the next phase

Stream	Area	Parameters & Scope	
		At Minimum	For Consideration
Antibiotics and Diagnostics	Antibiotics	Two select novel antibiotics already approved and marketed in Canada[57]	Either of: ▶ Four select novel antibiotics that are approved and marketed in Canada ▶ Two select novel antibiotics that are approved and marketed in Canada and two that are not yet approved (and can currently only be requested via SAP)[58]
	Diagnostics	Tests for selected antibiotics[59]	One to two rapid tests for pre-selected priority antibiotics that are not yet approved in Canada

Stream	Area	Parameters & Scope	
		At Minimum	For Consideration
Incentives and Financial Measures	Regulatory and policy incentives	Abstraction of existing product valuation and pricing for approved antibiotics and diagnostics	▶ Temporary exemption to approval process for selected antibiotics if applicable ▶ Exclusion from regular HTA/ Valuation/Product Listing Agreement processes (products new to Canada)
	Financial incentives	Guaranteed revenue for manufacturer(s) of chosen antibiotics (and long-term savings for HNHB)	Guaranteed revenue for manufacturer(s) of all chosen antibiotics/diagnostics (and long-term savings for Ontario healthcare)
	Financial mechanisms	Costs of select antibiotics/diagnostics are covered by federal envelope (not by hospital budget)	Costs of select antibiotics/diagnostics are covered by federal envelope (not by hospital budget)

Stream	Area	Parameters & Scope	
		At Minimum	For Consideration
Stewardship and Quality Assurance	Stewardship	Stewardship program inclusive of protocols/guidelines, expert resources (i.e., stewardship pharmacists and ID specialists), tools, and an information system ('app') to guide providers implemented in each hospital in scope	Nothing additional
	Quality Assurance (QA)	QA program inclusive of policies/ procedures, expert resources (e.g., QA lead, stewardship pharmacists and ID specialists), tools and information system to track adherence to stewardship protocols/guidelines	Nothing additional

Stream	Area	Parameters & Scope	
		At Minimum	For Consideration
Information Management Systems	Stewardship	Application enabling providers to access antibiotics guidelines provided by ACC Initiative program team	▶ Interfacing with Pharmacy/ Drug database/ ordering system ▶ Interfacing/integration with EMR and/or other systems to gather data required for QA program
	Distribution and Procurement	Selection of dedicated system and customization to AAC program requirements	▶ Interfacing with Stewardship app ▶ Interfacing/integration with Pharmacy systems to track utilisation of products and enable JIT orders ▶ Interfacing/integrations with analytics tool (e.g., Tableau) and designated reporting systems (e.g., CARSS)

Stream	Area	Parameters & Scope	
		At Minimum	For Consideration
Evaluation and Continuous Improvement	Stewardship	▶ Operationalization of evaluation framework and independent evaluation of initial and subsequent phases ▶ Establishment of Continuous Improvement processes across the system to refine the overall solution and adapt to evolving needs	Nothing additional

4.2 PROJECT METHODOLOGY & STRUCTURE

Project Management

We recommend a mixed approach to project management and execution, integrating best practices in project management, business analysis, and agile approaches from the Project Management Institute (PMI) to address both overall business needs and information technology implementation requirements. We also recommend applying the principles of Organizational Change Management and Process Improvement and marrying them with Project Management practices to ensure a comprehensive and cohesive approach to meeting objectives and delivering a sound model. Stakeholders along the entire provisioning pathway should feel prepared to adopt and use optimized processes and systems so that patients can be cared for in the best manner.

While this approach comes at an apparently greater cost, it has proven to pay off in the form of reduced effort duplication, fewer issues, and judicious risk management.

Project Structure

In following with project management best practices, this initiative will be structured with the appropriated governance bodies.

General Governance

- A project-specific governance will be established.
- In the event that the pan-AMR Governance model is being implemented, high-level governance may be provided by that entity to ensure that this project progresses according to plan and is in alignment with broader pan-Canadian objectives; however, the project's Steering Committee will be responsible for guiding the project team and charged with significant decision-making power (e.g., the appropriate reallocation of funds).

Advisory Committee

- An advisory committee will be struck to provide objective input. This committee will have the power to advise on and influence project direction, but it is in no way a decision-making body.

Steering Committee

- A representative steering committee composed of subject matter experts will set strategic priorities and guide the project team on execution.

Project Team

- The project team will be a mixture of consultants, vendors, and employees of the stakeholder organizations, who, together, will execute upon specific and broad project mandates. This team will facilitate project administration, communication, consultation, and work to implement new technologies.

Working Groups

- Working groups will be established to define and craft specific work packages as follows:
    - Market Access – Incentives & Financial Measures
    - Data Collection & Analytics
    - Antibiotics & Diagnostics
    - Stewardship & Quality Assurance
    - Information Management & Systems
    - Evaluation & Continuous Improvement

4.3 PROJECT LIFECYCLE, KEY ACTIVITIES, AND DELIVERABLES BY STAGE

The following table introduces the expected activities and deliverables to support the Initial Implementation (Pilot) at each stage of the project lifecycle.

Contract Award & Teaming

- Contract Awarding
- Teaming

Implementation & Costing

Initiation

- Background Documentation Review
- High-Level Plan / Project Timelines Validation
- Stakeholder Analysis
- Governance Structure Development
- Project Initiation
- Project Charter Development
- IMS Privacy & Security Requirements Identification
- — Gate Approval —

Planning

- Initial Scope/ Deployment Definition
- Current State Analysis / Process Mapping
- Future State Design
- Gap Analysis
- Master Plan Development
- Development of Other Supporting Documentation
- — Gate Approval —

Vendor and Systems Selection

- Call for Tender
- Vendor Selection

Execution

Stream 1 — Project Governance & Management

- Project Governance
- Project Management
- Change Management
- Business Analysis/ Process re-engineering & improvement
- Communications
- Training

Stream 3 — Antibiotics & Diagnostics

- Clinical evidence/demand data review
- Selection of products to include in current Phase

Stream 2 — Data collection & Analytics

- Datasets, data collection, and reporting requirements
- Data collection integrations / Analytical tools selection
- Reports enhancements/design

Stream 4 — Data collection & Analytics

- Refinement of proposed incentives and financial measures, including:
    - Modelling of Incentives model
    - Modelling of savings and impact of measures on the healthcare system and the Canadian economy
- Establishment of legal and regulatory parameters
- Identification/operationalisation of required policy/ regulation changes
- Establishment of funding envelopes and incentives-related accounts

Stream 5 — Stewardship & Quality Assurance

- Establishment of Stewardship protocols, in line with AMR governance and surveillance protocols
- Development/edification of existing programs — including parameters/performance indicators
- Development of guidelines tailored to AAC initiative

Stream 6 — Information Management

- Detailed systems/process requirements
- Development/enhancements to existing systems
- Interfacing with relevant apps/tools
- Configuration of Stewardship App
- Privacy/Security Policies and Procedures
- Testing
- Training/Train-the-trainer packages

Stream 7 — Evaluation & Continuous Improvement

- Evaluation Plan Development
- Continuous Improvement Program Development
- — Gate Approval —

Go Live Preparation & Go Live

- Site Preparation
- User Acceptance Test (UAT)
- Production/Compliance Sign Off
- Training
- — Gate Approval –
- Go Live

Post-Go Live

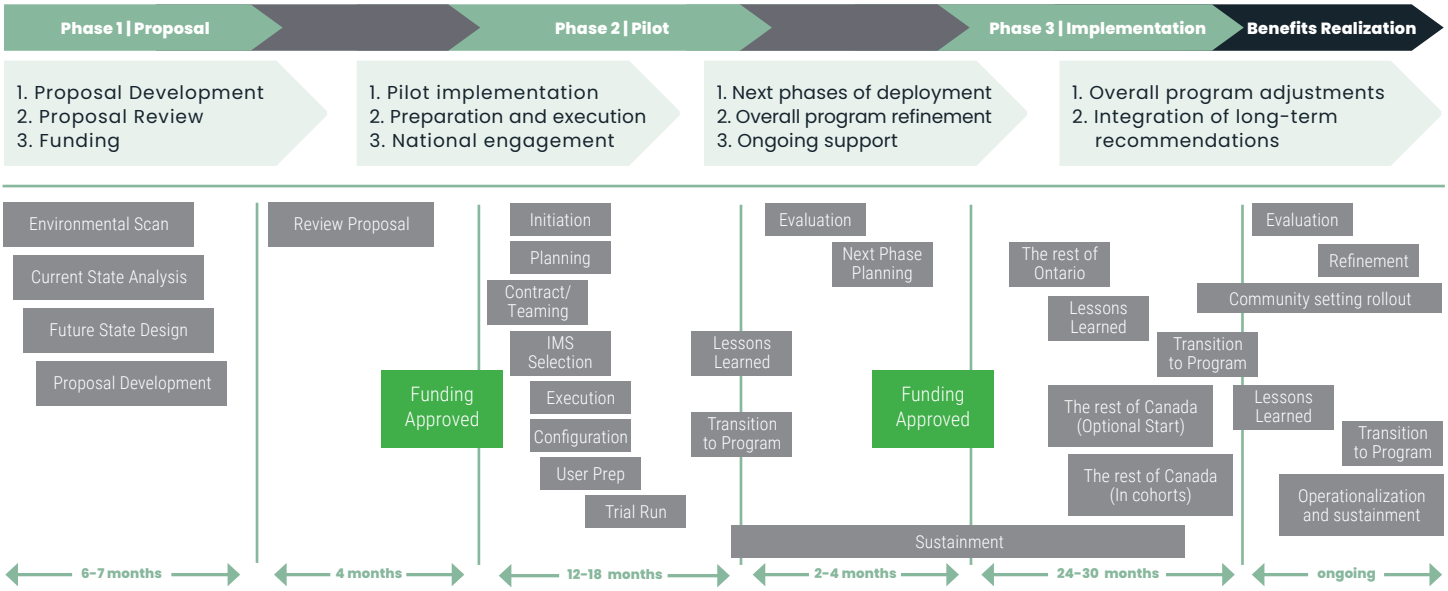
- User support, including troubleshooting, de-bugging, and additional training
- Lessons Learned
- Evaluation

> Stakeholders along the entire provisioning pathway should feel prepared to adopt and use optimized processes and systems so that **patients can be cared for** in the best manner.

4.4 END-TO-END IMPLEMENTATION

Project Timelines

The following diagram illustrates a high-level implementation plan for the entirety of the project, which is in line with the timelines assigned to the recommendations put forward in earlier sections. The sequencing of these activities was done carefully based on the information currently available to our team. These may be modified to accommodate new information.



Evaluation Framework & Key Measures

While a working group will be formed to develop and establish an evaluation program that is tailored to the initiative, our project team deemed it important to present an early version of an evaluation framework based on the Logic Model used by PHAC to demonstrate the benefits of the measures to be introduced:

Inputs	Activities	Initial Outcomes	Intermediate Outcomes	Long-Term Outcomes
▶ Skilled human resources and field expertise ▶ Regulatory/policy incentives (streamlining of regulatory processes for priority abx) ▶ Financial incentives (guaranteed revenue) ▶ Financial mechanisms (priority abx/dx funding envelopes) ▶ Stewardship program and information system ▶ Quality assurance program ▶ Improved ordering and distribution system	▶ Onboard/training resources ▶ Determine governance, surveillance, and stewardship protocols ▶ Refine and implement incentives and financial measures ▶ Develop and implement stewardship and QA Programs ▶ Implement/enhance/ integrate information systems ▶ Pilot solution on a small scale and evaluate ▶ Deploy solution across Canada	▶ Increased human and technological capacity to support stewardship and abx/dx provisioning ▶ Improved provisioning process in a designated region ▶ Increased access to limited number of priority abx/dx ▶ Improved diagnoses and dispensing decisions ▶ Increased number of patients with the right antibiotic at the right time ▶ Improved and timely access to select data and indicators	▶ Increased number of novel abx on formularies ▶ Increased number of priority abx/dx approved in Canada ▶ Increased access to priority abx/dx ▶ Increased turnaround/ capacity at hospitals ▶ Improved abx/dx utilisation ▶ Significant savings for the health care system ▶ Improved ability to make investment decisions ▶ More patients with quicker recoveries ▶ Improved data quality and completeness	▶ Improvements to the Canadian Economy ▶ Larger investments in novel antibiotics ▶ Reductions in incidence of AMR ▶ **Significant improvements to the health of Canadians**

Legend

abx = antibiotics
dx = diagnostics
initial = <1 year
intermediate = 1-2 years
long-term = 2-3 years

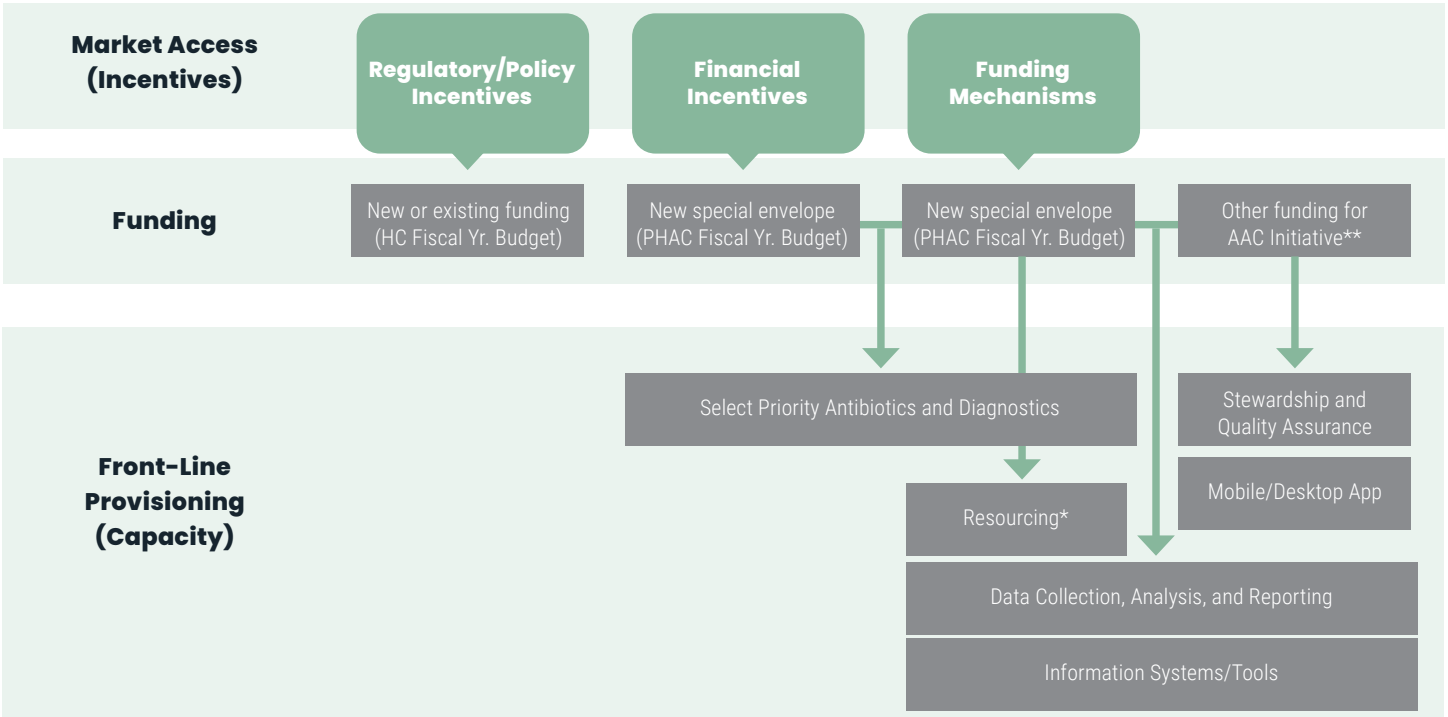
The model captures expected outcomes for several indicators; however, the list is not comprehensive. We anticipate that the Working Group will establish a robust list of indicators and data that will help fully measure the variables of interest in the context of this initiative.

4.5 FUNDING & COSTS

Funding Allocation

The table below illustrates how each of these proposed measures and components are proposed to be funded:

AAC Integrated Solution — Model Components



*Resources to include a full project team to support implementation and a small program team to support initiative on an ongoing basis.
**To support implementation and ongoing operations. Finding may come from a variety of sources.

While we understand that Provinces/Territories may want to manage funds that would be attributed via the new Priority Antibiotics and Diagnostics envelopes, it is also an option for the AAC Initiative Program to manage these – or at least to support allocation based on anticipated need per hospital and actual utilisation.

We highly recommend building some flexibility in the funding mechanism model so that funds may be re-allocated from one hospital to another at some point in the year if a particular situation (e.g., outbreak in a particular region) requires that an unusually high quantity of a specific antibiotic be consumed (this assumes that transfers would be done from (a) hospital(s) with lower than anticipated utilisation). To allow this, it will be important to ensure a centralized, real-time tracking of allocation and utilisation.

Because of the innovation and technology aspects to this antibiotic access and capacity initiative, there may opportunities to seek funding from other organizations, such as ISED (its Strategic Innovation Fund could support AMR innovation) or Canada Health Infoway.

Estimated Costs

The details of the estimated costs to implement and to sustain this initiative are provided ahead. As such, and in alignment with the Estimated Costs summary in Appendix 15, this subsection was divided into two components:

- **Implementation & Deployment Costs — 'one-time costs'**
- **Program Costs (Operation/Sustainment) — 'recurring costs'**

Please note the following pertaining to the various figures presented in this subsection:

- Implementation costs associated with the information systems were provided by two existing vendors that are already established in the areas that required coverage or enhancements
    - **Stewardship application**: Firstline, a Canadian company, is already established across several hospitals (covering exactly 20,900 beds) in Canada and can already support most of the functions required from a stewardship perspective. Some modifications and integrations with existing systems could be performed to fulfill additional functions, such as capturing dispensing information to compare with recommendation provided by the app.
    - **Ordering/Distribution application**: The Canadian Pharmaceutical Distribution Network is broadly established across Canada, as is their ordering system. They have established mechanisms for second-level approval of select drugs that can be co-opted to fit stewardship requirements for ordering of novel antibiotics.

IMPORTANT: The inclusion of these information systems in this proposal does not constitute endorsement over others that may meet objectives in the same or a better manner. They were chosen because of their existing presence in the market and their interest in and collaborative approach to this project. It is possible that a more in-depth field analysis would reveal other systems that are adequately or more appropriate to ensure the seamless flow of data/information, or yet that additional features are required to achieve the desired integrated solution.

- Salaries for the ACC Initiative team during implementation were factored into Operational Costs, but could be moved to Implementation Cost and thus included as project line items.
- Costs associated with antibiotics were estimated based on a model assuming Canada's participation in G7 efforts to improve the situation across the world.
- Costs for diagnostics were not available at this point and may vary upon the selected antibiotics, however manufacturers may opt to 'donate' diagnostic tests to use in the pilot if these are not already available at the designated sites.
- Costs associated with antibiotics/diagnostics used during the pilot were factored into Operational Costs, but could be moved to 'Implementation' and thus included as project line items.
- Costs do not include government savings that will be realized through:
    - a more effective utilisation of antimicrobials
    - a more effective utilisation of diagnostics
    - improved treatment outcomes
    - reduced complications and severe infections
    - reduced missed days of work

Implementation & Deployment Costs

Phase 2 – Initial Implementation (Pilot)

Two options are presented for consideration in planning for the initial deployment. In summary, they are:

1. Minimum Effort

- Include HNHB region hospitals that readily volunteer to participate in pilot
- Operationalize AAC Initiative team
- Implement Stewardship program (including Stewardship App & guidelines) and Quality Assurance Program
- Enhance designated distribution system for orders of select priority antibiotics
- Select and fund two priority antibiotics and their corresponding diagnostic tests to include in the program[48]

Advantages	Disadvantages	Estimated Costs
▶ Enables quicker implementation and demonstration of impact of initiative, thus allowing patients in HNHB, other Ontario regions and P/Ts to benefit earlier from what is to be established via this option (e.g., access to select antibiotics, stewardship program/app), and government/health care system to realize expected savings earlier	▶ Does not allow for the systematic capture of national data to inform certain decisions for Phase 3	▶ Just under $5.6 million, factoring dollars for time spent by salaried resources on implementation activities
▶ Is less costly up front, thus less risk linked to investment	▶ Does not allow to test the integrated solution at its full capacity	▶ Removing those costs, the project is forecasted to cost under $3.4 million
▶ Allows adjustments much faster and more easily since less has been established		▶ This amount does not include savings associated with the utilisation of the Stewardship App across the HNHB region. These should reach close to $2 million
▶ Gives other parties time to engage and work on other areas in parallel		

2. Optimum Effort

- Offers the same benefits as the Minimum Effort option, plus:
  - Work with all HNHB region hospitals to gain commitment to pilot
  - Establish data collection processes in larger geographical areas
  - Select and fund four priority antibiotics to include in the program
  - Select and fund one or two diagnostic tests for pre-selected priority antibiotics that are not yet approved in Canada to include in the program
  - Establish guaranteed revenue agreements with manufacturers for select antibiotics and diagnostics for a period of four years

Advantages	Disadvantages	Estimated Costs
▶ Allows for the systematic capture of national data to inform certain decisions for Phase 3	▶ Delays start of pilot and demonstration of impact of initiative, and deployment to other Ontario regions and P/Ts	▶ Just under $8.2 million, factoring in dollars to assign hospitals for staff time spent on implementation activities
▶ Engages all parties up front thus building momentum for subsequent phase	▶ Requires all stakeholders to be engaged at the onset and throughout, which might cause further delays, a slower pace of pilot initiation and refinement	▶ Removing those costs, the project is forecasted to cost $6.3 million
▶ Allows to test the integrated solution at its full capacity	▶ Is more costly up front, thus increases the risk linked to investment	▶ This amount does not include savings associated with the utilisation of the Stewardship App across the HNHB region. These should reach close to $2 million
▶ Enables gathering of information/input from stakeholders across the country, mitigating 'bad surprises' down the road		

Recommendation:

- We consider it critical to take immediate action towards achieving gains that will quicky and significantly improve patient care in Canada
- We also consider it important to establish processes at a national level and to participate in international initiatives to improve the situation for people across the world
- These two objectives cannot be achieved together under the same project; however, they can be achieved in parallel by two different teams — as long as there are regular touchpoints and exchanges to ensure alignment between what is being conceived and implemented by both teams.
- Therefore, we recommend that our government approves funding for Option 1 proposed for the AAC Initiative, and establishes a Data Collection task force under the AMR (governance model) umbrella to tackle the establishment of cohesive national data collection and collation processes that will inform decisions related to antibiotics and related diagnostics, as well as antimicrobials as a whole.
- This initiative would not only support several of the priority actions under the PHAC's Pan-Canadian Action Plan On AMR/AMU, but also prevent effort duplication and establish distinct processes, which should be cohesive.

The Costs of Scaling — Phase 3

The Rest of Ontario

Building on the momentum (including the 'still warm engagement' with stakeholders) and lessons learned gained from the initial implementation, we propose that the next stage focused on continuing deployment across Ontario.

ESTIMATED COST: Between $11.1 and $11.8 million, depending on scope (Option 1 or 2) and factoring dollars to assign hospitals for staff time spent on implementation activities. Removing those costs, the project is forecasted to cost between $7.6 and $8.2 million. These amounts do not include savings associated with the utilisation of the Stewardship App across Ontario. These should reach $17 million.

The Rest of Canada

While other provinces and territories may be given the opportunity to begin deploying the solution, the current plan is built around a later pan-Canadian scaling, so that lessons-learned can be applied before national-level investment is made.

ESTIMATED COST: Between $28.4 and $36.9 million, depending on scope (Option 1 or 2) and factoring dollars to assign hospitals for staff's time spent on implementation activities. Removing those costs, the project is forecasted to cost between $20.6 and $26.3 million.These amounts do not include savings associated with the utilisation of the Stewardship App across Canada. These should reach close to $39 million.

Program Costs (Operations & Sustainment)

Overall Program Management

The yearly costs associated with long-term planning, overseeing, and managing the day-to-day activities of the program are estimated to be less than $1.1 million. During the course of implementation/deployment, costs associated to this component are estimated to land just over $2.8 million.

Other operational program costs associated with infrastructure, information systems, and antibiotics during deployment are estimated to vary between $29.2 and $52.9 million, or between $7.3 and $13.3 million per year for four years, depending on the option chosen (minimum or optimum).

Yearly operational costs before antibiotic expenditures should remain below $2.9 million. Costs associated with antibiotics will vary based on the incentives model selected, as per the Market Access section ahead.

Note: These amounts do not include savings associated with the utilisation of the stewardship app and other savings to the health care system associated with reduced infections.

Market Access – Financial Incentives

From our review of existing and proposed incentives models, we surmise that Canada may opt to provide incentives under one of two options:

- A partially delinked model that sets the quantity of select priority antibiotics to be suppled yearly at a unit price that is representative of the true (public health) value of that antibiotic to Canadians for a total guaranteed revenue over an agreed-upon contract term (similar to the Sweden access model)

- A fully delinked model that bases the value of each guaranteed revenue agreement on Canada's agreed-upon investment towards the global antibiotic market and implies an unlimited supply of the select priority antibiotic (such as the UK subscription model)

The basis of the fully delinked model is that the 'investment' is not only made towards covering the production and distribution of the drug, but also towards the costs to research and develop it. Several variations of this model exist[60] and may be more or less relevant depending on where in its lifecycle an antibiotic is, or depending on the manufacturers' situation.

Neither choice is wrong, and a hybrid may be possible to allow an efficient management of antibiotic inventories and funds. Application of different models for different situations or manufacturers may also apply. As unbiased contributors to the solution, we recommend that our government further explores implications (operational and financial) for each of the models, with consideration to Canada's needs and what will be required to gain commitment by manufacturers to meet those needs.

To support this, we endeavoured to pair the seemingly best-suited model(s) to the corresponding estimated value (including financial incentives), along the three scenarios introduced in an earlier section. We expect that all figures provided will be further validated by government analysts and, where they were derived from international models, further adjusted using current exchange rates[61] and GDP/GDP share. The proposed models are as follows:

Select Priority Antibiotics already approved/marketed in Canada

Under a **partially delinked model**, guarantee manufacturers a revenue for a minimum set volume of select priority antibiotics at an agreed-upon unit price.

- Quantities to be based on a forecast derived from the current demand and adjusted to account for the actual demand once the financial barrier is removed (though funding envelopes allotted at the Federal level)
- For pricing, a recommendation is to start with current list price and adjust if needed – this could include removing any discounts that were previously granted at the next contract iteration.

- Contracts could be established for 3-4 years to allow reconsideration of volumes or other aspects, however this could be detrimental to price paid or tenure of relationship with a particular manufacturer.

Estimated value per select priority antibiotic for all of Canada:

- Floor:[64] $1.7 million
- Ceiling:[64] $10 million

NOTE: This model can only apply in the short-term if Canada opts to adopt a subscription model. At that point, Canada may decide to apply a subscription model to all antibiotics or only to those that were not already marketed in Canada.

Select Priority Antibiotics NOT yet approved in Canada

Remove or reduce the marketing authorization fee (aka 'filing fee').

- Estimated value per application: $437,009, if the drug has a new active substance, and $224,242, if the drug does not have a new active substance, in addition to the value associated with entering the market faster and selling the product earlier and at a fair price.

Under a **partially delinked model**, provide a guaranteed revenue for a minimum set volume of select priority antibiotics at an agreed-upon unit price.

- Quantities required should be estimated based on resistance patterns and a forecast for the expected use given incidences of infection and recommended treatment for the country.
- Until data collection processes are established to provide a comprehensive profile and enable this forecast, SAP data could inform demand trends as a start.
- For pricing, until the antibiotic valuation model has been redesigned to consider public health value and externality factors, one suggestion is to start with the government list price established in the U.S. Exchange rate could also be removed.
- Contracts could be established for 3-4 years to allow for reconsideration of volumes or other aspects, however this could be detrimental to price paid or tenure of relationship with a particular manufacturer.

Estimated value per select priority antibiotic for all of Canada:

- Floor:[64] $4 million
- Ceiling:[64] $12 million.

NOTE: This model can only apply in the short-term or not at all if Canada opts to adopt a Subscription model. At that point Canada may decide to apply a Subscription model to all antibiotics or only to those that were not already developed or approved in any jurisdiction.

Priority antibiotics yet to be developed/approved in any jurisdiction

Provide a guaranteed revenue under either a partially delinked or fully delinked model.

A partially delinked model could be based on:

- **(a)** A 'fixed volume' agreement (as derived from the Sweden Access model). Agreement with manufacturers would be established and adjusted yearly to arrive at a set minimum volume – as forecasted from incidences of infection(s) and the corresponding treatment considering resistance patterns – and a set price for any given antibiotic under this initiative would be established based on a new valuation model considering public health value and other externality factors. Contracts could be

established for 3-4 years to allow for reconsideration of volumes or other aspects, thus justifying higher average price paid per antibiotic.

Estimated value for any given select priority antibiotic:

- $7-8 million for all of Canada

- **(b)** Other variations involving, for instance, a market entry reward, which could be paid in one year,[62] after FDA licensure and allow the company to keep all sales revenues.

A **fully delinked model**, meanwhile, could be based on:

- A 'subscription' agreement (as derived from the UK 'Netflix' model).To secure participation by manufacturers and demonstrate Canada's commitment to the international effort to reduce AMR, a 10-year agreement would be established with participating manufacturers of select priority antibiotics, delinking the actual volume supplied from the value of the antibiotic to society. This model assumes commitment to an internationally agreed-upon valuation of these antibiotics and a financial investment by other interested countries based on their respective GDP. Commitment by other countries may vary and could extend to a small group, such as the G7, or a much larger group, such as the G20, which would reduce the share of the expected investment. Adoption of a partially or fully delinked model could also be considered. Estimated value per select priority antibiotic for all of Canada,[63] depending on the model selected would be:

Model	Low[64]	High[64]
Fully Delinked – SUB10 [65]	$6.6 million	$17.7 million
Fully Delinked – SUB10+ACQ [66]	$4.4 million	$9.5 million

- According to our industry partners, the SUB10+ACQ model may be ideally suited to Canadian companies with antimicrobials that have reached Phase-II[67] development, but require support to address funding gaps for product development and commercialization. For other companies, however, the situation is dire and this span of time doesn't sufficiently address the immediacy of their needs.

- Note that these assume that all G20 countries would commit to the international effort. A 30-40% increase might be expected if only G7 countries committed.

- Please refer to Appendix 16 for greater details.

IMPORTANT: The valuation for the antibiotics to be used during the initial implementation and subsequent deployments period (i.e., 3-4 years) was based on an approximated average of the Scenario 1 figures, which also aligns with figures presented in Scenario 3. We hope that this conservative number will amply cover what may be allotted towards antibiotics during that time. If manufacturers choose to donate antibiotics, the funds could be redirected towards diagnostics, an essential tool that is too often neglected in budget planning and allocations.

This proposed incentives framework is viewed as a great start, to serve as a base for discussions with stakeholders and a decision by Canada on how to move forward. These discussions can happen while the pilot is conducted (using current or – ideally – Scenario 1 figures). This may also allow time to assess the true public health value – taking all externalities into account – of antibiotics to Canadians.

The following table summarizes the incentives framework and the estimated value of bringing critical antibiotics to Canadians:

SCENARIO	REGULATORY/POLICY INCENTIVES	FINANCIAL INCENTIVES	ESTIMATED VALUE	
			Canada	Hospitals[6]
Select Priority Antibiotics **already approved/ marketed** in Canada	▪ **N/A**	▪ **Guarantee** manufacturers **revenue** for a minimum set volume of select products at an agreed-upon price[1]	▪ **Per contract per year**: • Floor: $4 – Ceiling: $10 million per antibiotic[2]	▪ **Per contract per year**: • Approximately $170k - 1 million per antibiotic[2]
Select Priority Antibiotics **NOT yet approved** in Canada	▪ **Reduce or waive Marketing Approval costs and/or requirements** under certain conditions	▪ **Guarantee** manufacturers **revenue** for a minimum set volume of select products at an agreed-upon price[1] (as the partially delinked Sweden model)	▪ ***Per application:*** $437,009, if the drug has a new active substance, and $224,242 if the drug does not have a new active substance), plus value associated to quicker market entry and ability to sell product. ▪ **Per contract per year**: • Floor: $4 million – Ceiling: $12 million • per antibiotic[3]	▪ **Per contract per year**: • Floor: $400k • Ceiling: $1.2 million per antibiotic[3]
Priority Agents/ Antibiotics **yet to be developed/ approved in any jurisdiction**	▪ Canada contributes its share towards the international effort to invigorated the antibiotics/ antimicrobial market by investing in Pull Mechanisms[4]	▪ **Guarantee** manufacturers a certain **revenue** based on retaining or adopting a(n): o ***Partially delinked model (such as Sweden's)*** o **Fully delinked model** based on a 10-year subscription[5] o SUB10 o SUB10+ACQ	▪ **Per contract per year**: o Approximate fixed price of $7-8 million per antibiotic[3] o Low: $6.6 million – High: 17.7 million per antibiotic[5] o Low: $4.4 million – High: 9.5 million per antibiotic[5]	▪ **Per contract per year**: o Approx. $700-800k per antibiotic[3] o $660 – 1.7 million per antibiotic[5] o $440 - 950k per antibiotic[5]

1. Quantities TBD based on forecast – derived from current demand and adjusted to predict future demand without present barriers – at an agreed-upon list price – derived from current list price and temporarily adjusted to reflect true value more closely and accurately.
2. Depending on the type and quantity of antibiotic needed.
3. Determined based on a fixed quantity of select products X the agreed-upon unit price (per a revised valuation considering PH benefits, etc).
4. This may also mean investing more into push incentives for local R&D but being able to deduct this amount from pull – subscription model investment described below.
5. These amounts are based on a 10-year commitment by all G20 countries to an overall valuation of the antimicrobial market and according to respective GDP share (Canada's was established at 1.6% for this purpose). Canada's market share, and thus financial commitment, would increase according to the reduction in GDP share of the countries that do not commit. For instance, if only the G7 countries were to commit, Canada might be expected to shell out 30-40% more.
6. This is assuming a 10% flat share of antimicrobial consumption by hospitals across the whole Canadian healthcare system.

Market Access — Other Incentives & Financial Measures

Part of the costs associated with developing and establishing policy and financial measures to support this initiative were included in the Implementation costs. The ongoing management was not estimated and assumed to be part of the regulatory and finance/ budgeting scope of existing resources in government, industry and other relevant stakeholder organizations.The value of diagnostics and of the funding envelopes to be attributed to hospitals for the new tests remain to be determined. This should be completed in the first stages of Phase 2.

Front-line Access – Provisioning

Costs associated with the ongoing procurement and distribution of antibiotics purchased /dispensed used under this program were not calculated because they are assumed to be part of the drug procurement scope of existing resources in government, industry and other relevant stakeholder organizations. Please see Appendix 15 for a detailed summary of costs.

4.5 SAVINGS

Savings to be achieved by this initiative will grow over time as all the measures are implemented, and the integrated solution is refined and becomes fully operational. Adoption of the Stewardship application and antibiotics guidelines will see immediate results. Direct, observable savings upwards of $39 million per year are anticipated. Refer to Appendix 21 for details. This means that our government could recoup its investment (and even profit from it) in the first year following completion of deployment across the country. Long-term savings – for which measures need to be established – are also expected as illustrated in Section 4 – Evaluation Framework.

4.6 THE STATUS QUO

If you've made it this far into our proposal, then you likely know the social and economic consequences of AMR; however, we feel that it bears repeating. To pull from the 2019 report *When Antibiotics Fail*:

- "An average of 26% of bacterial infections reported in Canada in 2018 were resistant to first-line treatment, with 14,000 deaths linked to those infections and 5,400 deaths directly attributable to antibiotic resistance"
- "Longer hospital stays and longer courses of treatment associated with drug-resistant infections cost the Canadian healthcare system more than $1 billion (CAD)"
- "The resulting impact on labor productivity cost the country's economy $2 billion"

These are the immediate costs of not 'doing anything' to prevent the situation from worsening. If we do not act now, the same report concludes that the rate of antibiotic resistance risks climbing to 40% by 2050, which could lead to 13,700 Canadian people dying each year from drug-resistant infections. If the cost of lives wasn't bad enough, this will also burden the Canadian hospital system with additional spending to the tune of $7.6 billion annually and result in economic losses of $21 billion a year.

With that in mind, investing less than one billion dollars over four years to course-correct is undoubtedly in Canada's best interest.

— 5 —

THANK YOU

Thank you for reading this proposal.

On behalf of the many stakeholders consulted for this work, we look forward to seeing how our recommendations and proposed solution develop into tangible measures that increase access to and capacity for novel antibiotics in Canada.

This work, in alignment with the priorities set forth by our federal leadership, will help slow the spread of antimicrobial resistance in Canada — before it's too late. The COVID-19 pandemic has shown us the importance of being prepared for major public health threats, and we believe that having the right suite of antibiotics on hand to treat infections caused by Canada's priority pathogens is a great way to demonstrate such preparedness.

We implore you to consider this proposal with urgency — as we've illustrated throughout this document, Canadian economic and societal health are at stake. The investment required to demonstrate the feasibility of our plans is a sliver of the investment that will be required to fix antimicrobial resistance, should it continue to worsen.

Please do not hesitate to connect with us if you have any questions or require any clarification.

We look forward to the next steps.

Lori Burrows
Project Chair
lori.burrows@mcmaster.ca

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21. Hospitals outside of Québec frequently wait for CADTH's recommendation before adding a new drug to their own formulary to prevent administering a drug that patients would have to pay out of pocket once discharged from hospital.

22. Hospitals manage their own negotiations through Group Purchasing Organizations, but see the product list price reduced to match that negotiated by the pCPA when applicable.

23. Because drug expenditures are at the hospital's discretion, most provinces/territories (except, for instance, British Columbia and Québec) do not extend their provincial formulary to public hospitals within that province/territory. Hospitals are responsible to review evidence and recommendations for each new product and to decide whether to add to their formulary, which consideration for the budgetary implications.

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40. Considerations should be given to supporting the capacity of labs to perform surveillance regarding antibiotic resistant organisms. This would have to be further explored – outside the scope of this proposal.

41. A role will remain for the SAP to support access to drugs not available under an incentive program.

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43. This includes ensuring that reviews are performed in parallel, so that diagnostic tests are available once new antibiotic is available in Canada, and considering the expedited approval of diagnostics for novel antibiotics. In the event that an antibiotic may not be approved and its corresponding diagnostic can be, consider deploying and using it regardless as an innovative and proactive way to narrow down diagnosis and identify needs for novel antibiotics.

44. A biomanufacturing funding envelope was just created that could support this measure: https://www.innovation.ca/news/budget-2021-boosts-bio-science-labs-future.

45. As/if savings are realized at the hospital, health region and Provincial/territorial levels, it will be at the Federal government's discretion to reduce or remove its contribution towards the antibiotics and diagnostics under this initiative.

46. Based on infection strains, resistance/susceptibility, efficacy and demand per diagnostics test and expressed by providers (incl., ID Specialists, Microbiologists, Physicians, Pharmacists). 'Status Quo' would apply for generic antibiotics and, in the short term, for other brand name antibiotics.

47. Implies establishing a fixed-price contract starting with Hospitals and eventually expanding to Community setting, requiring that manufacturer pay a penalty clause if supply requirement is not met, allowing for volumes to be adjusted after a few years based on utilisation data and trends of infection, and seeking commitments to invest in R&D/licensing of agents targeting priority pathogens; term could be set 2-3 years.

48. These funds would be in addition to regular hospital budgets and be determined based on hospital needs and data.

49. Diagnostics could include those for existing strains that could be treated by antibiotics that are not yet approved in Canada.

50. These will be selected among antibiotics only available via SAP. Proposing that 1-2 deemed essential be granted exceptions, as we have seen with the two Malaria Drugs

51. Conditions may include pre-existing approval by EMA and/or FDA, or dispensing sign off by an ID specialist or Stewardship Pharmacist following established standards.

52. May include expanding review to consider international data on efficacy of the antibiotics where already used, factors such as economics, ethics, equity, feasibility and antibiotic acceptability and, in the long-term, positive/negative externalities.

53. Variable or fixed lump-sum amounts to be attributed based on fair economic/public health value assessment.

54. Add-on payments may be granted at the discretion of HC/PHAC if a particular new agent shows promising results targeting priority pathogens, as an incentive to market in Canada in early global market stages.

55. This includes expanding access to rapid diagnostic testing at point-of-care.

56. Home and Community Care Support Services. (2021). Our Hospitals. Ontario Ministry of Health. http://www.hnhblhin.on.ca/aboutus/hsplist/OurHospitals.aspx

57. Refer to Appendix 7 for a list of 'already approved' antibiotics we recommend for selection.

58. Refer to Appendix 8 for a list of 'not (yet) approved' antibiotics we recommend for selection.

59. Once the antibiotics/diagnostics are chosen, manufacturers may choose to donate the selected products for the pilot period since the quantity will be very minimal.

60. As described in 'Estimating the appropriate size of global pull incentives for antibacterial medicines' by K. Outterson (2021).

61. This could include remodelling using a parity exchange rate rather than the current USD-CAD or other exchange rates.

62. This is what is referred to as MER1 in the recent publication 'Estimating the appropriate size of global pull incentives for antibacterial medicines' by Kevin Outterson (2021), where a MER1+ACQ (defined further below) model was proposed and valued between $1.8 and 5.2 million. MER1: Market entry reward paid in one year, which calculates the required size of a market entry reward pull incentive paid in a single installment after FDA licensure that allows the company to keep all sales revenues — also known as partially delinked.

63. These figures, along with the models presented in 'Estimating the appropriate size of global pull incentives for antibacterial medicines'), and adapted for Canada based on a conservative yet deemed ample GDP share among the G20 countries of 1.6%.

64. Floor/Ceiling vs. Low/High: Floor is the lowest estimated price Canada might pay for one year's supply of a particular priority antibiotic. Ceiling is the highest estimated price Canada might pay for one year's supply of

a particular priority antibiotic. 'Low' is the lowest estimated average price amount Canada might pay for any priority antibiotic brought under the program. High is the highest estimated average price Canada might pay for any priority antibiotic brought under the program.

65. SUB10: Fully delinked global subscription for antibiotics needed, paid over the course of ten years. It is the lowest price Canada will pay for one year's supply of a particular antibiotic.

66. ACQ: Acquisition of a Phase II–ready asset for a total acquisition price of $500 million (25 percent up front, 25 percent at Phase III start, 25 percent at FDA approval, and the balance in royalties over the patent term).

67. According to Outterson, "acquisition of a Phase II–ready asset is designed to calculate the pull incentives required by the acquirer in such circumstances, as they obtain a partially de-risked asset, thereby shifting uncertainties surrounding preclinical and Phase I development. Many antibacterials on the market today were transferred between companies, and many of these small companies plan to sell or outlicense their Phase II-ready assets to the AMR Action Fund or other commercial acquirers."

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APPENDIX 1: GLOSSARY OF TERMS

Access: The ability to deliver an appropriate antibiotic to a patient in a timely fashion.

ACQ: Acquisition of a Phase II–ready asset for a total acquisition price of $500 million (25 percent up front, 25 percent at Phase III start, 25 percent at FDA approval, and the balance in royalties over the patent term).

AMR Action Fund: Created by leading pharma companies, this fund aims to bring 2-4 new antibiotics to patients by 2030. They work with partners to create market conditions that enable sustainable investment in the antibiotic pipeline. The AMR Action Fund expects to invest more than $1 billion USD in smaller biotech companies and provide industry expertise to support the clinical development of novel antibiotics.

Antibiotic: A type of antimicrobial used to treat infections caused by bacteria (Government of Canada, 2017).

Antimicrobial Resistance (AMR): Antimicrobial resistance occurs when microbes (e.g., bacteria, viruses, fungi and parasites) evolve in ways that reduce or eliminate the effectiveness of antimicrobial medicines (e.g., antibiotics, antivirals, antifungals, and antiparasitics) to treat infections by killing or slowing microbial growth. When microbes are exposed to antimicrobials, they adapt and become more resistant. This contributes to increased AMR in humans, animals, crops, and in the environment (e.g., water, soil) through exposure to wastewater, consumer products, and animal manure. There are also many social and environmental factors that contribute to rising rates of AMR, including poor hygiene, inadequate infection prevention and control (IPC) practices, lack of awareness and education about AMR and appropriate antimicrobial use (AMU), insufficient access to health services, overcrowded housing conditions, and a lack of clean water.

Antimicrobial Stewardship (AMS): A system-wide approach that includes coordinated interventions designed to promote, improve, monitor, and evaluate the judicious use of antimicrobials to preserve their future effectiveness and promote and protect human and animal health (AMR Stewardship Task Group, 2017).

Canadian Agency for Drugs and Technologies in Health (CADTH): An independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence about the optimal use of drugs and medical devices.

The Canadian Anti-infective Innovation Network (CAIN): A consortium of over 80 Canadian leaders, researchers, clinicians, and policymakers from universities, companies, governments, and not-for-profit organizations that is committed to addressing AMR.

The Canadian Antimicrobial Resistance Surveillance System (CARSS): CARSS is Canada's national system for reporting on AMR and AMU. CARSS synthesizes and integrates epidemiological and laboratory information from Public Health Agency of Canada (PHAC) surveillance programs across the human and agricultural sectors to provide high-quality national data on AMR and AMU.

The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS): CIPARS monitors trends in antimicrobial use and antimicrobial resistance in selected bacterial organisms from human, animal and food sources across Canada. The program is based on several representative and methodologically unified surveillance components which can be linked to examine the relationship between antimicrobials used in food-animals and humans and the associated health impacts.

The Canadian Nosocomial Infection Surveillance Program (CNISP): CNISP is a collaborative effort between the Public Health Agency of Canada's Centre for Communicable Diseases and Infection Control (CCDIC), the National Microbiology Laboratory (NML), and sentinel hospitals across Canada. The objectives of CNISP are to provide national and regional rates and trends on selected healthcare-associated infections (HAIs) and antimicrobial resistant organisms (AROs)

Canadian Pharmaceutical Distribution Network (CPDN): CPDN is a pharmaceutical distribution channel to Canadian hospitals. CPDN procures pharmaceutical products from a number of drug manufacturers and consolidates them into a single shipment with a single invoice that drives hospital efficiencies.

Common Drug Review (CDR): A single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada. All jurisdictions are participating except Québec. INESSS assumes responsibility for a similar process in Québec.

Delinkage/Delinked: A proposed model for development of new pharmaceutical drugs where "delinking" refers to separating the profitability of a drug from its volume of sales. In the current business model, the pharmaceutical industry relies on the pricing and sales of its products to generate profits and to finance research and development of new drugs. This ability is dependent on the monopoly granted through patents. In the de-linkage model, other means (such as lump sums) would be used to reward companies for research and development in exchange for restricting the price charged for the product. This would allow the product to be sold at prices closer to production costs which would ensure better access, particularly for poor people and those who pay for their own treatment.

Distribution: Distribution is the process of making a product or service available for the consumer or business user who needs it. This can be done directly by the producer or service provider or using indirect channels with distributors or intermediaries. More specifically, distribution refers to the physical distribution of antibiotics from manufacturing facilities to other facilities such as depots and hospitals.

Factory Gate Price Ceiling: Factory gate price is the price of the product available at the factory, excluding any separately billed transport or delivery charge. Thus, factory gate price ceiling is the highest unit price a manufacturer may sell "out of the gate."

Formulary: A list of prescription drugs covered by a particular drug benefit plan.

Group purchasing organizations (GPOs): Companies that negotiate prices for drugs, devices, and other medical products and services on behalf of healthcare providers, including hospitals, ambulatory care facilities, physician practices, nursing homes, and home health agencies. Examples include HealthPRO and Mohawk Medbuy.

Health Technology Assessment (HTA): Health technology assessment (HTA) products involve assessments of new technologies or reassessments of existing technologies, evaluating clinical effectiveness and/or cost-effectiveness, and may include the ethical, legal, and social implications of health technologies on patient health and the health care system (CADTH, 2021).

Institut National d'Excellence en Santé et Services Sociaux (INESSS): INESSS is Québec's equivalent to CADTH. It aims to promotes clinical excellence and the efficient use of resources in the health and social services sector.

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR): A global collaborative organisation and platform, engaging 28 nations to curb antimicrobial resistance.

Jurisdictional formulary decision-making: The final step in the regulatory pathway at which point the drug is subjected to a Public Drug Benefit Plan review. This process results in recommendations for inclusion on more localized formularies.

Market: Pharmaceutical companies require incentives to invest in R& D to commercialize an antibiotic. Antibiotics that have been brought to market do not require the onerous SAP process and are therefore more accessible.

Marketing authorization: A process by which the federal government assesses the safety, efficacy, and manufacturing quality of a new drug. If it meets Health Canada standards, the manufacturer is given a Notice of Compliance (NoC) or a Notice of Compliance with Conditions (NoC/c). At this point, a monograph outlining indications and clinical claims can be made.

Notice of Compliance (NOC): A notification indicating that a manufacturer has complied with sections C.08.002 or C.08.003 and C.08.005.1 of the Food and Drug Regulations. Notices of Compliance are issued to a manufacturer following the satisfactory review of a submission. (Government of Canada, 2021).

Notice of Compliance with Conditions (NoC/c): An NOC/c is authorization to market a drug (i.e. a Notice of Compliance), with the condition that the sponsor undertake additional studies to verify the clinical benefit. The NOC, qualifying under the NOC/c policy, is issued under section C.08.004 of the Food and Drug Regulations.

One Health: One Health is a collaborative, multisectoral, and transdisciplinary approach with the goal of achieving optimal human, animal, plant, and environmental health outcomes while recognizing the interconnection between people, animals, plants, and their shared environment.

Pan-Canadian Action Plan (PCAP): A federal public policy document being developed to define specific commitments, measurable outcomes, and timeframes for important antimicrobial actions.

Pan-Canadian Pharmaceutical Alliance (PCPA): An alliance of the provincial, territorial and federal governments that collaborates on a range of public drug plan initiatives to increase and manage access to clinically effective and affordable drug treatments. One of PCPA's key roles is to conduct joint negotiations for brand name and generic drugs in Canada to achieve greater value for publicly funded drug programs and patients through its combined negotiating power.

The Patented Medicine Prices Review Board (PMPRB): An independent quasi-judicial body that is part of the Health portfolio, and operates at arm's-length from the Minister of Health. PMPRB protects and informs Canadian consumers by regulating the prices of patented medicines sold in Canada, and by reporting on pharmaceutical trends.

Price Listing Agreement (PLA): A negotiated agreement between a pharmaceutical manufacturer and a provincial drug plan for the plan to cover a specific drug at a reduced price, usually through the use of a rebate. PLAs allow drug plans to cover medications that otherwise would not be considered cost-effective or affordable and have become a de facto tool in the management of public drug plans in Canada.

Pricing Review: Following marketing authorization, the Patented Medicines Prices Review Board (PMPRB) reviews a drug and determines its maximum average potential price (MAPP).

Priority antibiotics: Antibiotics that are essential to treat complex, life-threatening infections posed by priority pathogens.

Priority pathogens: Pathogens deemed to be a public health priority.

Procurement: Procurement is the act of obtaining goods or services, typically for business purposes and on a relatively large scale. Procurement generally refers to the final act of purchasing but it also more broadly to the procurement process overall, which is critically important leading up to a final purchasing decision.

Pull incentive: An antibacterial drug development incentive that provides known return on investment; rewards only successful development.

Push incentive: An antibacterial drug development incentive for pharmaceuticals that lowers the cost of and de-risks R&D and supports both successful and unsuccessful R&D efforts.

Reimbursement review: Involves a common drug review, where experts consider comparative clinical and cost-effectiveness for new medicines. This process results in a formulary recommendation — list, do not list, or list with conditions.

Shared services organizations (SSOs): Medical or administrative services for which two or more hospitals or health care organizations agree to share responsibility. Examples include Health Shared Services BC (HSSBC), HSS Ontario, and Service New Brunswick.

Special Access Programme (SAP): Through Health Canada's SAP, health care professionals may request access to non-marketed drugs to treat patients with serious or life-threatening conditions. Access to these drugs is only considered when conventional therapies have failed, are unsuitable or are unavailable. An SAP authorization allows a manufacturer to sell a drug that has not been approved for sale in Canada (Government of Canada, 2021).

SUB10: Fully delinked global subscription for antibiotics needed, paid over the course of ten years. It is the lowest price Canada will pay for one year's supply of a particular antibiotic.

APPENDIX 2: STEERING COMMITTEE

Lori Burrows (Project Chair) is a microbiologist, a Fellow of the American Academy of Microbiology and the Canadian Academy of Health Sciences, and an international expert on bacterial virulence factors and antibiotic resistance. She is a Professor of Biochemistry and Biomedical Sciences at McMaster University, and the Interim Director of McMaster's Michael G. DeGroote Institute for Infectious Diseases Research.

Alfonso Iorio is Professor and Chair of the Department of Health Research Methods, Evidence, and Impact at McMaster University. He is Chief of the Health Information Research Unit and Lead of the Hamilton-Niagara Hemophilia Program. Dr. Iorio is past Chair of the Data and Demographics Committee of the World Federation of Haemophilia (WFH), Co-Chair of the World Bleeding Disorder Registry (WFH), a member of the GRADE Working Group, and a member of the COVID-END initiative.

Mark Loeb is Professor and Michael G. DeGroote Chair in Infectious Diseases in the Departments of Pathology and Molecular Medicine and Health Research Methods, Evidence, and Impact at McMaster University. Dr. Loeb is Co-Director of the McMaster WHO Collaborating Centre on Infectious Diseases.

Jacqueline McCarles is the Associate Director of Public Health Vaccines and AMR with Merck Canada. She has been working in the pharmaceutical industry for 22 years.

Wes Miyai is an Associate Director of Public Health and External Affairs at Merck. He is also the Vice-Chair of the Board of Directors of the Canadian Antimicrobial Innovation Coalition (CAIC).

Dani Peters is President of Magnet Strategy Group, a consulting firm that manages public affairs strategies in Canada and the United States. She is co-founder of the Cross-Border Health Foundation, an organization that fosters dialogue between Canada and the United States around common health priorities. Ms. Peters serves on the Industry Advisory Board for Bloom Burton & Co., a healthcare investment advisory firm in Toronto. She is also a Health Leader-in-Residence for the World Health Innovation Network (WIN), within the University of Windsor's Odette School of Business.

Jean-Éric Tarride is the Chair of Heath Technology Management, Director of the Centre for Health Economics and Policy Analysis (CHEPA), Professor of the Department of Health Research Methods, Evidence and Impact (HEI), and Associate Member of the Department of Economics at McMaster University. Dr. Tarride is also the Director of the Programs for Assessment of Technology in Health (PATH), The Research Institute of St. Joe's Hamilton, St. Joseph's Healthcare Hamilton.

Gerry Wright is a Distinguished University Professor in the Departments of Biochemistry & Biomedical Sciences and Pathology & Molecular Medicine at McMaster University. In response to the COVID-19 pandemic, Dr. Wright has recently launched Canada's Global Nexus for Pandemics and Biological Threats, of which he is the Inaugural Lead. Wright holds the Michael G. DeGroote Chair in Infection and Anti-Infective Research and a Canada Research Chair in Antimicrobial Biochemistry.

APPENDIX 3: SPONSORS

Canada's Global Nexus for Pandemics and Biological Threats works with and for decision-makers, system leaders, businesses, communities, and the public to develop and deploy relevant and timely solutions to prevent, prepare for and protect against pandemics and biological threats. This new interdisciplinary hub is based at McMaster University.

The Canadian Antimicrobial Innovation Coalition (CAIC) is a coalition of Canada's key players in the biomedical innovation industry and research-based organizations in collaboration with these industries. CAIC aims to engage the public, health sector and government in strategies to help protect Canadians from the dangerous rise in antimicrobial resistance (AMR).

Innovative Medicines Canada (IMC) represents Canada's innovative pharmaceutical industry, helping their members discover, develop, and deliver innovative medicines and vaccines.

Merck is a research-intensive biopharmaceutical company dedicated to providing leading innovations and solutions for today and the future.

GlaxoSmithKline (GSK) is a science-led global healthcare company that researches, develops, and manufactures pharmaceutical medicines, vaccines, and consumer healthcare products.

The David Braley Centre for Antibiotic Discovery at McMaster University was established with the vision of successfully addressing the antimicrobial resistance crisis.

The Michael G. DeGroote Institute for Infectious Disease Research (IIDR) at McMaster University is a world-leading centre of transdisciplinary infectious disease research.

APPENDIX 4: RESPONSES – BRIEF SURVEY ON ACCESS TO NEW ANTIBIOTICS

Enclosed are the results of a survey send to hospital pharmacists across Canada. While the response was not large, the consistency in answers was striking and appeared as a good indicator of the types of challenges pharmacists experience.

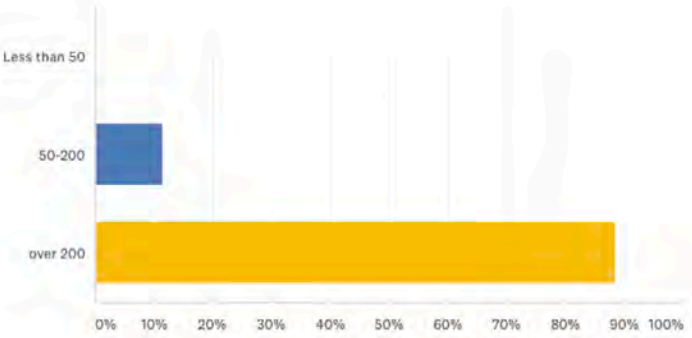
Hospital Pharmacists Survey – February 2021

Introduction — McMaster University recently launched the Global Nexus for Pandemics and Biological Threats (https://globalnexus.mcmaster.ca). One of our major areas of interest is antimicrobial resistance, and we are working with academic, clinical, government, and industry groups on addressing this slow-moving pandemic. We've identified access to new antibiotics as a potential area where we might make a difference. Of 15 antibiotics recently approved by the FDA, only one has been approved for use in Canada, and that happened only in summer of 2020. Even approved antibiotics can be challenging to access. We are interested in development of a centralized or depot model of antibiotic distribution that incorporates stewardship (especially important for smaller institutions that may lack the resources for a dedicated program) and surveillance (which drugs are being accessed, and for what purpose). We would love your opinion on this idea, and prepared a brief survey (10 questions, 3 minutes) to gauge your interest and get your feedback. Who knows, this might save you a lot of time and paperwork in the future! Thanks in advance for participating.

Question 1

How large is your institution (number of beds)?

Answered: 35 Skipped: 0

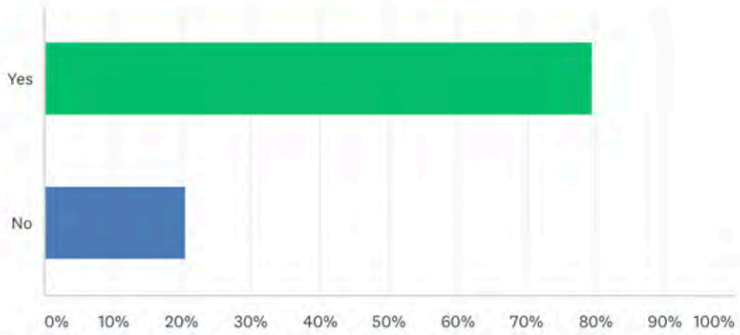


ANSWER CHOICES	RESPONSES	
Less than 50	0.00%	0
50-200	11.43%	4
over 200	88.57%	31
TOTAL		35

Question 2

Do you have an infectious diseases service?

Answered: 34 Skipped: 1

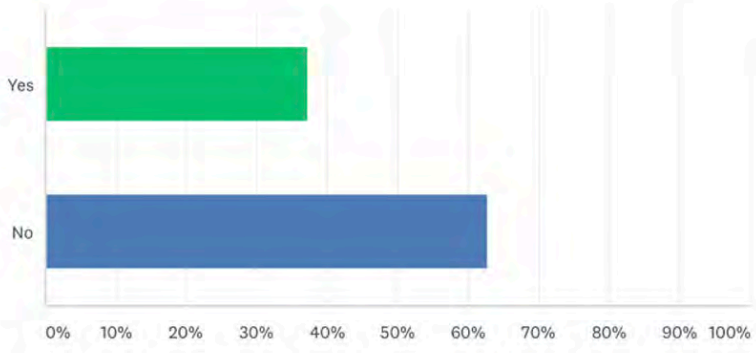


ANSWER CHOICES	RESPONSES	
Yes	79.41%	27
No	20.59%	7
TOTAL		34

Question 3

Are there standard procedures and/or stewardship guidelines in place for management of multi drug-resistant infections?

Answered: 35 Skipped: 0

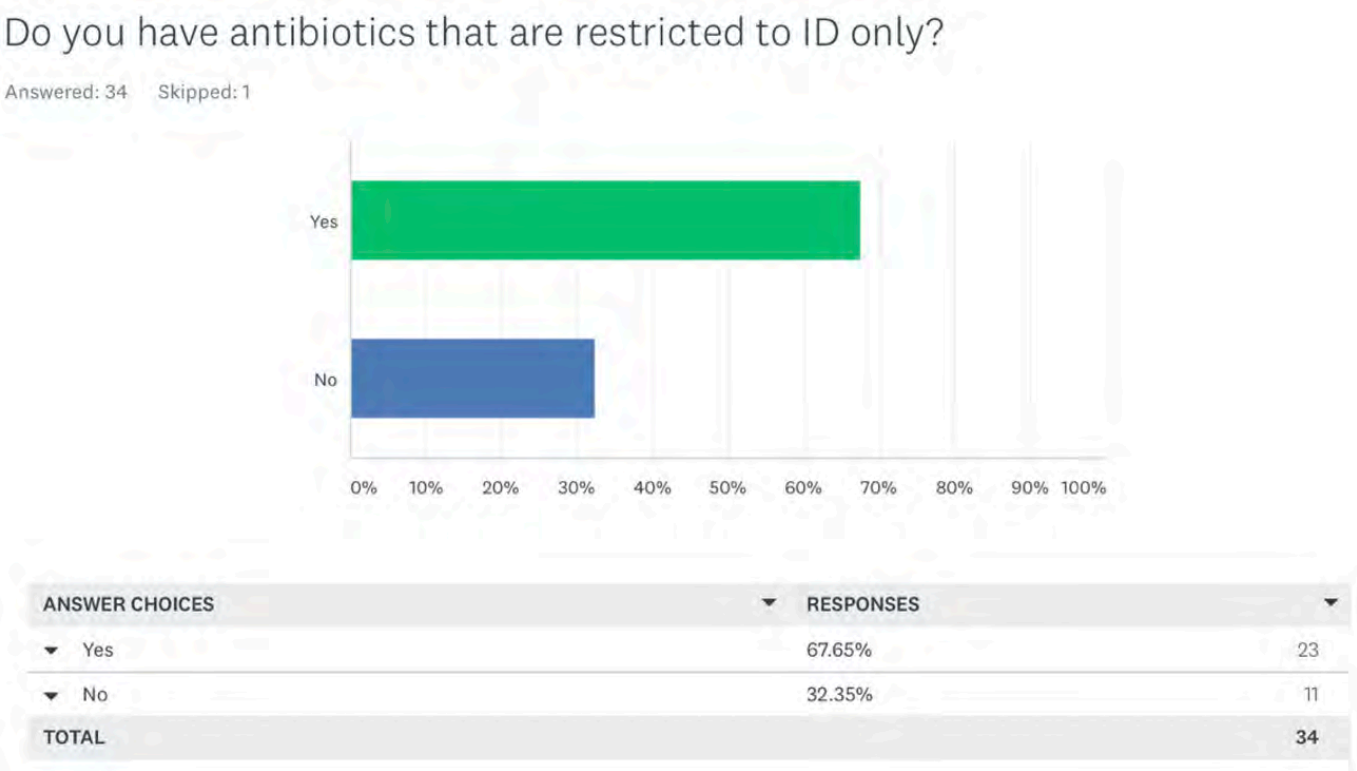


ANSWER CHOICES	RESPONSES	
Yes	37.14%	13
No	62.86%	22
TOTAL		35

Comments on Question 3

- ID consult/ASP review antimicrobial handbook and guidance including antibiogram
- Criteria of use by organism - but mostly ID service consult recommendations given complexities around drug access and availability
- It is not an automatic consult but highly recommended to consult ID for MDRO; ASP pharmacists screens cultures and discuss with MRP or make antibiotic selection suggestions based on discussion with ID
- Case by case basis between ID and ASP
- Empiric guidelines exist but definitive guidelines for treating specific mdr bugs do not exist.
- Hospital policy for surveillance and treatment guidelines.
- No specific guideline however on our ASP audit and feedback floors we would consult ID as appropriate (i.e. for complex infections and when have to use our ID restricted broadspectrum agents).
- Spectrum App Guidelines
- We have clinical guidelines for infectious syndromes, but not specifically as to how to manage MDR-infections.
- Guidelines for treatment of CROs, automatic ID/ASP consults for selected broad-spectrum antibiotics and/or bacteria that are MDR and/or difficult to treat.
- ID service consulted when MDR organisms are isolated and usually if suspected MDR organisms e.g. previous infections with MDR organisms
- We refer to IDSA guidelines or new studies We don't have any hospital wide standards or guidelines for specific MDR infections
- Our locally developed stewardship guidelines are posted on our program website. Specific guidelines and syndrome-based clinical summaries include recommendations for multi drug resistant pathogens.
- for Micro reporting - there are standards to follow.
  ASP - strongly recommend ID consultation, or strongly recommend ID consultation for use of a restricted antimicrobial more appropriate for the MDR organism
- we have infection control prevention initiatives but nothing specific towards MDRs. We have restricted use forms for meropenem/caspofungin but again nothing specific to MDROs.
- 48 hour PAF review of MDR infections (yearly)
- These are very rare at our institution and are all handled by ID consultation service (not including ESBL in this context, those are generally handled without ID but are reviewed by ASP PAF)
- Multi-drug resistant infections are often referred to the ID consult service for management at the discretion of the MRP. Given that most drugs to treat these infections are restricted to ID, this almost always happens.
- Usually would warrant ID consult
- We are fortunate and do not have MDRO's
- Guidelines are based on disease state rather than MDR status. However guidelines do address risk for MDR pathogens to help decide on appropriate treatment.

Question 4



ANSWER CHOICES	RESPONSES	
Yes	67.65%	23
No	32.35%	11
TOTAL		34

Comments on Question 4

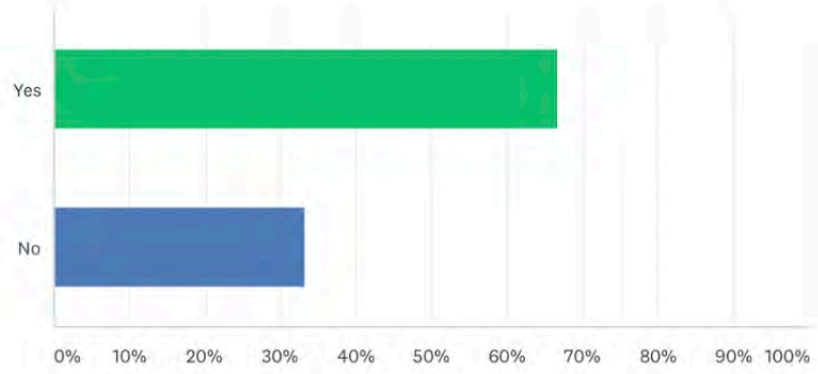
- Yes, many antibiotics have ID consult as a "criteria" for prescribing (but not directly enforced)
- Daptomycin, Amphotericin, Caspofungin
- Colistin, ganciclovir, voriconazole etc.
- Ceftobiprole ceftolozane/tazobactam daptomycin
- Carbapenems (although they can order and it is reviewed within 24 hours), antifungals (oncology and ID), fidaxomicin (ID and GI)
- About 25 drugs are restricted, but only a few are specifically restricted to ID consult. Meropenem, Ertapenem
- Just fidaxomicin
- Meropenem, cefepime, Zerbaxa, Colistin, Amikacin, ertapenem, imipenem, linezolid, daptomycin, fidaxomicin.
- Only remdesivir is restricted to ID only. We have "reserved" antibiotics that can only be used for select indications & otherwise require an ID/ASP consult. These include: pip-tazo, mero, erta, dapto, caspo, linezolid, moxi, and ceftazidime.
- Technically, no, as the two ID doctors do not want that. We strongly encourage either a formal or informal ID consult when certain antibiotics/infections are being treated. We are working to expand on which positive lab results/ infections identified by the lab to have a mandatory report to include the ID physicians.
- Fidaxomicin, daptomycin, ceftolozane-tazobactam
- Carbapenems, and certain ones restricted to TB service
- Daptomycin, linezolid, tigecycline, meropenem/erta, ceftolozane tazobactam

- Antibiotics: Amikacin, Daptomycin, Linezolid, Tigecycline Antifungals: Liposomal Amphotericin B (Ambisome), Anidulafungin, Caspofungin, Itraconazole, Voriconazole Antiviral: Ganciclovir
- Tigecycline, colistin, ertapenem, aztreonam, ceftobiprole, ceftolozane/tazobactam, cefepime, daptomycin, linezolid, doxycycline IV
- Fidaxomycin
- Colistin, Daptomycin (mandatory ID consult)
- Many broad-spectrum or specialized antimicrobial agents require an ID consult/approval prior to initiation of therapy.
- Amikacin, colistin, ceftobiprole, daptomycin, linezolid, meropenem
- Ceftolozane tazobactam; ceftobiprole; colistin; cefepime
- Daptomycin - Ertapenem - Linezolid – Tigecycline
- Daptomycin, linezolid, cefepime
- Meropenem (ICU/ID) Ceftoloazane/Tazobactam Colistin Moxifloxacin Daptomycin Linezolid
- Linezolid, daptomycin, amikacin, cefotaxime, colistin
- Daptomycin, ceftolozane-tazobactam, caspofungin, liposomal amphotericin, meropenem (the ICU can order as well)

Question 5

Do you believe there is unmet need for new antibiotics (e.g. those not on formulary) at your institution? Are there 'approved in Canada' antibiotics that your institution has chosen not to bring on formulary?

Answered: 33 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	66.67%	22
No	33.33%	11
TOTAL		33

Comments on Question 5

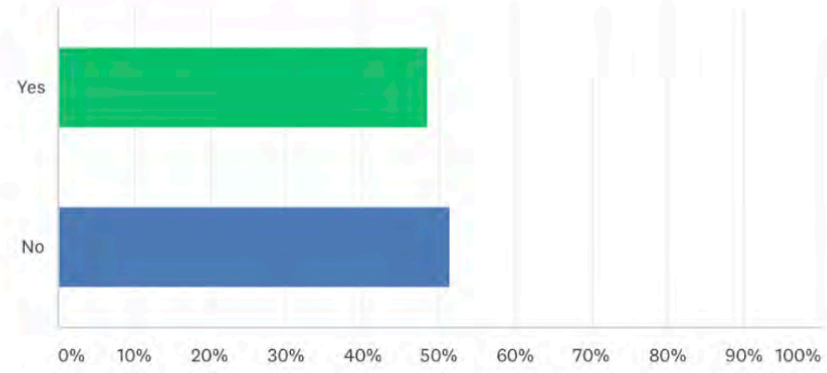
- IV amox-clav, daptomycin,tigecycline We have no ID resources....small hospital with very few resistant organisms - unless they are re-patriated from another institution.
- There is a need to better access to antimicrobials that are not approved in Canada yet.
- Amox/Clav IV, Fosfomycin IV, Telavancin IV not on formulary
- IV fosfomycin (expense), ceftobiprole
- Ceftol/Tazobactam was rejected for formulary due to lack of evidence and dosing unknowns.
- No to the first question, yes to the second question. If an antibiotic would be a therapeutic duplication with one on formulary, then don't carry it. There are some antibiotics that we have use non-formulary, since only comes up very occasionally.
- We are in process of reviewing a few newer agents for formulary addition (most recently brought forth IV fosfomycin to our P&T for approval with restrictions to ID).
- Yes and no. We have on occasion encountered an MDR organism that needed a non-formulary antibiotic (e.g., tigecycline, ceftolozane/tazobactam, colistin), but our Non-formulary request process did not prevent us from getting the drugs in a timely manner. We are in the process of doing formulary reviews for amox-clav IV & fosfomycin IV, but have no pursued any of the other new antibiotics for formulary yet.
- We have a significant IV drug abuse problem locally. We have experienced some treatment failures with the "usual and more readily available (i.e. less costly)" antibiotics to treat these infections. Very long and complicated courses have been required.
- Ceftobiprole
- We have not reviewed IV amoxicillin-clav, or IV fosfo yet.
- Ceftobiprole, iv clavulin as a couple.
- Even if a drug is non-formulary at my hospital, it doesn't mean it cannot be ordered if indicated for a patient. I think the bigger issue is the unmet need for new atbx that are approved elsewhere in the world but require Special Access to get. SAP drugs often result in delay of starting the most appropriate and effective therapy. E.g. Ceftaroline for MRSA (only available through Special Access). I think there is also an unmet need for drugs that are approved in Canada but not covered by ODB so patients who cannot afford to pay out of pocket for it cannot have access to it at home (e.g. ceftobiprole) - this has resulted in extended hospital stays for patients who require this IV atbx.
- Usually the high cost of new antibiotics has been the reason for not adding to formulary. The central development of a standard formulary submission including a pharmacoeconomic analysis for all new antibiotics which all hospitals could use would be very helpful. This would eliminate the need for each hospital to develop their own P&T formulary submission. Otherwise there may be a delay in reviewing new antibiotics for addition to formulary.
- Zerbaxa, Fosfomycin Only required if have MDR organisms that aren't sensitive to any agents that we have
- We assess the role of new antimicrobial based on our patient population's need. Even if a drug is non-formulary, a clinician can still prescribe it (with documentation). The bigger hurdle is Special Access Drugs, e.g. ceftazidime-avibactam.

- Some of the new agents for MDR organisms, such as ceftaz-avibactam would be useful
- I have had two cases where I believe ceftazidime/avibactam would have been the drug of choice and wish it was available. There are a few "approved in canada" abx that we have not added to formulary eg ceftolozane-tazobactam, fidaxomicin, IV fosfo. However, if we have a specific use case, we can fairly rapidly get internal approval for a onetime order.
- Amox/clav IV
- Fosfomycin IV
- We have not encountered many situations where we needed to. There was one inquiry about ceftolazone-tazobactam by ID recently, but never needed to use it.
- Inpatient rehab and complex continuing care, so there is more a need to steward existing antimicrobials.
- We could actually use daptomycin on formulary. Our ID consult service will recommend it in patients not responding adequately to vanco or sometimes our higher risk patients (we have a lot of endocarditis patients).

Question 6

Within the last year, have you applied for access to a new antibiotic through Health Canada's Special Access Program (SAP)?

Answered: 35 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	48.57%	17
No	51.43%	18
TOTAL		35

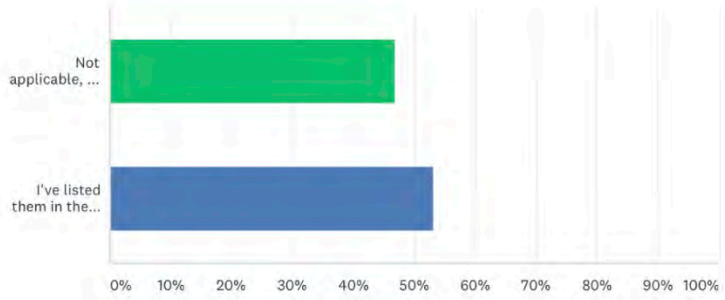
Comments on Question 6

- Variable (and I am not always involved in every SAP request), estimate ~1 request q2-4wks. we have a CF service that also does a large # of requests. Drug access is largely variable.
- 1-2 times per year tend to be approved days to receive drug
- I applied and was approved but we couldn't find a supplier in Canada it was dalbavancin - would be of benefit for OPAT , especially when we were trying to clear out inpatients to make way for COVID patients (in place of vancomycin OP)
- Every 2-3 weeks 100% approved on average, rarely requires more info 1-4 days to obtain drug
- Not an often request, maybe a few times per year. Usually get drug approved within a day or so. Haven't had any rejections as far as I know.
- Infrequently - 1-2/year
- 3-4 times per year. 100% approved. 1-3 weeks to receive drug. Usually try to borrow from other hospitals.
- Monthly, within 24 hrs, or to up to 3 weeks (cefiderocol)
- Proportion of requests approved - 80% 3-4 days (Depending on whether there is already a supply of the drug in Canada at a local distributor or if it's shipped from out of country)
- Probably once per month, approx 95% are approved, now usually takes 24-48 hrs (has become faster recently)
- A few times. Takes a week, sometimes more. This step causes undue delay in patient care.
- All approved- within a week
- We apply for SAP roughly 4-5 times a year. The majority of our submissions have been approved
- Doxycycline, 1/2, 2-3 months
- 1-2 times a year Both times approved more than 3-5 days
- 6x per year, 75% approval
- ~5 times per year, typically 100% approval. Usually takes a few days to get drug

Question 7

What is/are the top new antibiotic(s) you request most frequently via the SAP?

Answered: 32 Skipped: 3

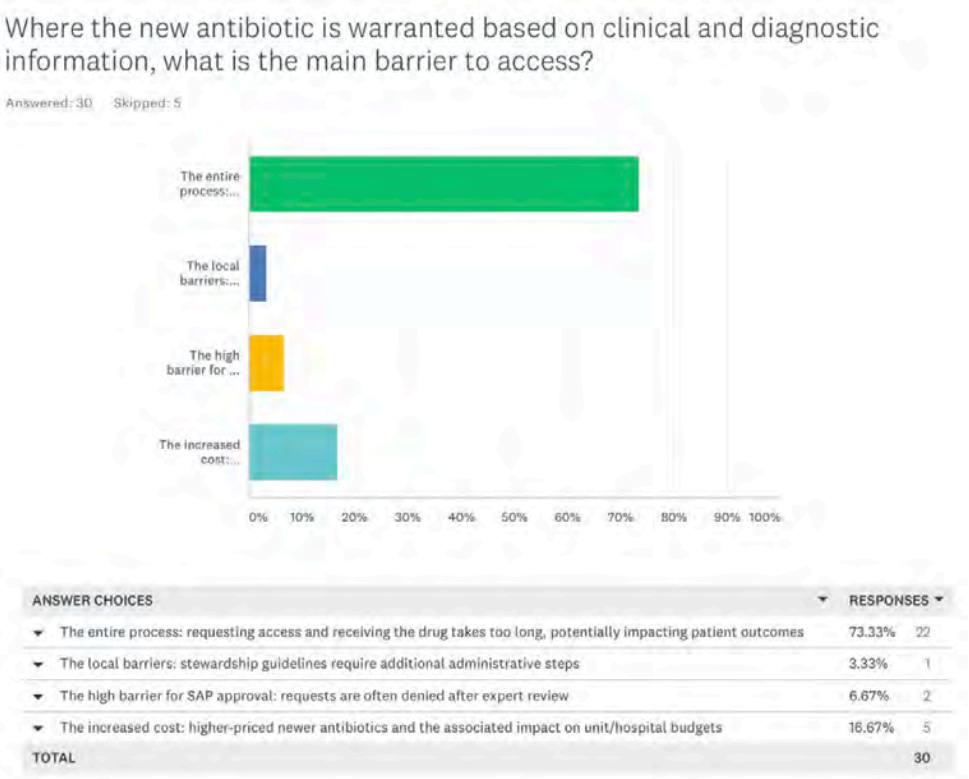


ANSWER CHOICES	RESPONSES	
Not applicable, I don't submit SAP requests.	46.88%	15
I've listed them in the comment box below.	53.13%	17
TOTAL		32

Comments on Question 7

- Clofazamine, ceftaroline, fluctosine, doxycycline IV, Ivermectin, mafenide cream, nevirapine, pristinamycin, quinidine, ribavirin, rifampin IV, - This is basically everything we have ordered via SAP over the past several years. Most are one time, many are for outpatients that are seen in our ID clinic since retail pharmacies in the past couldn't order SAP products directly. This has now changed, so may see this type of SAP request less. Aztreonam, ceftaroline, ceftaz/avi, isavuc, etc (x1 maribavir)
- IV rifampin ceftazidime avibactam aztreonam albendazole ceftaroline
- Ceftazidime/avibactam, albendazole, aztreonam, meropenem/vaborbactam
- I think the last one was ceftaroline
- Over 2020, most common SAP drugs I applied for included Remdesivir, an antiviral.
- Doxycycline IV Ivermectin (no longer SAP!)
- Ceftolazone tazobactam - a year ago
- Ceftazidime-avibactam, doxycycline IV, rifampin IV
- Ceftaroline
- Ceftaroline, foscarnet
- Aztreonam, fosfomycin IV, ceftaroline, ceftazidime/avibactam
- Ceftazidime-avibactam
- Ceftaroline
- Ceftazidime/Avibactam
- Ceftazidime/avibactam
- Cetazidime-avibactam

Question 8



ANSWER CHOICES	RESPONSES	
The entire process: requesting access and receiving the drug takes too long, potentially impacting patient outcomes	73.33%	22
The local barriers: stewardship guidelines require additional administrative steps	3.33%	1
The high barrier for SAP approval: requests are often denied after expert review	6.67%	2
The increased cost: higher-priced newer antibiotics and the associated impact on unit/hospital budgets	16.67%	5
TOTAL		30

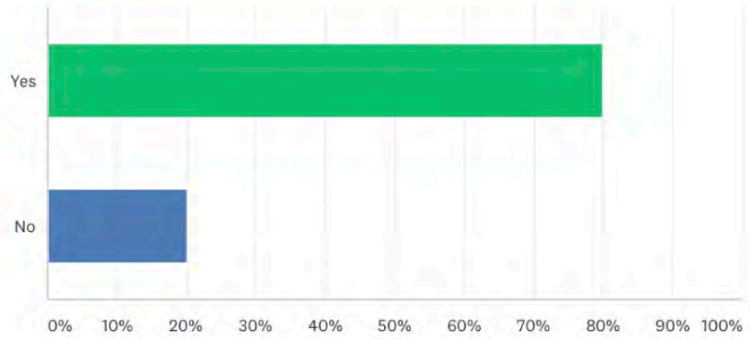
Comments on Question 8

- I have found that the expert review process at SAP offices take too long. This step seems to be out of the control of the SAP employees, but requires a lot of back and forth asking for papers and evidence.
- Review process to add a drug to formulary - need input from stakeholders, time it takes to do the clinical review, pull and analysis patient specific data if applicable.
- Small community hospital - small community budget
- We have logistical issues as well w.r.t. preparing the IV abx
- Ability to get susceptibility information from our microbiology lab either due to delays from the Public Health Micro or due to lack of CSLI breakpoints.
- All of the above may factor sometimes into the process. Sometimes SAP approval is the issue and other times it has been the higher cost.
- Our "ID service" is 2 ID docs - no other support. Stewardship adds some of the antibiotic reviews to our other duties

Question 9

Are you familiar with the depot model of malaria drug distribution that is managed by the Canadian Malaria Network, or the Canadian Blood Services model of haemophilia products distribution? Do you think a similar model would be useful for access to new antibiotics?

Answered: 35 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	80.00%	28
No	20.00%	7
TOTAL		35

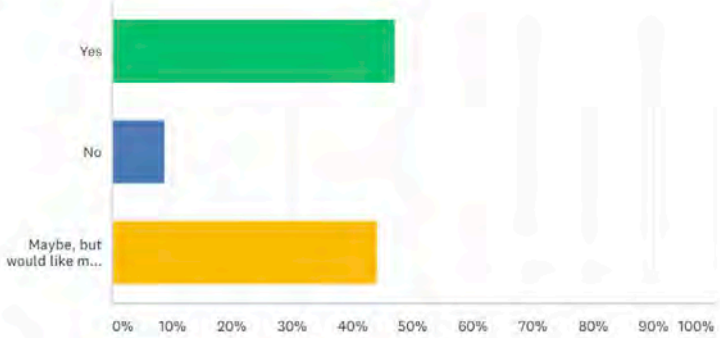
Comments on Question 9

- Subscription based model or similar for allowing access to MDR antibiotics
- Difficulty would be inventory i.e. knowing what to keep on hand; supply and demand
- Could cut down on transit time for SAP drugs, assuming a lot of the leg work for the clinical review process would be done centrally so could also cut down on time to get a new drug on formulary. Hopefully this network could also monitor, analyze, advise on antibiotic drug shortages?
- Familiar with the model, but not sure for my practice that it would be necessary.
- I have some familiarity with it. Might be useful. I would be interested in learning more.
- Just comes down to funding, but overall yes I think this would work for all SAP, and $$$ abx.
- Yes - would expedite access after approval
- I am familiar with the malaria drug distribution. I am not sure that a similar model would be useful for access to new antibiotics. The barrier I have run into is not the supply issue which I believe a central depot would address but the prohibitive cost of the new antibiotics which results in denial by management to bring the antibiotic in. This is also true for newer antibiotics that are on the Canadian market as well as antibiotics available through SAP.
- For the most part, I don't find there's much delay in getting in newer abx… it would mostly be for evenings or weekends where purchaser is not available
- There should be centralized guidelines for when to use abx/ and a provincial approach.
- Developing a Novel Antimicrobial Depot could help alleviate some of the barriers organizations face when trying to obtain these agents. It would cut down on time and improve overall awareness of access. The challenges in obtaining novel, non-market approved therapies significantly hampers their use in clinical practice. Making these agents more readily available and alleviating the burden from individual hospitals/hospital systems can have a meaningful impact on patient care.
- It makes sense. A centralized distribution centre would be helpful. If possible, integrating an ID consult service for hospitals without an ID physician may even make that an all in one service.
- N/A
- Would improve timely access
- Yes, but should be equally available regardless of geography. Also there will be a greater need for stewardship compared to the malaria network.

Question 10

Would you be interested in participating in development of a centralized or depot model for access to new antibiotics in Canada that incorporates stewardship, distribution, and surveillance while reducing paperwork and cost?

Answered: 34 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	47.06%	16
No	8.82%	3
Maybe, but would like more details first	44.12%	15
TOTAL		34

Comments on Question 10

- I would be interested. However, I am 0.2FTE ASP working a total of 3 days/week under my title of "Medication Safety & Antimicrobial Stewardship". Before I could commit I want to understand what would be required.
- I would like to be involved in the process.
- Timelines, does the project include all antimicrobials or just antibiotics, will the project include both new antibiotics on the market and available through SAP, and how is the project planning to implement a centralized/ depot model? Thanks.
- How it would work, cost of maintaining drug depot, how often do you think it will be utilized
- I am very interested in this model of access and curious to find out more. You can reach me. Thanks!
- I would definitely be interested in providing a Northern Ontario perspective. We have lower rates of resistance. This makes it difficult to carry more expensive new antibiotics given low use and risk of wasting. However, not carrying newer antibiotics in stock creates delays in initiating therapy when resistant organisms are isolate.
- I have actually been talking about this idea for several years. A CMN model for unapproved, rarely used yet important abx. As a small centre hospital pharmacist I wasn't even sure where to begin. I am not sure how I could help but I'd be interested in learning more! thanks for taking this on!
- I realize the day will come when we need such a drug; however, we have no MDRO's at our site.
- Would love to be involved.

APPENDIX 5: CONTRIBUTORS

The following people contributed to this project either through one-on-one interviews, broad consultations, survey responses, or other general input.

Kim Abbass	Nova Scotia Health
Lama Abi Khaled	Innovative Medicines Canada (IMC)
Christina Adams	Canadian Society of Hospital Pharmacists
James Anderson	International Federation of Pharmaceutical Manufacturers & Association
Christine Årdal	Norwegian Institute of Public Health
Anne-Sophie Belzile	Innovative Medicines Canada
Alka Bhalla	Correctional Service Canada
Lise Bondy	Western University
Daniel Brian Gregson	University of Calgary
Annie Brooks	Hamilton Health Sciences - Juravinski Hospital
Eric Brown	McMaster University
John Burrows	Novo Nordisk
Jo-Anne Cecchetto	Government of NWT Department of Health and Social Services
Stephanie Cheung	Mackenzie Health
Daniel Chiasson	Canadian Association for Pharmacy Distribution Management (CAPDM)
Judy Chong	Ontario College of Pharmacists
Jeannette Comeau	Dalhousie University
Mary Coughlin	Health Canada
Peter Daley	Memorial University of Newfoundland
Nick Daneman	Sunnybrook, University of Toronto
Gregory Deans	University of British Columbia/Fraser Health
Yuyi Deng	Health Canada
Rita Dhami	London Health Sciences Centres
Sav DiPasquale	Canadian Pharmaceutical Distribution Network (CPDN)
Christine Donaldson	HealthPRO
Francois Drolet	Roche Diagnostics
Ginette Dutrisac	Health Sciences North
Rainer Engelhardt	Public Health Agency of Canada (former senior official)
Bersabel Ephrem	Public Health Agency of Canada
Francois Farmer	Merck

Thomas Fear	Mackenzie Health
Judith Fisher	Nova Scotia Department of Health and Wellness
Cameron Forbes	Queensway Carleton Hospital
Susan Fryters	Alberta Health Services, Royal Alexandra Hospital
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Jérémie Lacroix	Health Canada
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Tim Lau Vancouver	General Hospital
Courtney Lawrence	University of Manitoba
Minh-Hien Le	Canadian Society of Hospital Pharmacists
Edmond Lee	Microbion Corp.
Anna Lee	Scarborough Health Network
Simon Lee	Ontario Ministry of Health
Daniela Leto	Hamilton Health Sciences
Elizabeth Leung	St. Michael's Hospital
Mitchell Levine	McMaster University
Joel Lexchin	University Health Network
Ryan Lock	GlaxoSmithKline
Yves Longtin	Jewish General Hospital
Sarah Lutes	Health Prince Edward Island
Ian MacKay	Health Canada
Anne MacLaurin	Healthcare Excellence Canada
Selina Manji	Ottawa-Carleton Pharmacists Association
William Martin	Public Health Agency of Canada
Jorge Martinez Cajas	Kingston Health Sciences Centre

Larissa Matukas	Unity Health Toronto
Bayan Missaghi	University of Calgary/Alberta Health Services
Chantal Morel	University of Geneva
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Andrew Morris	Sinai Health
Dario Moscoso	Humber River Hospital
Karen Mueller	SterileCare
Prev Naidoo	Whitehorse General Hospital
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N'kem Odita	Health Canada
Kevin Outterson	Boston University
Sheena Pang	William Osler Health System
Westley Partington	Health Canada
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Miranda So	University Health Network
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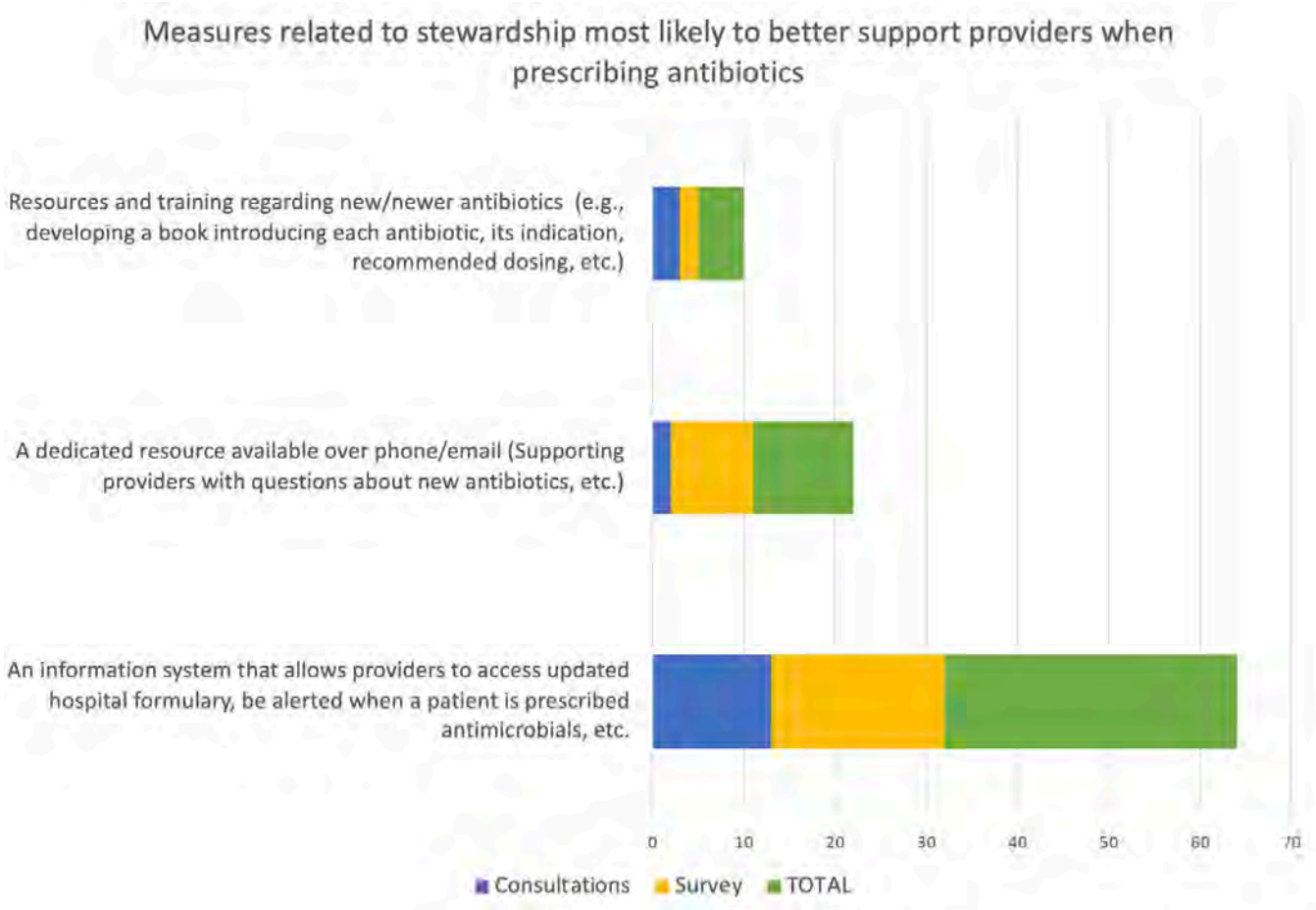
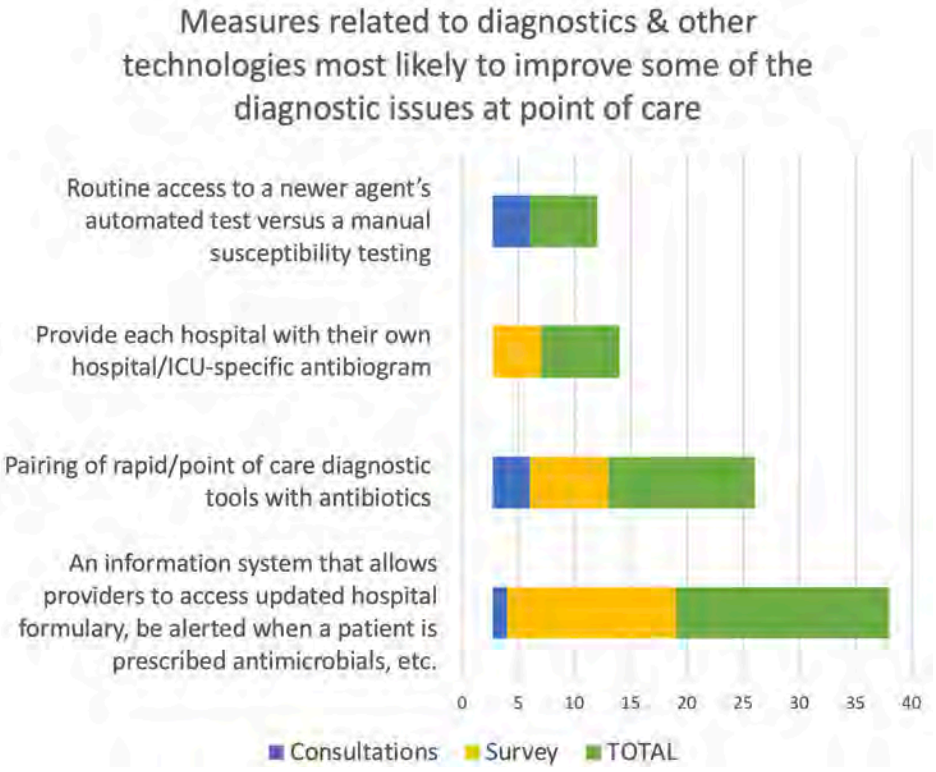
Evelyn Soo	Health Canada
Aleina Spigelman	Roche Diagnostics
Patrick Stewart	Health Canada
Jessica Tang	Health Canada
Daniel Thirion	University of Montreal
Jason Vanstone	Saskatchewan Health Authority
Divya Virmani	Island Health Authority
Justine Walker	Ontario Ministry of Health
Imani Williams	GlaxoSmithKline
Angie Wong	Ontario Ministry of Health
Steven Wong	Ontario Ministry of Health
Daisy Yang	Southlake Regional Health Centre

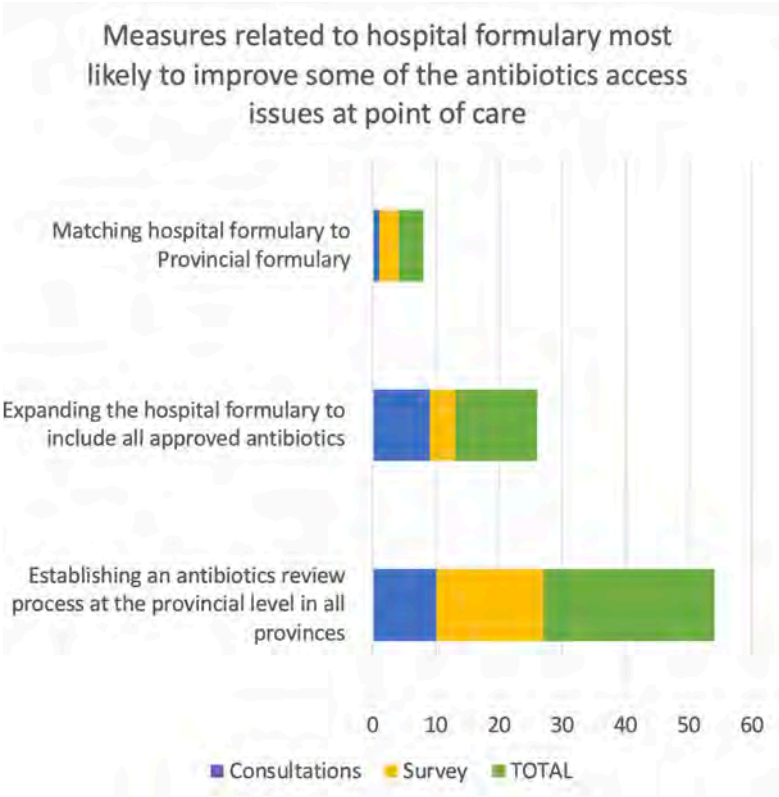
APPENDIX 6: CONSULTATIONS AND SURVEY DATA

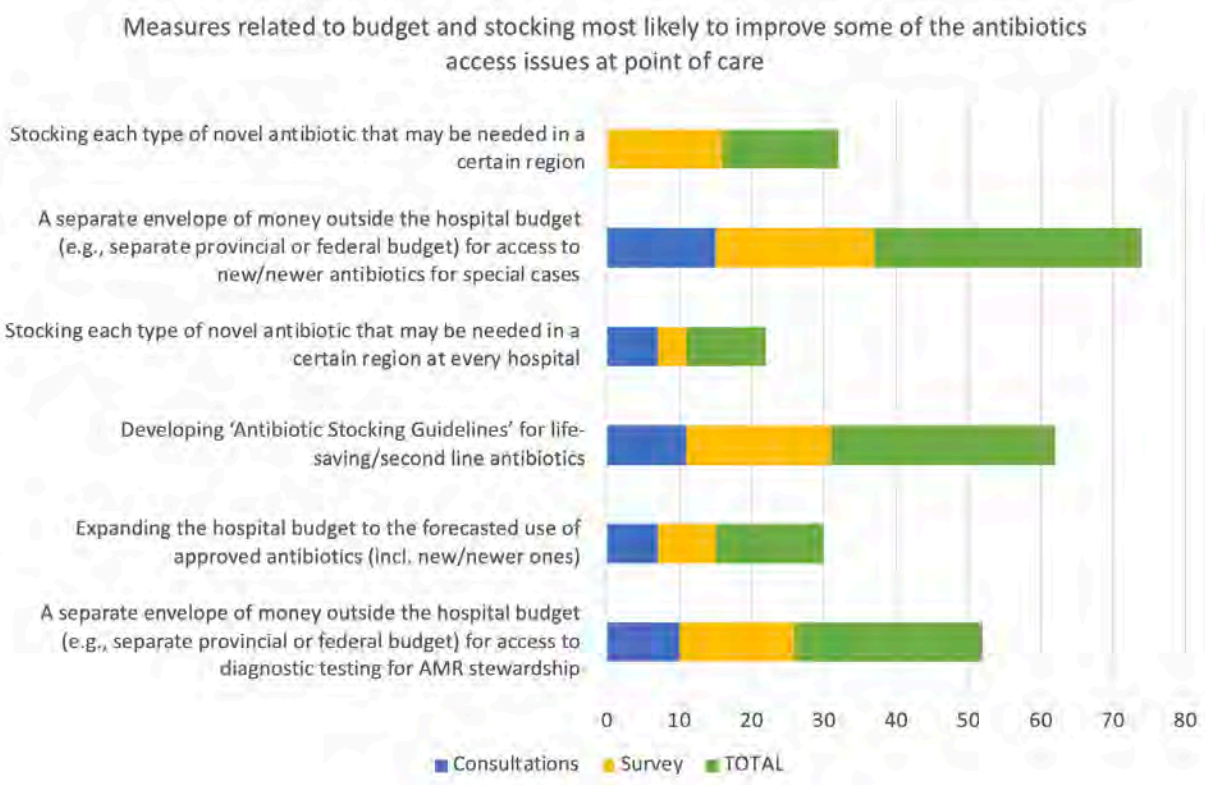
Individuals from various stakeholder organizations – academia, industry, government, healthcare, and more – were invited to participate in a series of virtual consultation sessions in August 2021. Following these consultation sessions, stakeholders who were unable to attend were invited to participate in an online survey.

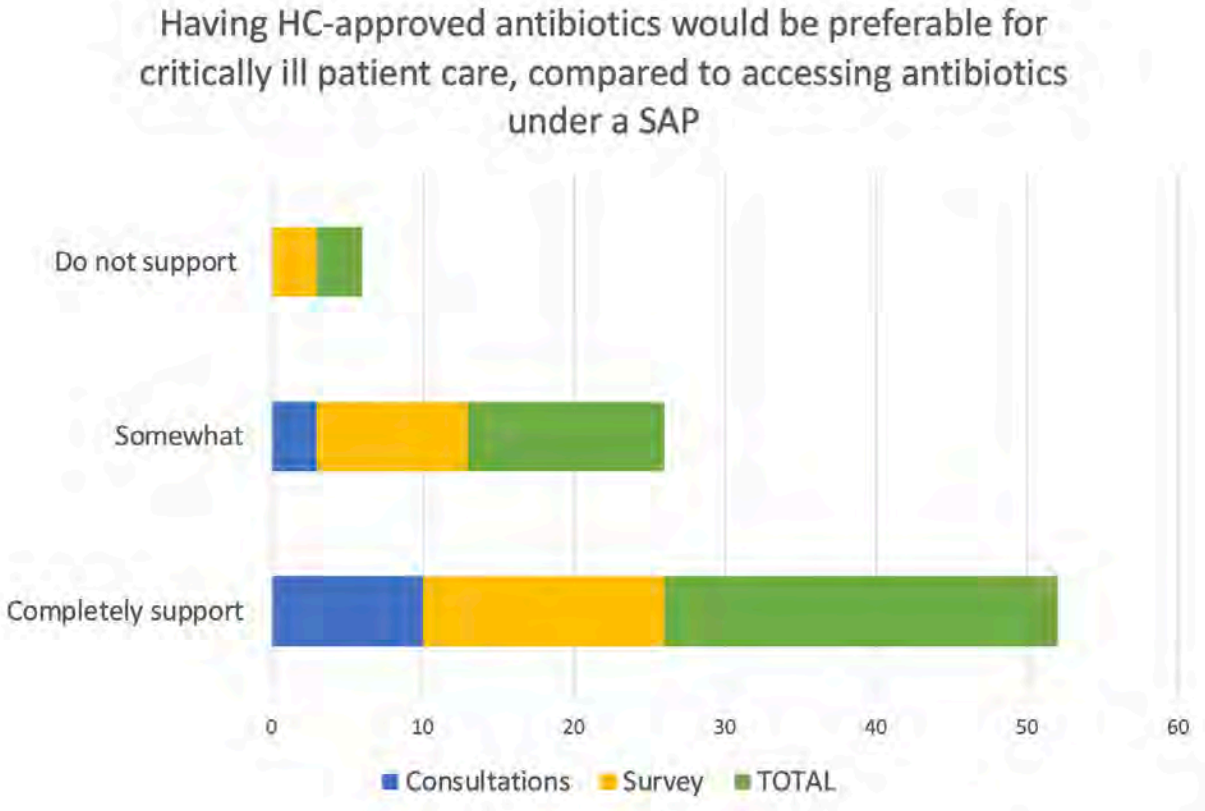
Structured quantitative data and open-ended qualitative data, based on 40 consultations participants and 34 survey respondents, were collected and are presented here.

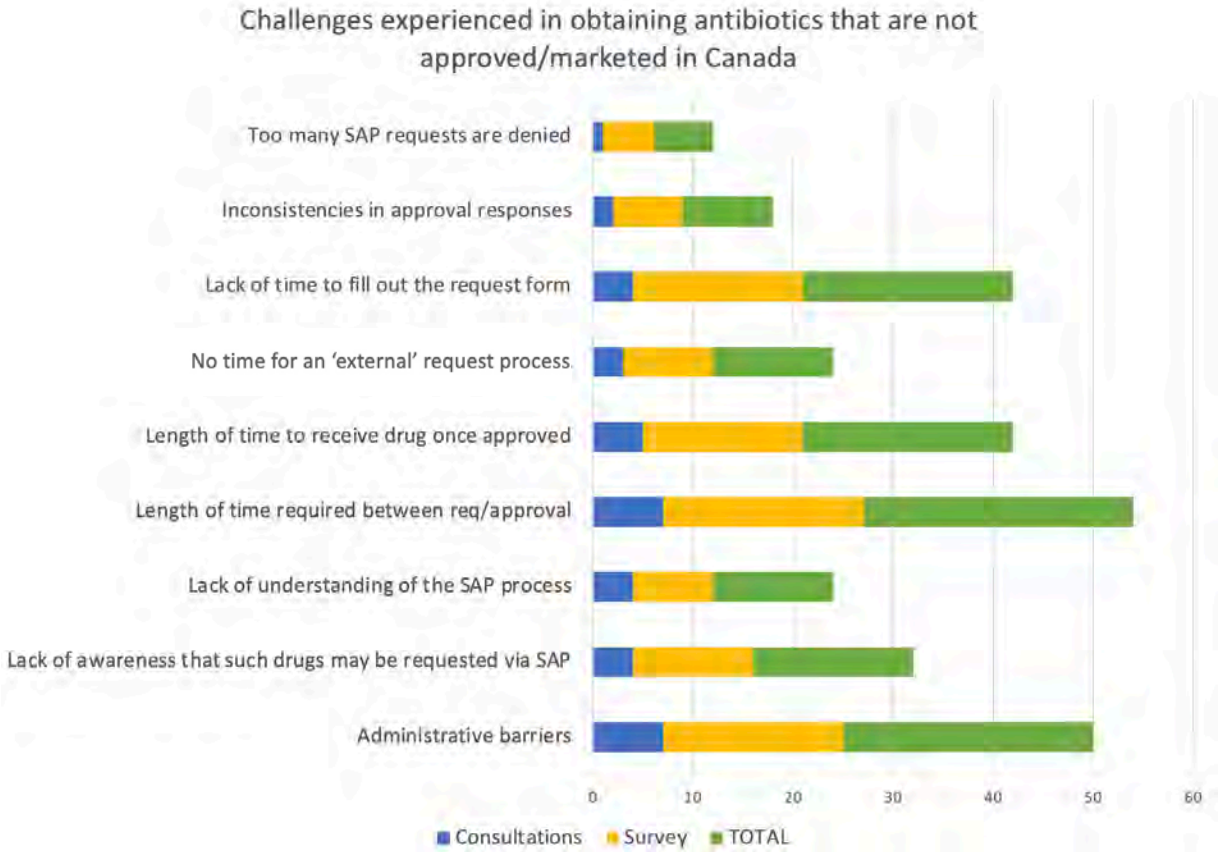


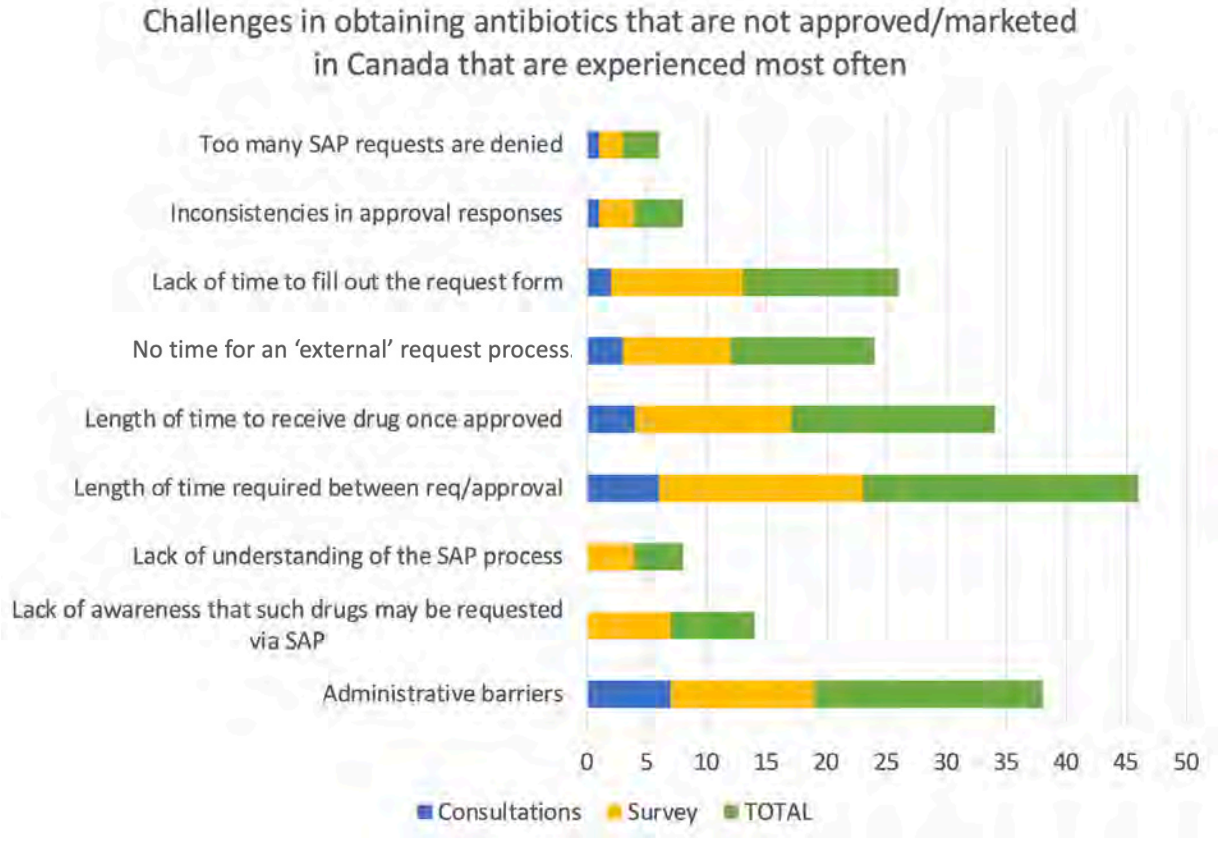

Measures related to diagnostics & other technologies most likely to improve some of the diagnostic issues at point of care
Routine access to a newer agent's automated test versus a manual susceptibility testing
Provide each hospital with their own hospital/ICU-specific antibiogram
Pairing of rapid/point of care diagnostic tools with antibiotics
An information system that allows providers to access updated hospital formulary, be alerted when a patient is prescribed antimicrobials, etc.
0 5 10 15 20 25 30 35 40
Consultations
Survey
TOTAL

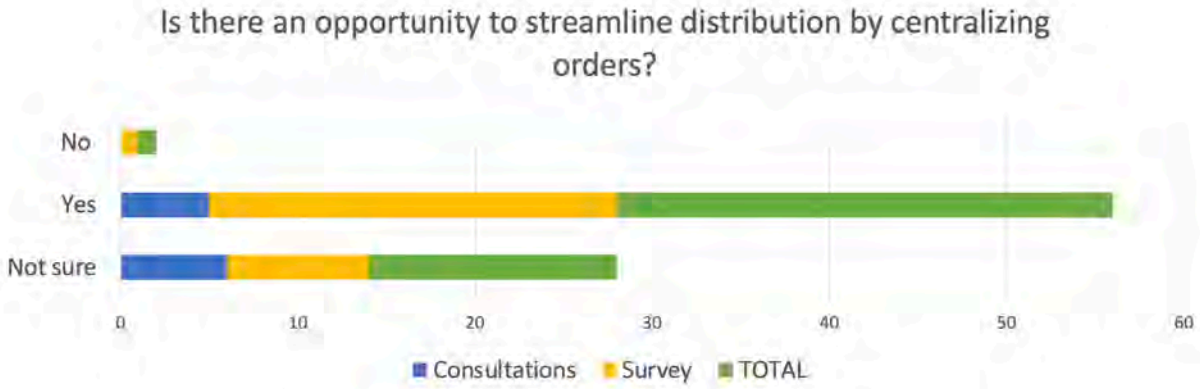

Measures related to hospital formulary most likely to improve some of the antibiotics access issues at point of care
Matching hospital formulary to Provincial formulary
Expanding the hospital formulary to include all approved antibiotics
Establishing an antibiotics review process at the provincial level in all provinces
0 10 20 30 40 50 60
Consultations
Survey
TOTAL

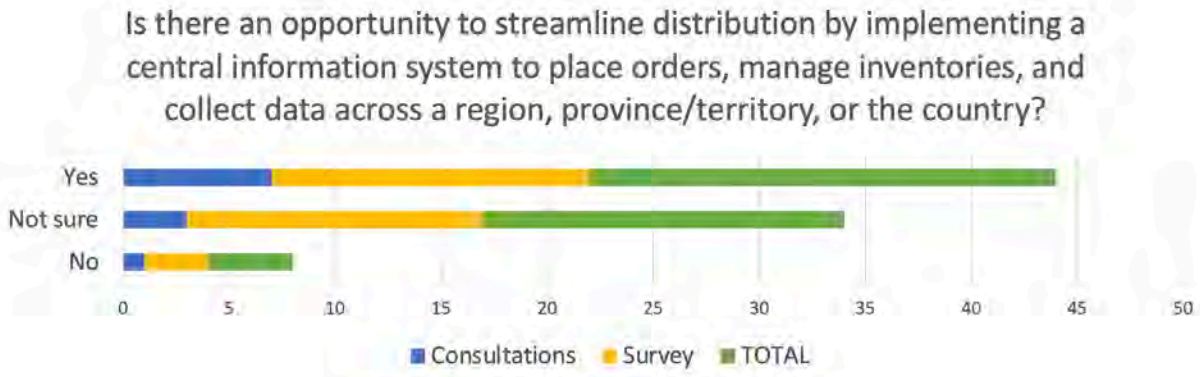

Measures related to budget and stocking most likely to improve some of the antibiotics access issues at point of care
Stocking each type of novel antibiotic that may be needed in a certain region
A separate envelope of money outside the hospital budget (e.g., separate provincial or federal budget) for access to new/newer antibiotics for special cases
Stocking each type of novel antibiotic that may be needed in a certain region at every hospital
Developing 'Antibiotic Stocking Guidelines' for life-saving/second line antibiotics
Expanding the hospital budget to the forecasted use of approved antibiotics (incl. new/newer ones)
A separate envelope of money outside the hospital budget (e.g., separate provincial or federal budget) for access to diagnostic testing for AMR stewardship
0 10 20 30 40 50 60 70 80
Consultations
Survey
TOTAL

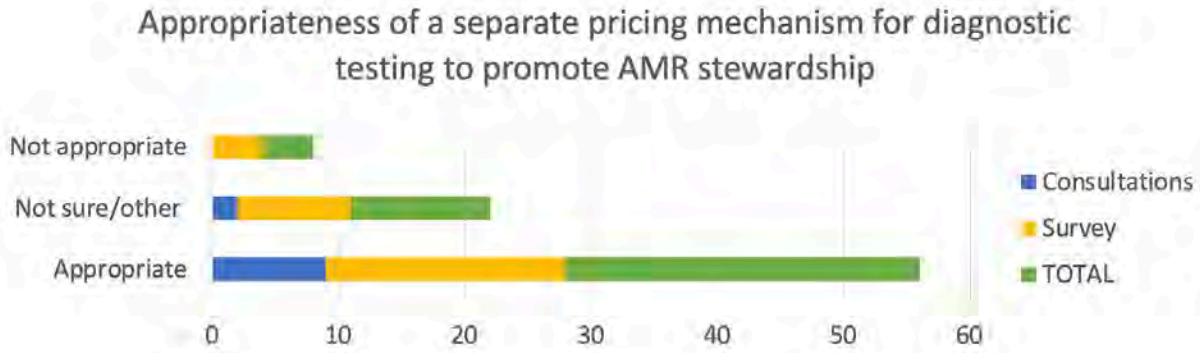

Having HC-approved antibiotics would be preferable for critically ill patient care, compared to accessing antibiotics under a SAP
Do not support
Somewhat
Completely support
0 10 20 30 40 50 60
Consultations
Survey
TOTAL


Challenges experienced in obtaining antibiotics that are not approved/marketed in Canada
Too many SAP requests are denied
Inconsistencies in approval responses
Lack of time to fill out the request form
No time for an 'external' request process
Length of time to receive drug once approved
Length of time required between req/approval
Lack of understanding of the SAP process
Lack of awareness that such drugs may be requested via SAP
Administrative barriers
0
10
20
30
40
50
60
Consultations
Survey
TOTAL

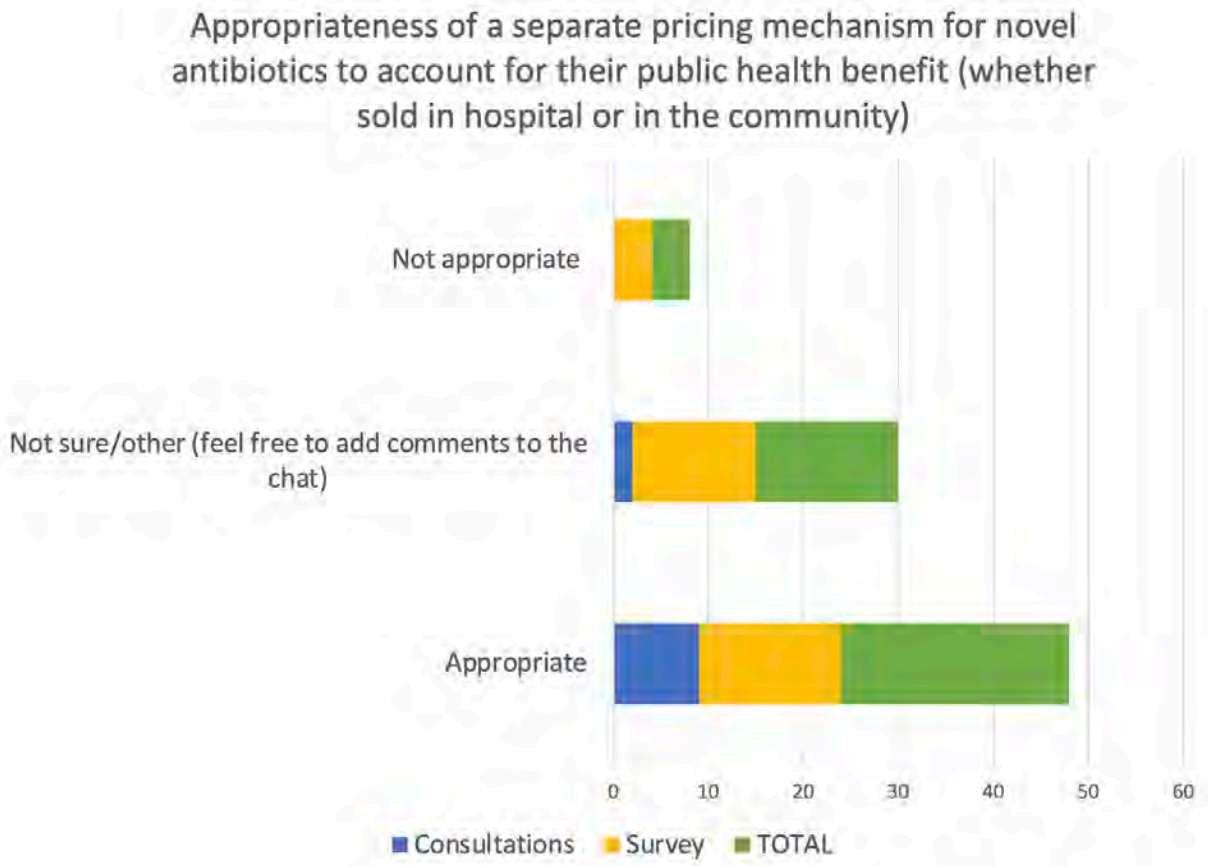

Challenges in obtaining antibiotics that are not approved/marketed in Canada that are experienced most often
Too many SAP requests are denied
Inconsistencies in approval responses
Lack of time to fill out the request form
No time for an 'external' request process
Length of time to receive drug once approved
Length of time required between req/approval
Lack of understanding of the SAP process
Lack of awareness that such drugs may be requested via SAP
Administrative barriers
0
5
10
15
20
25
30
35
40
45
50
Consultations
Survey
TOTAL

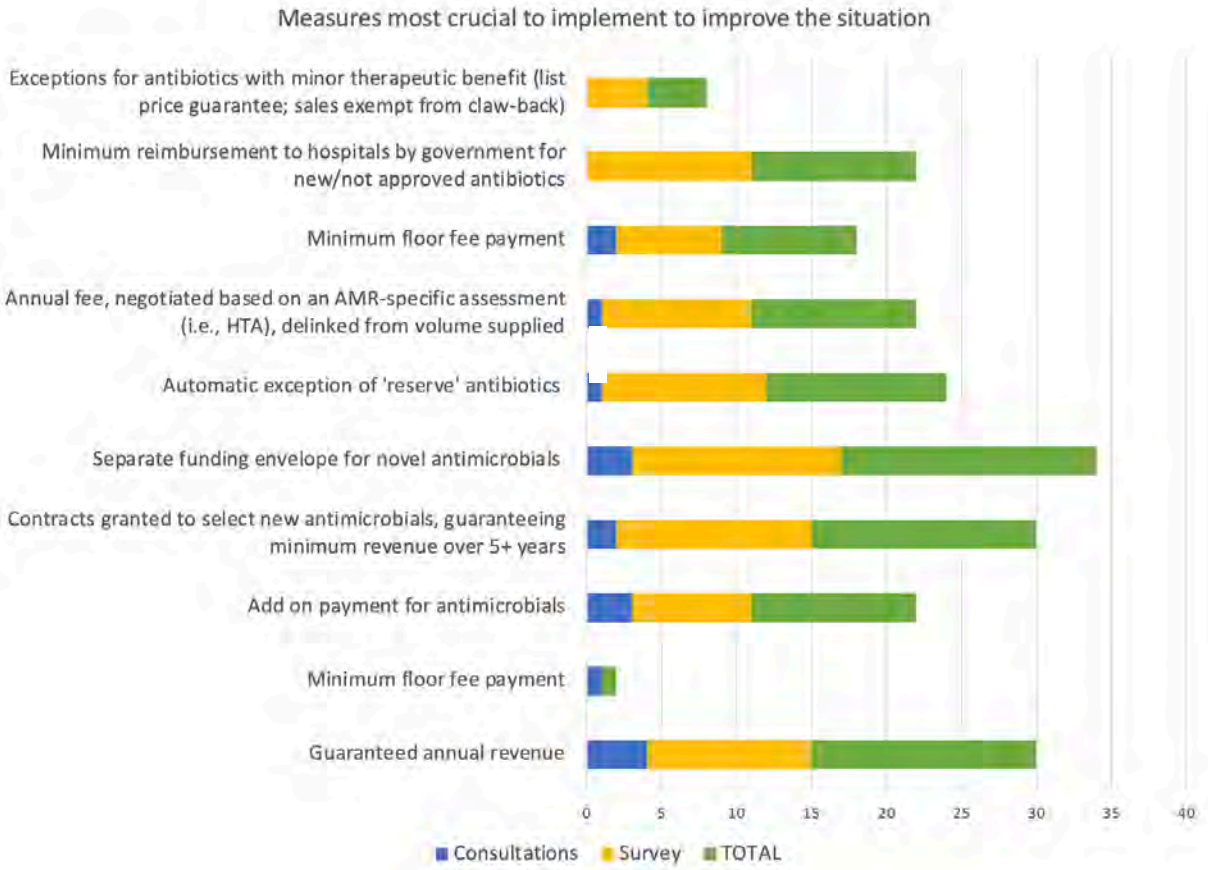

Is there an opportunity to streamline distribution by centralizing orders?
No
Yes
Not sure
0
10
20
30
40
50
60
Consultations
Survey
TOTAL


Is there an opportunity to streamline distribution by implementing a central information system to place orders, manage inventories, and collect data across a region, province/territory, or the country?
Yes
Not sure
No
0
5
10
15
20
25
30
35
40
45
50
Consultations
Survey
TOTAL


Appropriateness of a separate pricing mechanism for diagnostic testing to promote AMR stewardship
Not appropriate
Not sure/other
Appropriate
0
10
20
30
40
50
60
Consultations
Survey
TOTAL


A higher price ceiling and list price for certain antibiotics is justified if associated with a measurable public health benefit
Yes
Not sure/other
No
0
10
20
30
40
50
60
70
Consultations
Survey
TOTAL


Appropriateness of a separate pricing mechanism for novel antibiotics to account for their public health benefit (whether sold in hospital or in the community)
Not appropriate
Not sure/other (feel free to add comments to the chat)
Appropriate
0
10
20
30
40
50
60
Consultations
Survey
TOTAL


Measures most crucial to implement to improve the situation
Exceptions for antibiotics with minor therapeutic benefit (list price guarantee; sales exempt from claw-back)
Minimum reimbursement to hospitals by government for new/not approved antibiotics
Minimum floor fee payment
Annual fee, negotiated based on an AMR-specific assessment (i.e., HTA), delinked from volume supplied
Automatic exception of 'reserve' antibiotics
Separate funding envelope for novel antimicrobials
Contracts granted to select new antimicrobials, guaranteeing minimum revenue over 5+ years
Add on payment for antimicrobials
Minimum floor fee payment
Guaranteed annual revenue
0
5
10
15
20
25
30
35
40
Consultations
Survey
TOTAL

Appendices

The following statements were also collected from session attendees and surveys, and copied verbatim:

Observations
Stakeholders' prevailing thoughts

From Consultation Sessions

- The global pipeline for new antibiotics is dry, and Canada's marketplace doesn't inspire hope for change
- Novel antibiotics need help entering the market, but shouldn't be governed differently once they're more accessible

From Post-Consultation Survey

- Regulatory bodies need to be more evidence based about antibiotic selection
- If better patient outcomes could be quantified, the savings could be measured to promote adoption of higher priced new antibiotics
- It takes a long time to get antibiotics to remote communities
- Diagnostics is crucial to ensure both appropriate stewardship and managing costs associated with novel antibiotics
- The labs need to be amenable to testing susceptibility to alternative agents
- Regulatory bodies need to be more evidence based about antibiotic selection

Barriers
Obstacles that impact patient care

From Consultation Sessions

- Financial barriers are unequivocally the largest obstacle preventing more antibiotics from entering the Canadian marketplace
- Stewardship, while vital in the fight against antibiotic resistance, poses an obstacle to accessing novel antibiotics
- There is a lack of relevant data captured – or at least shared publicly – in this space
- Individual provincial approaches lead to variations across Canada that could make solutioning complex

From Post-Consultation Survey

- Health Technology Assessment (HTA) is a major barrier
- Newer innovations are valued against genericized medicines that are much lower priced, and the societal benefit is not taken into account in the valuations
- Comfort level (being told to try older agents first)
- Uncertainty about which antibiotics are on the SAP list and how to get it if it's not on the SAP list
- Sometimes HC will approve reasonably quickly, but the manufacturer/supplier delays their approval and/or shipping

Solutions
Ideas for addressing barriers

From Consultation Sessions

- Antibiotics could benefit from having their own program, separate from the Special Access Program (SAP)
- There is widespread appetite for establishing an antimicrobial information system

From Post-Consultation Survey

- Level the playing field so smaller and larger hospitals have equal access to novel antibiotics
- The novel antibiotics could be purchased by PHAC similarly to COVID-19 therapeutics, circumventing PMPRB, HTA and pCPA
- Establish a strategic stockpile of critical antibiotics
- Develop a list of significant pathogens and a list of required agents for treatment as a national standard and access need
- Conduct group purchasing to obtain a better deal from manufacturers
- Implement funding for drug access coordinators (like those at ON cancer centres) for inpatient AMU
- Establish a criteria-based approach
- Develop an online SAP process
- Educate patients in completing prescriptions
- Provide regular feedback to physicians on how their prescription could help reduce use of antibiotics
- Establish formal processes for reserving new antibiotics for only when older ones have proved to be ineffective
- Compare all the ways we treat patients with antibiotics
- Focus on much stronger policies about the use of antibiotics in agriculture
- Prioritize standardized access to diagnostic testing and base it on science
- Establish robust process to access the newest antibiotics for labs to test and create appropriate breakpoints (in Canada or follow international organizations)
- Measure diagnostic delays
- Expedite and streamline HC approvals
- Align drug approvals with the EU and USA

APPENDIX 7: DIFFICULT TO SECURE ANTIBIOTICS

The following antibiotics are approved in canada but reported by pharmacists as difficult to secure due to formulary and supply chain issues.

Antibiotic	Major Indication	Approval	Patented (Y/N)	Owner	Product
Ceftobiprole	▶ Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP) Caused by: Staphylococcus aureus (including MRSA), Streptococcus pneumoniae, Escherichia coli, and Klebsiella pneumoniae. ▶ Community-acquired pneumonia (CAP) Caused by: Staphylococcus aureus (including MRSA), Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae and Haemophilus influenzae.	FDA: Not Approved Health Canada: 2015	Y	Basilea	Zevtera
Ceftolozane/Tazobactam	▶ Complicated intra-abdominal infections (cIAI) caused by the following Gram-negative and Gram-positive microorganisms: Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius. ▶ Complicated urinary tract infections (cUTI), including pyelonephritis caused by the following Gram-negative microorganisms: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. ▶ Nosocomial pneumonia, including ventilator-associated pneumonia, caused by the following susceptible Gram-negative microorganisms: Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Serratia marcescens.	FDA: 2014 Health Canada: 2015	Y	Cubist/Merck	Zerbaxa
Daptomycin	▶ Complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillinresistant strains), Streptococcus pyogenes and Streptococcus agalactiae. ▶ Staphylococcus aureus bloodstream infections (bacteremia) including those with right-sidedStaphylococcus aureus infective endocarditis (native valve) caused by methicillin-susceptible and methicillin-resistant strains	FDA: 2003 Health Canada: 2019	N	N/A	Cubicin
Fidaxomicin	▶ Clostridium difficile infection (≥18 years of age)	FDA: 2011 Health Canada: 2012	Y	Cubist/Merck	Dificid

APPENDIX 8: ANTIBIOTICS NOT APPROVED IN CANADA, AND REPORTED BY PHARMACISTS AS NEEDED TO TREAT PATIENTS

Antibiotic	Major Indication	Drug Route	Dosage Form	FDA Approval	Owner	# Approved[1] 2018	# Approved[1] 2019	# Approved[1] 2020
Aztreonam	Pseudomonas/ CF (76%)	I.V.	Single-Use Vial	1986[2]	Gilead	14092	12281	10991
Cefiderocol	MDR Pseudomonas (100%)	I.V.	Vial	2019	Shionogi	0	266	1992
Ceftazidime-Avibactam	Pseudomonas (28%)	I.V.	Single-Use Vial	2015	Allergan	2074	4609	1930
Ceftaroline	MRSA (89%)	I.V.	Vial	2010	Allergan	3445	4243	2978
Clofazimine	Mycobacterium sp. (97%)	Oral	Capsule	1986[2]	N/A	102887	123806	132396
Doxycycline	Lymphatic cyst (35%)	I.V.	Single-Use Vial	1967	Galderma	3880	4023	1420
Fosfomycin IV	UTI (45%)	I.V.	Vial	1996	N/A	170	1615	210
Imipenem-cilastatin-relebactam (RECARBRIO)	None	N/A	N/A	2019	Merck	N/A	TBD	TBD
Meropenem/ vaborbactam	None	N/A	N/A	2017	Melinta	N/A	TBD	TBD
Minocycline (Minocin)	A variety of infections	I.V.	N/A	2002	(Melinta)	N/A	TBD	TBD
Plazomicin	None	N/A	N/A	2018	Cipla	N/A	TBD	TBD
Rifampin	Tuberculosis (50%)	I.V.	Vial	1971[2]	N/A	2754	4111	2520

Notes

1 Quantity approved corresponds to the unit based on dosage form – e.g., bottle, capsule, single/multiple-dose vial, tablet, syringe. The SAP team kindly provided data for the drugs of listed – Another extract request will be required to obtain the 2019-2020 data for drugs that came to our attention later in the project.

2 This is the initial approval year for the formulation put forward at the time. A different formulation was since produced that does not have marketing approval for Canada.

APPENDIX 9: REIMBURSEMENT & INCENTIVES MODELS

This document was prepared by the Canadian Antimicrobial Innovation Coalition.

Reimbursement Models to Address Antimicrobial Resistance Market Failures

A Canadian Biomedical Industry Perspective

(Updated 08-16-21)

New antimicrobials, diagnostics and antimicrobial alternatives are urgently needed to tackle the growth of antimicrobial resistance (AMR) and drug resistance; however, the global pipeline of these treatments remains limited.

The global COVID-19 pandemic has demonstrated the importance of public health preparedness and the devastating economic and social impact of infectious disease. With AMR already creating serious challenges to public health around the globe, it's imperative that innovation, together with stewardship, infection prevention & control and surveillance be advanced to mitigate the impact of AMR on our society.

As countries develop, pilot, and implement novel procurement and reimbursement models to bring more AMR treatments to their markets, Canada has yet to identify an appropriate and sustainable model that stabilizes and sustains a domestic AMR market. As other countries advance their AMR models, Canada has an opportunity to assess the benefits of their models while evaluating the appropriateness of these model for the Canadian market.

In response to this opportunity, the Canadian Antimicrobial Innovation Coalition (CAIC) has developed AMR incentive model principles and provided industry insight into the feasibility of the models of France, Germany, Sweden, the United Kingdom, and the United States in Canada.

AMR Incentives – Canadian Considerations

(1) Canada's federated health system requires an incentive model with a strong bottom-up approach with considerations of provinces, local health systems, and the patient.
- Provincial delivery systems must be factored into distribution and payment schemes.
- Incentive models should be patient centered.
- Consistent collaboration between infectious disease physicians, hospital pharmacists and microbiology labs is essential to ensure appropriate use.
- Consider incentive models inspired by other Federal-Provincial-Territorial (FPT) financing models, such as malaria medicines and blood products.

(2) Integrate stewardship into model.
- While stewardship is a requirement in incentive models in other jurisdictions, stewardship is not integrated into the model itself.
- By integrating stewardship into the model, the government realizes a direct return on its investment, thereby justifying the government financial contribution to the incentive program.
- Important to acknowledge limited incentives to use existing and new diagnostics. There is a need for incentives to encourage appropriate use and assist physicians in making determination when the newer/new antimicrobial is warranted.

- Consideration of innovative methods to support stewardship in hospital, pharmacies, and local health units.

(3) The market guarantee is essential, but also streamlined market access and Health Technology Assessment (HTA) processes can incentivize manufacturers to Canada.

- Canada's small market may require added benefits to attract industry for commercialization of AMR products.
- Canada's innovative SME community requires a stabilized and guaranteed market to develop AMR products.
- HTA and Market Access process in Canada can be lengthy, compared to other G7 countries. The lengthy market access process can discourage the introduction of novel products for AMR.
- There is a significant degree of time sensitivity in identifying and adopting medicines to tackle AMR.
- A more efficient, expedited HTA process for antimicrobials could provide an incentive on top of a financial incentive.

(4) Eligible medicines

- Health Canada's priority pathogen list can serve as a starting point for incentives, but it is also important to be flexible and allow for antibacterial candidates deemed essential for public health.
- The option to leave door open for antibiotic alternatives is crucial.
- Canadian incentive models should have considerations beyond antimicrobial treatments and applied to additional therapeutic and prevention options such as antibiotics, vaccines for AMR, anti-fungal treatments in context of AMR, and the use of antivirals.

Jurisdiction Comparison

The following provides an overview of the various incentive policies and mechanisms in France, Germany, Sweden, the United Kingdom, and the United States. As these policies and programs do not exist in Canada and are not designed for Canada's unique health system landscape, CAIC has provided analysis to these programs from the lens of the program's suitability in Canada to assist in the building of a 'Made in Canada' solution.

Country	Program	Timeline	Mechanism Type	Antimicrobials/Pathogens Targeted	Canadian Perspective - CAIC
France	Exception for antibacterials with ASMR level IV (minor)	In effect since 2015	Medicines with' moderate' or higher added therapeutic benefit are guaranteed a price not lower than the lowest price across 4 reference countries. This is extended to antibacterials with 'minor' added therapeutic benefit.	Antibacterials assessed as being ASMR level IV (minor)	• "Strategic Contract for the Health Industry and Technologies," which describes reciprocal commitments between government and industry aligns with CAIC's recommendations with respect to creating implementable solutions for AMR incentives, both from industry and government. • A strategic contract demonstrates that both industry and government commit to sustaining and building a market for antimicrobials, diagnostics, vaccines and antibiotic alternatives, while supporting objectives with respect to stewardship. Framework agreement provides an option for the pharmaceutical company to request a pricing increase if planning to cease production or commercialization of a product with no alternatives on the market. This step could be implemented through PCPA but presumably through procurement this is less likely to happen. • Carve-out for high-cost medicines and diagnostics used in hospitals will be a challenge to implement in Canada at a national, coordinated level. However, the carve-out in France aims to alleviate strain in global hospital budgets, which otherwise stands as an obstacle to accessing new/newer antibiotics. This is a similar challenge in Canada, but given the administration of healthcare, the solution will need to be structured under an FPT model. • HTA exception for antibacterials that allows for pricing that better reflects product value is a principle we support. In France, the approach is to extend minimum price guarantees to antibacterials with "minor" therapeutic benefit to address the reimbursement process that undervalues based on non-inferiority trials. However, given the dire market for antibacterials, diagnostics, vaccines and antibiotic alternatives, the arrangement is too abstract to incentivize market entry.
	Exception for antibacterials with ASMR level IV (minor)	In effect since 2015	Sales of certain medicines exempted from turnover liable to claw back	Antibacterials and other medicines used in combatting AMR	
	Price renegotiation for medicines at risk of shortages	In effect since 2015	Companies may request permission for a price increase from the reimbursement authority, if continued commercialisation would otherwise not be viable	This mechanism has been used for antimicrobials, though details are confidential.	
Germany	Changes in § 35 SGB V	In effect since 2017	Ad hoc exception of antimicrobials from internal price reference groups	Decided by reimbursement authority ad hoc taking into consideration resistance patterns	• Invites the reimbursement authority to consider resistance patterns when determining if a therapeutic provides value. Similarly, resistance patterns should be factored into Canada's incentive programs to demonstrate value for the new/newer antibacterial, diagnostics, vaccines and antibiotic alternatives. • Germany legislation also enables reimbursement to pursue individual pricing arrangements for Reserve Group. Allows for degressive pricing- pay a higher unit price for pre-defined volume

Country	Program	Timeline	Mechanism Type	Antimicrobials/Pathogens Targeted	Canadian Perspective - CAIC
					and lower price when volume exceeded. In practice it would be difficult to administer a program that is consistent across provinces unless flexibility in pricing engagements is managed at national level under a federal procurement model?
	Fair Health Insurance Law -Faire Kassenwettbewerbsgesetz	In effect since March 2020	Automatic exception of 'reserve' antibacterials from internal price reference groups, accelerated reimbursement review process following EMA approval	'Reserve' antibacterials	• Exempts reserve group antibacterials from HTA process and automatic exemption from certain price controls. Exempted from early benefit assessment, automatically qualify as having therapeutic benefits in context of pricing negotiations. Also exempted from being included in internal reference pricing groups. Similar type of exemptions would make a significant difference in Canada by alleviating administrative, PMRPB and time burden associated with new drug entry in Canada. • Have a DRG carve out like France – this positive in the sense that the cost burden is taken away from global hospital budgets but need to be implemented in a different way in Canada more under a FPT procurement model or national/provincial fund.
Sweden	PHAS pilot study	First procurement call planned for early 2020, pilot study to run through 2022	PHAS sets a minimum guaranteed annual revenue for selected originator antibacterials, in exchange for a guaranteed supply volume	"Critical" pathogens in the WHO	• Sweden's approach is to ensure access to products for which current demand volume may be too low to attract the proprietor to market the medicine Sweden. Canada's limited market size presents a similar obstacle to drug sponsors to introduce antibacterial drugs in Canada. • The pilot mode ensures availability of originator antibacterials that may not otherwise be marketed in Sweden due to small market size. We noted the comment that this model may not create a substantial incentive for R&D, however if Sweden, Canada and other countries followed the same model, and extended it to diagnostics, vaccines and antibiotic alternatives, would this create a level of certainty at the global level that could sustain R & D? • In addition, this model could be paired with other incentives to stimulate R&D, such as regulatory incentives that allow for smaller clinical trials and push incentives. • Sweden's focus on priority pathogen list "PPL" could be broadened in Canada as there may be pathogens not on the WHO or HC Priority Pathogen list but may still be desired to improve quality of care and/or respond to emerging public health priorities

Country	Program	Timeline	Mechanism Type	Antimicrobials/Pathogens Targeted	Canadian Perspective - CAIC
				Priority Pathogens List [1]	• An open procurement call under the pilot is feasible in Canada under a federal procurement model. Similarly, PSPC in consultation with PHAC could establish a minimum annual guaranteed revenue. In Sweden, the revenue is based on the cost of a "security stock" at 50% above the average European list price. In Canada, would a basket price be applied? In some cases, antibacterials are listed in the U.S. only or EU only. • Like Canada, in Sweden pharmaceuticals are reimbursed regionally. Regional health departments pay the list price for the selected antibacterials with the difference made up at national level if the guaranteed annual revenue not reached through regional procurement. In Canada, this could be a challenge to administer from a financial perspective. • We believe setting up provincial procurement would draw out the process and create a disincentive to participate in a Canada AMR incentive program. • A national tender program with guaranteed annual revenue to acquire antibacterial, then distributed under a regional program would work more efficiently. Provincial governments could contribute to the national fund.

[1] World Health Organization. Global priority list of antibiotic-resistant bacteriato guide research, discovery, and development of new antibiotics. 27 Feb2017. Available: https://www.who.int/medicines/publications/WHO-PPL-Short Summary 25Feb-ET NM WHO.pdf?ua=1.

Country	Program	Timeline	Mechanism Type	Antimicrobials/Pathogens Targeted	Canadian Perspective - CAIC
United Kingdom	Innovative models for the evaluation and purchase of antimicrobials	Product selection completed in 2020, HTA completed in 2021, commercial negotiations to be concluded in early 2022	Annual fee, negotiated based on AMR-specific HTA, delinked from volume supplied	Pathogens on the WHO Priority Pathogens List[2]; two antimicrobials to be selected in the pilot model – one approved in the last 1.5–3 years, and late-stage pipeline product expected to be approved by the end of 2020	• Objective of model is to arrange procurement of new valuable antibacterials on basis of a multi-year contract paid through annual payment or fee for which the manufacturer would provide as many doses of the antibacterial as needed. • Setting a price/cost that would incentivize industry is an important principle to incentivize industry to participate, while also delinking sales from volume to achieve public health outcomes. • UK payment fee established a ceiling payment. The ceiling payment, combined with a tendering process could ultimately disincentivize manufacturer participation by reducing the fee below the ceiling fee. The annual payment should instead treat the antibiotic as a unique product with a minimum floor payment. • Negotiated on AMR-specific HTA, delinked from volume specified. Note that in Canada, HTA process can be lengthy, which can serve as a barrier for newer antimicrobials, diagnostics, vaccines and antibiotic alternatives, especially given Canada's relatively small market size. HTA embedded in procurement process, upfront could be a more suitable approach. • UK pathogens selected on WHO priority list – Canada could apply Health Canada's priority pathogens list, but list can be more expansive to include other antibacterials that fulfill a public health need. • Two antimicrobials selected one late-stage product and one approved in last 1.5-3 years. Similarly, Canada's program should create an early adopter market for available and newer antibacterials, diagnostics, vaccines and antibiotic alternatives. For example, as Canada has adopted a limited number of antibacterials approved by the FDA since 2010, Canada may consider prioritizing 1-2 newer antibacterials that are currently available in other jurisdictions, including transitioning a product from Special Access Program.
United States	GAIN Act	In effect since 2012	5 years of additional market exclusivity, faster regulatory review	Antibacterial or antifungal drug-resistant pathogens and other qualifying pathogens (QIDP pathogens)	• Extra 5 years of data exclusivity and faster regulatory review. While not sufficient as a market pull mechanism on its own, the GAIN Act has helped emerging companies maintain and build value into their AMR programs, at a time that is otherwise difficult to raise funding from private investors. Regulatory.
	Updates in IPPS rule	In effect since October 2019	Increased reimbursement of cost to hospitals for procurement of newer antibacterials	Antibacterial or antifungal drug-resistant pathogens and other qualifying pathogens (QIDP pathogens)	• Increased reimbursement of cost to hospitals for procurement of newer antimicrobials, diagnostics, vaccines and antibiotic alternatives • While this will be difficult to implement at a federal level, but possible under a provincial program. In principle an incentive that offsets the cost of using newer antimicrobials, diagnostics, vaccines and antibiotic alternatives to hospitals is essential to remove barriers to patient access to newer AMR products
	DISARM legislation	Proposed, still under discussion	Reimbursement of antibacterial expenditures separately from general in-patient expenditures	Antibacterial or antifungal drug-resistant pathogens and other qualifying pathogens (QIDP pathogens)	• Reimbursement of antibacterials expenditures separate from in-patient expenditures. In principle, an incentive that removes cost burden from global hospital budgets to access newer/new antimicrobials, diagnostics, vaccines and antibiotic alternatives is essential to remove barriers to access for patients. QIDP definition does not exist in Canada – Canada may need to define own list – incorporating priority pathogen list with flexibility to include other targets deemed important to public health
	PASTEUR Act	Proposed, still under discussion	Contracts granted to selected new antimicrobials guaranteeing minimum guaranteed revenues over 5+ years	To be defined, if the Act is passed, by a specially created Committee on Critical Need Antimicrobials	• Contracts granted to selected new antimicrobials guaranteeing revenues over 5+ years. • Suitable in Canada as a procurement contract facilitated under a FPT distribution model. • Should include diagnostics, vaccines and antibiotic alternatives to procurement program • Includes resources for stewardship and surveillance, an aspect we support for Canadian incentive program
	Civica Rx	Contracts signed for manufacture of first antibacterials in May 2019	Contract manufacture of antibacterials to avoid shortages and price hikes and ensure more stable supply	Medicines susceptible to shortages, as identified and prioritized by Civica Rx members. To date, vancomycin (Watch) and daptomycin (Reserve)	• Contracts signed for manufacturers – contract manufacture to avoid shortages. • Can occur in Canada with generic pharmaceuticals (?)

ASMR – amélioration du service médical rendu (added therapeutic benefit).

[2] World Health Organization. Global priority list of antibiotic-resistant bacteriato guide research, discovery, and development of new antibiotics. 27 Feb2017. Available: https://www.who.int/medicines/publications/WHO-PPL-Short Summary 25Feb-ET NM WHO.pdf?ua=1.

APPENDIX 10: RECOMMENDATIONS & PROPOSED MEASURES

Recommendations were developed in consideration of the key issues identified throughout the various consultations held. The latter were summarized as:

General Issues	
1	No concrete actions/ initiatives seen on AMR/AR
2	Limited number of manufacturers producing new antibiotics
3	Limited availability of antibiotics that treat multi-resistant infections in Canada
4	Lack of national/ provincial coordination/ availability of data
5	Information on newer antibiotics that may treat multi-resistance infections is sparse / not readily available
6	Hospital budgets not sufficient to cover all costs related to the treatment of multi-resistant infections
Access to antibiotics that are not marketed in Canada	
7a	Lack of awareness or understanding related to the SAP process
7c	Length of time required (e.g., fill out SAP forms, between submission & approval, to receive drug once approved)
7f	No time for an 'external' request process delaying treatment
Stewardship	
8	Deficits in resources/ tools supporting clinical decisions and stewardship
9	Challenges associated with diagnostics (incl., lack of in-hospital tests, length of time to get test results from PH labs, not knowing where advanced tests are available)

The following matrix demonstrates how each of the proposed actions/measures addresses one or more of the key issues.

Notes/ Legend: Measures are listed in the order they should be tackled, not in priority order. Font colour indicates measures is to be tackled and mostly completed: Within 1 year of receiving Phase 2 funding; Within 2-3 years of receiving Phase 2 funding; Within 3-4 years of receiving Phase 2 funding		General Issues						Access to antibiotics that are not marketed in Canada			Stewardship	
		1	2	3	4	5	6	7a	7c	7f	8	9
Recommended Measure	**Stream**	No concrete actions on AMR/AR	Limited number of new antibiotics	Limited availability of new antibiotics in Canada	Lack of data	Information on newer antibiotics sparse	Hospital budgets not sufficient	Lack of awareness (SAP)	Length of time required	No time for 'external' process	Deficits in resources/ tools	Challenges associated with diagnostics
1 Form an AAC Task Force (aka coordinating body, or action group)* to establish partnerships and obtain engagement/participation/input from members of key organizations - e.g., AMMI-Canada, CAIC, CAPDM, CMA, Global Nexus, HC, international entities (incl., CARB-X), PHAC, Colleges of physicians and surgeons.	Governance/ Project & Program Management	✓										
2 Establish the AAC Task Force as the leading entity for the AAC initiative and all related implementation activities, including piloting of the new integrated solution/model.	Governance/ Project & Program Management	✓										
3 Working closely with government and industry partners, establish process to proactively identify priority/essential antibiotics to meet current and future needs in order to inform licensing approval and enable product listing.	Regulatory Incentives	✓	(✓)	✓						✓		
4 Establish pricing/procurement mechanisms for essential/ priority antibiotics administered in hospitals that could be managed through a federal, provincial/territorial, or F/P/T program.	Financial Mechanism		✓	✓								
5 Expedite/streamline the Marketing Approval of select priority antibiotics that qualify for Accelerated Review and were already approved in EU/US.	Regulatory Incentives			✓								
6 Create/enable a special funding envelope outside of the hospital budget (e.g., separate provincial or federal budget) for access to priority antibiotics.	Financial Mechanism						✓					

Notes/ Legend:
Measures are listed in the order they should be tackled, not in priority order.
Font colour indicates measures is to be tackled and mostly completed:
Within 1 year of receiving Phase 2 funding
Within 2-3 years of receiving Phase 2 funding
Within 3-4 years of receiving Phase 2 funding

			General Issues						Access to antibiotics that are not marketed in Canada			Stewardship	
			1	2	3	4	5	6	7a	7c	7f	8	9
	Recommended Measure	Stream	No concrete actions on AMR/AR	Limited number of new antibiotics	Limited availability of new antibiotics in Canada	Lack of data	Information on newer antibiotics sparse	Hospital budgets not sufficient	Lack of awareness (SAP)	Length of time required	No time for 'external' process	Deficits in resources/ tools	Challenges associated with diagnostics
7	Create/enable a special funding envelope outside of the hospital budget (e.g., separate provincial or federal budget) for diagnostic testing supporting AMR stewardship (e.g., access to a newer agent's automated test versus a manual susceptibility testing).	Financial Mechanism						✓					✓
8	Gather data from health centres where antibiotics of interest are already in use (in Canada or internationally) to inform 1) inclusion decision for AAC initiative across phases; 2) providers on specifications of newer drugs (e.g., indication, efficacy).	Antibiotics; Stewardship; Data					✓					✓	
9	Establish national requirements for yearly submissions of relevant data - incl., bacterial pathogens / infections, corresponding indicated antibiotic(s), adverse events, efficacy, resistance.	Data				✓	✓						
10	Establish a systematic process at the F/P/T levels to assess and disseminate evidence/ recommendations related to antibiotics recently approved for sale in Canada in view to inform formulary decisions by P/Ts and hospitals.	Antibiotics; Stewardship					✓					✓	
11	Establish data collection and reporting systems for a more ubiquitous accessibility to data - e.g., bacterial pathogens / infections, corresponding indicated antibiotic(s), adverse events, efficacy, resistance - to enable routine clinical decisions and improve overall programs.	Data; Technology				✓	✓						
12	Leveraging information systems, establish mechanism to: ❑ ensure up-to-date information about antibiotics/diagnostic tests for rare infections are available to providers - incl., location of accredited testing facilities ❑ share summaries of evidence for recently approved/unapproved novel antibiotics ❑ support clinical practice and stewardship (e.g., updated hospital formulary, guidelines, antibiogram and other relevant data; alerts when an antibiotic is dispensed; guidance with prescribing); ❑ provide user-defined reports with relevant data/statistics.	Antibiotics; Data; Stewardship; Technology				✓	✓		✓	✓	✓	✓	✓
13	Streamline distribution by leveraging/implementing a central information system to place orders, track/manage inventories and backlogs, as well as collect usage-related data across a region, province/territory, or the country.	Antibiotics; Data; Technology						✓					
14	Establish 'Canada-centric' banks of resistant isolates for susceptibility testing and diagnostics validation.	Data; Stewardship				✓						✓	✓
15	Develop a Communications Plan and target messaging according to audiences (e.g., ID specialist, Pharmacist, Administrators) to improve awareness/know-how amongst those who may interact with AAC initiative and peripheral programs (e.g., SAP).	Governance/ Project & Program Management							✓			✓	
16	Support SAP request process by enabling electronic submissions via AAC Initiative (incl., ability to assign/modify request priority and handling status) and by guiding providers throughout request submission (e.g., manufacturing details; approval by the manufacturer for drugs such as cefiderocol).	Antibiotics; Technology								✓			
17	Establish measures to reduce time lags to access essential antibiotics that are not marketed in Canada - e.g., stocking quantities of those most requested on Canadian soil, digitize process to obtain manufacturer approval (or remove requirement altogether) and ordering once approved by HC/manufacturer.	Antibiotics; Technology											
18	Develop 'Hospital Antibiotic Stocking Guidelines' for priority antibiotics and operationalized across sites.	Antibiotics; Stewardship						✓				✓	
19	Review existing stewardship programs/tools and establish 'net new' or strenghten as/where applicable.	Stewardship										✓	

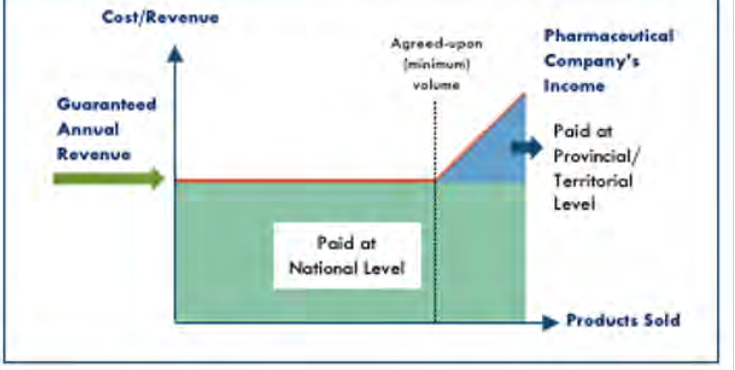
Notes/ Legend:
Measures are listed in the order they should be tackled, not in priority order.
Font colour indicates measures is to be tackled and mostly completed:
Within 1 year of receiving Phase 2 funding
Within 2-3 years of receiving Phase 2 funding
Within 3-4 years of receiving Phase 2 funding

	Recommended Measure	Stream	General Issues						Access to antibiotics that are not marketed in Canada			Stewardship	
			1	2	3	4	5	6	7a	7c	7f	8	9
			No concrete actions on AMR/AR	Limited number of new antibiotics	Limited availability of new antibiotics in Canada	Lack of data	Information on newer antibiotics sparse	Hospital budgets not sufficient	Lack of awareness (SAP)	Length of time required	No time for 'external' process	Deficits in resources/ tools	Challenges associated with diagnostics
20	Assess opportunities to expand capacity by adding new distribution centres or leveraging existing depots for antibiotics most needed in the country	Antibiotics						✓					
21	Establish 'Just in Time' (JIT) delivery and replenishment processes using essential newly-established antibiotic demand forecasts for priority antibiotics.	Antibiotics						✓					
22	Work with hospitals to ensure that all priority antibiotics are included in their respective formularies.	Antibiotics						✓					
23	Increase the availability of rapid diagnostics (e.g., susceptibility tests) at point-of-care, and appropriately pair them with antibiotics where feasible .	Stewardship; technology						✓				✓	✓
24	Collaborate with international entities to define solutions to establish demand, value and procurement standards related to novel antibiotics.	Governance/ Project & Program Management	✓	✓									
25	Develop and publish comprehensive reports related to antibiotic resistance, susceptibility and usage/demand for certain antibiotics to enable market access and other operational/provisioning decision by manufacturers.	Antibiotics; Data		✓	✓	✓	✓						
26	Establish national forecasts of antibiotics required by Canadian patients (incl., for those approved/not approved, older/newer, and not yet in the pipeline).	Antibiotics; Data		✓		✓	✓						
27	Invest in Canadian R&D efforts supporting: ❑ efficient/cost-effective strategies (e.g., partnerships with accelerators/incubators like CARB-X) ❑ development of antibiotics that will treat infections caused by 'priority' pathogens as identified by HC ❑ innovative solutions/ technologies that may be used as an alternative solution to the use of antibiotic ❑ local production of API required for essential antibiotics ❑ use of diagnostic technologies for/with priority antibiotics to optimize appropriate use.	Antibiotics; Technology (diagnostics)		✓									
28	Work with hospital administrators and providers to further identify/define access barriers and determine whether systematic solutions may be applied by the AAC initiative.	Antibiotics						✓				✓	✓
29	Collaborate with partners to harmonize the Marketing Approval / HTA processes to: ❑ include the systematic consideration of programmatic factors such as economics, ethics, equity, feasibility and antibiotic acceptability in developing evidence-based recommendations ❑ reduce costs and overall length of market entry process.	Regulatory Incentives			✓								
30	Develop and establish an antiotic valuation model that reflects public health and stewardship benefits.	Regulatory Incentives		✓	✓								✓

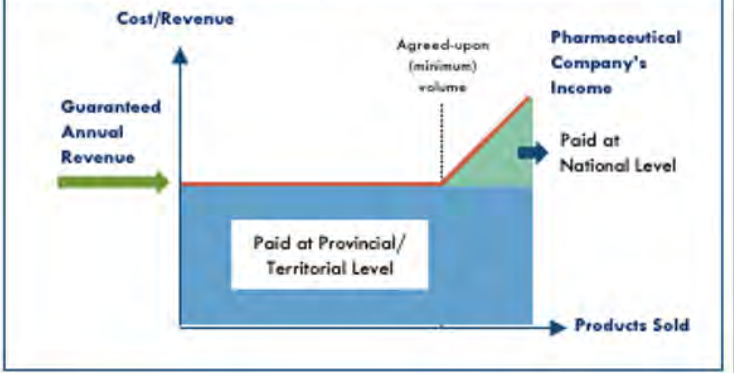
** Under the AMR Governance umbrella if/when it is established.*

APPENDIX 11: OTHER GUARANTEED REVENUE PAYMENT OPTIONS CONSIDERED

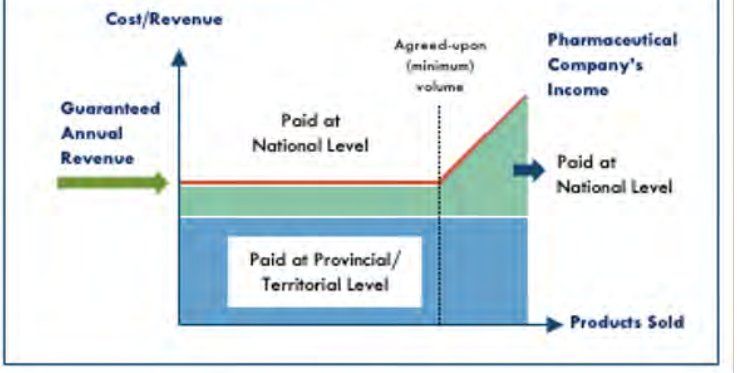
Option 1 – P/Ts only pay for delta for anything sold beyond guaranteed revenue/ agreed-upon volume



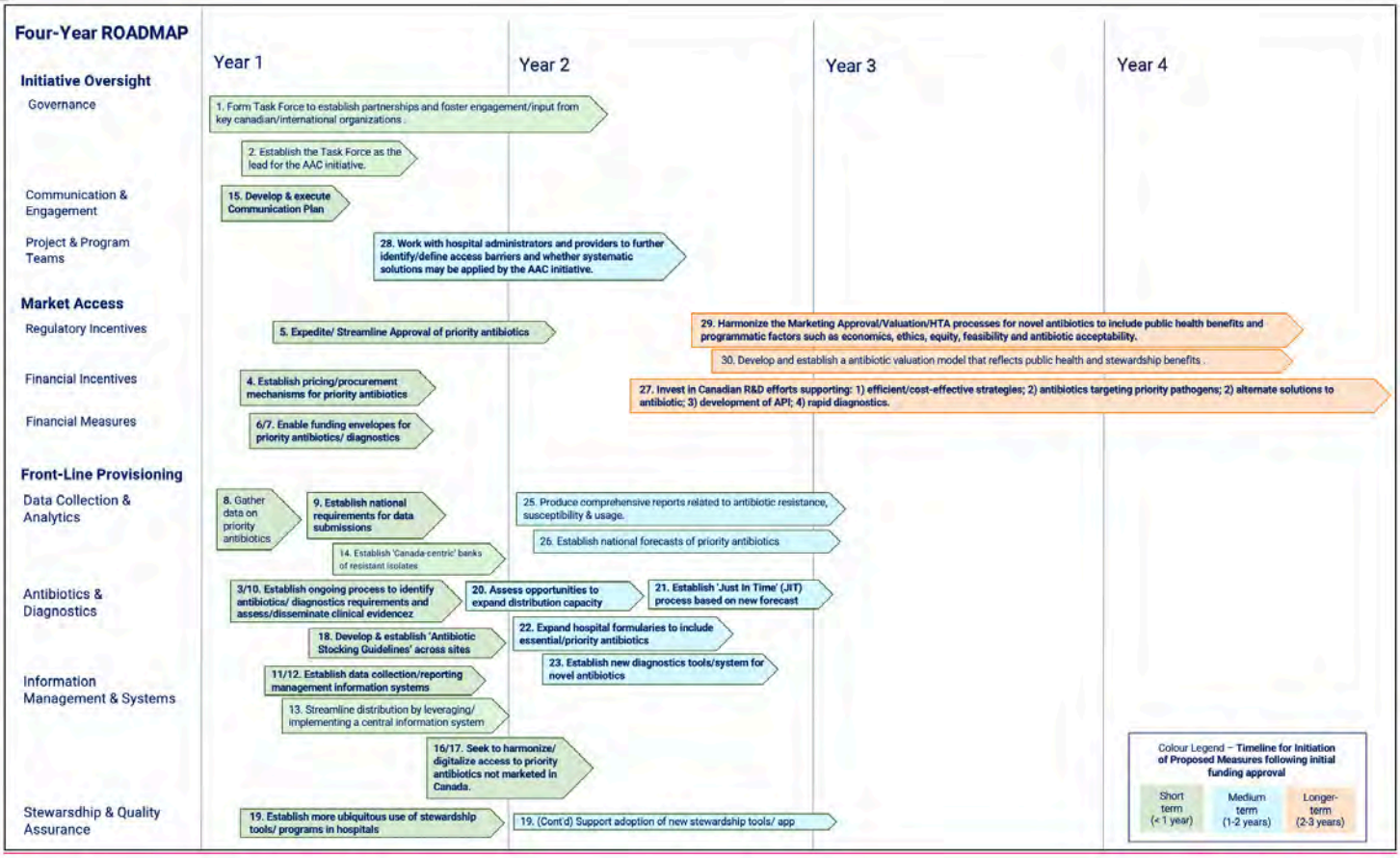
Option 2 – Federal level pays for products sold beyond guaranteed revenue/ agreed-upon volume



Option 3 – Federal level pays for delta between 'average product price' and agreed upon list price for all products sold*



APPENDIX 12: RECOMMENDATIONS IMPLEMENTATION ROADMAP



APPENDIX 13: SAMPLE STEWARDSHIP APP – FIRSTLINE

Firstline, a Stewardship solution vendor already established in several hospitals in Canada, kindly provided this proposal in support of our proposed Stewardship program objectives.

Challenges

1. Providers lack the guidance for appropriate prescribing at the point of care
2. Hospitals don't have the resources to build, maintain and/or provide effective guidance to their providers
3. Hospitals and providers may lack the knowledge of novel antibiotics or how to implement their use

Goals

1. Improve antimicrobial prescribing across Canada
2. Make it easy for every hospital in Canada to learn about novel antibiotics, add them to their formulary and implement them in their practice

Solution

- An end to end solution to help hospitals build guidelines based on the latest evidence and deliver it to their providers.

Discover & discuss new information

- Discussions is a focused space for infectious diseases professionals across Canada to have in-depth conversations on the latest evidence and complex clinical questions.
- Community Library allows hospitals and organizations to share clinical resources, including treatment guidelines, new pathogens and novel antibiotics.

Develop local guidance based on the latest evidence

- Content builder allows hospitals to create interactive clinical guidelines that are optimized for the point of care.
- With Community Library, hospitals can easily discover & adapt clinical resources from other organizations.
- Content subscriptions notify hospitals when the original source has updated a copied guideline or monograph. It allows hospitals to merge those updates while preserving local changes--keeping their resources always up-to-date.

Deliver real-time guidance to providers

- Mobile and web apps, designed for use at the point of care. Algorithmic, just the right amount of information and always accessible (even without wifi).
- Providers have access to trusted information from their hospital that includes treatment guidelines, formulary information (incl. novel antibiotics) and resistance data.

Results

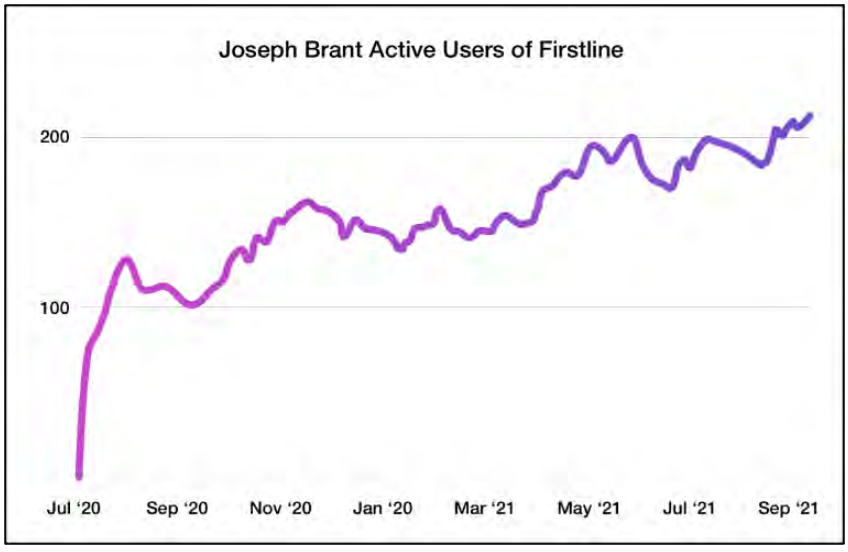
- Hospitals are significantly improving prescribing behaviour by using Firstline. We believe that making succinct local guidelines designed for use at the point of care leads to higher uptake of guidance among providers, and better prescribing decisions. The result is less antimicrobial use overall, leading to less C.difficile infections and ultimately, significant savings for hospitals many times the cost of Firstline.

Results

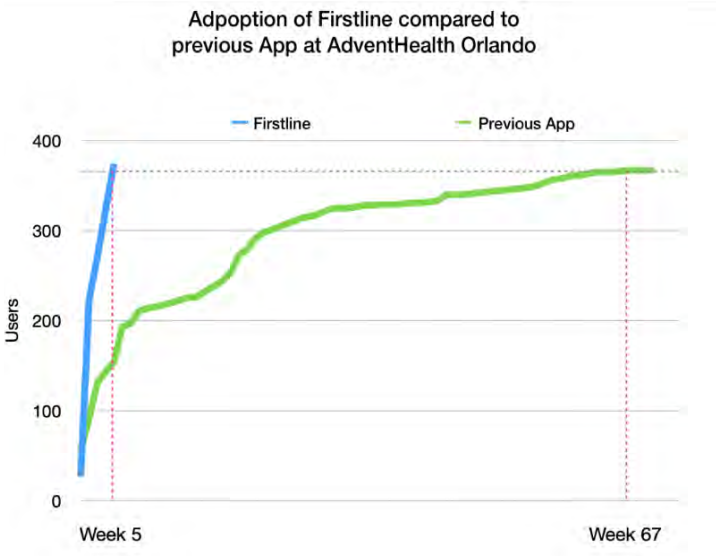
- Increases use of guidance.

Joseph Brant Hospital, a customer and member of the Hamilton Niagara Haldimand Brant LHIN, launched Firstline in July 2020 to deliver antimicrobial prescribing and COVID guidelines to 194 physicians.

At launch, they had an immediate surge of active users (over 100 in the first month) followed by long-term sustained use.



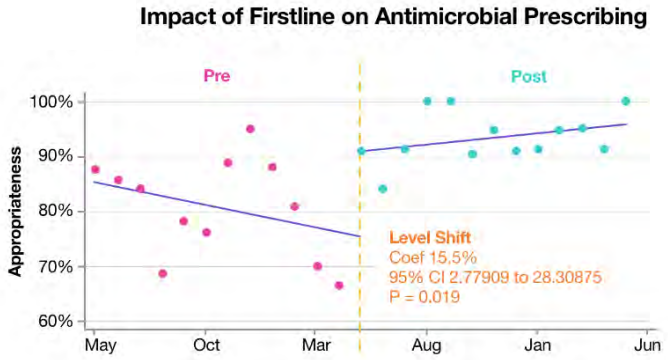
Before the implementation of Firstline, AdventHealth Orlando was using a different mobile application to deliver guidelines to their providers. After switching to Firstline, they reached the same user activity in only a fraction of the time.



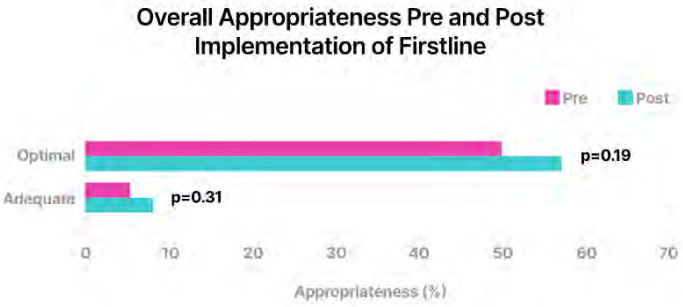
Results:

- Increases appropriate prescribing.

IWK Health Centre in Nova Scotia measured an immediate 18% increase in appropriateness, resulting in over 90% appropriateness. At present, IWK has over 1,000 providers actively using their guidelines on Firstline. Pre-publication of Evaluating Impact of Incorporating Clinical Practice Guidelines for Management of Infectious Diseases into an Electronic Application.



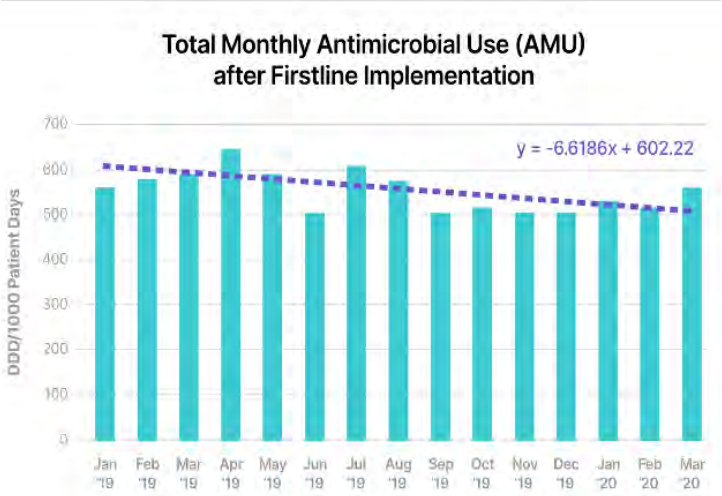
Eastern Health in Newfoundland measured an increase in optimal and adequate prescribing, resulting in significant reductions of antimicrobial utilization. This according to a publication of Impact of a mobile decision support tool on antimicrobial stewardship indicators in St. John's, Canada.



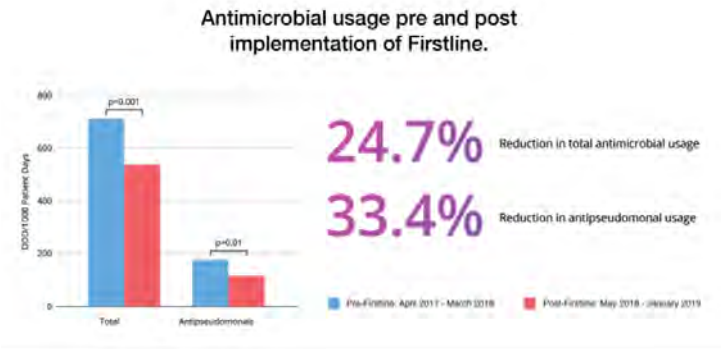
Results:

- Reduces utilization of antimicrobials.

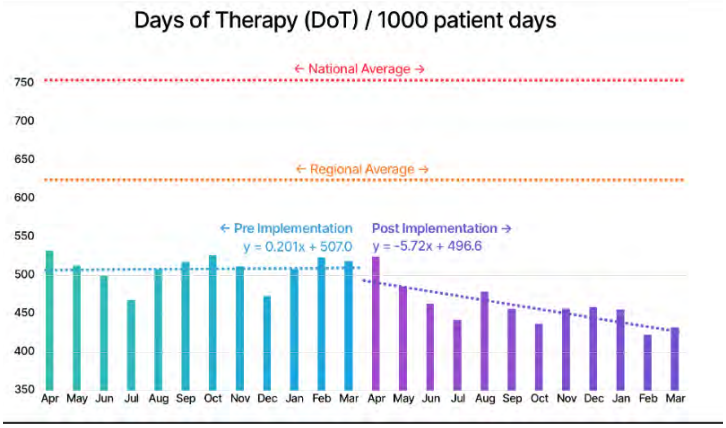
Over a 12-month period, Eastern Health measured a reduction in antimicrobial utilization by 6.6 DDD/1000 patient days per month. This according to a publication of impact of a mobile decision support tool on antimicrobial stewardship indicators in St. John's, Canada.



After the implementation of Firstline, Saskatoon Health Area observed a significant reduction of antimicrobial use (25%) with over 700 active users of the platform.



Eastern Maine Medical Center (EMMC) previously had stable antimicrobial utilization that was already below the regional average. After implementing Firstline, EMMC observed an even further reduction in antimicrobial use and received the Antimicrobial Stewardship Center of Excellence designation from the Infectious Disease Society of America. From an article, "Creating a Culture of Antimicrobial Stewardship."



Results:

- Lowers hospital-acquired infections.

Eastern Health determined the impact of regional implementation of the app on population-based Clostridioides difficile infection (CDI) rates and cost, including a one-year study period. The pre-survey included 184 prescriptions, and the post-survey included 197 prescriptions. CDI declined by 0.3 cases per month, resulting in 10 cases avoided.

Results:

- Saves hospitals' money.

Eastern Health saw significant cost savings associated with reduced AMU, resulting in $403.98 saved per bed per year ($222K) and reduced CDI, resulting in $148.96 saved per bed per year ($82K).

Using Firstline, hospitals across Canada have reported a pattern of cost reductions due to reduced antimicrobial use and C.diff avoidance.

Annual *C.diff* cost savings

Firstline Customer	Beds	Cases Avoided	Cost avoided (est. $12K/case)	Savings/bed
12-hospital system	2383	52	$624K	$261
2-hospital system	551	7	$82K	$149
Total	**2934**	**59**	**$706K**	**$240**

Annual antimicrobial cost savings

Firstline Customers	Beds	Hospitals	Abx savings	Savings/bed
12-hospital system	2383	12	$500,000	$210
Acute care hospital	70	1	$13,749	$196
3-hospital system	676	3	$121,000	$179
12-hospital system	2591	12	$736,790	$284
2-hospital system	551	2	$222,053	$403
Total	**6271**	**30**	**$1,593,592**	**$254**

Results:

- Saves hospitals' time via reduced need for interventions.

An antimicrobial stewardship program in Canada observed a significant reduction in interventions. On average, it is estimated to take 10 minutes to do an intervention. The result of lowered interventions saved over 400 person hours.

	Intervention rate	Interventions	Person hours
Before implementation	50.84%	6404	1067
After implementation	31.18%	3928	654
Savings			**413**

Time saved creating guidelines

On average, hospitals have 30 different clinical guidelines for treating infectious diseases. It takes hospitals approximately 150 hours to create each guideline (4,500 hours total). When hospitals have copied & adapted guidelines from the Firstline Library, it has saved them over 120 hours for each guideline. If all 30 guidelines are copied and adapted, this results in over 3,600 hours saved.

Background Information

Overview

Firstline is the highest-rated mobile platform for infectious diseases, used by over 100,000 healthcare providers. Firstline empowers providers with the latest guidelines for the treatment and management of infectious diseases, including COVID-19. With a primary focus on information design and ease of use, Firstline has seen high adoption and usage rates, 98% provider satisfaction and over a million clinical decisions made.

Platform

The Firstline Platform allows healthcare organizations to deliver customizable clinical guidelines to their frontline healthcare providers. Using a proprietary web-based application, administrators are able to rapidly create and update guidelines, formulary information and resistance data, which are instantaneously delivered to end users through a mobile app available for both iOS and Android devices. Healthcare organizations can send messages to every healthcare worker's phone, ensuring that critical alerts and protocol changes are not missed.

Antimicrobial Resistance

Firstline is an award-winning global technology leader in the fight to tackle antimicrobial resistance, working with 100s of hospitals and healthcare organizations around the world and empowering prescribers to reduce antimicrobial misuse. Through the use of the Firstline Platform, healthcare organizations have seen over 25% reductions in prescribing and up to 90% appropriateness of prescribing.

Global Presence

Firstline is the provincially adopted platform for Saskatchewan, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland and Yukon and is used by 100s of hospitals and healthcare organizations in Ontario, Alberta, British Columbia and Quebec to deliver clinical guidance to over 30,000 healthcare providers. Our experience with these rollouts have demonstrated the power of our collaborative mobile platform to expedite the creation and dissemination of critically important clinical guidance directly to healthcare providers. Firstline is used around the world, currently working with over 300 hospitals across 11 countries and rapidly growing. Firstline works with global partners including the World Health Organization, Food and Agricultural Organization, Oxford University, New York City Department of Health, Université de Genève, AdventHealth and UCLA.

Firstline Community

The current healthcare ecosystem is disconnected as hospitals, clinical experts, providers, public health and industry often work in silos. To address this issue, Firstline has developed a global platform that empowers healthcare organizations and clinical leaders to collaborate and improve the diagnosis and treatment of infectious diseases. In doing so, the Firstline platform has opened up to include public health, industry and clinical experts to create the most advanced clinical decision support platform; an ecosystem that includes every stakeholder.

How can Firstline help this project?

The Firstline Library was purpose-built to facilitate the sharing and maintenance of guidance and clinical resources between organizations. The project team will have the ability to create monographs for novel antibiotics that can be shared with hospitals participating in the project. The participating institutions are then able to integrate these antibiotic monographs directly into their local formulary and guidelines.

Firstline Subscriptions makes it easy for participating hospitals to stay up-to-date with the latest updates to the novel antibiotic monographs provided by the project team. The project team will have the ability to update information centrally and push out updates to all participating hospitals. Once accepted, these updates will be merged into the hospital's own formulary and guidelines and disseminated directly into the hands of their providers.

The project team and participating hospitals will have the ability to track what groups of providers and the frequency at which they are referencing the drug monographs. Additional data can be collected using in-app surveys and forms.

The Firstline Community also offers a space for the project team and participating hospitals to actively discuss questions and provide feedback in private or open forums.

Testimonials: embraced by providers & ASPs

- "This is one of the best evidence-based medicine programs that I use." - ASP Lead
- "Great resource for local data and abx prescribing. So convenient to have the app at your fingertips." - App Store
- "The reach we have achieved with Firstline is bigger than we could have imagined and helps us to empower and engage users. It's really phenomenal how mobile apps and technology can change behavior." - ASP Lead
- "Fantastic Point of Care Tool - must have for ER and IM physicians. Use this augmented approach to ensure proper antibiotic stewardship." - App Store
- "Firstline has been great at responding to our needs. When we ask for something they adjust it and push it out there. The responsiveness is one of the biggest benefits of this program." – Physician

Contact information

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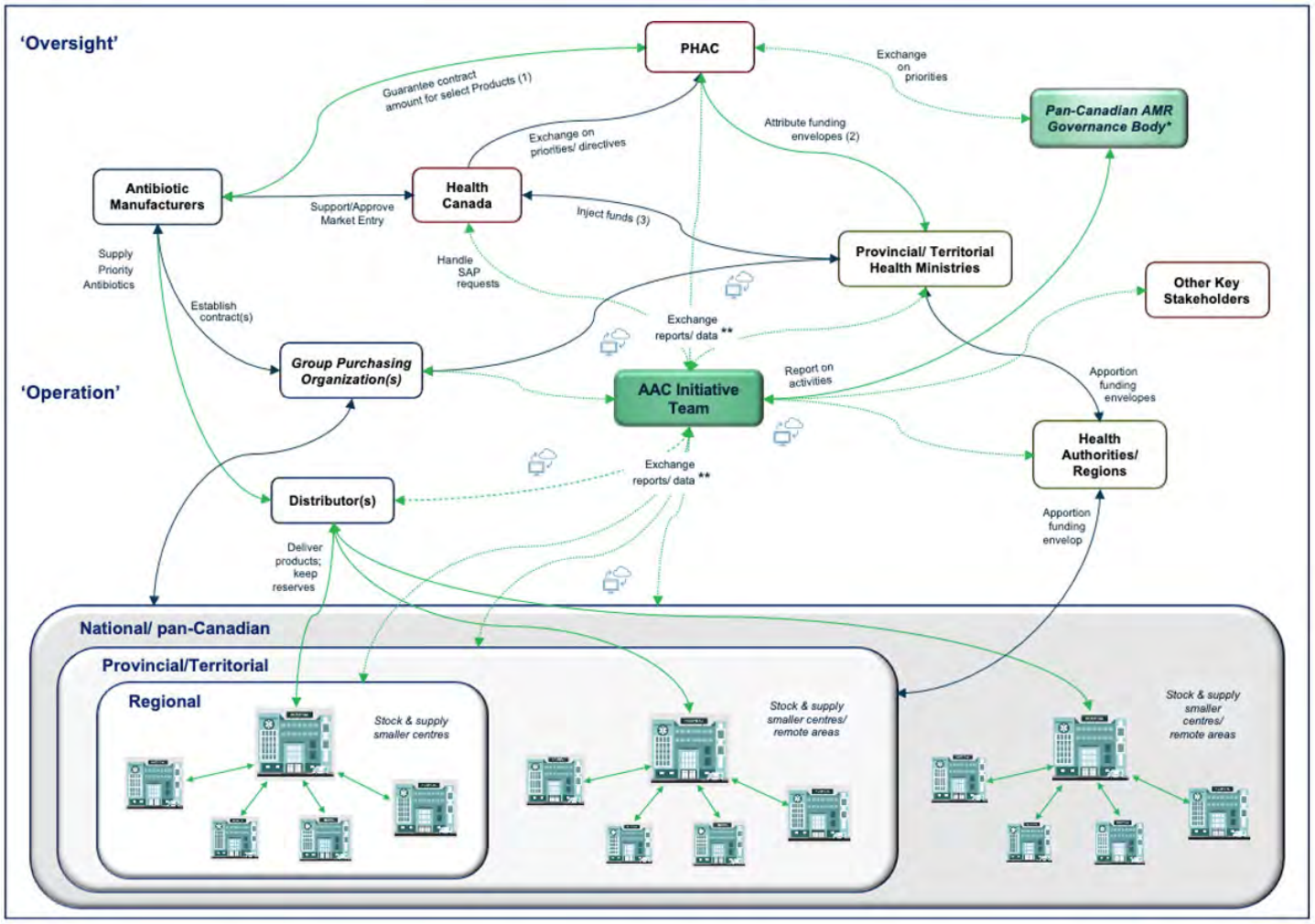
APPENDIX 14: A SECOND INTEGRATED SOLUTION OPTION WE CONSIDERED



LEGEND

- Arrows and the corresponding text boxes between entities are meant to illustrate relationships in the context of the *AAC initiative* only.
  - ◄► indicates a relationship that already exists and that may/may not remain the same per the proposed model.
  - ◄► indicates a new relationship or a new activity within an existing relationship.
  - ◄- -► indicates a relationship that is more 'informational' than 'transactional'.
- Text boxes highlight the key function of the entity or relationship between organizations and are not meant to identify all functions.

Refers to an information system being used to support processes and information/data* transfer between stakeholders

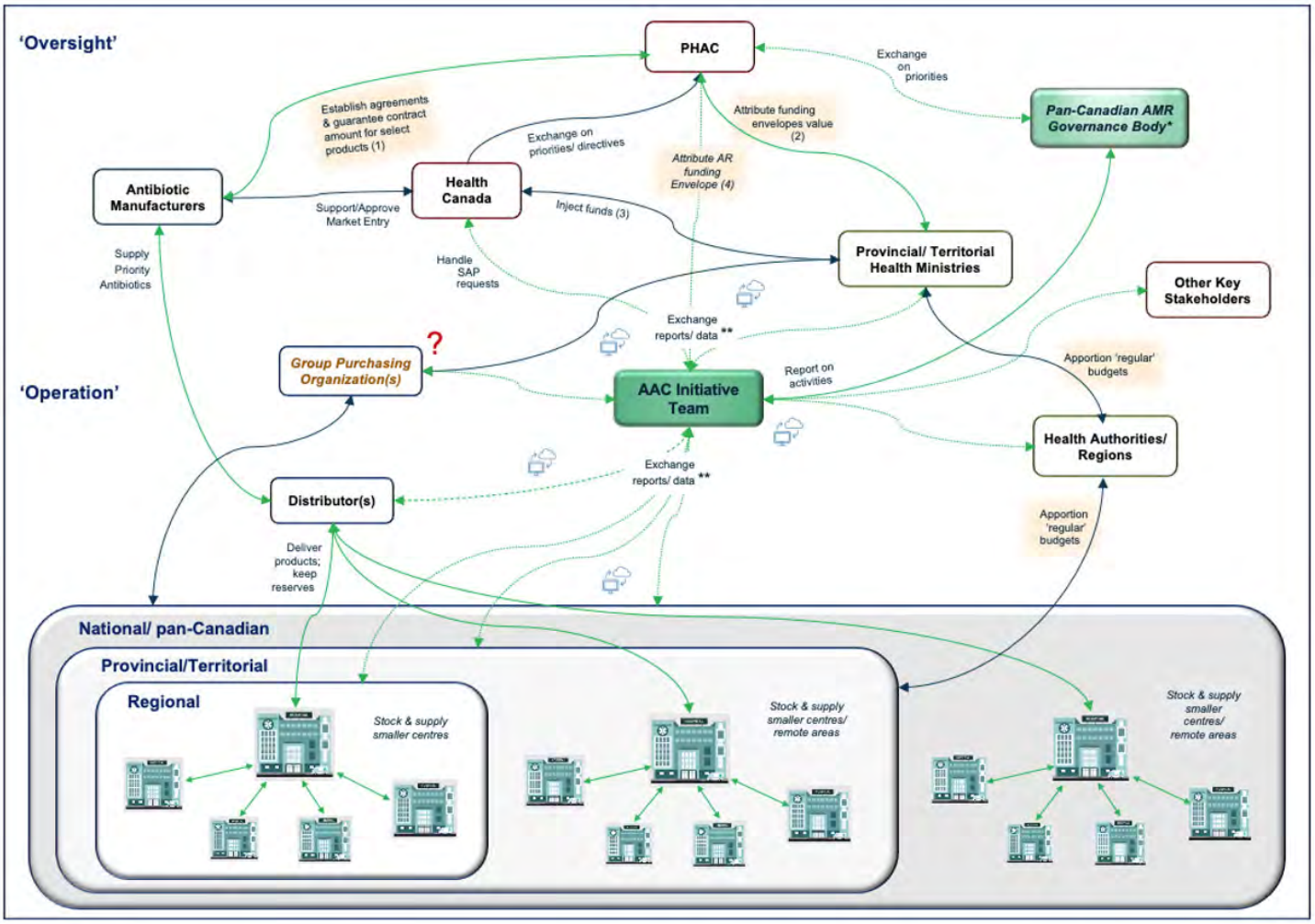
- Green and grey boxes, such as those below, indicate a new entity, process or measure to be established under this initiative.
- The grey boxes also correspond to these deployment timelines/geographical areas:

Phase 2 (Pilot) – **HNHB**	Phase 3 – **Rest of Ontario**	Phase 4 – **Rest of Canada**

* If/when the proposed AMR Governance Centre or Network is implemented.

** *Data to include:* Bacterial pathogens / infections, lab results/diagnosis, corresponding indicated antibiotic(s), adverse events, efficacy, resistance, utilisation, and costs

Key Differences between the selected model and the second considered are highlighted in yellow below:



LEGEND

- Arrows and the corresponding text boxes between entities are meant to illustrate relationships in the context of the *AAC initiative* only.
  - indicates a relationship that already exists and that may/may not remain the same per the proposed model.
  - indicates a new relationship or a new activity within an existing relationship.
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** *Data to include:* Bacterial pathogens / infections, lab results/diagnosis, corresponding indicated antibiotic(s), adverse events, efficacy, resistance, utilisation, and costs

APPENDIX 15: ESTIMATED SUMMARY OF COSTS

Option 1 – Minimum Effort

Estimated Costs [1]	Option 1 - Effort: Minimum in Phase 2 / Greater in Phase 3 (36-42 months)			
Project Costs (Implementation)	**Phase 2 - HNHB (Pilot)**	**Phase 3 - a. Rest of Ontario**	**Phase 3 - b. Rest of Canada**	**TOTAL**
Resources Time				
Contract Award/Teaming	$ 51,144	$ 15,343	$ 25,572	**$ 92,058**
Initiation	575,365	575,365	575,365	**1,726,094**
Planning	671,259	671,259	671,259	**2,013,777**
Vendor/Systems Selection	95,894	23,974	-	**119,868**
Execution				
STREAM 1 - Project Governance & Management	1,598,236	6,392,942	19,178,827	**27,170,005**
STREAM 2 - Data collection & Analytics	255,718	306,861	460,292	**1,022,871**
STREAM 3 - Antibiotics & Diagnostics	95,894	23,974	47,947	**167,815**
STREAM 4 - Incentives & Financial Measures	127,859	191,788	332,433	**652,080**
STREAM 5 - Stewardship & Quality Assurance	255,718	281,289	383,577	**920,584**
STREAM 6 - Information Management Systems	239,735	479,471	958,941	**1,678,147**
STREAM 7 - Integration, Evaluation & Continuous Improvement	127,859	127,859	255,718	**511,435**
Go Live Preparation & Go Live	191,788	287,682	767,153	**1,246,624**
Post-Go Live	255,718	383,577	767,153	**1,406,447**
Subtotal: Resources	**$ 4,542,186**	**$ 9,761,384**	**$ 24,424,236**	**$ 38,727,806**
Other Resources-related Expenses				
Hardware & Software [2]	$ 40,000	$ -	$ 8,000	**$ 48,000**
Travel [3]	716,100	1,074,150	2,148,300	**3,938,550**
Subtotal: Resources Time & Travel Expenses	**$ 5,298,286**	**$ 10,835,534**	**$ 26,580,536**	**$ 42,714,356**
Information Systems - Set up				
Stewardship Application [4]	$ 30,000	$ 510,000	$ 1,170,000	**$1,710,000**
Ordering/Distribution System [5]	60,000	88,000	88,000	**236,000**
Interfaces / Integrations [6]	200,000	400,000	600,000	**1,200,000**
Subtotal: Information Systems	**$ 290,000**	**$ 998,000**	**$ 1,858,000**	**$3,146,000**
Total Implementation Costs	$ 5,588,286	$ 11,833,534	$ 28,438,536	$ 45,860,356
Contingency [7]	**$ 558,829**	**$ 1,775,030**	**$ 5,687,707**	**$8,021,566**
Total Implementation Costs (minus Salaried Resources)	**$ 3,432,434**	**$ 10,893,884**	**$ 31,411,564**	**$ 51,167,242**

Program Costs (Operation)	Phase 2 - HNHB (Pilot) [8]	Phase 3 - a. Rest of Ontario	Phase 3 - b. Rest of Canada	TOTAL
AAC Team/Operation				
Salaries over 3 years (Including Benefits)				
Direction	$ 88,500	$ 177,000	$ 265,500	**$ 531,000**
Clinical Expertise/ Core Team	295,833	250,322	725,363	**1,271,518**
Support Services	74,488	171,100	223,463	**469,050**
Subtotal: Salaries	**$ 458,821**	**$ 598,422**	**$ 1,214,325**	**$ 2,271,568**
Additional Staff-related Operating Costs				
Building Occupancy - Room Rental [9]	$ -	$ 7,200	$ 10,800	**$ 18,000**
Professional Services	-	4,495	6,743	**11,238**
Technology & Telecommunications [10]	-	68,639	102,959	**171,598**
Training & Development	*See Implementation*	18,000	27,000	**45,000**
Travel	*See Implementation*	121,950	182,925	**304,875**
Subtotal: Staff/Operational Costs	**$ -**	**$ 220,284**	**$ 330,426**	**$ 550,710**
Total: AAC Team	**$ -**	**$ 818,706**	**$ 1,544,751**	**$ 2,822,278**
Other Program Costs				
Products Costs				
Antibiotics [11]	$ 655,070	$ 5,726,968	$ 17,354,448	$ 23,736,486
Diagnostics -Not Available at present [12]	TBD	TBD	TBD	TBD
Subtotal: Resources	**$ 655,070**	**$ 5,726,968**	**$ 17,354,448**	**$ 23,736,486**
Information Systems - Licensing				
Stewardship Application [13]	$ 87,575	$ 771,350	$ 1,765,275	$2,624,200
Ordering/Distribution System [14]	25,000	60,000	60,000	145,000
Subtotal: Information Systems	**$ 112,575**	**$ 831,350**	**$ 1,825,275**	**$ 2,769,200**
Total Operational Costs	**$ 767,645**	**$ 7,377,024**	**$ 20,724,474**	**$ 29,327,964**
Contingency [7]	**$ 76,764**	**$ 1,106,554**	**$ 4,144,895**	**$ 5,328,213**
TOTAL COSTS (Implementation & Operation)	**$ 6,991,524**	**$ 22,092,142**	**$ 58,995,613**	**$ 88,538,099**
TOTAL COSTS - Minus Salaried Resources (Implementation)	**$ 4,276,844**	**$ 19,377,462**	**$ 56,280,933**	**$ 85,823,419**

Option 2 – Optimum Effort

Estimated Costs [1]	Option 2 - Effort: Optimized in Phase 2 / Distributed in Phase 3 (42-48 months)			
Project Costs (Implementation)	**Phase 2 - HNHB (Pilot)**	**Phase 3 - a. Rest of Ontario**	**Phase 3 - b. Rest of Canada**	**TOTAL**
Resources Time				
Contract Award/Teaming	$ 76,715	$ 23,015	$ 38,358	**$ 138,088**
Initiation	863,047	863,047	863,047	**2,589,142**
Planning	1,006,888	1,006,888	1,006,888	**3,020,665**
Vendor/Systems Selection	143,841	35,960		**179,802**
Execution				
STREAM 1 - Project Governance & Management	2,397,353	4,195,368	25,172,211	**31,764,932**
STREAM 2 - Data collection & Analytics	575,365	632,901	772,140	**1,980,406**
STREAM 3 - Antibiotics & Diagnostics	143,841	35,960	71,921	**251,722**
STREAM 4 - Incentives & Financial Measures	287,682	287,682	460,292	**1,035,657**
STREAM 5 - Stewardship & Quality Assurance	383,577	383,577	498,650	**1,265,803**
STREAM 6 - Information Management Systems	359,603	719,206	1,078,809	**2,157,618**
STREAM 7 - Integration, Evaluation & Continuous Improvement	191,788	191,788	383,577	**767,153**
Go Live Preparation & Go Live	287,682	431,524	1,150,730	**1,869,936**
Post-Go Live	383,577	575,365	1,150,730	**2,109,671**
Subtotal: Resources	**$ 7,100,961**	**$ 9,382,282**	**$ 32,647,350**	**$ 49,130,593**
Other Resources-related Expenses				
Hardware & Software [2]	$ 40,000	$ -	$ 8,000	**$48,000**
Travel [3]	540,525	810,788	2,702,625	**4,053,938**
Subtotal: Resources Time & Travel Expenses	**$ 7,681,486**	**$ 10,193,070**	**$ 35,357,975**	**$ 53,232,531**
Information Systems - Set up				
Stewardship Application [4]	$ 30,000	$ 510,000	$ 1,170,000	**$ 1,710,000**
Ordering/Distribution System [5]	72,000	100,000	120,000	**292,000**
Interfaces / Integrations [6]	400,000	400,000	400,000	**1,200,000**
Subtotal: Information Systems	**$ 502,000**	**$ 1,010,000**	**$ 1,690,000**	**$ 3,202,000**
Total Implementation Costs	$ 8,183,486	$ 11,203,070	$ 37,047,975	$56,434,531
Contingency [7]	**$ 818,349**	**$ 1,680,461**	**$ 7,409,595**	**$ 9,908,404**
Total Implementation Costs (minus Salaried Resources)	**$ 6,287,155**	**$ 10,168,851**	**$ 41,742,890**	**$63,628,255**

Program Costs (Operation)	Phase 2 - HNHB (Pilot)	Phase 3 - a. Rest of Ontario	Phase 3 - b. Rest of Canada	TOTAL
AAC Team/Operation				
Salaries over 3 years (Including Benefits)				
Direction	$ 88,500	$ 177,000	$ 265,500	**$ 531,000**
Clinical Expertise/ Core Team	295,833	250,322	725,363	**1,271,518**
Support Services	74,488	171,100	223,463	**469,050**
Subtotal: Salaries	**$ 458,821**	**$ 598,422**	**$ 1,214,325**	**$ 2,271,568**
Additional Staff-related Operating Costs				
Building Occupancy - Room Rental [9]	$ -	$ 7,200	$ 10,800	**$18,000**
Professional Services	-	4,495	6,743	**11,238**
Technology & Telecommunications [10]	-	68,639	102,959	**171,598**
Training & Development	*See Implementation*	18,000	27,000	**45,000**
Travel	*See Implementation*	121,950	182,925	**304,875**
Subtotal: Staff/Operational Costs	**$ -**	**$ 220,284**	**$ 330,426**	**$ 550,710**
Total: AAC Team	**$ -**	**$ 818,706**	**$ 1,544,751**	**$ 2,822,278**
Other Program Costs				
Products Costs				
Antibiotics [11]	$ 1,310,140	$ 11,453,936	$ 34,708,897	**$47,472,972**
Diagnostics -Not Available at present [12]	TBD	TBD	TBD	TBD
Subtotal: Resources	**$ 1,310,140**	**$ 11,453,936**	**$ 34,708,897**	**$ 47,472,972**
Information Systems - Licensing				
Stewardship Application [13]	$ 87,575	$ 771,350	$ 1,765,275	**$ 2,624,200**
Ordering/Distribution System [14]	25,000	60,000	60,000	**145,000**
Subtotal: Information Systems	**$ 112,575**	**$ 831,350**	**$ 1,825,275**	**$ 2,769,200**
Total Operational Costs	**$ 1,422,715**	**$ 13,103,992**	**$ 38,078,923**	**$ 53,064,451**
Contingency [7]	**$ 142,271**	**$ 1,965,599**	**$ 7,615,785**	**$ 9,723,655**
TOTAL COSTS (Implementation & Operation)	**$ 10,566,821**	**$ 27,953,121**	**$ 90,152,277**	**$ 129,131,040**
TOTAL COSTS - Minus Salaried Resources (Implementation)	**$ 7,852,141**	**$ 25,238,442**	**$ 87,437,597**	**$ 126,416,360**

Notes & Assumptions for Cost Charts in Appendix 15

1. At this stage, requirements are still high-level so costs were generally 'grossly' estimated based on previous experience with such implementations/deployments - they will need to be validated once requirements are refined. The team has greater confidence in the initial implementation (Pilot) estimates than the estimates for the subsequent phase stages because the later present a greater number of 'unknowns' at this point.
2. These include equipment for the Program Team, which can be capitalized and included in Project Costs.
3. Includes travel for the Consulting members of the Project Team as well as for the Program Team, assuming that they will be required to travel to 'client sites' (unlike the Salaried members of the Project Team who are already onsite).
4. Costs provided by Firstline, which has deployed its Stewardship Application across Eastern Health in Nova Scotia and a few hospitals within HNHB in Ontario.
5. Assumption is that initial configuration cost for Option 1 will be on the lower end quoted by CPDN due to minimal scope in Year 1, but will increase as more information is obtained from other stakeholders in the later stages of deployment, while it will be higher in Option 2 at the beginning but less in subsequent stages as a greater pan-Canadian effort will have been completed front and less changes will be required later.
6. Simple interfaces only may be possible, but budget allows for deeper integrations, which would be desirable in some cases (e.g., analytics components to extract data from Hospital EHR and ordering system. Number of systems to interact with TBD.
7. Contingency fees were established above the total fees including salaries resources at a rate of 10% for HNHB, 15% for the rest of Ontario, and 20% for the rest of Canada.
8. Salaries adjusted to a partial year; option to include time spent on 'implementation' under the Project Costs section.
9. Proposal that Program Team be virtual with opportunities to sporadically use space for meetings at client/other sites (including at McMaster, AMR governance offices). Allocation is for eventual meeting room rentals for face-to-face meetings.
10. These include administrative/corporate items — systems that are required to deliver program 'content' are included below.
11. Implies two types of antibiotics in Option 1, and four in Option 2. These will be selected by a committee of experts — ID specialists, Pharmacists, Physicians — at the beginning of Phase 2. Dollar amounts were derived from an adaptation of the partially delinked Sweden access model, thus would need to be validated and/or modified if a different model was selected. Other assumptions/ models may be applied to align with true value of antibiotics and reflect Canada's desired commitment and financial capacity to support this initiative and the overall antimicrobial market. Whether the number of units that manufacturers could supply with this figure will be sufficient to meet Canadian demand is TBD leading to Phase 2 funding allocation.
12. Because diagnostic tests report on the antibiotic that a particular infection should be susceptible to, determination of these costs will require: selection of the priority antibiotics to include in the program and assessment of current diagnostic tests 'inventory' at deployment sites so that they can purchase the number desired to test for the potential efficacy of the select antibiotics against given infections.
13. Annual fees (i.e., user licenses) are based upon CIHI's report on the number of active beds at each of the hospital where the Application is to be deployed.
14. Annual fees (i.e., user licenses) vary between $3,000-5,000 depending on reporting requirements.
15. IQVIA is a Healthcare Data Science company that collects and collates hospital data. As no response was obtained follow-ing a request for quote, this figure is an estimate and would need to be validated. Annual fees would need to be estimated.

APPENDIX 16: PROGRAM COSTS – YEARLY – FOLLOWING DEPLOYMENT

Program Costs (Operation)	TOTAL
AAC Team/Operation	
Salaries (Including Benefits)	
Direction	$ 177,000
Clinical Expertise/ Core Team	483,575
Support Services	148,975
Subtotal: Salaries	**$ 809,550**
Additional Staff-related Operating Costs	
Building Occupancy - Room Rental [1]	$ 7,200
Professional Services	4,605
Technology & Telecommunications [2]	72,781
Training & Development	22,000
Travel	156,550
Subtotal: Staff/Operational Costs	**$ 263,136**
Total: AAC Team	**$ 1,072,686**
Program-related Costs	
Information Systems - Licensing	
Stewardship Application [3]	$ 1,765,275
Ordering/Distribution System [4]	60,000
Subtotal: Information Systems	**$ 1,825,275**
Total Operational Costs	**$ 2,897,961**
Contingency [6]	**$ 434,694**
TOTAL ESTIMATED COSTS - Before cost of Antibiotics/ Diagnostics	**$ 3,332,655**
Other Program Costs	
Antibiotics Costs [7]	
Partially Delinked Model	34,708,897
TOTAL - After cost of Antibiotics - Partially Delinked	**$ 38,041,552**
Fully Delinked Model	48,409,600
TOTAL - After cost of Antibiotics - Fully Delinked	**$ 51,742,255**
Diagnostics Costs	
Not Available at present [8]	

Notes & Assumptions

1 Proposal that Program Team be virtual with opportunites to sporadically use space for meetings at client/other sites (including at McMaster, AMR governance offices). Allocation is for eventual meeting room rentals for face-to-face meetings.

2 These include administrative/corporate items - systems that are required to deliver program 'content' are included below.

3 Annual fees (i.e., user licenses) are based upon CIHI's report on the number of active beds at each of the hospital where the Application is to be deployed.

4 Annual fees (i.e., user licenses) vary between $3,000-5,000 depending on reporting requirements.

5 IQVIA is a Healthcare Data Science company that collects and collates hospital data. As no response was obtained following a request for quote, this figure is an estimate and would need to be validated. Annual fees would need to be estimated.

6 Contingency fees were established above the total fees including salaries resources at a rate of 10% for HNHB, 15% for the rest of Ontario, and 20% for the rest of Canada.

7 Implies two (2) types of antibiotics in Option 1, and four (4) in Option 2. These will be selected by a committee of experts - ID specialists, Pharmacists, Physicians - at the beginning of Phase 2.

8 Partially delinked model figures correspond to amounts derived from both an adaptation of Sweden model and the Subscription model presented by K.Outterson and were provided as starting numbers.

9 Because diagnostic tests report on the antibiotic that a particular infection should be susceptible to, determination of these costs will require 1- selection of the priority antibiotics to include in the program; 2- assessment of current diagnostic tests 'inventory' at at deployment sites - to purchase the number desired to test for the potential efficacy of the select antibiotics against given infections.

APPENDIX 17: ESTIMATED COSTS – PROJECT TEAM

As per the previous Costs Summary table, costs associated to the Project Team's time on the initiative from Year 1 to 4 (Phases 2-3) were established for each of the stages of the project. The tables enclosed in this appendix detail the anticipated resources and other assumptions used to establish overall resourcing costs.

This first table presents the costs for salaried resources for the duration of the pilot (Phase 2). Costs expected to incur over the course of Phase 3 were extrapolated from Phase 2 costs based on the expected complexity of the deployment (i.e., rest of Ontario being less complexed than Canada), as well as the team's ability to leverage materials produced in Phase 2 for the subsequent phase/waves of deployment.

Project Team

Salaried Resource	Qty	FTE	Yearly Salary [1]	TOTAL - 12 Mths (Col D*E*M)	TOTAL - 18 Mths (Col D*1.5)
Executive Sponsor(s) [2]	**2**	**0.2**	**$ 80,000**	**$ 32,000**	**$ 48,000**
Business Sponsors [3]					
Government Administration [4]	10	0.1	$ 110,000	$ 110,000	$ 165,000
Hospital Administration	10	0.15	338,773	254,080	381,120
Infectious Disease Specialty	5	0.25	174,200	217,750	326,625
Laboratory	4	0.25	111,000	111,000	166,500
Information Technology	3	0.25	155,000	116,250	174,375
Pharmacy	8	0.25	112,900	225,800	338,700
Procurement/Contract	3	0.1	120,000	36,000	54,000
Total	**43**		**$ 1,121,873**	**$ 1,070,880**	**$ 1,606,320**
Managers/Specialists					
Data Analysis/ Decision Support	2	0.5	$71,000	$71,000	$ 106,500
Finance/ Health Economy	2	0.25	85,000	42,500	63,750
Government Administration [4]	12	0.25	77,500	232,500	348,750
Hospital Administration	8	0.25	102,625	205,250	307,875
Infectious Disease Specialty	20	0.05	88,550	88,550	132,825
Laboratory	4	0.25	80,500	80,500	120,750
Information Technology	5	0.5	105,000	262,500	393,750
Miscellaneous (Admin/clerks)	3	0.5	44,000	66,000	99,000
Nursing	3	0.25	84,500	63,375	95,063
Pharmacy	5	0.25	102,500	128,125	192,188
Primary Care Physician	40	0.05	170,000	340,000	510,000
Privacy	1	0.1	79,000	7,900	11,850
Procurement/Contract	1	0.2	80,500	16,100	24,150
Security	1	0.1	75,000	7,500	11,250
Total	**107**		**$ 1,245,675**	**$ 1,611,800**	**$ 2,417,700**
TOTAL - Salaries	**152**		**$ 2,447,548**	**$ 2,714,680**	**$ 4,072,020**

Travel - Not applicable [5]

Notes

1 Average of the low and high range for this role, including benefits

2 Assumes 1 Executive Sponsor at the highest relevant program level of the funding organization(s) and 1 Exec Sponsor representing the group(s) ofdeploying hospitals.

3 Assumes Business Sponsors at a director level from the relevant program of the funding organization(s) and deploying hospitals.

4 Assumes representation by managers and subject-matter experts from the relevant program areas at the Federal/Provincial/Territorial levels.

5 Assumes involvement of individuals on site being deployed, virtual meetings, and/or travel by the contracted members of the project team to the sites. Other related travels may be considered by the sponsoring organizations at a later time.

This second table presents the costs for contracted resources for the duration of the pilot (Phase 2). Costs expected to incur over the course of Phase 3 were extrapolated from Phase 2 costs based on the expected complexity of the deployment (i.e., rest of Ontario being less complexed than Canada), as well as the team's ability to leverage materials produced in Phase 2 for the subsequent phase/waves of deployment.

Project Team					
Contracted Resource	**Qty**	**FTE**	**Hourly Rate [1]**	**TOTAL - 12 Mths [2]**	**TOTAL - 18 Mths (Col O*1.5)**
Project Management					
Project Manager	2	0.9	$ 130.00	$ 421,200	$ 631,800
Project Coordinator	2	0.9	90.00	291,600	437,400
	5			**$ 955,800**	**$ 1,433,700**
Business Analysis/ Process Engineering					
Business Architect	1	0.5	$ 140.00	$ 126,000	$ 189,000
Senior Business Analyst	1	1	130.00	234,000	351,000
Business Analyst	2	0.5	120.00	216,000	324,000
	4			**$ 576,000**	**$ 864,000**
Technical Team					
Network Architect	1	0.25	$ 140.00	$ 63,000	N/A
Solutions Architect	1	0.25	140.00	63,000	N/A
Interfacing/Integration specialist	1	0.25	140.00	63,000	N/A
Development Team	3	0.25	140.00	189,000	N/A
	6			**$ 378,000**	**$ 378,000**
Other					
Health Economist	1	0.25	$ 140.00	$ 63,000	$ 94,500
Privacy Specialist	1	0.25	130.00	58,500	87,750
Security Specialist	1	0.25	130.00	58,500	87,750
Change Management Specialist	1	0.25	110.00	49,500	74,250
Trainer	1	0.1	110.00	19,800	29,700
Communications Specialist	1	0.2	100.00	36,000	54,000
	6			**$ 285,300**	**$ 427,950**
TOTAL - Consulting	**21**			**$ 2,195,100**	**$ 3,292,650**

Travel [3]	**Qty**	**Days**	**# attendees**	**Total**	**Total**
Project Kick off	1	0.5	15	$ 29,250	$ 29,250
Steering Committee meeting (monthly)	5	0.5	3	$ 29,250	$ 43,875
Advisory Committee meeting (monthly)	5	0.5	3	$ 29,250	$ 43,875
Working Groups meetings (2-4 monthly)	20	1	5	$ 200,000	$ 300,000
Change Management sessions/meetings	10	0.5	2	$ 39,000	$ 58,500
Training	7	3	2	$ 33,600	$ 33,600
Total				**$ 360,350**	**$ 540,525**
Total - Contracted Resources				**$ 2,555,450**	**$ 3,833,175**

Notes & Assumptions

1. Based on Canadian senior health informatics contractor rates.
2. Established based on 7.5 hour/week day over 48 weeks (incl., vacations/blackouts): 1800
3. Assumes 1 out of 2 SC/AC meetings and 1 out of 4 WG meetings are held face-to-face; all other are held virtually. Approximate cost per trip based on average airfare to Toronto, Hotel, per diem, etc: $2,000. Travels days are only relevant for purpose of determining Per Diem eligibility: $100. Attendees based on relevance/requirement of role to attend particular meeting and may include 'guests' from AMR Governance entity

APPENDIX 18: ESTIMATED COSTS – PROGRAM TEAM

As per the Costs Summary table above, costs for the Program Team were established for the years of deployment and yearly after that. The tables below illustrate the base costs and assumptions used to establish overall costs. The first table presents the total costs for the pilot, with the minimum effort (12 months) and optimum effort (18 months) scenarios.

Program Team - Year 2				
Salaries	**Qty**	**FTE**	**Yearly Salary[1]**	**Total**
Director	1	1	$ 177,000	$ 177,000
Infectious Disease Specialist[3]	2	0.75	77,511	116,267
Stewardship Pharmacist[3]	2	0.75	66,611	99,917
Data Librarian/ Analyst	2	0.75	106,200	159,300
Executive Assistant/Coordinator	1	1	82,600	82,600
Accountant/Bookkeeper	1	0.75	88,500	66,375
Total	**9**			**$ 701,458**
Potential reductions in salaries, if AMR Governance model is implemented[3]:				
Data Librarian / Analyst	1	0.75	$ 106,200	$79,650
Executive Assistant/Coordinator	1	1	82,600	82,600
Accountant/Bookkeeper	1	0.75	88,500	66,375
Total	**3**			**$ 228,625**
Travel[4]	**Qty[5]**	**Days[6]**	**# attendees[7]**	**Total**
Onboarding/Intro	10	3	2	$40,400
AGM/Board meetings	3	0.5	3	17,550
Strategic/Planning meetings	2	1	10	40,000
Knowledge Exchange/Training	2	2	5	24,000
Total				**$ 121,950**
Technology & Telecommunications			**Yearly/ Staff**	**Total**
Software - MS 365 / Teams	1		$31	$ 279
Analytics Tableau	1		840	7,560
Website	1		25,000	50,000
Technical Support - 24/7	1	Ad hoc	1,200	10,800
Total				**$ 68,639**
Miscellaneous	**Qty**	**Daily**	**Yearly/ Staff**	**Total**
Building Occupancy - Room Rental[8]	24	300		$ 7,200
Training & Development			$ 2,000	18,000
Professional Fees				
Payroll			55	495
Auditing/ Income Tax Report				4,000
Contingencies (10%)				44,891
Total				**$ 74,586**
Program Team - Year 2 Total				**$ 966,633**
TOTAL (with potential reductions)				**$ 738,008**

Notes & Assumptions	
1 Includes benefits for F/T positions - established at 18% above salary:	1.18
2 1 resource = 1 FTE; 2nd resource = 0.5 FTE.	
3 If AMG Governance entity is established, AAC could potentially leverage some of the resources that are common to both - i.e., Librarian, data analyst, administrative assistant, and the accounting team.	
4 Cost per trip based on average airfare to Toronto, Hotel, per Diem, etc:	$2,000
5 Assumes one (1) out of two (2) meetings is held virtually.	
6 Travels days are only relevant for purpose of determining Per Diem eligibility:	$100
7 Attendees based on relevance/requirement of role to attend particular meeting and may include 'guests' from AMR Governance entity.	
8 Assumes a virtual team for day-to-day, with office/conference room booking on occasion.	

Program Team - Year 3 and 4				
Salaries	**Qty[1]**	**FTE**	**Yearly Salary[2]**	**Total**
Director	1	1	$ 177,000	$ 177,000
Infectious Disease Specialist[3]	3	0.75	77,511	174,400
Stewardship Pharmacist[3]	3	0.75	66,611	149,875
Data Librarian/ Analyst	2	0.75	106,200	159,300
Executive Assistant/Coordinator	1	1	82,600	82,600
Accountant/Bookkeeper	1	0.75	88,500	66,375
Total	**11**			**$ 809,550**
Potential reductions in salaries, if AMR Governance model is implemented[4]:				
Data Librarian / Analyst	1	0.75	$ 106,200	$79,650
Executive Assistant/Coordinator	1	1	82,600	82,600
Accountant/Bookkeeper	1	0.75	88,500	66,375
Total	**3**			**$ 228,625**
Travel[5]	**Qty[6]**	**Days[7]**	**# attendees[8]**	**Total**
Onboarding/Intro	10	3	2	$ 60,000
AGM/Board meetings	3	0.5	3	17,550
Strategic/Planning meetings	2	1	10	40,000
Knowledge Exchange/Training	3	2	5	39,000
Total				**$ 156,550**
Technology & Telecommunications			**Yearly/ Staff**	
Software - MS 365 / Teams	1		$31	$ 341
Analytics Tableau	1		840	9,240
Website	1		25,000	50,000
Technical Support - 24/7	1	Ad hoc	1,200	13,200
Total				**$ 72,781**
Miscellaneous	**Qty**	**Daily**	**Yearly/ Staff**	
Building Occupancy - Room Rental[9]	24	300		$ 7,200
Training & Development			$ 2,000	22,000
Professional Fees				
Payroll			55	605
Auditing/ Income Tax Report				4,000
Contingencies (10%)				49,176
Total				**$ 82,981**
Program Team - Yearly (Yr 3/4) Total				**$ 1,121,862**
TOTAL (with potential reductions)				**$ 893,237**

Notes & Assumptions	
1 Plans for an increment of resources as deployment progresses across the country.	
2 Includes benefits for F/T positions - established at 18% above salary:	1.18
3 1 resource = 1 FTE; 2nd resource = 0.5 FTE.	
4 If AMG Governance entity is established, AAC could potentially leverage some of the resources that are common to both - i.e., Librarian, data analyst, administrative assistant, and the accounting team.	
5 Cost per trip based on average airfare to Toronto, Hotel, per Diem, etc:	$2,000
6 Assumes one (1) out of two (2) meetings is held virtually.	
7 Travels days are only relevant for purpose of determining Per Diem eligibility:	$100
8 Attendees based on relevance/requirement of role to attend particular meeting and may include 'guests' from AMR Governance entity.	
9 Assumes a virtual team for day-to-day, with office/conference room booking on occasion.	

APPENDIX 19: ESTIMATED COSTS – INFORMATION SYSTEMS

		Year 1 of Implementation		
		Set up Fee	Annual Fee	TOTAL
		HNHB	HNHB	
# of Beds		N/A	3503	
Stewardship Application				
Firstline	Fixed	30,000	87,575	$ 117,575
Distribution Application				
Canadian Pharmaceutical Distribution Network	Low	30,000	3,000	$ 33,000
	High	50,000	5,000	$ 55,000
Sub-Total	Low	$ 60,000	$ 90,575	$ 150,575
	High	$ 80,000	$ 92,575	$ 172,575
Interfaces /Integrations		400,000		$ 400,000
TOTAL - Information Systems	Low			$ 550,575
	High			$ 723,150

		Year 2 of Implementation		
		Set up Fee	Annual Fee	TOTAL
		Rest of Ontario	All of Ontario	
# of Beds		N/A	30854	
Stewardship Application				
Firstline	Fixed	$ 510,000	$ 771,350	$ 1,281,350
Distribution Application				
Canadian Pharmaceutical Distribution Network	Low	30,000	$3,000	$ 33,000
	High	50,000	5,000	$ 55,000
Sub-Total	Low	$ 540,000	$ 774,350	$ 1,314,350
	High	$ 560,000	$ 776,350	$ 1,336,350
Interfaces /Integrations		$ 400,000		$ 400,000
TOTAL - Information Systems	Low			$ 1,714,350
	High			$ 3,050,700

		Year 3 of Implementation		
		Set up Fee	Annual Fee	TOTAL
		Rest of Canada	All of Canada	
# of Beds		N/A	70611	
Stewardship Application				
Firstline	Fixed	$ 1,170,000	$ 1,765,275	$ 2,935,275
Distribution Application				
Canadian Pharmaceutical Distribution Network	Low	$ 30,000	$3,000	$ 33,000
	High	$ 50,000	$5,000	$ 55,000
Sub-Total	Low	$ 1,200,000	$ 1,768,275	$ 2,968,275
	High	$ 1,220,000	$ 1,770,275	$ 2,990,275
Interfaces /Integrations		$ 400,000		$ 400,000
TOTAL - Information Systems	Low			$ 3,368,275
	High			$ 6,358,550

		TOTAL	Year 4*	TOTAL
		ALL FEES COMBINED	Annual Fee	ALL FEES COMBINED
			All of Canada	
# of Beds			70611	
Stewardship Application				
Firstline	Fixed	$ 4,334,200	$ 1,765,275	$ 6,099,475
Distribution Application				
Canadian Pharmaceutical Distribution Network	Low	$ 99,000	$3,000	$ 102,000
	High	$ 165,000	$5,000	
Sub-Total	Low	$ 4,433,200	$ 1,768,275	$ 6,201,475
	High	$ 4,499,200	$ 5,000	$ 4,504,200
Interfaces /Integrations		$ 1,200,000		$ 1,200,000
TOTAL - Information Systems	Low	$ 5,633,200	$ 1,768,275	$ 7,401,475
	High	$ 10,132,400	$ 1,773,275	$ 11,905,675

Notes & Assumptions

- Costs for HNHB implementation assume deployment to all hospitals in that region. Deployment to Hamilton Health Sciences, Joseph Brant and St-Joseph's (As per minimum scope), would reduce initial costs by approximately $43,525.
- Set-up fee for Firstline is $5,000/ institution - An institution may be a group of hospitals under the same corporation or a single hospital.
- Set-up fee for CPDN is a tailored customization/configuration of the system to meet client-defined requirements - it varies between $30-50k per installation/client. The fee was included for each set of deployments as a safety net.
- Annual Fee for Firstline = $25/bed; for CPDN = flat $3-5k per initiative - unlimited # of users.
- Firstline is already established in several institutions (equating 20,900 beds), which was taken into account in fees calculations.
- Estimated cost per integration to another relevant system: $200,000.

APPENDIX 20: MARKET ACCESS – FINANCIAL INCENTIVES

			Canada's G20 share based on GDP - Using 1.4% vs 1.6% share for comparison					
Scenario: All G20 Countries Subscribe (from K. Outterson Paper)			With Canada's Share at Current Value:		1.40%	With Canada's Share at 2015 Value:		1.60%
Model		**Total market value over 10 years**	**USD - 10 yrs**	**CAD - 10 yrs**	**CAD - 1 yr**	**USD - 10 yrs**	**CAD - 10 yrs**	**CAD - 1 yr**
Partially Delinked - MER1 + ACQ	lower	$ 900,000,000	$ 12,600,000	$ 15,624,000	$ 1,562,400	$ 14,400,000	$ 17,856,000	$ 1,785,600
	Best Est	**$ 1,600,000,000**	**$ 22,400,000**	**$ 27,776,000**	**$ 2,777,600**	**$ 25,600,000**	**$ 31,744,000**	**$ 3,174,400**
	upper	$ 2,600,000,000	$ 36,400,000	$ 45,136,000	$ 4,513,600	$ 41,600,000	$ 51,584,000	$ 5,158,400
Fully Delinked - SUB10 + ACQ	lower	$ 2,200,000,000	$ 30,800,000	$ 38,192,000	$ 3,819,200	$ 35,200,000	$ 43,648,000	$ 4,364,800
	Best Est	**$ 3,100,000,000**	**$ 43,400,000**	**$ 53,816,000**	**$ 5,381,600**	**$ 49,600,000**	**$ 61,504,000**	**$ 6,150,400**
	upper	$ 4,800,000,000	$ 67,200,000	$ 83,328,000	$ 8,332,800	$ 76,800,000	$ 95,232,000	$ 9,523,200
Fully Delinked - SUB10	lower	$ 3,300,000,000	$ 46,200,000	$ 57,288,000	$ 5,728,800	$ 52,800,000	$ 65,472,000	$ 6,547,200
	Best Est	**$ 4,200,000,000**	**$ 58,800,000**	**$ 72,912,000**	**$ 7,291,200**	**$ 67,200,000**	**$ 83,328,000**	**$ 8,332,800**
	upper	$ 8,900,000,000	$ 124,600,000	$ 154,504,000	$ 15,450,400	$ 142,400,000	$ 176,576,000	$ 17,657,600

*USD-CAD Exchange rate (Oct.29, 2021): 1.24

APPENDIX 21: ESTIMATED STEWARDSHIP-RELATED SAVINGS

The following are the savings estimated to be realized as a result of implementing the Firstline Stewardship App, based on reports by Eastern Health related to observed reductions of *C. diff* cases and a more appropriate usage of Antimicrobials.

Estimated Savings				
Following activation of Stewardship App across:	**HNHB**	**Ontario**	**Canada**	**Yearly After**
Savings related to use of App on AMU & C.Difficile[16]	**$ 1,933,656**	**$ 17,031,408**	**$ 38,977,272**	**$ 38,977,272**
TOTAL ESTIMATED SAVINGS		Cummulative over project life:	**$ 57,942,336**	
		Cummulative over the 4 yrs of deployment:		**$ 96,919,608**
Net Cost of Implementation - Recouped at the end of the first year following implementation			*Based on Option 1:*	**$ 47,358,781**
			Based on Option 2:	**$ 6,765,840**
Cost of Status Quo [16]				
Estimated Annual Costs of AR to Canadian HC System				$ 1,000,000,000
Resulting impact on labour productivity				$ 2,000,000,000

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