The antibiotic resistance *tsunami*

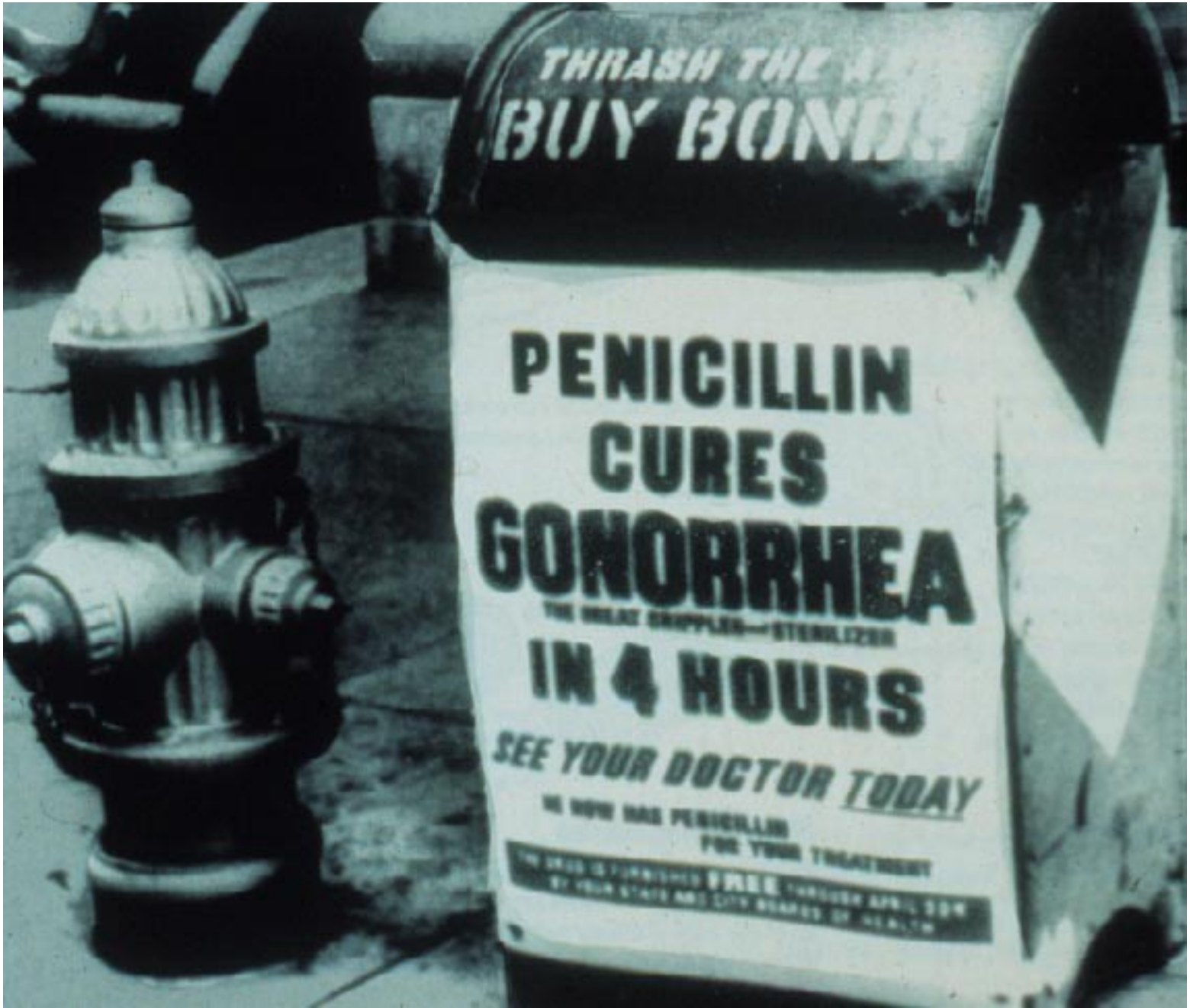
And how do we deal with it?

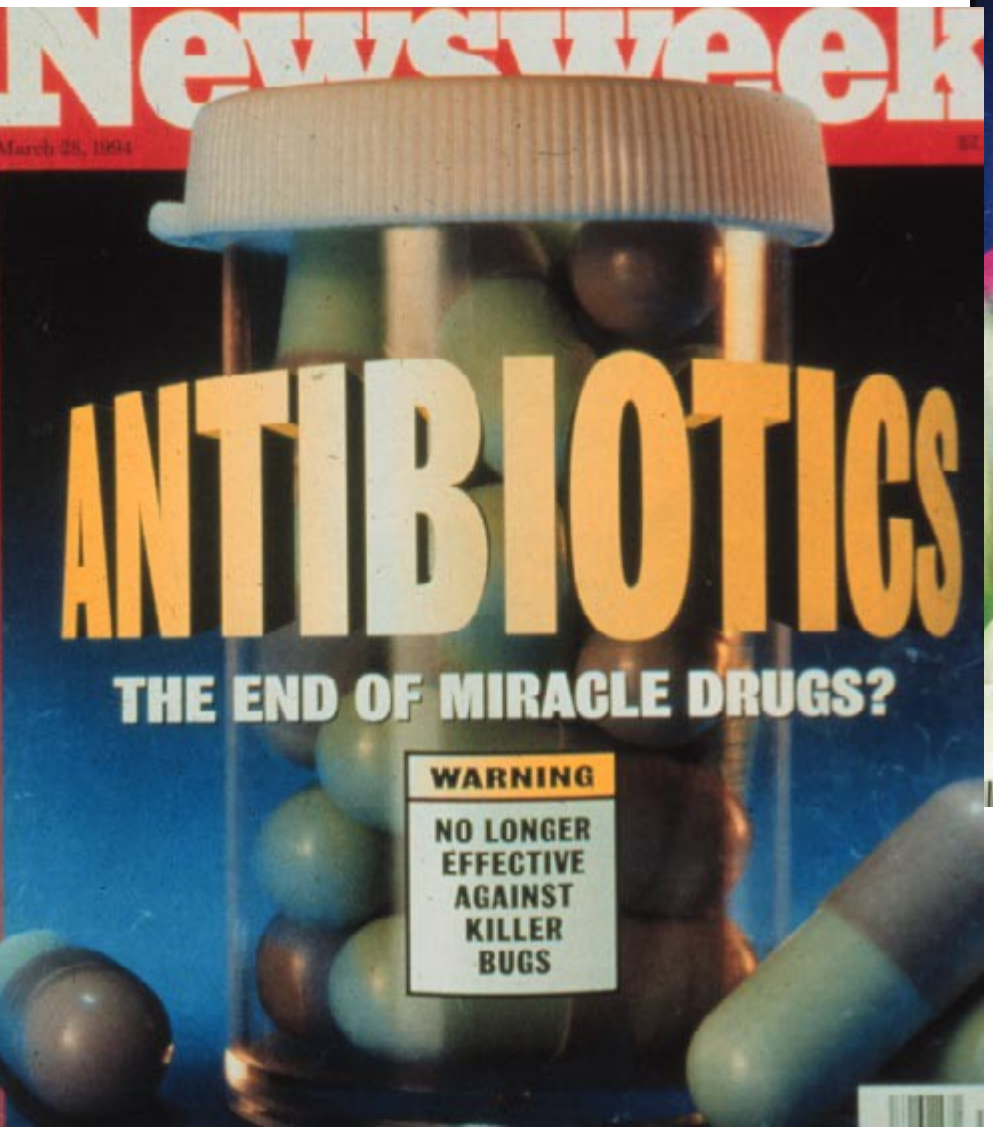
Global crisis of antimicrobial resistance in medicine

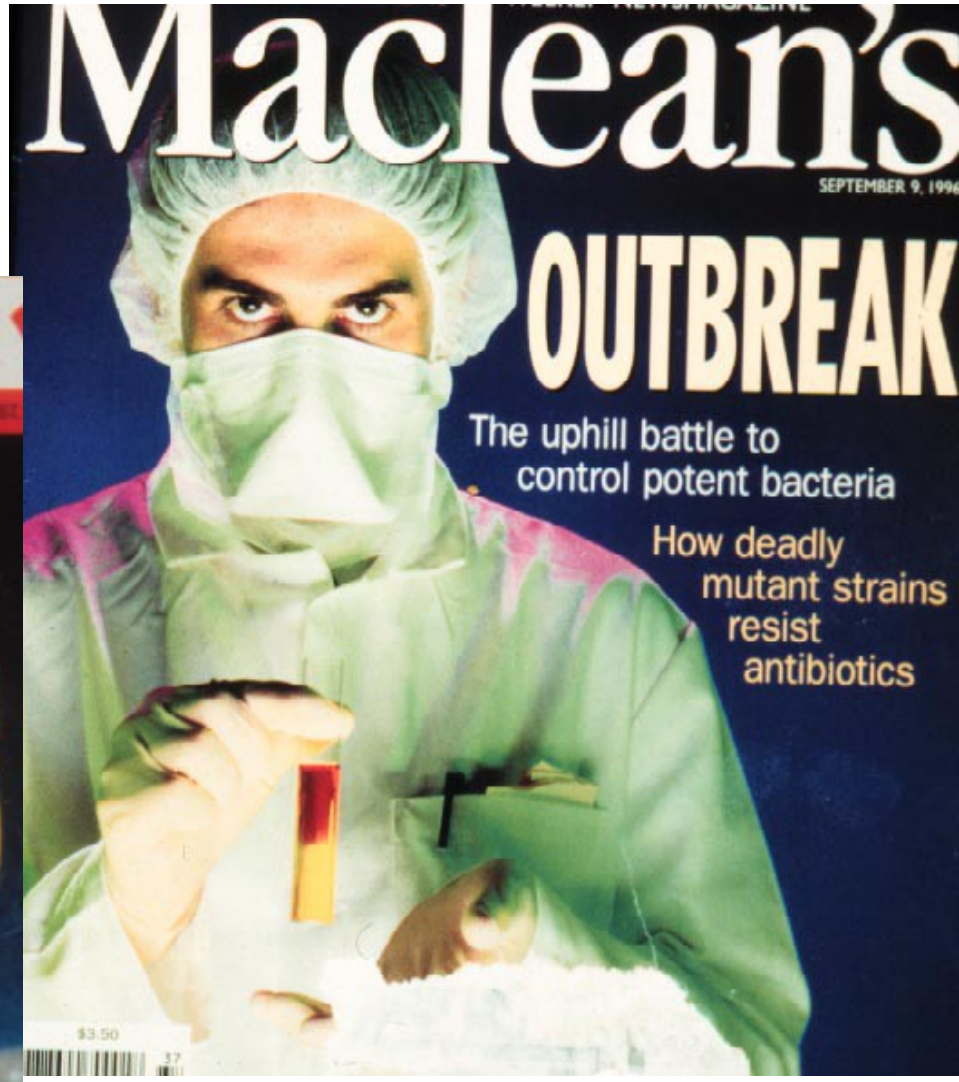
Global crisis of antimicrobial resistance in medicine

Modern medicine is built on antibiotics

From this


BUY BONDS
PENICILLIN
CURES
GONORRHEA
IN 4 HOURS
SEE YOUR DOCTOR TODAY


Newsweek
March 28, 1994
ANTIBIOTICS
THE END OF MIRACLE DRUGS?
WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS


Maclean's
SEPTEMBER 9, 1996
OUTBREAK
The uphill battle to control potent bacteria
How deadly mutant strains resist antibiotics
$3.50

To this?

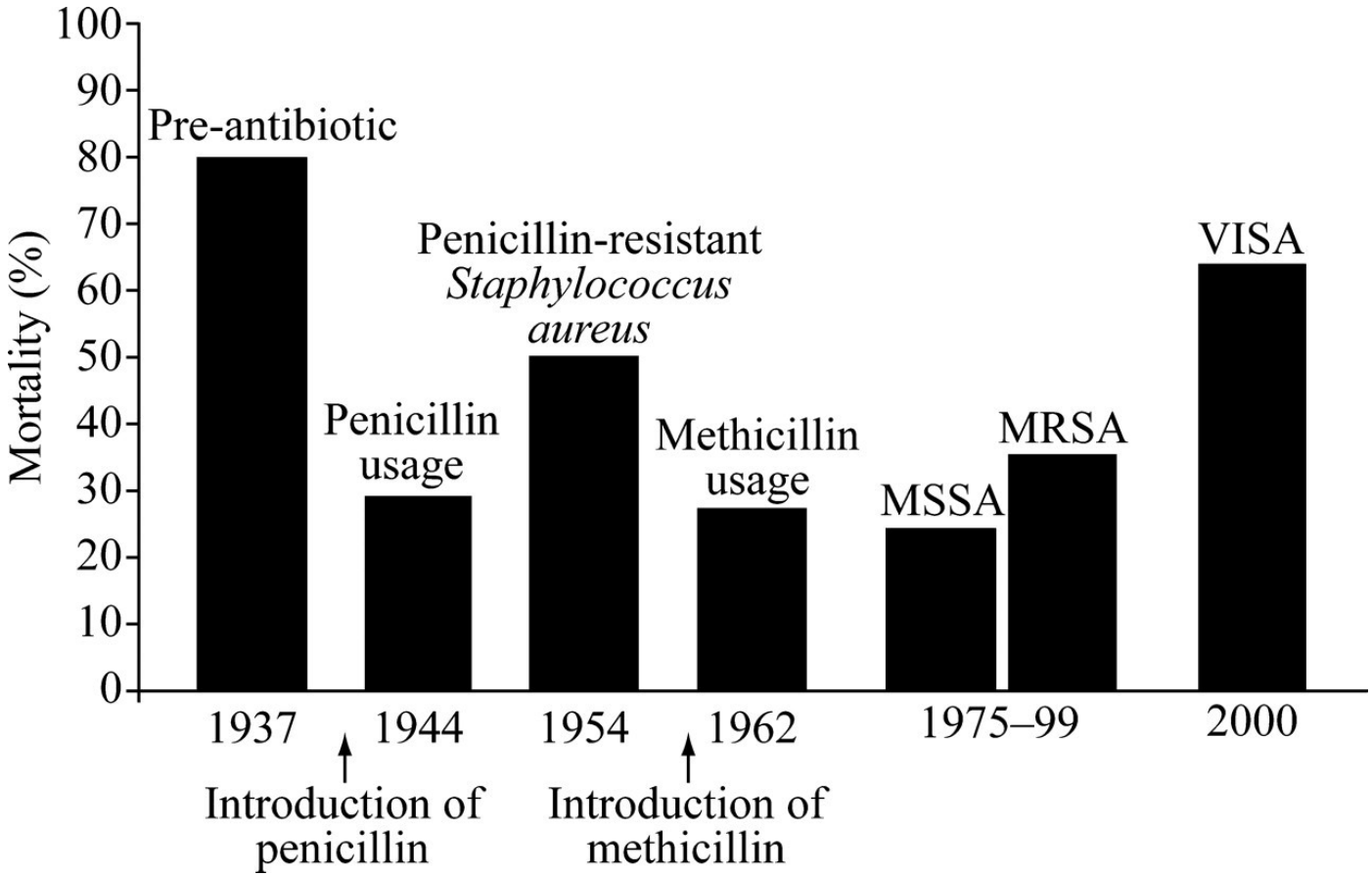
Antibiotic resistance is

- Increasing dramatically
- Associated with bad outcomes
- Caught everyone “off guard”
- A global threat to humanity

The medical resistance crisis

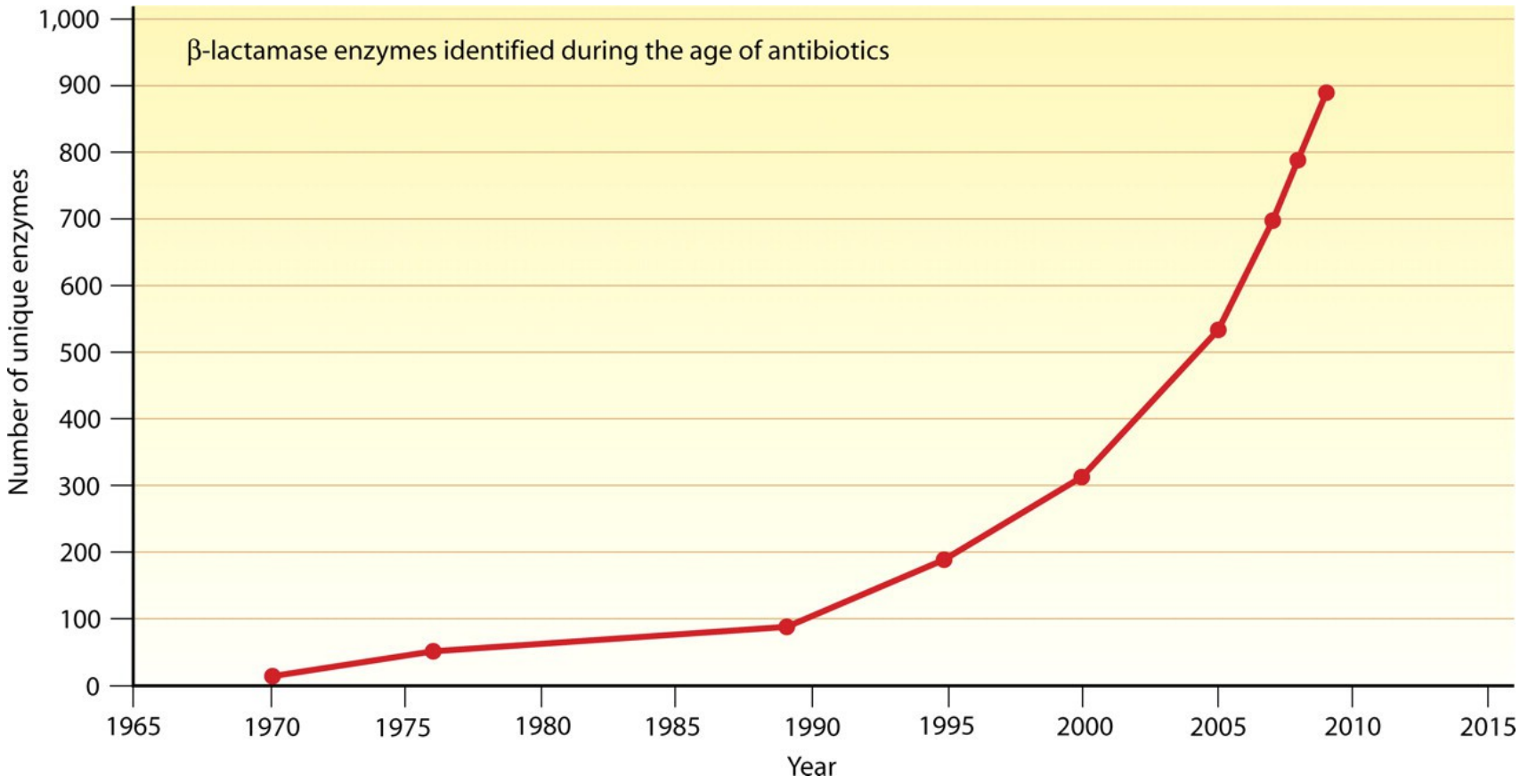
- Cumulative effect of widespread and extensive use in people for 60+ years
- Inappropriate use
- Numerous influences
- Ability of bacteria to become resistant, of resistance genes to spread
- The underestimated “bystander” effect

Mortality rates of staphylococcal bacteraemia over time



Dancer, S. J. J. Antimicrob. Chemother. 2008 61:246-253; doi:10.1093/jac/dkm465

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



Davies, J. et al. 2010. Microbiol. Mol. Biol. Rev. 74(3):417-433

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.

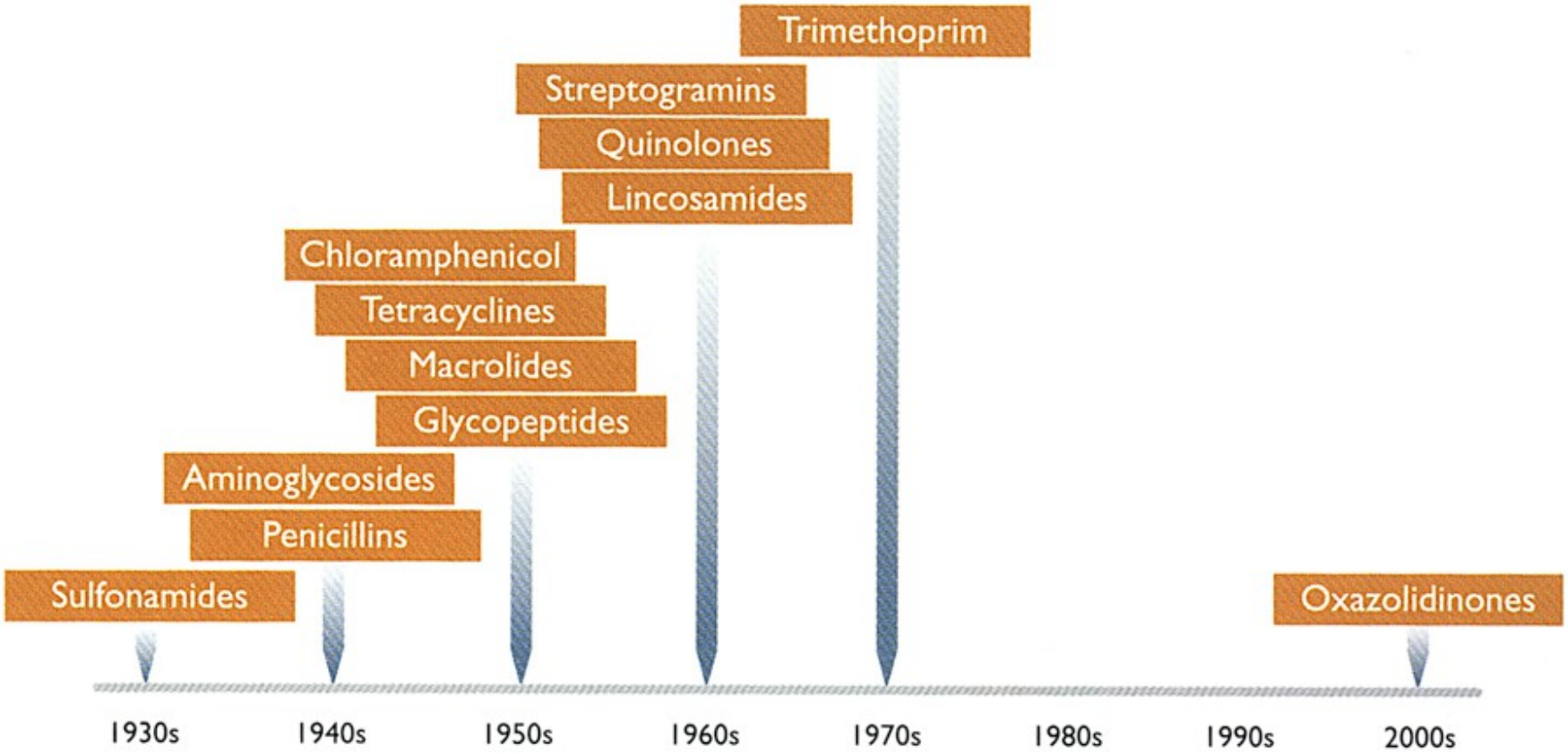
Source: Review's own analysis.

Review on Antimicrobial Resistance

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

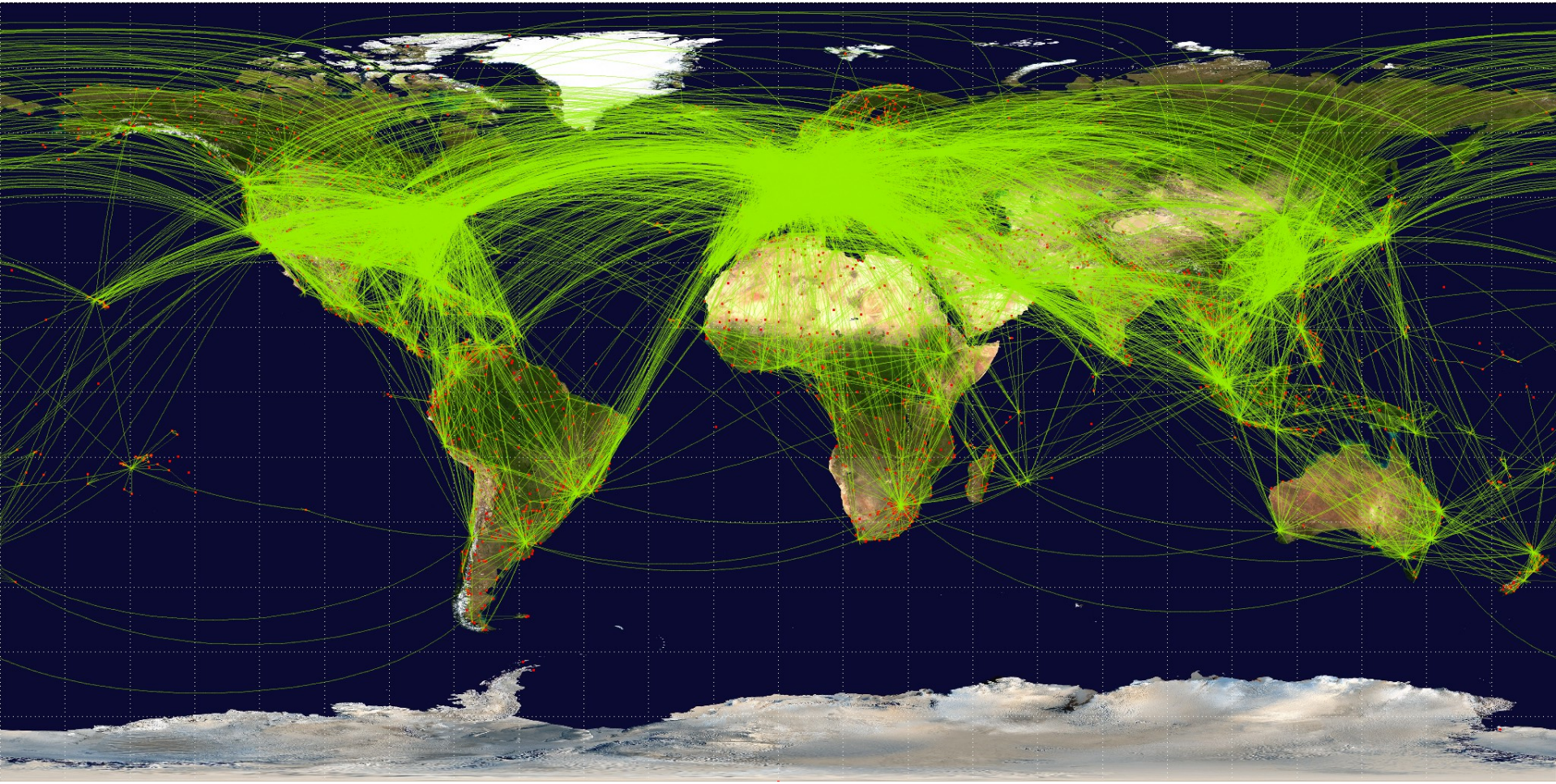
Introduction of new antibacterial classes



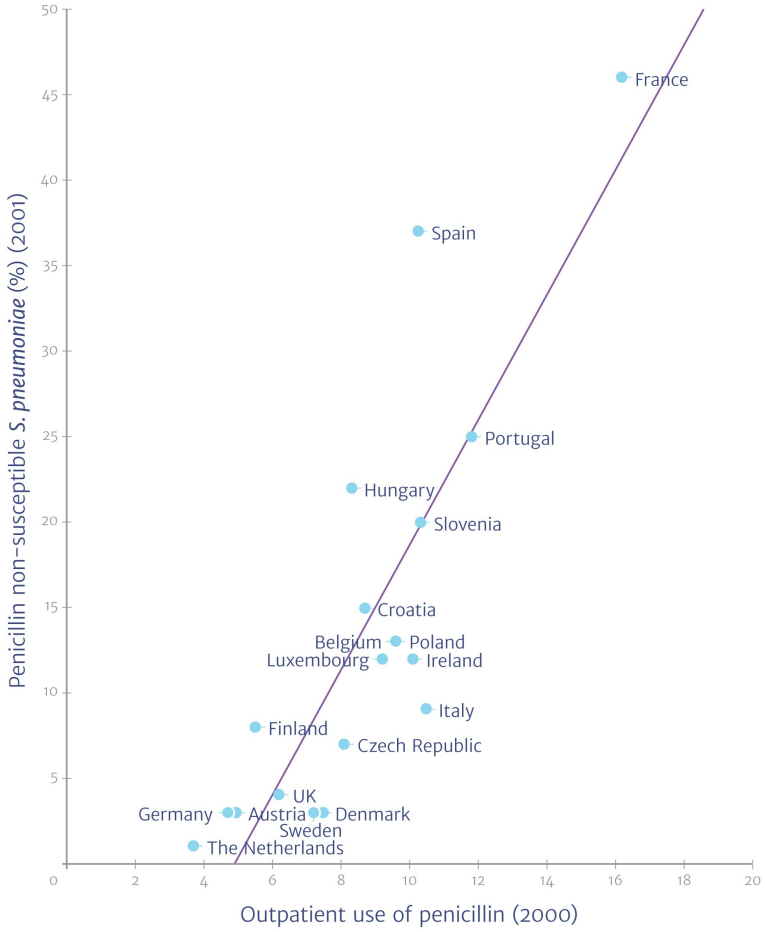
Source: Monnet DL, 2004

Resistance is a global problem

Rapid movement of people: Air



THERE IS A HIGH CORRELATION BETWEEN ANTIBIOTIC USE AND RESISTANCE



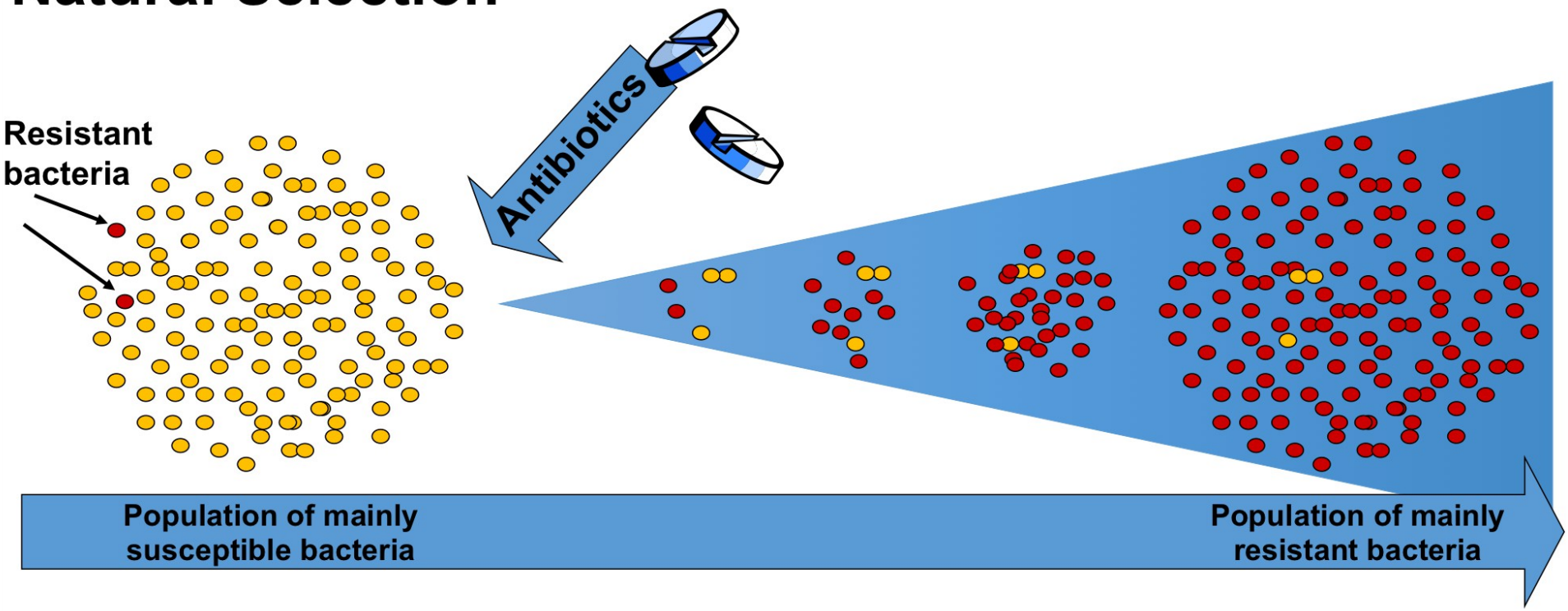
Source: Goossens H, Ferech M, Vander Stichele R, et al. *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet 2005; 365(9459): 579-87.

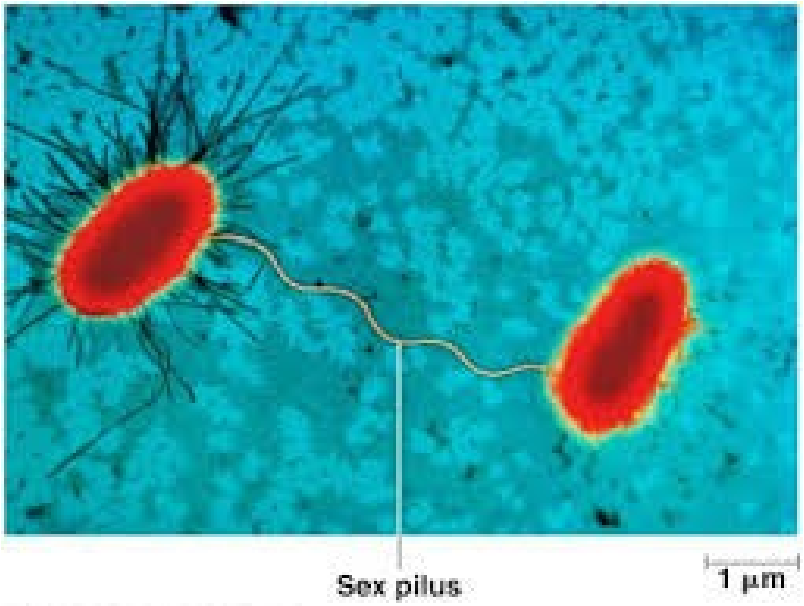
Review on Antimicrobial Resistance

Evolution of resistance

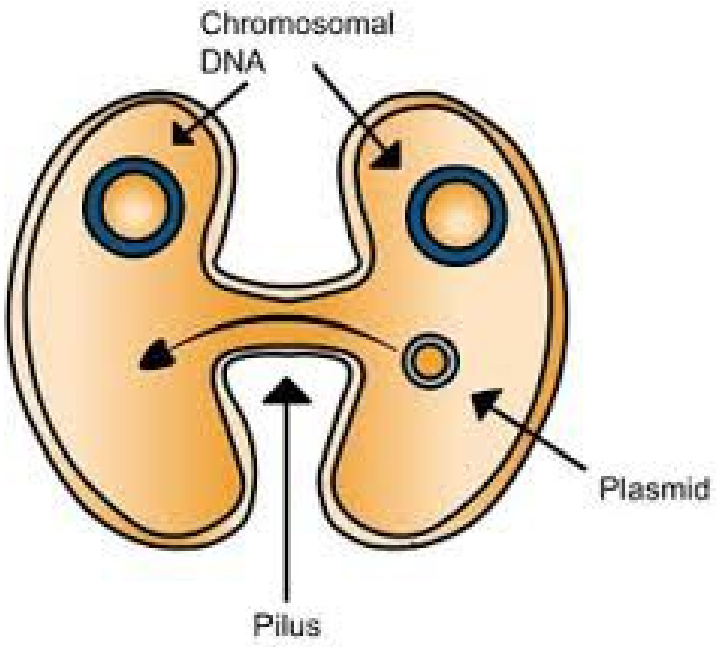
- Complex process
- Combination of genetic change and
- Movement of resistance genes through different bacterial populations
- Antibiotic selection required

Natural Selection

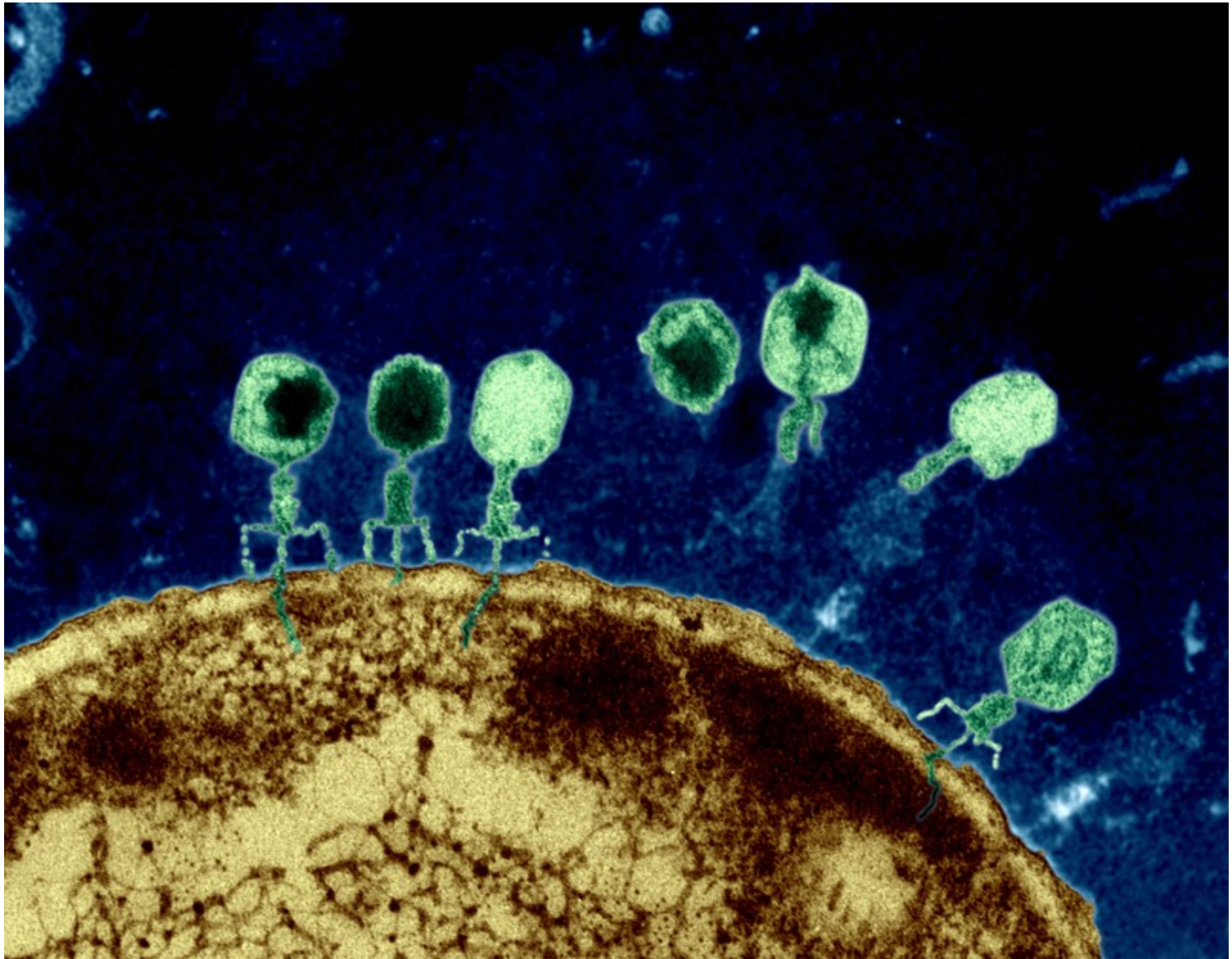




Plasmids and the spread of resistance



Bacterial viruses can spread resistance

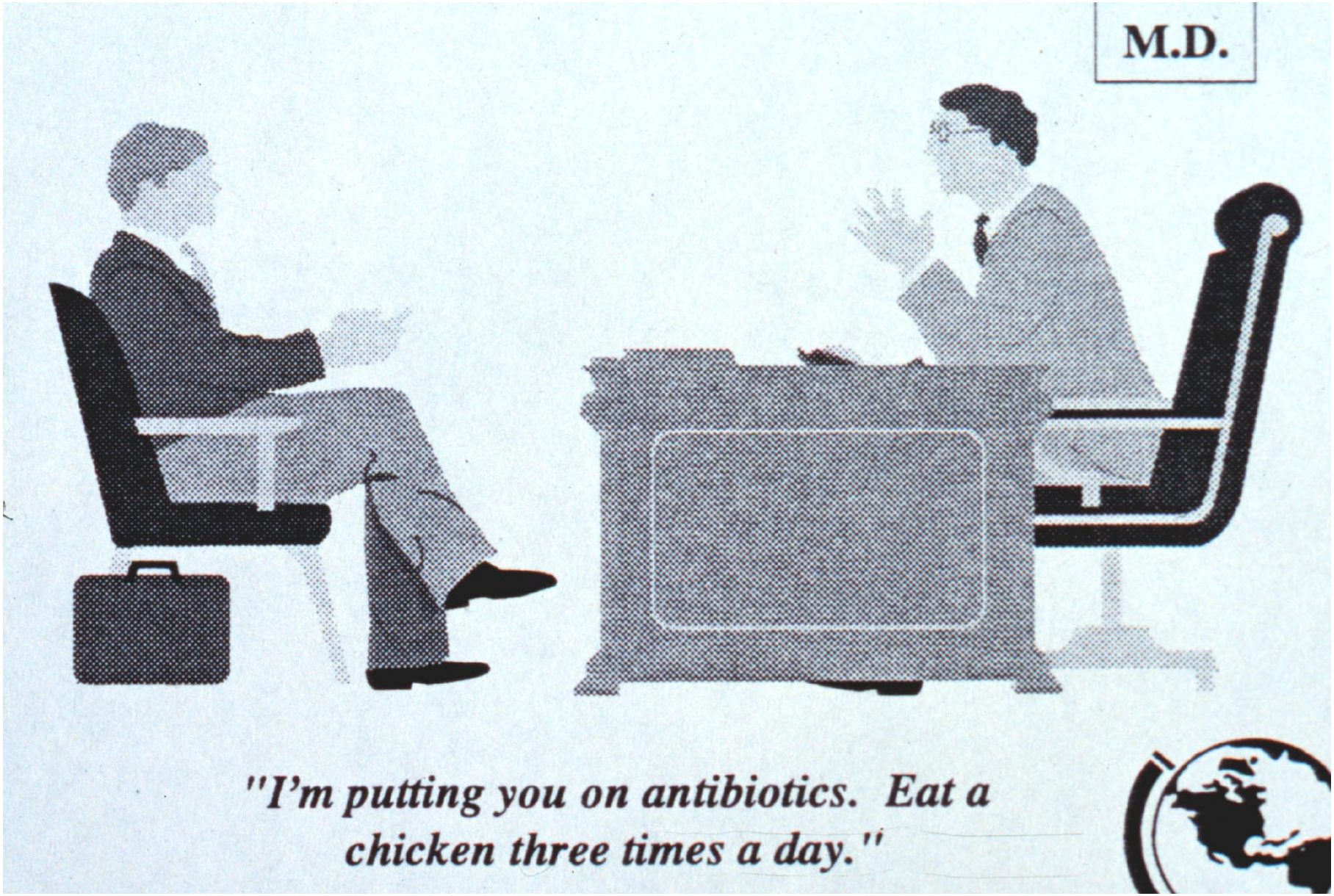


Resistance in human pathogens

The agricultural connection?

NATIONAL POST

Superbugs spreading in Canada due to lax laws governing antibiotics use by farmers



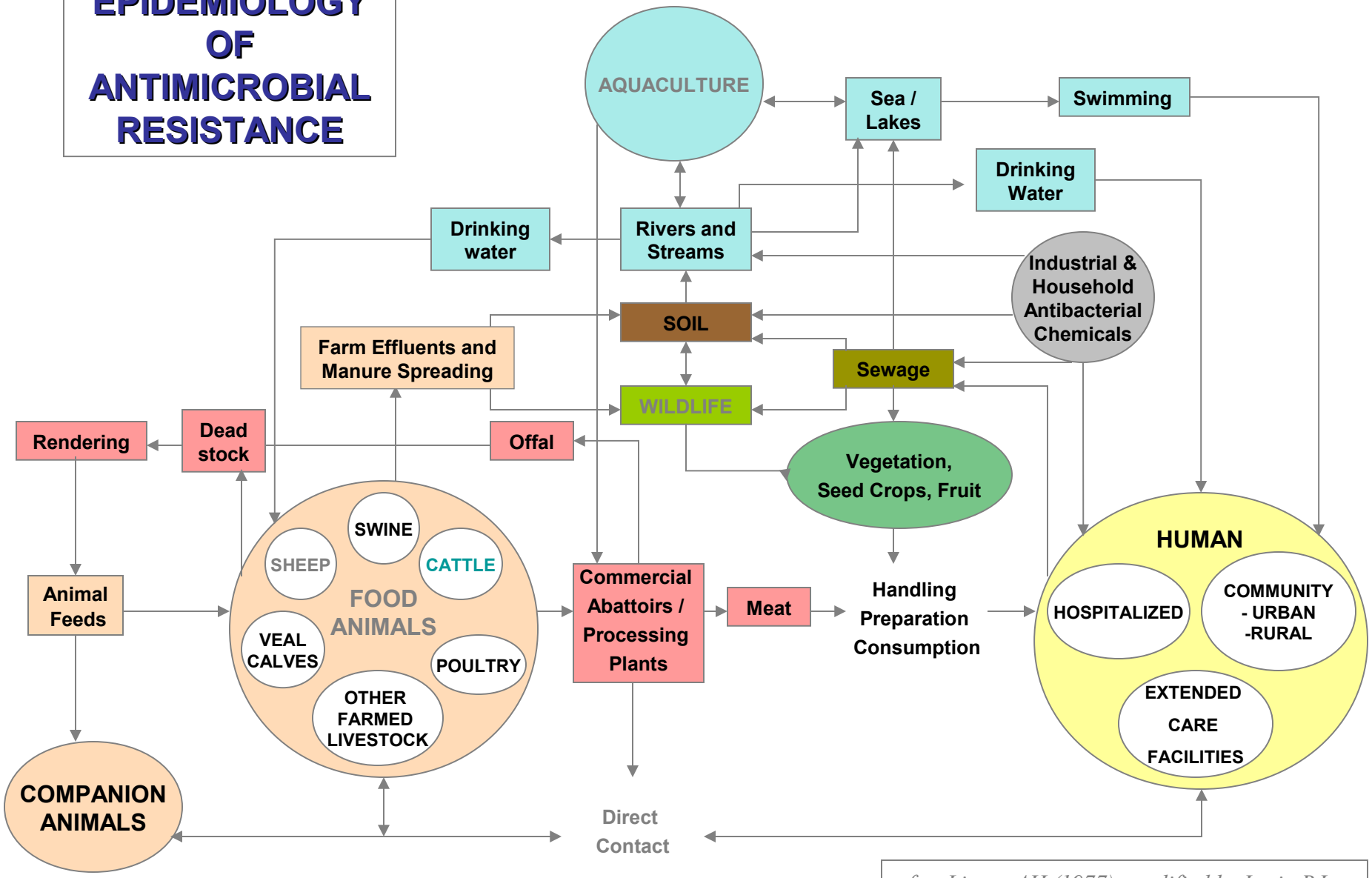
"I'm putting you on antibiotics. Eat a chicken three times a day."

Antibiotics used in food animals for:

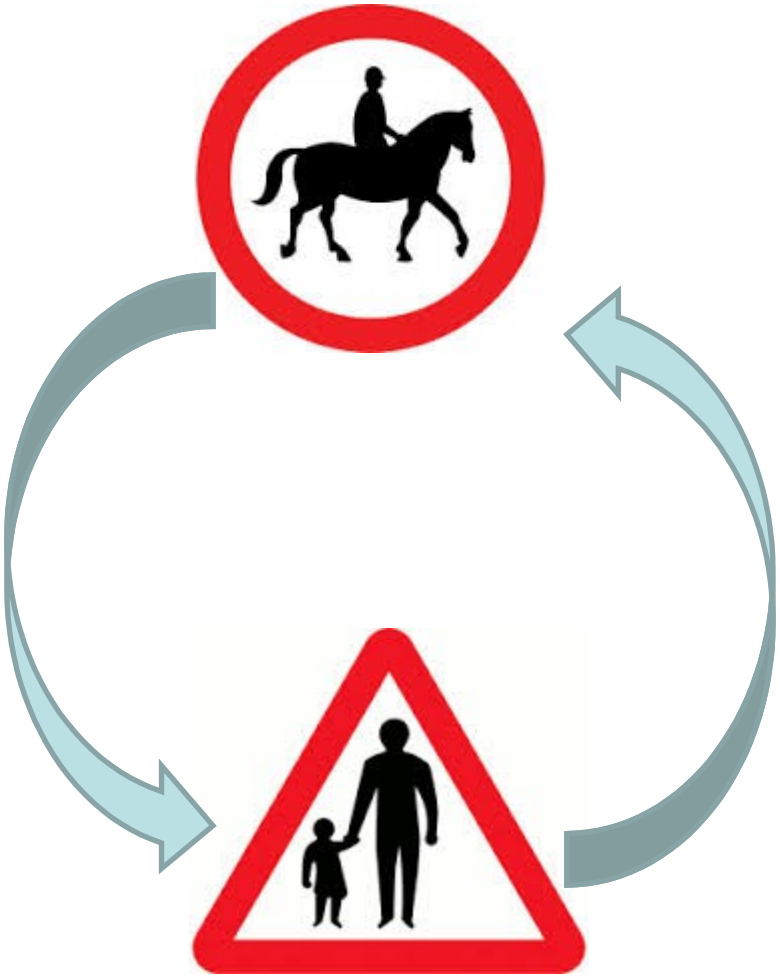
- Treatment of disease
- Prevention of disease (“subtherapeutic”)
- Growth promotion
- Majority without veterinary prescription
- Issue is development and the spread of resistant bacteria and of resistance genes

What is contribution of animal (agricultural) use of antibiotics to resistance in human pathogens?

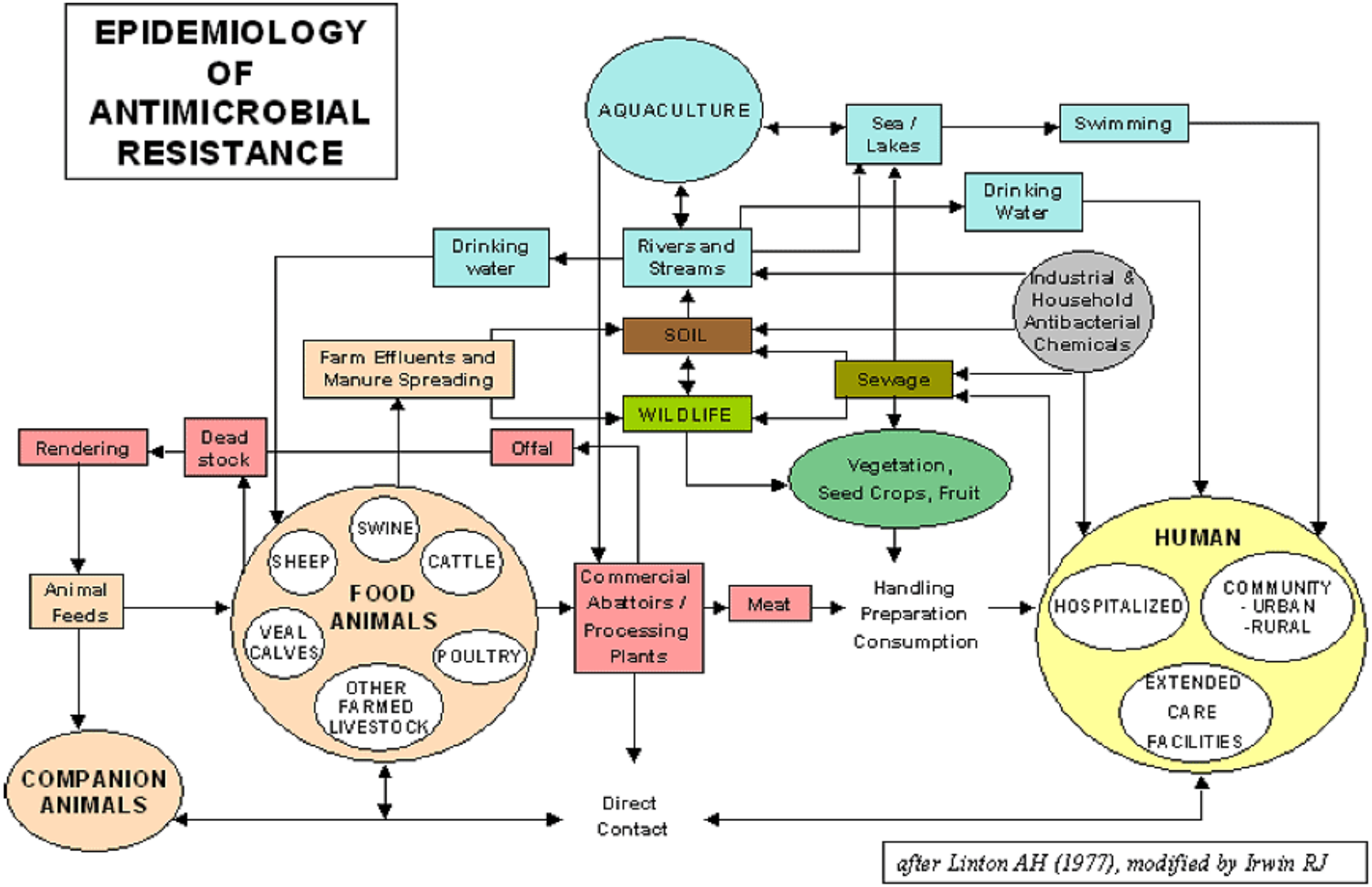
EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE



after Linton AH (1977), modified by Irwin RJ



Epidemiology of equine MRSA



Resistance ANYWHERE is potentially resistance EVERYWHERE

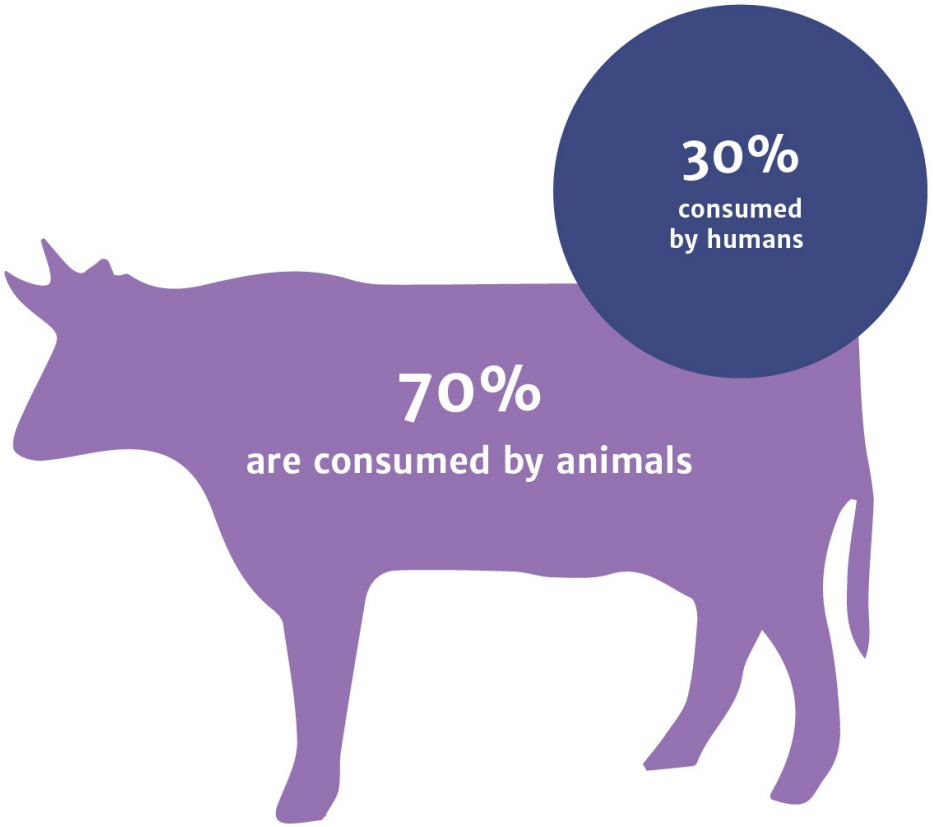
World Health Organization

2001

WHO Global Strategy for Containment of Antimicrobial Resistance

“Nobody is exempt from the problem, nor from playing a role in the solution.”

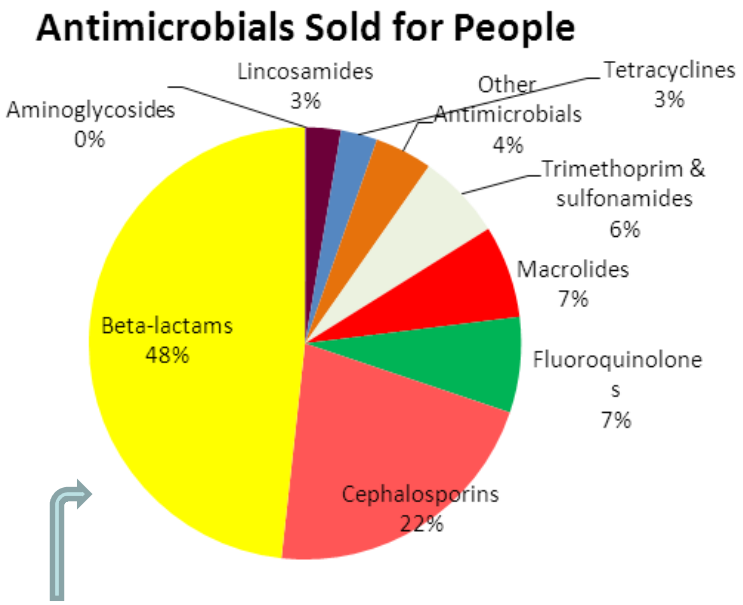
ANIMALS IN THE USA CONSUME MORE THAN TWICE AS MANY MEDICALLY IMPORTANT ANTIBIOTICS AS HUMANS



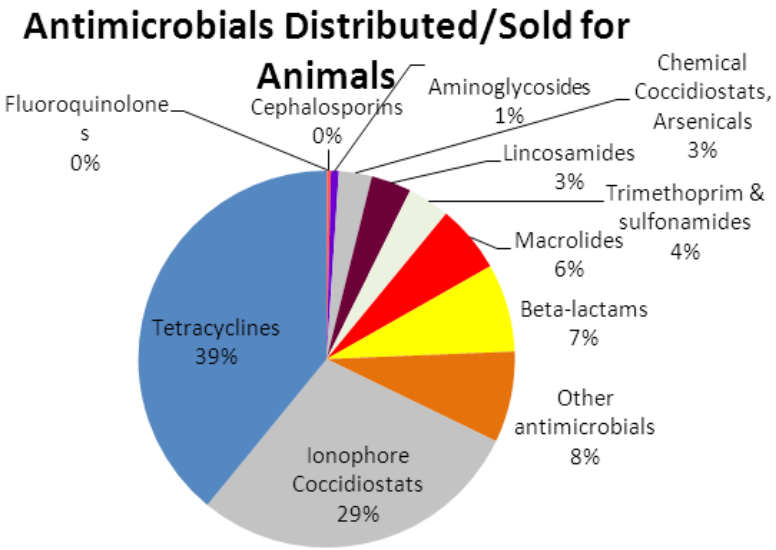
Source: Animal consumption figure of 8,893,103kg from FDA, 2012. Human consumption of 3,379,226kg in 2012 based on calculations by IMS Health. The figures are rounded from 72.5% used in animals and 27.5% used in humans.

Review on Antimicrobial Resistance

Antibiotics used in animals and humans, Canada, 2013



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

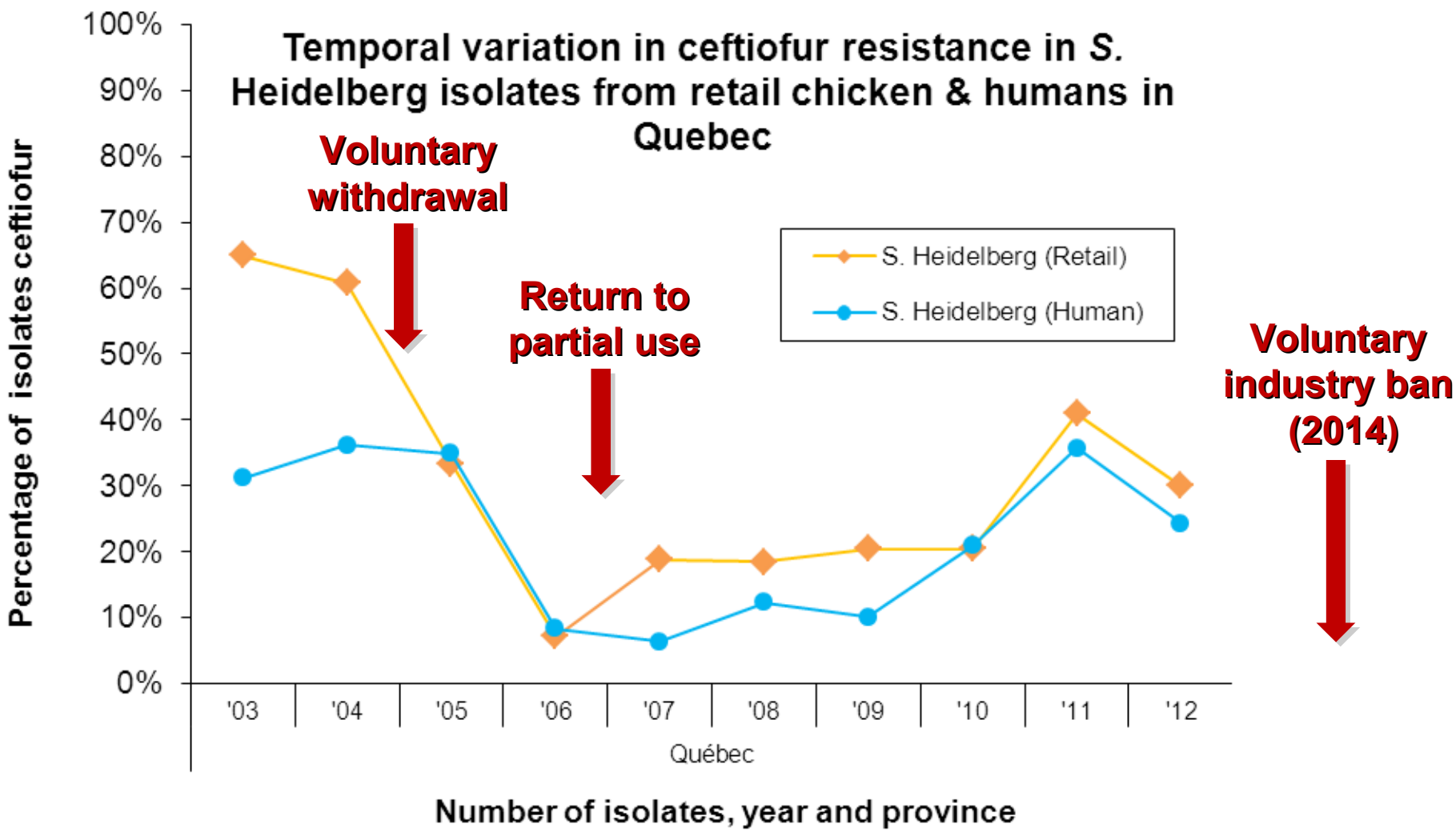
Priorities and ranking agricultural use, 2013

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

In 2013, Canada was not meeting international standards or national recommendations

Overall ranking: C-

Salmonella Heidelberg story: CIPARS



Auditor General of Canada
Vérificateur général du Canada

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

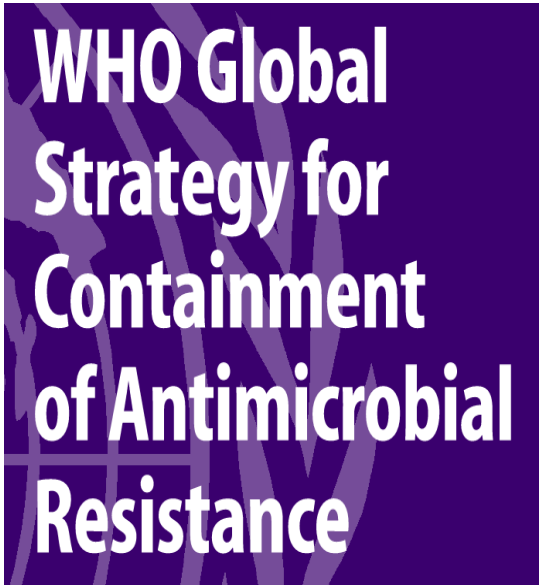
Very critical of PHAC's and Health Canada's failure to address international standards and national recommendations around animal use of antibiotics

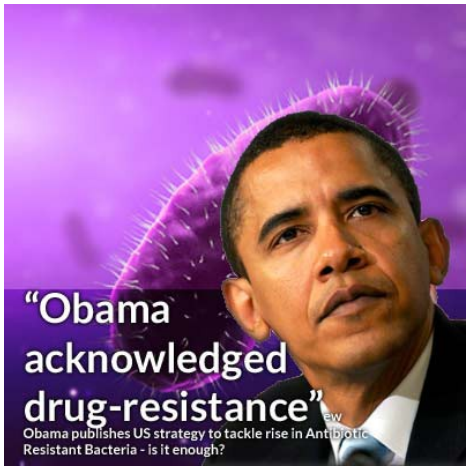
Major recent developments

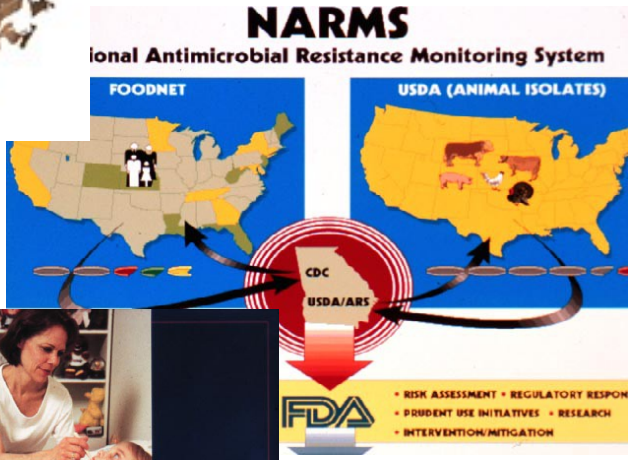
G8 Science Ministers agree to collaborate on antimicrobial resistance

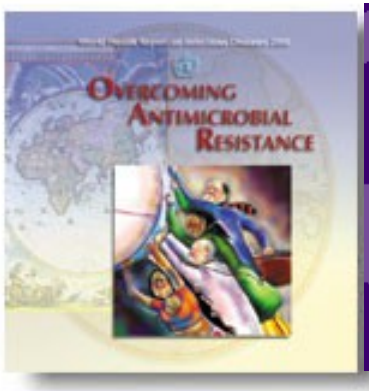
2013

G8 Science Ministers agree to collaborate on antimicrobial resistance, 2013









Major recent developments

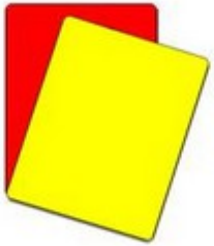
- U.S. Food and Drug Administration: Phasing out growth promotional use of antibiotics; Veterinary oversight of antibiotics for food animals (December 2013)
- Health Canada (VDD) and Canadian Animal Health Institute agree to align with the U.S. FDA actions (April 2014)

Federal ***Action*** Plan March 2015

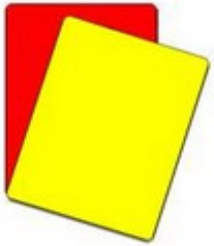
- Commitment to leadership
- Building surveillance of use in agriculture
- Veterinary oversight of food animal use
- Remove growth promotion use
- Address OUI and API issues
- Alternatives to antimicrobials – support for innovation, with enabling regulation
- Changes by December 2016

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

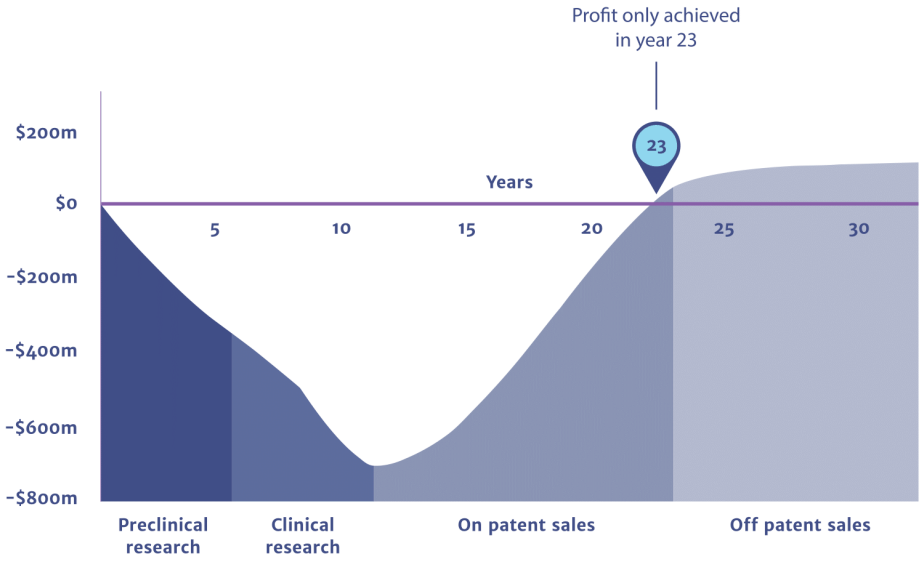
- Preserve existing agents
- Prevent emergence of resistance, rapid diagnostics
- Support new drug development, interventions
- Support new diagnostics
- Share surveillance data internationally
- Better understand emergence and spread of resistance

TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Surveillance
- Rapid diagnostics
- Human capital
- Drugs
- Global Innovation Fund
- International coalition for action

Review on Antimicrobial Resistance

CUMULATIVE PROFITS FROM ANTIBIOTIC RESEARCH



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 2002 and forward projections provided by IMS health and selected pharmaceutical companies. More detail on the modelling can be found at amr-review.org

Review on Antimicrobial Resistance

HIGH-LEVEL MEETING ON ANTIMICROBIAL RESISTANCE

21 SEPTEMBER 2016, UN HEADQUARTERS, NEW YORK

Bacteria can change

Bacteria can change

So can we