Antimicrobial-Resistance Drugs: From Drug Discovery to Access Is Canada Prepared for Their Entry?

CADTH Symposium 2018

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Dr. Lucye Galand, Health Canada
Dr. Sameeh Salama, Fedora Pharmaceuticals
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What is antimicrobial resistance (AMR)?

- AMR develops when microorganisms evolve so that treatments become less effective, and sometimes do not work at all.

- AMR occurs naturally, but inappropriate or over use of antimicrobials increases emergence and spread.
Significant Global Human and Economic Impacts

- AMR can spread quickly around the world
- By 2050, 10 million deaths worldwide, overtaking diabetes and cancer combined
- The global economy could fall between $2 and $6 trillion USD

Worldwide deaths attributable to AMR every year (compared to other major causes of death)

The State of Antimicrobial Resistance in Canada

1 in 16 patients admitted to hospitals will get a multi-drug resistant infection

That is more than 20,000 hospital patients developing a drug-resistant infection each year

In Canada, overall rates of AMR in Canada remain stable and are similar and/or lower than many other countries in the world

However, rates of resistance for some infections have shown increases

- rates of AMR Neisseria gonorrhoea over past 10 years
- Rates of MRSA

Many Canadians know someone who has been impacted directly (e.g. infection) or indirectly (e.g. burden of care) by drug-resistant infections
Global Response to AMR

The **G7 and G20** have been seized with the issue for several years

- Global AMR Research and Development Collaboration Hub (June 2017)

**UN General Assembly High Level Meeting** (September 2016)

- Agreement to develop and implement national action plans
- Only 4th health issue taken up in 72 years
One Health Linkages of Antimicrobial Resistance
### PAN-CANADIAN FRAMEWORK ON ANTIMICROBIAL RESISTANCE AND ANTIMICROBIAL USE

#### SURVEILLANCE

Strong, integrated surveillance systems are needed to provide a comprehensive picture of AMR and AMU in Canada.

#### INFECTION PREVENTION AND CONTROL

To contain the spread of resistant organisms and reduce AMR and AMU, standardized infection prevention and control approaches, programs and policies must be in place.

#### STEWARDSHIP

Programs and policies that highlight education, awareness raising as well as professional and regulatory oversight will be required to reduce inappropriate prescribing, dispensing and use of antimicrobials in humans and animals and to conserve the effectiveness of new and existing antimicrobials.

#### RESEARCH AND INNOVATION

Responses to AMR must be evidence-based and will require increased knowledge, innovative tools and collaborative approaches to better understand resistance and the development of new treatments and strategies.

### OUTCOMES

#### OPPORTUNITIES FOR ACTION

- Engage with stakeholders to ensure coordination at all levels to move towards robust and comprehensive surveillance systems with defined objectives and the required capacity for AMR and AMU data collection.
- Establish coordinated platforms and mechanisms to link AMR and AMU data, in particular from human health, animal health and agriculture sectors.
- Enhance coordinated technical guidance for data collection, collation and comparison, including developing standardized definitions of AMR and priority microorganisms in humans and animals.
- Engage all levels of government and stakeholders to take action within their realm of responsibility:
  - Deliver communication, education/training programs and tools on evidence-based IPC practices and strategies for all stakeholders and professionals in human and animal health.
  - Facilitate and promote the application and oversight of IPC best practices, including immunization, through policy/guidelines development, standard-setting and knowledge translation.
- Work with communities and stakeholders to build capacity and reduce inequalities in delivering comprehensive and effective IPC programs in the human and animal health sectors.
- Invest in IPC research to expand knowledge about and improve the effectiveness and sustainability of IPC practices across human and animal health.
- Support the development of a pan-Canadian antimicrobial stewardship network to provide ongoing leadership and coordinated action across human and animal health sectors, while respecting the roles and responsibilities of each level of government.
- Implement a robust system for collecting AMU data to support continuous improvement of stewardship across the human and animal health sectors.
- Develop governance tools, such as regulations and organizational accreditation requirements as well as consistent standards for prescribing, dispensing and distributing of medically important antimicrobials for medical and veterinary use, while respecting the roles and responsibilities of each level of government.
- Build knowledge about antimicrobial stewardship through enhanced and coordinated educational curricula for prescribers (including continuing education opportunities), dispensers and end users of antimicrobials as well as public awareness programs and activities, which highlight the impact of AMR and AMU.
- Support a cross-sectoral, multidisciplinary research network to facilitate antimicrobial discovery, best practices, behavioural research and economic and production impacts across sectors and jurisdictions.
- Explore mechanisms to develop the capacity and appropriate infrastructure required to further support the development of human and veterinary medicines and alternative tools.
- Establish a fast-tracked cost effective process for licensing antimicrobial drugs, alternatives to antimicrobials and new diagnostic tools in Canada to incentivize pharmaceutical investment without compromising safety, efficacy and quality.
Canada’s Strengths

- Clinical trials
  - Canada ranks 4th globally in number of clinical trials

- Drug discovery
  - New antimicrobials and vaccines

- Antimicrobial Alternatives
  - Adjuvants, immunomodulation, etc.

- Diagnostics
  - *Antimicrobial Resistance: Point of Care Diagnostics in Human Health*
Challenges to Drug Development and Access

Tomorrow’s Antibiotics: The Drug Pipeline

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

Source: Antibiotic resistance threats in the United States, 2013, CDC, 2013
Next Steps

How can we leverage Canadian expertise and strengths to respond to the threat of AMR and collaborate with others internationally?
AMR and Innovation: The Regulator’s Perspective

April 17, 2018

Dr. Lucye Galand, A/Director
Bureau of Gastroenterology, Infection and Viral Diseases
Therapeutic Products Directorate
Roles and Responsibilities for AMR/AMU in Canada

Under the Pan-Canadian Framework for Action

Health Canada - Health Products and Food Branch Mandate

Regulate the market authorization of antimicrobial drugs/biologics/medical devices for humans and animals, and set policies and standards related to the safety and nutrition of the food supply.
Health Canada Roles

- **Stewardship**
- **Surveillance**
- **Infection Prevention and Control**
- **Research and Innovation**
Health Canada Actions – Stewardship

Overseeing labelling changes to strengthen appropriate use of antimicrobials
- Removing growth promotion claims from medically important antimicrobials for animal use
- Adding stewardship logos to labelling of antimicrobials for veterinary use
- Adding stewardship statements to product monographs of antimicrobials for human use

Implementing regulatory changes for veterinary antimicrobials
- At least 14 medically important antimicrobials for veterinary use switched to required prescription for use
Health Canada Actions – Stewardship

Review of clinical efficacy indications for selected antibacterial classes

- Re-examination of the efficacy of fluoroquinolones for the following indications:
  - Acute bacterial sinusitis
  - Acute bacterial exacerbation of chronic bronchitis
  - Uncomplicated acute bacterial cystitis
  - Acute uncomplicated gonorrhea

- Restrictions, adjustment and/or removal of some indications for self-limiting infections for some members of the fluoroquinolone classes

Working with partners/stakeholders to strengthen healthcare professionals oversight of medically important antimicrobials

- Patient and Outreach Initiatives to promote prudent prescribing and use under a One Health Approach
Health Canada Actions – Research and Innovation

Developing alternative policy options and regulatory pathways to incentivizing innovation for human antimicrobial products
  o Proposed Pathogens of Interest List
  o Regulatory Review of Drugs and Devices

Increased international collaboration on the harmonization of guidelines and technical data requirements for the scientific review of novel therapeutic products for human use:
  o TATFAR, ACSS Consortium Teleconference cluster (Infectious Diseases), NCE WG, ICH

Participating in Genomics Research and Development Initiative (GRDI) project on AMR
Proposed Pathogens of Interest List

Publication of a Notice in Spring 2018 focused on a Proposed Pathogens of Interest List, which is anticipated to:

- Inform sponsors of the bacterial pathogens in most urgent need of innovative therapeutic drugs/devices in Canada
- Assist Health Canada in prioritizing the review of new antimicrobials
- Provide guidance to sponsors on the existence of current regulatory enablers
- Guide the development of new tools and policy approaches by Health Canada

Health Canada will be seeking comments as part of a public consultation on the Proposed List
Regulatory Pathways Currently Available

The following regulatory pathways are already available in HPFB to facilitate market entry in Canada:

- Priority Review of Drug Submissions
- Notice of Compliance with Conditions (NOC/c)
- Extraordinary Use New Drugs
- Access to Drugs in Exceptional Circumstances
- Fecal Microbiota Therapy (FMT)
- Submissions relying on Third-Party Data
- Fee Remissions
Considerations for Successful Innovation

AMR innovation is a shared responsibility
- Along the product and market lifecycle continuum
- Between academia, industry, government, HTA organizations and the healthcare system

Advancement and development of new antibiotic candidates, non-traditional therapeutics, and/or biologics/vaccines at all stages
- Recognizing the scientific challenges in R&D, pre-clinical development and early clinical stages

Creation of new incentives and open collaborative partnerships
- Push versus pull systems of incentives

Improved diagnostics
- Rapid “point-of-care” tests that can be used to identify bacterial infections, susceptibilities and resistance profiles
Considerations for Successful Innovation

New antibiotics alone will not be sufficient to mitigate the threat of AMR
  - Development should go hand in hand with:
    - One Health approach to infection prevention, detection and control
    - Fostering of appropriate use of existing and future antibiotics through stewardship measures.

Surveillance remains the major cornerstone of success

What is Canada’s place in the Global AMR Innovation Strategy?
Next Steps

Continue discussions with government partners, (PHAC, CIHR, ISED), international counterparts and other stakeholders (industry, academia)

Determine what roles and responsibilities HPFB is best positioned to take in developing an innovation incentives bundle

Establish a structured approach to develop and implement new policy tools and regulatory approaches to incentivize innovation
Canada’s AMR Research & Innovation: Opportunities and challenges

CADTH April 17, 2018

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www.fedorapharma.com
2018 updated FDA Approval of new parenteral antibiotics

- Vabomere(BL-BLI) (2017)
- Delavance (lipoglycope) (2014)
- Oritavancin (lipoglycope) (2014)
- Zerbaxa (ceftz-Taz) (2014)
- Telavancin (lipoglycope) (2013)
FDA Approved Antibacterial vs. Anticancer Agents: 1998-2018

Source: CenterWatch
CDC Biggest Threats (2013 Report)-combined with ESKAPE pathogens

**Urgent Threats:**
- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- *Neisseria gonorrhoeae*

**Serious Threats:**
- Multidrug resistant *Acinetobacter*
- Drug resistant *Campylobacter*
- Fluconazole-resistant *Candida*
- Extended-spectrum *Enterobacteriaceae* (ESBL)
- VRE
- Multi-drug resistant *Pseudomonas aeruginosa*
- Drug-resistant non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* serotype *typhi*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

www.fedorapharma.com
Challenges facing antibiotic discovery: “valley of death”
Canada’s AMR innovation gap

Canada’s challenges can be summarized in 4 main categories:

1. Discovery
2. Commercialization
3. Clinical Research
4. Health System Adoption
Canada’s AMR innovation gap

More specifically, Canada’s discovery support system challenges include:

1. Resource/Funding availability: **Push/Pull strategies**

2. Training and *retention* of translational teams: *The Medicinal Chemistry Challenge*

3. IP Management and strategies

4. Regulatory knowledge
Suggested Readings

DECLARATION BY THE PHARMACEUTICAL, BIOTECHNOLOGY AND DIAGNOSTICS INDUSTRIES ON COMBATING ANTIMICROBIAL RESISTANCE

January 2016

Antimicrobial and antibiotic resistance play a crucial role in modern medicine. These are crucial medicines to other issues for growth and are not only necessary to treat life-threatening infections, but are also vital for implementing most common surgical procedures and many chronic treatments such as chemotherapy and HIV and transplant medicines. They also play a crucial role in the health of animals.

The increase in bacterial resistance to antibiotics has been dramatic, and combating this crisis has a top priority for global policy and public health. There is particular concern that antibiotics are being overprescribed, and they are being replaced by new, more resistant drugs, including some antibiotics and antifungals. Inadequate approaches to treating and preventing infections.

Innovations that have been implemented and are widely acknowledged to be the result of a combination of science and business. This has impacted antibiotic development over several years. The pharmaceuticals, biotechnology, and diagnostics industries have an important role to play, and we are committed to doing our part. Leadership by other sectors is also crucial, and we will continue to be part of the solution for AMR, as well as the actions of governments and public health organizations. (See also the London 5 Year Review of AMR Declaration) and the leadership and policy of the International Organization for Dairy (IO), the WHO, and the CDC, the public health and policy bodies of the World Health Organization (WHO), and the European Commission, and the European Food and Veterinary Health Commission (EFSA), and the European Food and Veterinary Health Commission (EFSA). In addition, we support a progression of effective approaches to combat global antimicrobial resistance.

A Pan-Canadian Framework for Action

DRIVE-AB REPORT
Revitalizing the antibiotic pipeline
Stimulating innovation while driving sustainable use and global access

EMBARGOED UNTIL 15th January 2016

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

FEDORA PHARMACEUTICAL INC

www.fedorapharma.com
Antibiotics HTA Challenges
2018 CADTH Symposium

Simon Yunger
Hoffmann-La Roche, Canada
Agenda

- Challenges
- Global Initiatives
- Proposed Value Framework
- Next Steps
### Misalignment between Antibiotic Clinical Trials and Current Frameworks

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Ethical and practical constraints</strong></td>
<td>Antibiotic trials are designed primarily as non-inferiority trials</td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>Given trial size and duration, recruitment is difficult and not always feasible, especially for resistant patients</td>
</tr>
<tr>
<td><strong>Generalizability</strong></td>
<td>The patients that physicians treat on a regular basis are often excluded from RCTs due to exclusion criteria e.g. immunocompromised, severe patients</td>
</tr>
<tr>
<td><strong>Other Data Sets</strong></td>
<td>Other data sets alongside microbiology data and PK/PD studies are used to draw conclusions relating to efficacy</td>
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| **Patient Reported Outcomes** | Demonstrating benefits in health economic or patient reported outcomes is difficult due to the acute nature of the disease  
Patients with serious in-hospital infections are likely to have co-morbidities, are typically frail/elderly and often too sick to complete PRO instruments |

- Propose novel incentive models to reinvigorate antibiotic R&D
- A work package was formulated to assess gaps in the current HTA of antibiotics and propose solutions
Global Initiatives to Problem Solve

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<tr>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
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Antibiotics Value Forum (Feb 2017)

Assessing the Value of New Antibiotics: Additional Elements of Value for Health Technology Assessment Decisions

Sarah Karlberg Schaffer, Peter West, Adrian Towe, Christopher Henshall, Jorge Mestre-Ferrandiz, Robert Masterton and Alastair Fischer

May 2017
Antibiotics Value Forum (Feb 2017)

• **WHAT**
  – Multi-stakeholder meeting to discuss antibiotic value demonstration challenges and align on perspectives on how to establish value
  – Propose a novel value framework to assess unique value of antibiotics

• **WHO**
  – Payers / health economists, KOLs, industry (Roche, GSK & MSD), Dame Sally Davies (CMO for England), and Marco Caveleri (EMA)
  – Co-led by Office of Health Economics (OHE) & Academy of Infection Management (AIM)

• **WHY**
  – Identify tangible next steps to create a pragmatic definition of value that can be used to guide decision making for all relevant stakeholders
  – Publish findings for referencing
**Proposed Value Framework for Antibiotics**

**Traditional HTA Requirements**

<table>
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<tr>
<th>Health Gain (Clinical efficacy, microbiological, quality of life)</th>
<th>Traditional HTA Requirements</th>
</tr>
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<tbody>
<tr>
<td>▪ Superiority RCTs</td>
<td>▪ Non-inferiority trials</td>
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<thead>
<tr>
<th>Unmet Need (Severity, alternatives)</th>
<th>AMR Specific HTA</th>
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<tbody>
<tr>
<td>▪ Evidence of length of QOL of current therapies</td>
<td>▪ Priority pathogen lists</td>
</tr>
<tr>
<td>▪ Captured in Clinical Trials/Modelling Studies</td>
<td>▪ Epidemiology studies (AMR rates for particular pathogens)</td>
</tr>
</tbody>
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| Cost Offsets                                                    | Not Collected                |
| ▪ Modelling Studies                                             | ▪ Not Collected               |

| Productivity Benefits                                           | Not Collected                |
| ▪ Modelling Studies                                             | ▪ Not Collected               |
# Proposed Value Framework for Antibiotics

## Additional Benefits Relevant to Antibiotics

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<thead>
<tr>
<th>Benefit Description</th>
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<tbody>
<tr>
<td><strong>Transmission</strong></td>
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<tr>
<td>- Controlling the spread of infection to other patients and the wider population</td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
</tr>
<tr>
<td>- Having treatments available in case of future outbreaks</td>
</tr>
<tr>
<td><strong>Enablement</strong></td>
</tr>
<tr>
<td>- Enabling other procedures (such as chemotherapy and surgery) to proceed in the knowledge that possible infections may be treated</td>
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<tr>
<td><strong>Diversity</strong></td>
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<tr>
<td>- Evidence that using a range of different antibiotics to treat a pathogen across a population of patients reduces the risk of resistant strains of the pathogen developing</td>
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<tr>
<td><strong>Novel Action</strong></td>
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<tr>
<td>- Antibiotics with a novel mechanism of action are valuable in the fight to combat AMR because there is a lower likelihood that pre-existing resistance to them exists</td>
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Next Steps from an HTA Perspective

Discuss and align on most appropriate value benefits

Develop technical models to incorporate into HTA frameworks
Doing now what patients need next