Beating Superbugs: Innovative Genomics and Policies to Tackle AMR

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Editor’s Preface

Launched in 2009, GPS: Where Genomics, Public Policy and Society Meet is a series hosted by Genome Canada to facilitate a dialogue between federal policymakers and researchers exploring issues at the interface of genomics and its ethical, environmental, economic, legal and social aspects (or GE3LS).

Overarching themes for the series and specific topics are selected on the basis of their importance and timeliness, as well as the “ripeness” of the underlying scholarship. Accordingly, the series focused on “Genetic information,” whereas in year two, attention shifted to “Translational Genomics”. The third series, “The Innovation Continuum” broadens the discussion by casting the process of innovation in a broader societal context. The 2014 series focuses on the bioeconomy. The concept of the bioeconomy is meant to capture economic activities, and their related products and services, which result from new discoveries in the biosciences, including genomics.

At the core of these exchanges is the development of policy briefs that explore options to balance the promotion of science and technology while respecting the many other considerations that affect the cultural, social, or economic well-being of our society.

Co-authors of the briefs are leaders in their field and are commissioned by Genome Canada to synthesize and translate current academic scholarship and policy documentation into a range of policy options. The briefs also benefit from valuable input provided by invited commentators and other experts who participate in GPS events. Briefs are not intended to reflect the authors’ personal views, nor those of Genome Canada. Rather than advocating a unique recommendation, briefs attempt to establish a broader evidence base that can inform various policymaking needs at a time when emerging genomic technologies across the life sciences stand to have a profound impact on Canada.

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Executive Summary

The world is in danger of losing effective antibiotics as a result of the evolution and spread of antimicrobial resistance (AMR). Resistant bacterial pathogens are spreading across more than 250 infectious diseases of concern in Canada. As a multi-sectoral issue, AMR must be addressed both scientifically and through appropriate national policies. It calls for new drugs, the prudent use of existing ones, and innovation in finding alternatives to current practices that select for AMR. Because of the strong links of AMR across humans, animals and the environment, a One Health paradigm—which links the human, animal and environment/ecosystem health domains—must underpin successful AMR policy development. Tackling AMR effectively will require input from scientists and policy makers, as well as antimicrobial users (clinicians, farmers, patients) and suppliers in the private sector. It will also require the involvement of the genomics field in order to understanding how AMR genes evolve, move through communities and become expressed.

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I. Context

Antibiotics enable modern medicine. Not only are they used to treat infection, they also allow physicians to undertake a wide range of life-saving and pain-relieving practices. Cancer chemotherapy, major surgeries, organ transplants and artificial joints all depend on the infection control afforded by antibiotics. Agriculture relies extensively on antibiotics to maintain healthy herds of food animals, treat infections that can result in massive economic losses, and promote animal growth in high-intensity farming.

It is not an understatement to consider antibiotics as one of the highest-impact discoveries of the 20th century. They have profoundly changed society: infections are now responsible for less than 5% of deaths, whereas in the pre-antibiotic era of the 1920s infections were the major cause of mortality (57%) (Statistics Canada 2015; Statistics Canada 2014).

Today, however, we are in danger of losing effective antibiotics as a result of the evolution and spread of antimicrobial resistance (AMR). Resistant bacterial pathogens are spreading across more than 250 infectious diseases of concern in Canada. Some examples include methicillin resistant Staphylococcus aureus (MRSA), carbapenem-resistant Enterobacteriaceae (CRE) (e.g., NDM-1, KPC); vancomycin-resistant Enterococci (VRE); multidrug resistant Salmonella species; multidrug resistant tuberculosis (MDR-TB); Neisseria gonorrhoeae (N. gonorrhoeae); and Clostridium difficile (Cdiff). The lay press frequently refers to such microbes as ‘superbugs’, particularly when they have become resistant to multiple antimicrobials.

One of the reasons for the AMR crisis is that the environment is an unexpectedly large reservoir of antibiotic resistance genes. These have been built up over millennia (D’Costa et al 2006; D’Costa et al 2011) and continually re-seeded and selected through the use of antimicrobial drugs in human and animal medicine, along with activities of modern agriculture, wastewater treatment and industry that result in a release of antimicrobials into the environment. The genes encoding resistance elements do not respect national borders, or even the traditional biological boundaries of species. Instead, many of them are mobile moving not only from mother

What's in a name?

The antibiotics field includes many terms with overlapping definitions. This paper uses the terms ‘antibiotic’ and ‘antimicrobial’ interchangeably, noting that ‘antibiotic’ denotes a particular class of antimicrobials, which is the most prevalent and predominantly targeted at bacteria. ‘Antimicrobial’ includes ‘antibiotic’ microbe-killing drugs as well as other products that act on parasites and fungal infections.

Antibiotics: Attributed to Selman Waksman, the pioneer of antibiotic discovery, this term formally refers to compounds produced by microorganisms that inhibit the growth of another microorganism. Over time, this definition has expanded in most areas to include synthetic compounds as well as those produced by microbes, and to focus only on compounds that affect bacteria.

Antimicrobial agents: Chemical substances that inhibit the growth of microbes (e.g. bacteria, fungi, parasites). The category hence includes antibiotics, antifungals and antiparasitics.

Antiseptics: Chemical substances that inhibit the growth of microbes, generally with a non-specific mechanism applied topically (e.g. alcohols and detergents).
to daughter cells but between species and general (Perry and Wright 2013). The so-called ‘resistome’—the totality of antibiotic resistance genes in the environment and the clinic—is in constant flux, challenging the long-term efficacy of all antibiotics.

The results of this phenomenon may be catastrophic. As Figure 1 shows, a 2014 UK government report predicts that 10 million people will die as a result of unchecked AMR by the year 2050, with a blow to the global economy of $100 trillion U.S.

Figure 1

![Figure 1: AMR now and AMR in 2050](source: Review on Antimicrobial Resistance 2014)

While Canadians can all be considered at risk generally, some may be at heightened risk from an antimicrobial-resistant infection. They include seniors, children, aboriginal peoples and people with compromised immune systems (including those who are in hospital care for illness or surgery or are undergoing routine outpatient treatments such as chemotherapy or dialysis). It is open to speculation whether the growing migration of peoples occurring currently in the world will have an impact on the dynamics of AMR in receiving countries, including Canada (World Health Organization 2016).

Yet despite the threat of AMR to the health and wealth of countries around the world, and the growing clinical need for new antibiotic drugs, few new drugs are coming to market. The reasons for this are complex but include a challenging economic environment for new antibiotics, complex national and international regulatory landscapes, and ultimately very difficult scientific barriers. As a multi-sectoral issue, AMR must be addressed both scientifically and through appropriate national policies. It calls for new drugs, the prudent use of existing ones, and innovation in finding alternatives to current practices that select for AMR.

Because of the strong links of AMR across humans, animals and the environment, a One Health paradigm—which links the human, animal and environment/ecosystem health domains—must be the framework for successful AMR policy development. The One Health approach has developed during the past decade into a globally-adopted paradigm that is inter- and multi-disciplinary, multi-jurisdictional and international in scope. It focuses on the dynamics of interactions across domain interfaces. International pressure for a One Health approach has increased in recent years, with the World Health Organization (WHO), the World Organization for Animal Health (OIE) and the G7 taking a leading role.

Tackling AMR effectively will require input from scientists and policy makers, as well as antimicrobial users (clinicians, farmers, patients) and suppliers in the private sector. A Canadian AMR strategy should engage physicians, patients, farmers, veterinarians and pet owners for a comprehensive approach to the issue. It must address alternatives to antibiotics, beneficial sanitary practices, the impact on cost of product and other trade relevant factors. As well, it must include an effective informative communications approach to each of the relevant sectors as well as the general public.

As perhaps the most significant challenge facing the health care sector thus far in the 21st century, AMR has received increased international attention over the past decade from international organizations. The WHO has called for all member countries to develop national action plans to address the AMR issue, and do so in a globally coordinated effort. The World Health Assembly endorsed the WHO Global Action Plan on AMR in May 2015. In November 2014, Canada released its federal framework for action, which was followed by a high-level federal action plan on AMR in March 2015.

The field of genomics must play an important role in the success of the federal framework on AMR. AMR is the outcome of the activities of microbial genes. These genes are influenced by their host organisms, environments and the massive selection pressure exerted by antibiotics. In the presence of high levels of antibiotics, microbes are placed in an ‘adapt or die’ mode. The sheer numbers of microbes in the environment (10,000–50,000 different species in 1 gram of soil) and their remarkable adaptability ensure that with selection, mechanisms of antibiotic resistance will emerge. Furthermore, increasingly we are realizing that even sub-lethal concentrations of antibiotics result in dramatic impacts at the level of gene expression. Furthermore, bacteria have developed multiple strategies to share genetic information. Such mobile genetic elements have proven to be highly diverse, able to accommodate multiple antibiotic resistance cassettes, and their distribution capacity vexingly difficult to predict.
Understanding how AMR genes evolve, move through communities and become expressed is vital to the success of Canada’s Action plan on AMR. Successful stewardship requires deep understanding of selection of AMR gene expression and mobilization. Accurate AMR surveillance depends on rapid diagnostics, advances in genome sequencing and bioinformatics tools for gene identification and mining. Finally genomic-based platforms are essential for the development of new antibiotic drugs and alternatives to antibiotics that may prove less susceptible to resistance.

The objectives of this report are to describe the challenges of AMR in the context of the Action Plan’s three areas of focus: surveillance, stewardship and innovation, and provide options to guide policy to address them. In particular, the role of genome sciences and expertise is highlighted as this area of scientific expertise must be harnessed to achieve the common goal of preserving the advances that we have enjoyed in the antibiotic era.

II. Issues

Canada’s Action Plan for AMR is based on three key areas that public health investigators across the globe agree must be addressed: Surveillance, Stewardship and Innovation. Genomics is vital to success in each area.

1. Surveillance

Effective surveillance of a global phenomenon such as AMR requires open access to data across public and private sectors, and among national and international jurisdictions. Understanding and cataloguing the existing diversity and mechanisms of resistance elements currently circulating in pathogens in human and animal reservoirs is vital to managing AMR risk [see Figure 2]. We need to understand the mechanisms by which this complex global reservoir seeds new resistance in disease-causing bacteria in order to develop practices and policies that minimize gene mobilization.

The complex interplay of resistance genes found in non-pathogenic environmental bacteria, along with their potential to be captured by pathogens, is largely unknown and unexplored. Most AMR genes on mobile elements likely originate in these non-pathogenic bacteria, since resistance is pervasive and ancient in this group. Figure 3 below illustrates a conceptual model of the environmental pathways that can result in an increased risk of human and animal infection with antibiotic-resistant bacteria.

Canada currently lacks well-coordinated surveillance of human and animal pathogens and their associated AMR profiles. National coordination is complicated by Canadian federalism, with relevant responsibilities in this domain distributed among the provinces.
and territories. There appear to be no policies directing federal and provincial jurisdictions to cooperate on AMR. The result is a pastiche of ad hoc studies that do not capture the benefit of a coordinated comprehensive approach.

Similarly there is a lack of coordination with other governments and our trading partners to integrate data from various locations into an international network of AMR surveillance. The WHO Global Action Plan on AMR calls for international collaboration, including surveillance; and in late 2015, the WHO initiated a program to support the development of national plans on AMR in all of its member states, facilitated by the provision of advice through a coordinated body of contracted experts made available to countries in need. Another recent international initiative, the Global Health Security Agenda, which was initiated in 2014 and currently involves over sixty countries, has made AMR as one of its action priorities (Seoul Declaration 2015).

The need for international collaboration is increasingly important in view of rapidly emerging economies such as China and India, where few effective controls exist on the use of antibiotics and consequently selective pressures that maintain and enrich AMR are stronger. The threat of the antibiotic resistance element NDM-1 demonstrates the need for collaboration in surveillance [see box below].

A brief history of NDM-1

The antibiotic resistance element NDM-1 has emerged as a severe global health challenge. It confers resistance to penicillin, cephalosporin, and carbapenem antibiotics, which are the mainstays of antibiotic therapy in the community and in the hospital. Furthermore, NDM-1 is found on genetic elements that always contain genes conferring resistance to many other classes of antibiotics; hence bacteria that acquire NDM-1 are invariably multi-drug resistant, frequently to all currently available drugs. The first report of NDM-1, in 2009, was from a strain of *Klebsiella pneumoniae* isolated from a patient in Sweden who had recently been hospitalized in New Delhi, India. By convention, the new gene was named for the city of origin and its biochemical function (New Delhi Metallo-beta-lactamase) and numbered ‘1’ as the first gene of its kind.

Since 2009, the NDM element has spread to many other pathogenic bacteria (including *Pseudomonas, E. coli,* and *Acinetobacter*) and has spread to dozens of countries across the globe. It has also been found widespread in the environment and water supply in India and Pakistan, which contributes to its dispersal. The U.S. Centers for Disease Control and Prevention have classified NDM-containing enteric bacteria as an ‘urgent threat’, their highest level of antibiotic resistance concern.
The world is truly a global village from the perspective of drug-resistant pathogens, since modern trade and transportation enable microbes and their resistance genes to travel the world in a matter of hours to days. This is illustrated by the global spread of drug-resistant Enterobacteriaceae, in particular ones carrying the KPC gene that confers resistance to penicillin, cephalosporin and carbapenem antibiotics (Nordmann et al 2011; and see Figure 4).

Another concern about globalized AMR development and its link to agricultural practices relates to the MCR-1 gene. This gene is linked to resistance to the antibiotic colistin, one of the last-resort antibiotics for human use (Yang 2016). Initially reported by Chinese researchers in 2015, MCR-1 has since been found (through targeted global surveillance) in E. coli in livestock, meat products and human patients, including one Canadian patient who likely became infected outside of Canada. The MCR-1 gene is easily shared with other microbes, making a potentially wide range of pathogens to colistin. However, the use of colistin and other polymyxin antibiotics in livestock production is widespread and growing. With bacterial strains now harboring both MCR-1 and carbapenemase genes, we have effectively entered the post-antibiotic era.

Surveillance must take advantage of bacterial genomic and metagenomic data, which is increasingly easier to obtain using next generation-sequencing infrastructure. These data must be monitored to track and model outbreaks and identify new points of entry of new pathogens and associated AMR genes. Surveys of resistance elements in non-pathogenic environmental bacteria can serve as an early warning with respect to new genes that may emerge in pathogens.

Critical to the success of such genome surveys are well-funded central repositories of molecular AMR information and bioinformatic tools to interrogate sequence data. Grassroots efforts in Canada have established the Comprehensive Antibiotic Resistance Database (CARD) which is being accessed by investigators and clinicians across the globe (McMaster University n.d.). However, these resources do not have dedicated funding and are not well integrated with international efforts in other sectors (such as the GenBank initiatives that are working to harness and analyze genetic information to address AMR occurrence and risk) (National Center for Biotechnology Information 2015).

Figure 4

A) Worldwide geographic distribution of Klebsiella pneumoniae carbapenemase (KPC) producers. Gray shading indicates regions shown separately: B) distribution in the United States; C) distribution in Europe; D) distribution in China.

Source: Nordmann et al 2011
2. Stewardship

Prescribing ‘the right antibiotic for the right infection’—that is, targeting antibiotics very specifically to an identified infectious organism—lessens the selective pressure for the emergence and establishment of AMR. Overuse of antibiotics is a significant contributor to the maintenance of AMR in bacterial populations and in the human health clinic.

Rates of antimicrobial use in agriculture are likely even higher, particularly in resource-poor areas of the globe where antibiotics are plentiful and cheap. In Canada and in the U.S., agricultural practice in recent years accounts for about 80% of all antibiotic use (Public Health Agency of Canada 2007; Martin et al 2015). In Canada, the issue is further complicated by ‘own-use importation’ of antimicrobials (in which a person can import such drugs without prescription, often over the internet), as well as off- or extra-label use of antimicrobials in animal health practice (i.e. for disease indications other than as defined by the drug registration).

Antibiotic use in the growth and care of food animals varies worldwide. Canada appears to be a moderate consumer of antimicrobials in livestock, but global consumption is projected to rise overall by 67% from 2010 levels by 2030, and nearly to double in Brazil, Russia, India, China, and South Africa (Van Boeckel et al 2015). The increase is likely driven by growth in consumer demand for livestock products in middle-income countries and a shift to large-scale farms where antimicrobials are used routinely.

Increasing evidence links AMR in human pathogens with prior selection in agriculture through the use of identical or similar antibiotics in this sector. Even the use of antibiotic alternatives such as metals (e.g. zinc) selects for mobile resistance elements that include resistance genes to drugs used in human medicine (Seiler et al 2012). The economic drivers of these practices are complex, and in many countries are not subject to rigorous regulation or scrutiny. The problem is exacerbated by increased globalization, which moves agricultural products across borders with ease.

The culture of prescribers (veterinarians and physicians) also must be addressed. Antibiotics can be prescribed by many health care practitioners regardless of their experience or knowledge in infection control and AMR. Expectations among patients and animal owners that antibiotics are necessary as a first response to any illness leads to over-prescription and a ‘tragedy of the commons’ in which individual decisions undermine a resource of value to society as a whole. New animal management practices to avoid infection and the spread of pathogens would further reduce the need for antibiotic use, and thus the spread of AMR.

Successful stewardship efforts require reliable and sensitive diagnostics, for which the use of genomic technologies holds the greatest advantage. The ability to provide accurate results rapidly is an integral requirement for effective diagnostics, not just for identification of the infectious disease organisms, but also its AMR characteristics. Here there is a knowledge gap and a need for innovation and markets. Price points in agriculture (i.e. the low profit margins typical for animal and plant production) make it challenging to adopt diagnostics that are costly or require specialized laboratory expertise or equipment; hence, simple paper-based diagnostics would be transformative by decreasing unnecessary use of antibiotics, and therefore lessening the selection pressure for AMR.

Until recently there has been no central effort to champion the stewardship agenda in Canada. This changed in 2015, when the Public Health Agency of Canada was mandated to lead interdepartmental federal efforts on AMR and develop and implement a horizontal policy driven agenda for AMR that integrates the scientific knowledge base in policy considerations.
3. Innovation

The AMR crisis will require new antibiotic drugs, antibiotic adjuvants (compounds that potentiate antibiotics and/or block resistance), alternatives to antibiotics (e.g. probiotics, prebiotics, bacteriophage products), vaccines, and new practices. Genomic techniques and knowledge are at the core of many of these efforts, both in the discovery and development phases as well as in the deployment and evaluation phases to support surveillance efforts.

The pharmaceutical sector faces challenges in developing new antibiotic drugs. This sector, which has traditionally been the source of new antimicrobial medicines to address AMR, has been leaving the field for scientific/technical, regulatory, and financial reasons during the past decade. (Not the least of these reasons is the short lived use of any new antibiotic, since onset of resistance is rapid.) There are currently no ‘big pharma’ private companies pursuing discovery research on new antibiotics with internal research and development programs in Canada—and only a very few in the world.

Much of the burden of discovery and development has been diverted to small and medium biotechnology in Europe and the U.S., where successful innovations tend to be acquired by large pharmaceutical companies. In Canada, however, the lack of a robust research and development biotechnology industry, and associated investment culture, means that AMR has not been an attractive area for entrepreneurial research activities and venture capital investment.

Substantial innovation to address AMR has been pursued in academia. Investments through the Canadian Institutes for Health Research (CIHR) and the Natural Sciences and Engineering Research Council (NSERC) in Canada, as well as similar agencies in other countries, have enabled innovation in AMR-directed research focused on the pre-clinical realm.

Moving these discoveries from the laboratory into clinical use has been challenging, however, in light of the so-called ‘valley of death’ for entrepreneurs who require significant outside investment to de-risk the development of promising drug candidates and

Current and potential antimicrobial therapies

For the past century, treatment and control of infection in medicine and agriculture have used hygiene, vaccines, and antimicrobial agents. Going forward, hygiene (including access to clean water and good sanitation) remains the most cost-effective mechanism to prevent and control infection. It is relatively low in cost yet has immense benefit. Many parts of the world still do not have access to hygienic conditions, resulting in reliance on other strategies such as antibiotic use, which selects for resistance.

Vaccines remain the best solution to prevent disease and control the spread of outbreaks. By preventing infection in the first place, disease is kept in check and can even be eradicated (e.g. smallpox). Many highly effective vaccines are available for common infections; however, it has been challenging to prepare effective vaccines for all infectious agents. For example, despite over a century of effort, no effective vaccine for tuberculosis exists; as a result, tens of millions remain infected and over 1.3 million die each year. Efforts to develop and improve vaccines are desperately needed.

Antibiotics remain the most effective therapy to treat active infections. Antibiotics are small molecules, produced by microbes or in the lab by chemists, that inhibit bacterial growth. The rise of resistance is greatly impacting the efficacy of these drugs. Identifying new antibiotics has proven very challenging to the pharmaceutical sector, and many companies no longer actively pursue these medicines. As a result, there is a growing innovation gap in antibiotic discovery and development.

Antibiotic adjuvants are molecules that can be used to extend the useful lifetime of existing antibiotics. These adjuvants either directly block resistance or otherwise increase the potency of antibiotics. Co-formulated with antibiotics, versions of these combination drugs have been in use for two decades. There is great opportunity to expand this area of research to identify other combinations that preserve existing antibiotics.

New antimicrobial strategies include the use of phage (viruses that infect bacteria) to eradicate disease-causing bacteria; the identification of drugs that do not kill bacteria but rather prevent infection (anti-virulence); therapies to boost the host immune response; and pre- and pre-biotics that alter the host microbiome (the collection of microbes that live in and on all animals and humans) to improve health and immune response. All of these strategies require rigorous evidence-based assessment; however, initial efforts show promise as alternates that do not select for antibiotic resistance.
diagnostics. Other countries have put in place approaches to overcome this (for instance the U.S. National Institute of Allergy and Infectious Diseases (NIH), with its preclinical services platform). In Canada, public-private partnerships for AMR developments have been difficult to find. The National Research Council has a refreshed mandate to assist in bridging from discovery to commercialization, and should be able to contribute to AMR innovation by drawing on its extensive experience in microbiology, genetics and drug development but it will not be trivial to achieve competence or critical mass in this area.

III. Policy Environment

AMR is a ‘wicked’ public health problem because of its biological complexities as well as chronic policy and system failures. One of its biggest challenges is a lack of coordination among many sectors and actors within Canada that do not easily collaborate. The time is right for the development of nationally coordinated Canadian AMR policies that engage the country’s 13 provincial and territorial health systems as well as the health care system administered federally for Canada’s Inuit and First Nations and the so-called ‘federal population’ including the armed forces. Such coordination must extend to the veterinary public health sector spread across Canada’s diverse jurisdictions.

The desired national Canadian approach should ideally be congruent with international efforts emerging in several global sectors in response to the AMR crisis. These include international organizations such as the WHO (which has released a Global Action Plan on AMR); international initiatives such as the Global Health Security Agenda (GHSA) recent declarations on AMR by G7 countries; and recommendations from the Organization for Economic Co-operation and Development (OECD) (Cecchini 2015). Policy frameworks to address AMR have been released by major trading partners including the EU (European Union 2016), U.S. (White House 2015a, 2015b; Centers for Disease Control and Prevention 2015) UK (UK Government 2013) and Australia (Government of Australia 2015) and other countries are increasingly following suit. The U.S. is writing AMR measures into law through the Generating Antibiotic Incentives Now (GAIN) Act, which encourages investment in antimicrobial development and instructs policy makers (such as the Food and Drug Administration) to align their regulations with the clinical need for new drugs. These initiatives are being supported by funders such as the Gates Foundation, the Welcome Trust, U.S. National Institutes of Health (NIH) and in Canada the Canadian Institutes of Health Research (CIHR).

In 2015, Canada’s federal government released its Action Plan for AMR, which provides a high-level framework for policy development and action. No detailed agenda for its implementation has yet been made public; nor is a specific genomic agenda linked to the action plan, although genomic studies will figure prominently in solutions to the AMR crisis. Within the federal framework there have been recent efforts to develop a common Genomics Research and Development Initiative (GRDI), led by the National Research Council and uniting relevant departments and agencies of the federal government (e.g. the Public Health Agency of Canada, Agriculture and Agrifood Canada, the Canadian Food Inspection Agency and Environment Canada, all of which have responsibilities impacted by AMR). These efforts should be linked with those of provincial agencies as well as with organizations outside of the public sector in order to develop a comprehensive Canadian AMR agenda.

Integration across the health and agricultural sectors is especially important given the realization that only a One Health approach can adequately address the AMR crisis. The World Organization for Animal Health (OIE) has identified AMR as a priority for its member states (World Organization for Animal Health 2015). In Canada, the Canadian Veterinary Medical Association has put out a position statement and guidance documents on prudent antimicrobial use in production and companion animals (Canadian Veterinary Medical Association 2016). Canada’s animal production sector is also responding to the issue, as evidenced by a 2012 survey report on AMR released by the National Farmed Animal Health and Welfare Council (NFAHW Council 2012). The sector is gathering information and developing policies on AMR and antimicrobial use that can be accepted by its constituency.

IV. Policy Options

A) Surveillance

Surveillance is a key element for AMR response. There is a great need for comprehensive data-gathering efforts to monitor the flow of AMR genes in real time within and among microbial reservoirs, across the country and planet, in each of the human health and animal health and production sectors. Such surveillance requires cooperation of provincial health and agriculture networks with federal authorities to pool data and share information and material (e.g. bacterial strains and gene sequence data) in an unencumbered, seamless and timely manner. Indeed, the Canadian Food Inspection Agency should make AMR surveillance as a ‘farm-to-fork’ priority, assuring that AMR surveillance is implemented along the entire value chain of food production from the grower to the consumer.

Canada should partner with international agencies to gather and share data in order to monitor the global tides of AMR based on models of gene and pathogen movement. Integrating AMR data
with movement of goods (including animals and animal products) and people would enable the development of evidence-based risk assessment guidelines that can inform foundation for new policy strategies.

Recent findings suggest that surveillance of AMR should be extended to include companion animals, which are exhibiting increases in AMR similar to humans and may be an additional reservoir. Surveillance should include the extent and patterns of antimicrobial usage in companion animals, including cascade use of antimicrobials (particularly with respect to human-authorized antimicrobials).

A new Canadian Antimicrobial Surveillance System (CARSS), spearheaded by the federal government, will combine existing government-supported human and animal surveillance systems in the initial phase of its development. Eventually it will also integrate environmental AMR information into a comprehensive One Health approach. CARSS is to be ‘evergreen’ and adaptable to the rapidly changing surveillance needs required for progress on AMR and antimicrobial use. It will also establish national targets and performance measures.

AMR surveillance must adopt a genomics view, which requires investment in bioinformatics platforms and tools that are globally cohesive or open-sourced in order to facilitate data sharing. In order to enable the evolution of such a comprehensive surveillance platform, Canada needs more experts trained in both bioinformatics and genomics.

B) Stewardship

Stewardship preserves our existing drugs and enables us to protect these precious resources and allow their sustainable use for as long as possible. The principle of stewardship should be adopted by medical practitioners, whether physicians, clinicians or veterinarians, as well as naturopaths, farmers and Canadians in general. Stewardship policies should be based on the ‘right drugs for the right bugs’ formula in order to eliminate inappropriate prescription of antibiotics in the health and agricultural sectors. Success will require the cooperation of stakeholders such as Canadian Medical Association, the Canadian Veterinary Medicine Association, the private sector, and academia, including the curricula in medical and veterinary schools, as well as the essential communication with patients, clients, customers and the general public.

The development of evidence-based practices and incentives for ‘antibiotic-free’ agricultural practices has the potential to lessen the need for antibiotic use and consequently decrease AMR selection. Sanitary farming practices are being implemented in a few countries, demonstrating that reliance on antimicrobials for hygiene can be markedly reduced using proper infrastructure and policies without being an economic hardship to farmers.

C) Innovation

Soon after his discovery of penicillin in 1928, Alexander Fleming warned that he expected resistance to arise to this antibiotic, which readily occurred, as it has with all subsequent antibiotics. Today the AMR crisis demands massive global investments to develop new drugs, preserve old drugs and develop alternatives to antibiotics. New diagnostics are needed, including patient bedside tests that can accelerate diagnosis of infection and facilitate effective early treatment as well as feed into a national and global AMR surveillance database. Opportunities abound for large-scale public and public-private investments to prime innovation, both in academia and in small- and medium-sized biotech.

Public-private partnerships such as the ‘New Drugs for Bad Bugs’ program of the Innovative Medicines Initiative in Europe (Innovative Medicines Initiative 2010) seek to stimulate academic research in AMR-related drug discovery and to help bring candidate drugs closer to market. Also promising are efforts by the U.S. National Institutes of Health to de-risk academic discoveries through expert guidance and access to cutting-edge pre-clinical services. In the UK, the Longitude Prize has been established for advances in point-of-care diagnostics for AMR; and in the U.S., President Obama has proposed similar prizes to prime efforts in sensitive diagnostics.

Such efforts to accelerate the generation of new options to combat AMR may require modifications to regulatory policies for the development of new drugs and practices. The European Medical Authority and the U.S. Food and Drug Administration (FDA) are leading the way in modifying regulations for new drug approvals. Accompanied by policies that modify market exclusivity rules to encourage private sector development, such efforts are already having impact—for example, in the recent accelerated approval by the FDA of the new antibiotic Avicaz with only Phase II clinical trials data.

Canadian policy efforts to encourage the development of new antibiotic drugs are lagging by comparison with other countries.
Canada must systematically identify and remove barriers to research and development in AMR, and act to stimulate innovation and development in the national biotech and pharma sectors.

V. Implementation and Future Prospects

While many initiatives in the three domains of surveillance, stewardship and innovation already exist in Canada, these must be shared among jurisdictions in order to enable coordination and more rapid cost-effective advances. For instance, proven approaches such as the ‘Do Bugs Need Drugs’ community awareness program in Alberta and British Columbia could be adapted and expanded across other provinces and territories (Alberta Health Services 2016). A network-of-networks approach could support each of the segments of the various jurisdictions and sectors, maintaining their decision-making independence while creating a ‘greater whole’ through information and cost-sharing as well as congruent approaches to science and policy development.

As well as addressing the biological and clinical dimensions of the AMR challenge, Canada and the world must also grapple with the political economics of inaction. AMR demands a science-based strategy for collective global action. For instance, international agreement on antibiotic use in livestock is needed to establish global rules and thus a level competitive field for producers. Genuine engagement is needed with industrial sectors such as pharmaceuticals, livestock production and information technology.

The successes of international mega-projects such as the International Space Station and the Human Genome project show that science can be harnessed and funded to solve a large problem of global significance. It may be that the AMR crisis is even more complex than those precedents. Broad collaborative engagement in science and policy development is needed to address this crisis, and genomic sciences are vital to the agenda.

References


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