The antibiotic resistance *tsunami*

And how do we deal with it?
Global crisis of antimicrobial resistance in medicine
Global crisis of antimicrobial resistance in medicine

Modern medicine is built on antibiotics
From this image, we see a poster advertising the effectiveness of penicillin in curing gonorrhea within 4 hours. The poster encourages individuals to see their doctor today. Additionally, it mentions that the drug is furnished free through April 30th by your state and city boards of health.
ANTIBIOTICS
THE END OF MIRACLE DRUGS?

WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS

Maclean's
OUTBREAK
The uphill battle to control potent bacteria
How deadly mutant strains resist antibiotics

To this?
Antibiotic resistance is

• Increasing dramatically
• Associated with bad outcomes
• Caught everyone “off guard”
• A global threat to humanity
The medical resistance crisis

- Cumulative effect of widespread and extensive use in people for 60+ years
- Inappropriate use
- Numerous influences
- Ability of bacteria to become resistant, of resistance genes to spread
- The underestimated “bystander” effect
Mortality rates of staphylococcal bacteraemia over time

Numbers of unique beta-lactamase enzymes identified since the introduction of the first penicillin antibiotics

IF NOT TACKLED, RISING AMR COULD HAVE A DEVASTATING IMPACT

By 2050, the death toll could be a staggering one person every three seconds if AMR is not tackled now.

Source: Review’s own analysis.
Problem

• In past, dealt with resistance by developing another antibiotic
• Most antibiotics are variants of drug classes discovered in the 1940s
• New antibiotics cost billions to develop
• Resistance is developing and spreading rapidly
Introduction of new antibacterial classes

- Sulfonamides
- Penicillins
- Aminoglycosides
- Glycopeptides
- Macrolides
- Tetracyclines
- Chloramphenicol
- Lincosamides
- Quinolones
- Streptogramins
- Trimethoprim
- Oxazolidinones

Source: Monnet DL, 2004
Resistance is a global problem
Rapid movement of people: Air
THERE IS A HIGH CORRELATION BETWEEN ANTIBIOTIC USE AND RESISTANCE

Evolution of resistance

• Complex process
• Combination of genetic change and
• Movement of resistance genes through different bacterial populations
• Antibiotic selection required
Natural Selection

Resistant bacteria

Antibiotics

Population of mainly susceptible bacteria

Population of mainly resistant bacteria
Plasmids and the spread of resistance
Bacterial viruses can spread resistance
Resistance in human pathogens

The agricultural connection?
Superbugs spreading in Canada due to lax laws governing antibiotics use by farmers
"I’m putting you on antibiotics. Eat a chicken three times a day."
Antibiotics used in food animals for:

- Treatment of disease
- Prevention of disease ("subtherapeutic")
- Growth promotion
- Majority without veterinary prescription
- Issue is development and the spread of resistant bacteria and of resistance genes
What is contribution of animal (agricultural) use of antibiotics to resistance in human pathogens?
Epidemiology of equine MRSA
Resistance ANYWHERE is potentially resistance EVERYWHERE
“Nobody is exempt from the problem, nor from playing a role in the solution.”
ANIMALS IN THE USA CONSUME MORE THAN TWICE AS MANY MEDICALLY IMPORTANT ANTIBIOTICS AS HUMANS

30% consumed by humans
70% are consumed by animals

Source: Animal consumption figure of 8,893,103 kg from FDA, 2012. Human consumption of 3,379,268 kg in 2012 based on calculations by IMS Health. The figures are rounded from 72.5% used in animals and 27.5% used in humans.
Antibiotics used in animals and humans, Canada, 2013

**Antimicrobials Sold for People**
- Beta-lactams: 48%
- Cephalosporins: 22%
- Other Antimicrobials: 4%
- Aminoglycosides: 3%
- Tetracyclines: 3%
- Lincosamides: 3%
- Trimethoprim & sulfonamides: 6%
- Macrolides: 7%
- Fluoroquinolones: 7%

**Antimicrobials Distributed/Sold for Animals**
- Tetracyclines: 39%
- Ionophore Coccidiostats: 29%
- Cephalosporins: 6%
- Aminoglycosides: 1%
- Lincosamides: 5%
- Trimethoprim & sulfonamides: 4%
- Macrolides: 6%
- Beta-lactams: 7%
- Other antimicrobials: 8%

Includes quantities of antimicrobials from community pharmacies and human hospitals.

- based on kg active ingredients
- ionophores & chemical coccidiostats included
How was Canada doing in agricultural use of antibiotics?

2013
<table>
<thead>
<tr>
<th>Priority</th>
<th>Issue</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Create a national system to monitor use of antimicrobials in food animals</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>Terminate growth promotion if drugs used in humans</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>Stop the importation, sale and use of antimicrobials not evaluated and registered by Health Canada (“Own use”, “Active Pharmaceutical Ingredients”)</td>
<td>F</td>
</tr>
<tr>
<td>4</td>
<td>Monitor resistance and take corrective action if needed</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Prescription only of antibiotics for food animals</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>Develop an extra-label use policy, which ensures no endangerment to human health</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>Follow OIE guidelines re fluoroquinolones and 3rd generation cephalosporins</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>Initiate Veterinary Feed Directive to ensure veterinary oversight of critically important drugs</td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>Develop national leadership and oversight in Canada</td>
<td>C</td>
</tr>
</tbody>
</table>
In 2013, Canada was not meeting international standards or national recommendations.

Overall ranking: C-
**Salmonella Heidelberg story: CIPARS**

Temporal variation in ceftiofur resistance in S. Heidelberg isolates from retail chicken & humans in Quebec

- **Voluntary withdrawal**
- **Return to partial use**
- **Voluntary industry ban (2014)**

Number of isolates, year and province
AG appeal

- Potential gaps in the federal regulation of antibiotics in food-producing animals

- Petition: 342

- Issue(s): Agriculture, human/environmental health, and federal–provincial relations

- Petitioner(s): Ad Hoc Committee on Antimicrobial Stewardship in Canadian Agriculture and Veterinary Medicine

- Federal Departments and Agencies Responsible for Reply: Agriculture and Agri-Food Canada, Canada Border Services Agency, Health Canada, Public Health Agency of Canada
Auditor General’s Report
April 2015

Very critical of PHAC’s and Health Canada’s failure to address international standards and national recommendations around animal use of antibiotics
Major recent developments
G8 Science Ministers agree to collaborate on antimicrobial resistance

2013
G8 Science Ministers agree to collaborate on antimicrobial resistance, 2013
Major recent developments

• U.S. Food and Drug Administration: Phasing out growth promotional use of antibiotics; Veterinary oversight of antibiotics for food animals (December 2013)

• Health Canada (VDD) and Canadian Animal Health Institute agree to align with the U.S. FDA actions (April 2014)
Federal Action Plan March 2015

• Commitment to leadership
• Building surveillance of use in agriculture
• Veterinary oversight of food animal use
• Remove growth promotion use
• Address OUI and API issues
• Alternatives to antimicrobials – support for innovation, with enabling regulation
• Changes by December 2016
Federal *Action* Plan March 2015

- Commitment to leadership
- Surveillance of use and resistance in human and veterinary medicine
- Stewardship
- Innovation
Danish “yellow card” system for vets and farms?
“Yellow card” system for hospitals and physicians?
How are the coming changes coordinated?
How are the coming changes coordinated?

Public Health Agency of Canada leading
Health Canada, Agriculture and AgriFood Canada, Canadian Institutes of Health Research
How are the coming changes coordinated?

Federal-Provincial-Territorial jurisdictional issues
How are the coming changes coordinated?

Incredibly chaotic process at the moment
We’re entering a whole new paradigm in our relationship with antibiotics
We’re entering a whole new paradigm in our relationship with antibiotics

We need to reduce use to where the benefits are clear and substantial
We are entering the golden age of microbiology
We are entering the golden age of microbiology

Numerous improvements in diagnosis and novel antibacterial development
G8 Science Ministers agree to collaborate on antimicrobial resistance

- Preserve existing agents
- Prevent emergence of resistance, rapid diagnostics
- Support new drug development, interventions
- Support new diagnostics
- Share surveillance data internationally
- Better understand emergence and spread of resistance
CUMULATIVE PROFITS FROM ANTIBIOTIC RESEARCH

Profit only achieved in year 23

Source: Review's own modelling of the discounted average expenditure and revenue for a sample of antibiotics R&D projects based on historical input dating back to 2001 and forward projections provided by IMS health and selected pharmaceutical companies. More detail on the modelling can be found at amr-review.org
Bacteria can change
Bacteria can change

So can we