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**MULTI-STAKEHOLDER ANTIMICROBIAL STEWARDSHIP
EXPERT FORUM**

**Canadian Institutes of Health Research and Merck Canada
November 17-18, 2016
Toronto, Canada**

Workshop Report



At the Canadian Institutes of Health Research (CIHR), we know that research has the power to change lives. As Canada's health research investment agency, we collaborate with partners and researchers to support the discoveries and innovations that improve our health and strengthen our health care system.

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Executive Summary

Background

There is an urgent need to change society's perceptions about antibiotics. Decades of easy access to these relatively inexpensive and highly effective drugs has generated an air of complacency that now threatens the health of future generations. Resistance to current antibiotics of clinical relevance is now widespread in humans, livestock and the environment. It is essential that the antimicrobial resistance transmission pathways are better understood and that interventions are designed and implemented to mitigate the emergence and impact of antimicrobial resistance.

A multi-pronged approach for preserving antibiotics for human use is required that will: protect the remaining effective antibiotics by limiting their use in health and in agriculture; preserve new drugs coming to market by restricting their use to situations where no other options are available; explore innovative alternatives to antibiotics in health and agriculture; and incentivize industry to invest in new antibiotic discovery, supported by the development of rapid diagnostics.

Canada is committed to global efforts to overcome the challenges created by antibiotic resistance and there are many federal and provincial initiatives in place to guide progress. Research is the driver of innovation, and CIHR has invested in research initiatives and activities to find solutions to antimicrobial resistance. The current multi-stakeholder forum represents the next step in a shared commitment to invest in the development of strong and effective antimicrobial stewardship programs for Canada and beyond.

The Forum brought together more than 80 participants from multiple disciplines and sectors to share their expertise in a one-day workshop comprised of keynote presentations, panel discussions, plenary sessions, and a breakout session. A high level summary of the recommendations generated is presented in Table 1.

Table 1: Summary of Workshop Recommendations

Theme	Recommendations
Antibiotic Innovation	From a pharmaceutical company perspective, antibiotic prioritization through global threat assessment studies would assist in guiding investment and new program development. To further incentivize companies to invest in new drug programs, new models of antibiotic discovery and development are needed that provide a mix of "push and "pull" incentives, de-link profit from volume (at least partially), and provide access to innovative new clinical trials that take into account the challenges posed by antimicrobial resistance. It was recommended that the solution to many of these problems is to engage the appropriate stakeholders early in the process to generate the public/private partnerships required to mitigate risk and reduce individual costs, from discovery through to the post marketing evaluation phase. Research is needed to determine how best

	to implement these recommendations to drive antibiotic innovation in Canada.
Innovative Interventions In Antimicrobial Stewardship	Behavioural research is needed to better understand the determinants of decision making in the health (prescribers and patients), and agri-food sectors and how best to implement change to reduce inappropriate prescribing and the misuse of antibiotics. Studies are also needed on how to adapt antimicrobial stewardship programs across health care settings and tailor them to meet the needs of special populations. Best practices are needed on the most effective ways to educate health care professionals, veterinarians, and the public on the risks associated with antimicrobial resistance, and the urgent need to protect existing antibiotics. As antibiotic resistance is unlikely to be eradicated, research is also needed on viable, cost-effective alternatives in the health and agri-food sectors.
Innovative Metrics and Outcomes	Workshop participants repeatedly emphasized the need for more comprehensive, reliable and accessible Canadian surveillance data on antimicrobial resistance and antibiotic prescribing and use to inform stewardship efforts. Pilot projects were called for to demonstrate the feasibility of linking data from electronic health records to related health information at a jurisdictional or provincial level in a way that could be scaled up across the country to support antimicrobial stewardship programs. It was recommended that linkage to existing resources, such as the Canadian Health Infoway and the Canadian Primary Care Sentinel Surveillance Network, be explored. An environmental scan was called for of the metrics currently used to assess prescribing practices and appropriateness of use across the country to inform the selection of common metrics going forward and to support pilot studies on "adjusted" metrics in acute care settings to allow justifiable comparisons.
Laboratory and Technology	Workshop participants recommended studies on the role of laboratory services in antimicrobial stewardship programs, including: how to forge better real time linkages between the laboratory and clinic; behavioural studies on the factors influencing the use of laboratory services by health care workers; and the most effective mechanisms to educate policy makers on the need for rapid susceptibility diagnostics. Further studies were recommended on the appropriateness of point-of-care diagnostics; potential unintended consequences; the impact of rapid diagnostics on important outcomes; and the potential of innovative new diagnostics for use in health care and in animal welfare.
Knowledge Mobilization	Workshop participants recommended an initial environmental scan of successful Canadian and international social marketing campaigns aimed at raising public awareness about antimicrobial resistance and stewardship to identify best practices. Pilot projects were also suggested to determine best practices for promoting community engagement across a whole jurisdiction, including hospitals, clinics, outpatient settings, veterinary clinics, and the public.

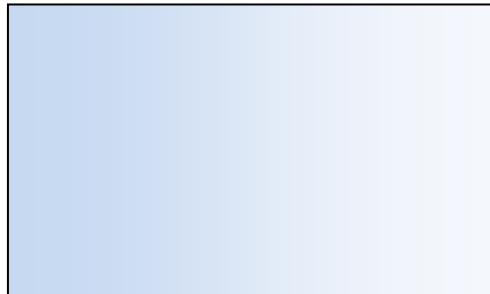
Next Steps

The workshop recommendations will inform CIHR senior management as they consider collaborative opportunities for innovation in antimicrobial stewardship. One such timely opportunity is the upcoming launch of a European Union's Joint Programming Initiative in Antimicrobial Resistance (JPIAMR) program, with a focus on antimicrobial stewardship. Many workshop participants expressed enthusiasm for exploring international partnerships with a view to potentially submitting an application to this Call for Applications. It is hoped that other research

opportunities may be generated through current federal and provincial activities in antimicrobial stewardship, including the Canadian Antimicrobial Stewardship Action Plan.

Background

Antibiotics have been one of the greatest therapeutic successes in modern medicine, saving millions of lives each year. As drugs that are easy to administer, fast acting, highly effective, and relatively inexpensive, antibiotics have been widely used in clinical practice to control bacterial infections, as



well as in the agriculture and agri-food sectors, to support infection control and enhance productivity. The downside to this success story, however, is that antibiotics rapidly generate resistance in the bacteria they target, rendering them therapeutically impotent. This situation is compounded by the fact that most of the new antibiotics produced in the last 40 years, represent essentially minor modifications of compounds to which bacteria have already developed resistance. The increasing shortage of

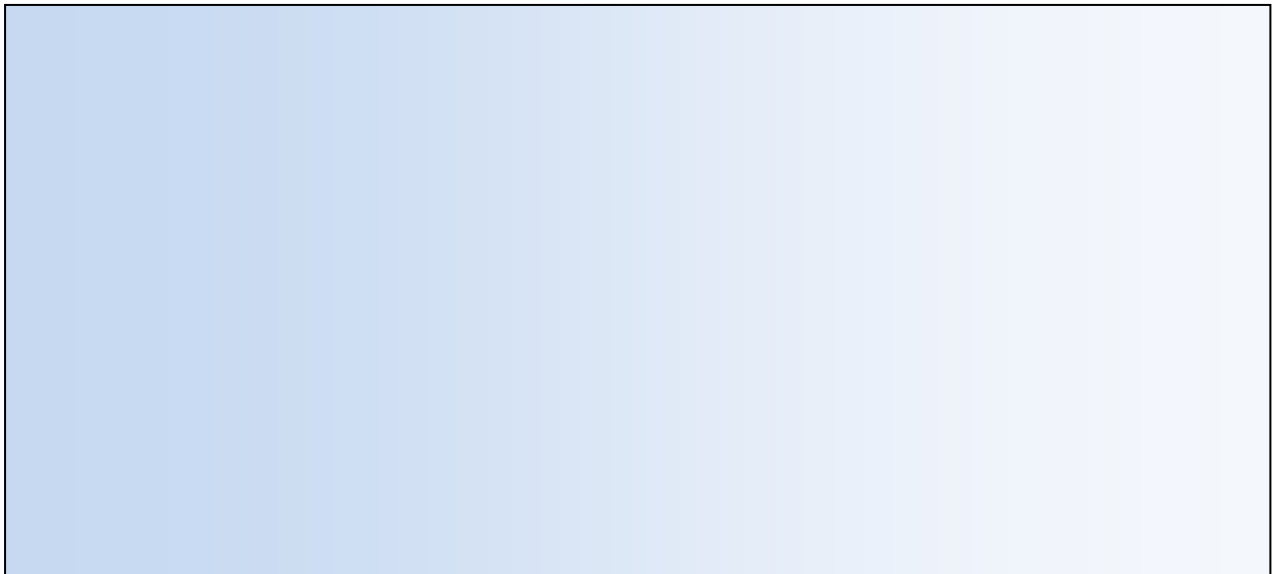
effective antibiotics has become a global health crisis that threatens our ability to: cure common bacterial infections; safely perform complex surgeries; deliver cytotoxic therapies; and treat minor injuries. The rising tide of antibiotic resistance also contributes to increased health care costs due to lengthened hospital stays, and the need for additional diagnostic tests and potentially more expensive treatments.

In 2015, the World Health Organization launched the "*Global Action Plan on Antimicrobial Resistance*"; and the following year the United Nations General Assembly called for an acceleration of global commitments to combat antimicrobial resistance, including antibiotic resistance. Along with many other countries, Canada has risen to the challenge through the launch of a number of federal and provincial initiatives aimed at developing reliable surveillance systems; improving infection control; reducing the generation of resistance at source; curbing the unnecessary use and overuse of antibiotics in the health and the agri-food sectors; developing new antibiotics and other novel therapeutics; and preserving the effectiveness of those antibiotics critical in human health. Antimicrobial stewardship programs have been launched in many countries, including Canada, in an effort to restrict antibiotic use to situations where no other viable options exist and ensure that, when needed, the appropriate antibiotic is prescribed at the right dose, frequency and duration to optimize outcomes while minimizing adverse effects. In today's world, the principles of antimicrobial stewardship are called for wherever antimicrobial agents are used, including hospitals, long term care facilities, community settings, and in the agri-food and veterinary environments.

As the Canadian Institutes of Health Research (CIHR) is a recognized leader in research and innovation in priority health areas, including antimicrobial resistance, the current collaboration on the *Multi-Stakeholder Antimicrobial Stewardship Expert Forum* will consolidate and advance joint activities in the antimicrobial resistance field, especially with respect to antibiotic stewardship, an area that has only relatively recently become a topic of global interest and concern. With the advice and support of a small but committed expert steering group, the CIHR Institute of Infection and Immunity organized a workshop to bring together stakeholders from multiple disciplines and sectors to build on ongoing initiatives and generate recommendations for innovative strategies in

antimicrobial stewardship and antibiotic innovation. The workshop participants and steering committee members are listed in Appendix 1.

Workshop Objectives



Workshop Format

The workshop was comprised of a keynote presentation on economic incentives for antibiotic development in the United States (US), four presentations on current Canadian strategies and activities related to antimicrobial resistance and antibiotic stewardship and two panel presentations to stimulate discussion and lay the groundwork for a two-hour breakout session (see Workshop Agenda, Appendix 2). Participants were divided into four multidisciplinary, multi-sector groups for the breakout session and asked to identify research gaps and opportunities and recommend potential actions for each of the three themes: Innovative Antimicrobial Stewardship Interventions; Innovative Metrics and Outcomes; and Laboratory and Technology, as well as an additional theme on Mechanisms for Antibiotic Innovation. Groups were asked to also discuss strategies for knowledge mobilization across all themes. For each research area identified, groups were asked to consider the rationale and anticipated impact of their recommendations. Breakout group discussions were summarized in a plenary session, followed by a discussion of next steps.

Key Messages From the Presentations

DAY 1 - November 17th

The workshop began on the evening of November 17th with a networking dinner and a brief welcoming address from representatives of the sponsoring organizations: Marc Ouellette, Scientific Director of the CIHR Institute of Infection and Immunity (III) and Mauricio Ede, formerly from Merck Canada Inc., followed by an keynote presentation by Joseph Larsen from the Transatlantic Task Force on AMR and Deputy Director of BARDA.



Joseph Larsen, BARDA

Economic Incentives for Antibiotic Development: An Overview

The US Biomedical Advanced Research and Development Authority (BARDA) focuses on the development and purchase of vaccines, drugs, therapies and diagnostic tools for public health emergencies. In 2010, BARDA established the Broad Spectrum Antimicrobials (BSA) program to develop novel anti-bacterials and anti-virals. BARDA is also a lead partner in the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), one of the world's largest public-private partnerships focused on the preclinical discovery and development of new antimicrobial products.

The Pharmaceutical industry evaluates the overall risk/benefit and profitability of pursuing drug development using the metric Net Present Values (NPV). NPV is the sum of all the investment costs of development and the expected value of future revenues, taking into account the discounted rate of the value of money over time. An NVP of about \$200 million is recommended to incentivize investment. This is easily achievable for neurological or musculoskeletal drugs, for example, where the NPV range can be as large as \$720 million - \$1.15 billion, but for antibiotics NPVs of approximately \$50 million are the norm. This fact alone may explain the reluctance of many pharmaceutical companies to invest in antibiotic development when the return on investment is so much greater for other therapeutics, especially those used to treat chronic health conditions.

Antibiotics are relatively inexpensive, compared to many other drugs; are taken only for a short time period; and rapidly generate resistance which renders them ineffective and makes them the only drugs for which use diminishes utility. Efforts in antibiotic stewardship require that new antibiotics are "protected" for situations in which generic drugs have failed in order to preserve their effectiveness, further reducing the commercial return for investors. The result is that few companies are willing to invest in antibiotic innovation and those that do generally do not see the project through to market. There are currently about 37 candidate antibiotics in phase II/III clinical development compared to more than 500 in oncology. These figures strongly suggest that new and alternative market structures are needed to provide more dependable and sustainable markets for antibiotics and incentivize innovation in antibiotic discovery.

Incentives for antibiotic innovations should cause minimal disruption, and conserve existing antibiotics without restricting patient access. Both the BARDA and CARB-X models have successfully used a mix of "push and pull" incentives to encourage new antibiotic innovation. "Push" Incentives provide direct support and payment for the "effort" of developers by underwriting the cost of the "effort", e.g. grants, contracts, tax credits. "Pull" incentives provide an incentive for private sector engagement by creating viable market demand or providing rewards for success, eg. advanced market commitments, prize/milestone payments, tax credits, regulatory incentives. Another incentive for investment would be a move away from a model that assesses revenue based on the number of units sold, i.e a de-linkage of profit from volume. Partial rather than full de-linkage is recommended, where a company owns the intellectual property rights and manufactures and sells the product in return for a series of payments over several years attached to

milestones, such as introduction to market, meeting public health objectives, launch of educational campaigns, etc. In this model, payments are smaller than full de-linkage but are easier to sustain as payments generate a known return on investment and the model provides an opportunity to meet public health objectives. Other incentive models might include tradeable exclusivity vouchers from government to extend a product's exclusivity.

In summary, there is a growing consensus on the need for economic incentives for antibacterial drug development. A mix of push and pull incentives and models that delink profits from volume of sales are favoured that will reward innovation while achieving public health objectives. There is currently a window of political opportunity to launch pilot studies on new models of antibiotic innovation for one or two antibiotics that, if successful, can be scaled up over time.

DAY 2 - November 18th

Day 2 began with a welcome and introductory remarks that acknowledged the interest of two additional CIHR Institutes: the Institute of Population, and Public Health, and the Institute of Health Services and Policy Research, in potential collaborations with III as they move forward in their efforts to address the challenges of antimicrobial stewardship.



Frank Plummer, Public Health Agency of Canada

Challenges in Antimicrobial Resistance and Antibiotic Stewardship: A Canadian Perspective

Although the 2016 Canadian Antimicrobial Resistance Surveillance Report suggests that overall rates of antimicrobial resistance in Canada have stabilized, areas of growing concern remain. One example is the increase in multi-drug resistant *Neisseria gonorrhoeae*, an indication of a looming public health crisis with the possible emergence of untreatable gonorrhoea. Another reason for a lack of complacency is the unsettling statistic that antibiotic use in humans is higher in Canada than in 50% of EU countries, and higher in animals than 70% of EU countries. Even more troubling, is 2014 data showing that 73% of the antibiotics used in food production animals, in Canada, belong to the same classes used in human medicine. A One-Health approach is essential for understanding antimicrobial transmission pathways between humans, animals and environment. Challenges include a lack of adherence to prescribing guidelines; gaps in stewardship practices; insufficient education/awareness programs; and a lack of comprehensive evidence to inform stewardship interventions and measure effectiveness over time. For effective antimicrobial stewardship, a coordinated approach across disciplines and sectors is needed that includes more comprehensive surveillance data, evaluation, impact assessment, audit, feedback, and research to identify the most appropriate diagnostics and the most promising stewardship practices across the health care system, especially at the community level.



Lindsay Noad, Public Health Agency of Canada

Overview of Federal and National Activities

Canada has already made progress in meeting commitments, made at the World Health Assembly in 2015 and United Nations General Assembly in 2016, to use a One-Health approach to coordinate Canada's activities in antimicrobial resistance among all levels of federal, provincial and territorial governments, as well as across a wide range of sectors and external stakeholders. Two key documents which frame federal actions and are guiding the development of national plans are now available: the *2014 Antimicrobial Resistance and Use in Canada: A Federal Framework for Action*, and the *2015 Federal Action Plan on Antimicrobial*

Resistance and Use in Canada. Priority areas for pan-Canadian action have been identified and include: surveillance, stewardship, infection prevention and control, and research and innovation. Expert task groups have now been convened to identify existing actions, gaps and propose recommendations in each of these four areas. Achievements to date include: integrating surveillance activities; closing surveillance gaps; implementing regulatory and policy changes for veterinary antimicrobials; strengthening awareness campaigns; and research initiatives to improve diagnostics. Several other stakeholders are undertaking complementary actions, such as HealthCareCAN's National Healthcare Stewardship Action Plan; the Canadian Veterinary Medical Association's Pan-Canadian Framework on Veterinary Oversight; and the National Farmed Animal Health and Welfare Council's national stewardship efforts in the agri-food sector.



**Andrea Johnston, Agriculture and Agri-Food Canada, and
Richard Rusk, Medical Officer of Health, Government of Manitoba**
Overview of National AMR Stewardship Task Group Activities

The Antimicrobial Resistance Stewardship Task Group, which is co-chaired by the two presenters, was created with a mandate to use a One-Health perspective to:

- Provide the Federal/Provincial/Territorial Antimicrobial Resistance Steering Committee with advice and recommendations for health care in hospital and community settings, and animal health in the veterinary and on-farm/agri-food settings;
- Identify existing best practices, expertise, tools, and resources, while also identifying gaps and opportunities; and
- Produce a report, by January 2017, with recommendations for priority areas for action to inform the development of the pan-Canadian framework on antimicrobial stewardship.

One of the first tasks undertaken was a comparison of the definitions of antimicrobial stewardship used in two key documents released in 2016 by the National Farmed Animal Health and Welfare Council, and the Communicable and Infectious Disease Steering Committee Task Group of Antimicrobial Use and Stewardship. Considerable overlap was evident in the recommendations in the two documents, suggesting that the health and agriculture communities are in broad agreement and share a common goal of improving stewardship in both sectors through collaboration.

Jennifer Kitts, HealthCareCAN

Key Learnings From the Canadian Action Roundtable on Antimicrobial Stewardship

In June 2016, more than 50 “Champions of Change” convened at the Canadian Roundtable on Antimicrobial Stewardship to discuss the key features of a Canadian Antimicrobial Stewardship Action Plan, spanning all health care settings. Based on these deliberations and consultations from across the healthcare system, HealthCareCAN and the National Collaborating Centre on Infectious Diseases (NCCID), with support from the Public Health Agency of Canada, developed, *Putting the Pieces Together: a National Action Plan on Antimicrobial Stewardship*. This Action Plan lays out ten key actions necessary to preserve the effectiveness of antimicrobials in Canada.

The first of the ten key actions identified in the Action Plan calls for a national network of key stakeholders in antimicrobial stewardship (called “AMS Canada”) to lead and coordinate human national stewardship projects in Canada as part of a One-Health approach to combating antimicrobial resistance. A transitional steering group for this network convened in October 2016. AMS Canada’s transitional steering group committed to the following initial activities:

- Developing an evaluation protocol to assess progress in national antimicrobial stewardship efforts;
- Modeling strategies for educating the public on antimicrobial resistance and antimicrobial stewardship; and
- Developing and promoting national guidelines on antimicrobial use for primary care practitioners treating common infections.

A second feature of the Action Plan, relevant to CIHR’s deliberations on antimicrobial stewardship, concerns the development of an Antimicrobial Stewardship Research and Development Fund. Action item number 6 of the Action Plan proposes establishing an antimicrobial stewardship research development fund to be supported by an investment of \$10 million over five years. Research gaps in antimicrobial stewardship knowledge include the following:

- A lack of evaluation of stewardship programming;
- A lack of understanding around resources required for effective stewardship;
- A lack of targets and benchmarks for antimicrobial use in facilities and community care;
- A dearth of rapid and precise diagnostic tools;
- Deficits in our understanding of the causes and predictors of inappropriate antibiotic prescribing; and,
- Gaps in our knowledge around the challenges of antimicrobial stewardship deployment in hard-to-reach populations.

Key Messages From the Panel Discussions

Panel 1: Research Gaps and Innovation for Antimicrobial Stewardship in Different Settings



Nick Daneman, Sunnybrook Health Sciences Centre, Toronto

A lack of reliable data on antibiotic use is a huge barrier to antimicrobial stewardship efforts. No standardized benchmarks currently exist for prescribers or facilities, resulting in a huge variation in antibiotic usage that is determined more by the historical practice of the health care practitioner prescribing the drug than any patient driven measure or system standard. The development of effective stewardship programs requires better correlation between practice outcomes to determine how to set appropriate standards for when an antibiotic should be prescribed, what kind of antibiotic is required, and the duration of treatment. The current lack of sustainable databases makes it challenging to implement consistent stewardship practices or determine how much variation is necessary or appropriate, as well as how much of the inappropriate or unnecessary prescribing is amenable for intervention.



John Conly, University of Calgary, Calgary

In order to oversee antibiotic use, we first need to be able to accurately measure the doses administered. The most commonly used metrics to measure antibiotic usage in acute care settings include Defined Daily Dose (DDD), Days of Therapy (DOT), and Length of Therapy (LOT). All these metrics have their relative strengths and weaknesses, with some being more appropriate for defined patient groups such as pediatrics or complex cases such as transplant patients, some requiring patient-level data, and some being more

amenable to institutional and intra-country comparisons. For benchmarking and comparison, standard metrics are needed that discriminate between the prescribed dose of antibiotics and the dose actually administered to the patients. These two values may be very different and the data suggest that the amount of antibiotics given to patients may be significantly overestimated if only the prescribing data is used. Adjusted metrics of antibiotic use are needed in order to compare studies and distinguish between patient groups, comorbidities and complications.



Lindsay Nicolle, University of Manitoba, Winnipeg

Establishing effective antimicrobial stewardship programs will require a culture change towards routinely incorporating diagnosis before treatment to identify whether an infection is present and, if so, what the infectious agent is and which antibiotics it is susceptible to, as well as considering alternatives to antibiotic therapy and using antibiotics only as a last resort. There also needs to be a recognition that infection control differs according to health care setting - one size does not fit all. For example, long term care facilities are characterized by intense antibiotic use, high prevalence of resistant organisms, and diagnostic limitations. However the patients in these facilities are often asymptomatic even when carrying antibiotic resistant organisms. Upon transfer back to an acute care setting for emergency health care, however, these patients may serve as a reservoir of resistant infections that can easily spread causing significant morbidity or even death in high risk patients. Increased surveillance for antibiotic use and resistance is needed along with clinical trials in different health care settings that use the appropriate outcome measures such as quality of life and the impact on the care facility. More studies are also needed to address the needs of special populations such as Northern, rural and First Nation communities.



Warren McIsaac, University of Toronto

More than 88% of hospitals have funding and dedicated resources to develop and implement antibiotic stewardship policies. In the community setting, however, where 80% of antibiotic use occurs, there are no accreditation requirements, no resources dedicated to ASP activities, and few, if any, clinical level antibiotic stewardship programs. Fortunately there are many grass roots efforts across the country that provide a rich body of evidence on interventions to reduce antibiotic prescribing that are effective at a community level and complement those that are available in hospitals. An ongoing, programmatic, coordinated approach is needed to sustain these efforts and gain a greater understanding of the epidemiology of antibiotic resistance in the community. Access to surveillance data remains a challenge in Canada, as we have no counterpart to the National Ambulatory Care Survey in the US. This survey of community-based physicians collects data, including diagnosis and prescribing information to show trends and changes over time. As electronic medical records have penetrated about 80% of practices in Ontario, alone, prescribing information can now be captured electronically opening the door to studies on numerator/denominator issues, coding differences and the appropriateness of antibiotic prescribing.



Scott McEwen, Ontario Veterinary College, University of Guelph

Canadian Antimicrobial Resistance Surveillance System (CARSS) data on antibiotic use in agriculture show that about 80% of the medically important antibiotics consumed in Canada are for food animals (77%), companion animals (1%) and plants (1%). The huge exposure to antibiotics in the agri-food sector is known to drive resistance rates in enteric bacterial pathogens of humans and increase the pool of resistance

genes in food and the environment. Some countries, such as the Netherlands and Denmark, have seen dramatic reductions in antibiotic use in agriculture following national regulatory policies, e.g. mandating reductions of 50-70%. A similar top-down, regulatory approach is needed in Canada where there are currently big gaps in federal and provincial policies needed to reduce unnecessary and/or inappropriate antibiotic use in agriculture. There are also opportunities for change at the veterinarian and farmer level through education; guidelines; benchmarking; improved diagnostics; better husbandry; and access to cost effective alternatives to antibiotics such as vaccines, and probiotics. Some elements are already falling into place as a result of the extensive discussions during the last 15-20 years that have primed commodity groups for change.

Panel 2: Stimulating Innovation - Multi-Stakeholders Perspective



Allan Coukell, The Pew Charitable Trusts, US

The road to effective antibiotic stewardship must follow two pathways: slowing the growth of resistance through conservation (infection control, reducing inappropriate use in humans and animals, making better use of existing drugs), and the discovery, development and marketing of new antibacterial agents. To inform stewardship policies, we need to fully understand the drivers of inappropriate antibiotic use in outpatient settings and develop appropriate interventions to reduce inappropriate prescribing across all health care settings. At the same time we need to reduce unnecessary antibiotic use in agriculture and the environment especially for those antibiotics of current or potential importance in human health. National goals for reducing inappropriate use would facilitate stewardship activities, including tracking antibiotic prescriptions; monitoring patterns of use and trends; identifying where improvement is needed; studying the social components of prescribing; informing stakeholders about progress and opportunities; and galvanizing public and political attention and support. Core elements of stewardship programs should include leadership commitment, targets, accountability, drug expertise, tracking, reporting, and education.



Joseph Larsen, Barda, US

The panel presentation summarized the keynote presentation given the previous evening (see page 7), reiterating the need for a new model for antibiotic innovation based on public/private partnerships, that incentivize industry to engage in novel drug development. CARB-X was proposed as an example of a highly successful multinational program, which currently has a portfolio of about 20 antibacterial candidates and aims to move a minimum of 2 candidates into clinical development within five years. The convening and funding power of CARB-X shows great potential as a catalyst for change.



Jackie Arthur, Public Health Agency of Canada

The Canadian Antimicrobial Resistance Surveillance System (CARSS) is the national coordinating program for the Public Health Agency of Canada's surveillance systems and programs. Since 2015, CARSS has been gathering information about antimicrobial resistance and use in humans and food animals across the country. The 2016 report highlights a number of information gaps in existing surveillance systems. For example, only limited data on antimicrobial resistance and use is available from small, non-academic hospitals and no data is available for rural and northern health care settings and First Nations communities. Data is

also limited in the community and non-traditional health care settings, e.g. dentists, long term care facilities, and overall there is little information on the links between antibiotic prescribing practices and patterns of resistance and spread. The Public Health Agency of Canada is working with its partners to try to address these gaps through ongoing federal initiatives on antimicrobial resistance and use surveillance and stewardship.



Jennifer Chan, Merck Canada Inc.

A major barrier to antibiotic innovation is the fact that bacteria are constantly evolving and the therapeutic window is narrowing. In addition there are many challenges in the design of clinical trials, enrollment is difficult and the regulatory path is complex. On the economic front, limited returns for novel antibiotics lead to limited investment. However, many pharmaceutical companies, including Merck, are committed to the challenge. At the 2016 World Economic Forum, in Davos Switzerland, which brought together 13 leading companies with a common goal of developing a roadmap on stewardship and innovation, Merck committed to:

- Expanding support for the Centers of Excellence Antimicrobial Stewardship Program from 521 hospitals in 26 countries to 1,000 hospitals in 40 countries by 2019;
- Creating a global network for antimicrobial stewardship training and support;
- Supporting education on antimicrobial stewardship including specific information regarding responsible and appropriate use of antimicrobial medicines;
- Scaling up partnerships with diagnostics companies to develop antibiotic susceptibility testing and rapid diagnostics to support appropriate use of novel antibiotics;
- Ensuring promotional activities advance antimicrobial stewardship and protect the utility of antibiotics by encouraging their correct use;
- Exploring new value-based contracting models with payers and providers;
- Ensuring Merck manufacturing discharges are meeting Environmental Quality Criteria;
- Ensuring antibiotics are only used by those who need them;
- Improving access to antibiotics globally; and
- Exploring new partnerships between industry and the public sector.

Multi-stakeholder, multi-sector efforts are needed to transform societal perceptions of the value of antibiotics, address reimbursement challenges, and advance novel incentive models. Industry is committed to being an integral part of this effort.



Karl Weiss, Jewish General Hospital; McGill University, Montreal

To have an impact on antimicrobial stewardship, Canada needs innovative, integrated, biomedical federal policies with clear objectives, similar to the policies that exist in countries, such as Switzerland and Israel. Any policy on antimicrobial stewardship should always integrate both the human and animal perspectives. One suggestion would be for Canada to focus on just one or two areas where the opportunity exists to become a world leader. For example:

- **Data collection and analysis:** Increased investment in information technology is needed to support better measurement of antibiotic consumption in humans and animals and across all health care settings, not just acute care hospitals.
- **Diagnostics:** Investment is needed in new technologies and devices, including point-of-care diagnostics in agriculture and across all health care settings.

- **Antibiotic Discovery:** Although perhaps not a particular strength in Canada, there is the potential for the discovery of new therapies that could change the landscape, as happened with the introduction of "biological therapies" for inflammatory bowel diseases. Potential alternatives to antibiotics might include phage therapy, probiotics as replacements or adjuncts to traditional antibiotics, microbiome manipulations, and vaccines.
- **Clinical epidemiology:** Canada is well placed to create a clinical trials network for infectious diseases that builds on existing centres of excellence. Such a network would provide an attractive option for companies with new products to test, as they would have timely access to a network of centres across the country, rather than navigating a competitive landscape.

Workshop Recommendations

Workshop recommendations were drawn from the breakout group discussions, as well as from the presentations, panel discussions, question periods, and plenary sessions. Table 2 summarizes the areas that were identified as having unanswered questions in need of innovative research solutions.

Table 2: Research Areas by Theme

Topics	Antibiotic Innovation	Innovative AMS Interventions	Innovative Metrics and Outcomes	Laboratory and Technology
Research Areas	Building public/private partnerships	Modifying antibiotic prescribing	Improving data linkage and integration	Improving linkages between laboratory and clinic
	Incentivizing antibiotic discovery and innovation	Tailoring antimicrobial stewardship efforts to populations and health care settings	Developing appropriate metrics, including adjusted metrics	
	Integrating novel antibiotics into the health care system	Developing alternatives to antibiotics		
Cross Cutting Theme	Knowledge Mobilization			

ANTIBIOTIC INNOVATION

BUILDING PUBLIC/PRIVATE PARTNERSHIPS

Rationale: The inevitability of antibiotic resistance makes antibiotic innovation a risky undertaking characterized by high drug discovery costs; uncertainty in the use of the antibiotic at launch; difficulties in predicting penetration of the antibiotic into the market; low return on investment relative to other therapeutics; potentially short effective lifespan; and an overall fragile market

environment. However, research and development aimed at producing new antibiotics remains a priority for industry, governments, the medical community, and the public. Innovative new models of drug development are encouraged, based on sharing risks and costs between governments and industry, while integrating the different perspectives of multiple stakeholder groups.

Recommendation:

- Support research to inform best practices in the development of novel public/private partnerships to incentivize antibiotic research and development in the Canadian context.

Anticipated Impact: New public/private partnerships will be created to incentivize antibiotic innovation.

INCENTIVIZING ANTIBIOTIC INNOVATION

Rationale: The barriers to antibiotic innovation must be removed in order to attract early investment in antibiotic research and development. A mix of push and pull incentives are needed to: improve return on investment; reward innovation; minimize disruptive effects; and ensure conservation without impacting patient access. De-linkage models should also be pursued to de-link profit from volume of units sold, as well as mechanisms to encourage innovators to see their new products through to marketing.

Recommendations:

- Support research to identify where new antibiotics are needed most, e.g through antibiotic prioritization, global treat assessments.
- Support pilot projects to determine the most effective incentives for antibiotic innovation in the Canadian context.
- Support pilot studies on a de-linkage model for select antibiotics to demonstrate efficacy.

Anticipated Outcomes: Increased activity in Canadian antibiotic innovation and the creation of new market models to serve as an example for other countries.

INTEGRATING NOVEL ANTIBIOTICS INTO THE HEALTH CARE SYSTEM

Rationale: Clinical trials for antibiotics present challenges not encountered for drugs that do not rapidly generate resistance. Limited approval is required in trials of a new antibiotic that restricts their use in order to preserve effectiveness. A balance is needed between preserving the effectiveness of a new antibiotic, allowing affordable access to those patients who need it, and providing an adequate return on investment.

Recommendations:

- Support innovative new clinical trials models for antibiotics, perhaps through the creation of a Canadian Clinical Trials Network for infectious diseases, that allows companies with new products a single point of entry to a network of testing centres across the country.
- Support evaluation research to determine whether new antibiotics on the market are being used appropriately and as intended.

Anticipated Impact: Guidelines will be developed to protect new drugs without restricting patient access. Canada will become the "go-to" place for clinical testing of new antibiotic candidates.

INNOVATIVE AMS INTERVENTIONS

MODIFYING ANTIBIOTIC PRESCRIBING

Rationale: Antibiotic prescribing across Canadian health care settings is highly variable for reasons that are poorly understood but that result in the overuse and inappropriate use of antibiotics, contributing to the generation of antimicrobial resistance and adverse collateral effects such as *C. difficile* infections. Real-time, reliable data on antibiotic prescribing practices in both inpatient and outpatient settings is required, as it is difficult to practice antimicrobial stewardship at a patient level in the absence of consistent information on the reason for the antibiotic, the kind of antibiotic needed, the dosage required, and the appropriate length of therapy. As most antibiotics are actually used in the agri-food sector, a one health approach is essential for understanding the antibiotic resistance transmission pathways between humans, animals and environment and for a better understanding of the broader issues at play in antimicrobial resistance, antibiotic usage and prescribing behaviours. For stewardship to be effective, a multidisciplinary approach is needed that incorporates program sciences, information technology, industrial engineering, behavioural science, implementation science, veterinary science and animal husbandry. In addition universal access is needed to the new technologies available through electronic developments, to promote information sharing within and across sectors.

Recommendations:

- Support behavioural research to explore the determinants of decision making in the health (prescribers and patients) and agri-food sectors, including the role of guidelines versus regulations.
- Support research, including clinical trials, to determine the most appropriate and effective interventions to impact antibiotic prescribing behaviour and decision making at a local and a systems level. *For example create a Canadian network in antibiotic resistance to evaluate interventions across the health and agriculture sectors.*
- Support research to determine best practices for training health care professionals, and veterinarians, on the appropriate use of antibiotics.
- Support research to provide real time feedback on the impact of interventions, including cost-effectiveness studies to inform decision making and investment .

Anticipated Impact: Antibiotic prescribing will be more consistent across prescribers, institutions and patient populations and the unnecessary/inappropriate use of antibiotics in medicine, agriculture, and the environment will be curbed, reducing the generation and impact of resistance. Prescribing guidelines and goals will be established that can be implemented at a local level, initially, to establish best practices that can be scaled up across the country.

ANTIMICROBIAL STEWARDSHIP ACROSS DIFFERENT POPULATIONS AND SETTINGS

Rationale: Antibiotic stewardship needs differ depending on the patient population and the health care setting. For humans, antibiotics are used in the community, long term care facilities, nursing homes, and acute care hospitals and for animals they are used on the farm, industrial feed lots, or

for companion animals in homes. Patient populations of particular concern are hard to reach and vulnerable groups, including indigenous populations such as First Nations, Metis and Inuit, those living in rural and remote locations, the frail elderly, immigrants, refugees and other ethnic groups, and anyone who is marginalized and disenfranchised. More data is needed on antibiotic resistance patterns and antibiotic use in all these groups, so that stewardship programs can be appropriately tailored to individual needs, while meeting national goals and standards.

Recommendations:

- Support research on the linkages between practices, patterns of resistance and antibiotic usage in different populations and settings to inform antimicrobial stewardship programs.
- Support research to promote optimal antibiotic prescribing and determine the appropriate interventions for different populations and different settings.

Anticipated Impact: Antibiotic prescribing and use will be tailored to meet the needs of special populations across multiple settings.

ALTERNATIVES TO ANTIBIOTICS

Rationale: It is unlikely that antibiotic resistance can ever be prevented and so concurrent with stewardship efforts to preserve the antibiotics it is essential to protect new ones coming to market, and pursue practical and cost-effective alternatives to traditional antibiotics for use in both the health and agriculture sectors. Several potential alternatives already exist, such as new compounds with novel modes of action, immune modulation, phage therapy, microbiome manipulation and vaccines. With respect to the microbiome, it is important to understand the off target effects of antibiotics, not just their effects on pathogens. For example, *C.difficile* infections are a common manifestation of the collateral damage caused by prolonged antibiotic use, especially in large tertiary care hospitals. Studies are needed to determine if giving probiotics with antibiotics might be effective in preventing these infections, or at least reducing their morbidity. More information is also needed about which antibiotics have the greatest impact on the normal gut flora and the selection for resistance, and a better understanding of the resistome, and microbial community structure and diversity.

Recommendation:

- Support research on potential alternatives for antibiotics in both the health and agri-food sectors.

Anticipated Impact: Antimicrobial stewardship efforts will be enhanced by the availability of alternatives or adjuncts to antibiotics, reducing the need for antibiotics and slowing the generation of resistance.

INNOVATIVE METRICS AND OUTCOMES

IMPROVING DATA LINKAGE AND INTEGRATION

Rationale: A common theme throughout the workshop was the need for more data, as well as better access to the data we already have. The availability of real time accurate data is a

prerequisite for antimicrobial resistance surveillance programs, providing information on antibiotic prescribing, and appropriate use in both human health and agriculture. Much of the data collected in inpatient and outpatient settings is fragmented and held in silos. This creates challenges in linkage and integration of information even in a single hospital although, theoretically, the technology is now available to consolidate this data. Real time data is already driving decision making in air transportation, banks, credit cards, and grocery chains, for example. As 70-80% of primary care physicians now have electronic medical records and hospitals are constantly building new information systems which could be designed to collect consistent and accessible antibiotic data, it should be possible to link this information electronically at a national level. One example is the recent launch, by the College of Family Physicians, of the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database - a pan-Canadian multi-disease electronic medical record surveillance system to improve patient management in chronic disease and neurological conditions.

Recommendations:

- Launch demonstration projects to show that electronic medical records and other forms of health information can be successfully linked at a jurisdictional/provincial level and scaled up across the country to support antimicrobial stewardship programs.
- Explore linkages to resources such as the Canadian Health Infoway and CPSCSSN as a means to support data linkage and management in antimicrobial stewardship programs.

Anticipated Impact: The functional linkage of existing electronic health data and other relevant health information will streamline investments and enhance the implementation of antimicrobial stewardship programs across facilities, patient groups and jurisdictions.

DEVELOPING APPROPRIATE METRICS

Rationale: Canada needs a validated composite measure of antibiotic resistance against which to benchmark the impact and cost-effectiveness of interventions in human health and agriculture; facilitate net comparisons across regions, facilities and patient/animal populations; and guide the implementation of those interventions most appropriate to individual settings. In addition, more information is needed on the metrics used to assess appropriate antibiotic use in Canada in both human and animal health and how these metrics compare with respect to ease of access and comparability. More precise metrics than those currently in use (e.g. number of kilograms of antibiotics in animals; defined daily dose, duration of treatment, and length of treatment in humans) are required that are tied to outcomes relevant to patient or animal welfare. In addition a common adjusted metric using consumed/administered versus dispensed antibiotics is needed for intra-and inter-hospital benchmarking in both adult and pediatric settings and different healthcare environments, as well as in animal welfare.

Recommendations:

- Develop and validate a composite measure for the burden of antimicrobial resistance that can be adapted across settings and sectors.
- Conduct an environmental scan of the metrics currently used to assess prescribing practices and appropriateness of use across the country to inform the selection of common metrics going forward.
- Support pilot studies on "adjusted" metrics in acute care settings to allow justifiable comparisons.

Anticipated Impact: The introduction and application of more concise metrics will better support comparative studies and benchmarking efforts in antimicrobial stewardship programs.

LABORATORY AND TECHNOLOGY

PROMOTING BETTER LINKAGES BETWEEN THE LABORATORY AND THE CLINIC

Rationale: There is currently an imperfect link between clinical laboratories and the health care professionals who use them, particularly in the community setting. Patients presenting in an outpatient setting with an infection are there to get help. Pressure is therefore brought to bear on the physician to prescribe an antibiotic and, in the absence a definitive diagnosis, many doctors will err on the side of caution prescribing an antibiotic for what may later turn out to be a viral infection. In addition, with no quick access to antibiotic susceptibility data, the physician may prescribe an ineffective antibiotic. The need for "rapid" diagnostics versus "point of care" diagnostics is unclear and depends on the circumstances. Critically ill patients may require immediate treatment, while ambulatory patient may be able to wait longer for treatment. This is an important distinction for the researchers and engineers designing diagnostic tests.

Recommendations:

- Support studies on the role of laboratory services in antimicrobial stewardship and how to forge better real time linkages between the laboratory and clinic.
- Support behavioural studies on the factors influencing the use of laboratory services by health care workers, and the mechanisms required to educate policy makers on the need to provide rapid susceptibility diagnostics.
- Support research to validate the appropriateness point-of-care diagnostics, monitor potential unintended consequences and test the impact of rapid diagnostics on important outcomes.
- Support research on the use of new technologies, eg. nanotechnology, in the development of innovative rapid diagnostics for use in health care, especially the outpatient setting, and also in animal welfare

Anticipated Impact: Health care workers will have real time information to determine if an antibiotic is needed and if so, which antibiotic will be effective, reducing the pressure on hospitals for further testing will be reduced.

KNOWLEDGE MOBILIZATION

Rationale: Public awareness programs on the dangers of antibiotic resistance are needed for all those working in the health, agriculture, agri-food and environment sectors. As antibiotic resistance rates continue to climb, stewardship programs to preserve clinically effective antibiotics and protect new products coming to market assume enhanced importance. In addition, steps must be taken to educate the public on the perils of counterfeit drugs imported from other countries, as well the basic principles of antibiotic resistance, including the necessity to complete a prescribed course of antibiotics and to discard any unused drugs immediately.

Recommendations:

- Conduct an environmental scan of successful Canadian and international social marketing campaigns geared towards increasing public awareness of antibiotic resistance and promoting optimal antibiotic use to identify best practices that could be shared.
- Support pilot projects to determine best practices for community engagement across a whole jurisdiction, including hospitals, clinics, outpatient settings, veterinarians, and the public.
- Support research to identify best practices for incentivizing health practitioners, pharmacists, institutions, and agri-food personnel to practice the principles of sound antimicrobial stewardship.

Anticipated Impact: The Canadian population will fully appreciate the dangers of antibiotic resistance and the necessity for antimicrobial stewardship programs and will work collaboratively to protect the viability of new and current antibiotics for future generations.

Next Steps

The CIHR leadership team will use the workshop recommendations to guide discussions on collaborative opportunities to move the antimicrobial stewardship research agenda forward in alignment with AMS Canada recommendations. CIHR is already actively engaged in a number of initiatives related to antimicrobial resistance, in areas such as transmission dynamics, new drug discovery, and diagnostics. An initiative on antimicrobial stewardship is particularly timely due to an upcoming international opportunity through the European Union's Joint Programming Initiative in Antimicrobial Resistance (JPIAMR) program. Previous JPIAMR calls have focused on target identification, transmission dynamics, and networking. The next launch to be released in January, 2017, entitled "Prevention and Intervention Strategies to Control AMR Infections" will include a focus on antimicrobial stewardship covering topics such as behavioural intervention strategies, rapid diagnostics, economic analysis, evaluation, education, and One Health pilot studies. JPIAMR programs enable researchers from three or more countries to combine their synergistic expertise, resources and infrastructures in an area of study to fast-track progress in a given field. Many Canadian researchers have already taken advantage of past opportunities and it is hoped that workshop participants will respond to the upcoming launch to advance international efforts in antimicrobial stewardship. In addition, the possibility new funding opportunities may arise in response to recommendations from the Canadian Antimicrobial Stewardship Task Force and other federal initiatives.