

97039: Global Health, Antimicrobial Drugs and Vaccines

Module 1: The growing pandemic of antimicrobial resistance

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Learning objectives

- Review the history and factors that drive antimicrobial resistance (AMR)
- Discuss *One Health strategy* for addressing antimicrobial resistance
- Compare management of AMR in high-income (HIC) vs. low and middle-income countries (LMICs)
- Examine lessons learned from the COVID-19 pandemic for managing cross-border transmission of antimicrobial resistance

What is a pandemic?

- Large-scale outbreak of infectious diseases
- Crosses international borders
- Causes disease and death in a large number of people

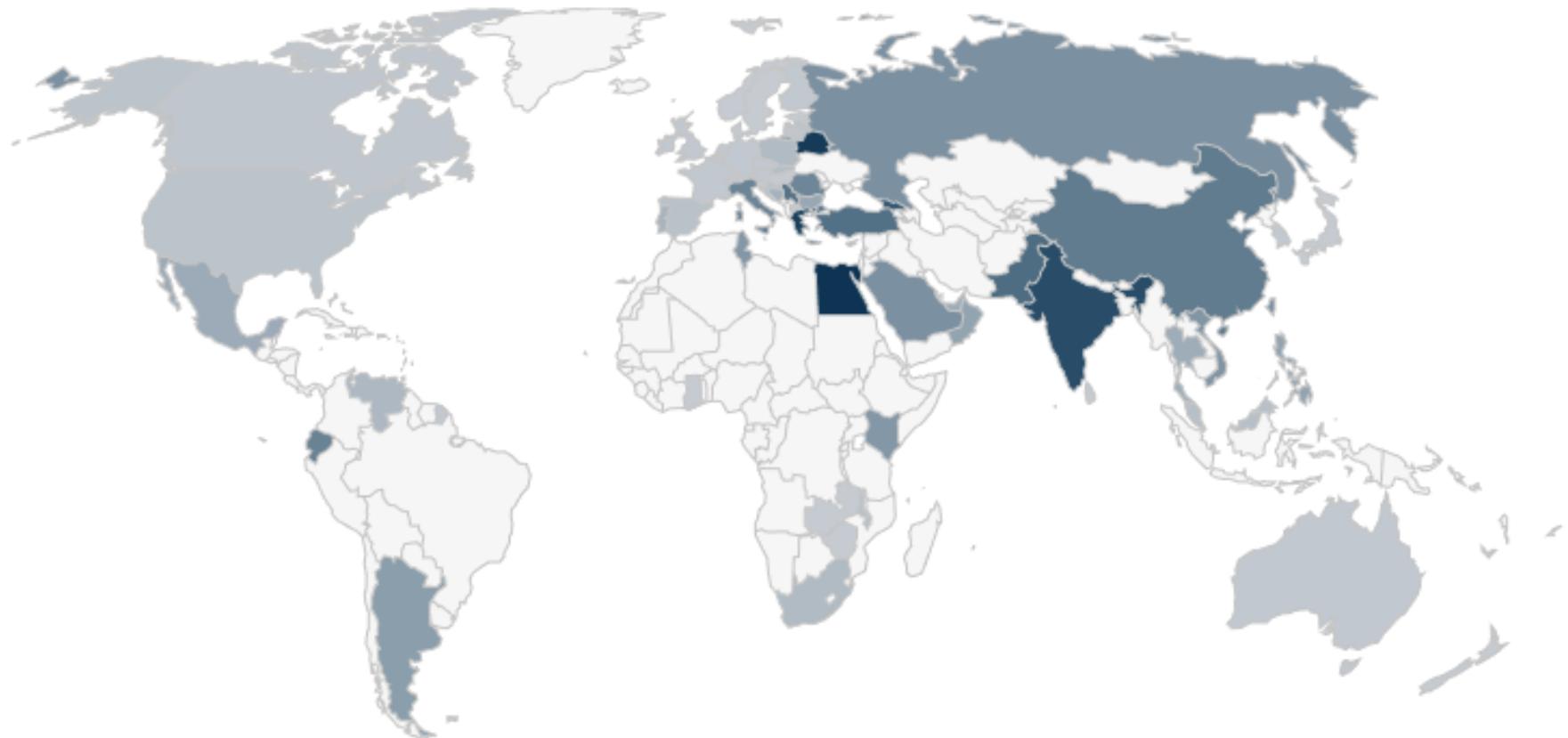
1. Large-scale outbreak of infectious diseases

Currently estimated number of deaths due to antibiotic-resistant infections per year:

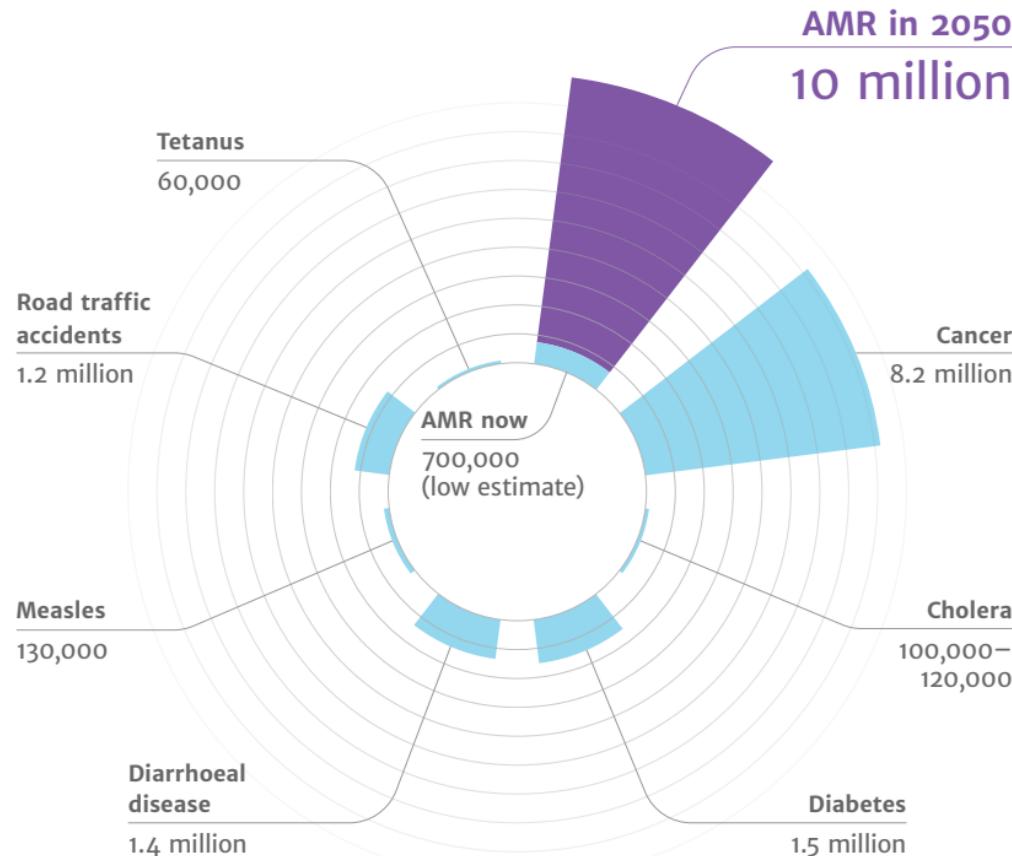
700,000 people (including 230,000 from MDR tuberculosis)

2. Crosses international borders

Resistance of *Klebsiella pneumoniae* to Carbapenems



3. Disease and death in a large number of people



Source: O'Neil Report on Antimicrobial Resistance

The future of antimicrobial resistance?

- The estimated total number of deaths due to AMR could climb to 10 million deaths globally per year by 2050
- Routine medical procedures or surgery will become more dangerous and associated with higher complication rates
- Immunosuppression, cancer chemotherapy and transplantations may carry unacceptable risk for many patients if infections cannot be effectively prevented and treated
- Economic and social progress in many countries will be dramatically impacted by increasing AMR leading to political and social instability

Changes in life expectancy over last 500 years

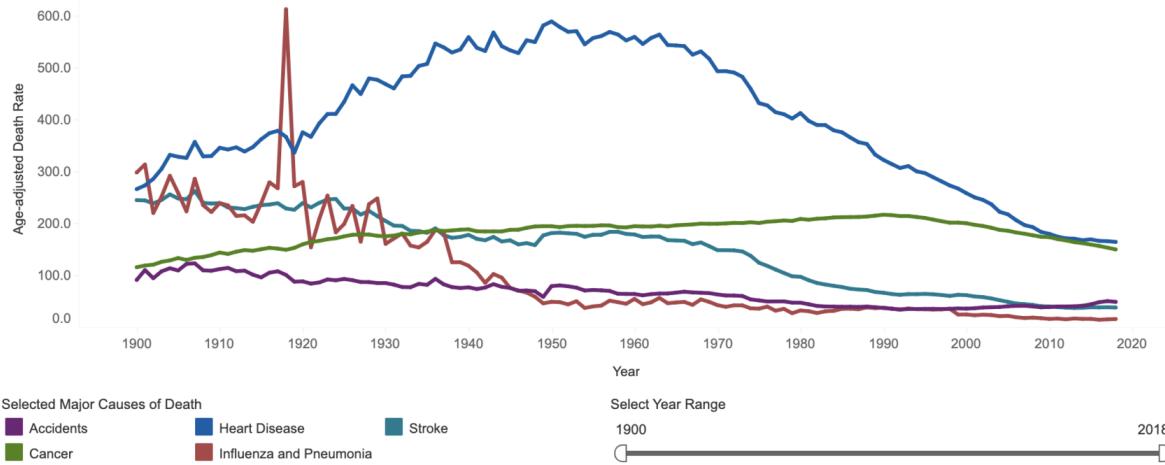
<https://ourworldindata.org/grapher/life-expectancy?tab=chart>

What factors reduced premature death due to communicable diseases?

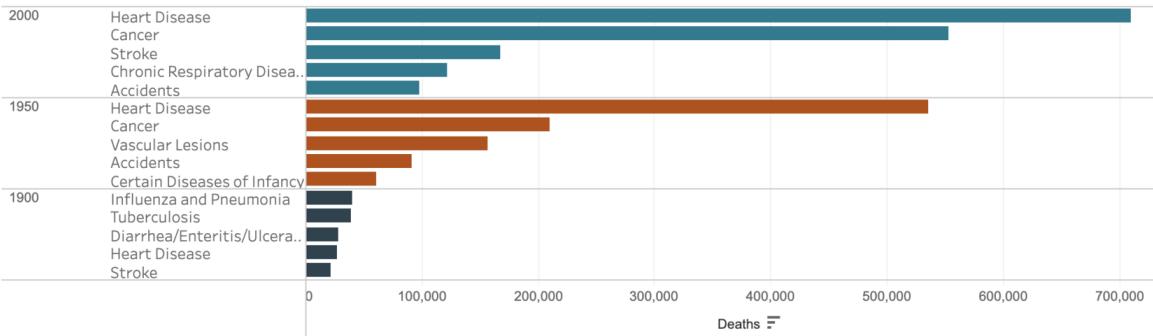
- Improved sanitation and drinking water (Mid 19th century)
- Immunization (Early 20th century)
- Antibiotics (Mid 20th century)

Infection rates began to fall in the early 1900s, long before antibiotics, on the basis of just implementing better sanitation!

Age-adjusted death rates, U.S. 1900-2018



Five Leading Causes of Death: United States, 1900, 1950, and 2000



A brief history of antibiotics and antibiotic resistance

Bacteria and antimicrobial resistance: Humans are not the cause...

Ancient "Antibiotic" Therapy



Chinese:

moldy tofu to treat inflammations and infections of the skin



Egypt:

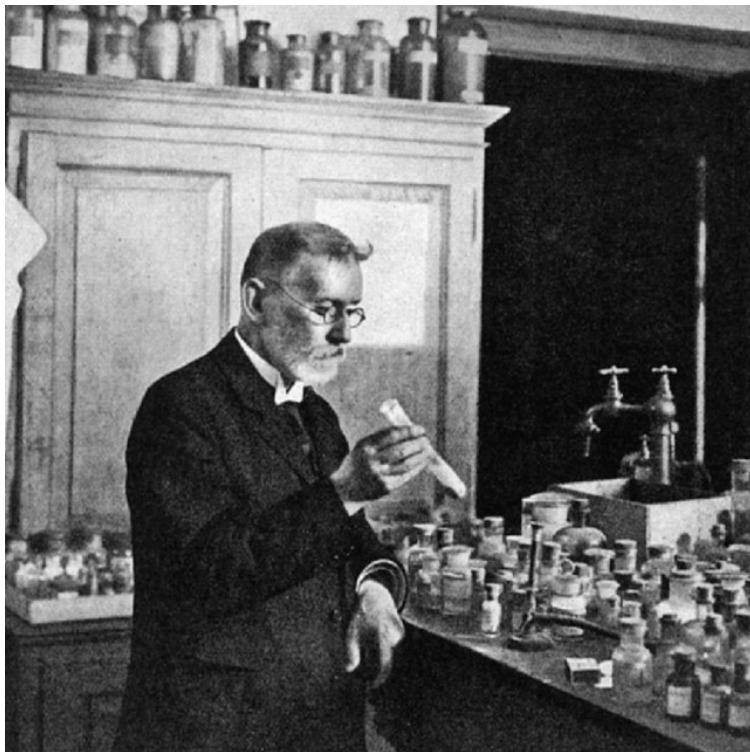
moldy bread to treat skin lesions



Greeks:

myrrh, wine, honey or caustic substances to treat wound infections

Early antibiotics



Paul Ehrlich (1854-1917)

"Magic bullet"- chemotherapy

arsphenamine (Salvarsan) 1909

The first treatment for syphilis
(*Treponema pallidum*)

Image: Wellcome Library, London

The beginning of the modern antibiotic era

Sir Alexander Fleming (1881-1955)



Image: Wellcome Library, London

The serendipitous discovery
of penicillin in 1928

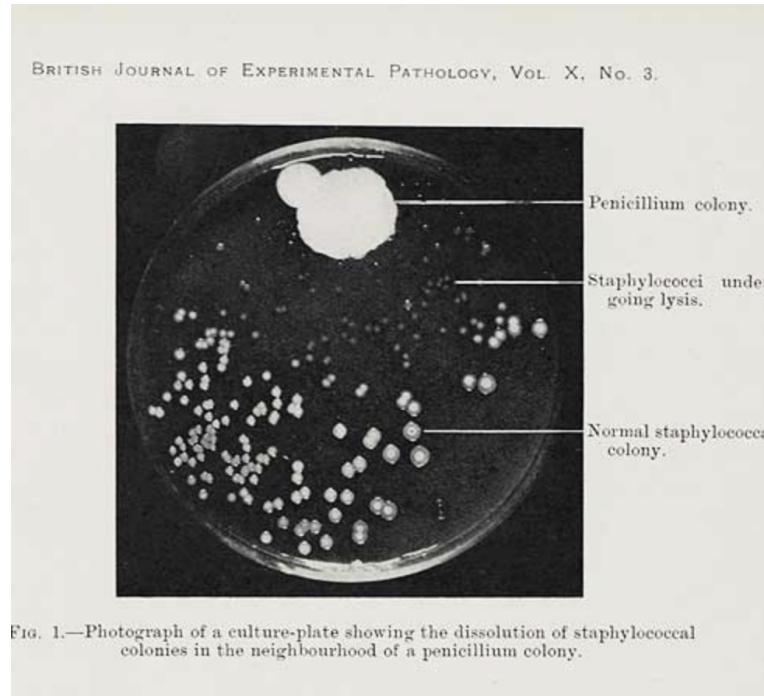
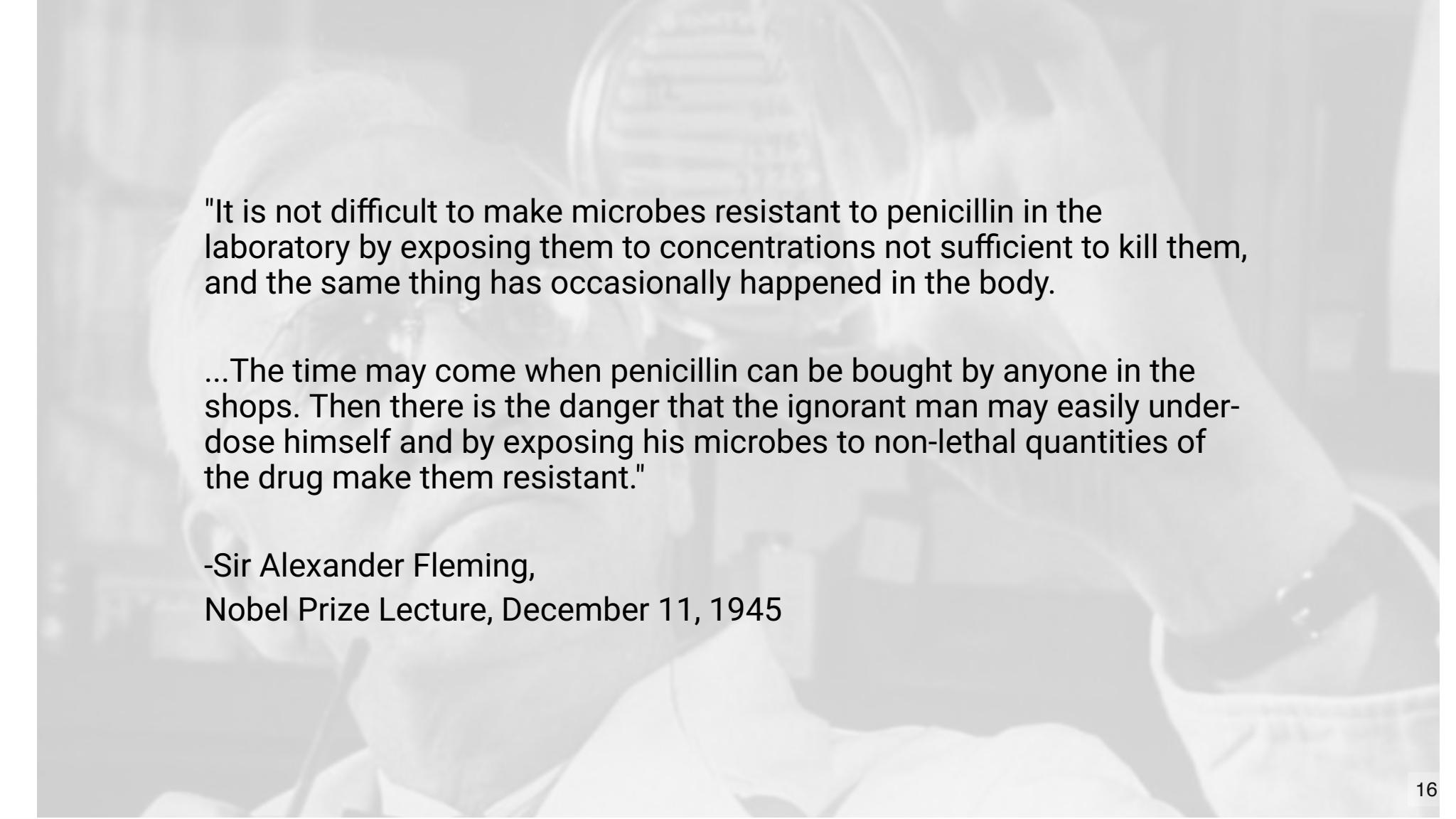


FIG. 1.—Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.

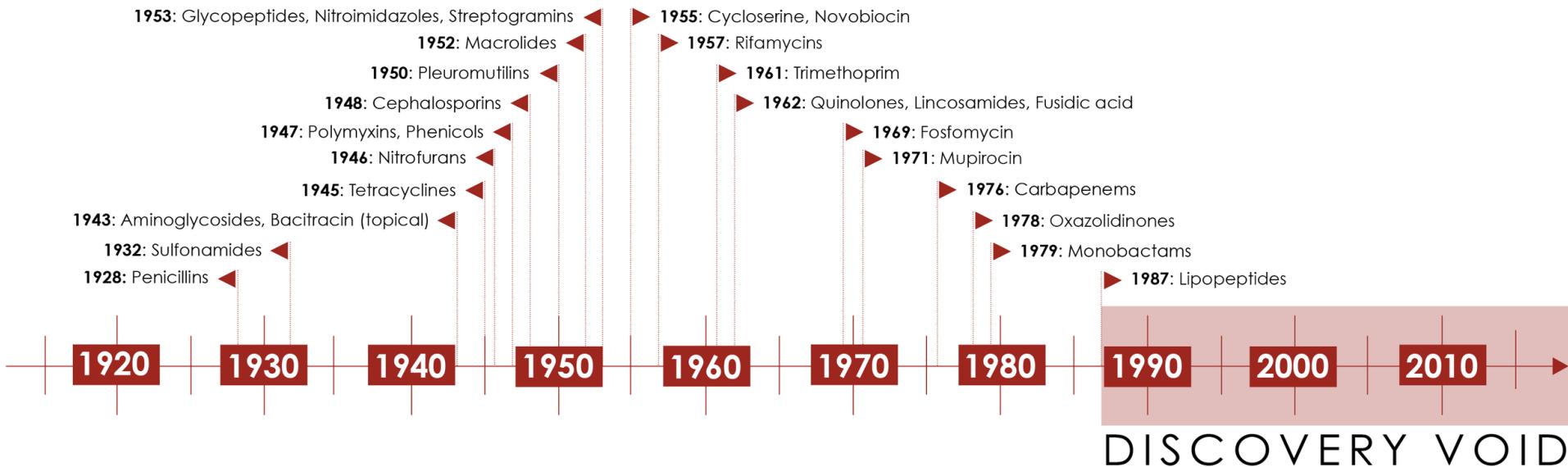


"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

...The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

-Sir Alexander Fleming,
Nobel Prize Lecture, December 11, 1945

Antibiotic development timeline



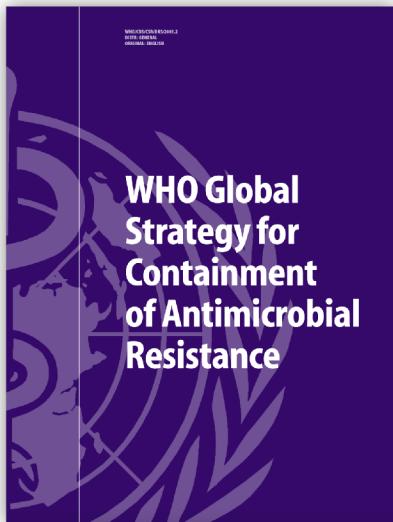
© ReAct Group 2015

Why is antibiotic discovery failing?

- Development of truly novel antibiotics is challenging
- Antibiotic discovery is time-intensive and high-risk
 - 10-15 years, 1 billion dollars investment *initially*
- Limited economic incentives for pharmaceutical companies
 - *Use of new drugs for resistant pathogens is often restricted to slow the emergence of resistance*

We will discuss these problems and solutions in Module 2

World Health Organization (WHO)



2001



2015



2019

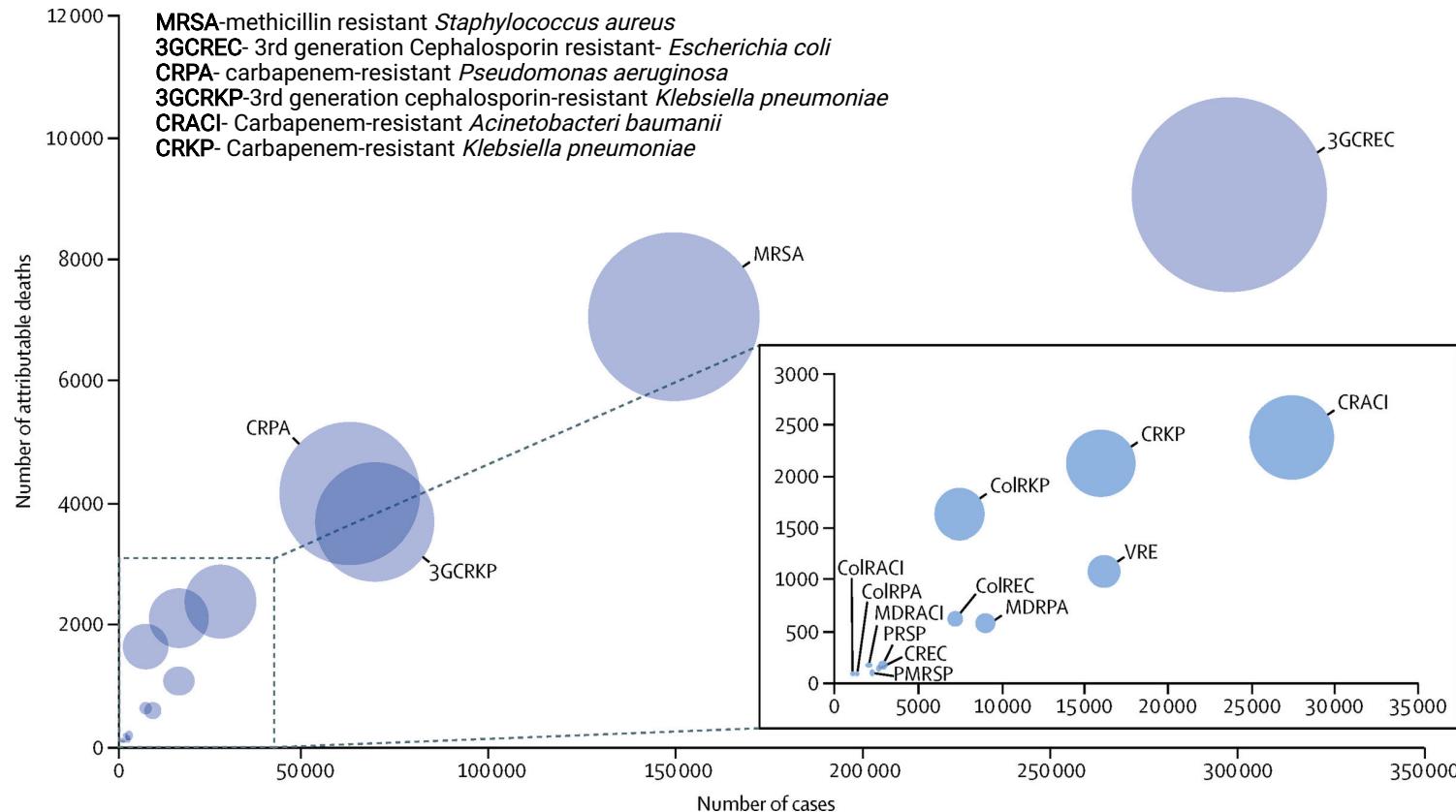
Establishment of global Antimicrobial Resistance
and Use Surveillance System (GLASS)

Global Research and Development Priorities for AMR

Priority	Pathogens included
Critical	<i>Acinetobacter baumannii</i> (Carbapenem-resistant) <i>Pseudomonas aeruginosa</i> (Carbapenem-resistant) Enterbacterales (3rd generation cephalosporin, carbapenem-resistant)
High	<i>Enterococcus faecium</i> , vancomycin-resistant <i>Staphylococcus aureus</i> , methicillin-resistant, vancomycin intermediate and resistant <i>Helicobacter pylori</i> , clarithromycin-resistant <i>Campylobacter</i> , fluoroquinolone-resistant <i>Salmonella</i> spp., fluoroquinolone-resistant <i>Neisseria gonorrhoeae</i> , 3rd gen. cephalosporin-resistant, fluoroquinolone-resistant
Medium	<i>Streptococcus pneumoniae</i> , penicillin-non-susceptible <i>Haemophilus influenzae</i> , ampicillin-resistant <i>Shigella</i> spp., fluoroquinolone-resistant

This table does not include *Mycobacterium tuberculosis*, which was already recognized as a global health priority pathogen

Which pathogens are associated with the highest mortality rates?



Common definitions of resistance used in literature

Resistance type	Definition
Multi-drug resistance (MDR)	Resistance to one agent in at least 3 antibiotic categories
Extreme drug resistance (XDR)	Resistant except to 2 or fewer antibiotic categories
Pan-drug resistance (PDR)	PDR- resistant to all agents in all antibiotic categories
Difficult-to-treat resistance (DTR)	DTR-requires the use of less-effective or more toxic "reserve" antibiotics

Magiorakos A-P et al. Clinical Microbiology and Infection. 2012:268–81.

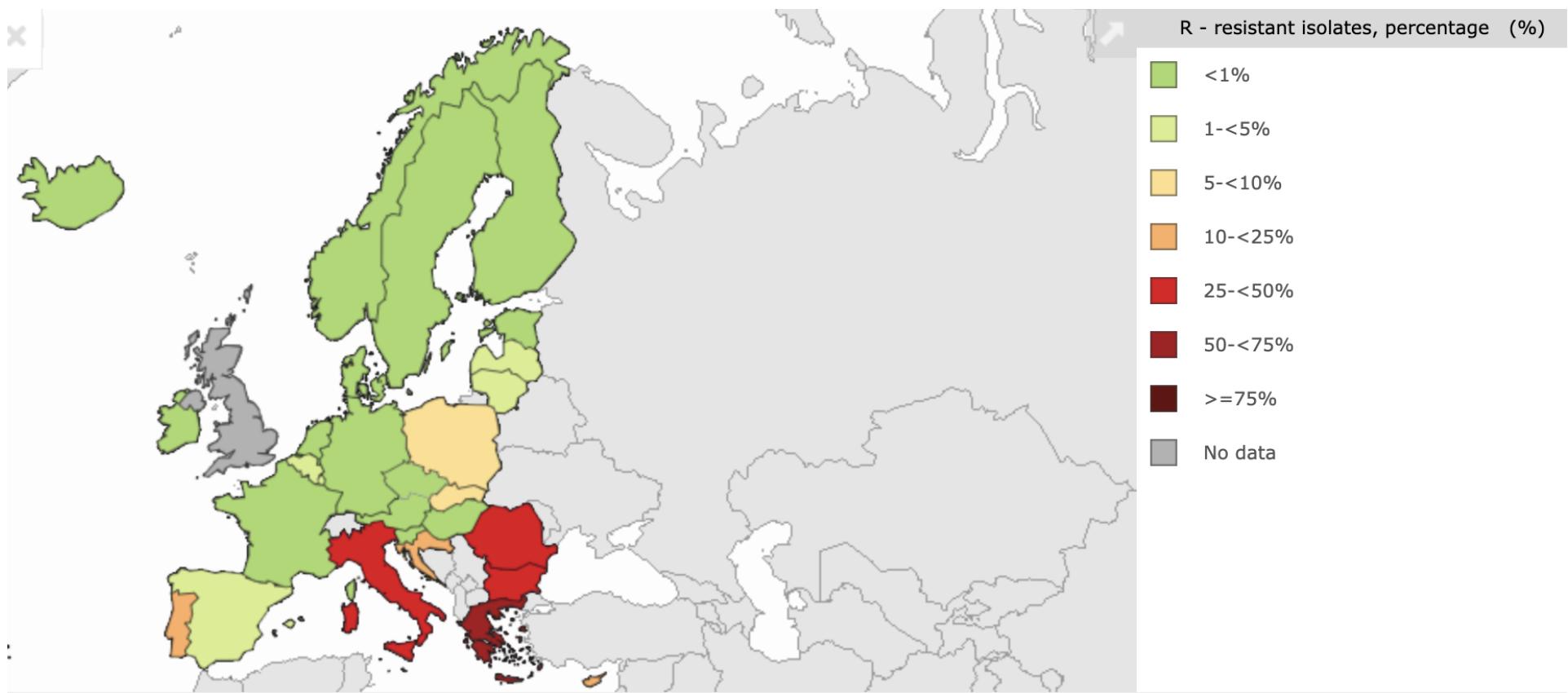
Kadri SS et al. Clinical Infectious Diseases. 2018:1803–14.

AMR situation in Italy-Gram negative bacteria

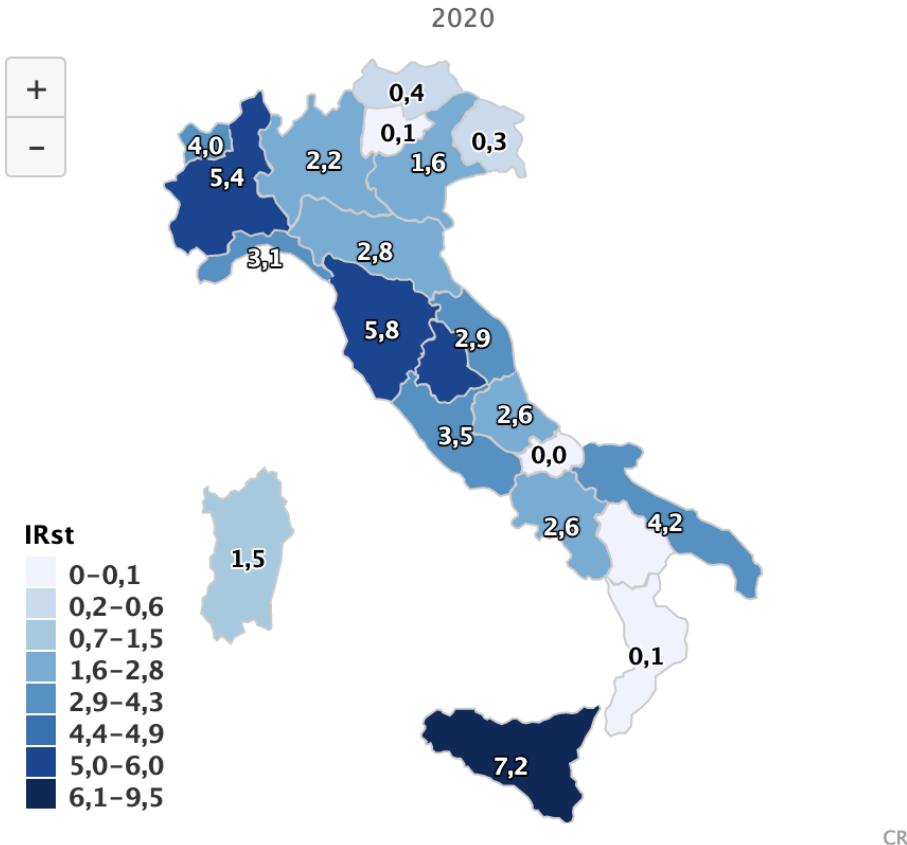
Southern Europe has among the highest resistance rates on the WHO priority pathogen list

- 26.4% of *Escherichia coli* are resistant to 3rd generation cephalosporins
- 29.5% of *Klebsiella pneumoniae* are resistant to carbapenems
 - Including 33.1% resistant to multiple drug classes
- 15.9% of *Pseudomonas aeruginosa* are resistant to carbapenems
- 80.8% of *Acinetobacter* spp. are resistant to carbapenems
 - 78.8% of species resistant to multiple drug classes
- Overall, higher antimicrobial resistance rates (around 40%) are observed in ICUs versus general medical wards

Carbapenem-resistance in *Klebsiella pneumoniae* in EU, 2020



Regional CRE bacteremia incidence per 100,000 Italian residents by region



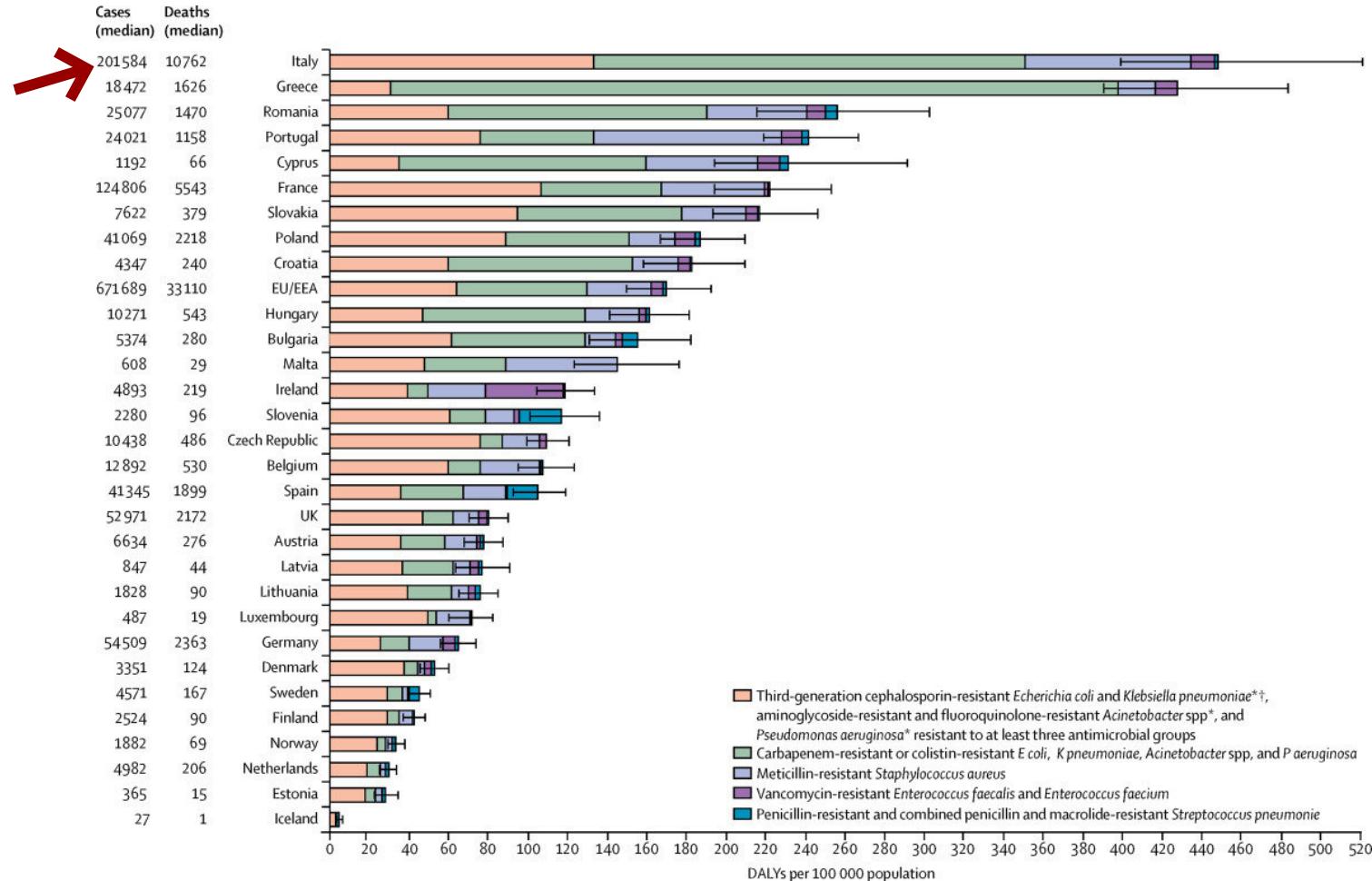
Source: [Micronet](#)

AMR situation in Italy-Gram positive bacteria

Southern Europe has among the highest resistance rates on the WHO priority pathogen list

- *Staphylococcus aureus*, the percentage of methicillin-resistant isolates (MRSA) remained stable around 34%, while a worrying trend continues to increase in the percentage of *Enterococcus faecium* isolates resistant to vancomycin, which in 2020 was equal at 23.6%
- *Streptococcus pneumoniae* isolates resistant to penicillin (13.6%) and those resistant to erythromycin (24.5%).

AMR situation in Italy-Predicted deaths



Cassini et al. Lancet Infect Dis 2019;19:55-66.

AMR in low-middle income countries (LMICs)

What factors contribute to AMR severity in LMICs?

- High population density
- Limited access to clean water, suboptimal sewage systems, poor sanitation
- Poor healthcare infection control practices
- Limited microbiology laboratory testing/surveillance
- Increasing consumption of antimicrobials in humans and animals
- Lack of regulation on antimicrobial use in farming, and pharmaceutical industry pollution



Image: Water Aid/Tom Saator

How are LMICs affected by AMR?

- Increased mortality and health costs
- Antibiotics effective against AMR are more expensive and not affordable for many patients
- Increasing use of antibiotics with efficacy against AMR leads to higher resistance to "last-line" antibiotics
 - Carbapenem consumption is increasing at a rapid pace in poor economies



Photo: Chandan Khanna/AFP/Getty Images

Klein, E. Y. *et al.* *The Lancet Infectious Diseases* 21, 107–115 (2021).

A close-up photograph of a person's hands holding a clear plastic petri dish. The dish contains a red agar medium with numerous small, white, circular bacterial colonies. The hands are positioned to support the dish from underneath.

**What are the drivers of
antimicrobial resistance?**

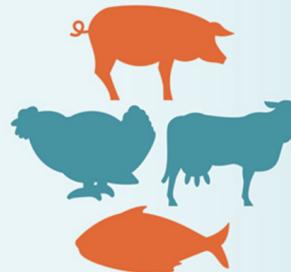
Factors driving antimicrobial resistance



Over-prescribing
of antibiotics



Patients
not taking
antibiotics as
prescribed



Unnecessary
antibiotics used
in agriculture



Poor infection
control in hospitals
and clinics

Poor hygiene
and sanitation
practices

Lack of rapid
laboratory tests

How does antibiotic resistance spread?

Antibiotic resistance is the ability of bacteria to combat the action of one or more antibiotics. Humans and animals do not become resistant to antibiotic treatments, but bacteria carried by humans and animals can.



- ① Animals may be treated with antibiotics and they can therefore carry antibiotic-resistant bacteria. ② Vegetables may be contaminated with antibiotic-resistant bacteria from animal manure used as fertilizer. ③ Antibiotic-resistant bacteria can spread to humans through food and direct contact with animals.



- ④ Humans sometimes receive antibiotics prescribed to treat infections. However, bacteria develop resistance to antibiotics as a natural, adaptive reaction. Antibiotic-resistant bacteria can then spread from the treated patient to other persons.



- ⑤ Humans may receive antibiotics in hospitals and then carry antibiotic-resistant bacteria. These can spread to other patients via unclean hands or contaminated objects. ⑥ Patients who may be carrying antibiotic-resistant bacteria will ultimately be sent home, and can spread these resistant bacteria to other persons.

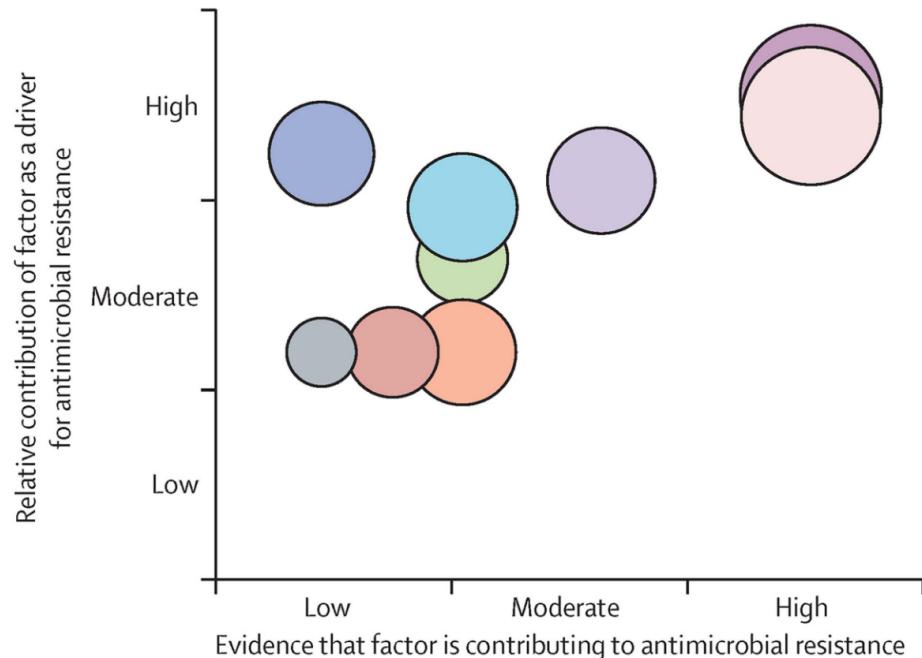


- ⑦ Travellers requiring hospital care while visiting a country with a high prevalence of antibiotic resistance may return with antibiotic-resistant bacteria. ⑧ Even if not in contact with healthcare, travellers may carry and import resistant bacteria acquired from food or the environment during travel.



Modifiable risk factors that drive antimicrobial resistance

- Human antimicrobial misuse or overuse
- Animal antimicrobial misuse or overuse
- Environmental contamination
- Health-care transmission
- Suboptimal rapid diagnostics
- Suboptimal vaccination
- Suboptimal dosing, including from substandard and falsified drugs
- Travel
- Mass drug administration for human health



Human antimicrobial misuse: *outside hospitals*

Outpatient settings account for **the majority** of antibiotics prescribed in human health care in the U.S.



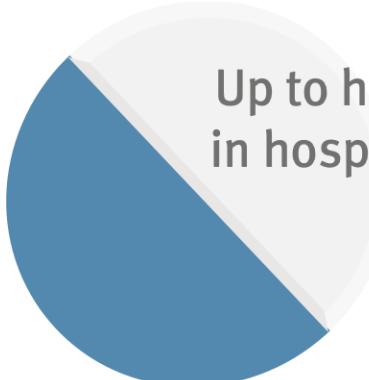
1 in 3

antibiotic prescriptions written in doctors' offices, emergency rooms, and hospital-based clinics is **unnecessary**—this equals about **47 million prescriptions** each year.



46% of all urgent care visits for diagnoses that do not require an antibiotic still result in an antibiotic prescription

Human antimicrobial misuse in hospitals

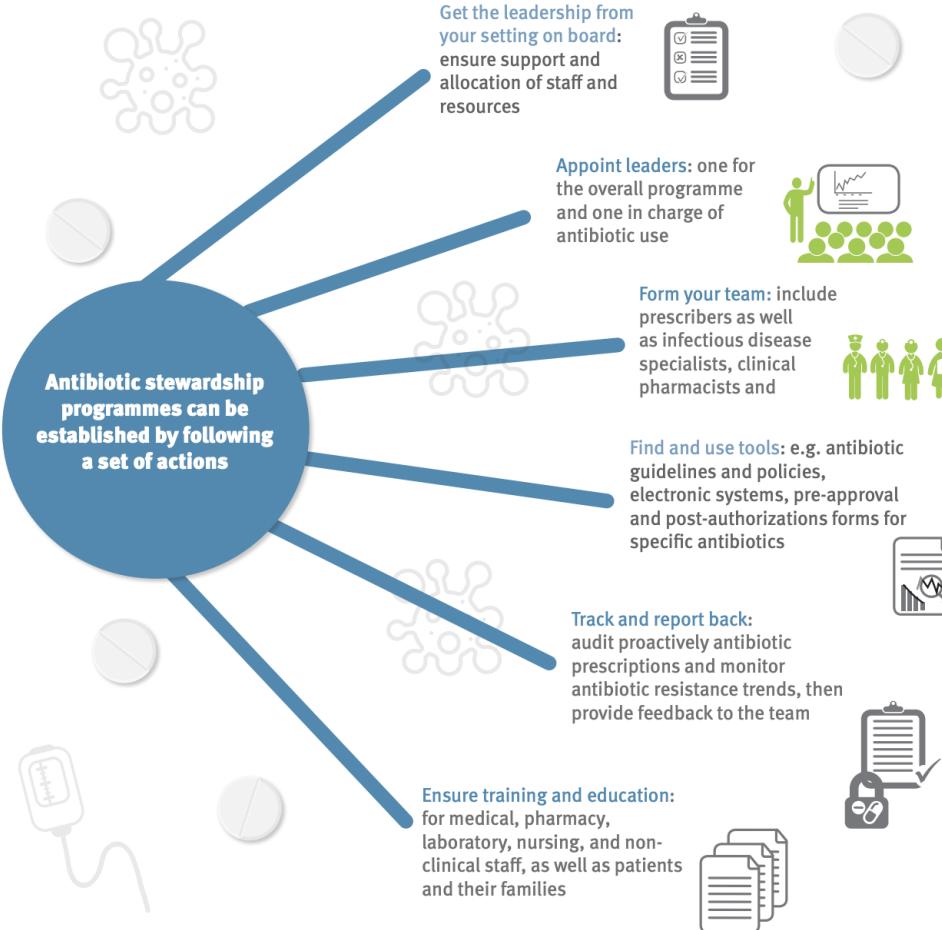


Up to half of all antibiotic use in hospitals is unnecessary or inappropriate

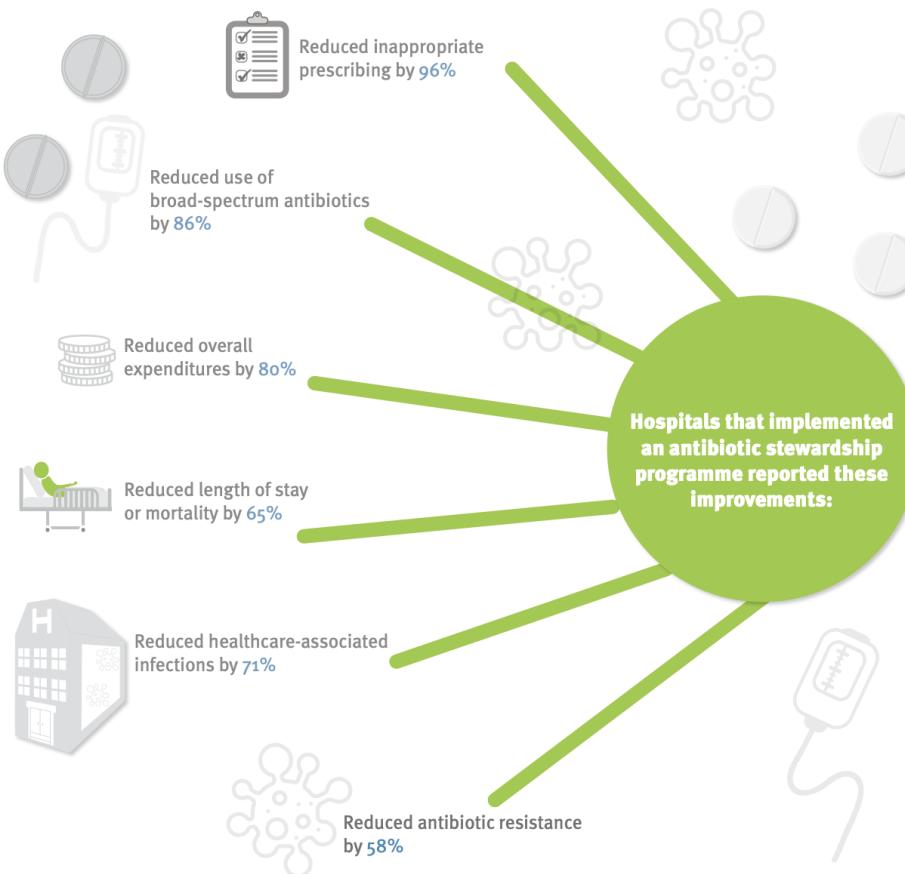


Antibiotic stewardship programmes can contribute to reduce antibiotic resistance in healthcare settings

Antimicrobial stewardship programs



Antimicrobial stewardship programs



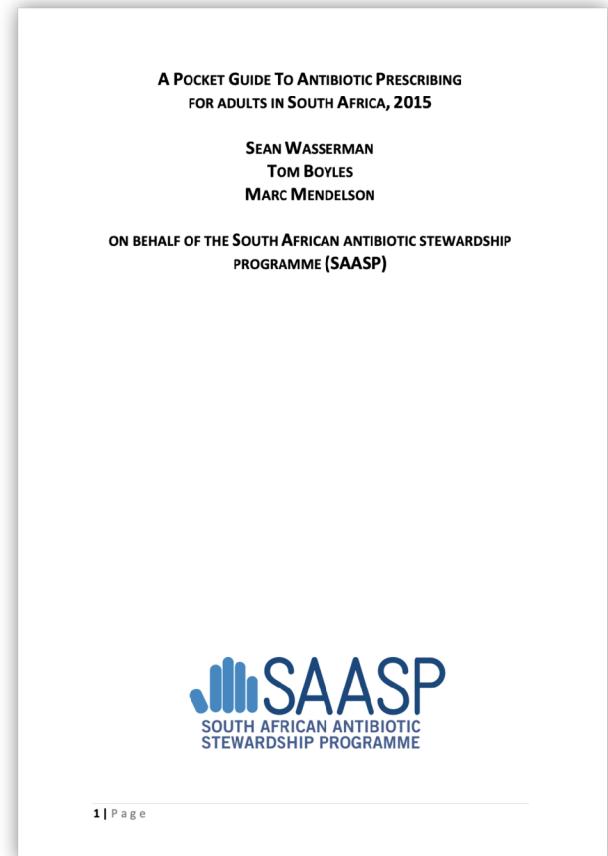
WHO- AWaRe Antibiotic List

<https://www.who.int/publications/i/item/2021-aware-classification>

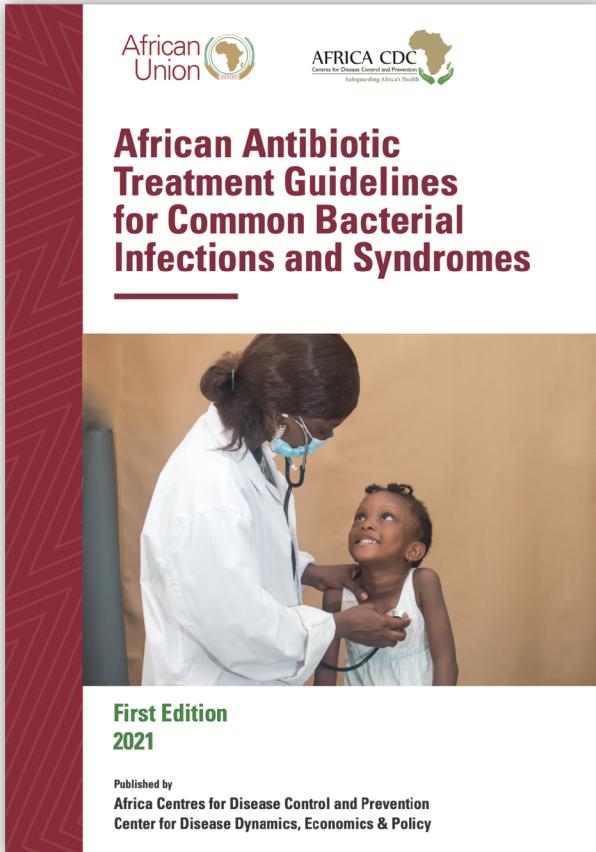
- The 2021 update of the AWaRe classification includes an additional 78 antibiotics not previously classified, bringing the total to 258.

Antimicrobial stewardship in Africa-2016

- Only 2 countries had national AMR plans
- 7 had overarching national infection prevention and control (IPC) policies
- 44 had essential medicines lists
- 43 had national medicines policies and treatment guidelines intimating rational use



Antimicrobial stewardship in Africa



https://africaguidelines.cddep.org/wp-content/uploads/2021/11/Guidelines_Adults_Peds_English.pdf

Antibiotic Stewardship Programs in Thailand:

Antibiotic Smart Use Program

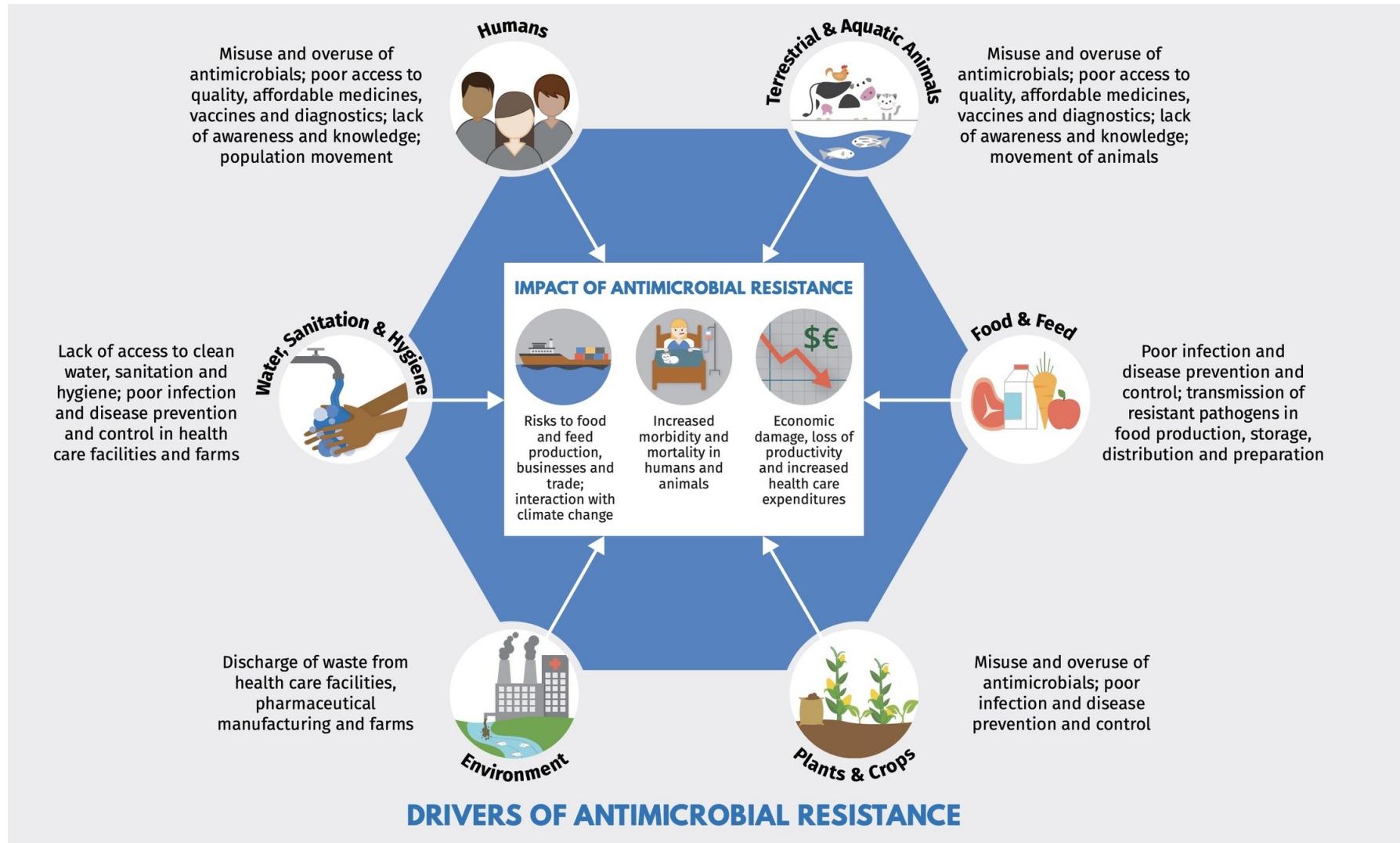


A self-diagnosis mirror in Thai pharmacies for patients who seek antibiotics for sorethroat

One-health approach to combatting antimicrobial resistance

What is meant by a one-health approach?

- Designing and implementing programmes, policies, legislation and research in a way that enables **multiple sectors engaged in human, animal, agricultural, and environmental health** to communicate and work together to achieve better public health outcomes



Antibiotic use in animals



Chicken farm in the United States of America. Image source: The Guardian

73% of all antibiotic use is in animals; 66% of human infections are zoonotic in origin

Long-term, low-dose mass antibiotic treatment for purposes of growth promotion

- Practice started in 1960's with observation of increased weight gain in cattle and chickens fed antibiotics
...now used to increase profits
- While antibiotic use has stabilized and decreased in HICs, it is increasing in LMICs where meat and milk consumption is increasing as poverty decreases



Factors influencing animal health used in food production

- The genetic stock of the animals
- Adequate nutrition
- Hygiene/stress of living conditions
- Adequate veterinary care

antibiotics are often used as low-cost substitutes for expensive hygiene measures

Only in the last 10 years
has antibiotics in livestock
begun to be reduced. New
EU regulations banning
metaphylaxis in 2022

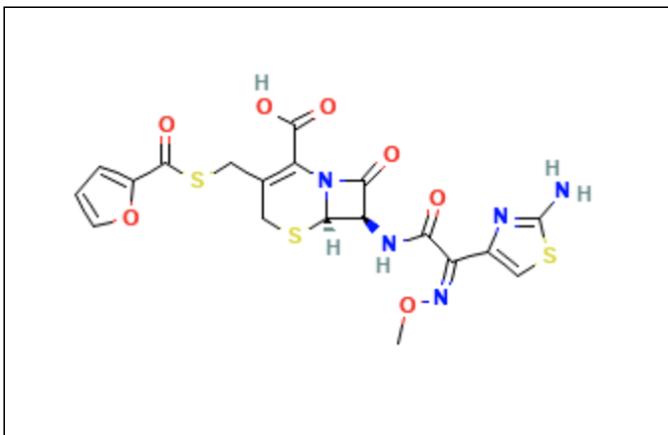
<https://ourworldindata.org/grapher/antibiotic-use-in-livestock>

<https://resistancebank.org/>



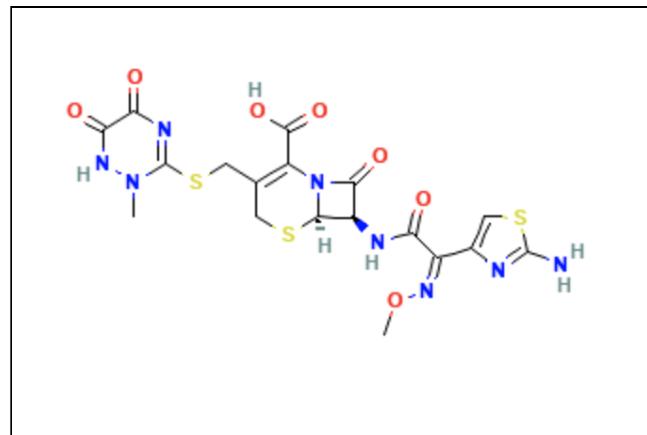
Chicken Farm in San Diego, California. Image: The Guardian

Used for
Metaphylaxis in animals



ceftiofurum

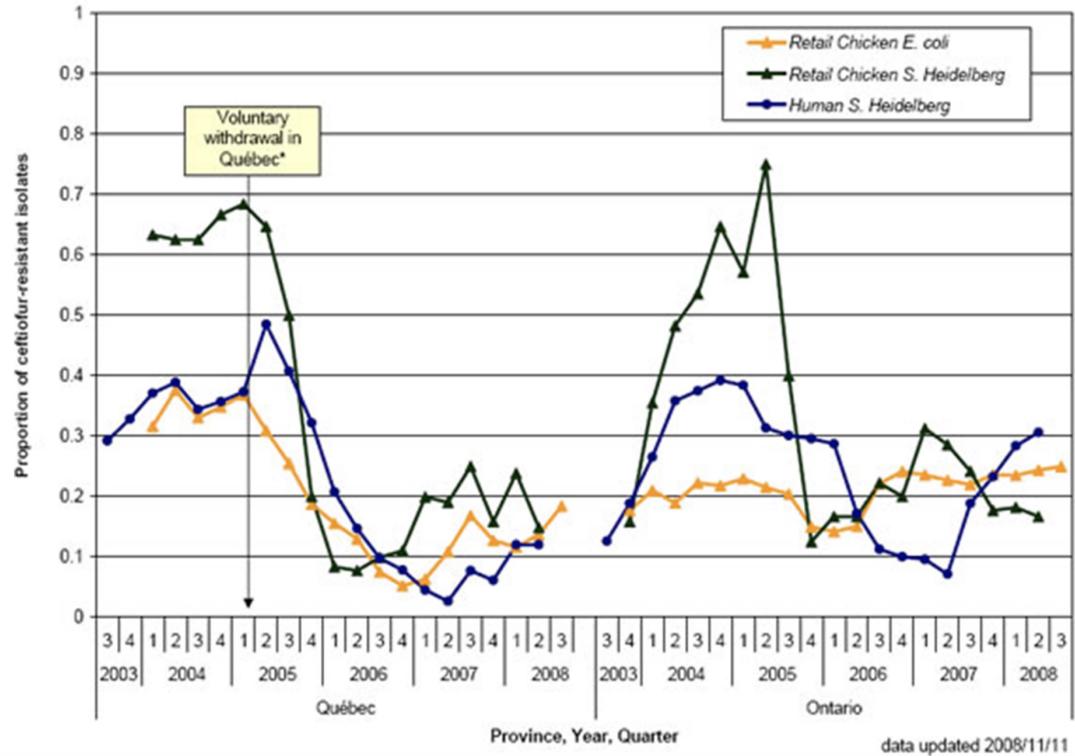
*Essential antibiotic
in humans*



ceftriaxone

Example- Cephalosporins

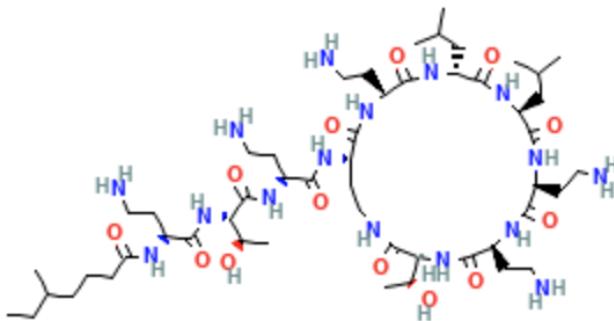
Outbreaks of multidrug resistant (MDR) *Salmonella* Heidelberg infections have been reported in humans working with cattle and chickens- associated with ceftriaxone (3rd generation cephalosporin) injection in young hatchlings



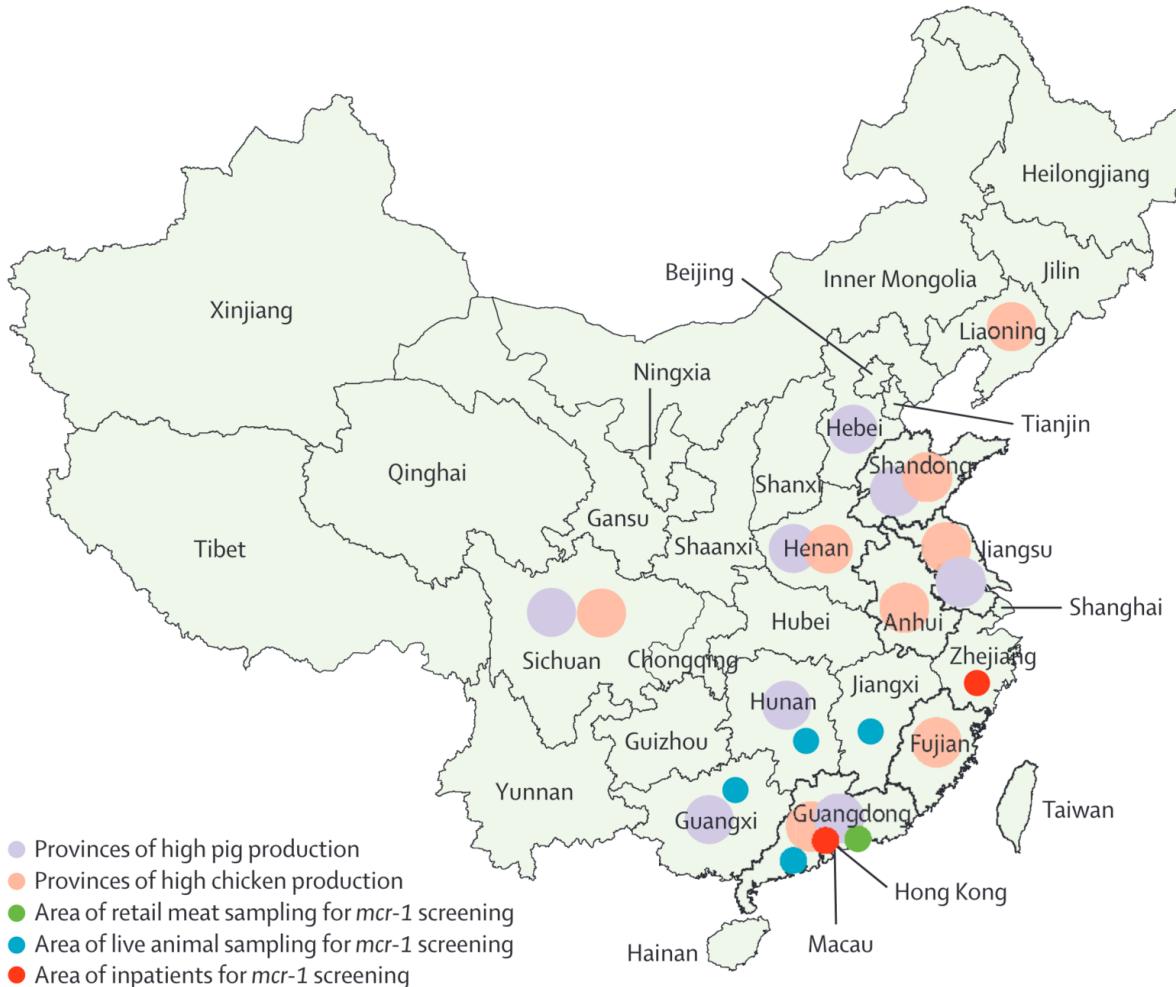


Pigs in cages, Quanzhou, China. Van Boeckel et al. *Science* 357, 1350–1352 (2017).

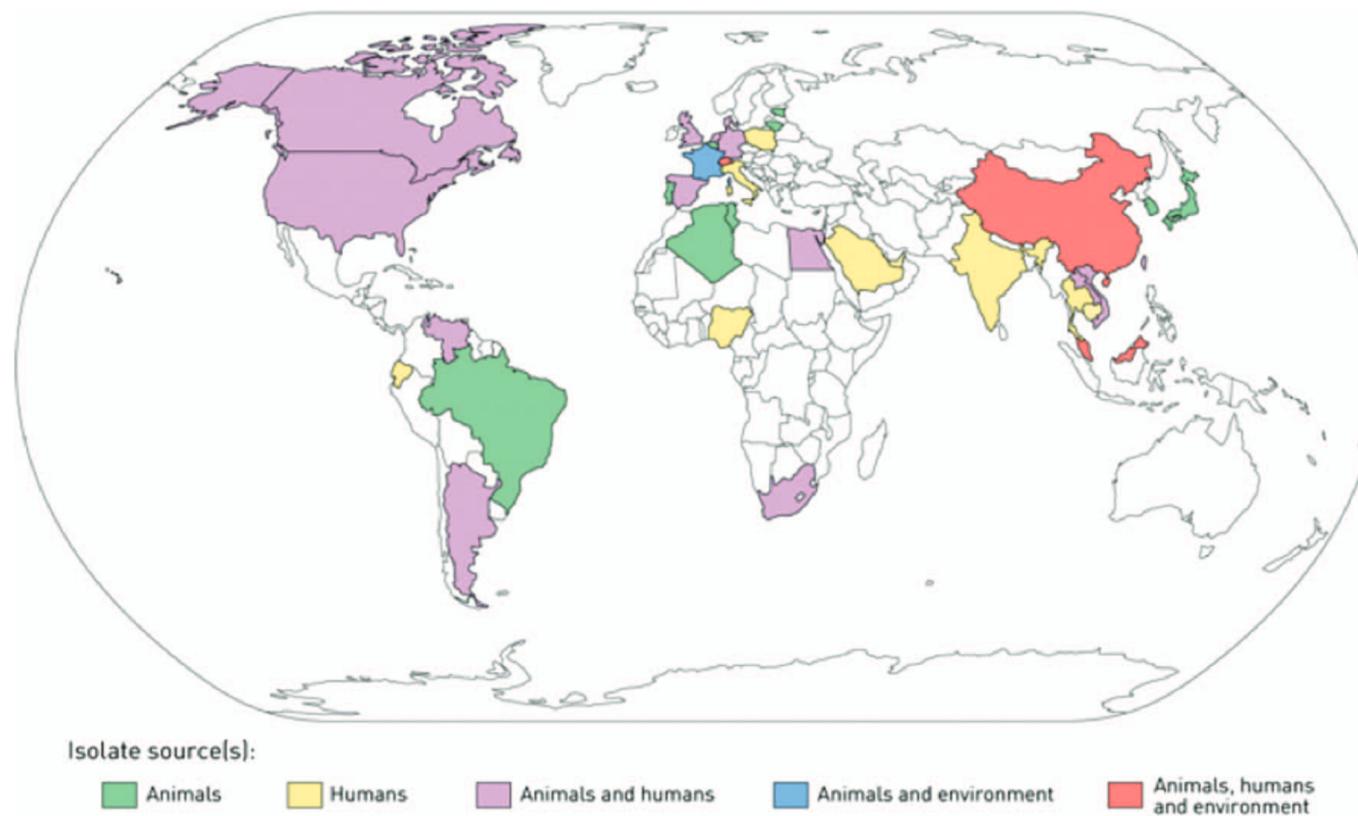
Example- Colistin



- Colistin-used in veterinary and human medicine for 50 years
- Intravenous colistin has surged in the last decade with the increase in carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*.
- Even as human use has increased, colistin continues to be used in Brazil, (formally Europe) and recently banned in China as growth promoting and antibiotic treatment for pigs, poultry and calves.

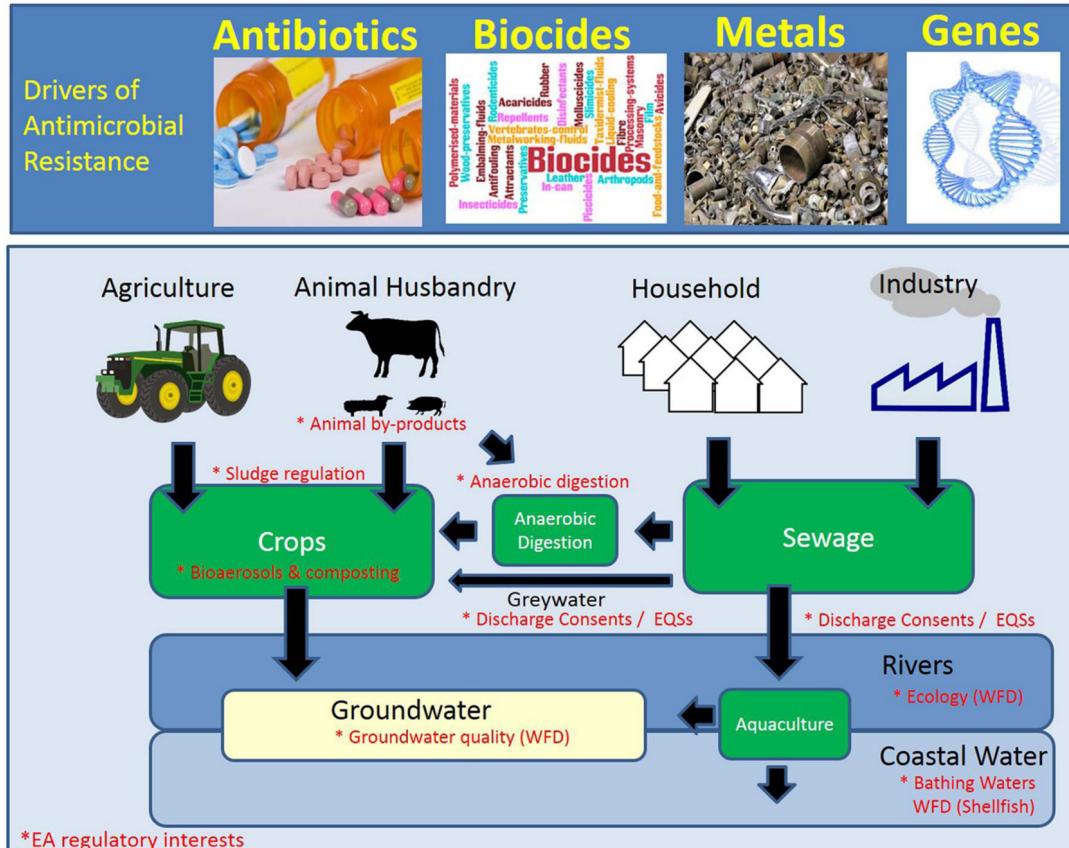


Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*



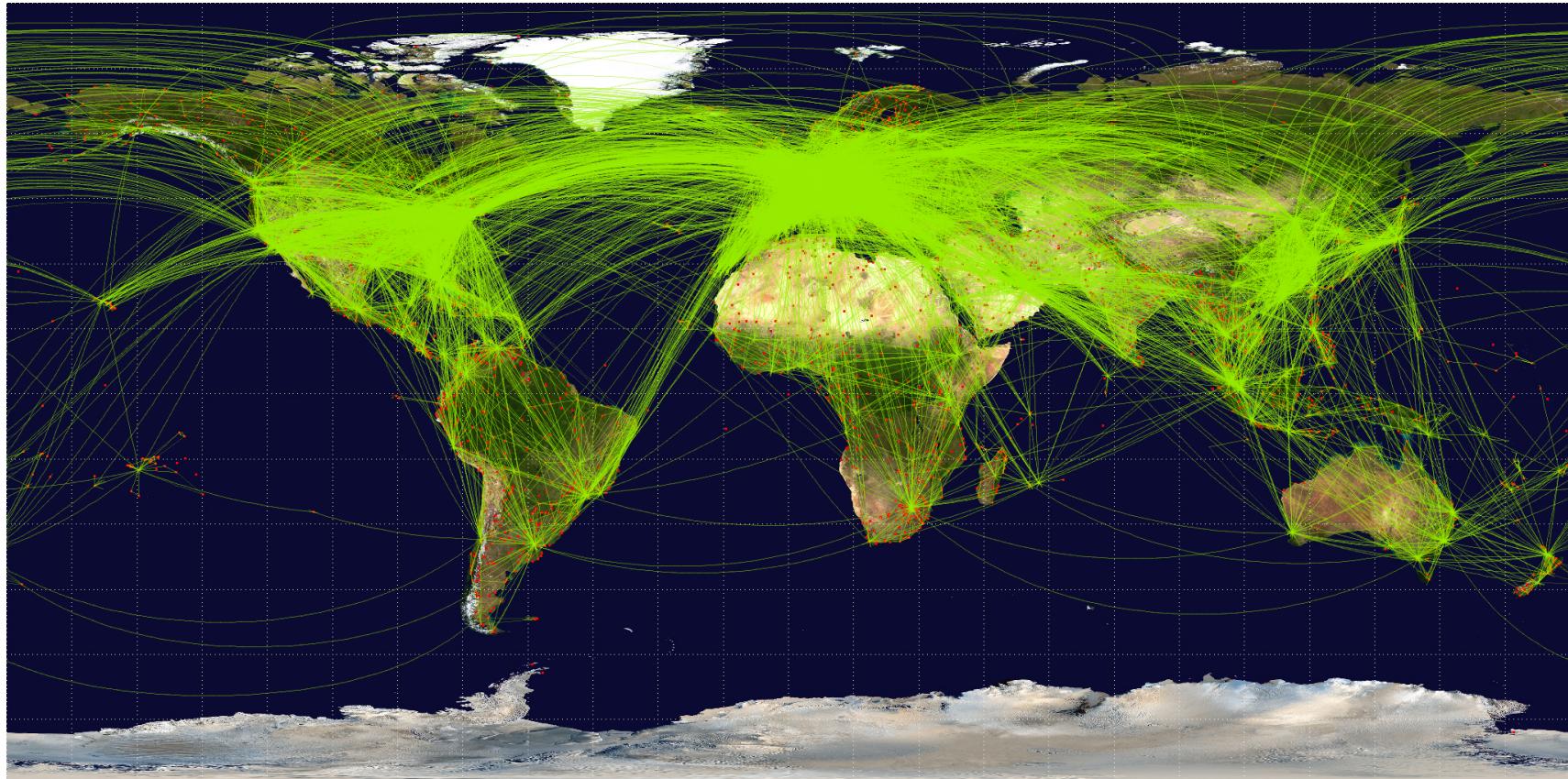
Frost, I, Van Boeckel, T. P., Pires, J., Craig, J. & Laxminarayan, R. Global geographic trends in antimicrobial resistance: The role of international travel. *Journal of Travel Medicine* **26**, taz036 (2019).

Environmental factors driving antimicrobial resistance



Singer, A. C., Shaw, H., Rhodes, V. & Hart, A. [Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators](#). *Frontiers in Microbiology* 7, 1728 (2016).

Cross-border spread of AMR



World airline travel routes 2014. Photo credit Jpatokal/Wikimedia (CC BY-SA 2.5)



WHO Pandemic Treaty 2024

Summary

- AMR is a persistent and growing global health threat that threatens to reverse a half-century of medical and economic progress
- Multiple modifiable risk factors are fueling an increase in AMR, with human and animal antimicrobial use/misuse a major driver-*One Health Approach is Needed*
- The dissemination of AMR is increasingly more rapid and does not respect borders- *international cooperation is essential*