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

CADTH Symposium 2018

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Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

Canadian Context on Antimicrobial Resistance

CADTH April 17, 2018

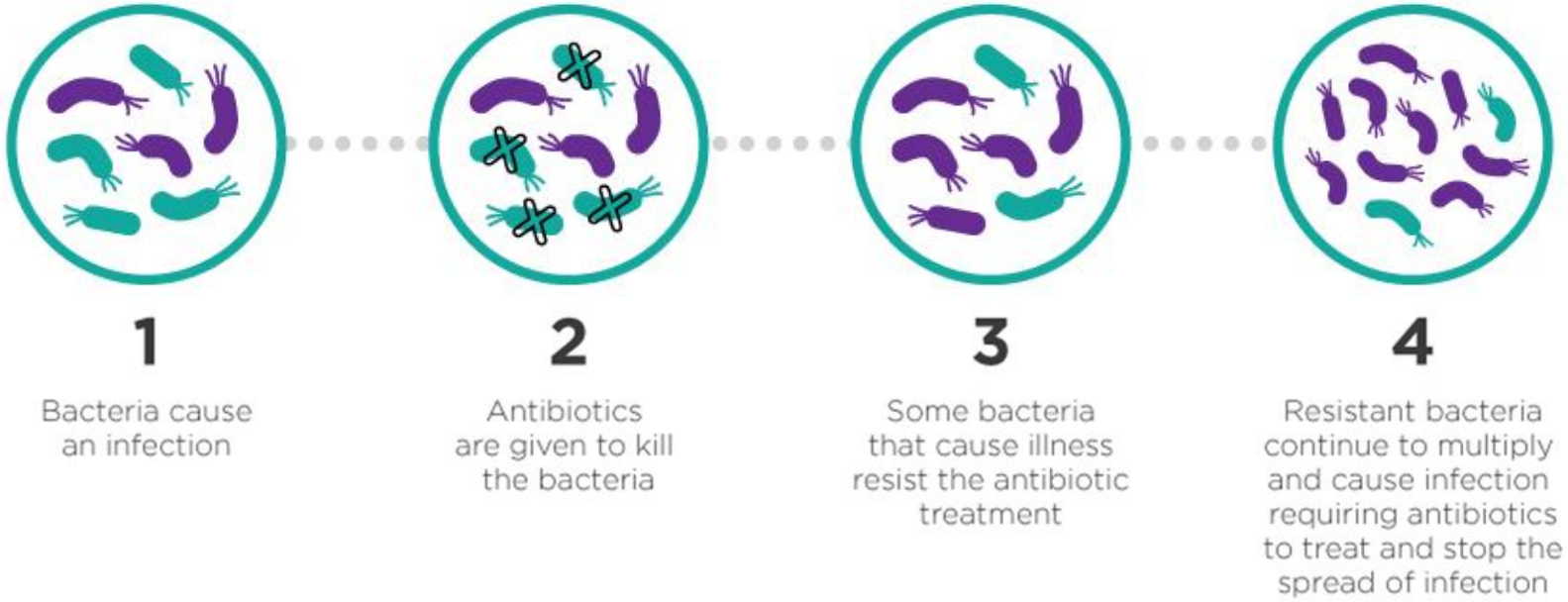
Dr. Howard Njoo, Deputy Chief Public Health Officer
Public Health Agency of Canada

PROTECTING AND EMPOWERING CANADIANS
TO IMPROVE THEIR HEALTH

What is antimicrobial resistance (AMR)?

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

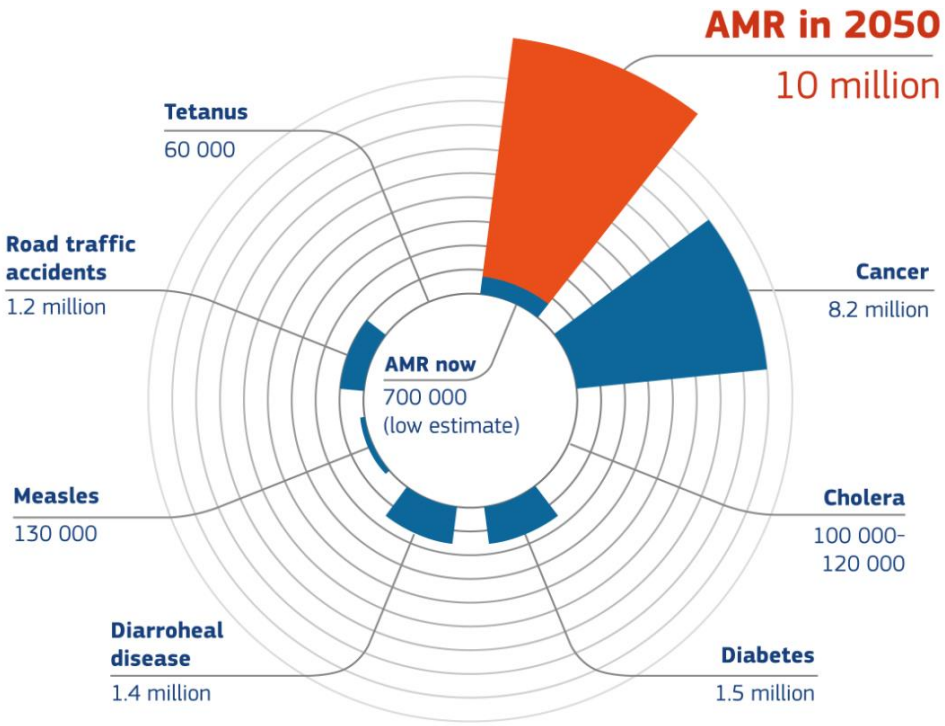
- AMR occurs naturally, but inappropriate or over use of antimicrobials increases emergence and spread



Significant Global Human and Economic Impacts

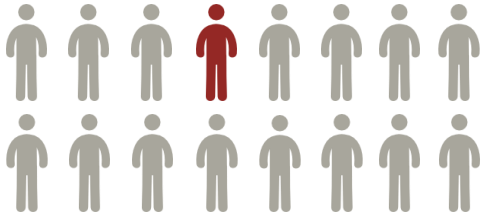
- AMR can spread quickly around the world
- By 2050, 10 million deaths worldwide, overtaking diabetes and cancer combined
- The global economy could fall between $2 and $6 trillion USD

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



Source: *The Review on Antimicrobial Resistance*, Jim O'Neill, 2014

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

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

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

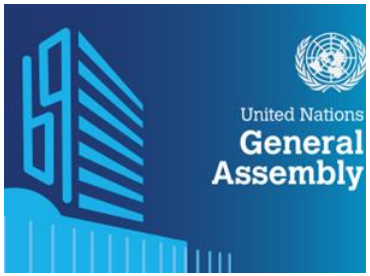
However, rates of resistance for some infections have shown increases

- ⬆ rates of AMR Neisseria gonorrhea over past 10 years
- ⬆ Rates of MRSA

Global Response to AMR

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

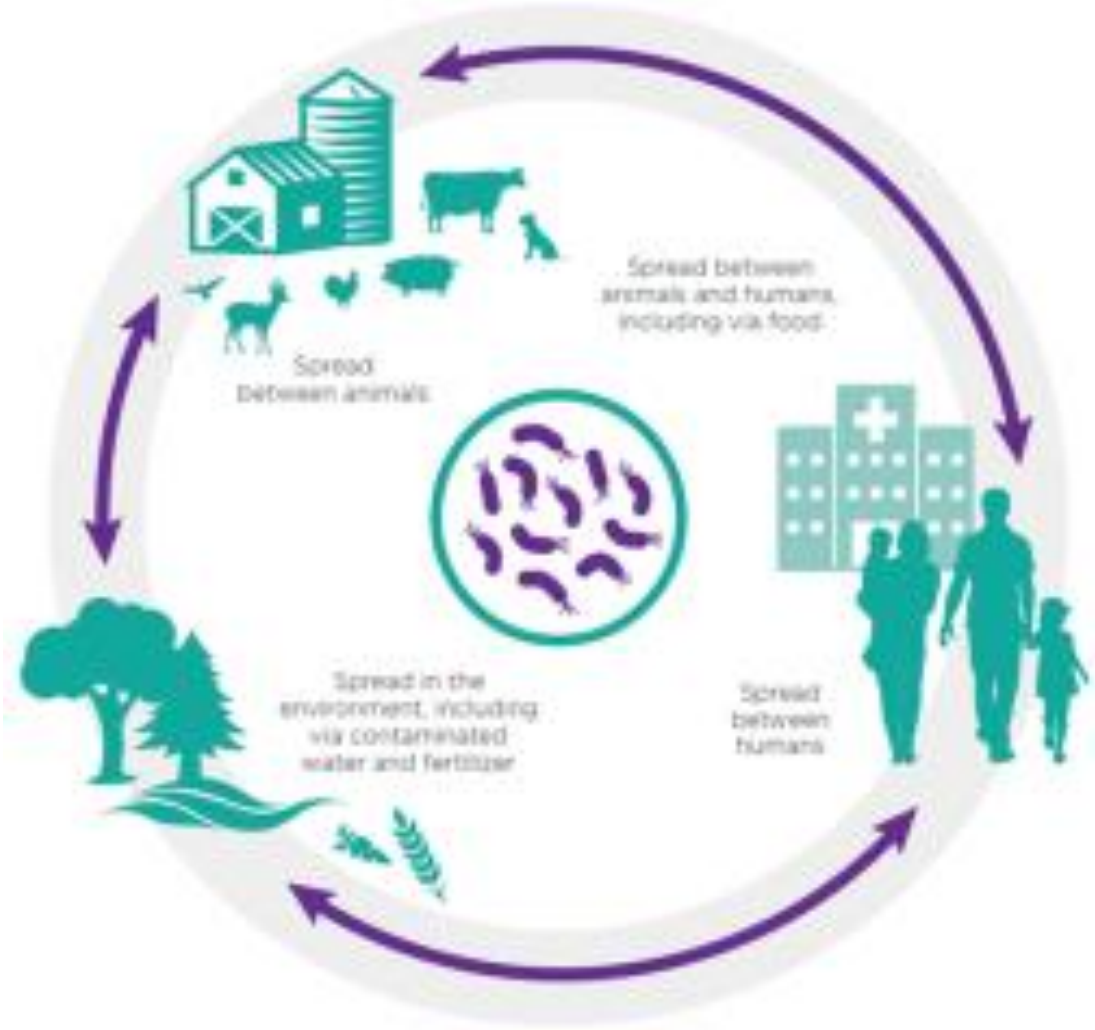
- Global AMR Research and Development Collaboration Hub (June 2017)



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	INFECTION PREVENTION AND CONTROL	STEWARDSHIP	RESEARCH AND INNOVATION

OUTCOMES

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

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.

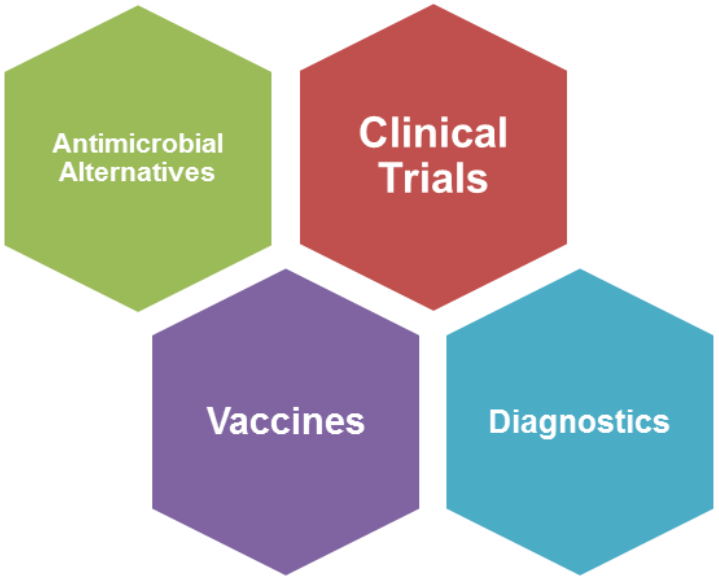
- Engage all levels of government and stakeholders to take action within their realm of responsibility:
  - A. Deliver communication, education/ training programs and tools on evidence-based IPC practices and strategies for all stakeholders and professionals in human and animal health.
  - B. Facilitate 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

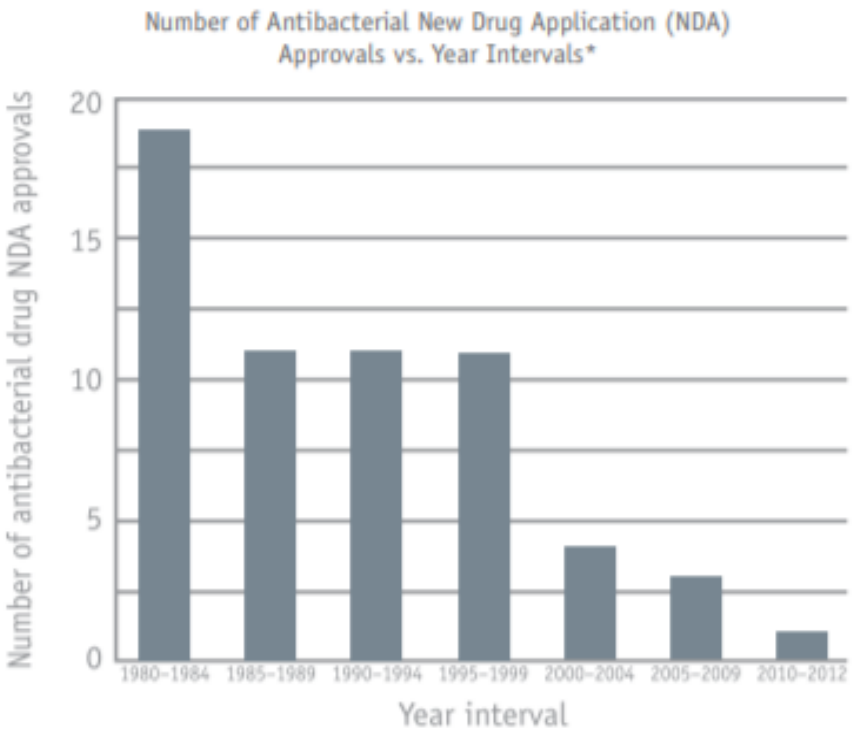
- Clinical trials
  - Canada ranks 4th globally in number of clinical trials
- Drug discovery
  - New antimicrobials and vaccines
- Antimicrobial Alternatives
  - Adjuvants, immunomodulation, etc.
- Diagnostics
  - *Antimicrobial Resistance: Point of Care Diagnostics in Human Health*



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.



*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents.
Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).

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?

Health Canada Santé Canada

Canada

AMR and Innovation: The Regulator's Perspective

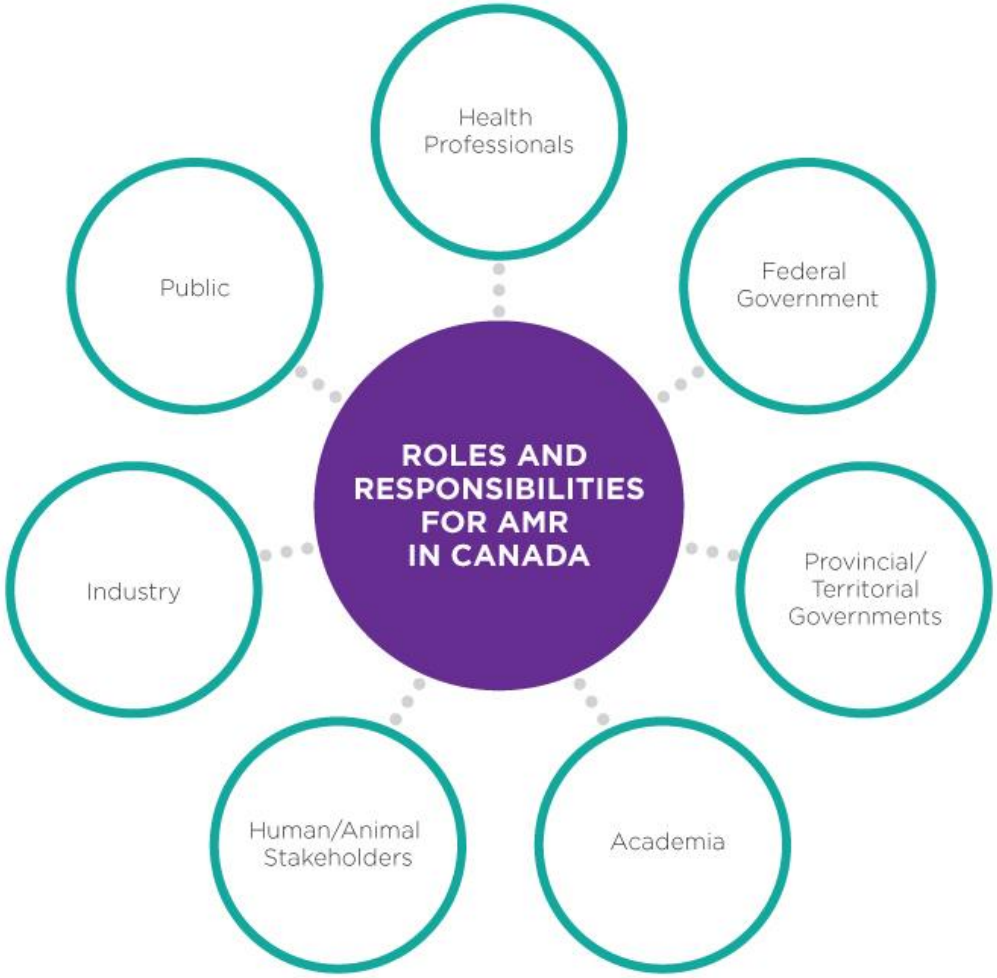
April 17, 2018

Dr. Lucye Galand, A/Director
Bureau of Gastroenterology, Infection and Viral Diseases
Therapeutic Products Directorate

YOUR HEALTH AND SAFETY... OUR PRIORITY.

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

- Proposed Pathogens of Interest List
- 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:

- 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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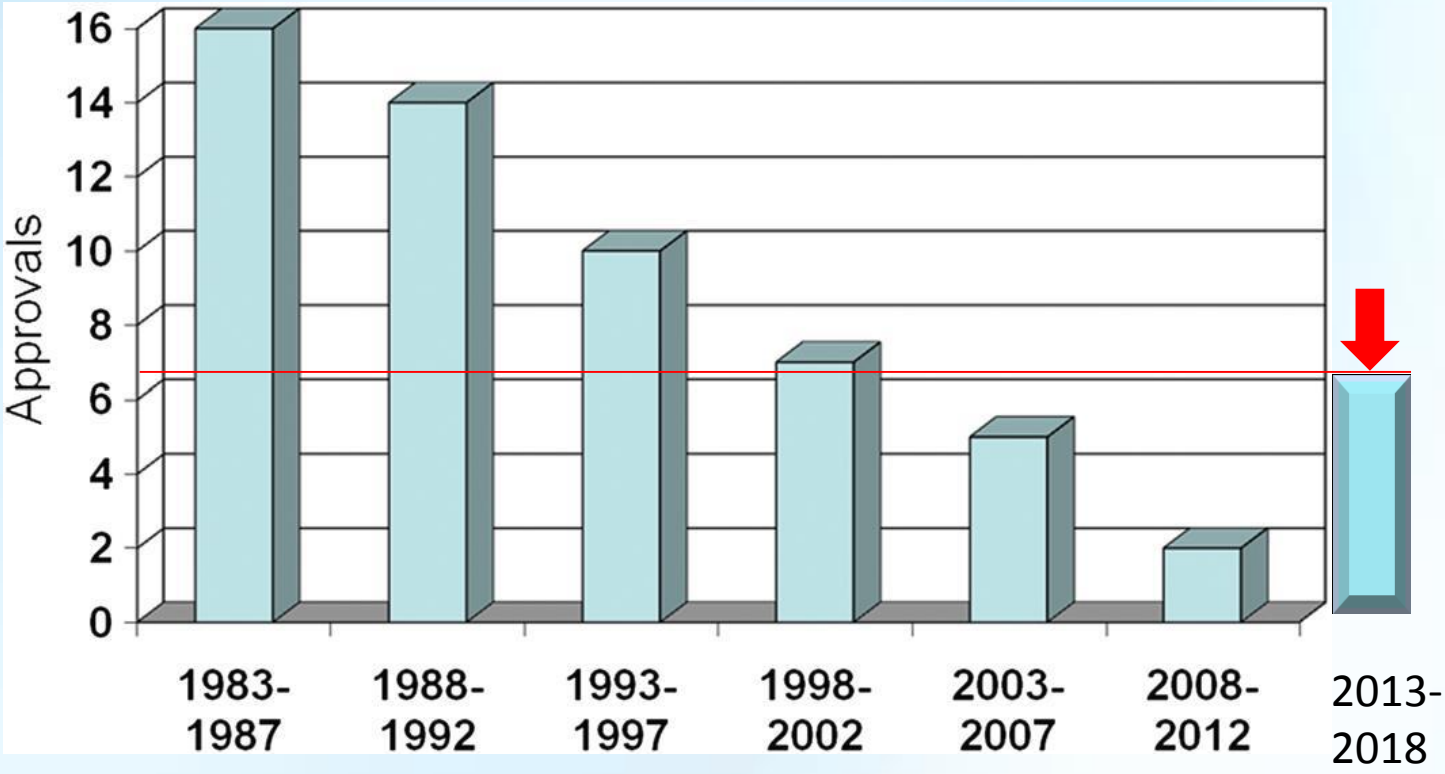
2018 updated FDA Approval of new parenteral antibiotics



- Vabomere(BL-BLI) (2017)
- Avycaz(BL-BLI) (2015)
- Delavance (lipoglycope) (2014)
- Oritavancin (lipoglycope) (2014)
- Zerbaxa (ceftz-Taz) (2014)
- Telavancin (lipoglycope) (2013)

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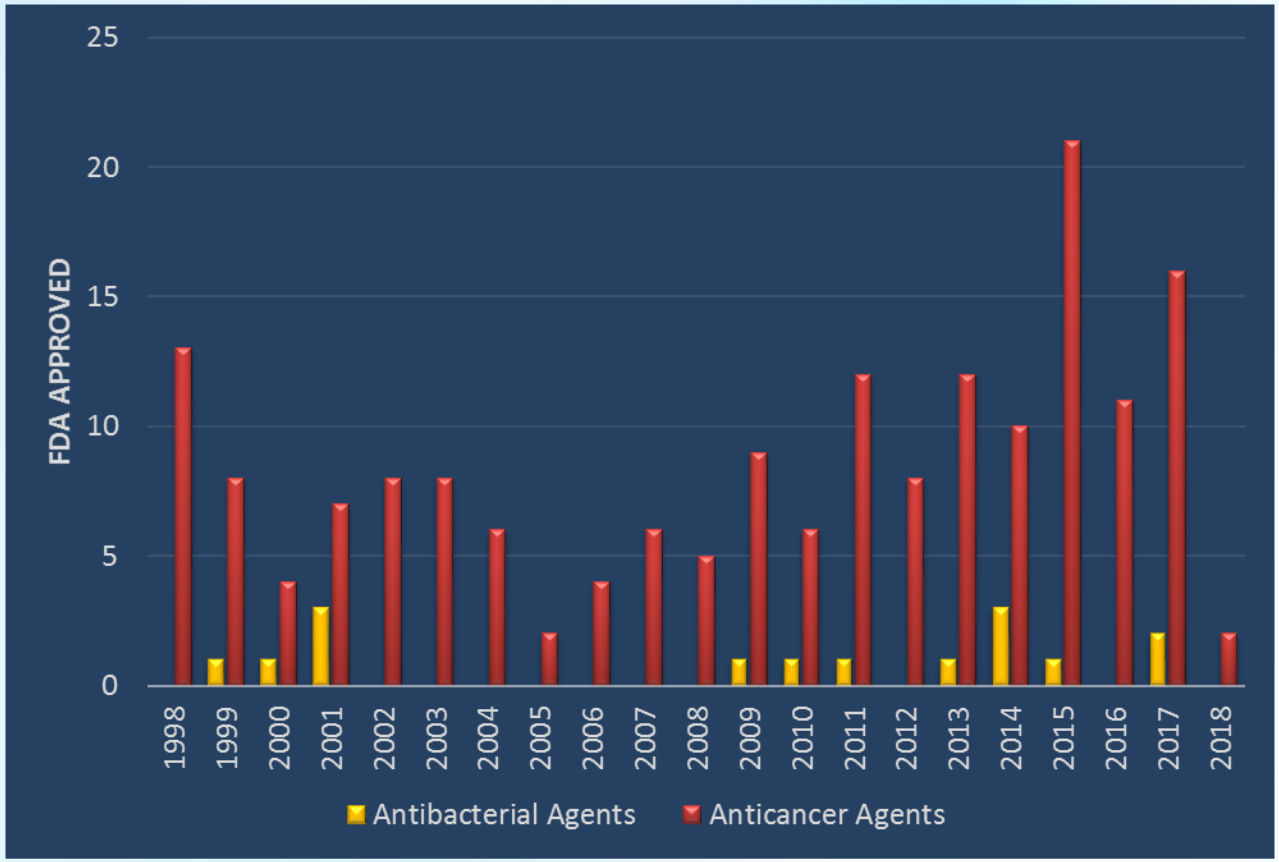
FDA Approved Antibacterial vs. Anticancer Agents: 1998-2018



Source: CenterWatch

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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

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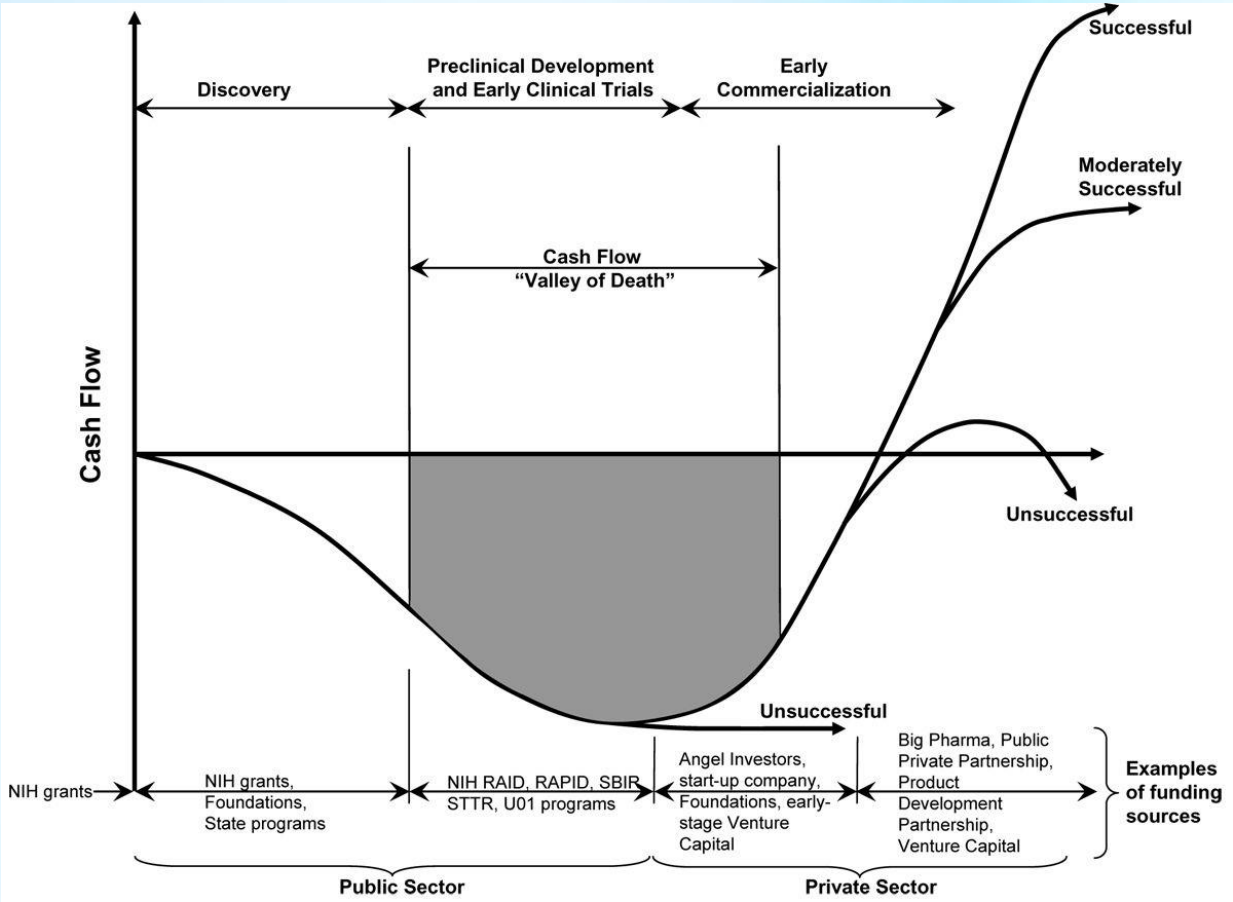
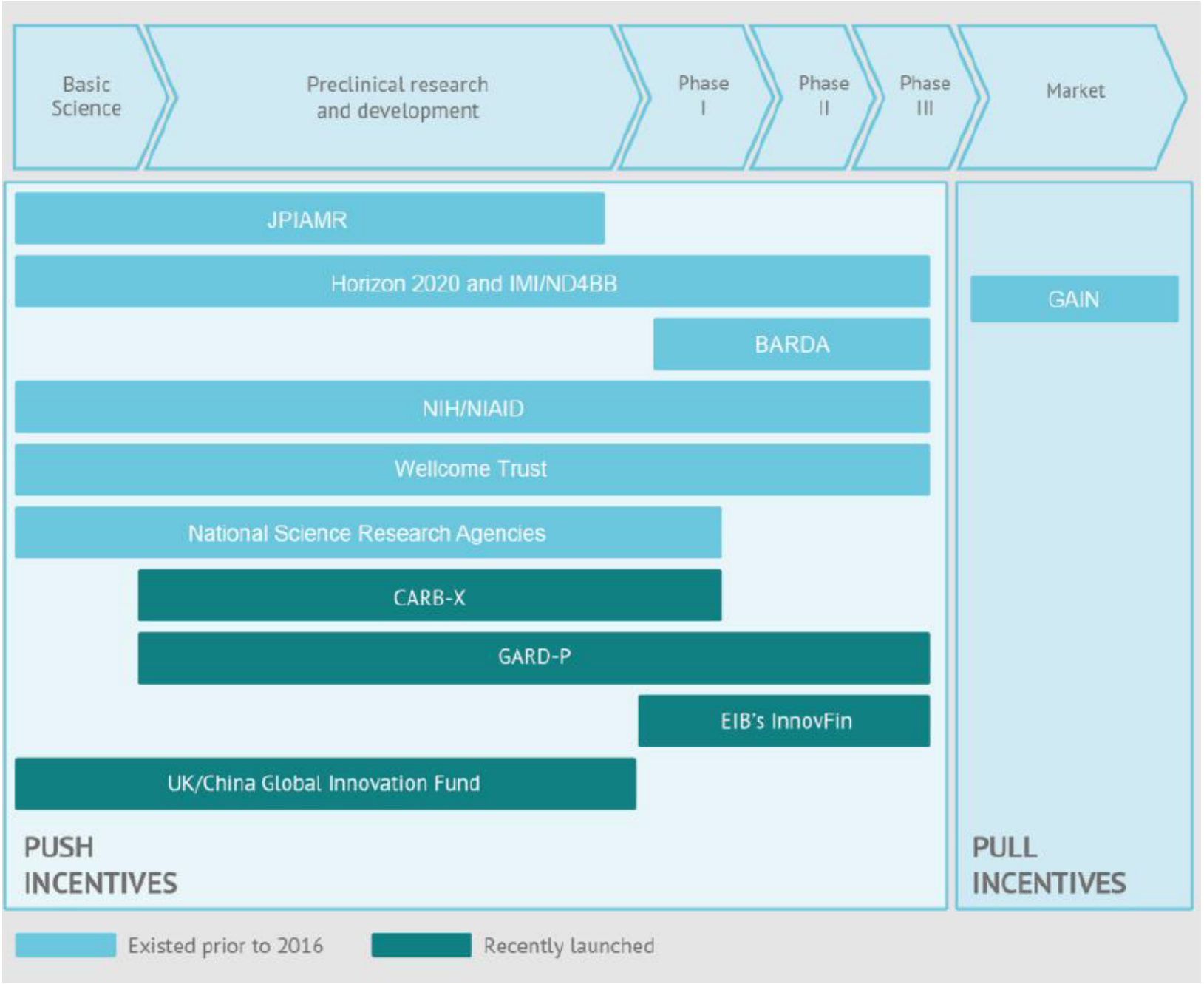
Challenges facing antibiotic discovery: "valley of death"





Adopted from: Drive-AB Report. Revitalizing the antibiotic pipeline. January 2018

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

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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

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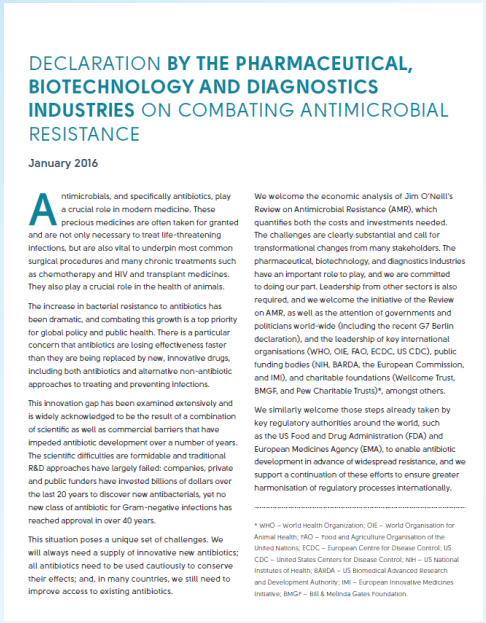
Suggested Readings



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

January 2016

Antimicrobials, and specifically antibiotics, play a crucial role in modern medicine. These precious medicines are often taken for granted and are not only necessary to treat life-threatening infections, but are also vital to underpin 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 growth is a top priority for global policy and public health. There is a particular concern that antibiotics are losing effectiveness faster than they are being replaced by new, innovative drugs, including both antibiotics and alternative non-antibiotic approaches to treating and preventing infections.

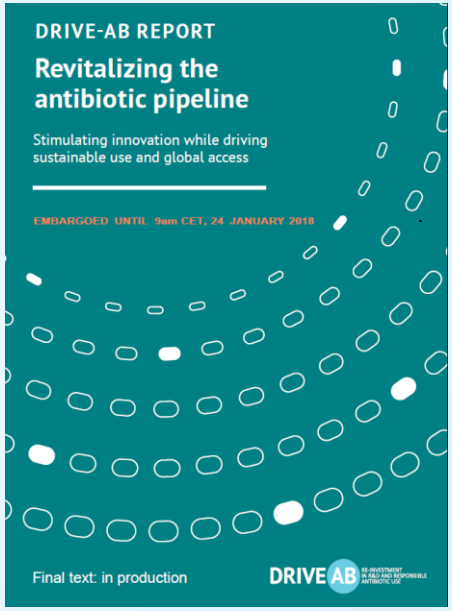
This innovation gap has been examined extensively and is widely acknowledged to be the result of a combination of scientific as well as commercial barriers that have impeded antibiotic development over a number of years. The scientific difficulties are formidable and traditional R&D approaches have largely failed: companies, private and public funders have invested billions of dollars over the last 20 years to discover new antibacterials, yet no new class of antibiotic for Gram-negative infections has reached approval in over 40 years.

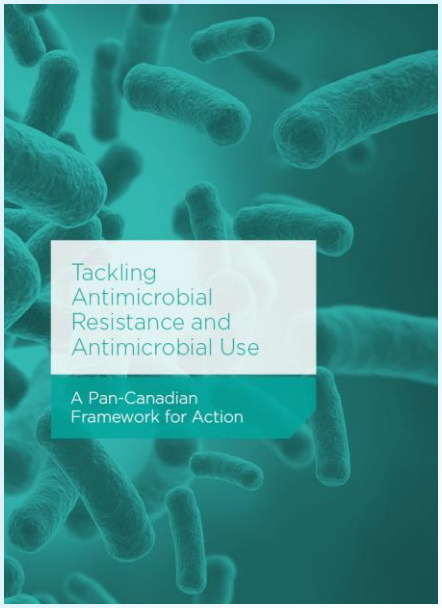
This situation poses a unique set of challenges. We will always need a supply of innovative new antibiotics; all antibiotics need to be used cautiously to conserve their effects; and, in many countries, we still need to improve access to existing antibiotics.

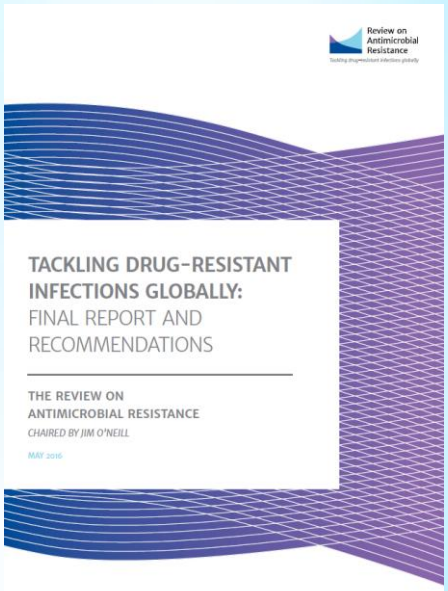
We welcome the economic analysis of Jim O'Neill's Review on Antimicrobial Resistance (AMR), which quantifies both the costs and investments needed. The challenges are clearly substantial and call for transformational changes from many stakeholders. The pharmaceutical, biotechnology, and diagnostics industries have an important role to play, and we are committed to doing our part. Leadership from other sectors is also required, and we welcome the initiative of the Review on AMR, as well as the attention of governments and politicians world-wide (including the recent G7 Berlin declaration), and the leadership of key international organisations (WHO, OIE, FAO, ECDC, US CDC), public funding bodies (NIH, BARDA, the European Commission, and IMI), and charitable foundations (Wellcome Trust, BMGF, and Pew Charitable Trusts)*, amongst others.

We similarly welcome those steps already taken by key regulatory authorities around the world, such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), to enable antibiotic development in advance of widespread resistance, and we support a continuation of these efforts to ensure greater harmonisation of regulatory processes internationally.

* WHO – World Health Organization; OIE – World Organisation for Animal Health; FAO – Food and Agriculture Organisation of the United Nations; ECDC – European Centre for Disease Control; US CDC – United States Centers for Disease Control; NIH – US National Institutes of Health; BARDA – US Biomedical Advanced Research and Development Authority; IMI – European Innovative Medicines Initiative; BMGF – Bill & Melinda Gates Foundation.

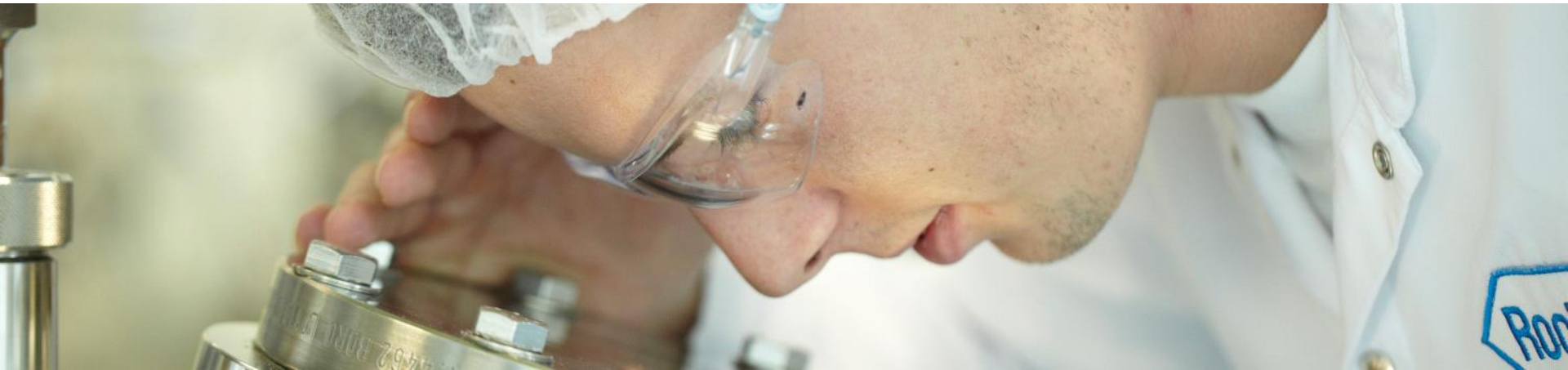






Antibiotics HTA Challenges
2018 *CADTH Symposium*

Simon Yunger
Hoffmann-La Roche, Canada



Agenda

- Challenges
- Global Initiatives
- Proposed Value Framework
- Next Steps

Misalignment between Antibiotic Clinical Trials and Current Frameworks

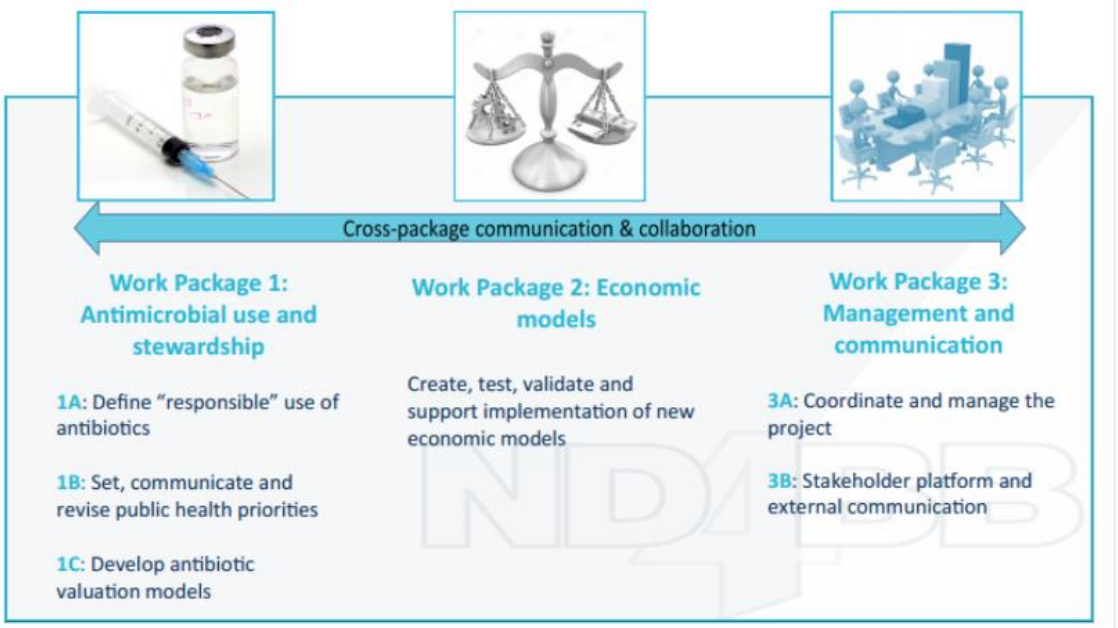
	Challenge
Ethical and practical constraints	▪ Antibiotic trials are designed primarily as non-inferiority trials
Recruitment	▪ Given trial size and duration, recruitment is difficult and not always feasible, especially for resistant patients
Generalizability	▪ The patients that physicians treat on a regular basis are often excluded from RCTs due to exclusion criteria e.g. immunocompromised, severe patients
Other Data Sets	▪ Other data sets alongside microbiology data and PK/PD studies are used to draw conclusions relating to efficacy
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

Global Initiatives to Problem Solve

EU Innovative Medicines Initiative (IMI) DRIVE-AB Project (Sept 2014-2017)

- 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

2014	2015	2016	2017



Global Initiatives to Problem Solve

2014	2015	2016	2017

Antibiotics Value Forum (Feb 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

	Traditional HTA Requirements	AMR Specific HTA
Health Gain (Clinical efficacy, microbiological, quality of life)	▪ Superiority RCTs	▪ Non-inferiority trials ▪ Non-RCT evidence of superiority e.g. microbiology, PK/PD data
Unmet Need *(Severity, alternatives)*	▪ Evidence of length of QOL of current therapies	▪ Priority pathogen lists ▪ Epidemiology studies (AMR rates for particular pathogens)
Cost Offsets	▪ Captured in Clinical Trials/Modelling Studies	▪ Not Collected
Productivity Benefits	▪ Modelling Studies	▪ Not Collected

Proposed Value Framework for Antibiotics

Additional Benefits Relevant to Antibiotics

	Benefit Description
Transmission	▪ Controlling the spread of infection to other patients and the wider population
Insurance	▪ Having treatments available in case of future outbreaks
Enablement	▪ Enabling other procedures (such as chemotherapy and surgery) to proceed in the knowledge that possible infections may be treated
Diversity	▪ 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
Novel Action	▪ 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

Next Steps from an HTA Perspective

Discuss and align on most appropriate value benefits

Develop technical models to incorporate into HTA frameworks

https://sarinasunbeam.deviantart.com/art/The-Antibiotic-Resistance-585612096

Doing now what patients need next