97039: Global Health, Antimicrobial Drugs and Vaccines

Module 1:Global Aspects 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-boarder transmission of antimicrobial resistance

Changes in life expectancy over last 500 years

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

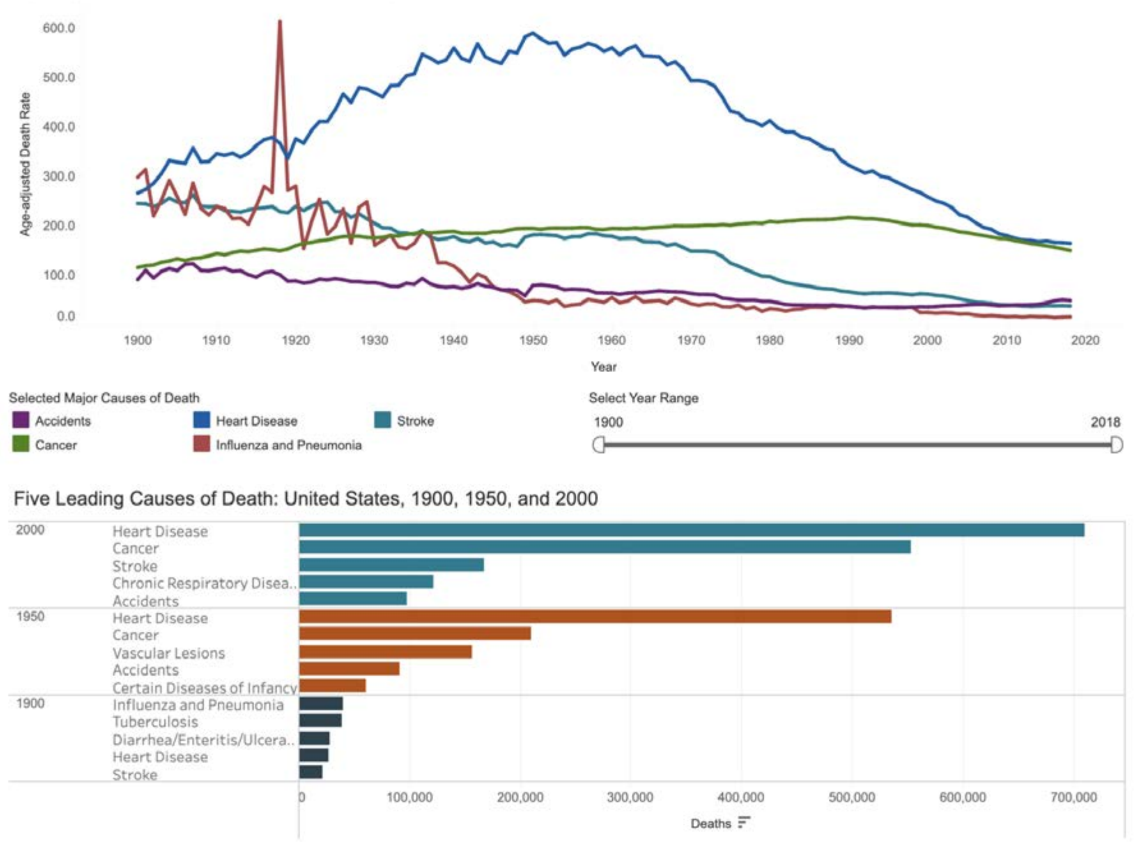
Source: Our World in Data

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



Source: National Center for Health Statistics

A brief history of antibiotics and antibiotic resistance

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

- Bacteria and antibacterial resistance emerged 2.5 billion years ago...humans 2 million years ago
- **It is likely that resistance mechanisms have been developed not only to *current* but also *future* antibiotics**
- Any antibiotic use, even appropriate use, will select for resistance
- In terms of Earth's biomass, humans are outnumbered by bacteria by 1000-fold
- Doubling time of bacteria approximately 20 minutes

PNAS Proc Natl Acad Sci USA 2018; 115:6506–6511.

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

All images: wikipedia

Early antibiotics

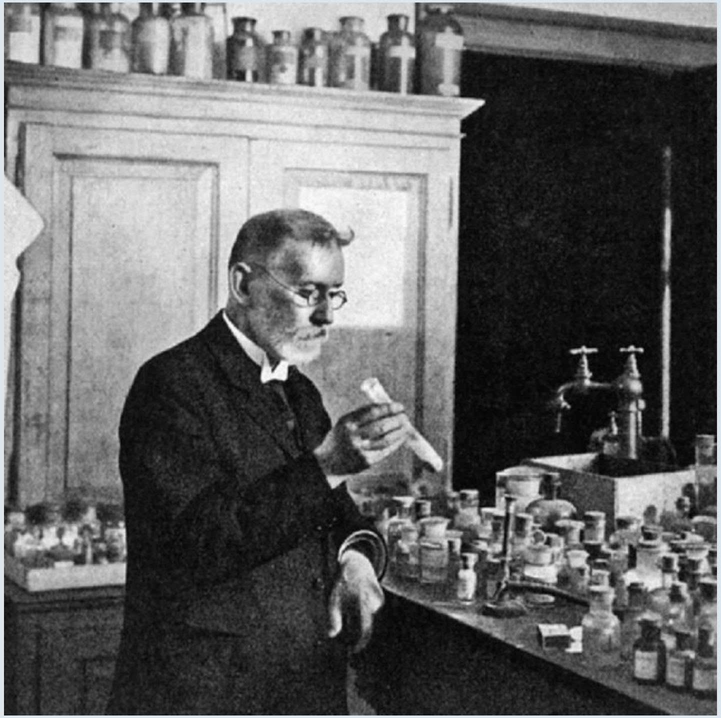


Image: Wellcome Library, London

Paul Ehrlich (1854-1917)

"Magic bullet"- chemotherapy

arsphenamine (Salvarsan) 1909

The first treatment for syphilis
(*Treponema pallidum*)

The beginning of the modern antibiotic era

Sir Alexander Fleming (1881-1955)

Image: Wellcome Library, London

The serendipitous discovery of penicillin in 1928

BRITISH JOURNAL OF EXPERIMENTAL PATHOLOGY, VOL. X, No. 3.

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

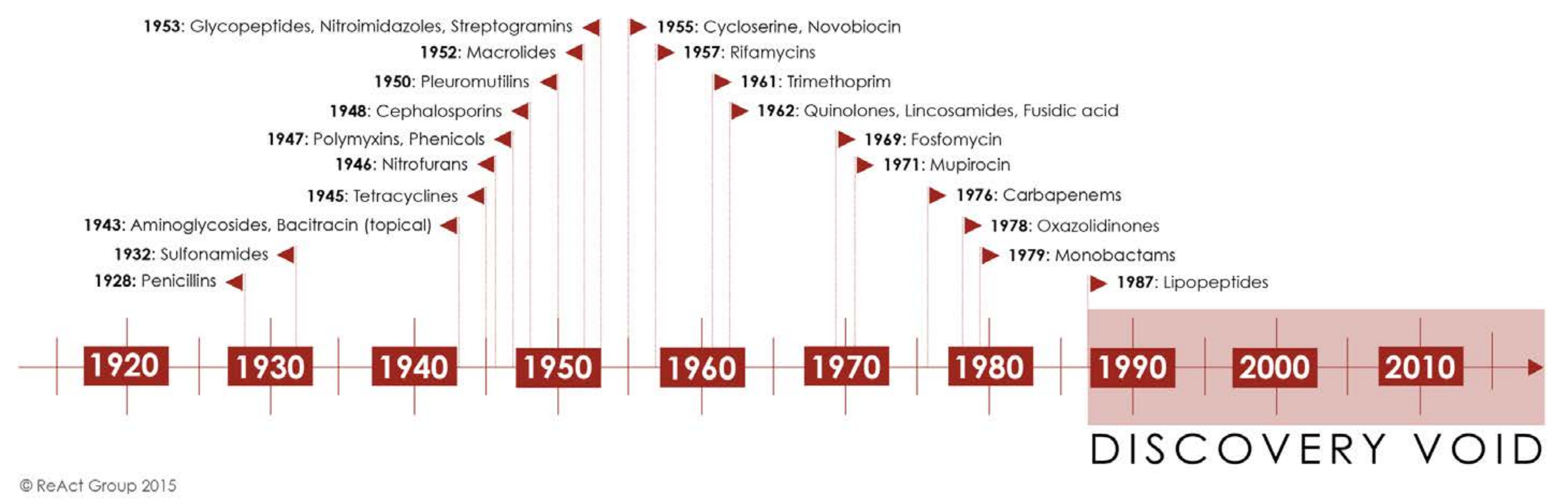
"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

...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



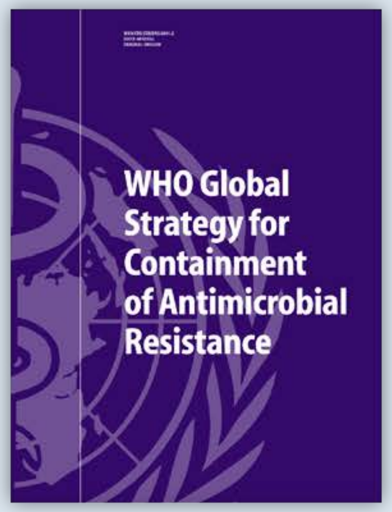
source: www.react.org

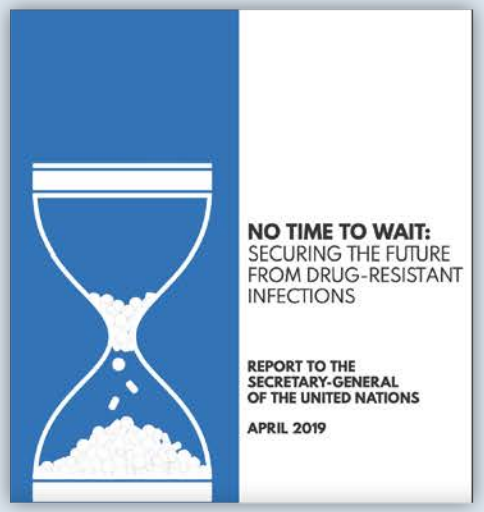
Why is antibiotic discovery failing?

- **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

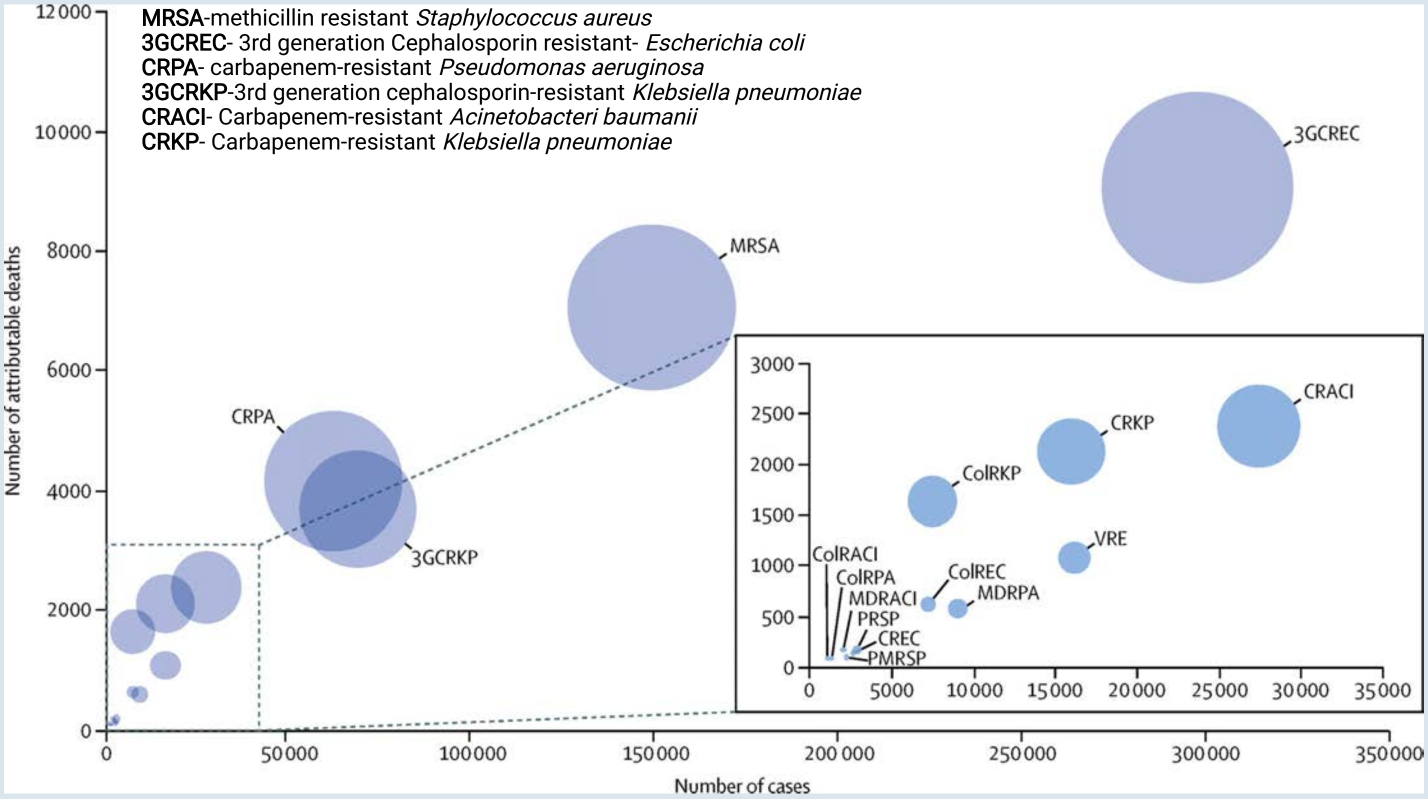
Priority	Pathogens included
Critical	*Acinetobacter baumannii* (Carbapenem-resistant) *Pseudomonas aeruginosa* (Carbapenem-resistant) Enterbacterales (3rd generation cephalosporin, carbapenem-resistant)
High	*Enterococcus faecium*, vancomycin-resistant *Staphylococcus aureus*, methicillin-resistant,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

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

Source:World Health Organization

Which pathogens are associated with the highest mortality rates?

MRSA-methicillin resistant *Staphylococcus aureus*
3GCREC- 3rd generation Cephalosporin resistant- *Escherichia coli*
CRPA- carbapenem-resistant *Pseudomonas aeruginosa*
3GCRKP-3rd generation cephalosporin-resistant *Klebsiella pneumoniae*
CRACI- Carbapenem-resistant *Acinetobacteri baumanii*
CRKP- Carbapenem-resistant *Klebsiella pneumoniae*



Cassini et al. Lancet Infect Dis 2019; 19: 56–66

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.

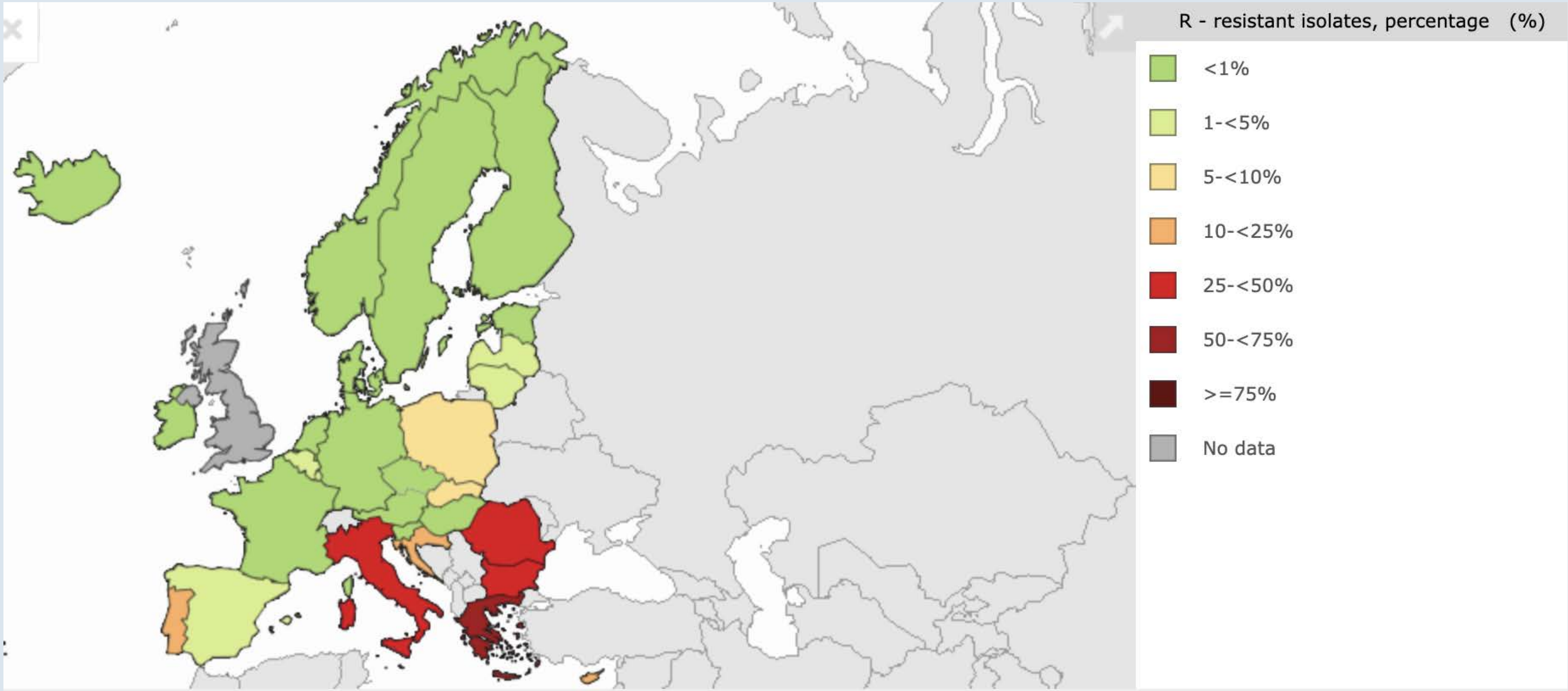
AMR situation in Italy-Gram negative bacteria

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

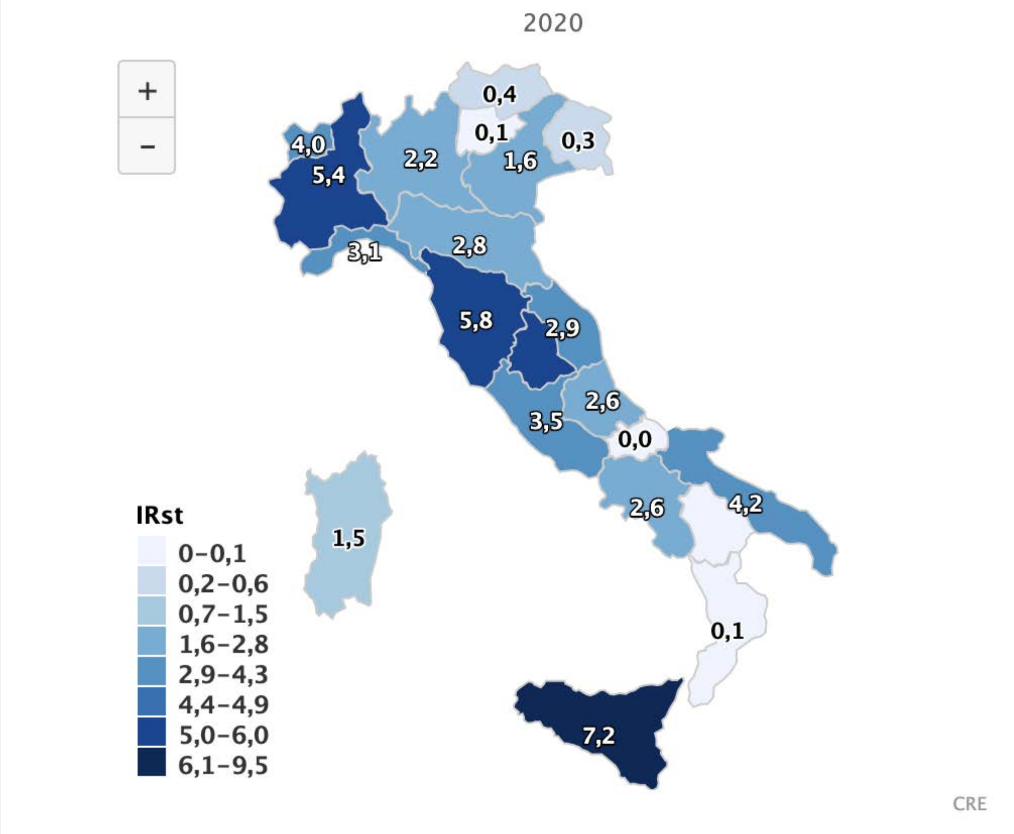
Source: Micronet Resistance Surveillance

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



Source: ECDC

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



Source: Micronet

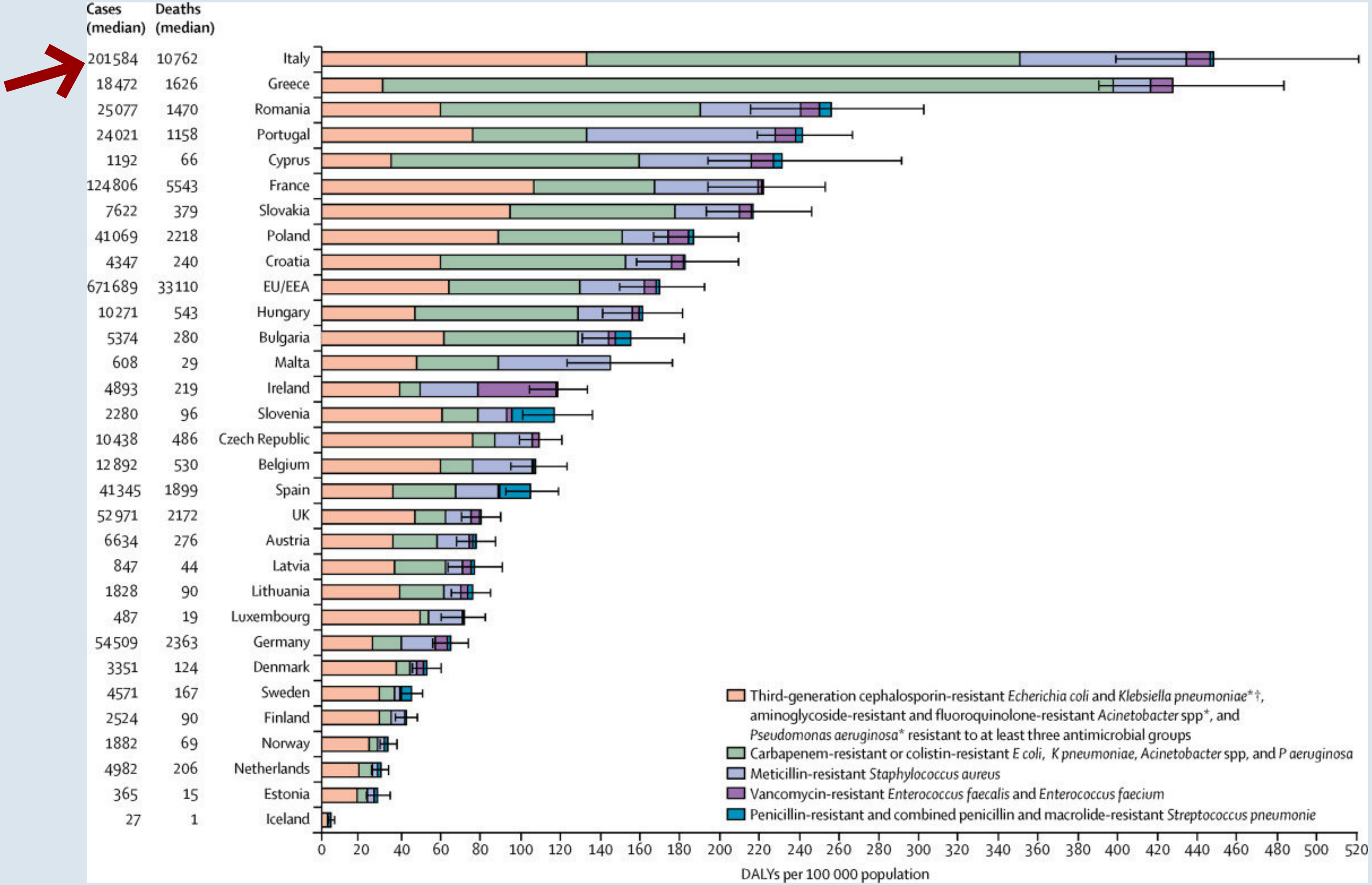
AMR situation in Italy-Gram positive bacteria

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%)**.

Source: Micronet Resistance Surveillance

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 spread in LMICs?

- High population density
- Limited of 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?

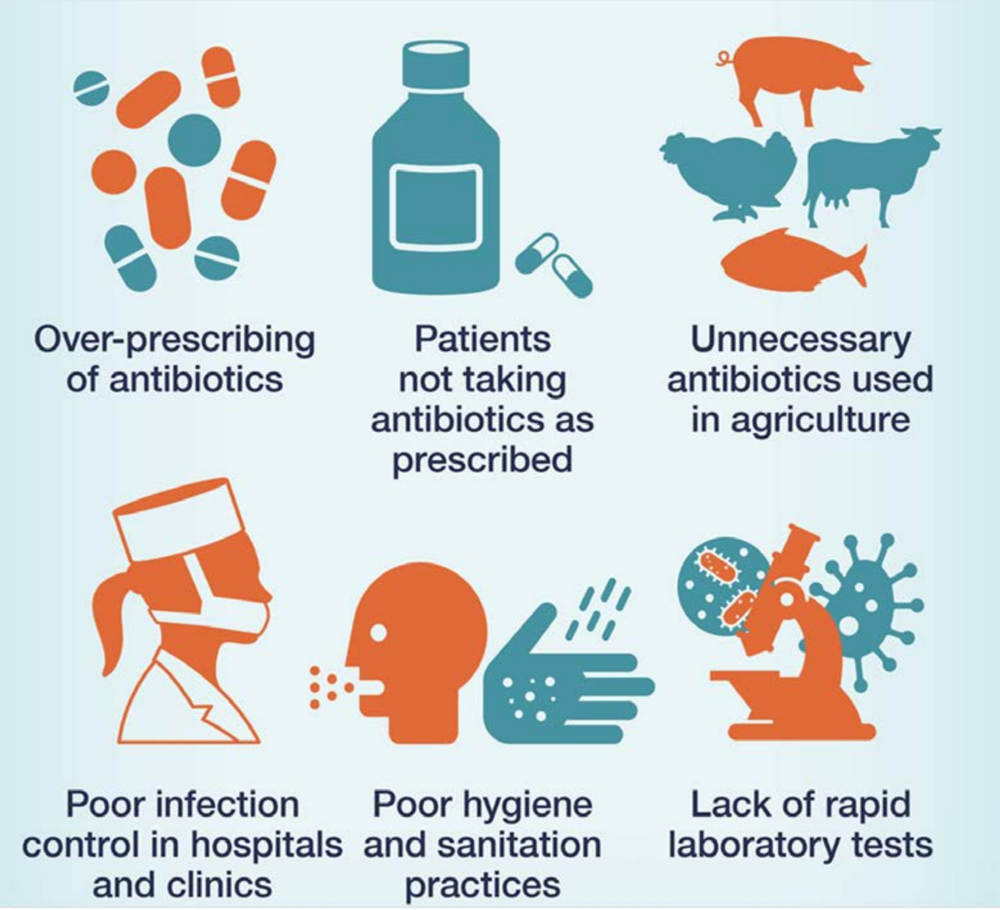
- Increased mortality and health costs
- Antibiotics effective against AMR are more expensive and not affordable for many patients
- Increasing use of antibiotics with efficacy against AMR leads to higher resistance to "last-line" antibiotics
  - Carbapenem consumption is increasing at a rapid pace in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

Photo: Chandan Khanna/AFP/Getty Images

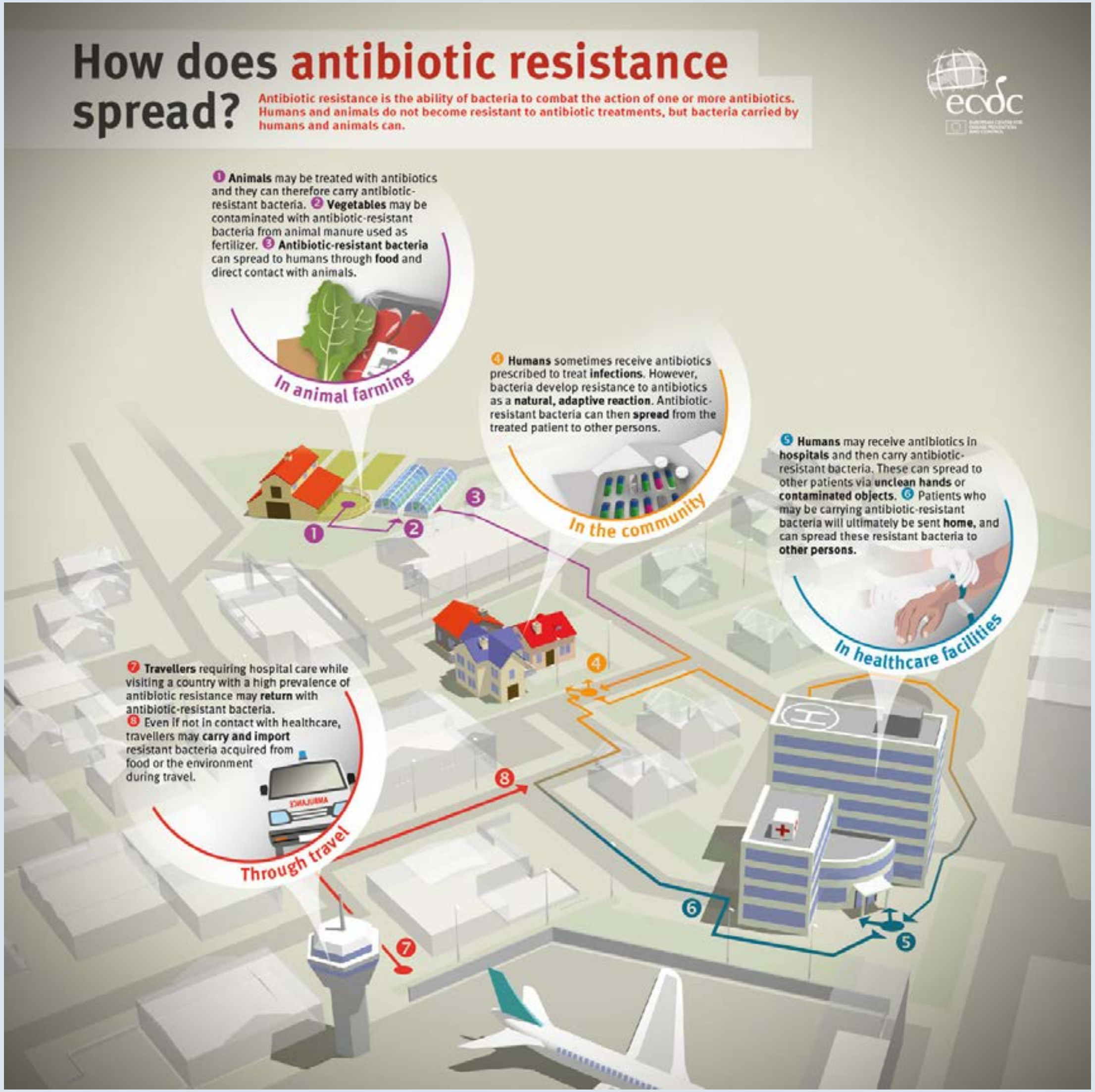
Klein, E. Y. *et al.* *The Lancet Infectious Diseases* 21, 107–115 (2021).

What are the drivers of antimicrobial resistance?

Factors driving antimicrobial resistance

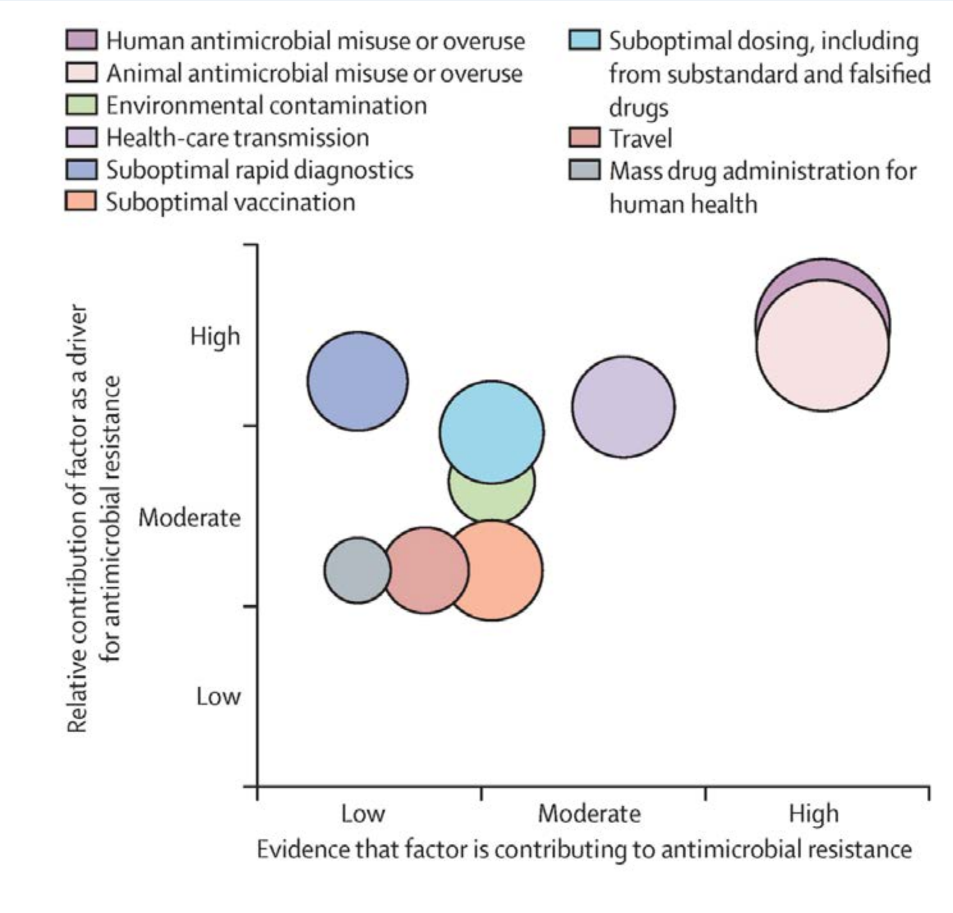


Source: U.S. CDC


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.
ecdc
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.
In animal farming
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.
In the community
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.
In healthcare facilities
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.
Through travel

Source: ECDC

Modifiable risk factors that drive antimicrobial resistance



Holmes AH et al. Lancet. 2016 Jan;387(10014):176–87.

Human antimicrobial misuse: *outside hospitals*

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

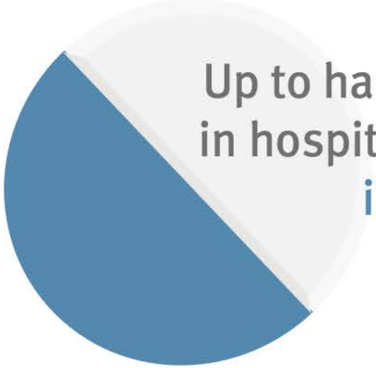
1 in 3

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

Source: Pew Research Trust

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

Source:ECDC

Antimicrobial stewardship programs

Source:ECDC

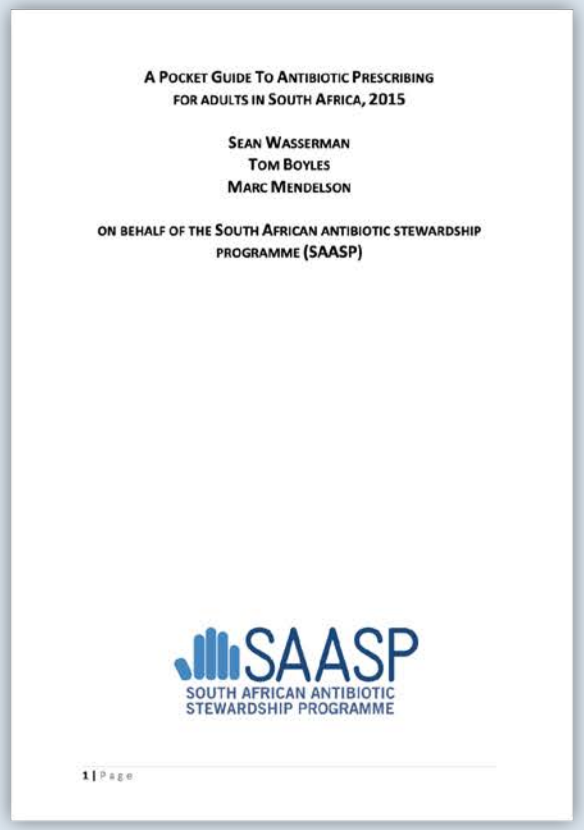
WHO- AWaRe Antibiotic List

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

- Antibiotics are classified into three groups:
  - **Access** (essential first-line agents)
  - **Watch** (high resistance potential, used in critically-ill)
  - **Reserve** (use only for MDR pathogens-last resort antibiotics)
- Takes into account the impact of different antibiotics and antibiotic classes on antimicrobial resistance, to emphasize the importance of their appropriate use.
- 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



A POCKET GUIDE TO ANTIBIOTIC PRESCRIBING FOR ADULTS IN SOUTH AFRICA, 2015

SEAN WASSERMAN
TOM BOYLES
MARC MENDELSON

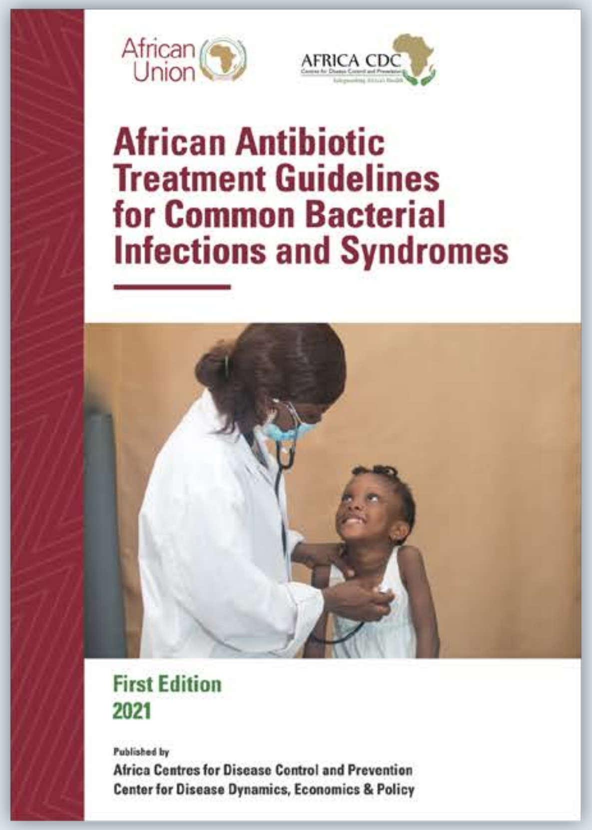
ON BEHALF OF THE SOUTH AFRICAN ANTIBIOTIC STEWARDSHIP PROGRAMME (SAASP)

SAASP
SOUTH AFRICAN ANTIBIOTIC STEWARDSHIP PROGRAMME

1 | Page

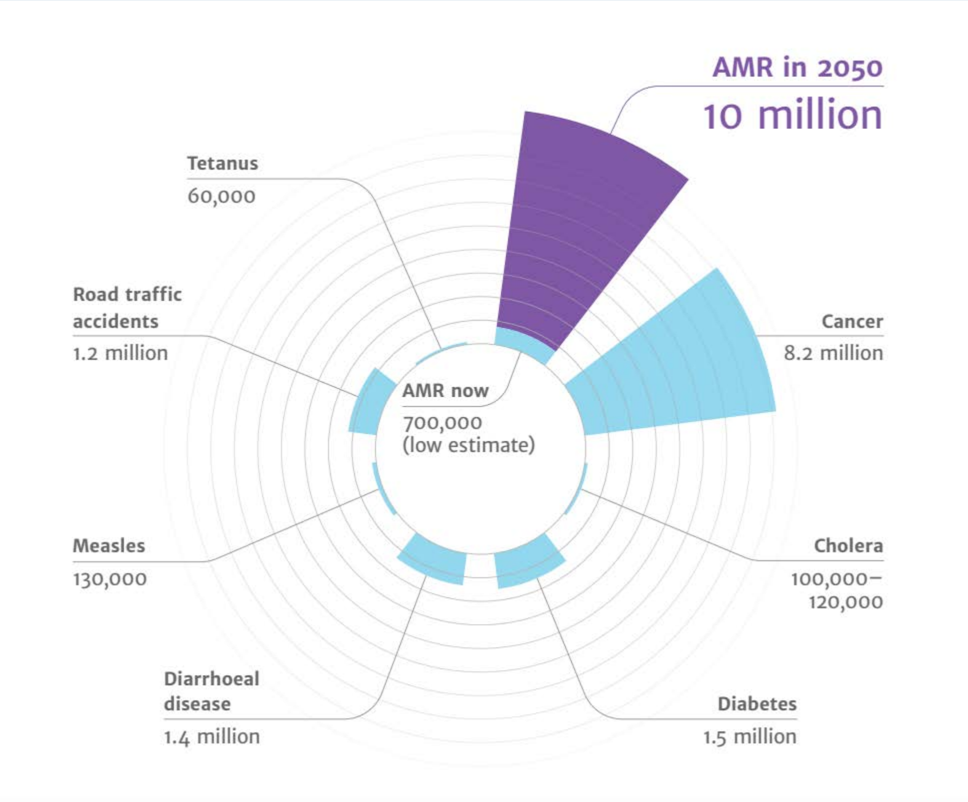
Essak et al. Journal of Public Health 2016; 39: 8–13

Antimicrobial stewardship in Africa



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

The future of antimicrobial resistance?
Mortality and cost estimates



66 trillion dollars

Source: O'Neil Report on Antimicrobial Resistance

The future of antimicrobial resistance?

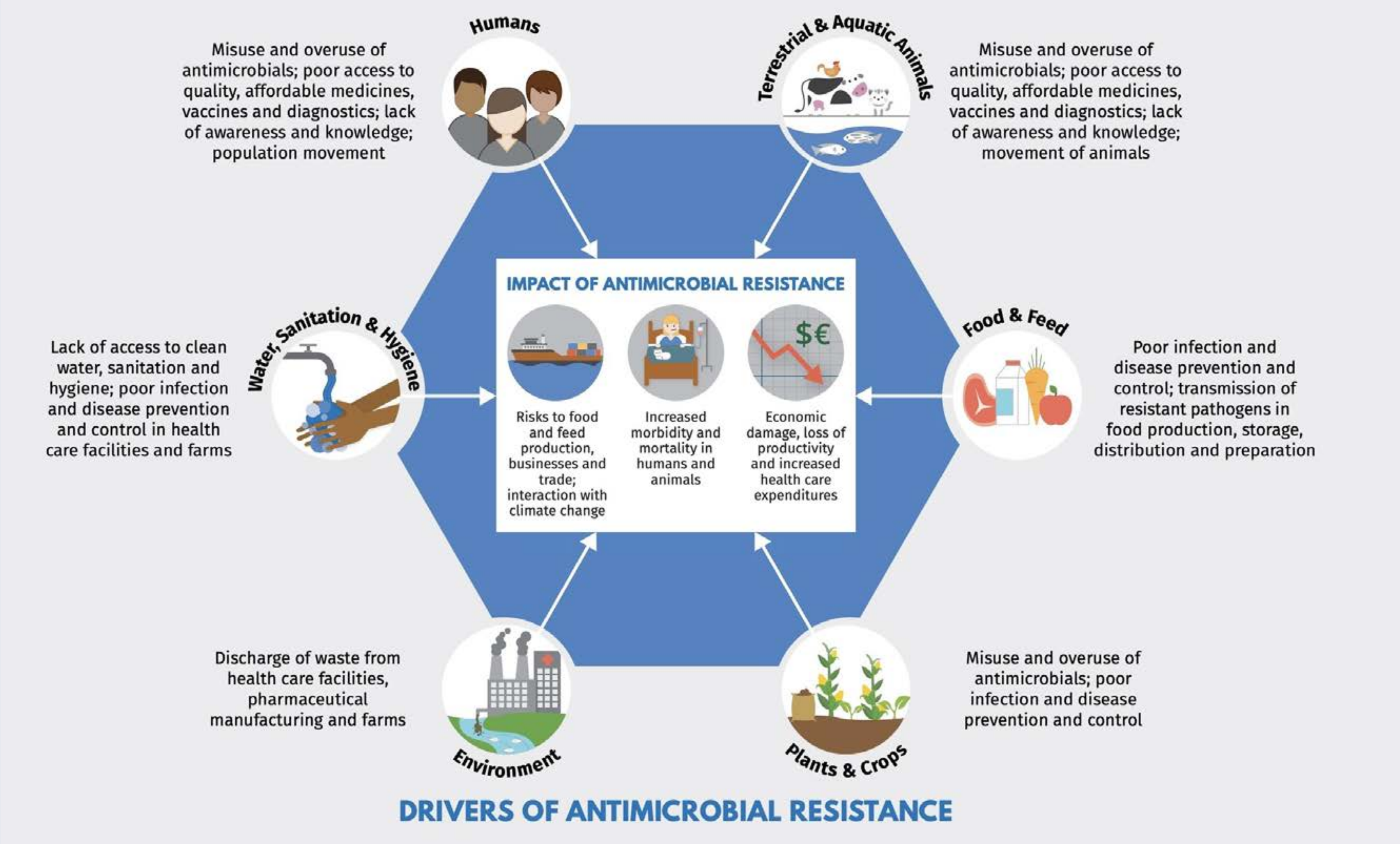
- The estimated total number of deaths due to AMR could climb to 10 million deaths globally per year by 2050
- Routine medical procedures or surgery will become more dangerous and associated with higher complication rates
- Immunosuppression, cancer chemotherapy and transplantations may carry unacceptable 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

Source: O'Neil Report on Antimicrobial Resistance

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


Humans
Misuse and overuse of antimicrobials; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; population movement
Terrestrial & Aquatic Animals
Misuse and overuse of antimicrobials; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; movement of animals
Water, Sanitation & Hygiene
Lack of access to clean water, sanitation and hygiene; poor infection and disease prevention and control in health care facilities and farms
IMPACT OF ANTIMICROBIAL RESISTANCE
$€
Risks to food and feed production, businesses and trade; interaction with climate change
Increased morbidity and mortality in humans and animals
Economic damage, loss of productivity and increased health care expenditures
Food & Feed
Poor infection and disease prevention and control; transmission of resistant pathogens in food production, storage, distribution and preparation
Discharge of waste from health care facilities, pharmaceutical manufacturing and farms
Environment
Plants & Crops
Misuse and overuse of antimicrobials; poor infection and disease prevention and control
DRIVERS OF ANTIMICROBIAL RESISTANCE

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

Boeckel, T. P. V. *et al. Proceedings of the National Academy of Sciences* 112, 5649–5654 (2015).

Factors influencing animal health used in food production

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

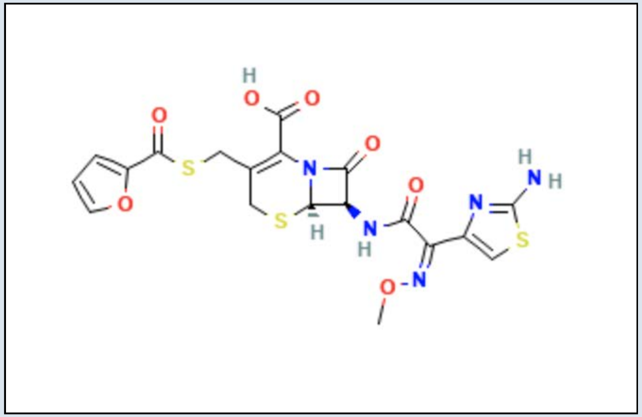
antibiotics are often used as low-cost substitutes for expensive hygiene measures

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

https://resistancebank.org/

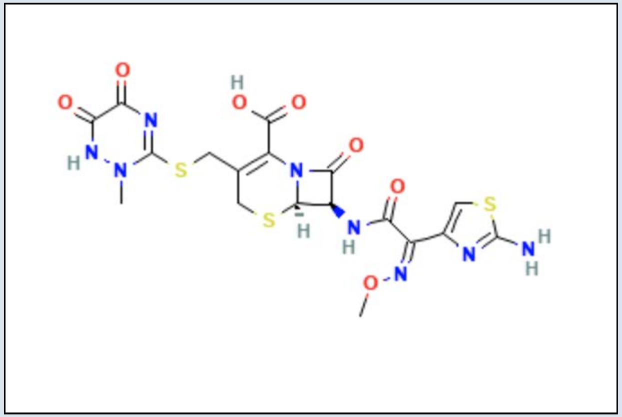
Used for

Metaphylaxis in animals



ceftiofurum

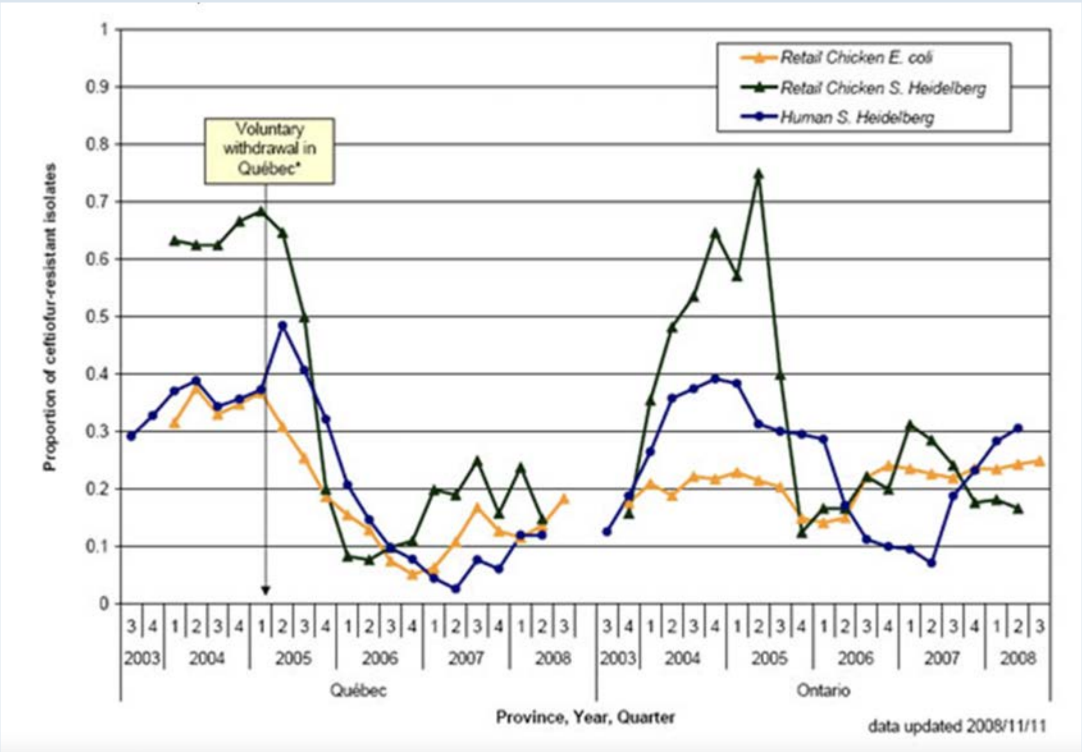
Essential antibiotic in humans



ceftriaxone

Example- Cephalosporins

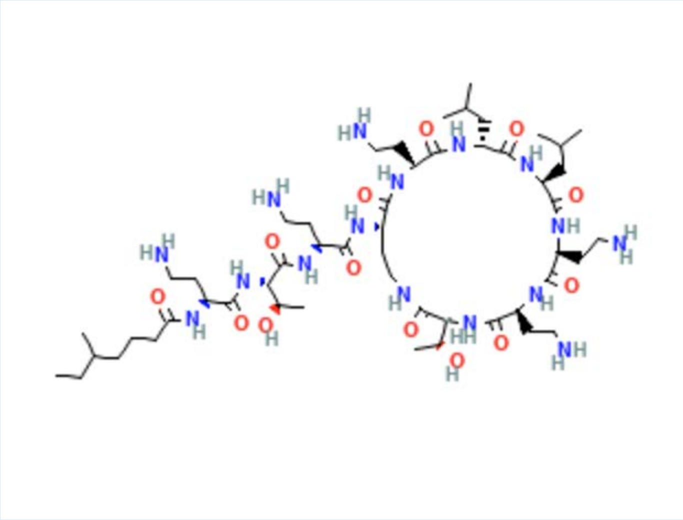
Outbreaks of multidrug resistant (MDR) *Salmonella* Heidelberg infections have been reported in humans working with cattle and chickens- assocaited with cetifior (3rd generation cephalosporin) injection in young hatchlings



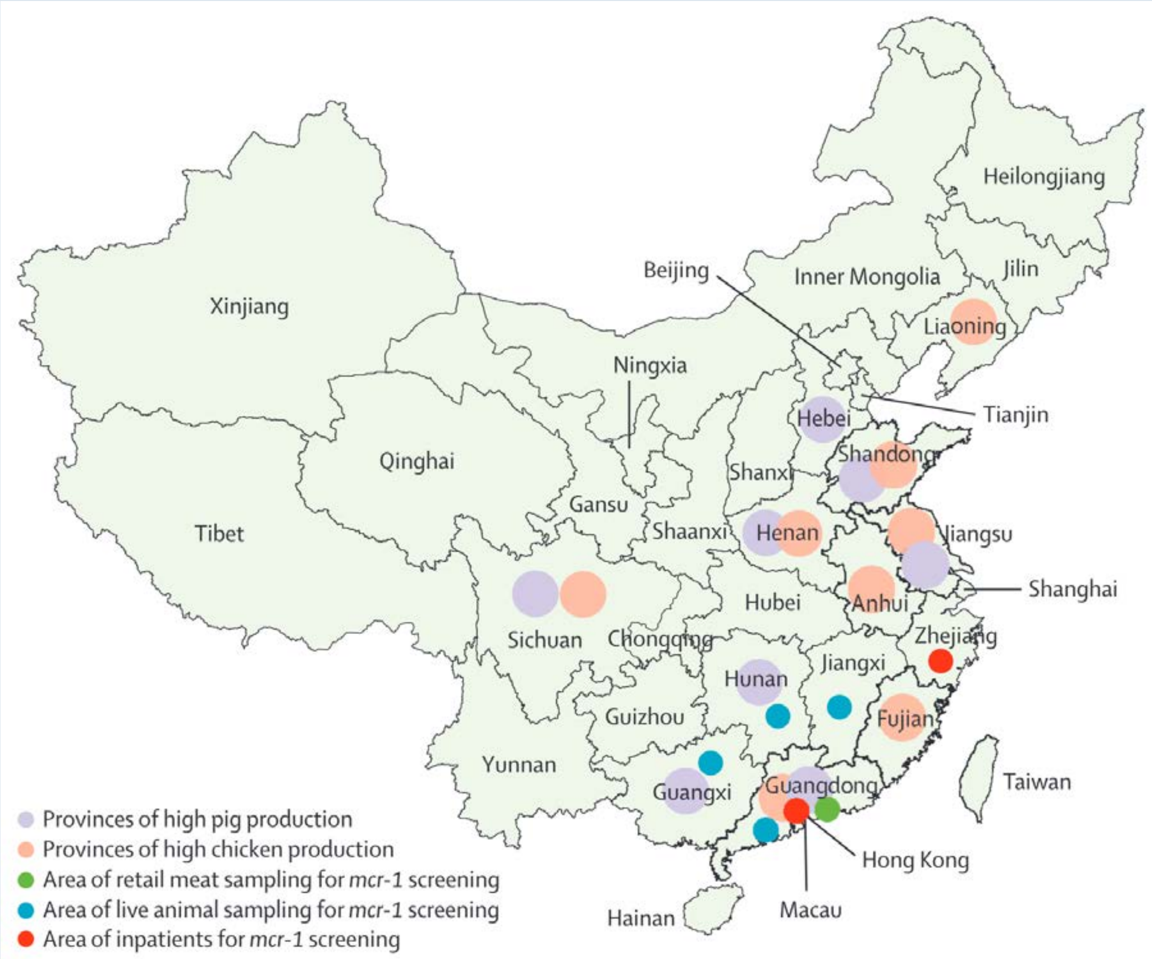
Publich Health Authority of Canada - UPDATE - Salmonella Heidelberg Ceftiofur-Related Resistance in Human and Retail Chicken Isolates - 2006 to 2008. (2009).

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

Example- Colistin

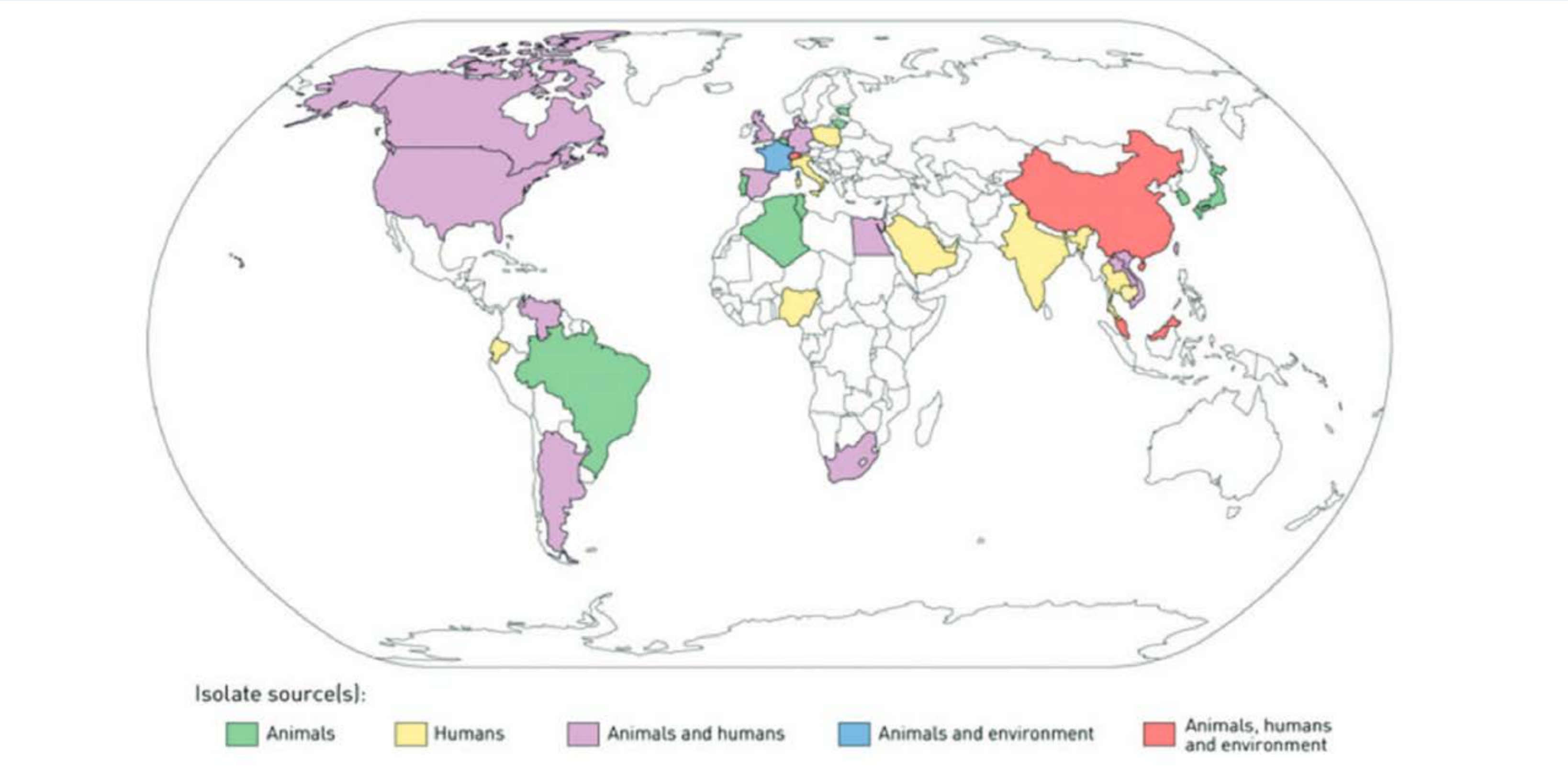


- Colistin-used in veterinary and human medicine for 50 years
- Intravenous colistin has surged in the last decade with the increase in carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae.*
- Even as human use has increased, colistin continues to be used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



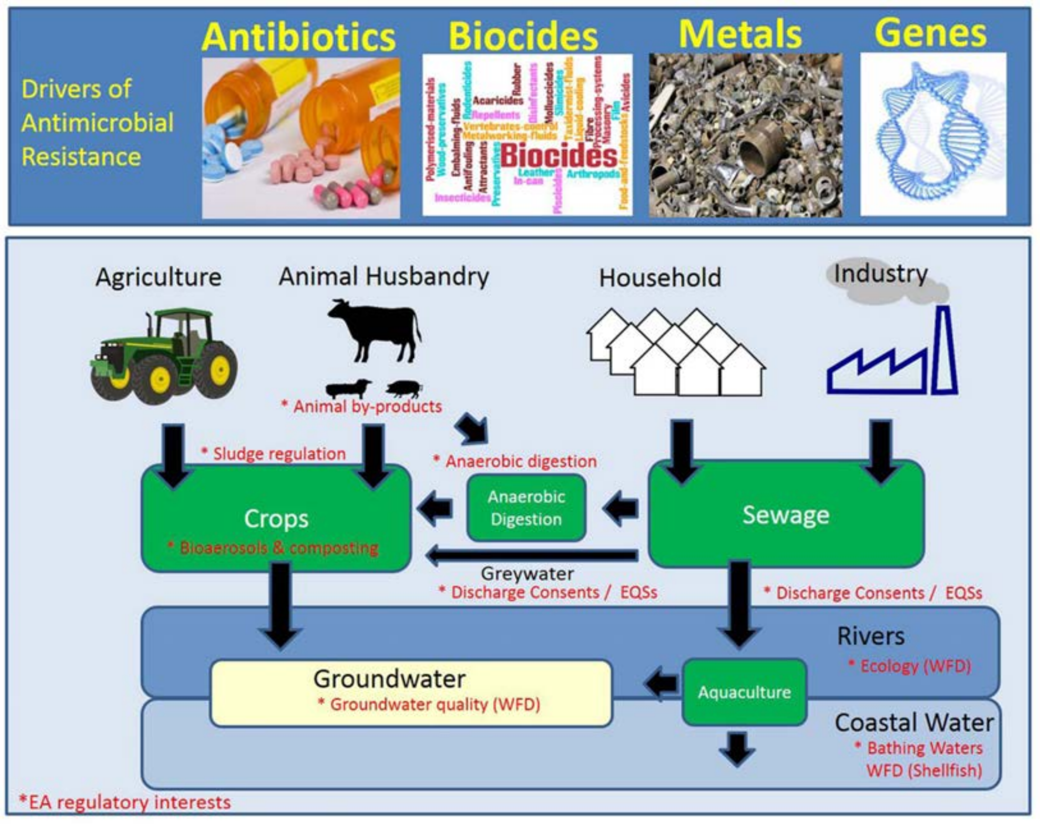
Liu, Y.-Y. *et al.* Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. *The Lancet Infectious Diseases* **16**, 161–168 (2016).

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)

Global success and shortcomings in the multilateral response to the COVID-19 pandemic

Domain	Success	Shortcoming
Research collaboration and information sharing	Sharing of information by researchers International research collaborations Public data repositories	Many regions and countries slow to learn policy lessons from elsewhere Lack of systemic global research governance Duplication of research studies
Vaccine discovery and development	Multinational initiatives to fund efforts such as the Coronavirus Global Response and the Coalition for Epidemic Preparedness Innovations Approval of vaccines and adjuvants Establishing the principle of equitable vaccine distribution through the COVAX Facility (despite failures in implementation)	Most funding from national efforts Most vaccine doses secured by rich countries through bilateral deals Trade barriers around vaccines and raw materials
Travel policies	Travel restrictions delayed spread from China in early 2020	Dissonant COVID-19 response policies between highly connected nations Restrictions on travel to countries of high infection incidence COVID-19 incidence contribute little to control in these countries

Singer, A. C. et al. *Frontiers in Microbiology* **7**, 1728 (2016).


WHO Pandemic Treaty 2024

Summary

- AMR is a persistent and growing global health threat that threatens to reverse a half-century or 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 boarders- *international cooperation is essential*