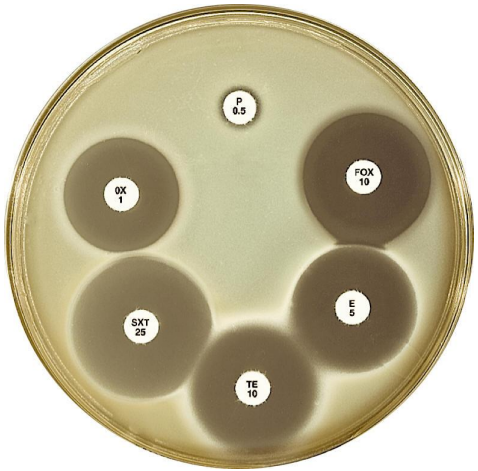
EPAH6052: Antimicrobial Resistance



DALHOUSIE UNIVERSITY

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Shared Hospital Laboratory
Public Health Alliance for Genomic Epidemiology

PUBLIC HEALTH ALLIANCE FOR GENOMIC EPIDEMIOLOGY

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Overview

1. Antimicrobials

- Properties of an (ideal) antimicrobial
- Types of antimicrobial
- Antibiotic mechanisms
- Antibiotic categories
- Antibiotic usage

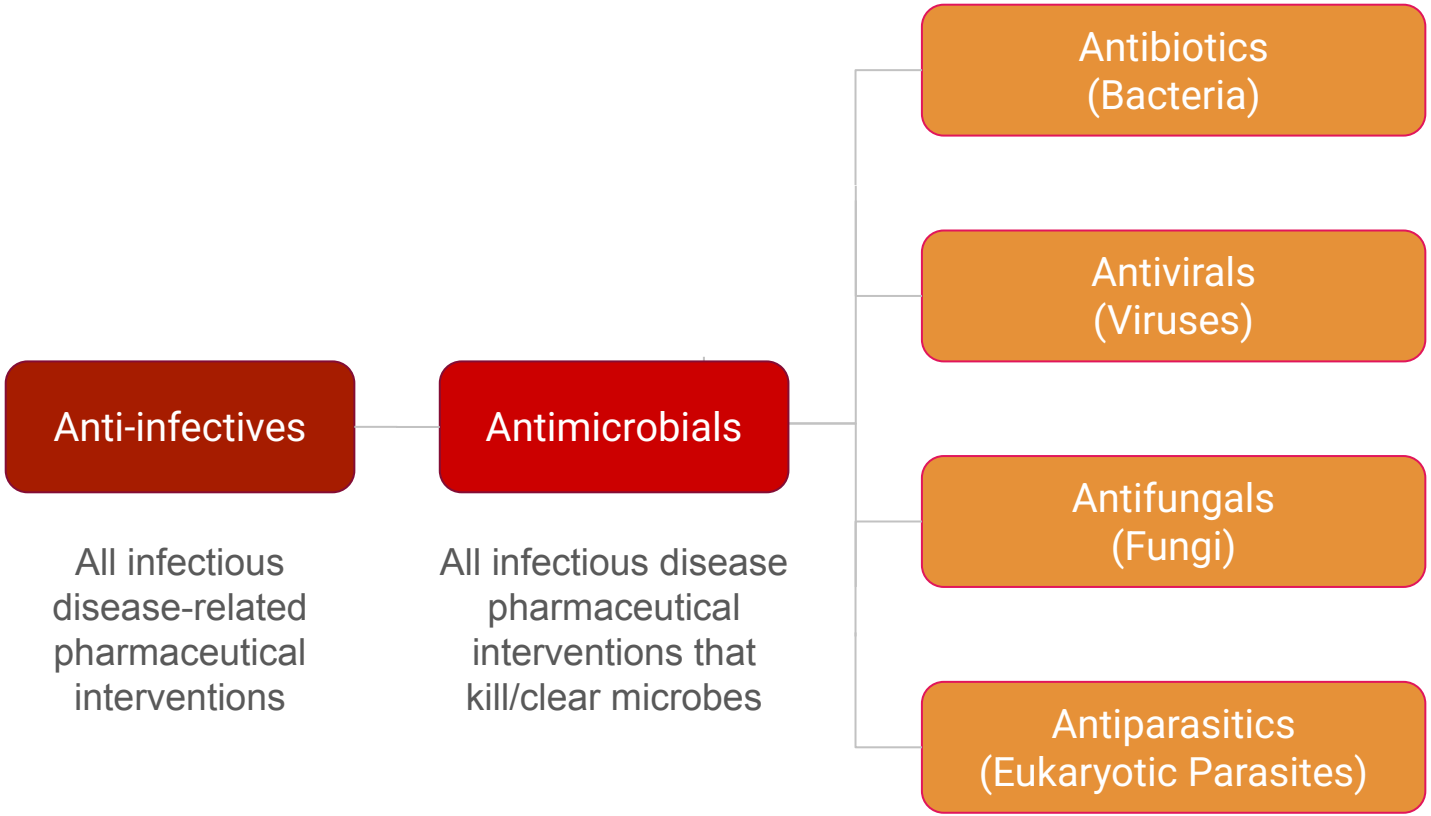
2. Antimicrobial Resistance

- Antibiotic Susceptibility Testing
- AMR mechanisms
- Origin and evolution of AMR
- Surveillance of AMR
- Burden of AMR

3. Solutions to Antimicrobial Resistance

- Improving Surveillance
- New Antimicrobials
- Alternatives to Antimicrobials
- Antimicrobial Stewardship
- Improved Rapid Diagnostics

Antimicrobials is an umbrella term



First, what does an ideal antimicrobial do?

Effective against pathogen -> pharmacodynamics

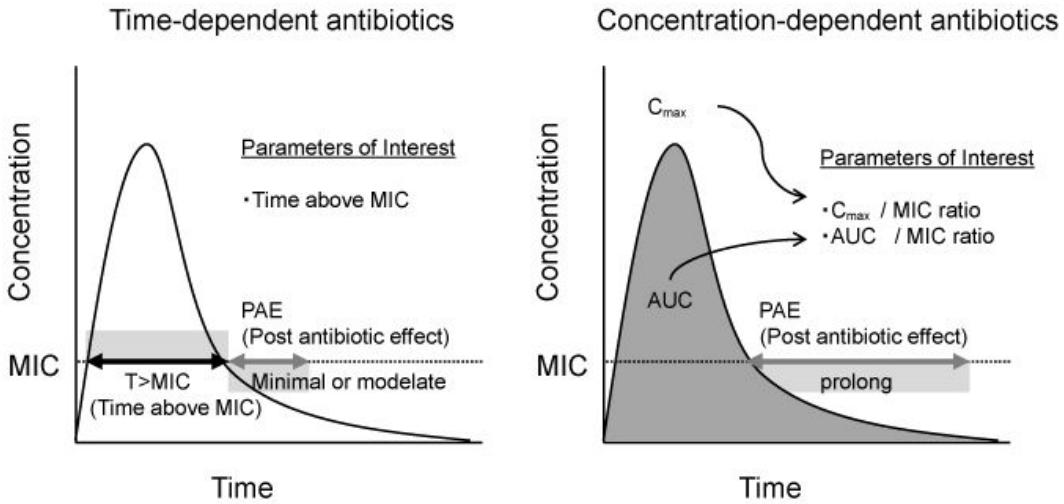
Pharmacodynamics - interaction of antimicrobial with microbe

Minimum Inhibitory Concentration (MIC) - concentration required to inhibit growth

Time-Dependent: Efficacy correlates with time above MIC (T>MIC) - more doses/extended release

Concentration-Dependent Killing: Efficacy correlates with peak concentration (Cmax/MIC) or AUC/MIC - 1 big dose/extended intervals

AUC/MIC-Dependent Killing: Total drug exposure over time relative to MIC - monitored individualised dosing



https://www.omicsonline.org/articles-images/JBB-S2-002-g002.html

Post-Antimicrobial Effect (PAE): Persistent suppression

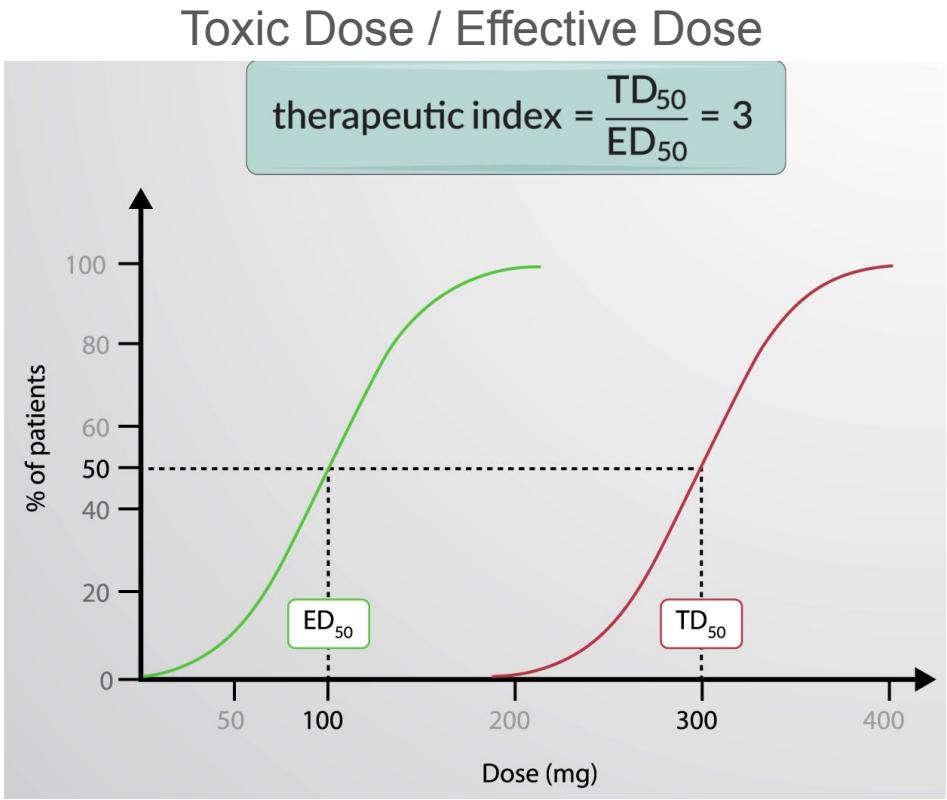
Eagle Effect: Lower efficacy at high doses

Inoculum Effect: Lower efficacy when lots of microbe

Low host toxicity -> high therapeutic index

- Host cells and microbial cells share similarities
- Antimicrobial can damage these shared aspects of host cell

- Toxic by-products from metabolic breakdown of antimicrobial
- Low Therapeutic Index (TI):
  - Therapeutic drug monitoring (TDM)
  - Adjustments for renal/hepatic impairment
  - Damage to sensitive systems (e.g., ototoxicity)



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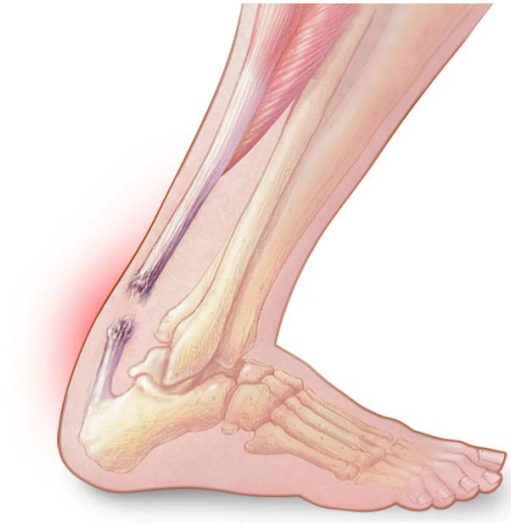
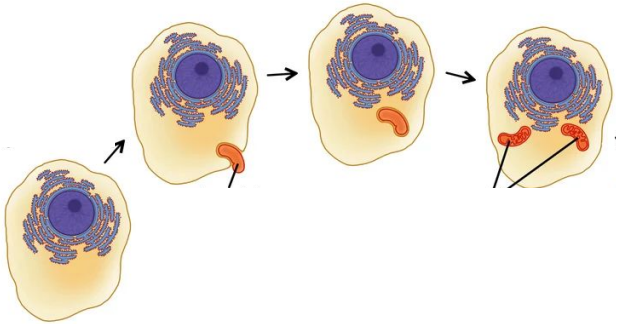
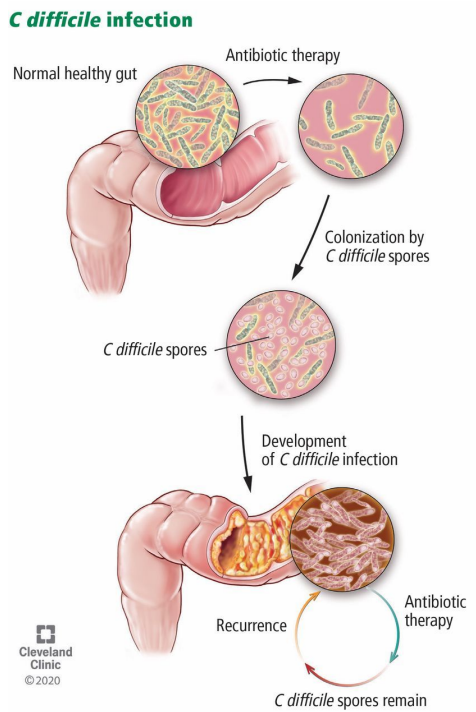
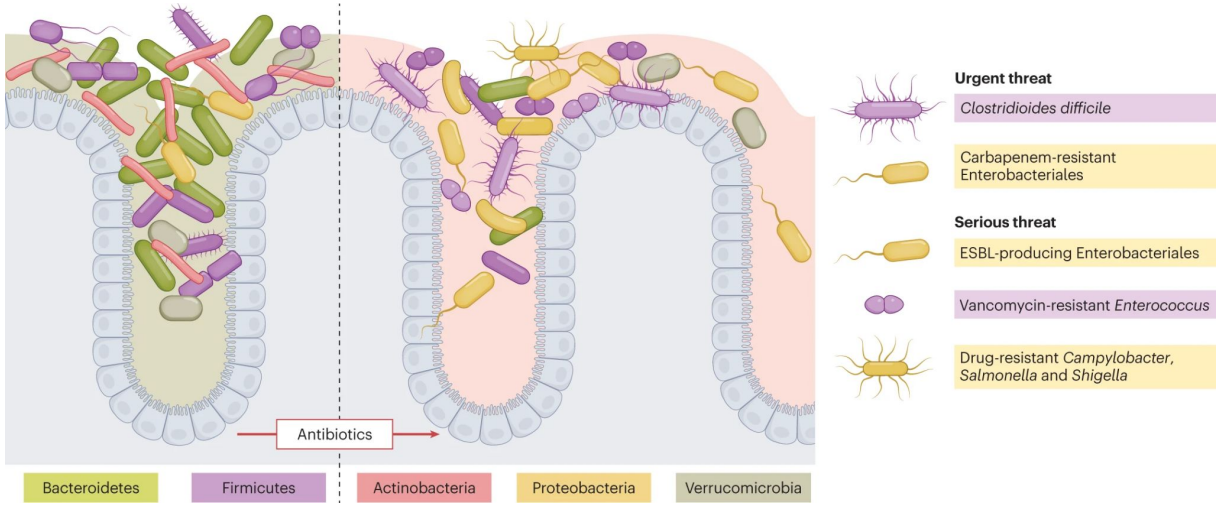




Selective action -> only kill the target pathogen



- Killing non-target microbes disrupts microbiome function
- Microbial diversity & competition is protective
- Microbiome has complex interactions with immune system
- Appropriate spectrum of activity (narrow vs broad)



Tsigrelis, Constantine. "Recurrent Clostridioides difficile infection: Recognition, management, prevention." Cleveland Clinic journal of medicine 87.6 (2020): 347-359.

Fishbein, Skye RS, Bejan Mahmud, and Gautam Dantas. "Antibiotic perturbations to the gut microbiome." *Nature Reviews Microbiology* 21.12 (2023): 772-788.

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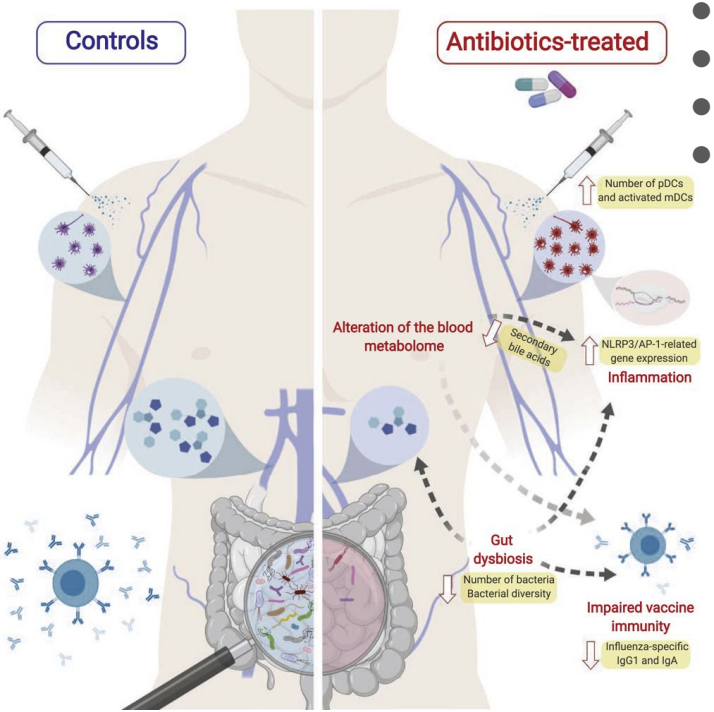

Hagan, Thomas, et al. "Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans." *Cell* 178.6 (2019): 1313-1328.

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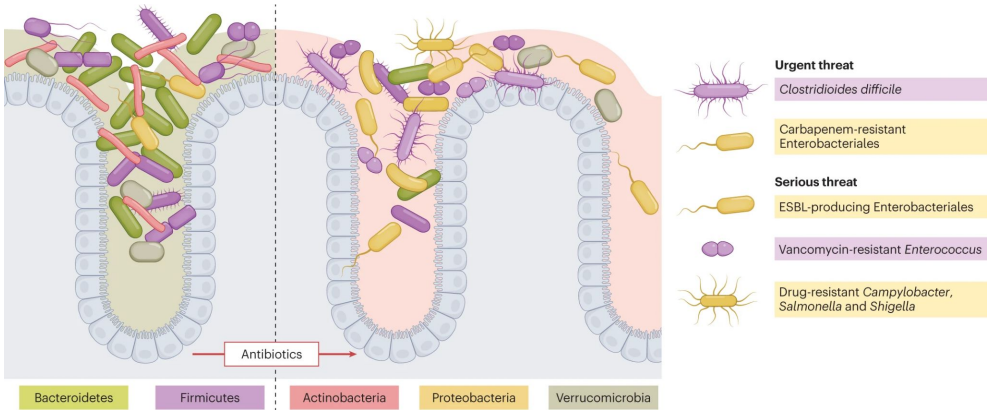

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Good pharmacokinetics -> drug gets where it needs to be

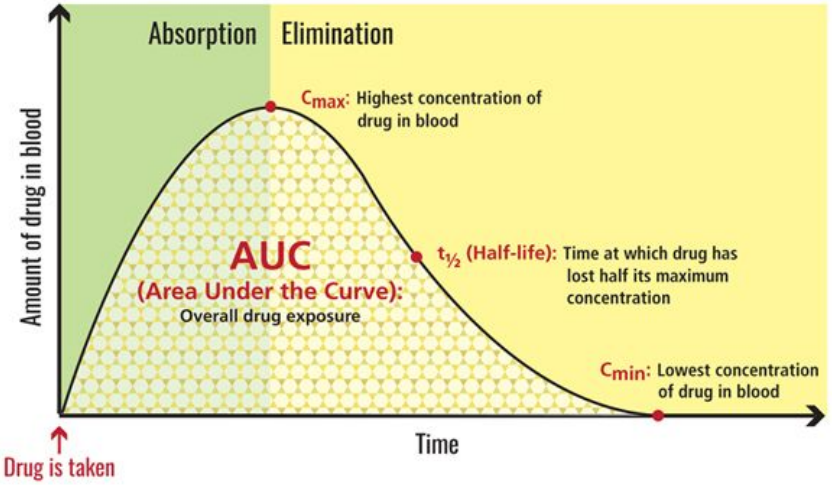
Absorption: high bioavailability and predictable kinetics robust to food/pH

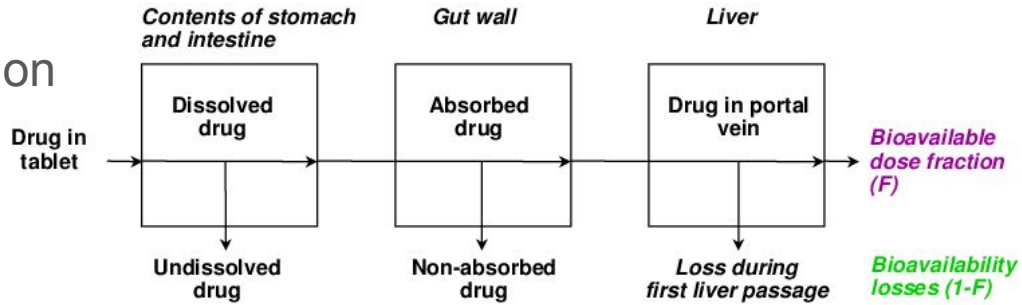
Distribution: high volume gets to infection sites (intracellular/CNS/bone/abscesses)

Metabolism: minimal complex breakdown to avoid drug-drug interactions or toxicity

Elimination: long half-life to reduce frequency of dosing and dual elimination (renal + hepatic)

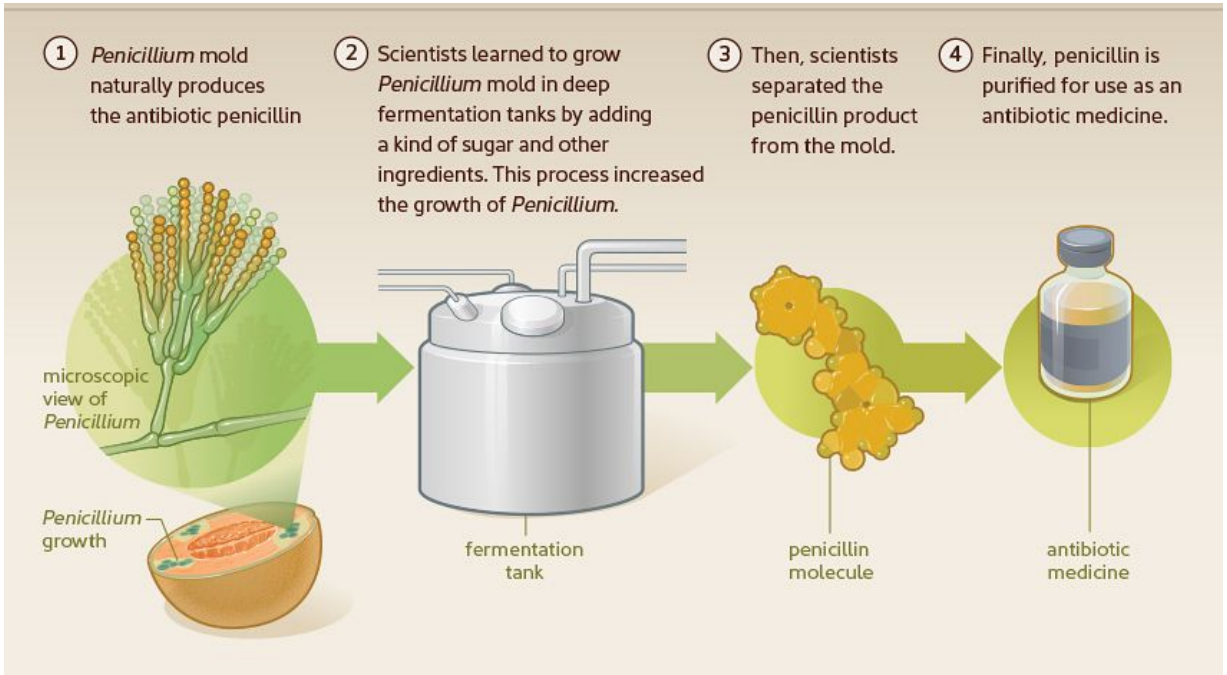
Same PK for all patients!





Cost-efficient to manufacture & ship at scale

15 years of work from discovery to large-scale production of penicillin (1929-1944)



In US Antimicrobials 42% more likely have shortages than average drug (and remain in shortage).

Fragile/unsustainable supply chains due to low margins

Small number of geographically concentrated manufacturers

Need coincides with civil/social disruption

https://www.nlm.nih.gov/exhibition/fromdnatobeer/exhibition-interactive/illustrations/penicillin-alternative.html

https://qualitymatters.usp.org/supply-chain-vulnerabilities-for-antimicrobial-medicines

Cost-effective to actually use

Cost effectiveness is a function of:

- **Direct costs** (acquisition, administration, monitoring)
- **Clinical Outcomes** (cure rates, mortality reduction, length of hospital stay)
- **Societal Impacts** (QALYs/DALYs, resistance, productivity)

Metrics:

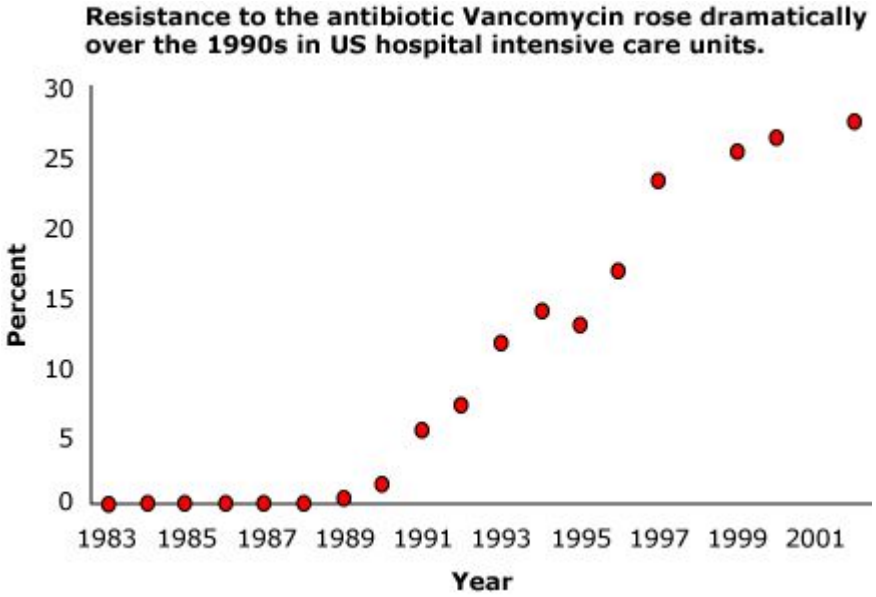
- **Cost per Life-Year Saved**
- **Cost per Cure/Clinical Success**
- **Cost-per Quality-Adjusted Life Year Gained**
- **Incremental Cost-Effectiveness Ratio (ICER):** difference in cost / difference in effect

Cost Effectiveness Thresholds:

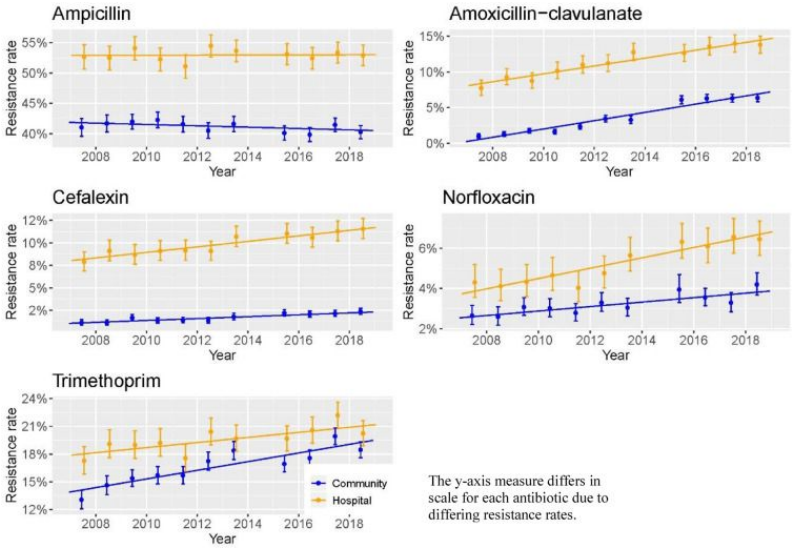
- **UK**: 20,000-30,000GBP / QALY (0.57-0.86 GDP per capita)
- **Canada**: $50,000 / QALY (0.93 GDP per capita)
- **WHO**: 1-3x GDP per capita per QALY (~i.e., $1,200USD to $1,500USD / QALY in Yemen or Burundi)

~191/635 (30.7%) of WHO Essential Medicine List are antimicrobials

Last: low propensity to lead to antimicrobial resistance!



Graph of Vancomycin resistance based on the National Nosocomial Infections Surveillance System Report, 2003

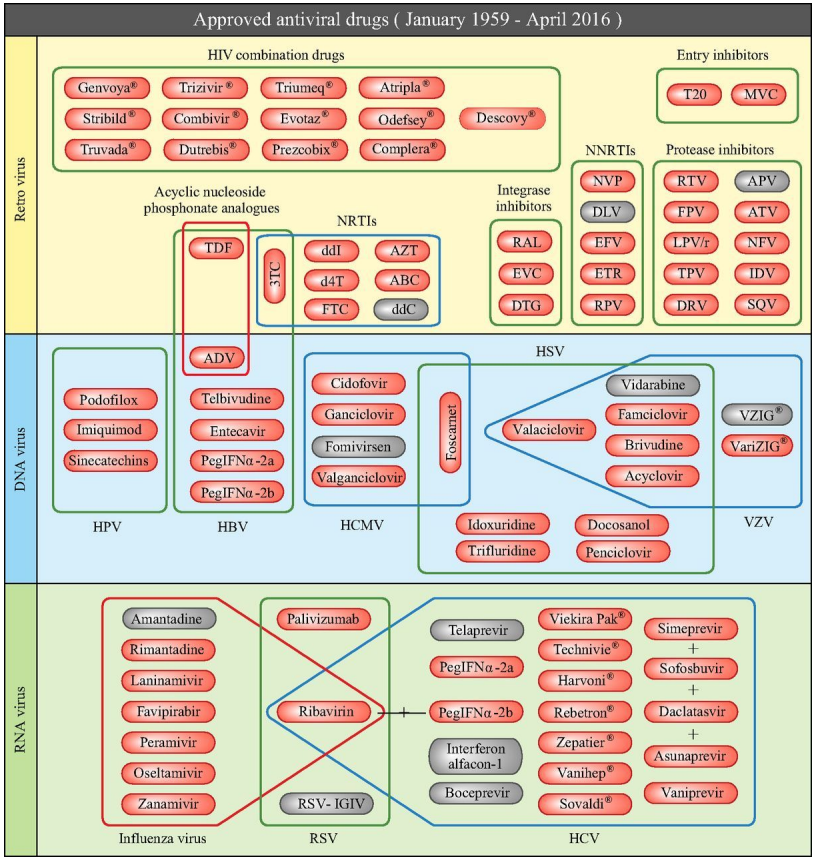


Keighley, Caitlin, et al. "Multi-year antimicrobial-resistance trends in urine Escherichia coli isolates from both community-based and hospital-based laboratories of an Australian local health district." Journal of Global Antimicrobial Resistance 31 (2022): 386-390.

Antibiotics will be most of today but let’s briefly discuss antivirals, antifungals, and antiparasitics

Antivirals - Viruses

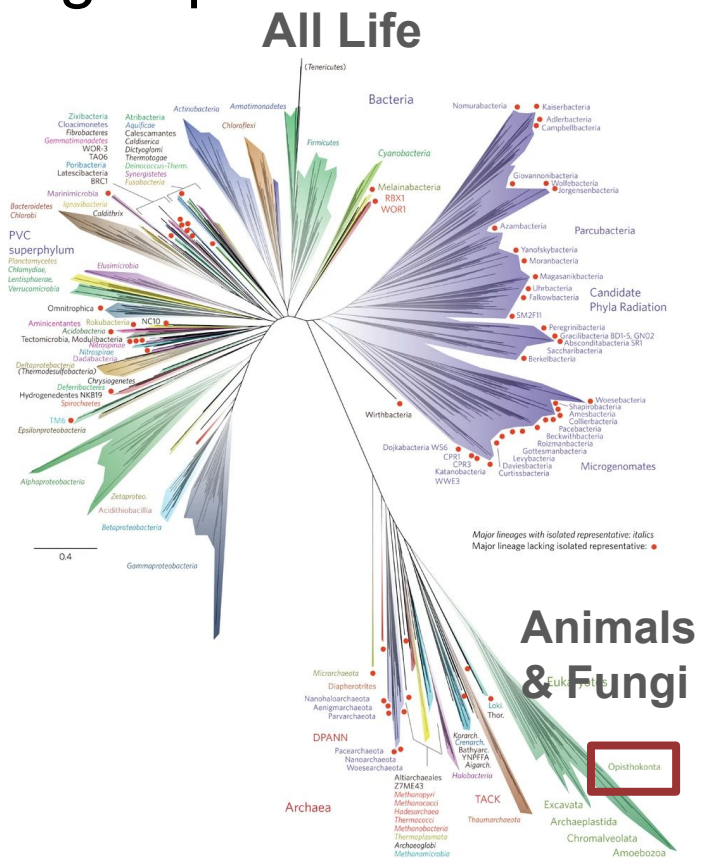
- Most antivirals target small number of viruses (HIV, HSV, Hep B/C, Influenza A/B)
- Retroviruses, DNA viruses, and RNA viruses largely distinct antivirals (broad and narrow spectrum antivirals e.g., remdesivir in RNA viruses vs rimantidine in influenza)
- Generally target/block specific viral proteins/functions (e.g., acyclovir) or push mutational rate beyond viability (e.g., paxlovid)
- Specificity challenging:
  - Viruses hijack host cell machinery
  - Toxicity is common
- Rapid emergence of resistance:
  - Viruses evolve quickly
  - Current avian influenza have resistance to ½ current flu antivirals
  - Combination therapies common e.g., HIV
- Recent focus on immunotherapies (i.e., antibodies targeting the virus that help your immune system fight them) - $$$



De Clercq, Erik, and Guangdi Li. "Approved antiviral drugs over the past 50 years." Clinical microbiology reviews 29.3 (2016): 695-747.

Antifungals - 4 main classes and growing importance

- Historically less prioritised - most invasive fungal disease associated with comorbidities/immunosuppression
- Emergence/growing burden of mycoses and antifungal resistance
  - Yeasts: *Candida, Cryptococcus*
  - Filamentous/moulds: *Aspergillus, Tinea.*
  - Both/dimorphic: *Coccidioides, Histoplasma, Blastomyces*
- Specificity challenging:
  - Mammal cells very similar to fungal
  - Toxicity/cross-reactivity common (and patients often frail)
- 4 main classes of antifungals:
  - Azoles (fluconazole)
  - Echinocandins (caspofungin)
  - Polyenes (amphotericin B)
  - Other (flucytosine)
- *Candida auris* - climate change-driven repeat resistant pathogen!



https://www.cdc.gov/candida-auris/tracking-c-auris/index.html

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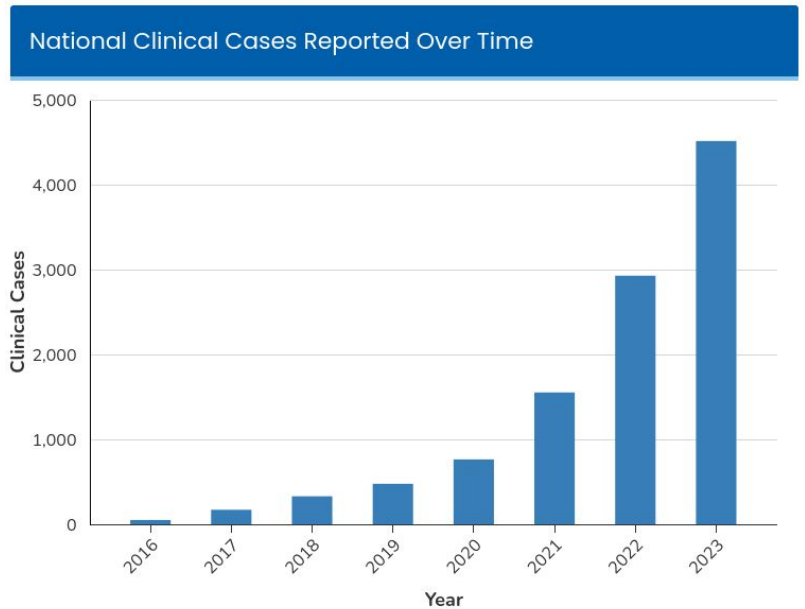
Mycology | Research Article | 30 June 2022

Candida auris Pan-Drug-Resistant to Four Classes of Antifungal Agents

Authors: Samantha E. Jacobs, Jonathan L. Jacobs, Emily K. Dennis, Sarah Taimur, Meenakshi Rana, Dhruv Patel, Melissa Gitman, SHOW ALL (19 AUTHORS), Vishnu Chaturvedi | AUTHORS INFO & AFFILIATIONS



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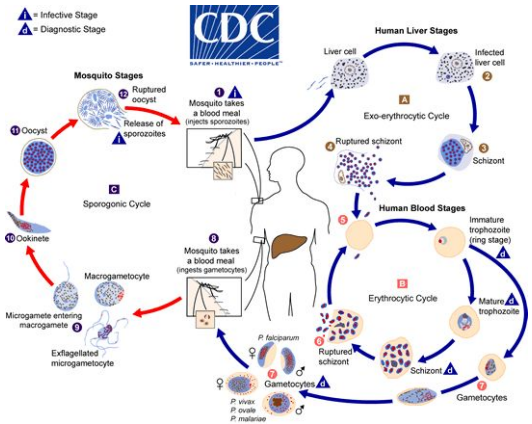
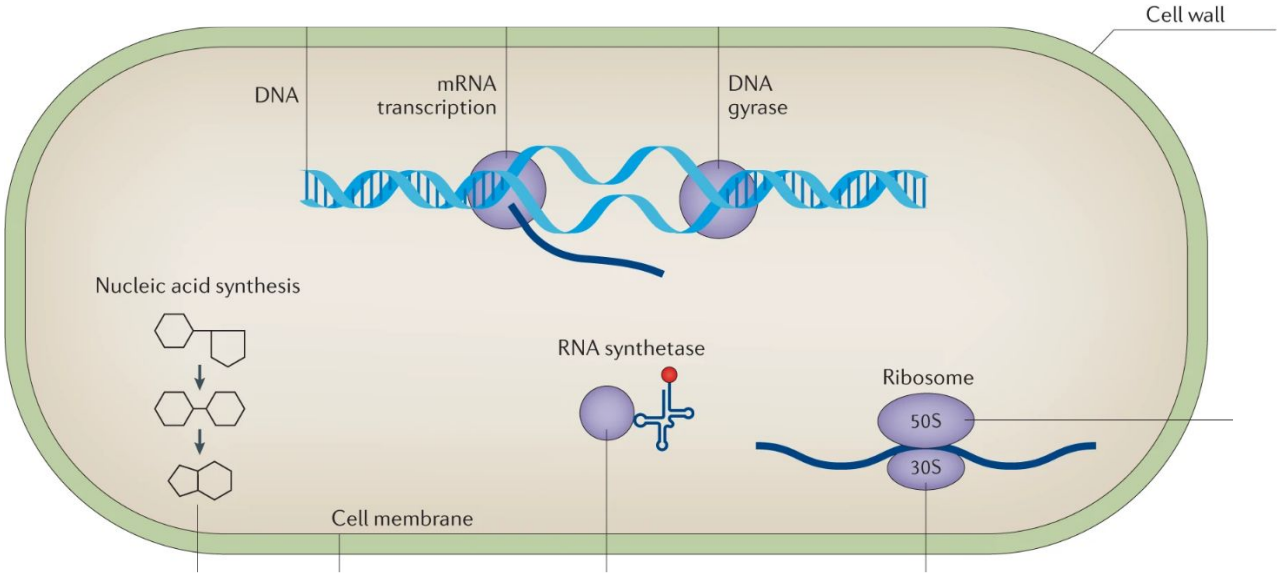
Antiparasitics - diverse and often quite toxic!

- Parasitic infections often chronic & highly morbid => high global burden
- Hard to develop: host toxicity problem and complex resistance
- **Antiprotozoals**:
  - Nitroimidazoles (Metronidazole/Tinidazole) - Anaerobic protozoa (*Trichomonas, Giardia, Entamoeba*)
  - Antimalarials (Artemisinin/Hydroxychloroquine/Atovaquone-proguanil) - Plasmodium species
  - Antifolates (Sulfadiazine + Pyrimethamine, Trimethoprim-sulfamethoxazole) - Toxoplasmosis
- **Anthelmintics**
  - Benzimidazoles (Albendazole/Albendazole) - nematodes, cestodes, some trematodes
  - Avermectins (Ivermectin) - Strongyloides, onchocerciasis, scabies
  - Praziquantel - nematodes/cestodes
- **Ectoparasiticides**
  - Pyrethroids (Permethrin) - scabies, lice
  - Organophosphates (Malathion) - resistant lice
- **Broad-spectrum**
  - Nitazoxanide - cryptosporidium and Giardia
  - Paromomycin - amebiasis and leishmaniasis.
  - Pentamidine - Pneumocystis and trypanosomiasis



Antimicrobial resistance is a problem for all types of antimicrobial but do a deeper dive on antibiotics!

Many antibiotics - few targets



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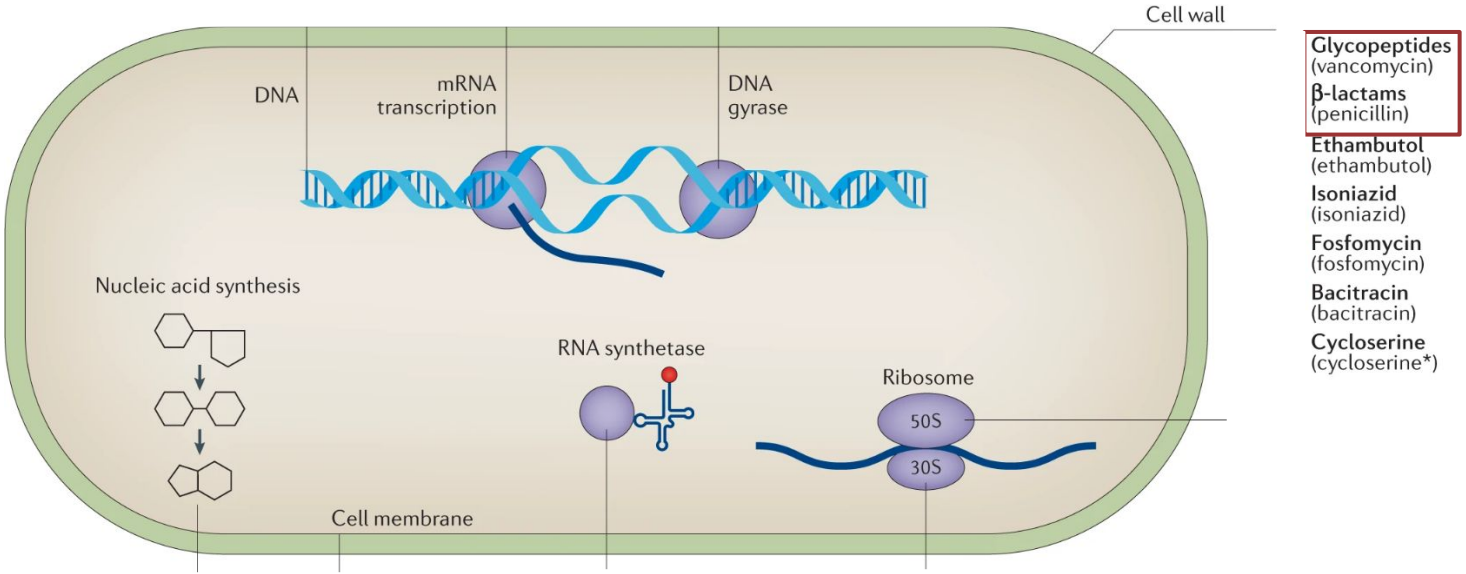

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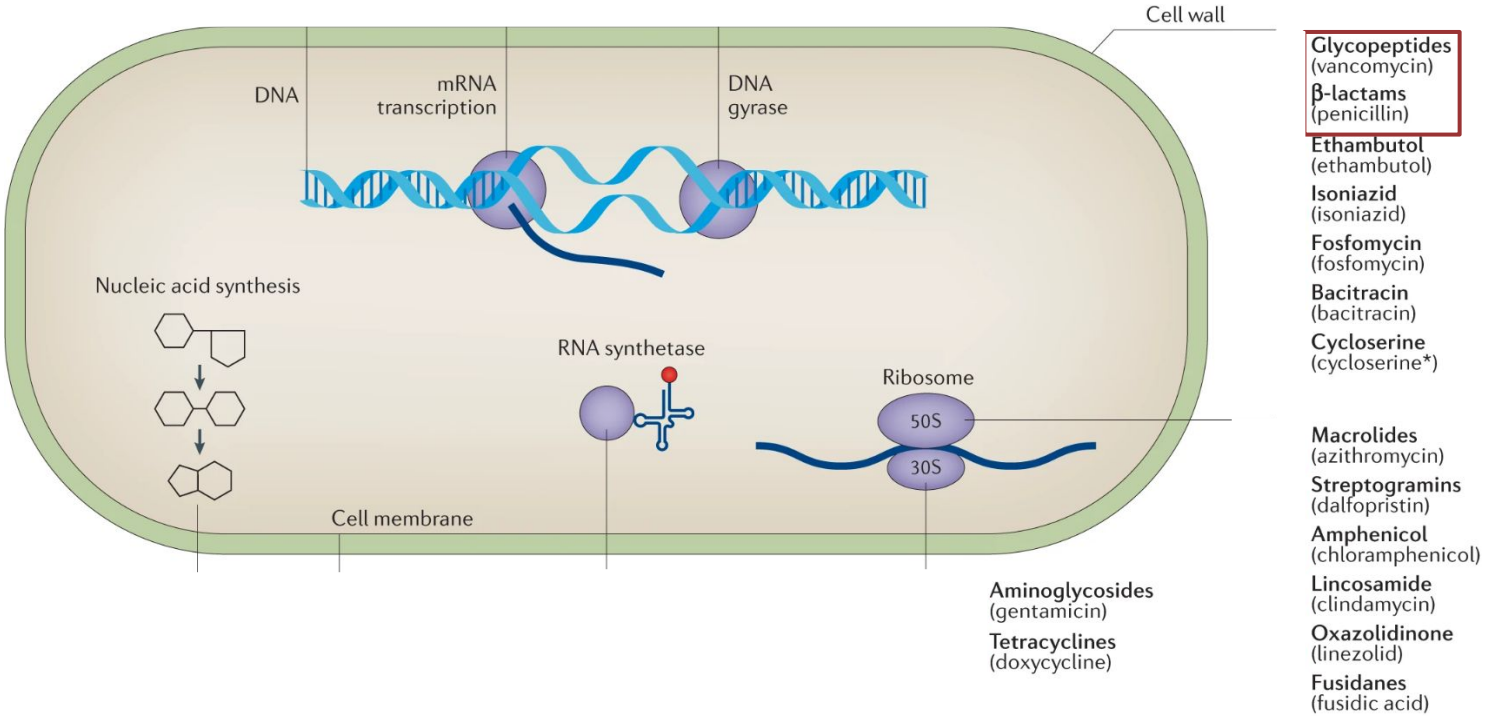

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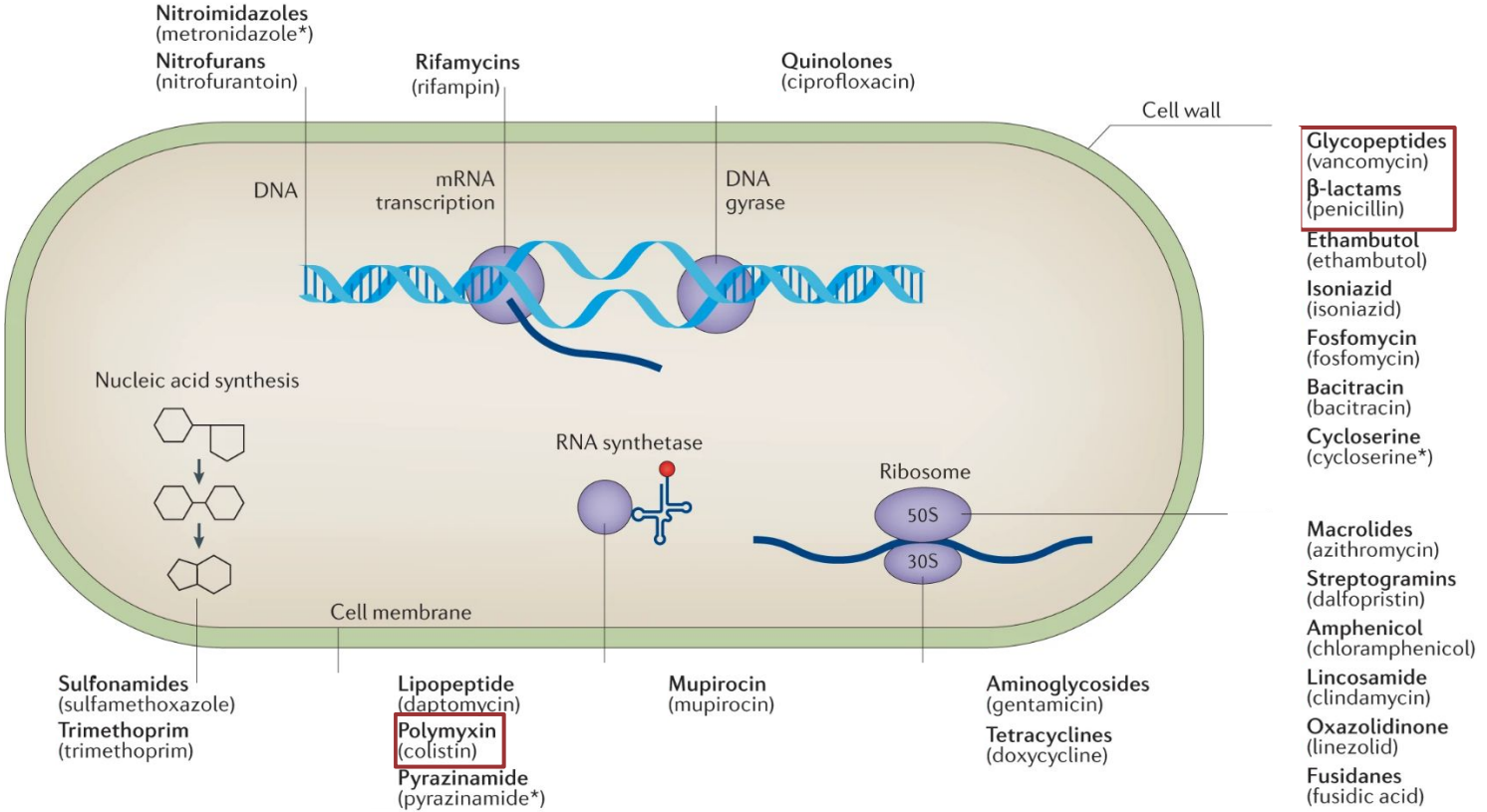

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Antibiotic Groupings - Family/Target

INHIBIT		CLASIFICATION		ANTIBIOTICS		
Cell Wall Synthesis	*Beta Lactams*	*Penicillins*		***Penicinillase – Sensible***		
			Natural Penicillins (narrow spectrum)	Penicillin G: Na, K, Procainic, Benzathine (IV, IM) Penicillin V: VO		
			Aminopenicillins (broad spectrum)	Ampicillin Amoxicillin		
			Penicinillase – Resistant *(very narrow spectrum)*			
			Nafcillin	Oxacillin	Dicloxacillin	
			Antipseudomonal *(extended spectrum)*			
			Carboxipenicillins	Ticarcillin Carbenicillin		
			Ureidopenicillins	Piperacillin Azlocillin Mezlocillin		
		Cephalosporins	1° Generation	Cefazolin	Cephalexine	Cephapirin
				Cefadroxil	Cephadrine	Cephalotin
			2° Generation	Cefuroxime	Cefamandole	Cefprozil
				Cefoxitin	Cefonicid	Cefmetazole
				Cefotetan	Cefaclor	
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime
				Cefpodoxime	Ceftizoxime	Cefotaxime
				Cefdinir	Ceftibuten	Cefixime
				Cefditoren		
			4° Generation	Cefepime	Cefpirome *	
			5° Generation	Ceftaroline		
		Carbapenems	Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams	Aztreonam			
		**** *Beta-lactamase inhib.*	Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	*Glycopeptides*	Vancomycin	Bacitracin		
			Teicoplanin	Polymyxin B		

Protein Synthesis	*30S*	*Amino-glycosides*	Gentamycin	Neomycin	Streptomycin	
			Amikacin	Tobramycin		
		Tetracyclins	Doxycycline	Demeclocylin *	Minocycline	
			Tetracyclin	Tigecyclin		
	50S	*Oxazolidonones*	Linezolid			
		Streptogramins	Quinupristin/Dalfopristin			
		Cloramphenicol				
		Macrolides	Erythromycin	Azithromycin	Clarithromycin	
		Lincosamides	Clindamycin	Lincomycin		
DNA topoisomerases	*Fluorquinolones*		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
			Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
	Quinolones		Nalidixic Acid			
Folic Acid Synthesis	*Sulfonamides*		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
	DHFR inhibitors		Trimethroprim (TMP)	Pirymethamine		
DNA (damage)	*Metronidazole*					
mRNA synth.	*Rifampim*					

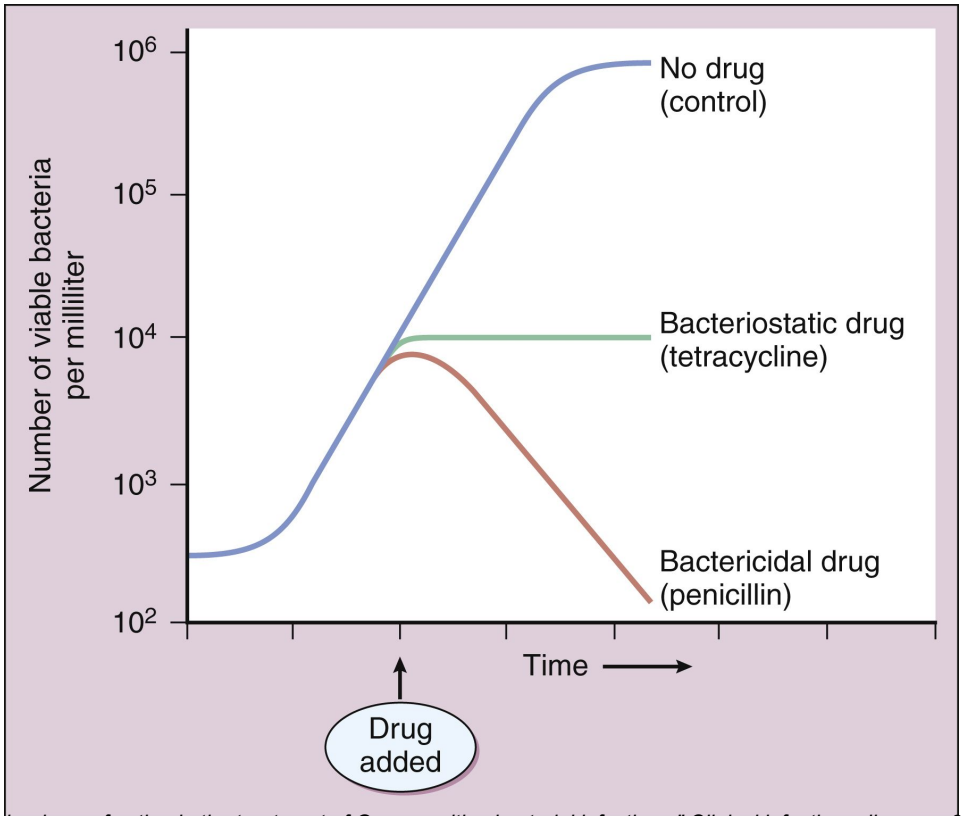
Antibiotic Groupings - Bacteriostatic/Bacteriocidal

- Bacteriostatic - prevents growth *in-vitro*
- Bacteriocidal - kills bacteria *in-vitro*
- Most ABX fall on spectrum
- Activity is organism/site-specific

Generally:

- Bacteriocidal for sterile sites (endocarditis/meningitis/osteomyelitis) or immunocompromised BUT adverse consequence of lytic/endotoxin surge
- Bacteriostatic can better control toxin production and may cause less damage to microbiome

BUT clinical relevance is **contextual**

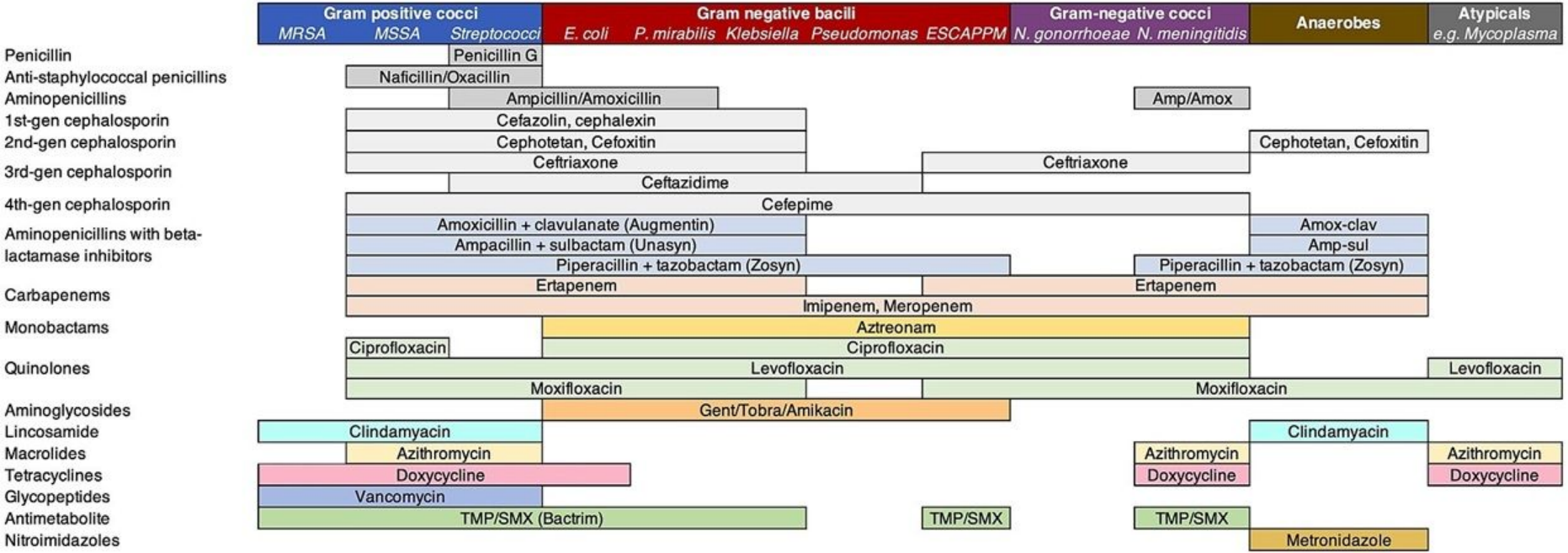


Pankey, George A., and L. D. Sabath. "Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections." Clinical infectious diseases 38.6 (2004): 864-870.

Antibiotic Groupings - Pharmacodynamics

Model	Optimized by...	Representation	Example
Time-Dependent Killing	...increasing the concentration time spent above the MIC	T>MIC	Beta-lactams
Concentration-Dependent Killing	...increasing the peak plasma concentration	C-max/MIC	Aminoglycosides
AUC-Dependent Killing	...increasing cumulative concentration exposure	AUC/MIC	Fluoroquinolones

Antibiotic Groupings - Organisms



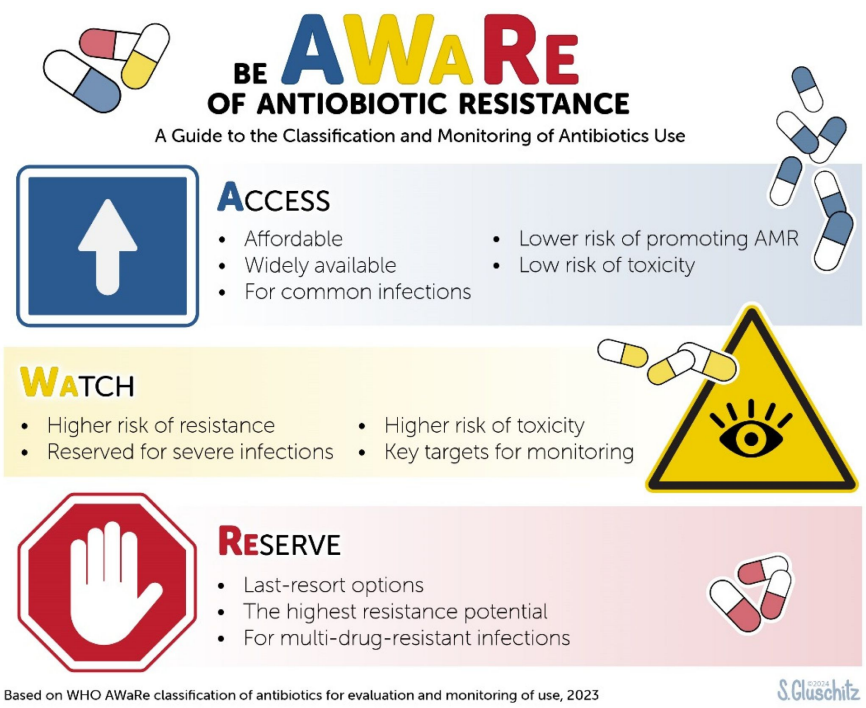
See github.com/aetherist/antibiogram for details. For educational purposes only. Consult your local antibiogram for clinical use.

TMP/SMX = Trimethoprim-sulfamethoxazole, MRSA = Methicillin-resistant Staphylococcus aureus, MSSA = Methicillin-sensitive Staphylococcus aureus, ESCAPPM = Enterobacter spp., Serratia spp., Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp. and Morganella morganii.

Antibiotic Groupings - Activity Spectrum

Narrow Spectrum	Broad Spectrum	Extended Spectrum
• 2nd generation cephalosporins • Amoxicillin • Ampicillin • Metronidazole	• 3rd generation cephalosporins (except ceftazidime) • Amoxicillin/clavulanate • Ampicillin/sulbactam	• Ceftazidime • 4th generation cephalosporins • Anti-pseudomonal penicillins • Aztreonam • Ertapenem • Ceftaroline • Fluoroquinolones • Aminoglycosides • Colistimethate

Antibiotic Groupings - Usage Categories



Antimicrobial Advice Ad Hoc Expert Group (AMEG) Categories

Category A
Avoid

- antibiotics in this category are not authorised as veterinary medicines in the EU
- should not be used in food-producing animals
- may be given to companion animals under exceptional circumstances

Category B
Restrict

- antibiotics in this category are critically important in human medicine and use in animals should be restricted to mitigate the risk to public health
- should be considered only when there are no antibiotics in Categories C or D that could be clinically effective
- use should be based on antimicrobial susceptibility testing, wherever possible

Category C
Caution

- for antibiotics in this category there are alternatives in human medicine
- for some veterinary indications, there are no alternatives belonging to Category D
- should be considered only when there are no antibiotics in Category D that could be clinically effective

Category D
Prudence

- should be used as first line treatments, whenever possible
- as always, should be used prudently, only when medically needed

Which antibiotics are actually used?

Challenging comparing antibiotics with different dosing

Ticarcillin (carboxypenicillin)

3 grams intravenously every 4 hours (~18g per day)

Lascufloxacin (fluoroquinolone)

75mg orally once per day

(Unusual antibiotics to show extremes)

J01CA04 AMOXICILLIN

amoxicillin 25mg/mL susp
Apo-Amoxi 125mg Susp
JAMP-Amoxicillin 125mg/5mL Susp
Amoxil 25mg/mL Susp (discontinued)

amoxicillin 50mg/mL susp
Amoxicillin 250mg Susp
Amoxicillin Sugar Reduced 50mg/mL O/L
Amoxicillin-250mg/5mL Susp
Apo-Amoxi 250mg Susp
JAMP-Amoxicillin 250mg/5mL Susp
Novamoxin 250mg Susp
Novamoxin Sugar Reduced 50mg/mL O/L
Sandoz Amoxicillin 250mg/5mL Susp
Amoxil 50mg/mL Susp (discontinued)

amoxicillin 250mg cap
Amoxicillin 250mg Cap
Apo-Amoxi 250mg Cap
Auro-Amoxicillin 250mg Cap
Jamp-Amoxicillin 250mg Cap
Novamoxin 250mg Cap
Amoxil 250mg Cap (discontinued)

amoxicillin 250mg chewable tab
Novamoxin 250mg Chewtab
Amoxil 250mg Chewtab (discontinued)

amoxicillin 500mg cap
Amoxicillin 500mg Cap
Amoxicillin 500mg Cap
Apo-Amoxi 500mg Cap
Auro-Amoxicillin 500mg Cap
Jamp-Amoxicillin 500mg Cap
Novamoxin 500mg Cap
Amoxil 500mg Cap (discontinued)

Normalised Units: Defined Daily Dose per 1,000

Defined daily dose (DDD): standardised statistical measure of drug consumption

Assumed average maintenance dose per day for a drug used for its main indication in 70kg adults*

Defined for all/most formulations of each drug in the Anatomical Therapeutic Chemical (ATC) Classification System by the WHO Collaborating Centre for Drug Statistics (Norwegian Institute of Public Health)

Patient Prescribed: Amoxicillin 500mg 4 times per day for 5 days

Dose per Day = 4 x 500mg = 2g

Amoxicillin DDD from WHO: 1.5g

Patient Receives Per Day: 2g / 1.5g = 1.3331DDD

Patient Total DDD = 5 * 1.333DDD = 6.666DDD

Prescribed daily dose (PDD): average dose prescribed according to a representative sample of prescriptions

Antimicrobial Usage/Consumption (AMU/AMC)

AMU: actual amount taken by patients

AMC: amount purchased/sold

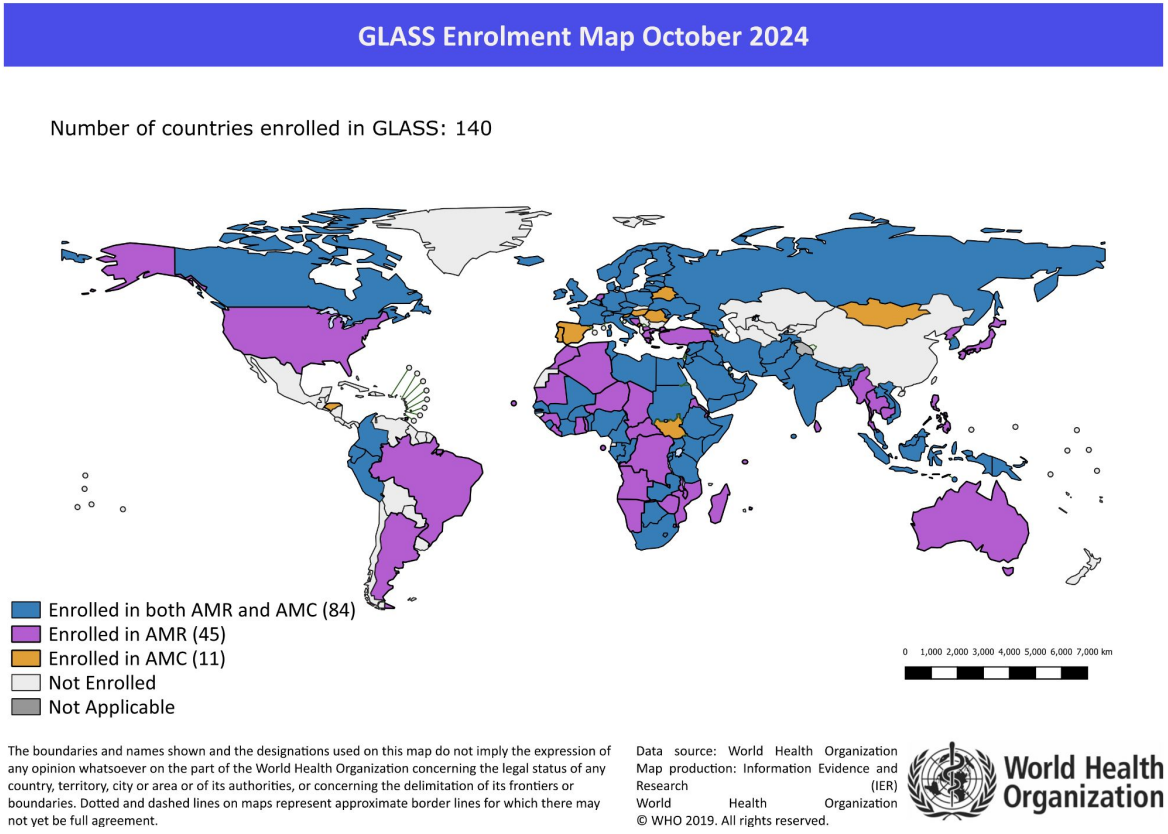
Buying lots of antimicrobials but using carefully: high AMC but low AMU

Global:

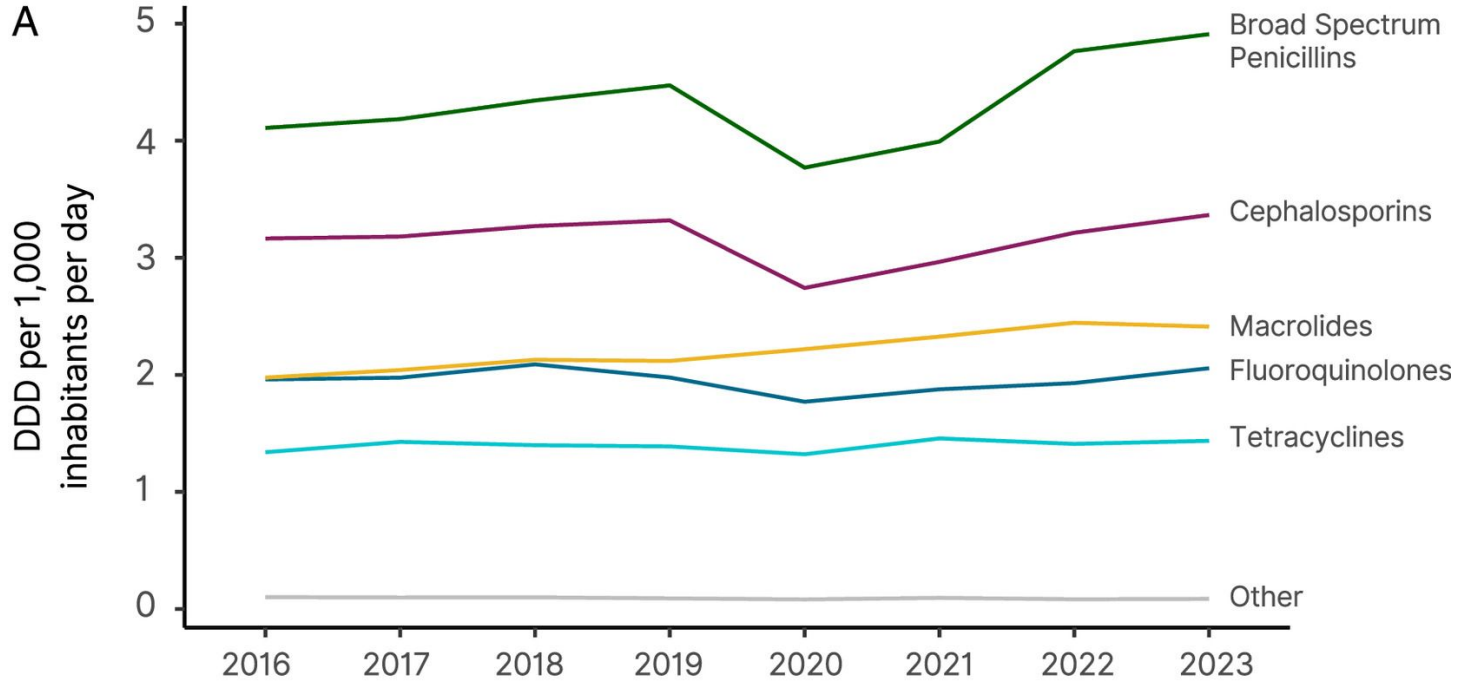
- IQVIA - USD$49 billion Market Capitalisation Contract Research Organisation - AMC
- WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) - AMU

Domestic:

- Canadian Antimicrobial Resistance Surveillance System (CARSS) - AMC & AMU

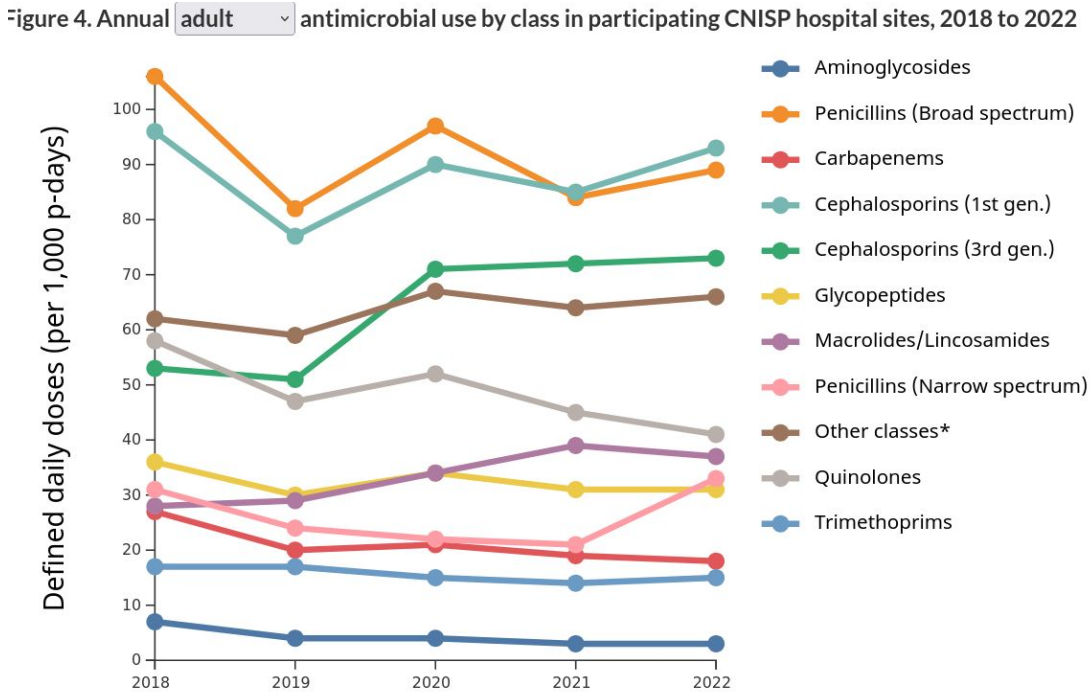


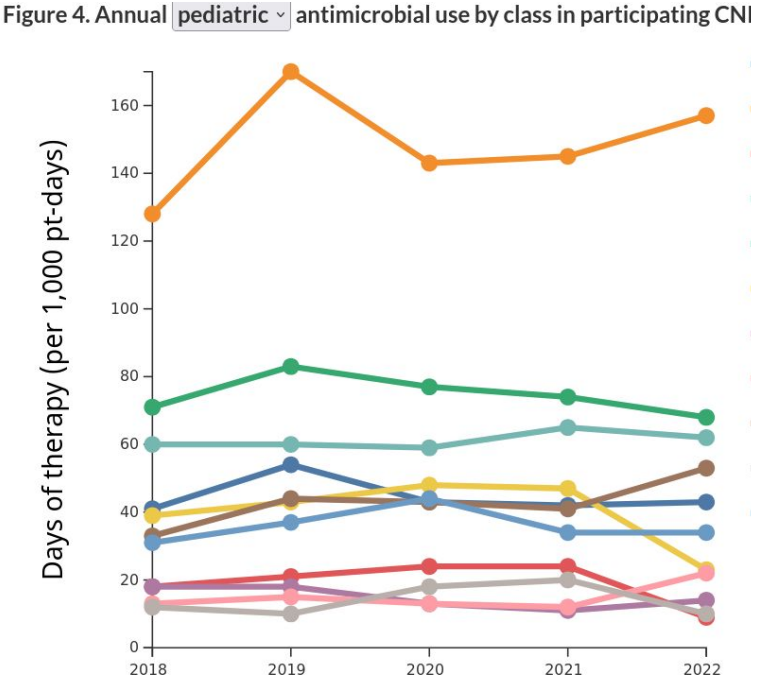
Globally: beta-lactams are majority of AMU



Klein, Eili Y., et al. "Global trends in antibiotic consumption during 2016–2023 and future projections through 2030." Proceedings of the National Academy of Sciences 121.49 (2024): e2411919121.

Hospitals vs Paediatric vs Community





What about animal usage?

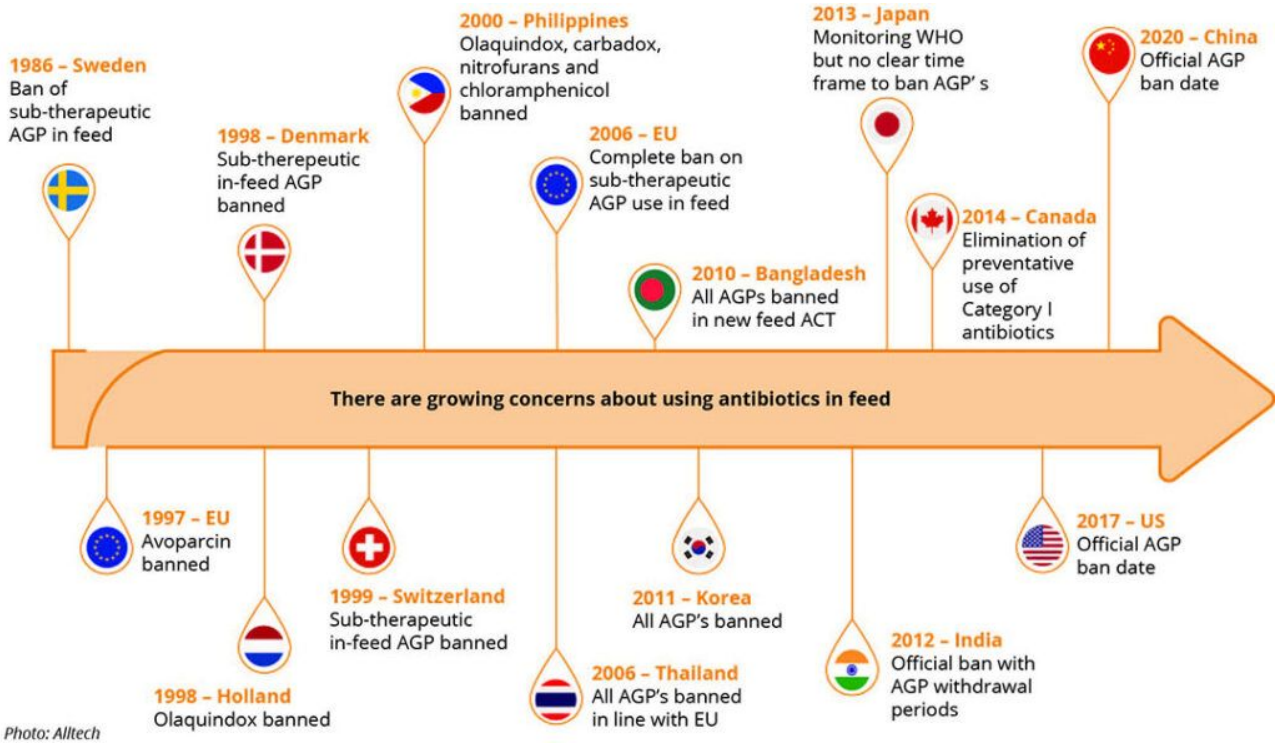
Antibiotics growth promoters

Subtherapeutic antibiotic doses

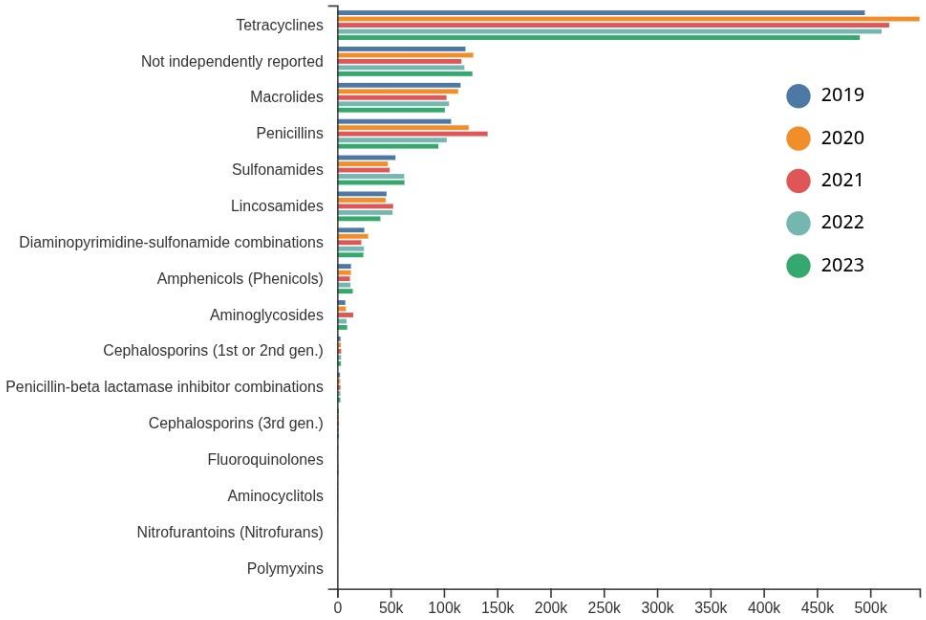
3-5% feed conversion efficiency and 5-10% weight gain in poultry

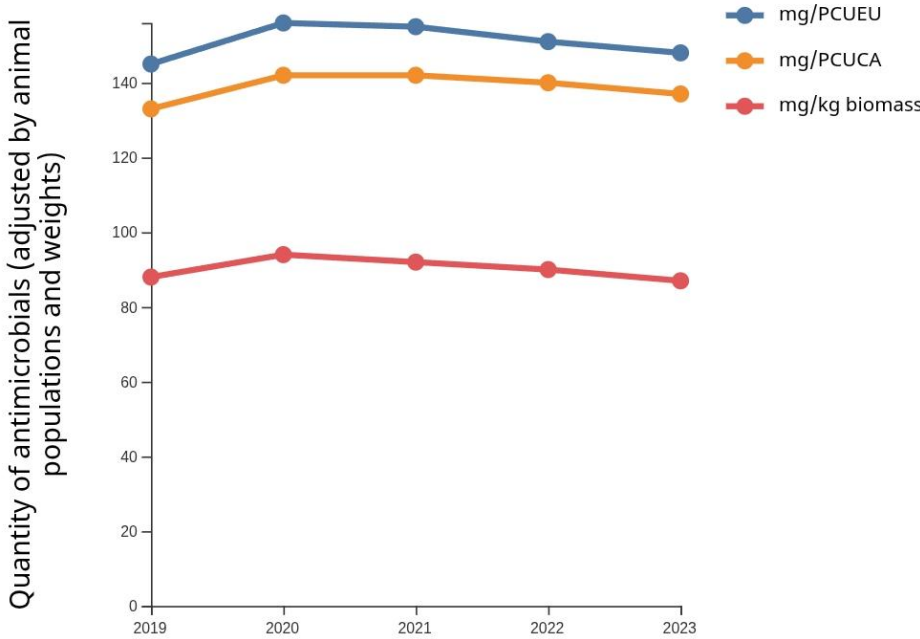
Mechanism unclear but potentially higher density, subclinical infection clearance, less bacterial consumption in guts

Relatively widely banned to some degree (but industry very resistant initially)



Normalisation challenging in animals





kg biomass: animal biomass average live weights at slaughter

PCU: Population correction unit, (number by average weight at treatment) - control differences in AMU at different production stages given majority of AMU occurs in relatively young animals below their weight at slaughter (EU vs CA)

Livestock vs Domestic/Companion Animals - very different use-patterns

Summary

1. Antimicrobials

- *Selective action, favourable PK/PD*
- *Antivirals/fungals/parasitics hard to develop due to overlap between host and microbe*
- *Antibiotics have many targets e.g., cell wall (beta-lactams), protein synthesis (macrolides & tetracyclines), and transcription (quinolones)*
- *Antibiotic organised into mechanistic families (or other properties/usage groups)*
- *Antibiotic usage driven by broad-spectrum penicillins in human and tetracyclines in animals*

2. Antimicrobial Resistance

- Antibiotic Susceptibility Testing
- AMR mechanisms
- Origin and evolution of AMR
- Surveillance of AMR
- Burden of AMR

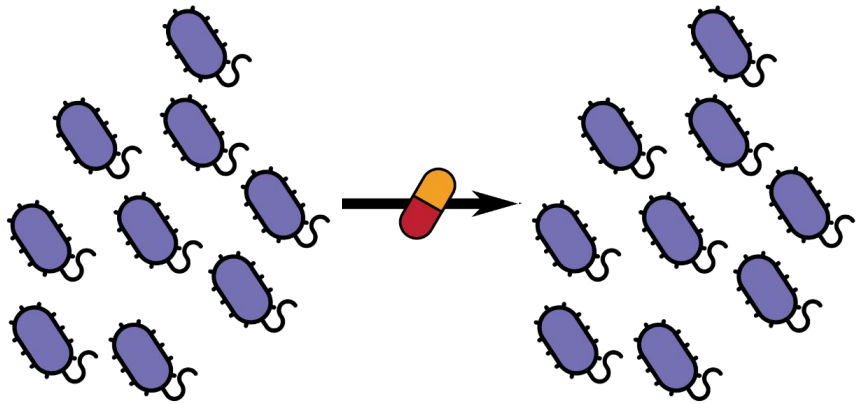
3. Solutions to Antimicrobial Resistance

- Improving Surveillance
- New Antimicrobials
- Alternatives to Antimicrobials
- Antimicrobial Stewardship
- Improved Rapid Diagnostics

So, what is antimicrobial resistance?

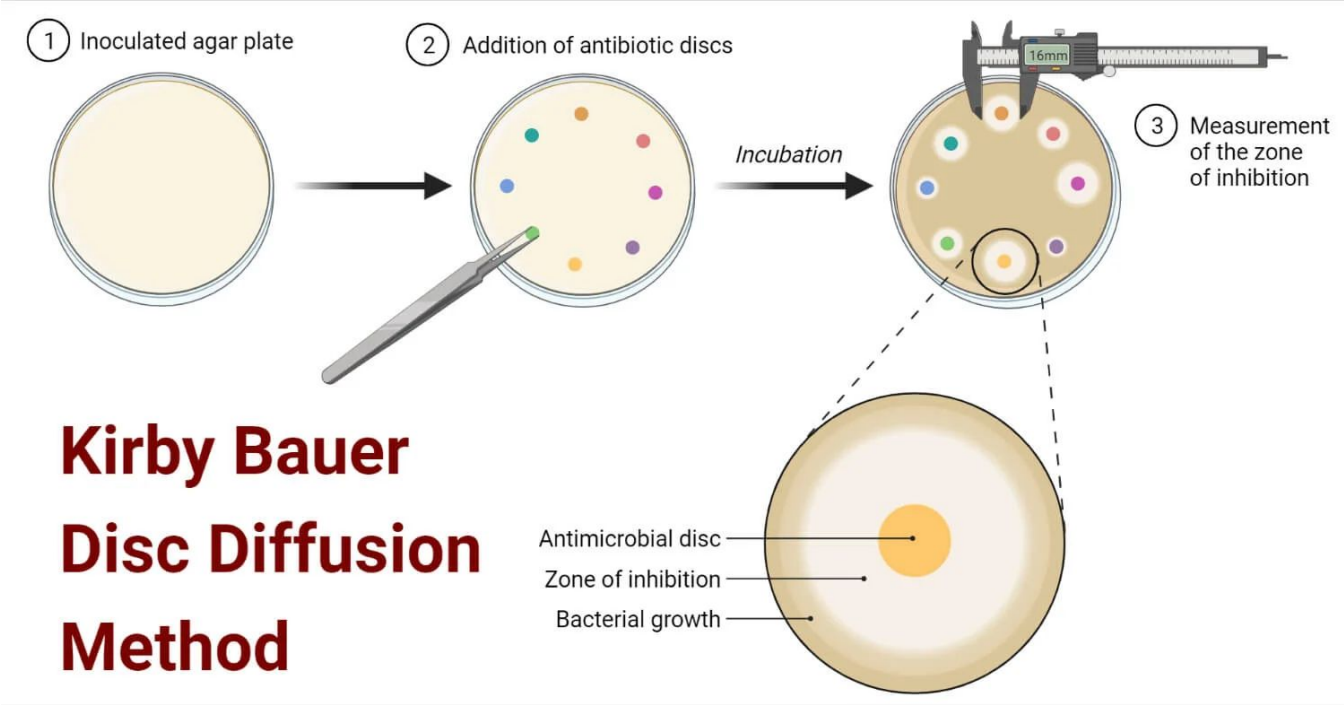
Antimicrobial resistance has 2 different definitions

1. **Antimicrobial resistance** (AMR) is when a specific microbe is shown to have an elevated minimum inhibitory concentration (MIC) to a specific antibiotic using *in-vitro* **Antibiotic Susceptibility Testing** (AST).
2. Alternatively, AMR is defined as when a specific microbe **is not inhibited or killed** by the **recommended dose** of a specific antibiotic at the **site of infection** *in-vivo*.



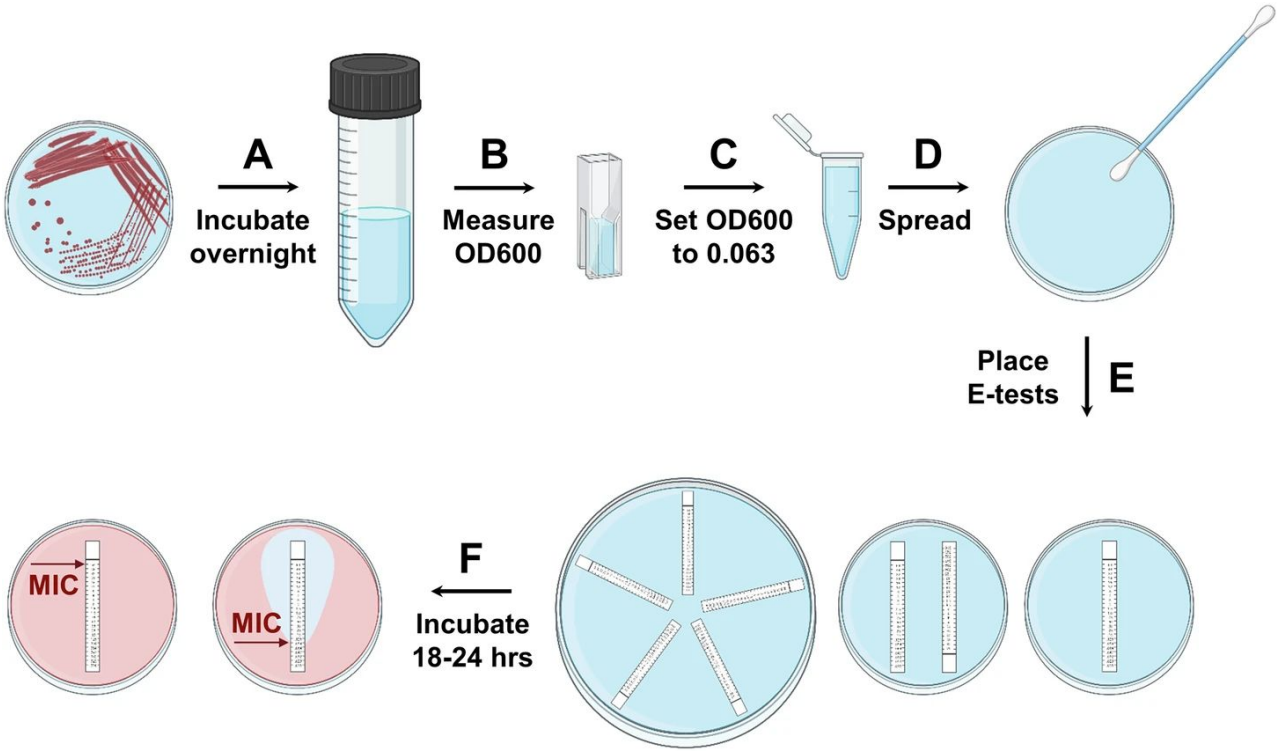
An infection caused by a resistant microorganism is unlikely to be cured by that antibiotic

Disk Diffusion Assays - Quick and Dirty



https://microbenotes.com/kirby-bauer-disc-diffusion/

Gradient diffusion testing (E-Test Strips)



Kadeřábková, N., Mahmood, A.J.S. & Mavridou, D.A.I. Antibiotic susceptibility testing using minimum inhibitory concentration (MIC) assays. npj Antimicrob Resist ***2****, 37 (2024). https://doi.org/10.1038/s44259-024-00051-6*

Aside: Vancomycin-dependent *Enterococcus*

Farrag, N. "Vancomycin-dependent enterococcus." Lancet 348 (1996): 1581-82.

Broth Microdilution (BMD) is gold standard

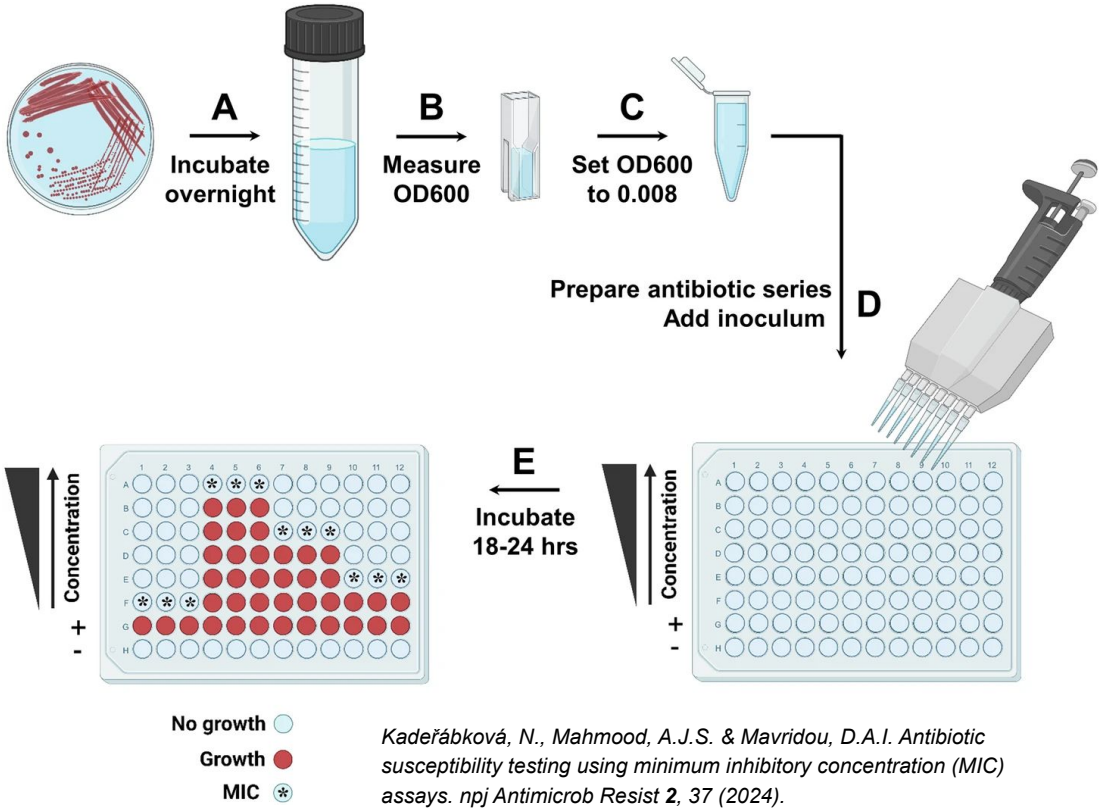
MIC values are typically reported as ranges (≤0.5, 1, 2, 4, 8, ≥16 µg/mL)

Censored (values above or below the lowest tested concentration)

2-fold dilution means MIC ordinal rather than continuous

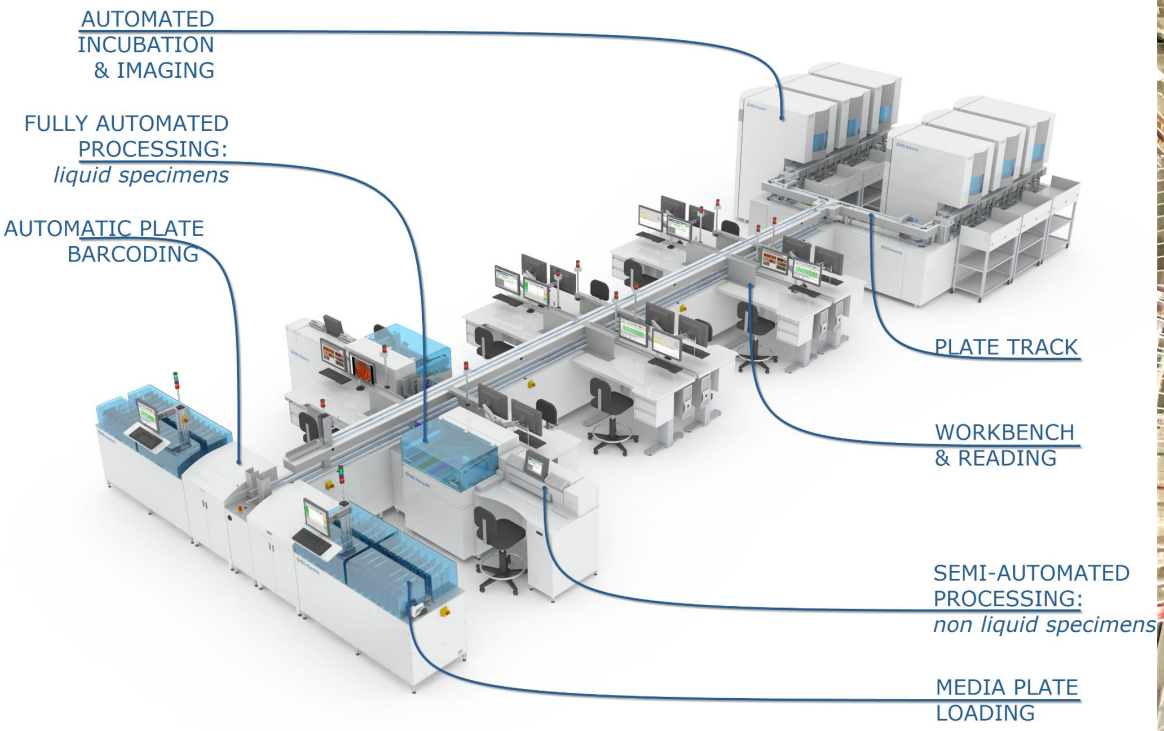
Non-normal residuals even when transformed

Technical variability requires dealing with replicates



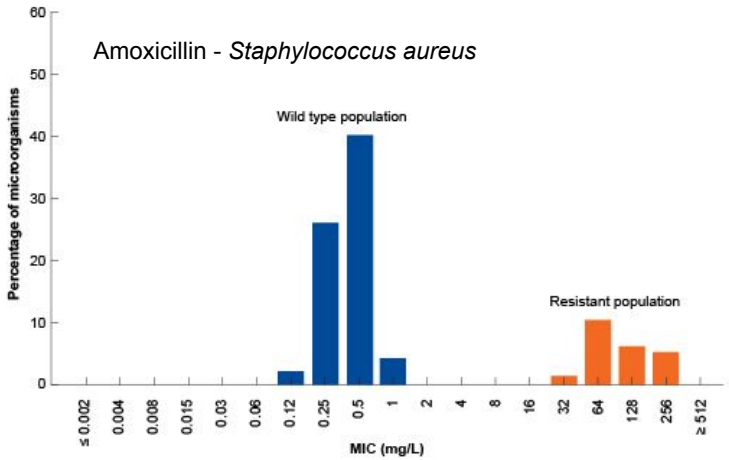
Kadeřábková, N., Mahmood, A.J.S. & Mavridou, D.A.I. Antibiotic susceptibility testing using minimum inhibitory concentration (MIC) assays. npj Antimicrob Resist ***2****, 37 (2024). https://doi.org/10.1038/s44259-024-00051-6*

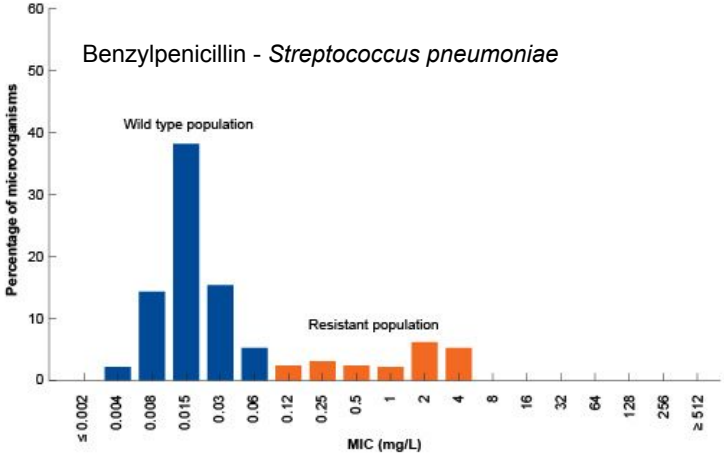
Modern clinical microbiology requires automation



Why do we have 2 different definitions of resistance?

Interpreting MICs - Epidemiological Cut-Offs (ECOFFS)





- ECOFF = highest MIC value of isolates without acquired AMR to specific antibiotic tested
- Split MIC distributions of “wild type” isolates from “resistant” isolates
- Clear ECOFF for some bug-drug combinations but challenging when distributions overlap
- Goal to detect acquired AMR that may, or may not, be clinically significant
- Primarily used in surveillance rather than to guide therapy in human or animal health

https://www.eucast.org/clinical_breakpoints_and_dosing/splitting_mic_wild_type_distributions

Interpreting MICs - Clinical Breakpoints

Susceptible:

MIC less or equal to safely achievable antibiotic concentrations at site of infection when a patient or animal following a standard dosing regimen.

Resistant:

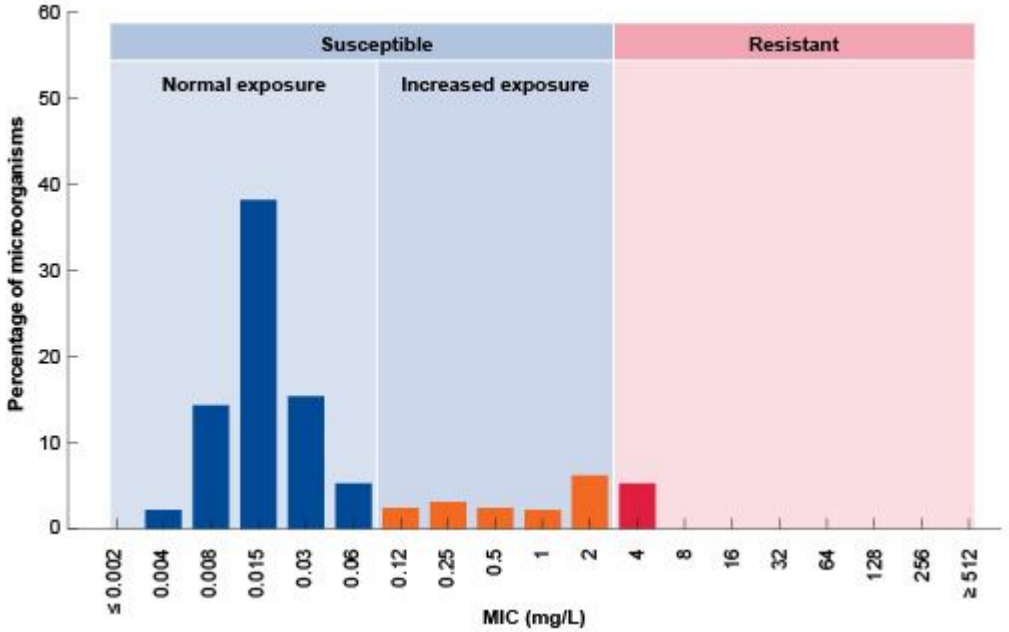
MIC higher than this safely achievable standard concentration

Intermediate (not all pathogen-antibiotics):

Grey-zone between definite susceptibility and definite resistance.

Susceptible Dose-Dependent (CLSI only):

Intermediate subcategory for drugs that can concentrate more at specific anatomical sites



Setting breakpoints is relatively complicated

Clinical breakpoints set collaboratively by expert committees (clinical microbiology, infectious diseases, pharmacy, basic science) for each antibiotic-bacteria pair:

- Antibiotic mechanism of action
- Known AMR mechanisms
- Clinical outcome data
- Pharmacokinetics and pharmacodynamics (PK/PD)
- MIC distributions and ECOFF values
- Difference types of infection (sometimes)

Tentative breakpoint published for consultation and refined before the final breakpoints (which are reviewed regularly)

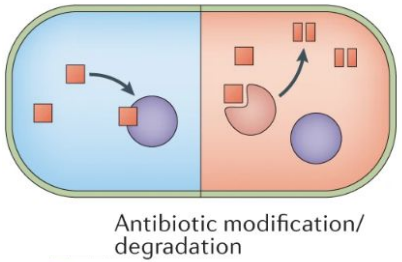
Animal and human breakpoints are not alway the same, as animals may metabolise some antibiotics differently and so may achieve different tissue concentrations.

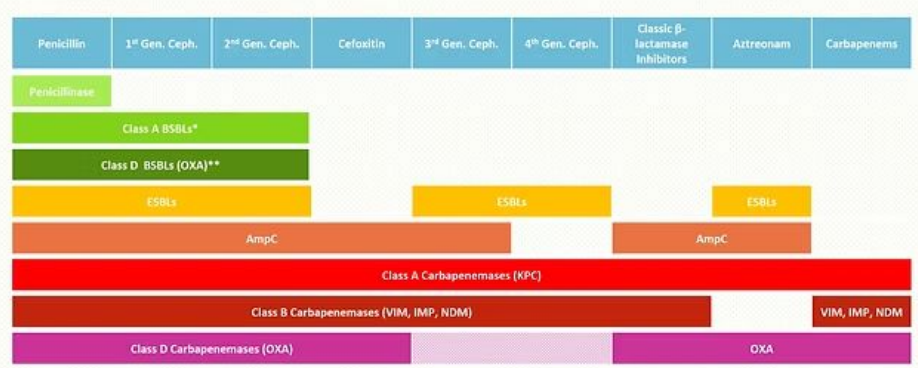
2 different sources with different priorities:

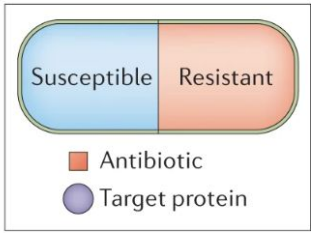
- Clinical & Laboratory Standards Institute (CLSI) - optimising laboratory standardization/reproducibility (private)
- European Committee on Antimicrobial Susceptibility Testing (EUCAST) - optimising clinical outcomes (public)

What are the primary mechanism of AMR?

Antimicrobial Resistance Mechanisms

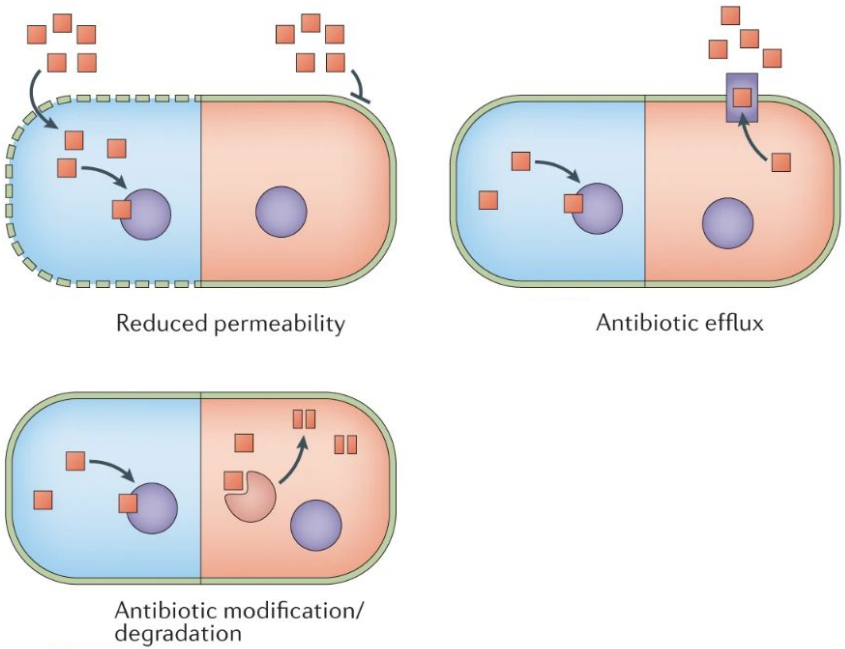


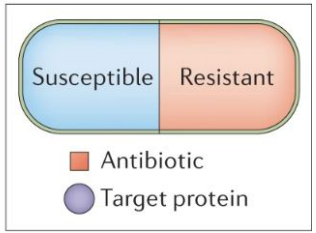




Boolchandani, Manish, Alaric W. D'Souza, and Gautam Dantas. "Sequencing-based methods and resources to study antimicrobial resistance." Nature Reviews Genetics 20.6 (2019): 356-370.

Antimicrobial Resistance Mechanisms





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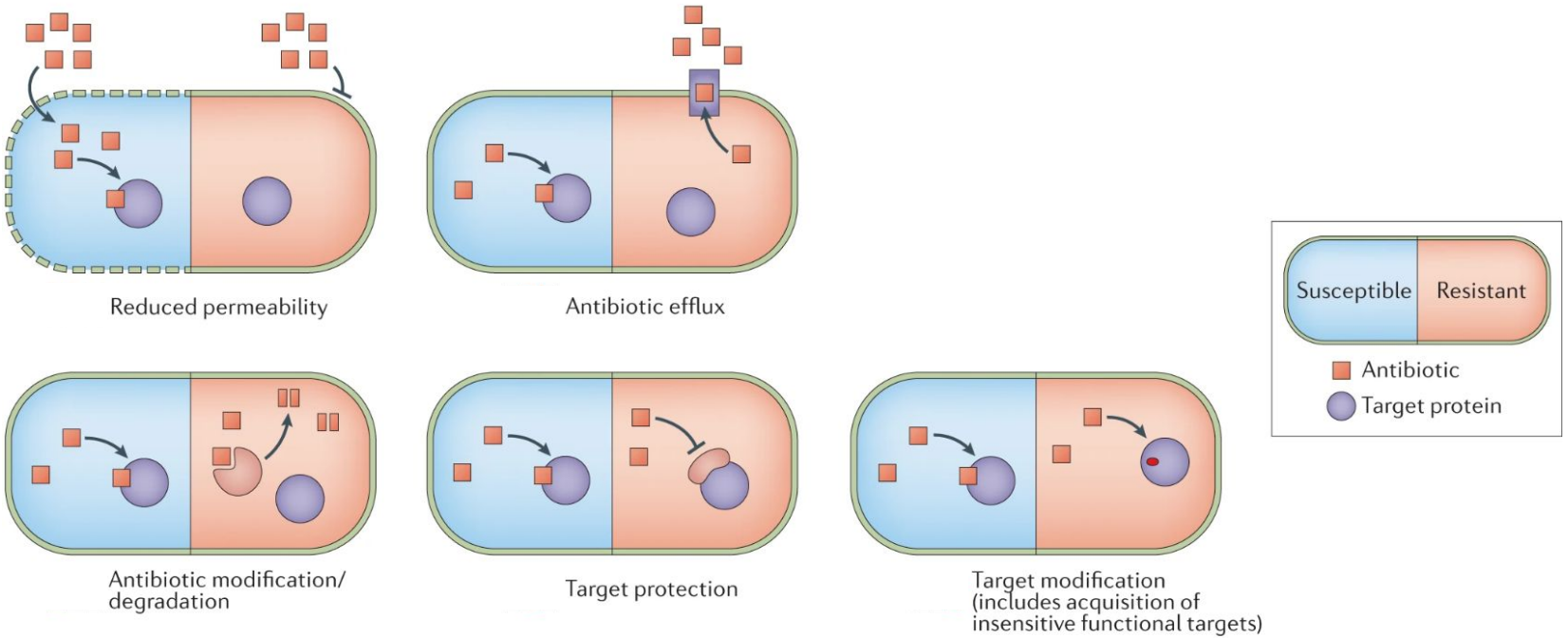

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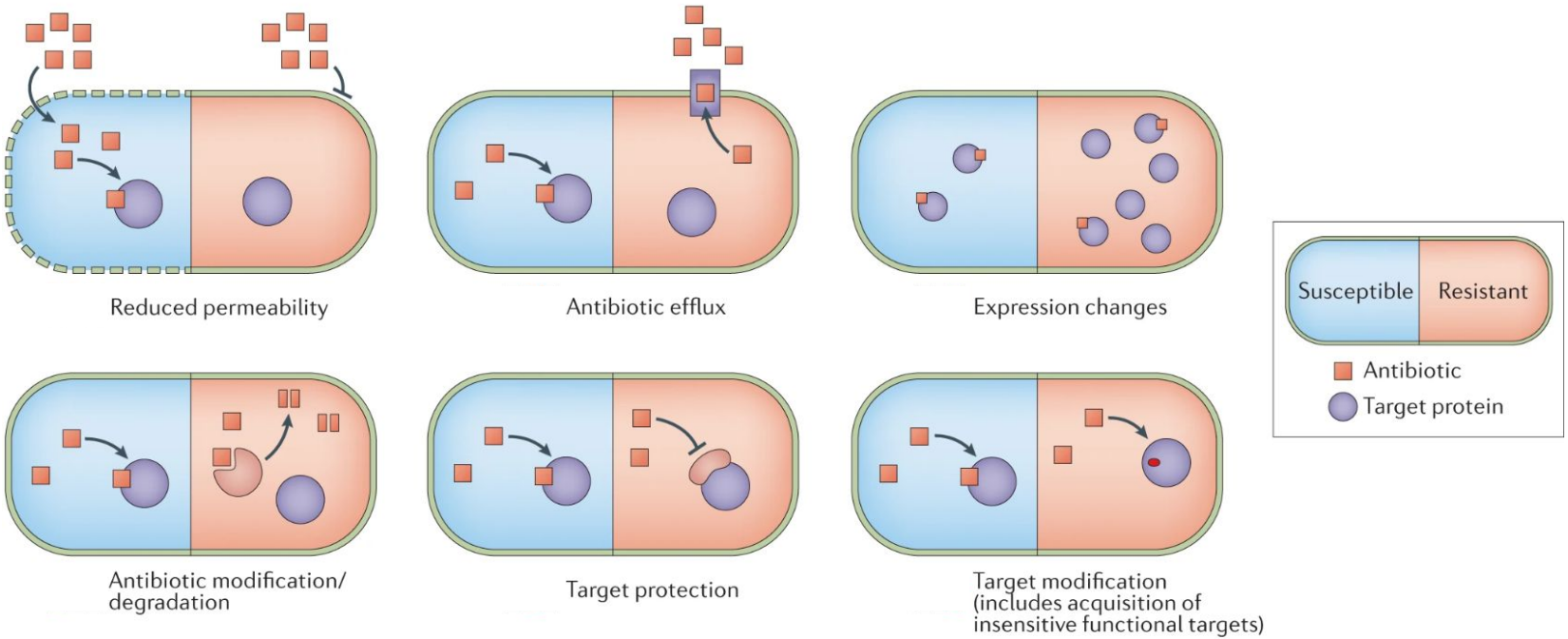
Antimicrobial Resistance Mechanisms



Boolchandani, Manish, Alaric W. D'Souza, and Gautam Dantas. "Sequencing-based methods and resources to study antimicrobial resistance." Nature Reviews Genetics 20.6 (2019): 356-370.

Where does AMR come from?

AMR is older than human use of antibiotics

Letter | Published: 31 August 2011

Antibiotic resistance is ancient

Vanessa M. D'Costa, Christine E. King, Lindsay Kalan, Mariya Morar, Wilson W. L. Sung, Carsten Schwarz, Duane Froese, Grant Zazula, Fabrice Calmels, Regis Debruyne, G. Brian Golding, Hendrik N. Poinar & Gerard D. Wright

Nature **477**, 457–461 (2011) | Cite this article

Diverse signatures of AMR in 30,000-year-old Beringian permafrost sediment cores

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

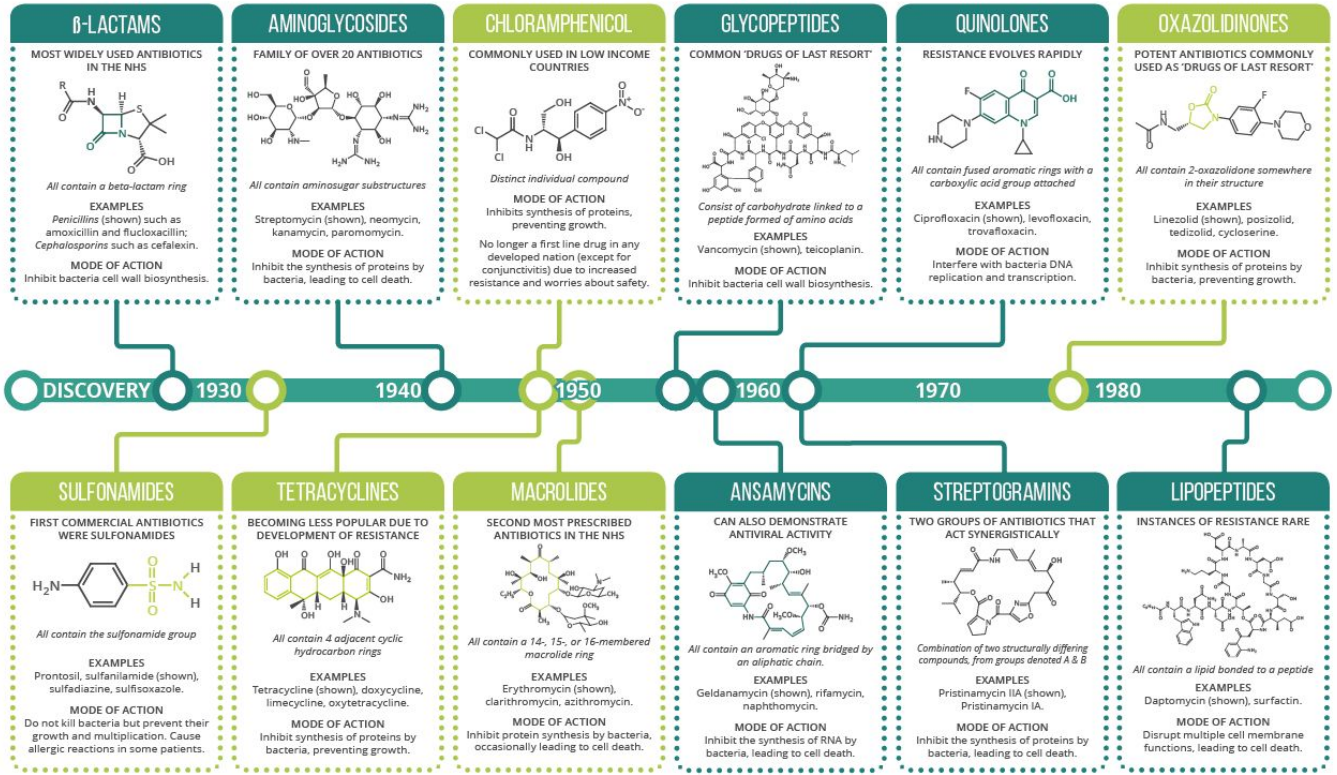
Kirandeep Bhullar, Nicholas Waglechner, Andrew Pawlowski, Kalinka Koteva, Eric D. Banks, Michael D. Johnston, Hazel A. Barton, Gerard D. Wright

Published: April 11, 2012 • https://doi.org/10.1371/journal.pone.0034953

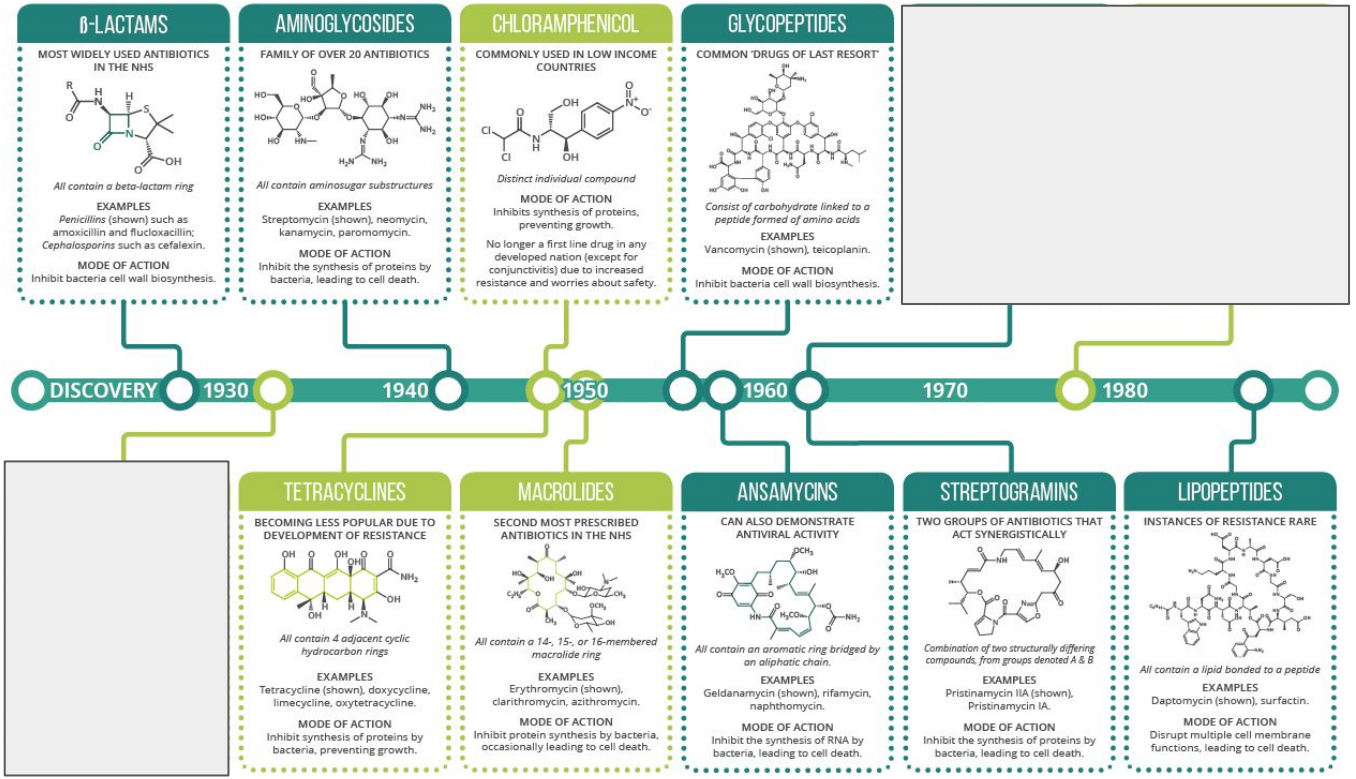
Lechuguilla Cave, New Mexico isolate for >4 million years: culturable bacteria highly resistant >= 14 antimicrobials

Why is AMR so old if antibiotics are only 80-120 years old?

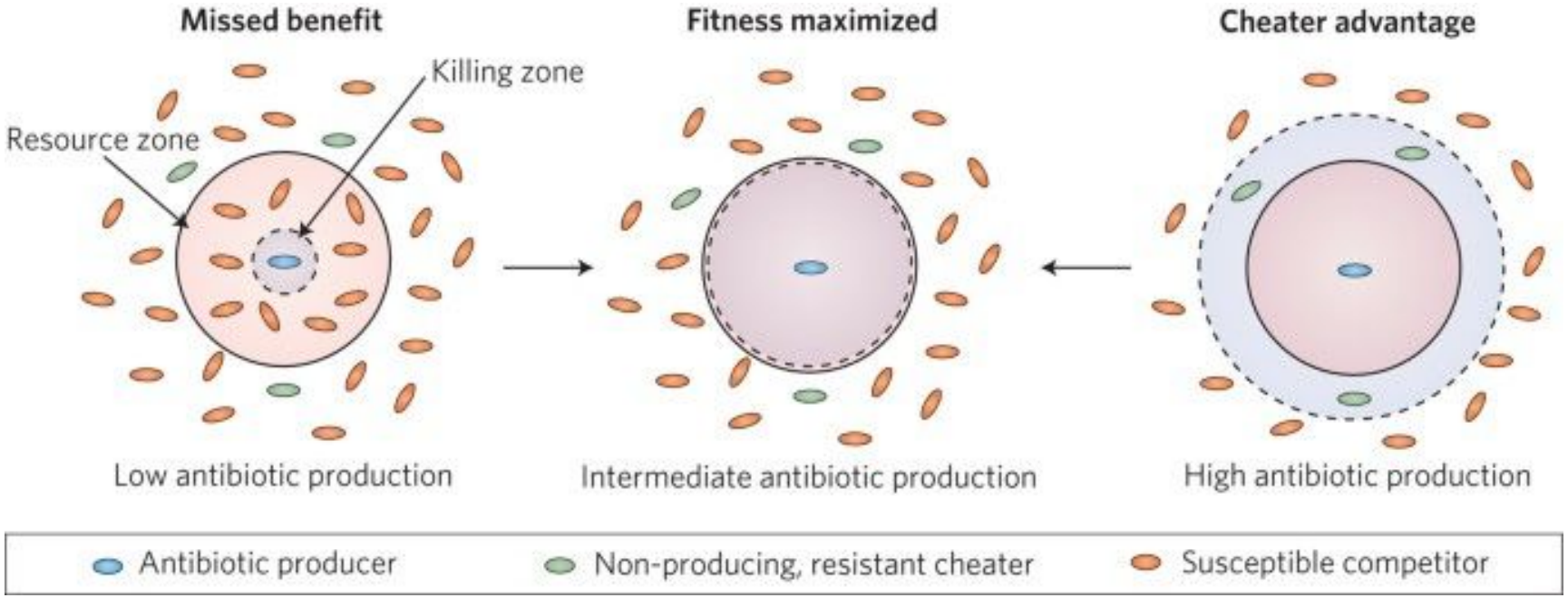
Most antibiotic classes are natural products



Most antibiotic classes are natural products



Antibiotic production is part bacterial ecology/competition



https://www.nature.com/articles/nmicrobiol2016225

So - what is the first bacteria resistant to antibiotics produced by a bacteria?

Antibiotic producers HAVE to be resistant or they die

- Penicillin producing *Penicillium chrysogenum* - Fungi so no cell wall
- Tetracycline producing *Kitasatospora aureofaciens* - Efflux

Biosci. Biotech. Biochem., **59** (10), 1835–1841, 1995

A Self-defense Gene Homologous to Tetracycline Effluxing Gene Essential for Antibiotic Production in *Streptomyces aureofaciens*

Tohru DAIRI,* Kazuo AISAKA, Ryoichi KATSUMATA, and Mamoru HASEGAWA†

Tokyo Research Laboratories of Kyowa Hakko Kogyo Co., Ltd., 3–6–6, Asahimachi, Machida-shi, Tokyo 194, Japan

Received January 13, 1995

- Streptomyces producing *Kitasatospora bikiniensis*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1979, p. 176–182 Vol. 16, No. 2
0066-4804/79/08-0176/07$02.00/0

Streptomycin Resistance in a Streptomycin-Producing Microorganism

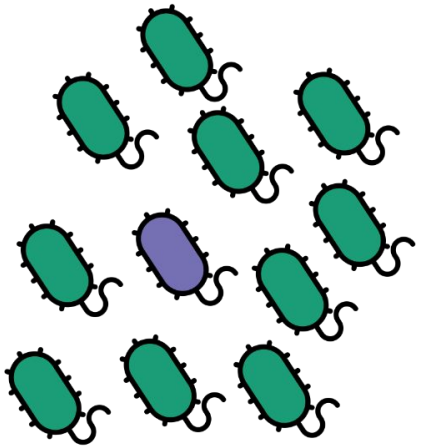
JANET M. PIWOWARSKI AND PAUL D. SHAW*

Department of Plant Pathology, University of Illinois, Urbana, Illinois 61801

Received for publication 23 May 1979

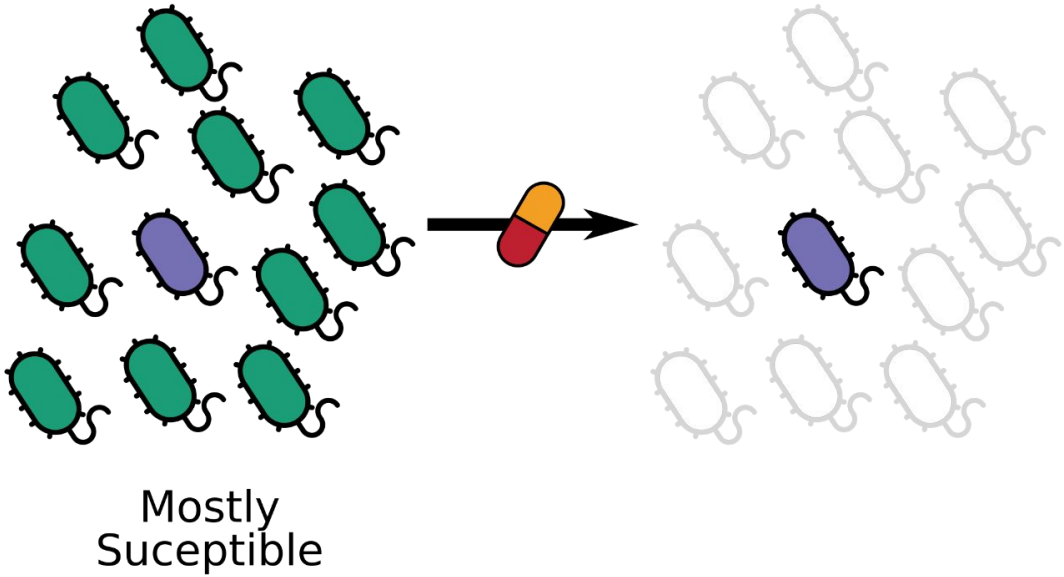
But how does a bacteria BECOME resistant?

AMR can rapidly evolve from random changes to DNA

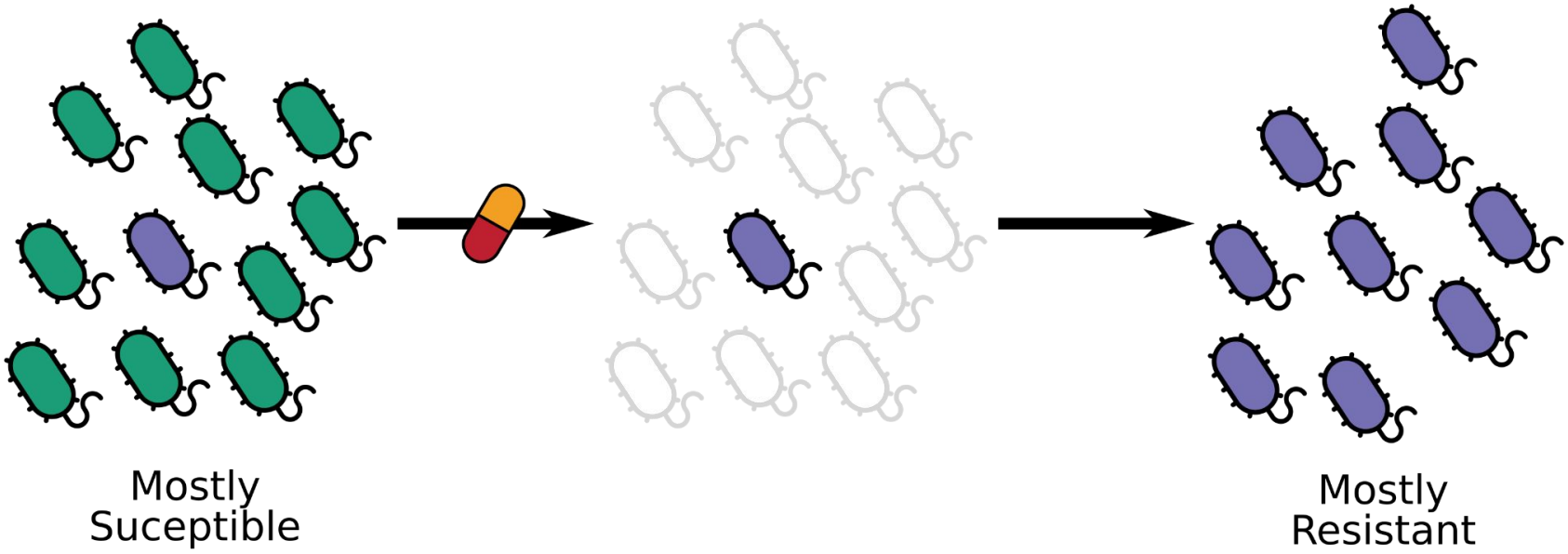


Mostly
Suceptible

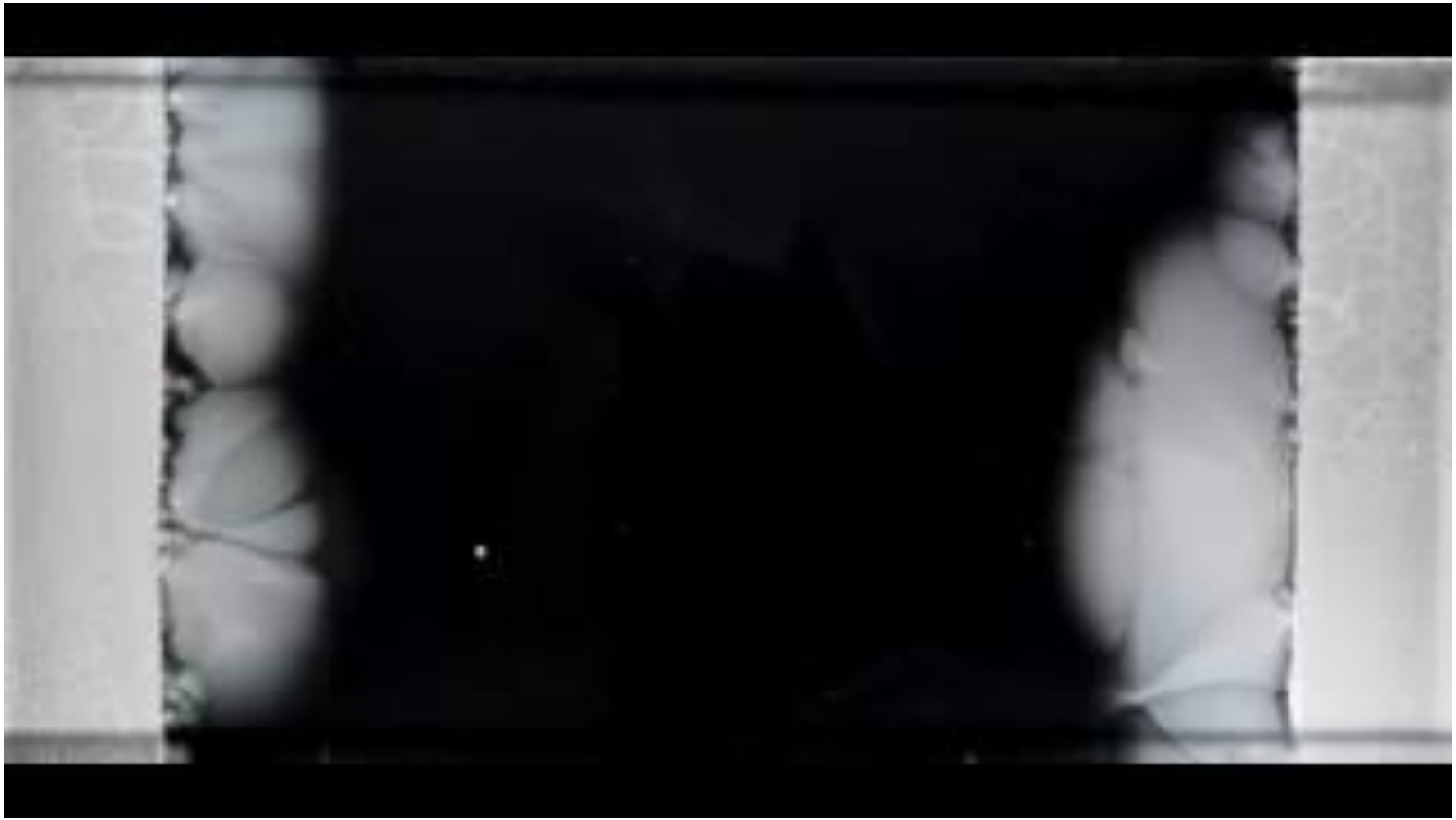
AMR can rapidly evolve from random changes to DNA



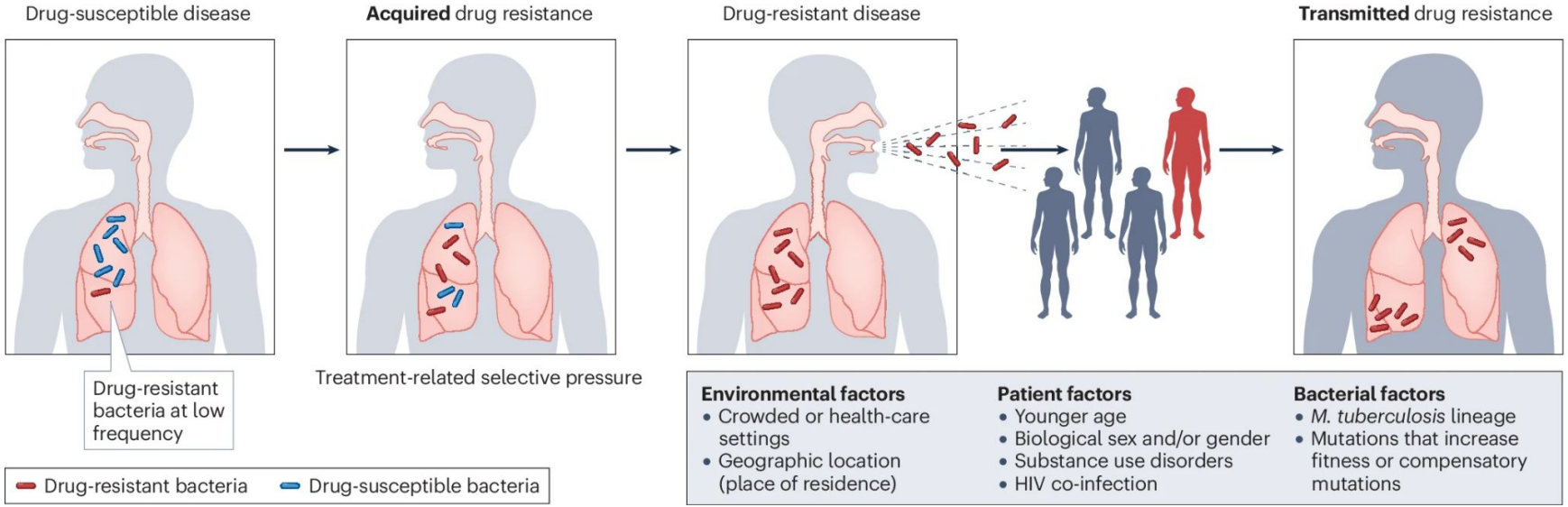
AMR can rapidly evolve from random changes to DNA



Can see in real-time: Megaplate Experiment

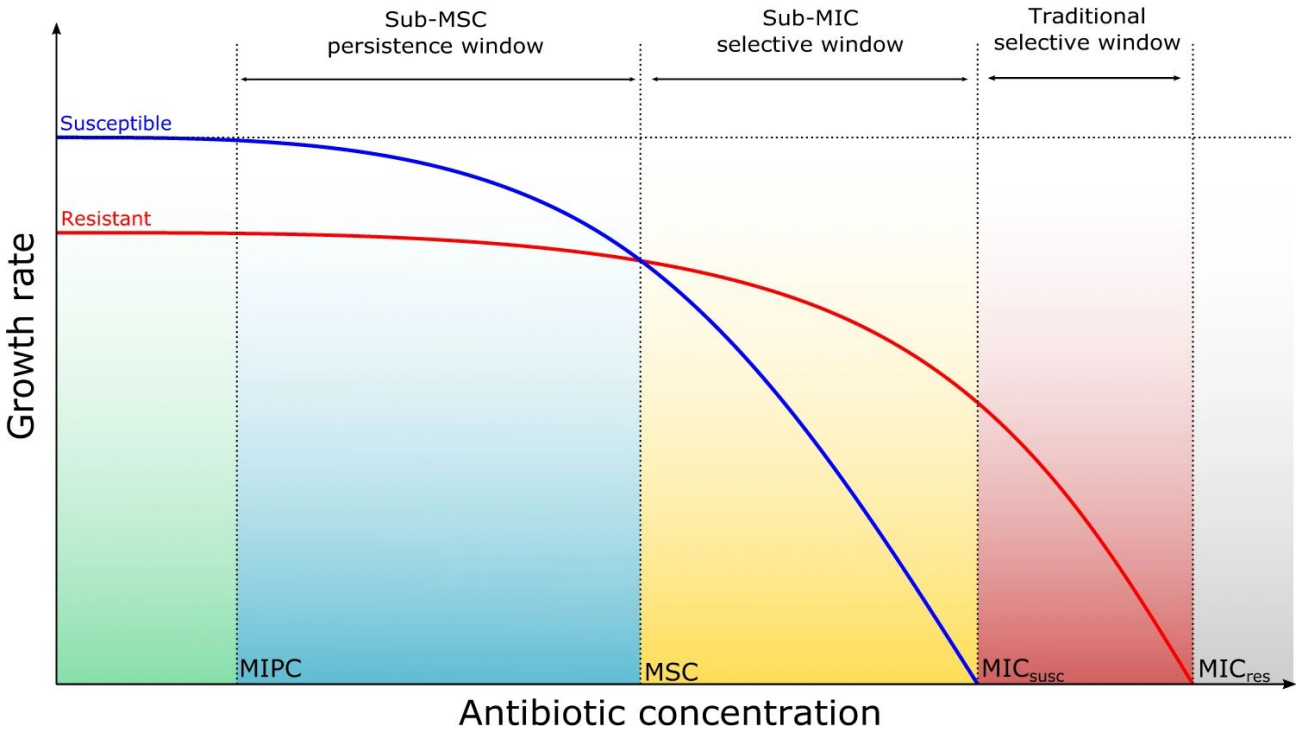


All tuberculosis resistance occurs via inherited mutation



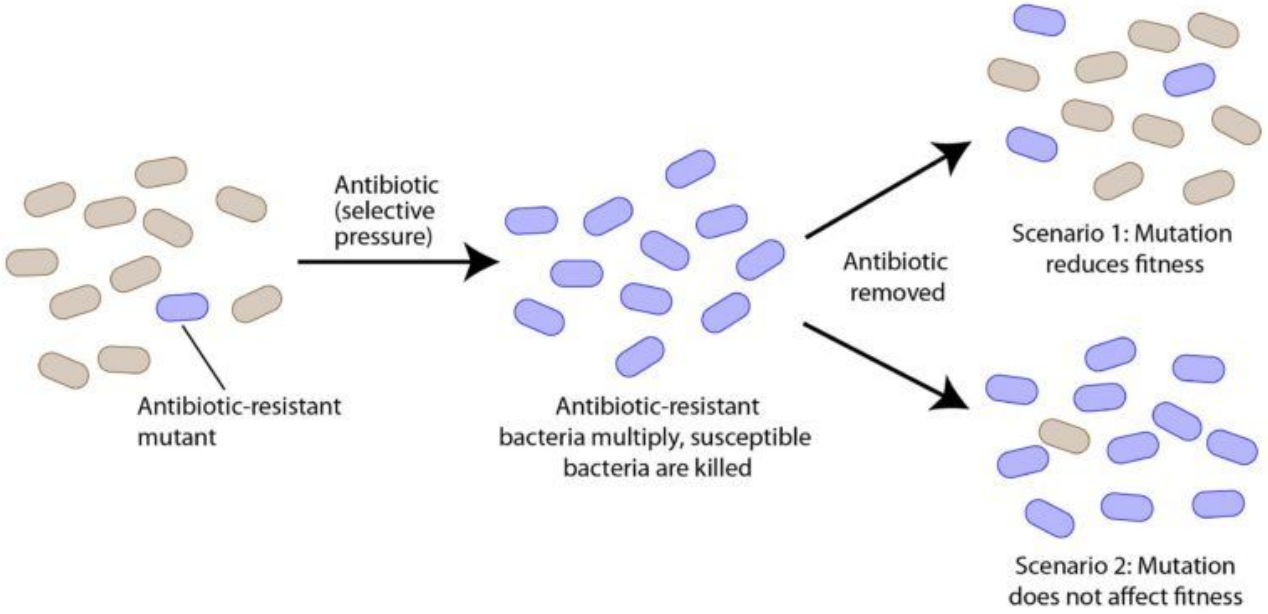
Farhat, M., Cox, H., Ghanem, M. *et al.* Drug-resistant tuberculosis: a persistent global health concern. *Nat Rev Microbiol* 22, 617–635 (2024). https://doi.org/10.1038/s41579-024-01025-1

Selective window drives fixation of these mutations



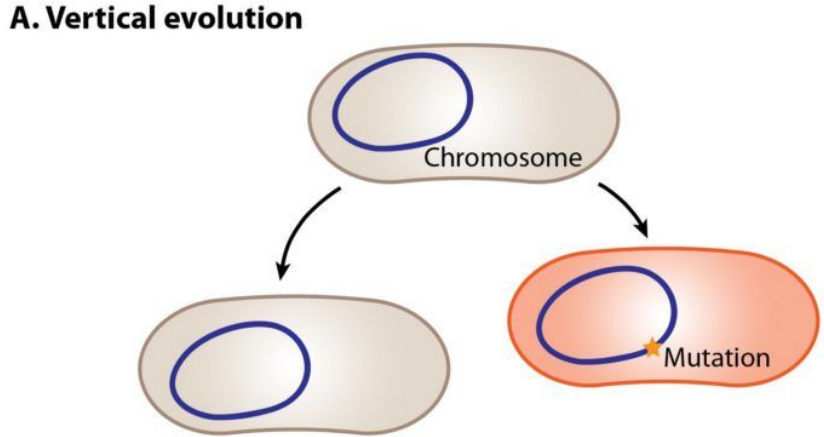
Stanton, I.C., Murray, A.K., Zhang, L. et al. Evolution of antibiotic resistance at low antibiotic concentrations including selection below the minimal selective concentration. Commun Biol 3, 467 (2020). https://doi.org/10.1038/s42003-020-01176-w

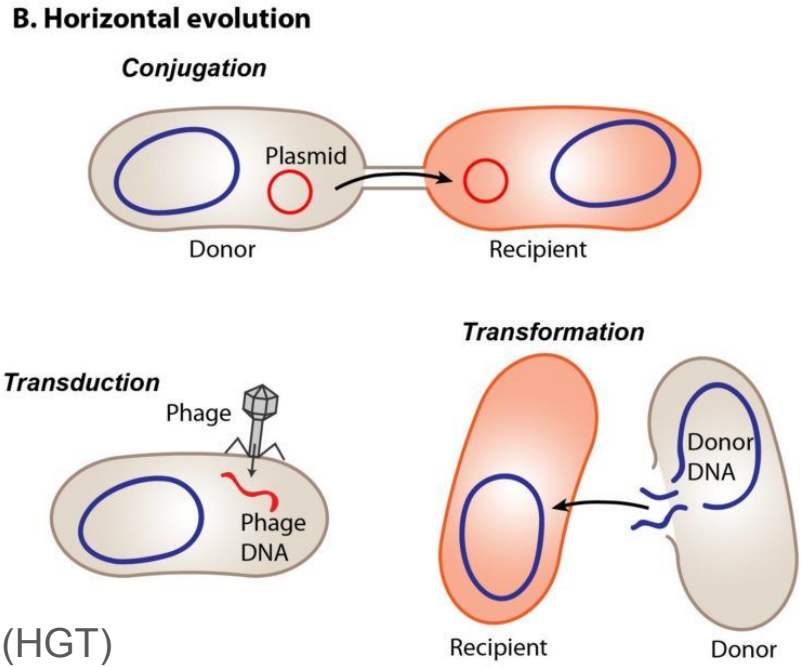
Mutational resistance can persist without antibiotic



Mutational resistance alone would be a problem but bacteria can acquire resistance another way!

AMR can be acquired from unrelated bacteria via LGT

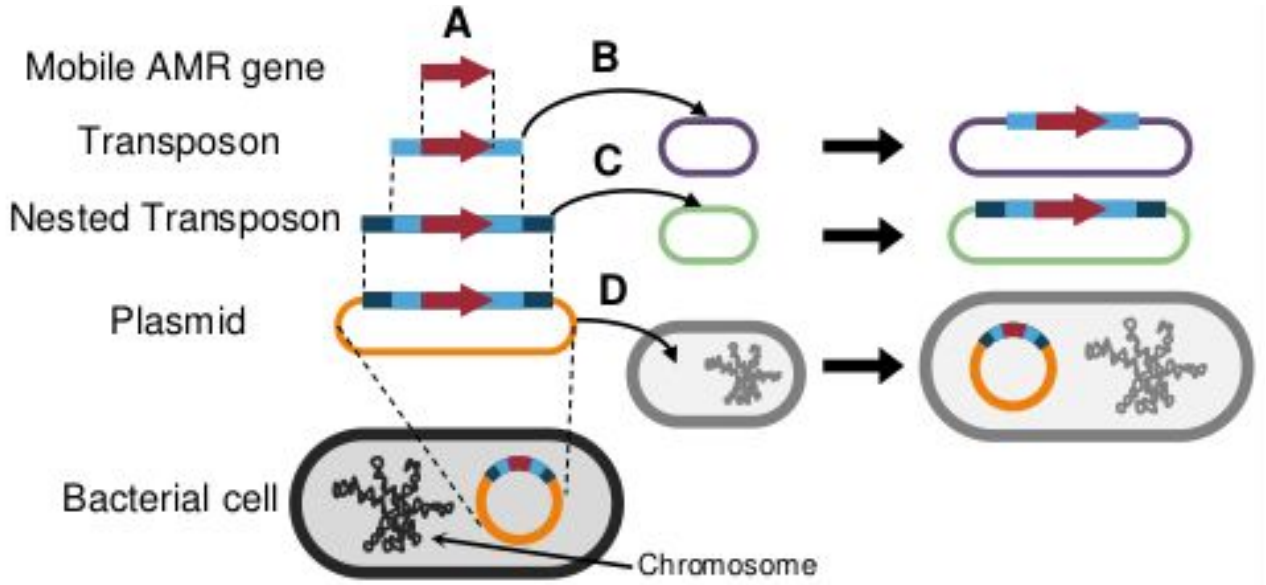




Lateral Gene Transfer (LGT) == Horizontal Gene Transfer (HGT)

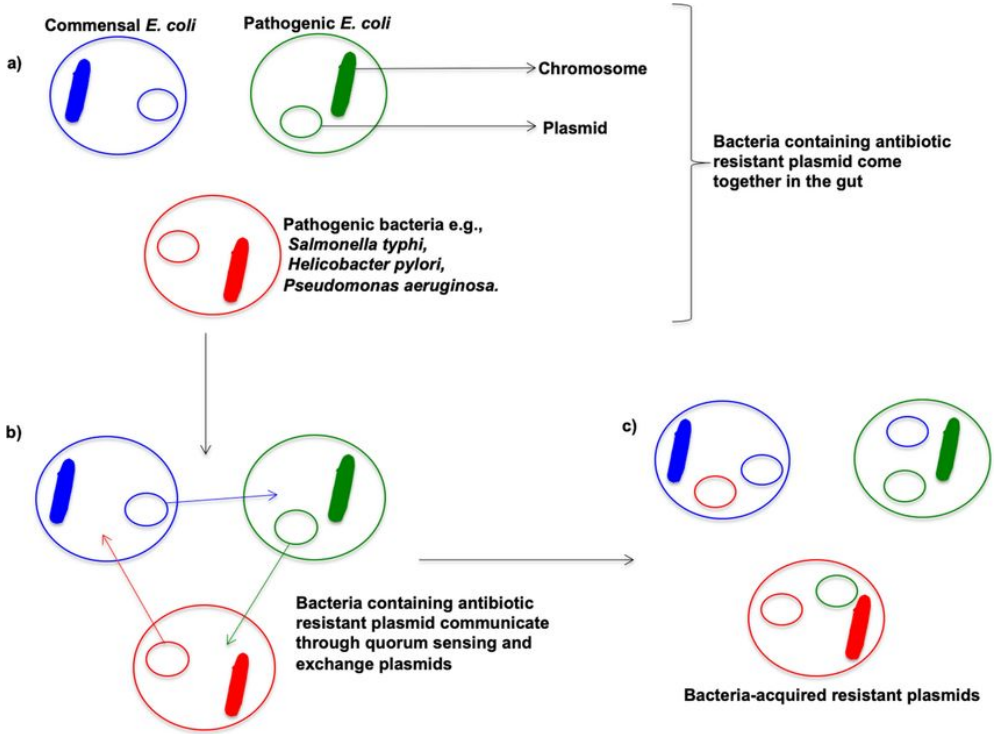
https://www.futurelearn.com/info/courses/introduction-to-bacterial-genomics/0/steps/45331

LGT can be complex - nested mobile DNA elements



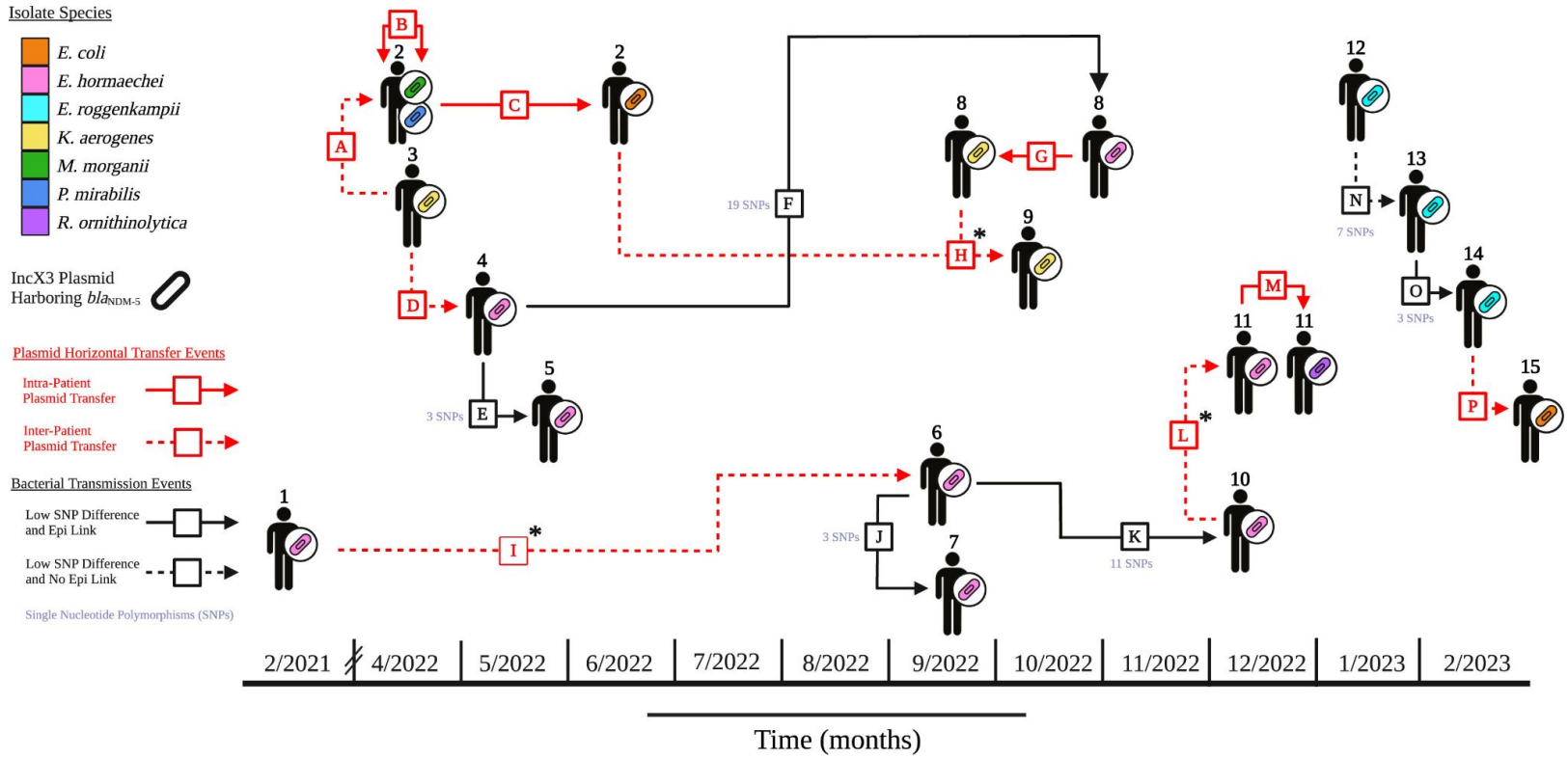
Sheppard, Anna E., et al. "Nested Russian doll-like genetic mobility drives rapid dissemination of the carbapenem resistance gene bla KPC." Antimicrobial agents and chemotherapy 60.6 (2016): 3767-3778.

LGT can happen within individual people or animals



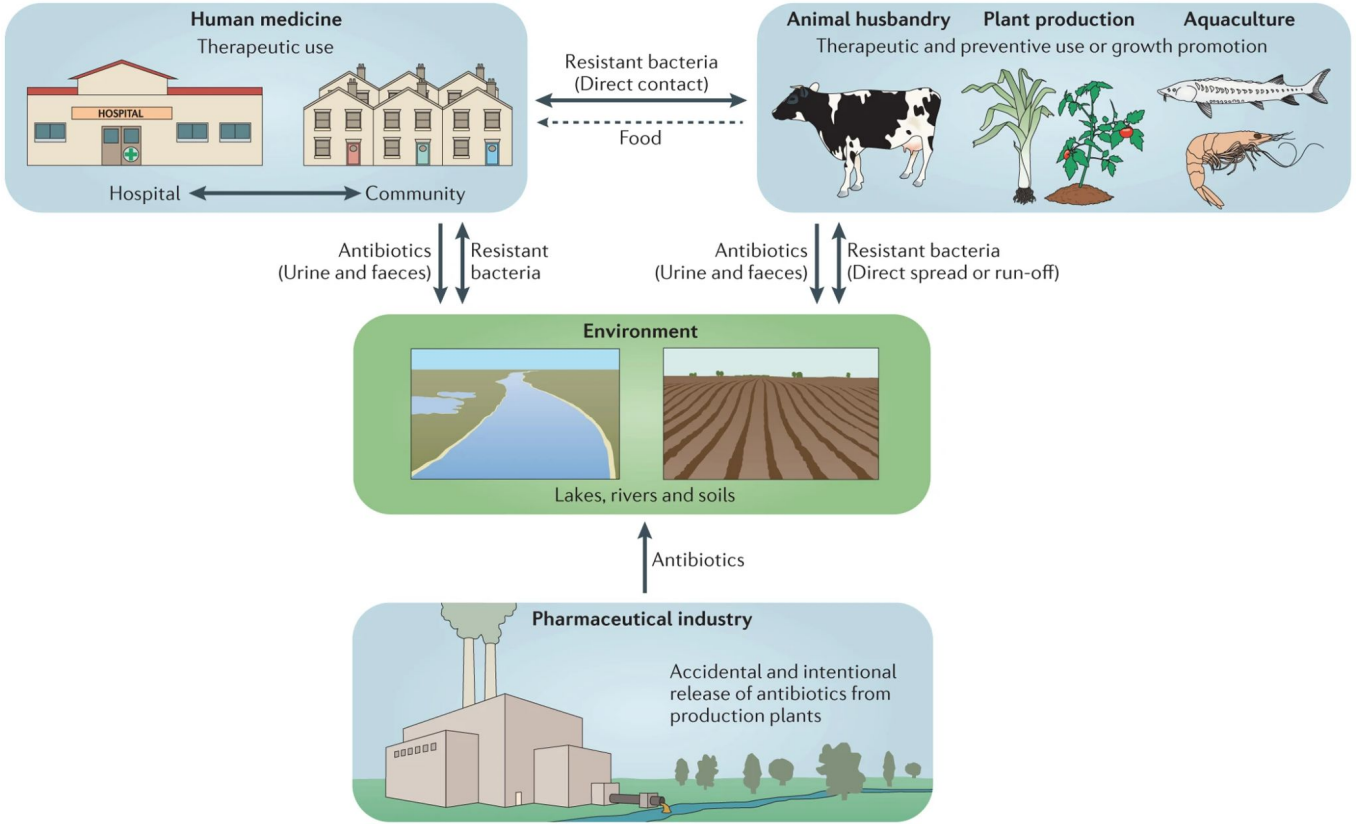
Nji, Emmanuel, et al. "High prevalence of antibiotic resistance in commensal Escherichia coli from healthy human sources in community settings." *Scientific reports* 11.1 (2021): 3372.

LGT can happen within hospitals



Raabe, Nathan J., et al. "Real-time genomic epidemiologic investigation of a multispecies plasmid-associated hospital outbreak of NDM-5-producing Enterobacterales infections." International Journal of Infectious Diseases 142 (2024): 106971.

LGT can happen between sectors



Andersson, Dan I., and Diarmaid Hughes. "Microbiological effects of sublethal levels of antibiotics." Nature Reviews Microbiology 12.7 (2014): 465-478.

How big a problem is AMR?

Antimicrobial Resistance impacts all antimicrobials

- Clinical Approval
- Resistance First Reported
- Resistance Same Year as Approval

Spagnolo, Fabrizio, Monica Trujillo, and John J. Dennehy. "Why do antibiotics exist?." *MBio* 12.6 (2021): e01966-21.

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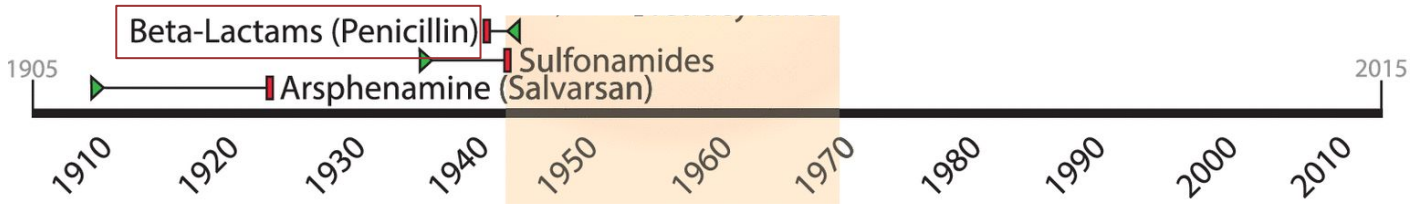

Spagnolo, Fabrizio, Monica Trujillo, and John J. Dennehy. "Why do antibiotics exist?." *MBio* 12.6 (2021): e01966-21.

Anti

- Clinic
- Resis
- Resis

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ*.

ALEXANDER FLEMING, F.R.C.S.

From the Laboratories of the Inoculation Department, St Mary's Hospital, London.

Received for publication May 10th, 1929.

WHILE working with staphylococcus variants a number of culture-plates were set aside on the laboratory bench and examined from time to time. In the examinations these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis (see Fig. 1).

Subcultures of this mould were made and experiments conducted with a view to ascertaining something of the properties of the bacteriolytic substance which had evidently been formed in the mould culture and which had diffused into the surrounding medium. It was found that broth in which the mould had been grown at room temperature for one or two weeks had acquired marked inhibitory, bactericidal and bacteriolytic properties to many of the more common pathogenic bacteria.

LETTERS TO THE EDITORS

The Editors do not hold themselves responsible for opinions expressed by their correspondents. They cannot undertake to return, or to correspond with the writers of, rejected manuscripts intended for this or any other part of NATURE. *No notice is taken of anonymous communications.*

IN THE PRESENT CIRCUMSTANCES, PROOFS OF "LETTERS" WILL NOT BE SUBMITTED TO CORRESPONDENTS OUTSIDE GREAT BRITAIN.

An Enzyme from Bacteria able to Destroy Penicillin

FLEMING[1] noted that the growth of *B. coli* and a number of other bacteria belonging to the coli-typhoid group was not inhibited by penicillin. This observation has been confirmed. Further work has been done to find the cause of the resistance of these organisms to the action of penicillin.

An extract of *B. coli* was made by crushing a suspension of the organisms in the bacterial crushing mill of Booth and Green[2]. This extract was found to contain a substance destroying the growth-inhibiting property of penicillin. The destruction took place on *B. coli*, it was not necessary to crush the organism in the bacterial mill in order to obtain the enzyme from it; the latter appeared in the culture fluid. The enzyme was also found in *M. lysodeikticus*, an organism sensitive to the action of penicillin, though less so than *Staphylococcus aureus*. Thus, the presence or absence of the enzyme in a bacterium may not be the sole factor determining its insensitivity or sensitivity to penicillin.

The tissue extracts and tissue autolysates that have been tested were found to be without action on the growth-inhibiting power of penicillin. Prof. A. D. Gardner has found staphylococcal pus to be devoid of inhibiting action, but has demonstrated a slight

Antimicrobial Resistance impacts all antimicrobials

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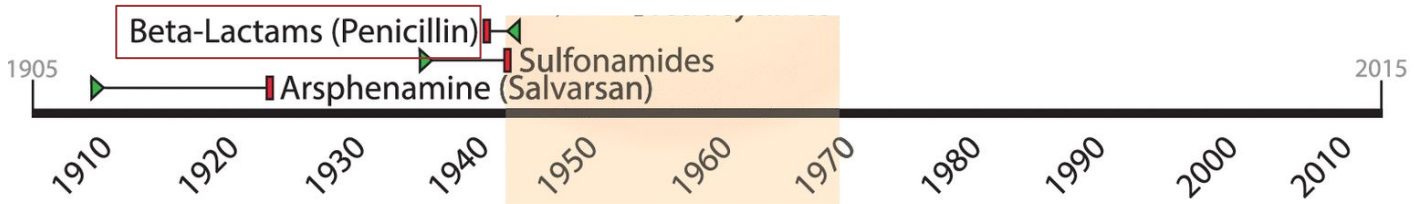
Penicillin treatment was started on 12 February 1941, with 200 mg (10 000 units) intravenously initially and then 300 mg every three hours. All the patient's urine was collected, and each morning I took it over to the Dunn Laboratory on my bicycle so that the excreted penicillin could be extracted to be used again. There I was always eagerly met by Florey and Chain and other members of the team. On the first day I was able to report that for the first time throughout his illness the patient was beginning to feel a little better. Four days later there was a striking improve-



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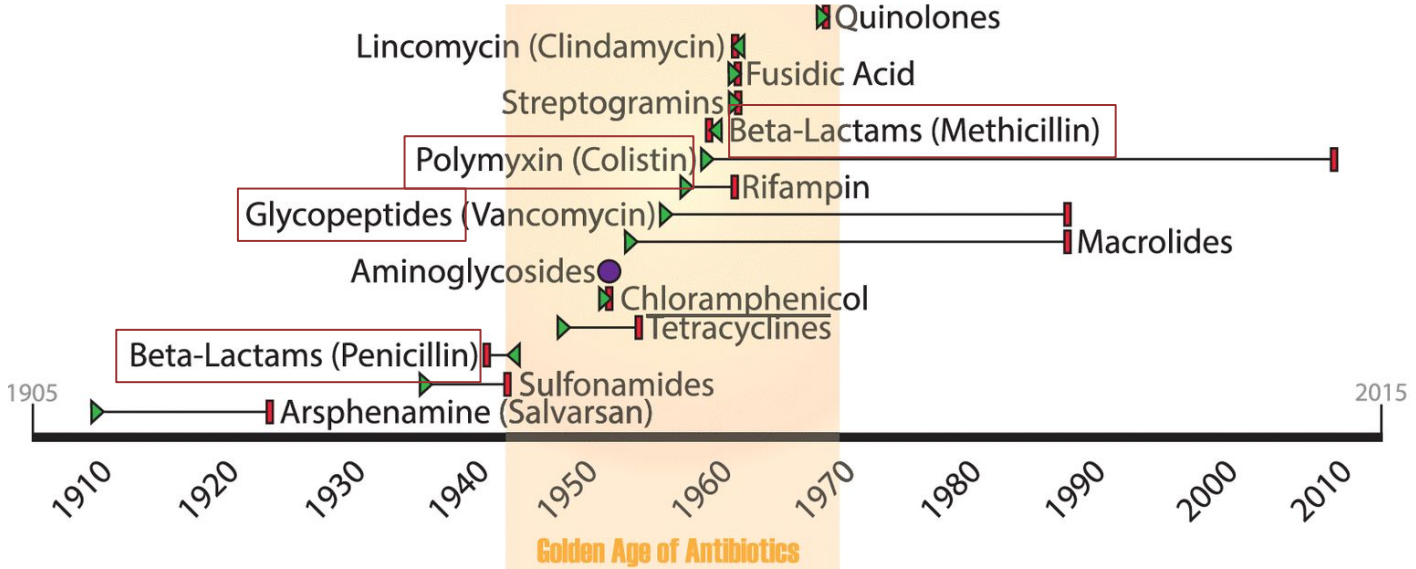

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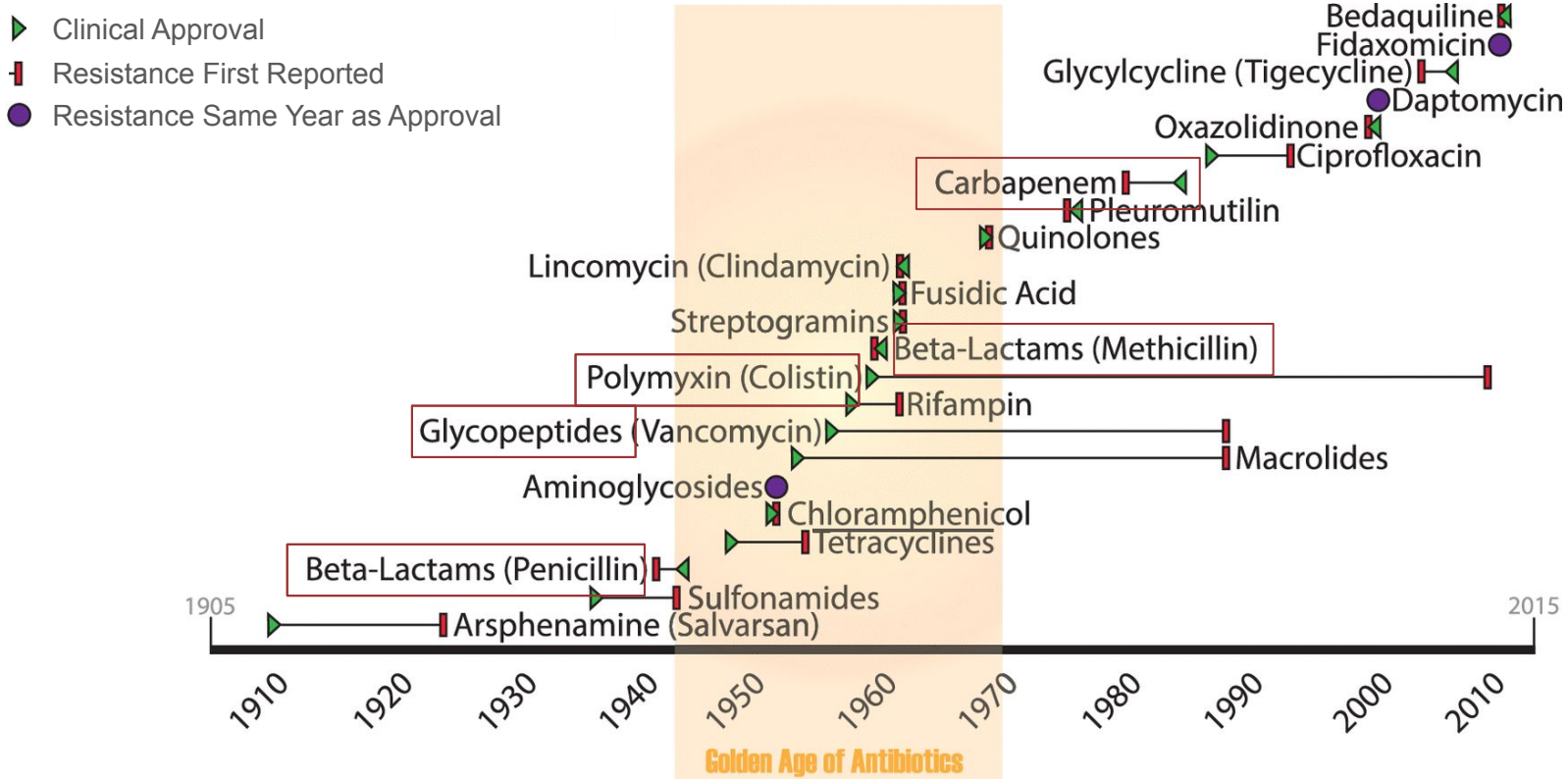


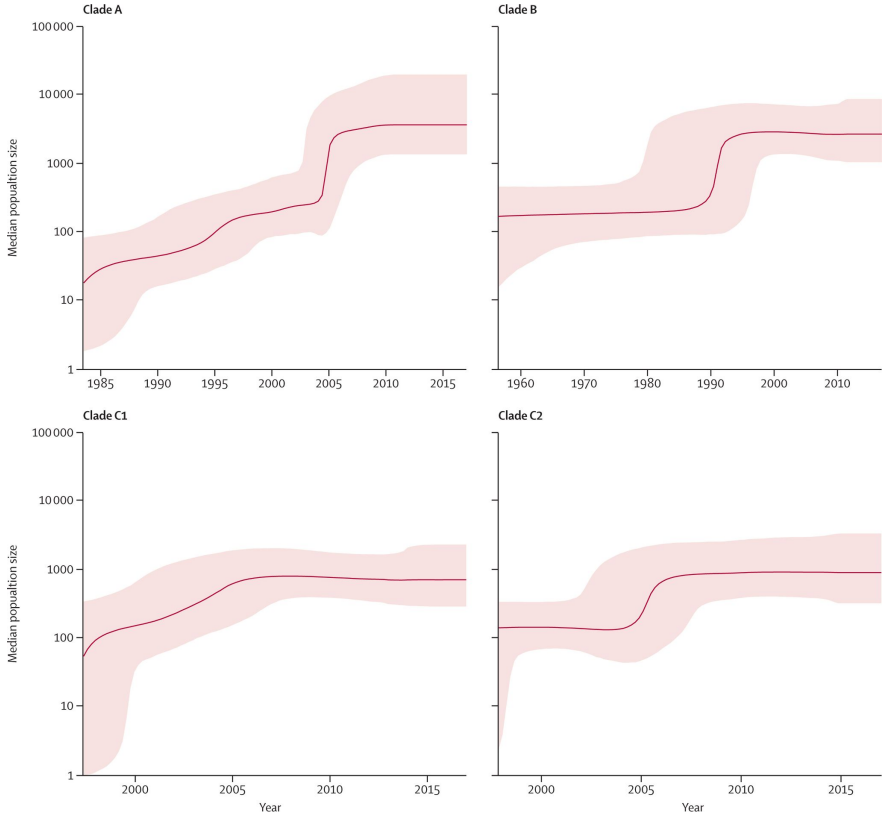
Spagnolo, Fabrizio, Monica Trujillo, and John J. Dennehy. "Why do antibiotics exist?." *MBio* 12.6 (2021): e01966-21.

Antimicrobial Resistances frequently co-occur

- Bacteria categorised based on degree of AMR:
  - Multidrug Resistant (MDR): AMR across ≥3 antibiotic classes
  - Extensively Drug Resistant (XDR): AMR to all but ≤2 antibiotics classes
  - Total/Pan-Drug Resistant (TDR/PDR): AMR to all antibiotic classes
- MDR more common in some priority pathogens e.g., ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp)*
- Rarely AMR not observed so far for some drug-bug combinations (e.g., penicillin resistance in *Streptococcus pyogenes*)

Acquisition of AMR can explode pathogen population size

- 2002-2017 Norwegian Surveillance Program (NORM) longitudinal cohort study of *E. coli* bloodstream infections (n=22,512)
- Genetic diversity of bacteria can be used to infer population size
- 3/4 subtypes of *E. coli* ST131 had near instantaneous population growth over 1-2 orders of magnitude
- Population explosions coincide with acquisition of CTX-M extended-spectrum β-lactamase



But how much AMR-related burden is there?

Integrated longitudinal surveillance across spatial scales

Surveillance Models:

- **Passive** - routine data collected during standard patient care (e.g., standard within-hospital microbiology)
- **Active** - systematic collection for surveillance with standardized protocols often including asymptomatic screening (MRSA/VRE screening, outbreak investigations, community carriage)
- **Syndromic** - monitor specific clinical manifestations related to AMR (e.g., treatment failures)
- **Sentinel** - network of selected representative sites for broader population or high-risk groups
- **Composite** - sampling of environmental aggregate mixed-sources (e.g., wastewater, feedlot, run-off, slaughterhouse effluent, aquaculture pond water, milk)

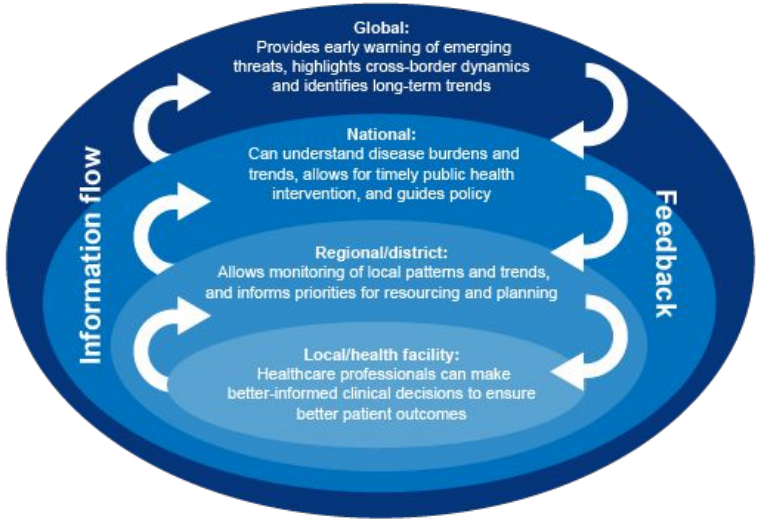
Geographic Scales:

- **Hospital** - internal microbiology
- **Regional** - hub labs/provincial public health reference labs
- **National** - national reference laboratories and sentinel coordination
- **Global** - large-scale data integration from networks of networks

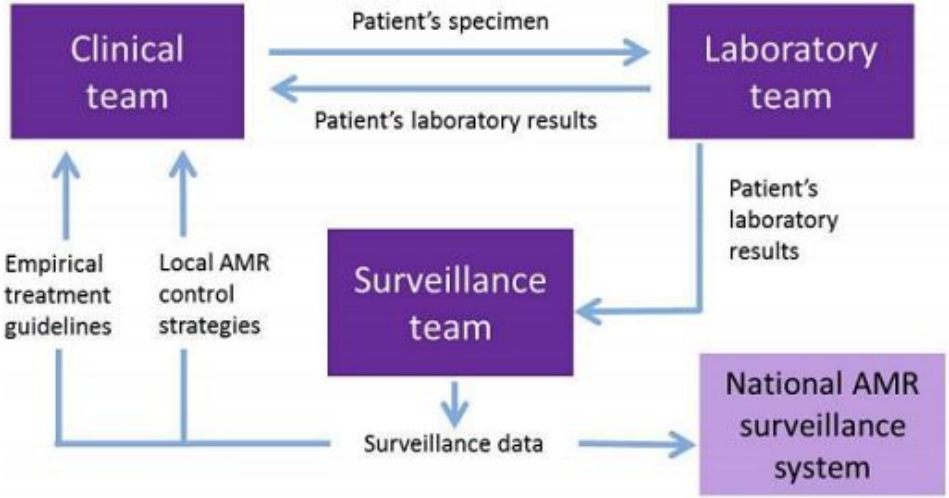
Subclinical and community hard to accurately surveill for humans and animals

Data collected includes some or all:

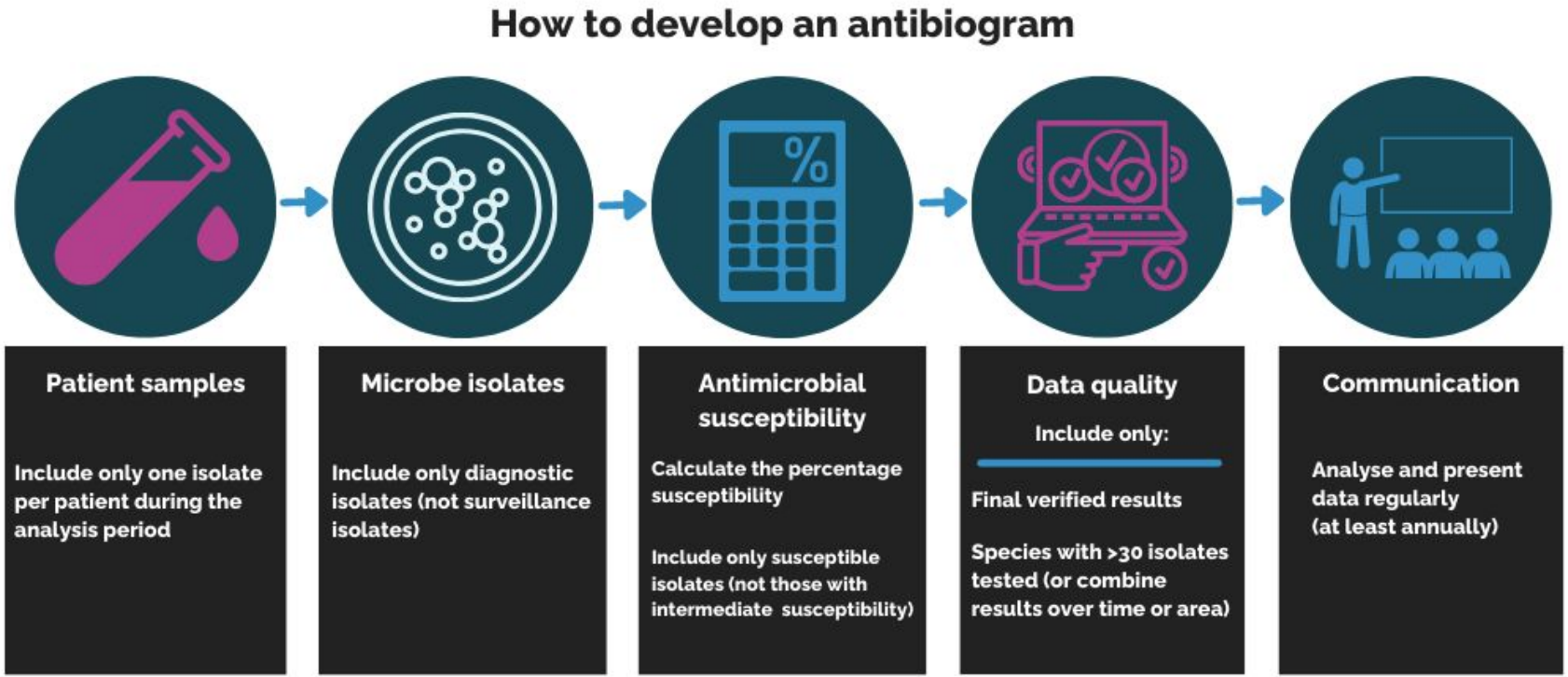
- Antibiotic Susceptibility
- Pathogen Typing Genome
- AMR Mechanism
- Treatment
- Clinical Outcomes



Local antimicrobial diagnostics and testing



Antibiogram - snapshot of local AMR incidence

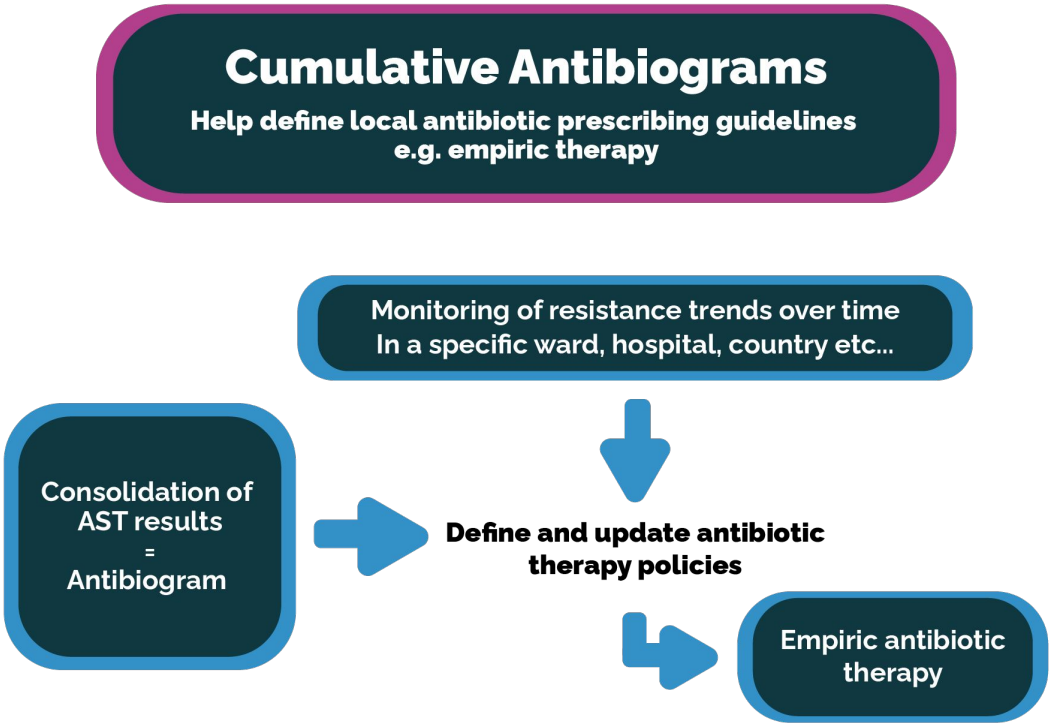


Antibiogram - snapshot of local AMR incidence

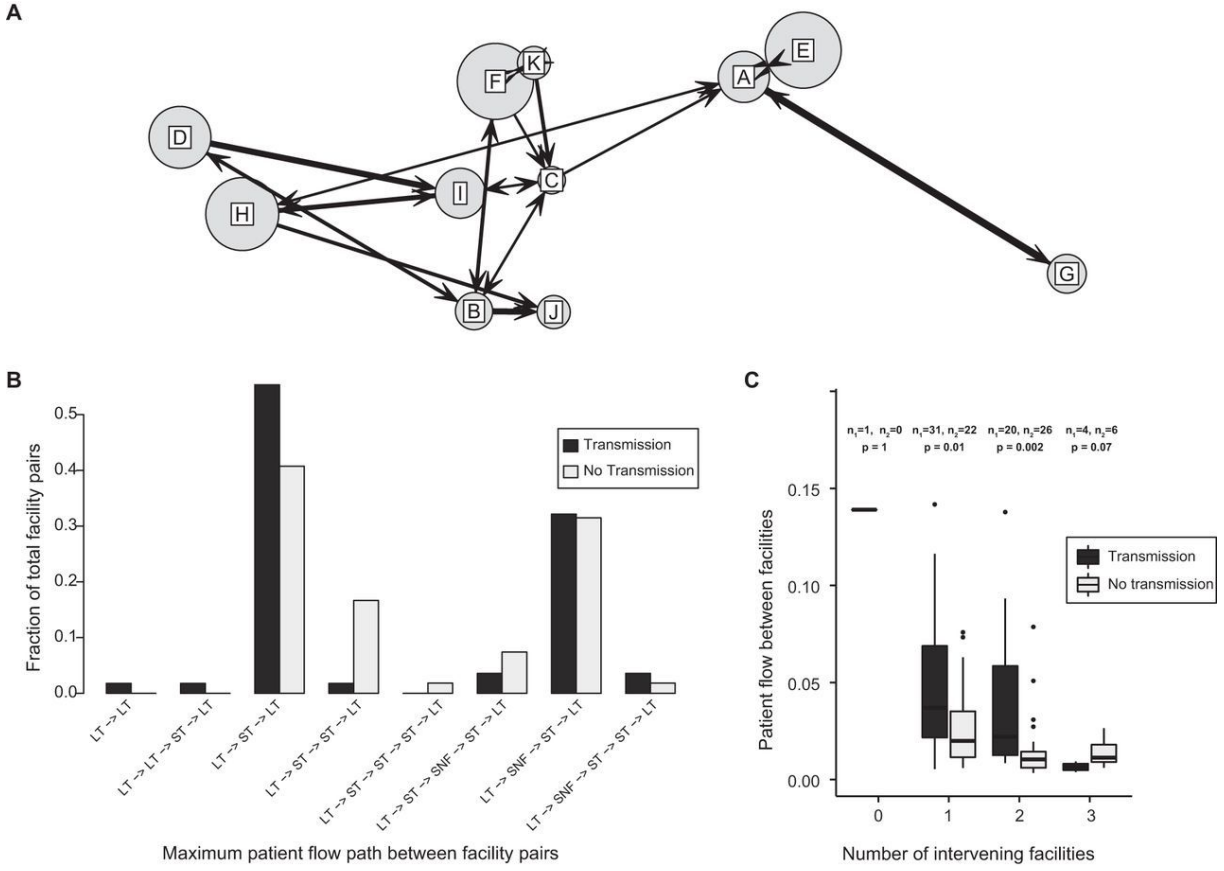
Gram-negative Bacteria	Isolates	β-Lactams																	
		Penicillins				Cephalosporins				Carbapenems			Aminoglycosides			FQ		Other	
	(N)	AMP	AMC	TZP	CZO	CXM	CTX	CAZ	FEP	IPM	MEM	ETP	AMK	GEN	TOB	CIP	ATM	SXT	NIT
Gram-negative bacteria (all)	34 932	28	69	89	59	63	73	-	83	91	95	96	95	880	85	68	69	68	76
Haemophilus influenzae	900	85	93	-	-	96	-	-	-	-	-	-	-	-	-	96	-	92	-
Moraxella catarrhalis	211	-	95	-	-	100	-	-	-	-	-	-	-	-	-	95	-	99	-
Enterobacteriaceae	27 972	28	70	92	60	-	75	-	84	95	99	98	98	89	87	67	79	68	-
Citrobacter koseri (diversus)	550	R	95	98	90	80	95	-	98	98	99	99	100	99	99	96	91	98	87
Enterobacter cloacae	802	R	R	86	R	51	79	-	92	91	98	94	99	93	93	86	86	89	48
Enterobacter aerogenes	543	R	R	85	R	R	82	-	95	65	98	98	100	95	94	85	88	92	25
Escherichia coli	16 810	36	74	93	59	66	71	-	81	99	99	99	99	89	86	62	76	60	94
Klebsiella pneumoniae	5 713	R	79	87	60	70	76	-	85	97	97	97	98	91	86	73	80	77	32
Klebsiella oxytoca	236	R	90	93	-	75	88	-	91	98	98	99	98	95	88	83	83	88	86
Morganella morganii	305	R	R	96	R	R	68	-	92	53	99	99	100	79	79	44	77	61	R
Proteus mirabilis	878	66	93	99	84	92	92	-	94	22	98	96	98	82	87	65	91	62	R
Providencia spp.	111	R	R	95	R	-	92	-	97	59	95	90	100	79	71	68	-	84	R
Salmonella spp. (non-typhoid)	566	86	92	99	-	-	97	-	99	-	-	-	-	-	-	-	-	96	-
Salmonella Typhi/Paratyphi	267	73	81	92	-	-	81	-	71	-	-	-	-	-	-	-	-	73	-
Serratia marcescens	652	R	R	95	R	R	91	-	97	71	98	98	100	97	89	87	98	98	R
Shigella spp.	79	37	72	98	-	-	65	-	78	-	-	-	-	-	-	52	-	48	91
Non-fermenting gram-neg rods	5 638	R	R	77	-	-	-	82	80	76	76	R	82	82	80	73	56	72	-
Acinetobacter baumannii	750	R	R	72	-	-	-	70	70	78	76	R	89	77	77	73	R	82	-
Pseudomonas aeruginosa	3 728	R	R	91	-	R	R	87	90	84	83	R	95	91	95	82	68	R	R
Stenotrophomonas maltophilia	479	R	R	R	-	-	R	66	-	R	R	R	R	R	R	-	R	87	-

FQ = fluoroquinolones, N = number, spp. = species, R = intrinsically resistant, (-) = no data available, or small number of isolates tested (N<30), or antimicrobial agent is not indicated, or not effective clinically.
Interpretation standard: CLSI M100 ED29:2019. Presentation standard: CLSI M39-A4:2014.
AMC = Amoxicillin/Clavulanic acid, **AMK** = Amikacin, **AMP** = Ampicillin, **ATM** = Aztreonam, **CAZ** = Ceftazidime, **CIP** = Ciprofloxacin, **CTX** = Cefotaxime, **CXM** = Cefuroxime, **CZO** = Cefazolin, **ETP** = Ertapenem, **FEP** = Cefepime, **GEN** = Gentamicin, **IPM** = Imipenem, **MEM** = Meropenem, **NIT** = Nitrofurantoin, **SXT** = Trimethoprim/Sulfamethoxazole, /Clavulanic acid, **TOB** = Tobramycin, **TZP** = Piperacillin/Tazobactam.

Antibiogram - snapshot of local AMR incidence



Regional surveillance - Long Term Acute Care Hospitals



Regional transmission map for carbapenem-resistant *K. pneumoniae* (CRKP) among 11 Los Angeles area LTACHs.

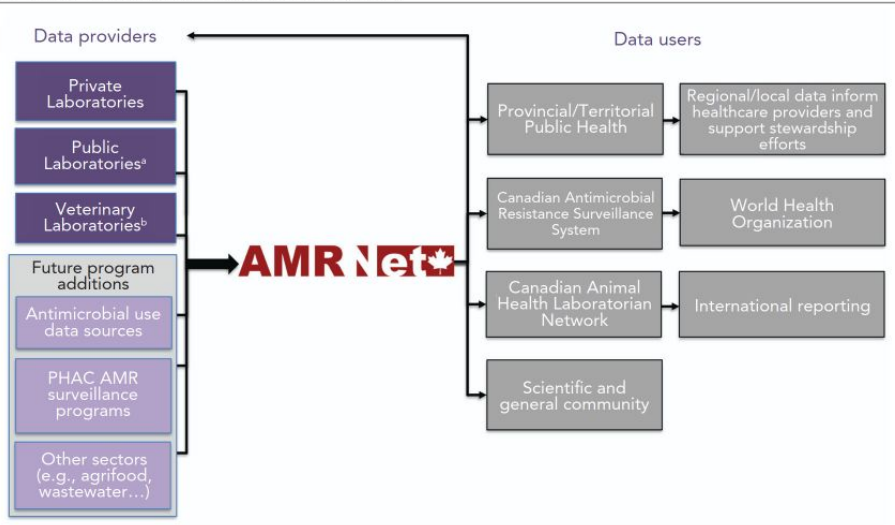
Han, Jennifer H., et al. "Whole-genome sequencing to identify drivers of carbapenem-resistant Klebsiella pneumoniae transmission within and between regional long-term acute-care hospitals." Antimicrobial agents and chemotherapy 63.11 (2019): 10-1128.

National - Canadian AMR Surveillance System (CARSS)

Consolidates data from 10 federal surveillance programs across human and animal health (across PHAC, CFIA, DFO, and HC-VDD)

- **AMRNet** - national laboratory-based surveillance system for human and animal (AMRNet-Vet) AMR data
- **Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)** - AMU/AMR for select bacteria from humans, animals and retail meat
- **Canadian Nosocomial Infection Surveillance Program** (CNISP) - hospital infections
- **National Microbiology Laboratory** (NML) - national reference laboratory
- **Canadian Primary Care Sentinel Surveillance Network (CPCSSN) -** community/primary-care AMU
- **Taxa-specific Programs**: Gonococcal Antimicrobial Surveillance Program (**GASP-Canada**), Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea (**ESAG**), National Laboratory Surveillance of Invasive Streptococcal Disease in Canada (**eSTREP**), Canadian Tuberculosis Laboratory Surveillance System (**CTBLSS**)
- **Veterinary Antimicrobial Sales Reporting** (VASR)

Figure 1: Data flow for AMRNet surveillance system



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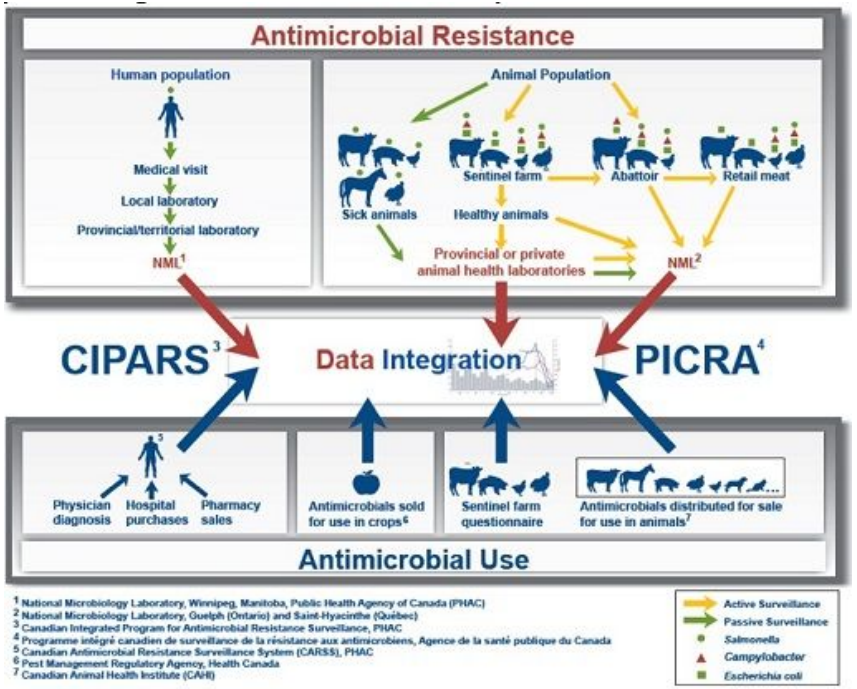

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Antimicrobial-Resistant G
Surveillance of Invasive S
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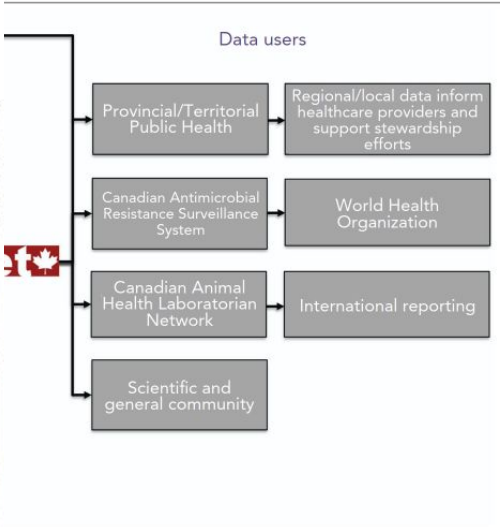
System (**CTBLSS**)
- **Veterinary Antimicrobial**

Public Health Agency not renewing contracts of over 800 employees, including 245 at Winnipeg lab: union

PHAC says contracts of temporary employees will end as COVID-19 funding dries up

CBC News · Posted: Jan 23, 2025 6:58 PM EST | Last Updated: January 23

The union representing Public Health Agency of Canada employees says contracts aren't being renewed for 800 employees, including 245 at the National Microbiology Lab in Winnipeg. (John Woods/The Canadian Press)

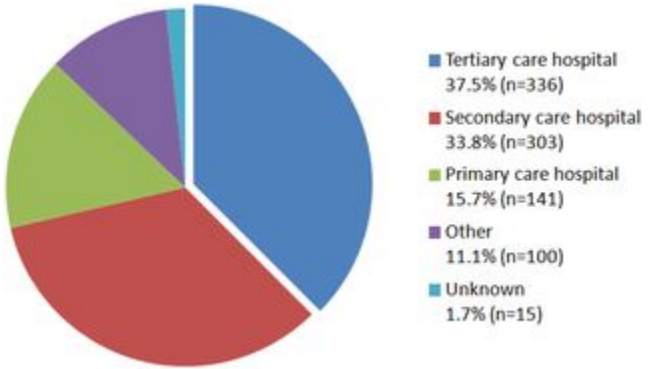


Regional - European Antimicrobial Resistance Surveillance Network (EARS-NET)

Expansion of earlier EARSS (1998-2010) - individual countries submit data in a standard format and EARS-NET collates/cleans/normalises

EARS-NET requires member countries to submit information on antimicrobial susceptibility results for specific pathogens causing invasive infections:

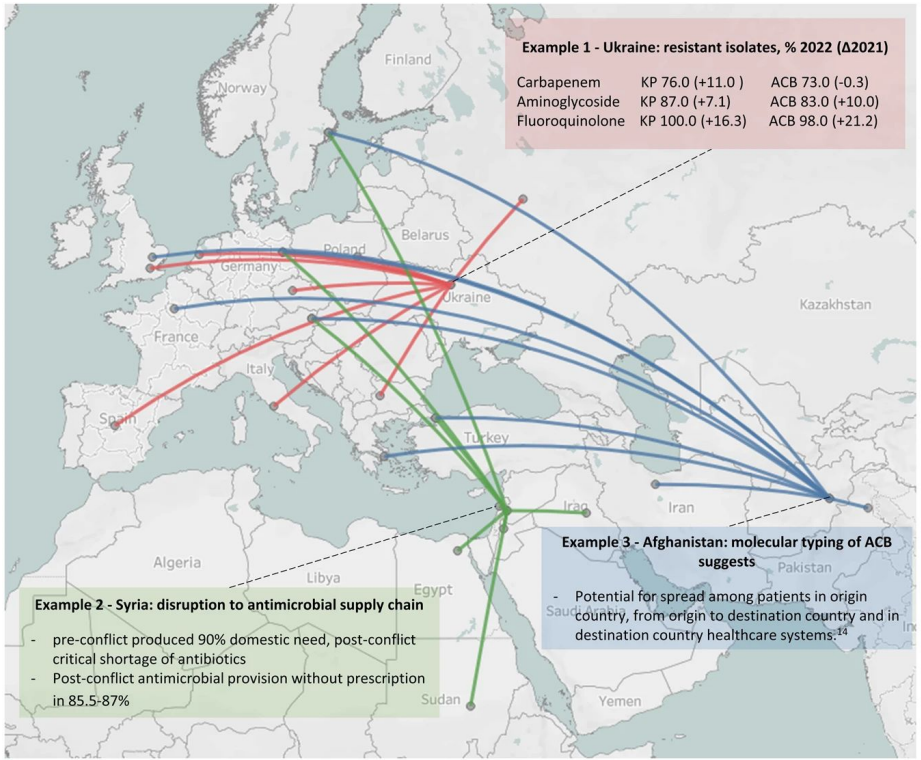
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter species*
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium.*



Heterogeneous population coverage (large surveillance networks vs sentinel sites)

Over-representing national referral centers and tertiary care hospitals

War, disruption, and displacement drives growth of AMR

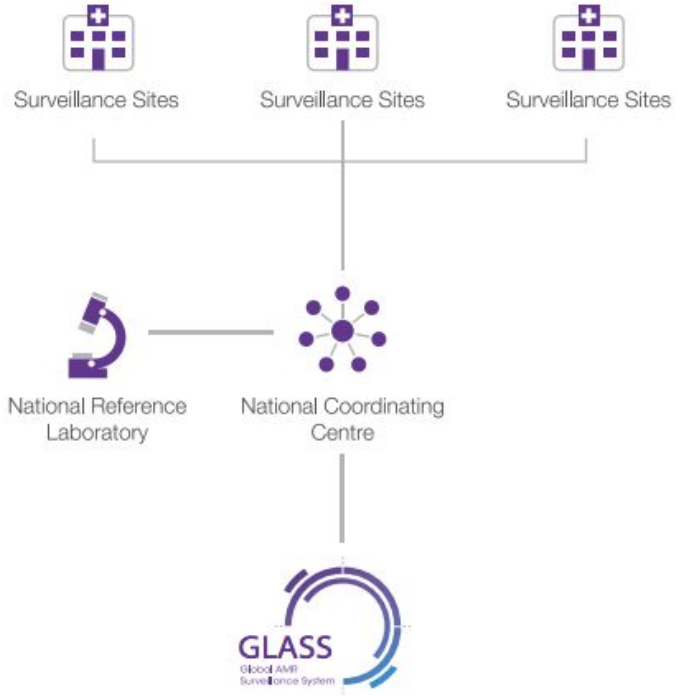


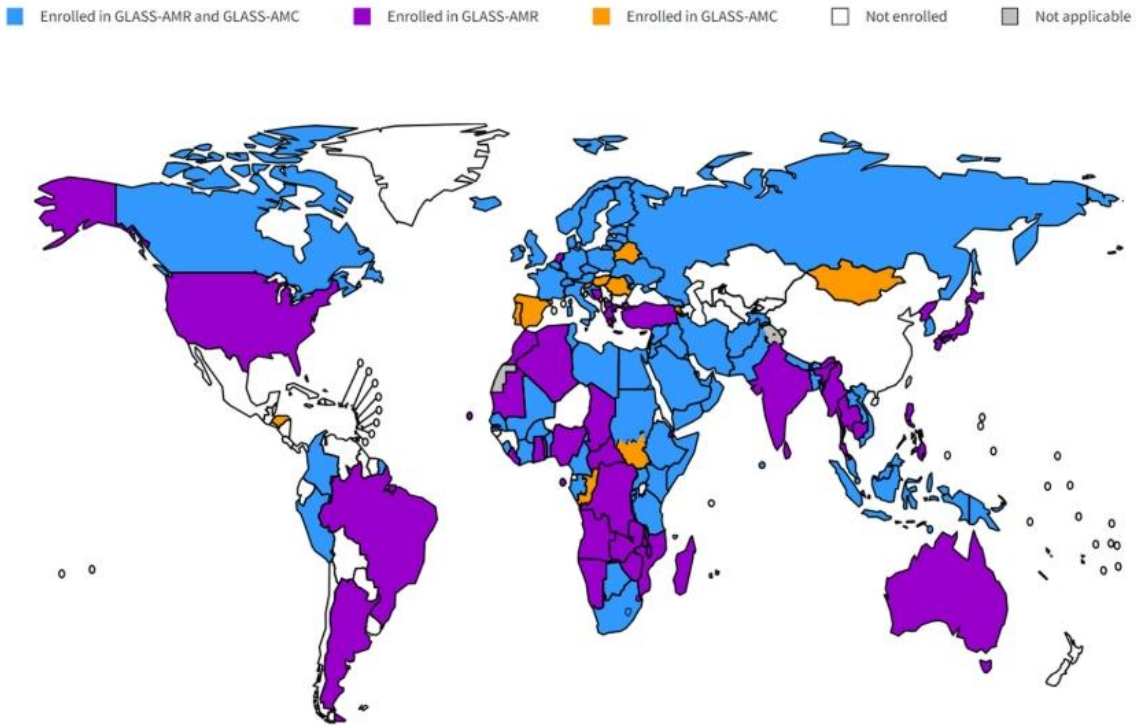
From	Population	Displaced to
Ukraine	6411343	Ukraine
	1275925	Russia
	1004382	Germany
	958519	Poland
	433638	Czechia
	183399	UK
	162672	Spain
	151750	Italy
	149231	Bulgaria
	103647	Netherlands
Syria	3535898	Turkey
	2224580	Syria
	817047	Lebanon
	660892	Jordan
	576793	Germany
	257439	Iraq
	145658	Egypt
	112432	Sweden
	93478	Sudan
	91167	Austria
Afghanistan	4457522	Afghanistan
	3413249	Iran
	1781419	Pakistan
	215677	Germany
	139394	Turkey
	74636	France
	52701	Austria
	38246	Greece
	28249	Sweden

KP = *Klebsiella pneumoniae* ACB = *Acinteobacter baumanii* Δ = change

Pallett, Scott JC, et al. "The contribution of human conflict to the development of antimicrobial resistance." *Communications medicine* 3.1 (2023): 153.

AMR Surveillance: WHO GLASS

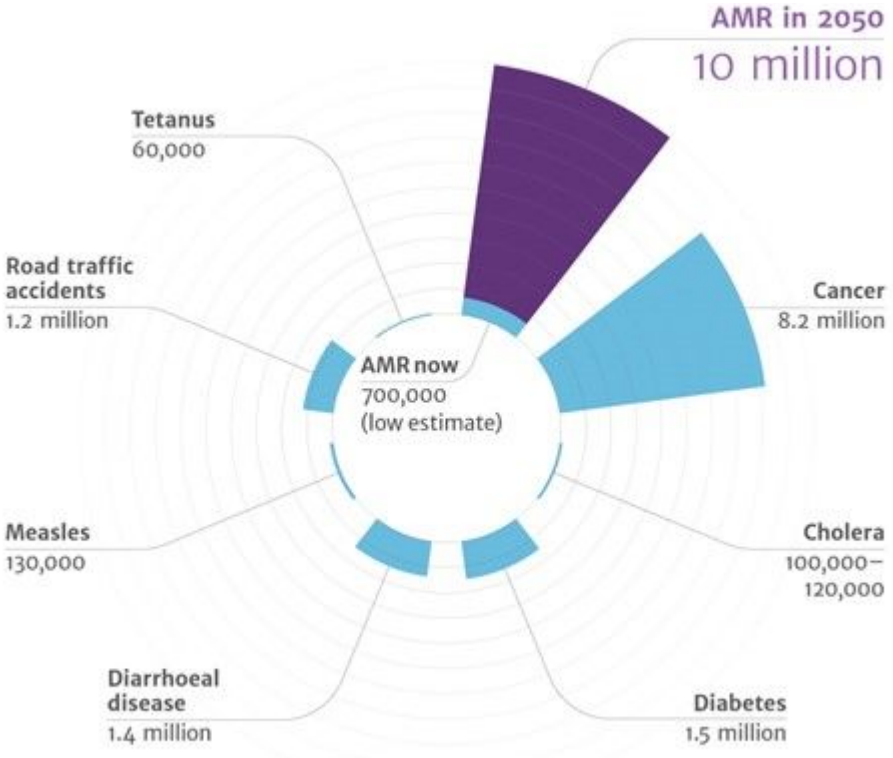




Combining these data sources to estimate current and future global burden of AMR

O’Neill Report

- KPMG created extrapolation from EARS-Net AMR-associated mortality data
  - EARS-Net only captures invasive disease for a subset of pathogens
  - Over-represents tertiary care
  - Europe only
  - Variability in frequency of blood culture sampling
  - => Biased estimation of current deaths
- Unclear method for extrapolating BSIs to other sites
- National estimates extrapolated from EARS-Net mortality by catchment or average rate multiplied by population
- Criticised by UK National Office for Animal Health for not adequately including antibiotic use in animals



de Kraker, Marlieke EA, Andrew J. Stewardson, and Stephan Harbarth. "Will 10 million people die a year due to antimicrobial resistance by 2050?." *PLoS medicine* 13.11 (2016): e1002184.

Other burden studies

- Many papers estimating effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for pathogen–drug pairs in specific locations

- US CDC 2013 & 2019 reports in USA for 18 pathogen-antibiotics pairs
- EU and European Economic Area for 2007–15 for 16 pathogen-antibiotic pairs

Cassini, Alessandro, et al. "Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis." The Lancet infectious diseases 19.1 (2019): 56-66.

- Thailand MDR burden in 2010 (Lim et. al.)

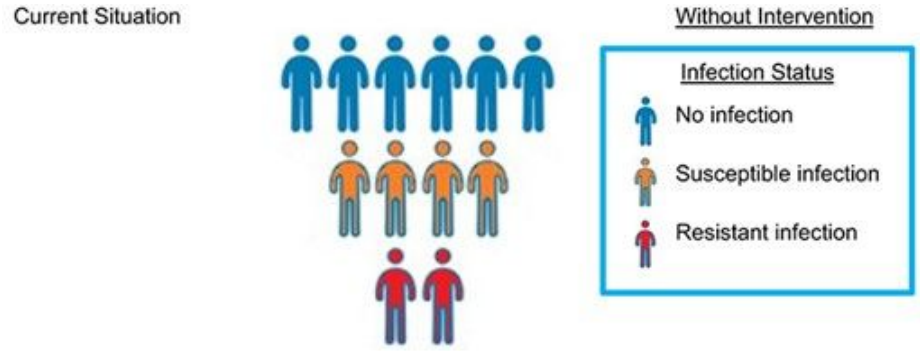
Lim, Cherry, et al. "Epidemiology and burden of multidrug-resistant bacterial infection in a developing country." elife 5 (2016): e18082.

- E. coli and K. pneumoniae resistant to 3rd generation cephalosporins and carbapenems in 193 countries in 2014 (Temkin et. al.,)

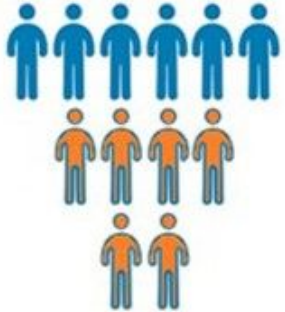
Temkin, Elizabeth, et al. "Estimating the number of infections caused by antibiotic-resistant Escherichia coli and Klebsiella pneumoniae in 2014: a modelling study." *The Lancet Global Health* 6.9 (2018): e969-e979.

Counterfactual Challenge in AMR Burden Estimation

*How much harm is done by antibiotic-resistant infections, **relative to the harm the same infections would do if they were susceptible** to all antimicrobial drugs that are normally effective against that species of bacteria?*



Susceptible-Infection Counterfactual

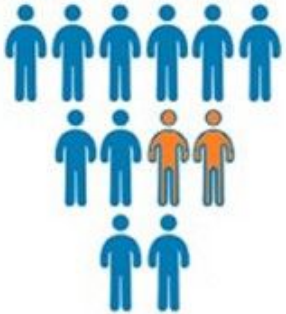


With Intervention

- Reduced human/veterinary antibiotic use (1, 7)
- Improved antibiotic choice (2)
- Vaccination reducing secondary infections (4b)
- New antibiotics (6)

*How much harm is done by antibiotic-resistant infections, **relative to a situation in which such infections did not occur** at all because they were prevented (e.g., by better infection control or a vaccine?)"*

No-Infection Counterfactual



With Intervention

- Infection prevention and control (3)
- Vaccination against bacterial pathogens (4a)
- Water, Sanitation and Hygiene (WASH) (5)
- Reduced livestock transmission (8)

de Kraker, Marlieke EA, and Marc Lipsitch. "Burden of antimicrobial resistance: compared to what?." Epidemiologic reviews 43.1 (2021): 53-64.
Dunachie, Susanna J., Nicholas PJ Day, and Christiane Dolecek. "The challenges of estimating the human global burden of disease of antimicrobial resistant bacteria." Current Opinion in Microbiology 57 (2020): 95-101.

Global Burden of Disease - AMR (IHME Study)

Estimate: Global burden (205 countries & territories) for 23 pathogens and 88 pathogen–antibiotic combinations using systematic literature reviews, hospital systems, surveillance systems

AMR attributable deaths

- *Most conservative estimate of AMR burden*
- Attributable deaths measures people who would not have died of infection if it was treatable (i.e., if there was no AMR) for whom resistance can be said to have caused their death.
- Counterfactual: resistant infections replaced by susceptible infection

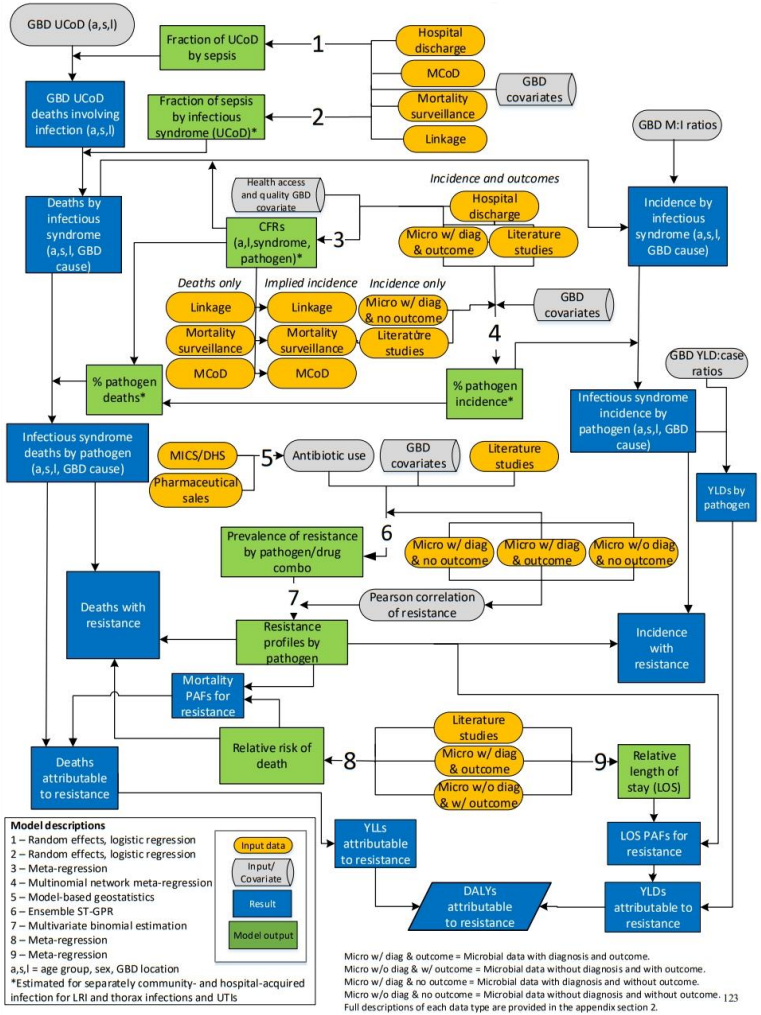
AMR associated deaths

- *Most inclusive estimate of AMR burden*
- Associated deaths measures people with a drug-resistant infection that contributed to their death. The infection was implicated in their death, but resistance may or may not have been a factor
- Counterfactual: resistant infections replaced by no infection

Data: 471 million individual records or isolates covering 7,585 study-location-years from literature, GBD partners, national surveillance systems, individual institutes, and industry

Global Burden of AMR Study

Source type	Number of study-location-years	Sample size	Sample size units	Estimation step								
				1: sepsis	2: infectious syndrome	3: case-fatality ratio	4: pathogen distribution	5: antibiotic use	6: prevalence of resistance	7: resistance profiles	8: relative risk of death	9: relative length of stay
Multiple cause of death	2980	120 871 372	Deaths									
Hospital discharge	391	192 533 415	Discharges									
Microbial or laboratory data with outcome	1102	3 060 802	Isolates									
Microbial or laboratory data without outcome	2302	145 067 113	Isolates									
Literature studies	607	701 356	Cases, isolates, or pathogen–drug susceptibility tests									
Single drug resistance profiles	158	8 648 390	Pathogen–drug susceptibility tests									
Pharmaceutical sales	1536	1536	Study-country-years									
Antibiotic use among children younger than 5 years with reported illness	203	151 455	Households surveyed									
Mortality surveillance (minimally invasive tissue sampling from Child Health and Mortality Prevention Surveillance)	7	870	Deaths									
Linkage (mortality only)	38	264 010	Deaths									
Grand total	**9324**	**471 300 319**										



Estimation steps 1 & 2: deaths in which infection played a role by infectious syndrome

- **Data**: Multiple Causes of Death (121 million deaths, 5.54 million death hospital discharges, 264,000 MCoD from 10 countries, 870 deaths from Child Health and Mortality Prevention Surveillance sites in 6 countries)
- **Estimate fraction of infection-related deaths** (sepsis cause/pathway to death) in GBD cause-specific mortality estimates
  - Communicable; Maternal; Neonatal; Nutritional; Non-Communicable; Injury

- **Subdivide sepsis deaths for each GBD category** into 12 infectious syndromes using logistic regression
  - Infections of bones, joints, and related organs; Bloodstream infections; Endocarditis and other cardiac infections; Meningitis and other bacterial CNS infections; Peritoneal and intra-abdominal infections; Lower respiratory infections and all related infections in the thorax; Bacterial infections of the skin and subcutaneous systems; Typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp.; Urinary tract infections and pyelonephritis.

Estimation steps 3 & 4: pathogen distribution for deaths and incident cases

- **Estimate pathogen-specific CFRs** by location and syndrome (Healthcare Access and Quality Index covariate) with Bayesian meta-regression
- **Calculate implied incidence per pathogen** by mapping CFR estimates onto pathogen-specific death data

- **Estimate the pathogen distribution per infectious syndrome** using multinomial estimation (trimmed constrained mixed effort model & network analysis)

Estimation steps 5-7: prevalence of AMR per pathogen

- **Data:** Microbiological data from 52.8 million bacterial using CLSI standards (largely high-income countries and tertiary referrals centers)

- **Estimate proportion resistant** for 88 pathogen-antibiotic combinations (drop
  - 88 combinations selected based on clinical relevance and minimum data availability
- **Estimate the prevalence of resistance** in each dyad by location with two-stage spatiotemporal modelling
- **Estimate AMC by location** (correlation between AMC and AMR)
- **Estimate resistance co-occurrence** (multidrug resistance)

Estimation steps 8 & 9: Relative risk of death resistant vs sensitive infections

- **Data**: 511,870 patients with death and AMR data; 455,909 with length of stay

- **Estimate relative risk of death** for each dyad R vs S - assumed the relative risk was the same for every syndrome, location, and age group
- **Estimate non-fatal excess risk** using relative increase in length of stay per dyad R vs S
- **Estimate population-attributable fraction** (PAF) for each resistance profile with resistance to at least one drug - proportional reduction in deaths or years lived with disability (YLDs) that would occur if all infections with the resistance profile of interest were instead susceptible (prevalence * relative risk / normalised over profiles)

Estimation Step 10: Putting it all together

AMR attributable burden per pathogen-antibiotic combination:

- **Years of Life Lost (YLL):** Deaths for each GBD category * Proportion sepsis-related * Proportion attributable to each syndrome * Proportion of syndrome deaths attributable to each pathogen * Mortality PAF for each resistance profile.
- **Years Living w/ Disability (YLDs):** syndrome incidence * Proportion of syndrome cases attributable to each pathogen * YLDs per incident case * non-fatal PAF
- **Disability-Adjusted Life Years (DALYs) = YLLs + YLDs**

AMR associated burden per pathogen-antibiotic combination:

- YLLs: Same calculation but using prevalence of resistance in deaths instead of PAF
- YLDs: Syndrome incidence * Proportion of infectious incident cases per pathogen * Prevalence of resistance * YLDs per incident case per syndrome

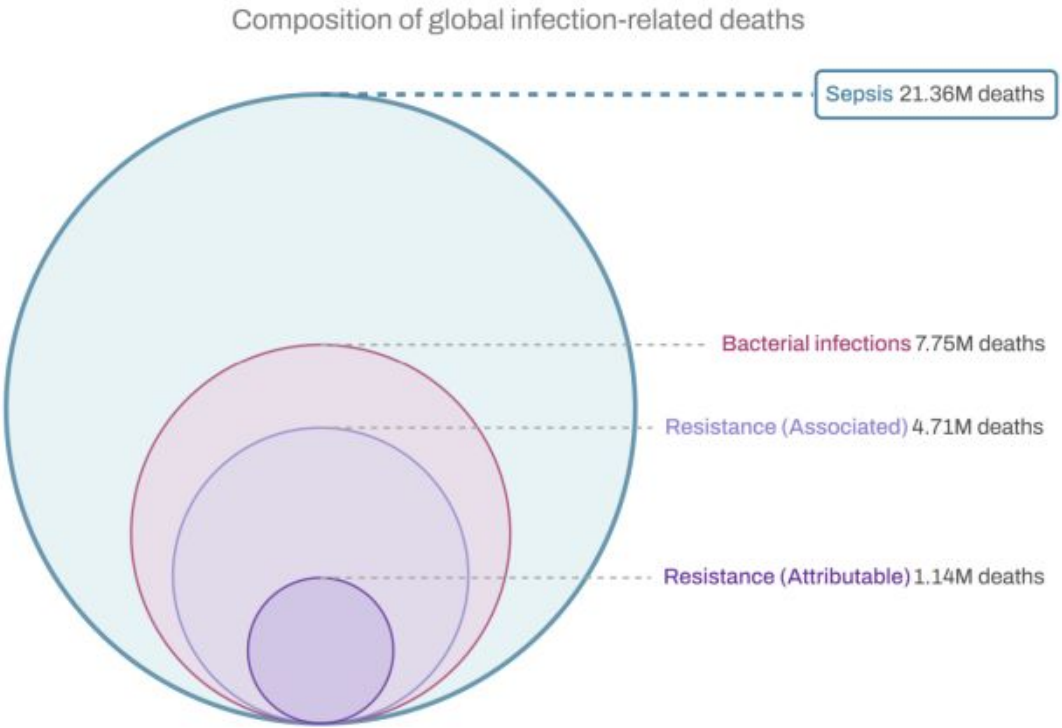
Data very sparse

- Highest burden regions have least data
- Sepsis (life-threatening organ dysfunction due to a dysregulated host response to infection) not only route to infection-related death (although probably majority)
- Big inferences drawn from very limited/biased data (especially towards tertiary care)
- Data for sepsis and infectious syndrome from only 16 high-income countries

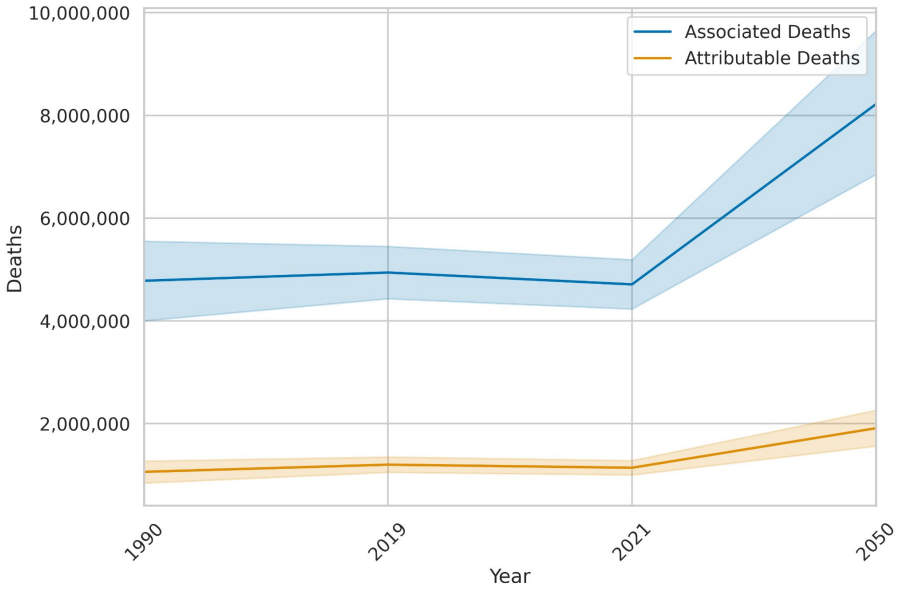
Region	1. Sepsis and Infectious Syndrome Models*	Fraction of countries represented in 1.	2. Case Fatality Rate	Fraction of countries represented in 2.	3. Pathogen Distribution	Fraction of countries represented in 3.	4. Fraction of Resistance**	Fraction of countries represented in 4.	5. Relative Risk	Fraction of countries represented in 5.
Andean Latin America	0	0/3	1,784	2/3	12,010	2/3	538,644	3/3	4,338	2/3
Australasia	320,909	1/2	94,818	1/2	6,294,677	2/2	4,653,832	2/2	5,211	2/2
Caribbean	0	0/19	2,858	5/19	6,225	5/19	68,078	10/19	529	1/19
Central Asia	0	0/9	43,852	2/9	2,785	1/9	304,341	9/9	6,065	1/9
Central Europe	0	0/13	371,112	10/13	627,844	11/13	3,148,864	13/13	397,885	10/13
Central Latin America	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Central Sub-Saharan Africa	0	0/6	0	0/6	770	2/6	40243	6/6	0	0/6
East Asia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Eastern Europe	0	0/7	118,754	4/7	64,212	5/7	968,565	7/7	102,904	4/7
Eastern Sub-Saharan Africa	292	3/15	6,388	4/15	68,791	9/15	474,280	14/15	3,436	2/15
High-income Asia Pacific	0	0/4	135,907	3/4	99,042	3/4	118,909,332	4/4	7,577	3/4
High-income North America	84,520,574	2/3	7,184,424	3/3	7,255,147	2/3	32,205,001	3/3	14,071,025	2/3
North Africa and Middle East	0	0/21	209,479	13/21	53,833	16/21	531,120	21/21	90,079	10/21
Oceania	0	0/18	0	0/18	20	1/18	4,297	12/18	0	0/18
South Asia	54	1/5	77,811	4/5	51,810	4/5	1,413,840	5/5	97,131	4/5
Southeast Asia	0	0/13	195,087	9/13	91,259	8/13	3,128,014	12/13	172,947	8/13
Southern Latin America	0	0/3	200,665	3/3	73,512	2/3	740,385	3/3	5,000	1/3
Southern Sub-Saharan Africa	4,696,789	1/6	80,717	2/6	4,699,304	2/6	910,509	6/6	1,051	1/6
Tropical Latin America	17,224,511	1/2	3,988,611	1/2	20,956,932	2/2	286,450	2/2	6,443	1/2
Western Europe	10,599,906	2/24	94,506,554	20/24	105,183,184	21/24	18,909,732	21/24	932,016	21/24
Western Sub-Saharan Africa	83	2/19	26,985	9/19	21,896	10/19	369,482	18/19	14,880	2/19

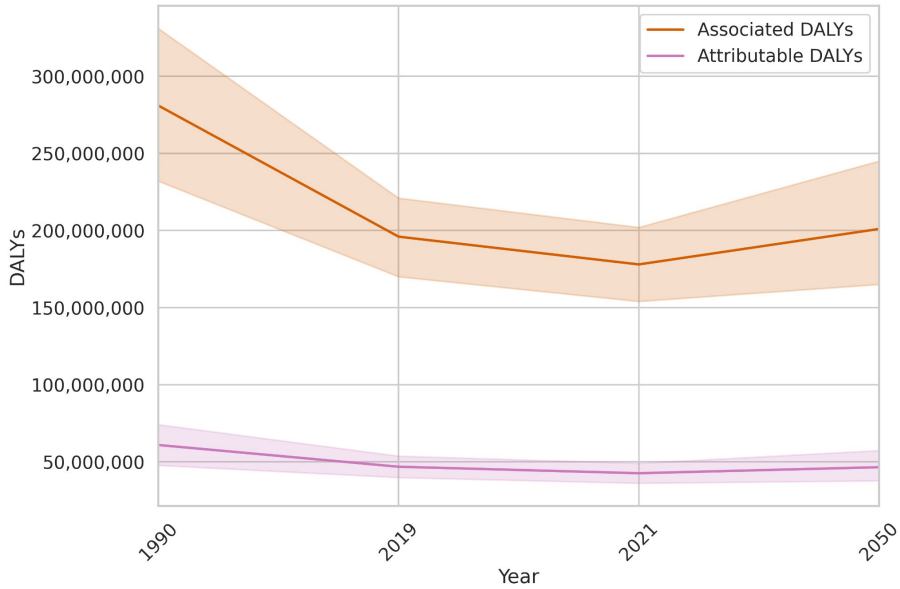
What does this surveillance tell us?

AMR small but notable subset of infection-related deaths



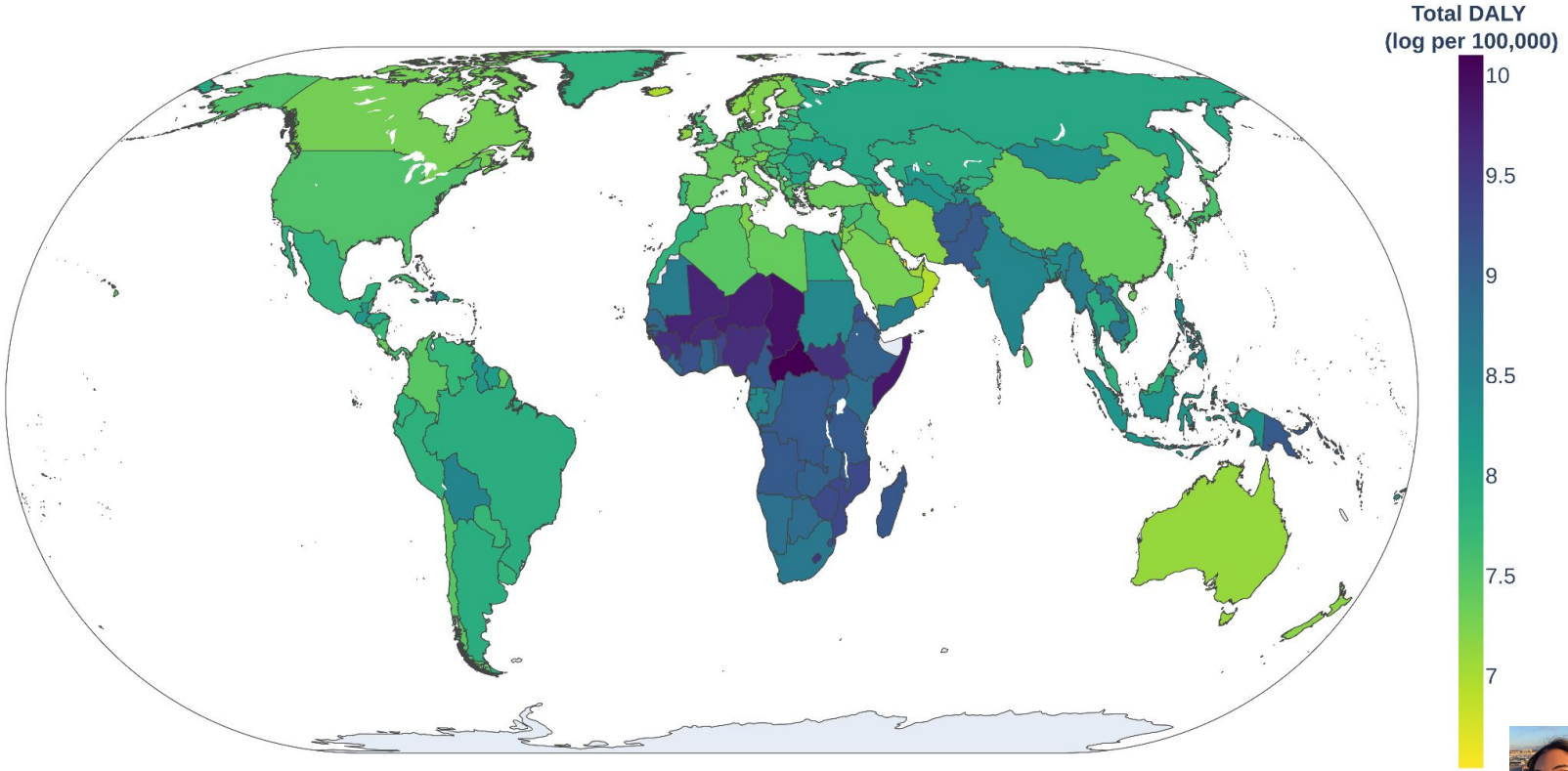
Considerable and Growing AMR Burden Globally



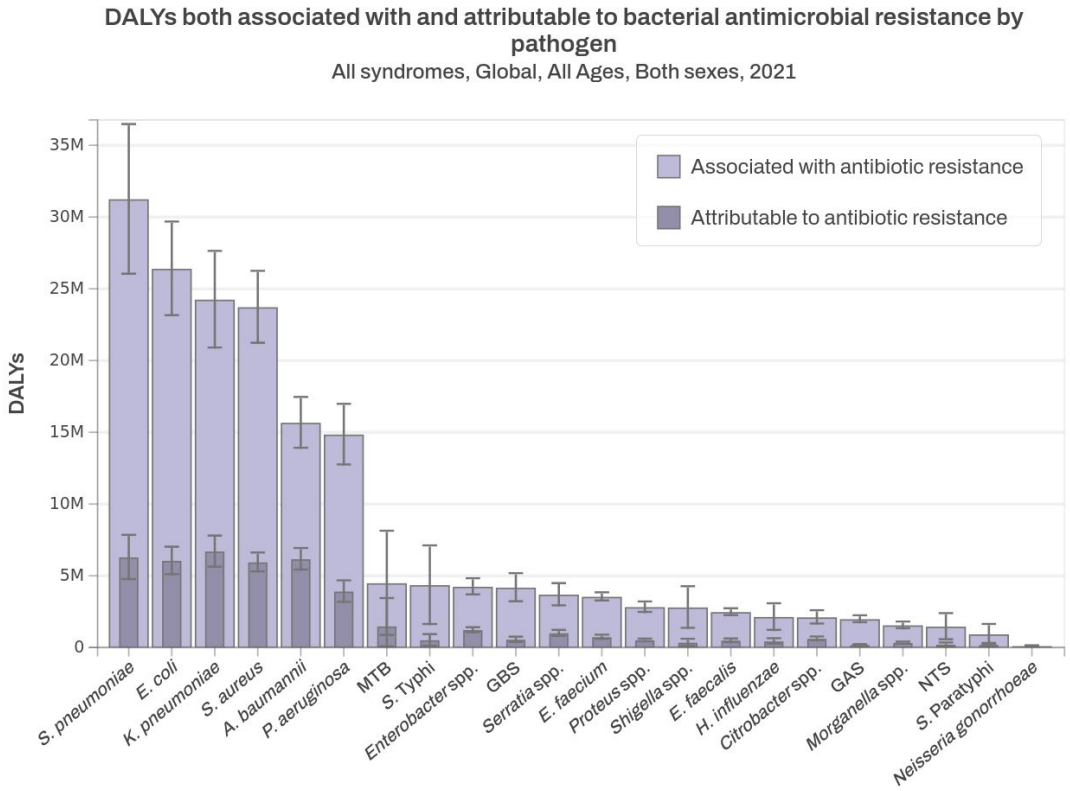


Data from: Naghavi, Mohsen, et al. "Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050." The Lancet 404.10459 (2024): 1199-1226.

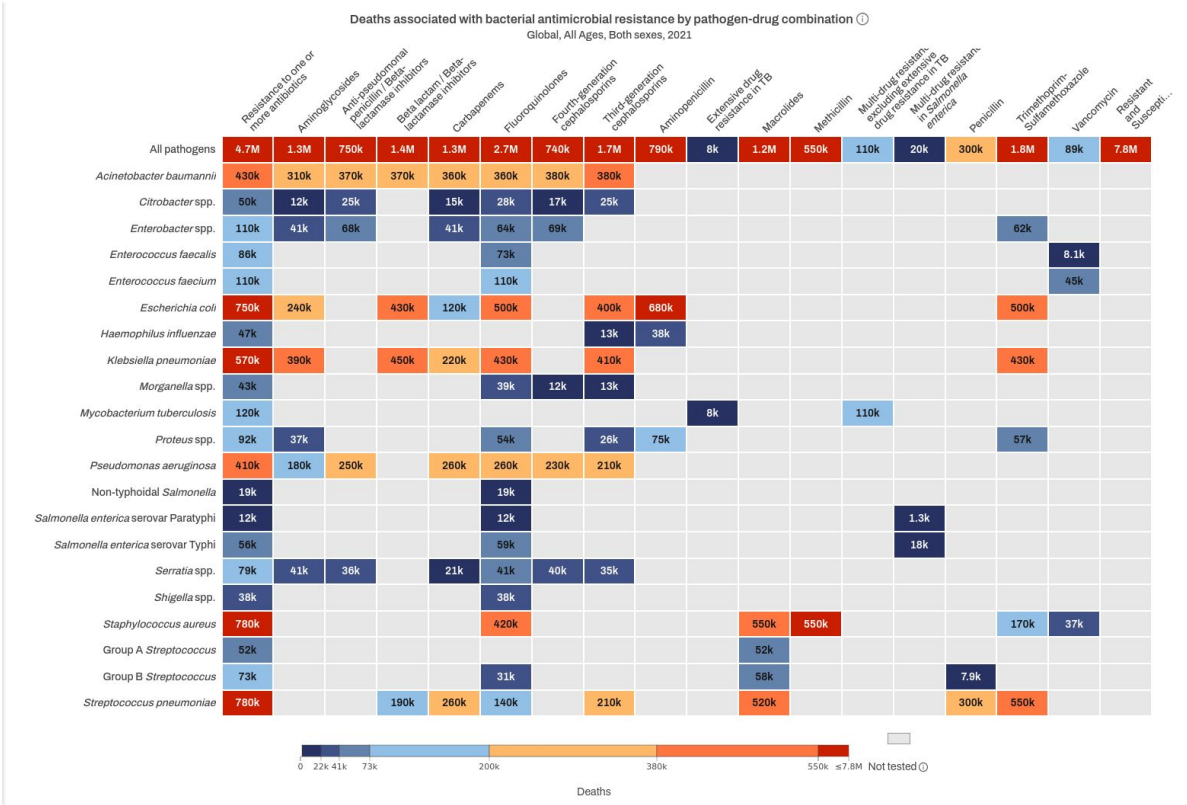
AMR Burden is unequally distributed globally



Burden of AMR higher in some organisms



Burden of AMR higher in some drug-bug pairs



Summary

1. Antimicrobials

- *Selective action, favourable PK/PD*
- *Antivirals/fungals/parasitics hard to develop due to overlap between host and microbe*
- *Antibiotics have many targets e.g., cell wall (beta-lactams), protein synthesis (macrolides & tetracyclines), and transcription (quinolones)*
- *Antibiotic organised into mechanistic families (or other properties/usage groups)*
- *Antibiotic usage driven by broad-spectrum penicillins in human and tetracyclines in animals*

2. Antimicrobial Resistance

- *Antibiotic Susceptibility Testing measures resistance measured but defining resistance is non-trivial and context dependent (i.e., ECOFFs vs Clinical Breakpoints)*
- *Many mechanisms of AMR (e.g., antibiotic inactivation, target modification, efflux/permeability)*
- *AMR is ancient and can evolves rapidly via mutation and LGT*
- *Surveillance of AMR is complicated and occurs at multiple geographic and technical scales*
- *High global burden of AMR but accurate measurement is difficult*

3. Solutions to Antimicrobial Resistance

- Improving Surveillance
- New Antimicrobials
- Alternatives to Antimicrobials
- Antimicrobial Stewardship
- Improved Rapid Diagnostics

What can we do about AMR?

National and international AMR action plans

National Action Plans

WHO Regional Office for Africa

1 January 2018

Burkina Faso: National multisectoral strategic plan to combat antimicrobial resistance (French)

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Ghana: National action plan for antimicrobial use and resistance

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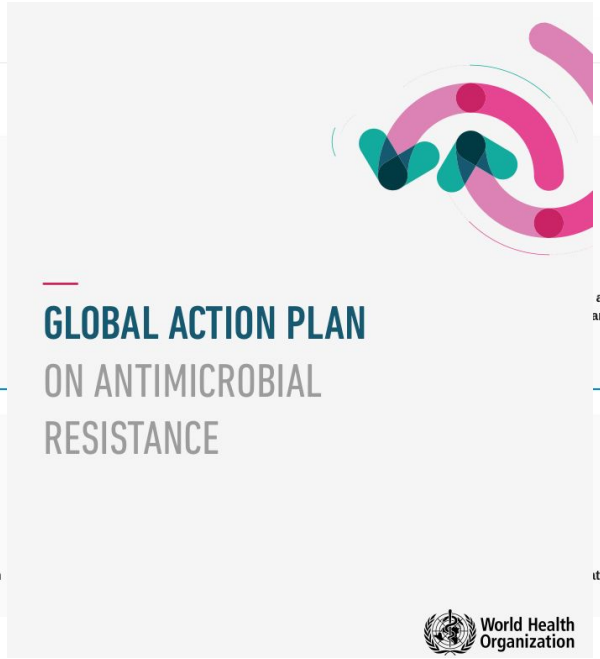
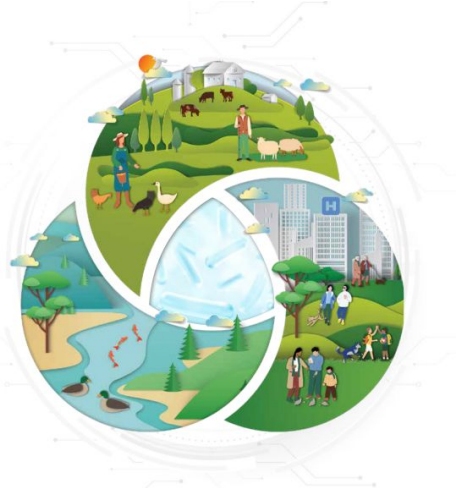




Pan-Canadian Action Plan on Antimicrobial Resistance

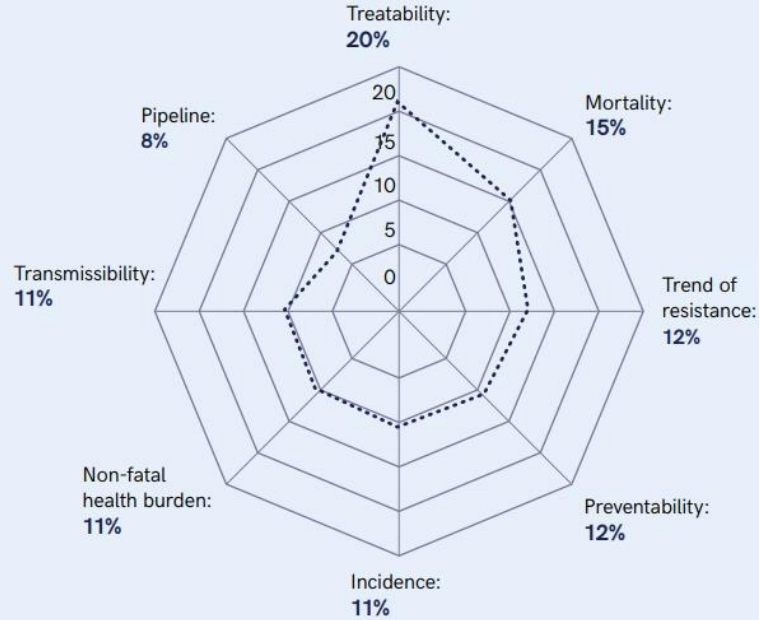
National and international AMR action plans

resistance 2017-2022

1. Better understanding of AMR and AMR evolution: surveillance, research
2. New antimicrobials
3. Better use of existing antimicrobials:
    - Fewer infections: vaccines, sanitation, healthcare access, public health
    - More efficient: rapid diagnostics, resistance profiles

Organization

WHO Priority Pathogens 2024



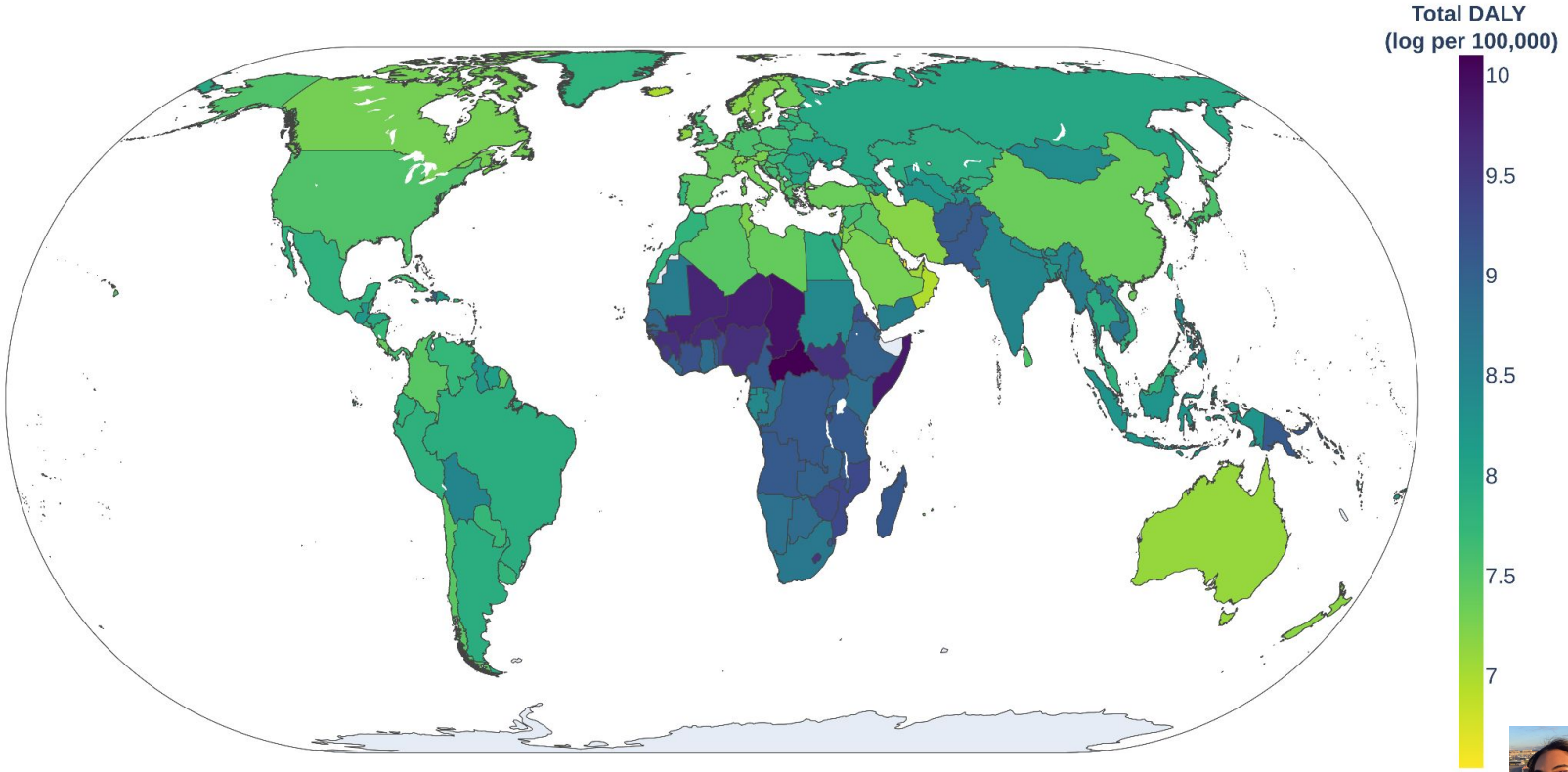
Spearman rank correlation = 0.9

Kendall's W = 0.871

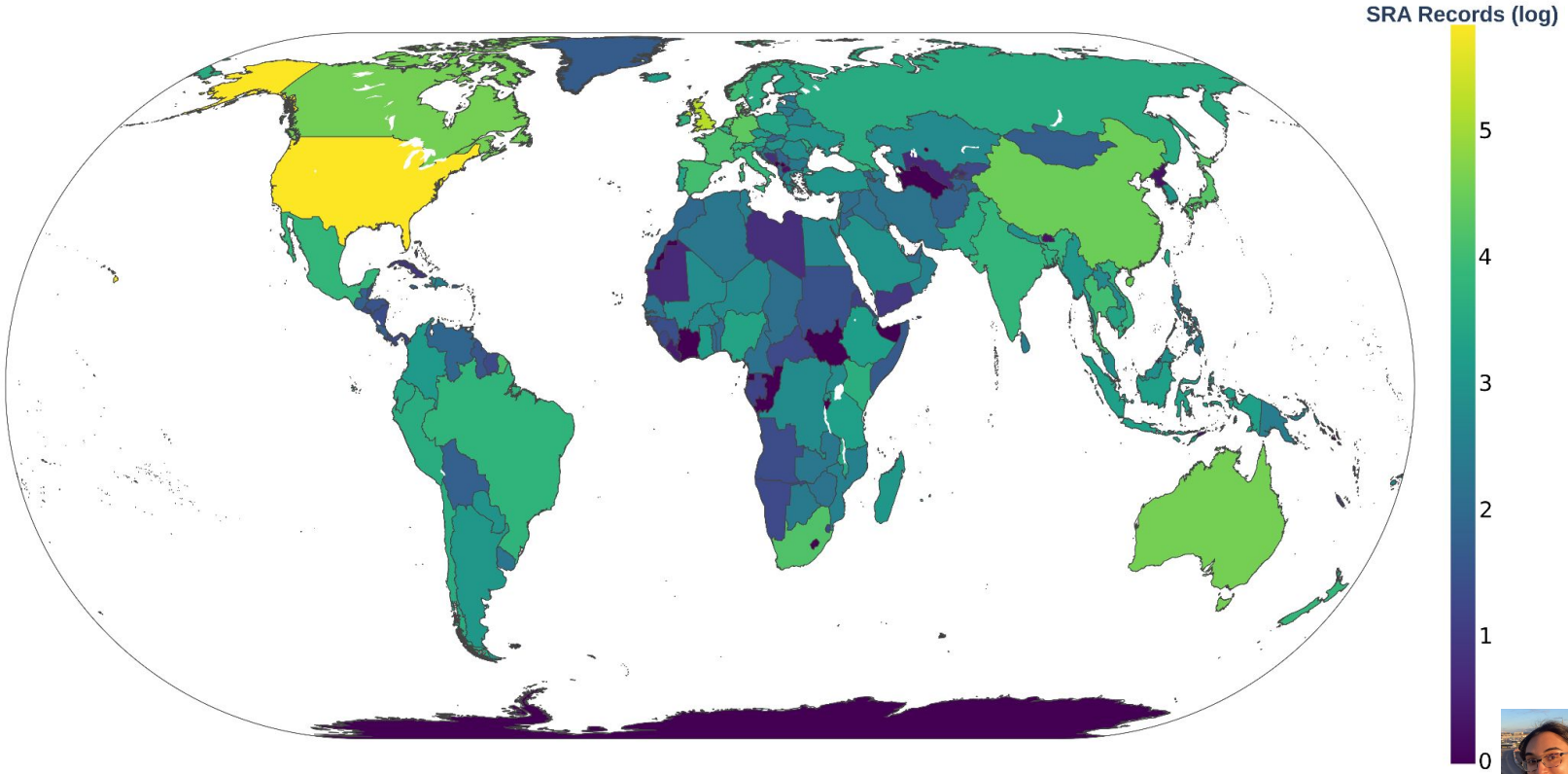
* PAPRIKA (Potentially All Pairwise RanKings of all possible Alternatives) is a robust decision-making approach for systematic evaluation and ranking of all conceivable pairwise alternatives to ensure comprehensive decision analysis. The method is a structured, thorough means of comparing and prioritizing diverse alternatives in making complex decisions.

Improve surveillance systems

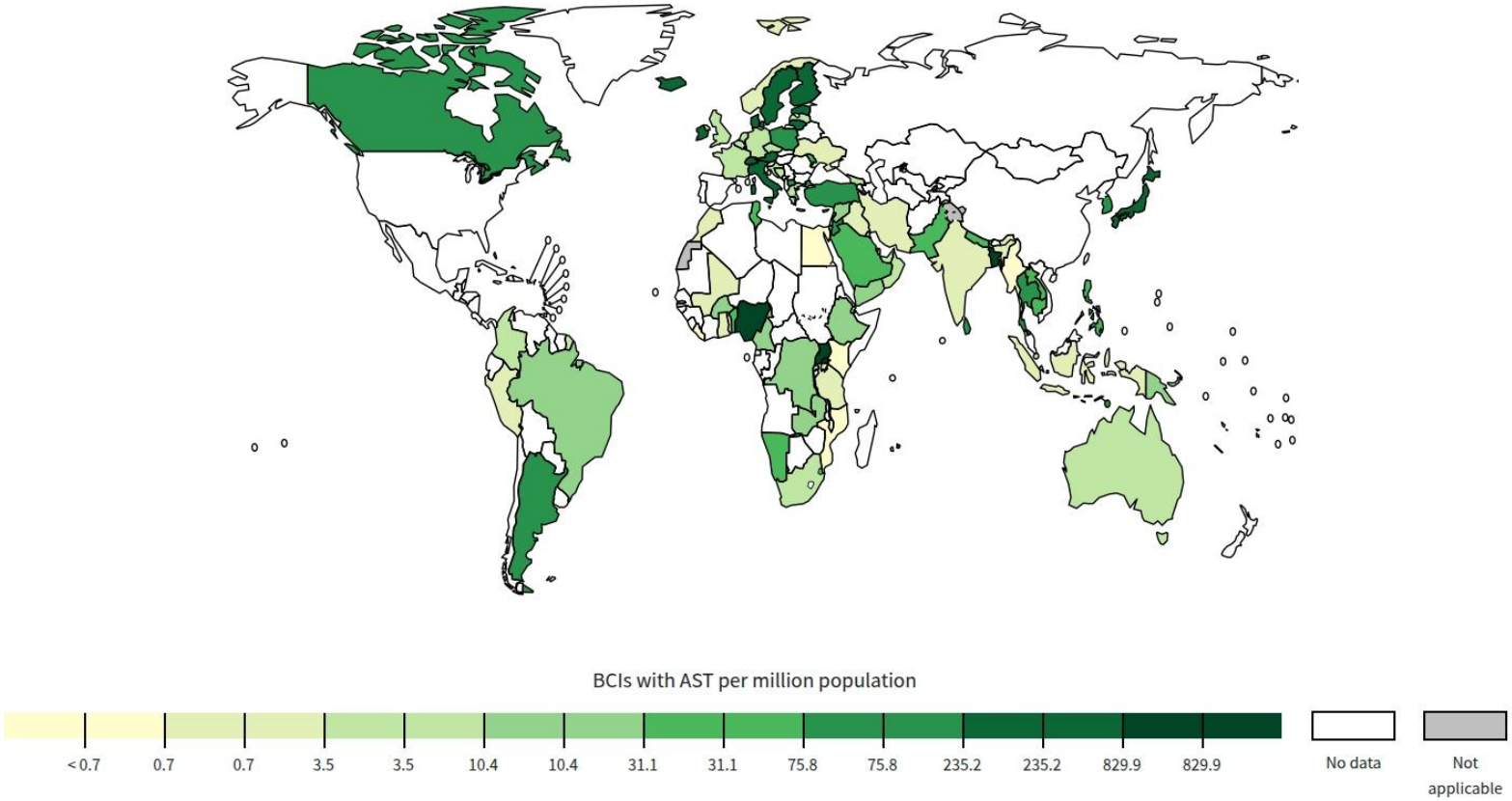
AMR surveillance mismatches with burden



AMR surveillance mismatches with burden



AMR surveillance mismatches with burden



Outbreaks easily missed - automated detection

clinisys™

LABWARE Results Count

LabVantage®

LIS/LIMS

Epic

Allscripts®

MEDITECH

EMR/EHR

AST Platform

WHONET

GLASS
Global Antimicrobial Resistance and Use Surveillance System

?

INSDC

DDBJ

ENA
European Nucleotide Archive

NCBI National Center for Biotechnology Information

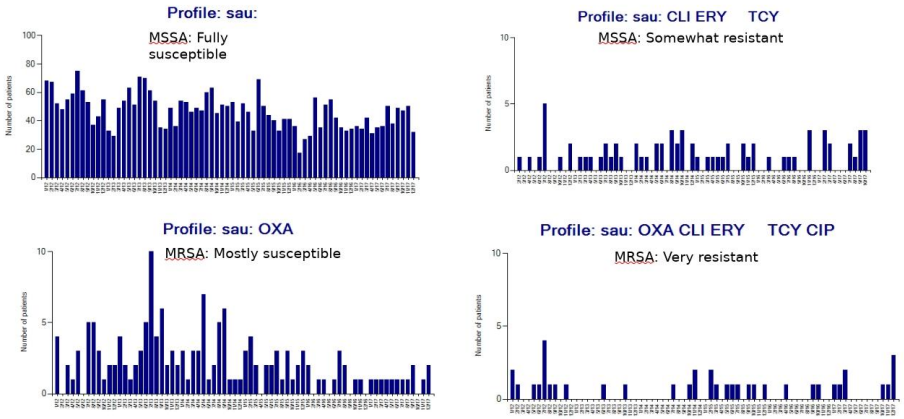
Automating outbreak detection

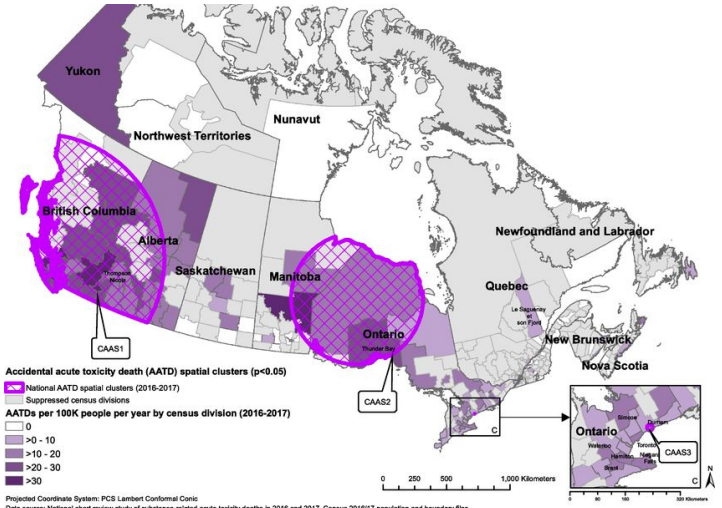
SaTScan (cluster detection scan statistic). Find a (multi-dimensional) region where data is significantly denser than background.

- *Run circles of various sizes across multidimensional count data:*
- *likelihood ~ (cases inside / expected inside) * (cases outside / expected outside)*
- *Monte carlo permutation test & multiple comparison correction*

Baker, Meghan A., et al. "A trial of automated outbreak detection to reduce hospital pathogen spread." NEJM evidence 3.5 (2024): EVIDoa2300342.

- Cluster randomised trial in 82 community hospitals
- Messed up by pandemic but pre-pandemic vs baseline: significant ~64.1% reduction in additional cases



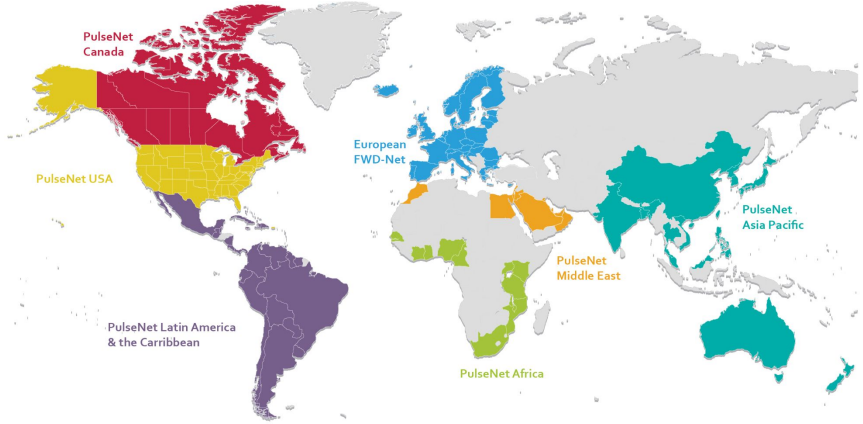


Demonstrating cost-effectiveness of genomic surveillance

PulseNet (human foodborne disease): CDC-led

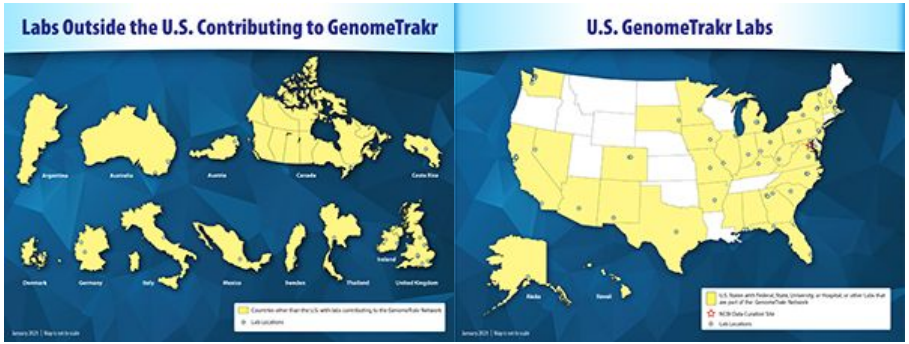
- **Recall Model (Direct Effects)**: attack rates * recovered product = *E. coli* cases reduced by 2,819 and *Salmonella* by 16,994 = $37 million cost averted
- **Process Change (Indirect Effects)**: natural experiment from PulseNet adoption = 266,522 *Salmonella*, 9,489 *E. coli*, and 56 *Listeria monocytogenes* annually = $507 million cost averted
- **Program Cost**: $7.3 million

Scharff, Robert L., et al. "An economic evaluation of PulseNet: a network for foodborne disease surveillance." American journal of preventive medicine 50.5 (2016): S66-S73.



GenomeTrakr (food & environmental): FDA-CFSAN-led

- **Social Value Model** = [Profit from food production] - [Public health burden] - [implementation costs]
- **Natural Experiment:** genomic adoption vs state-specific outbreaks = per 1,000 genomes: 6.09 fewer observed illnesses; +0.01 more outbreaks with -1.07 illnesses = $125-475 million cost averted per year
- **Program Cost**: $21.3 million per year (broke even by year 2).

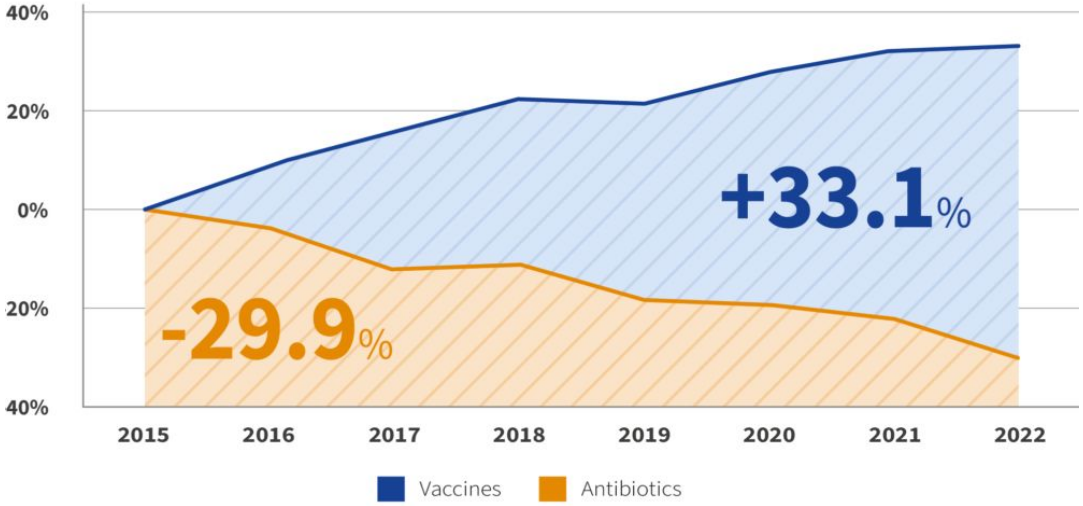


Brown, Brad, et al. "An economic evaluation of the whole genome sequencing source tracking program in the US." PLoS One 16.10 (2021): e0258262.

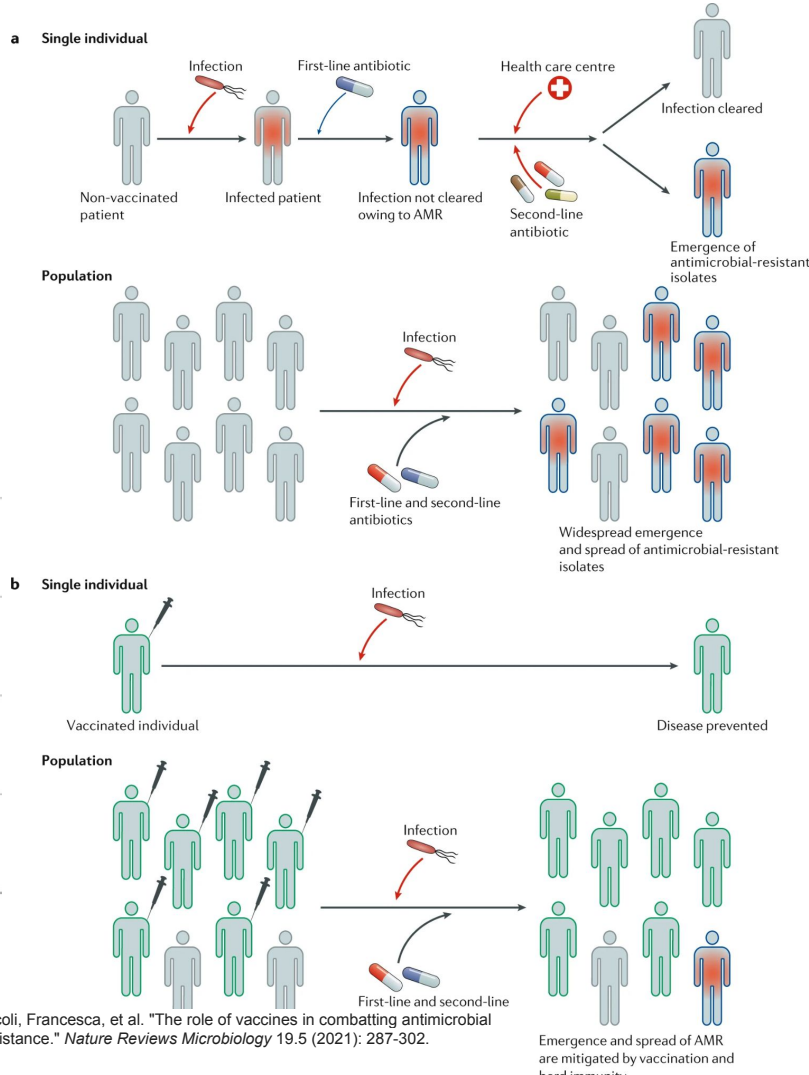
Reducing need for antimicrobials

Vaccination

- More infections prevented by vaccination
  => less use of antimicrobials
  => less AMR
- Animals: very cost-benefit sensitive
- Humans: vaccine hesitancy

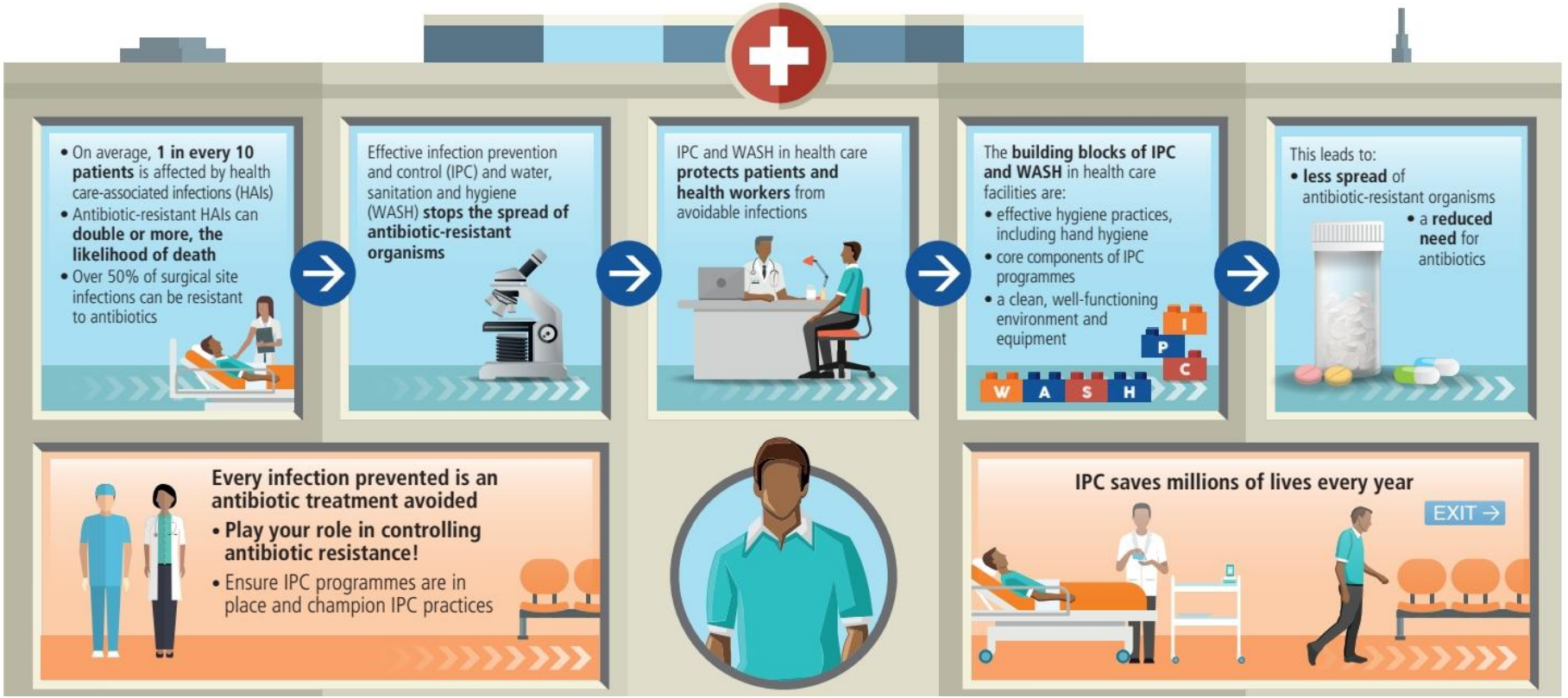


https://healthforanimals.org/animal-health-in-data/antimicrobial-resistance/animal-health-and-amr/

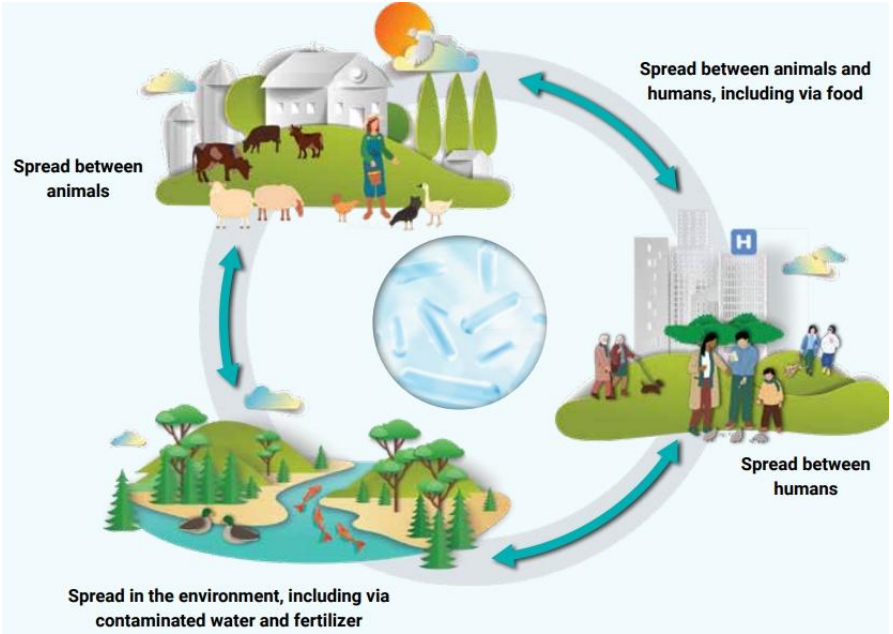


Micoli, Francesca, et al. "The role of vaccines in combatting antimicrobial resistance." *Nature Reviews Microbiology* 19.5 (2021): 287-302.

Infection Prevention & Control



Public Health & One Health interventions



Primary: Prevent infections
Secondary: Detect and treat early infections
Tertiary: Manage established infections

Water and sanitation:

- Safe water systems prevent waterborne diseases (cholera, typhoid, hepatitis A)
- Sewage treatment removes pathogens before environmental release
- Hygiene promotion reduces fecal-oral transmission routes

Food safety systems:

- HACCP protocols (Hazard Analysis Critical Control Points) prevent contamination during production
- Cold chain maintenance prevents bacterial growth during transport/storage
- Restaurant inspections ensure safe food handling practices

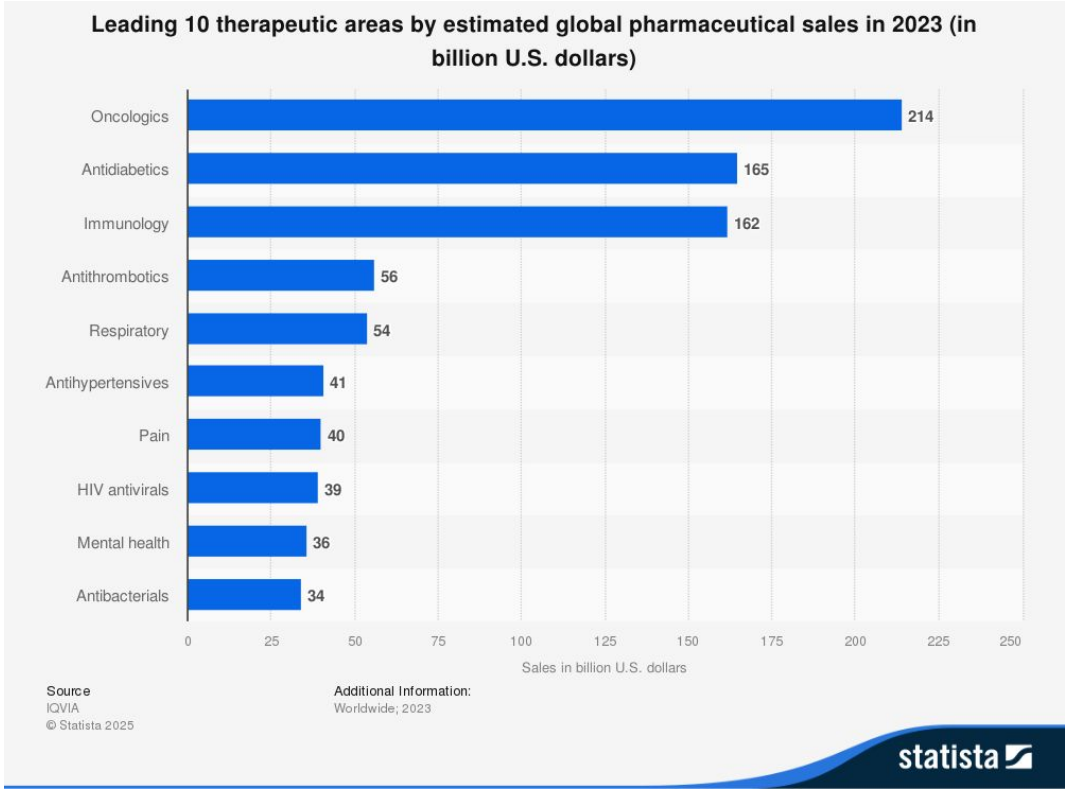
Air Quality:

- Ventilation standards in buildings reduce airborne transmission (crucial for TB)
- Air filtration systems remove pathogens from indoor environments
- Occupational respiratory protection prevents workplace exposures

Healthier Population

Developing novel treatments

Antimicrobials are not that “profitable”

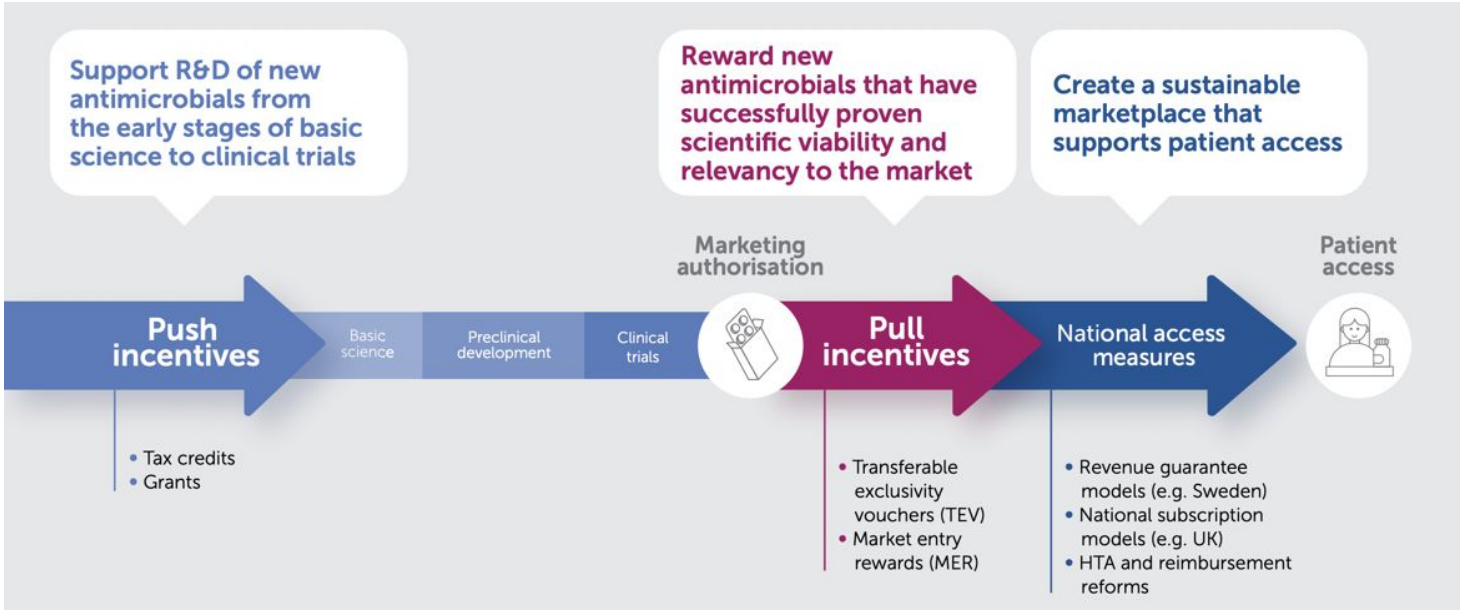


- **High development costs**: $1-3 billion typical cost, 10-15 year timeline
- **High failure rates**: 95% of antibiotic candidates fail in clinical trials
- **Limited market size**: Antibiotics mostly needed in LMICs and used briefly compared to chronic disease medications
- **Stewardship paradox**: New antibiotics deliberately restricted to preserve effectiveness
- **Generic competition**: Patent expiration leads to very reduced revenue

Other Challenges

- **Target saturation**: Most "easy" bacterial targets already exploited
- **AMR emergence**: New drug may not last long!
- **Clinical Trials**: few eligible patients and non-inferiority requirements

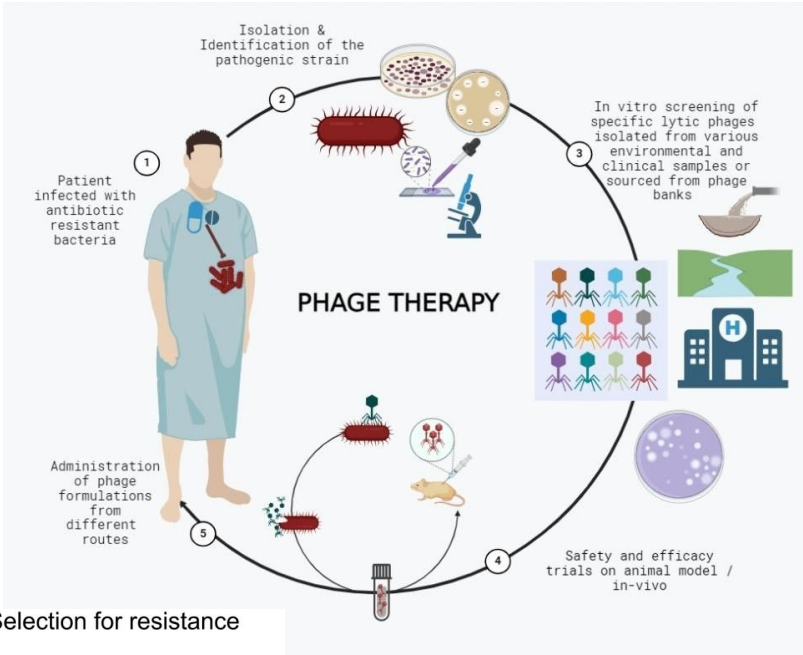
Push and pull incentives for antimicrobial development

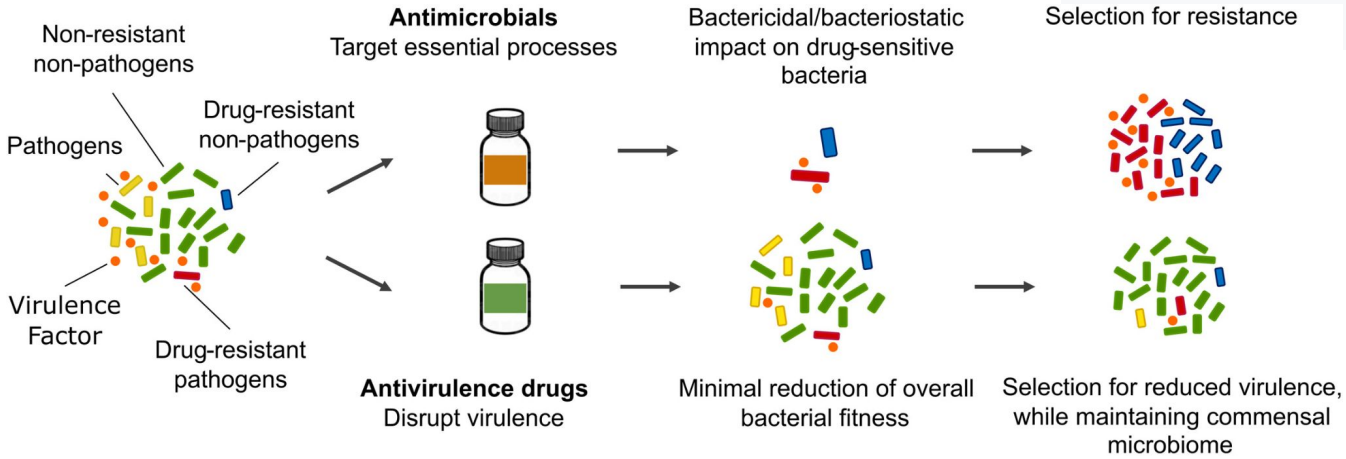


- **CARB-X program**: $500 million commitment to early-stage antibiotic development
- **Drugs for Neglected Diseases initiative (DNDi)**: Nonprofit drug development for tropical diseases
- **TB Alliance**: Focus on tuberculosis drug development
- **GARDP**: Nonprofit specifically for antibiotic development

Alternative treatments

- Phage therapy
- Antibiotic adjuvants:
  - Beta-lactamase inhibitors - Clavulanic acid, tazobactam, vaborbactam, relebactam…
    Efflux pump inhibitors - verapamil
  - Antibody-antibiotic conjugates
- Antivirulence drugs





More effective use of existing antimicrobials: Antimicrobial Stewardship

Antibiotic Stewardship

Leadership & Accountability: Designated physician-pharmacist team with institutional authority to implement changes and allocate resources.

Drug Expertise: Clinical pharmacists with infectious disease specialization provide real-time guidance on antibiotic selection, dosing, and duration..

Action: Active interventions including prospective audit-and-feedback, formulary restrictions, preauthorization requirements, and automatic stop orders.

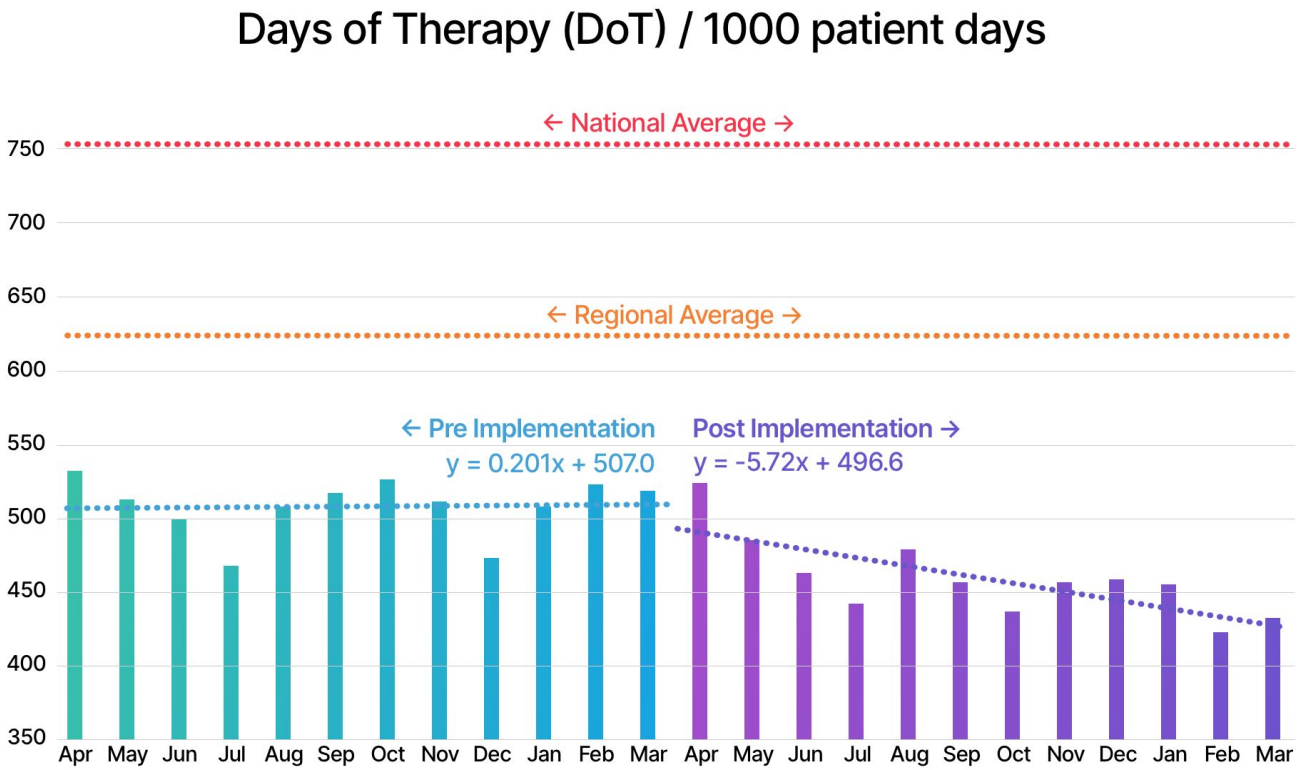
Tracking & Reporting: Monitor process metrics (antibiotic consumption, guideline adherence) and outcomes (infection rates, resistance patterns, length of stay).

Education: Ongoing training for all healthcare staff on appropriate antibiotic use, local resistance patterns, and program initiatives.

First Line, Second Line, Third Line Therapies

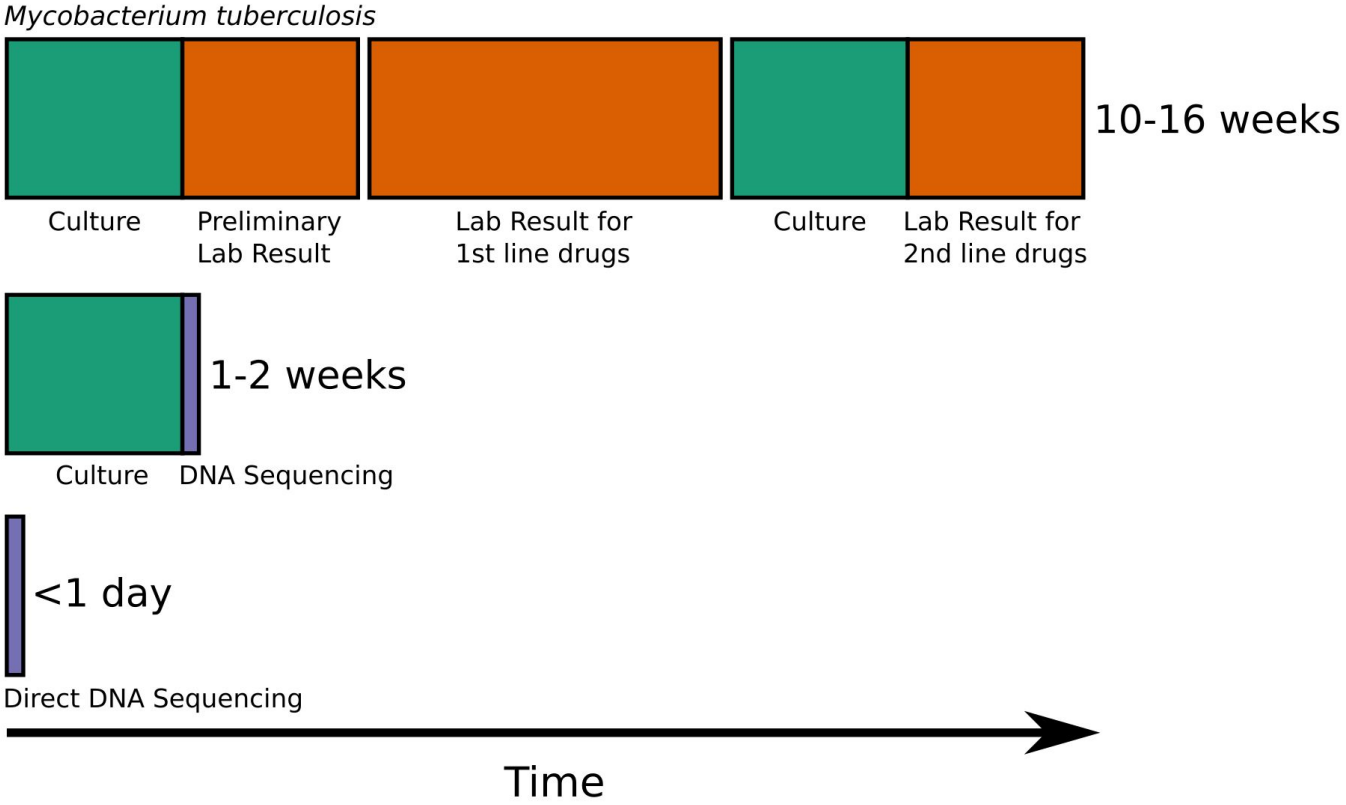
- Tiered treatment helps optimize outcomes while minimizing AMR and preserving potent antibiotics for serious infection.
- **First-line antibiotics**:
  - Initial, preferred treatments for most infections.
  - Generally effective, well-tolerated, have fewer side effects, and are less likely to promote antibiotic resistance.
  - Typically narrow-spectrum antibiotics that target the most common causative organisms.
  - UTI example: *Nitrofurantoin* or *trimethoprim-sulfamethoxazole* or **NOTHING** because effective against common UTI bacteria (*E. coli*), have good urinary tract penetration, and relatively few side effects
- **Second-line antibiotics:**
  - Used when first-line treatments fail, aren't tolerated, or specific circumstances preclude them (like allergies, resistance patterns, or severe infections).
  - May be broader-spectrum, have more side effects, or be reserved to prevent resistance development.
  - UTI example: Fluoroquinolones (like ciprofloxacin) or beta-lactams (like amoxicillin-clavulanate)
- **Third-line antibiotics**:
  - Typically reserved for serious infections, multidrug resistant organisms, or when first and second-line options have failed.
  - Often broad-spectrum, more expensive, may have significant side effects, or are considered "last resort" medications to preserve their effectiveness.
  - UTI example: Carbapenems or other broad-spectrum antibiotics
- Oral cheaper/easier than IV but potentially bigger impact on gut

Firstline: localised guidelines and antibiograms



Improved diagnostics

New genomic diagnostics enable targeted antibiotic therapies



Interpreting AMR genotype data requires lots of expertise

Proteus mirabilis isolate:

- terD
- qacEdelta1
- qnrA
- tetJ
- dfrA14
- sul1
- catA
- catB2
- blaSHV-12
- blaVIM-1
- aac(6')-Ib4
- mphA

- + 13 more AMR determinants

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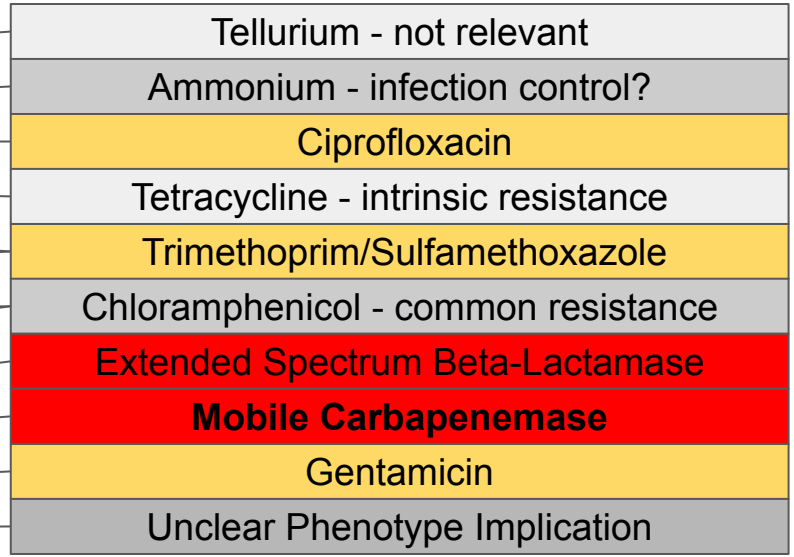
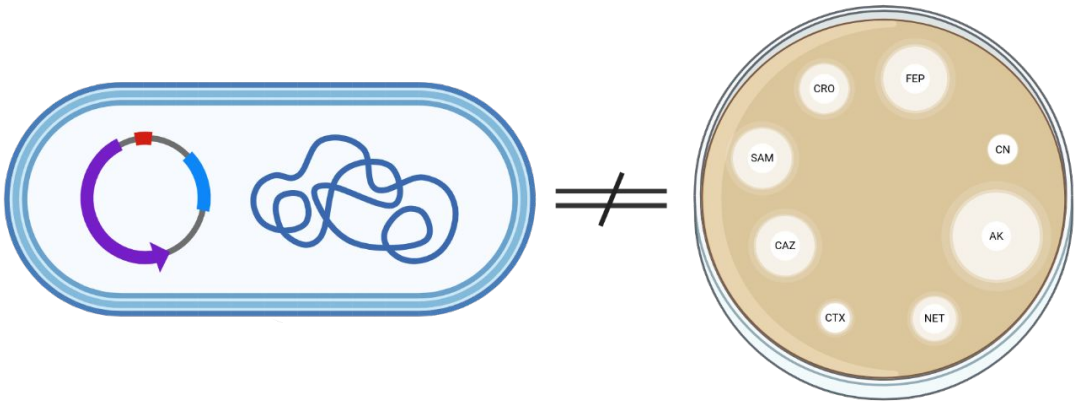


- \+ 13 more AMR determinants

Ad-Hoc Analysis & Expert Knowledge:

- Clinical
- Surveillance
- Infection Control
- Genomic
- Evolutionary
- Microbiological

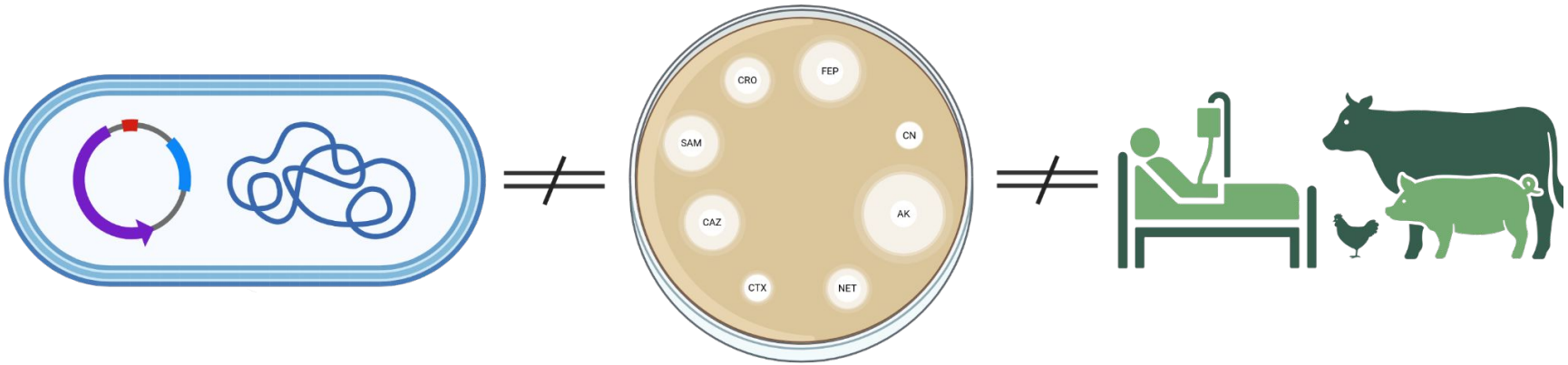
Clinical phenotype inference requires interpretative rules



AMR
Genotype

Lab
Phenotype

Clinical phenotype inference requires interpretative rules

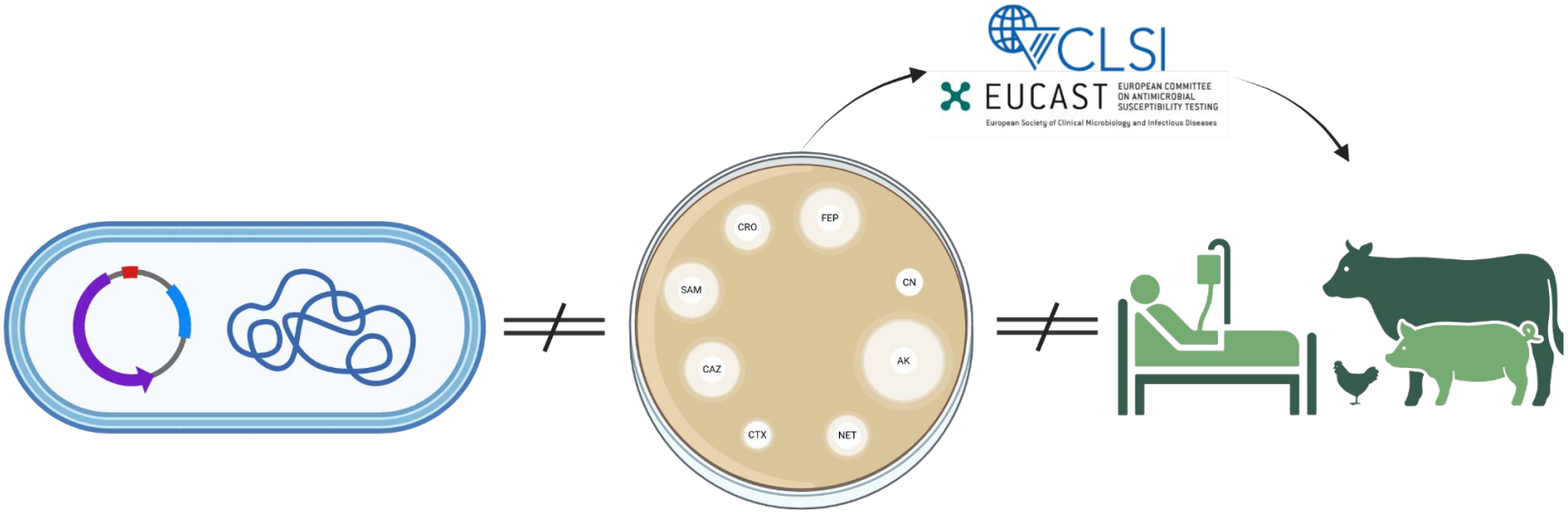


AMR Genotype

Lab Phenotype

Clinical Phenotype

Clinical phenotype inference requires interpretative rules



AMR Genotype

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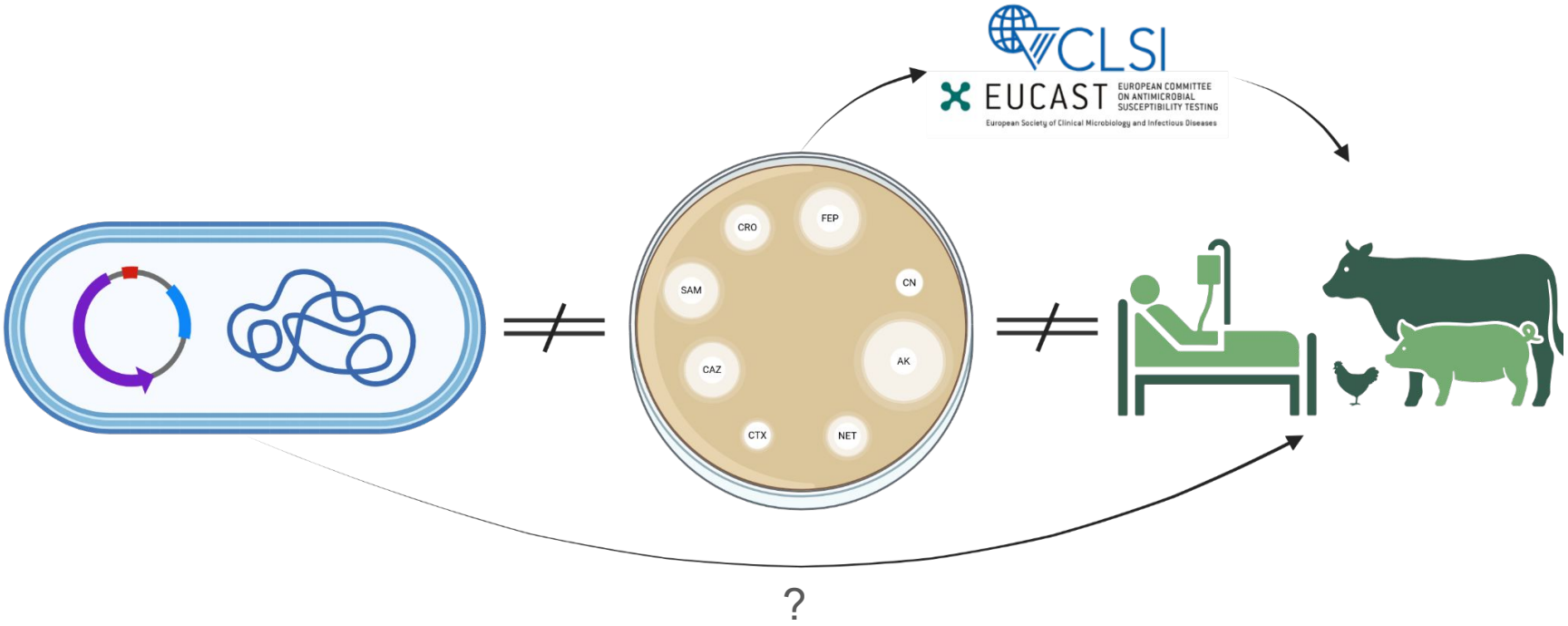

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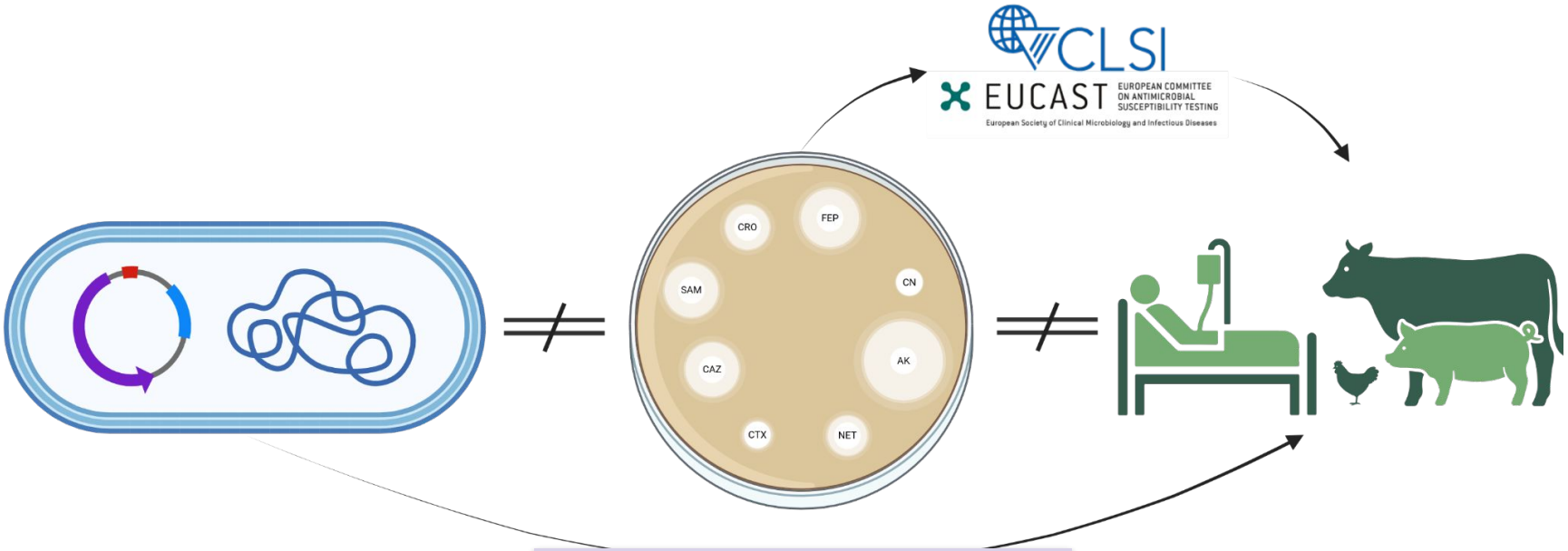
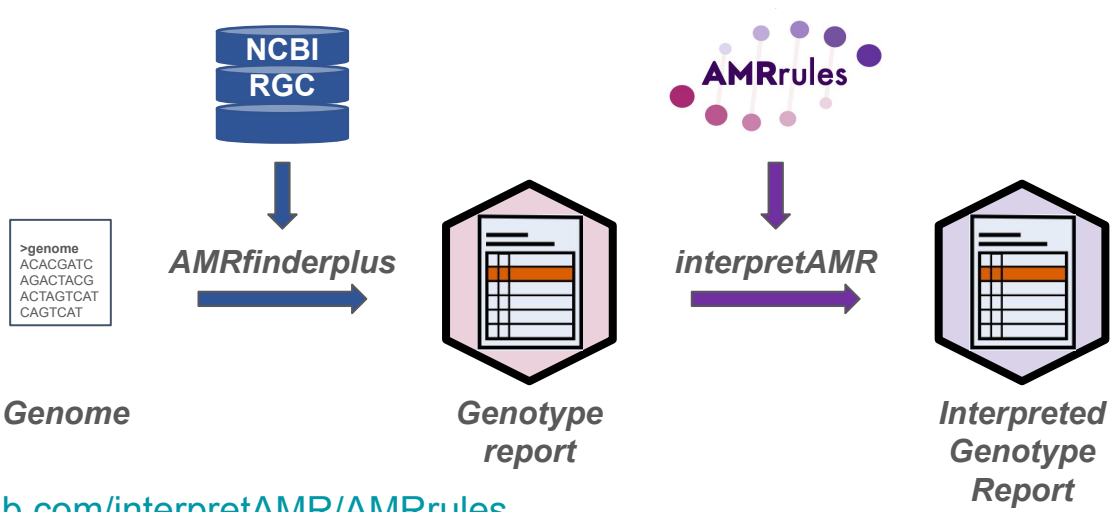


Missing rules for interpretation

What does **gene X** in **species Y** mean for **drug Z?**

AMRrules: creating AMR genotype interpretive rules



ESCMID
ESGEM-AMR
EUCAST
Public Health Alliance for Genomic Epidemiology

Dr. Kat Holt
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github.com/interpretAMR/AMRrules

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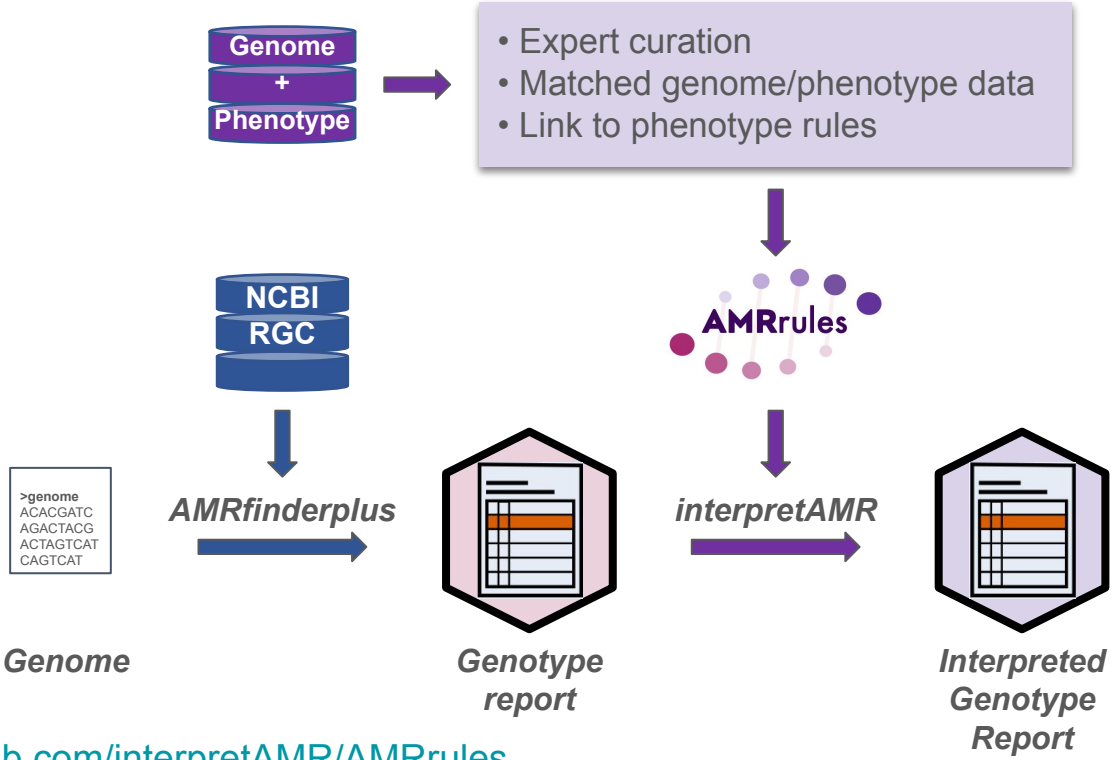

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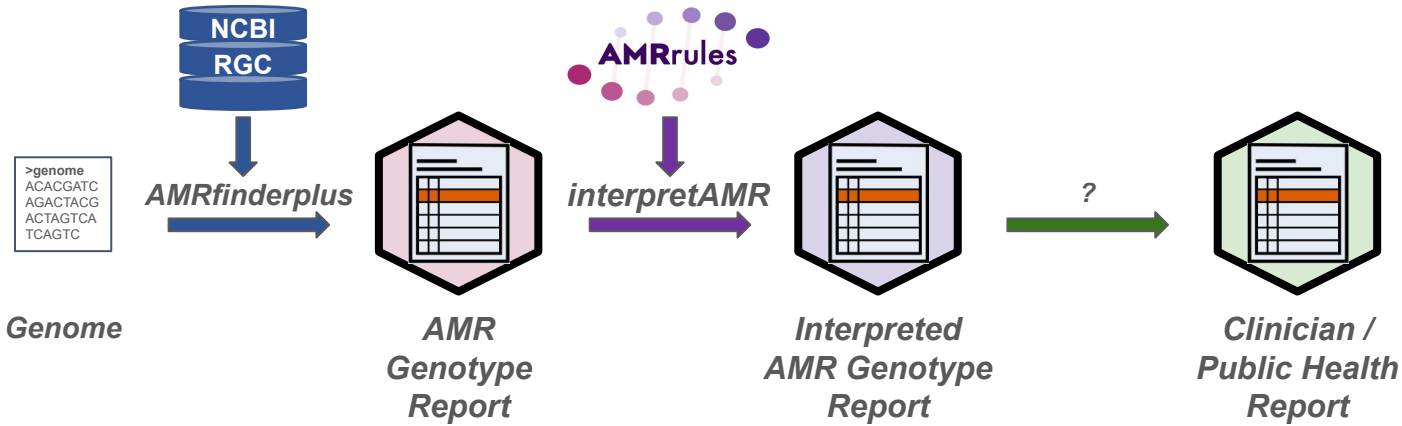
But more contextualisation of AMR genotypes needed



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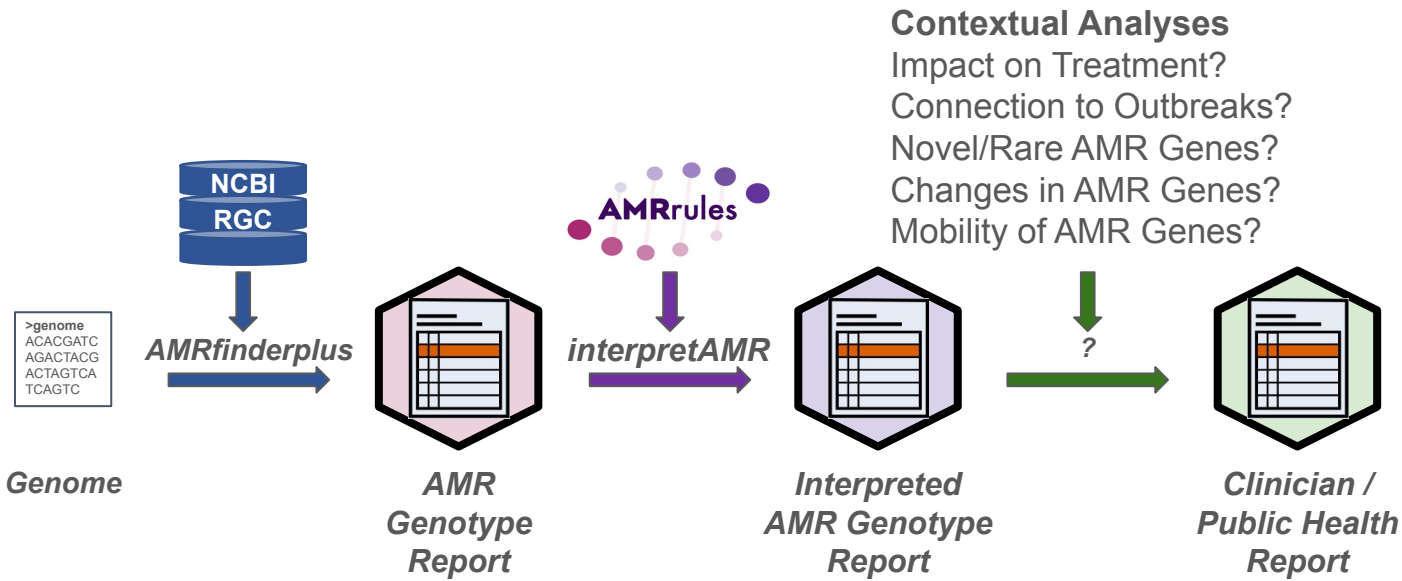
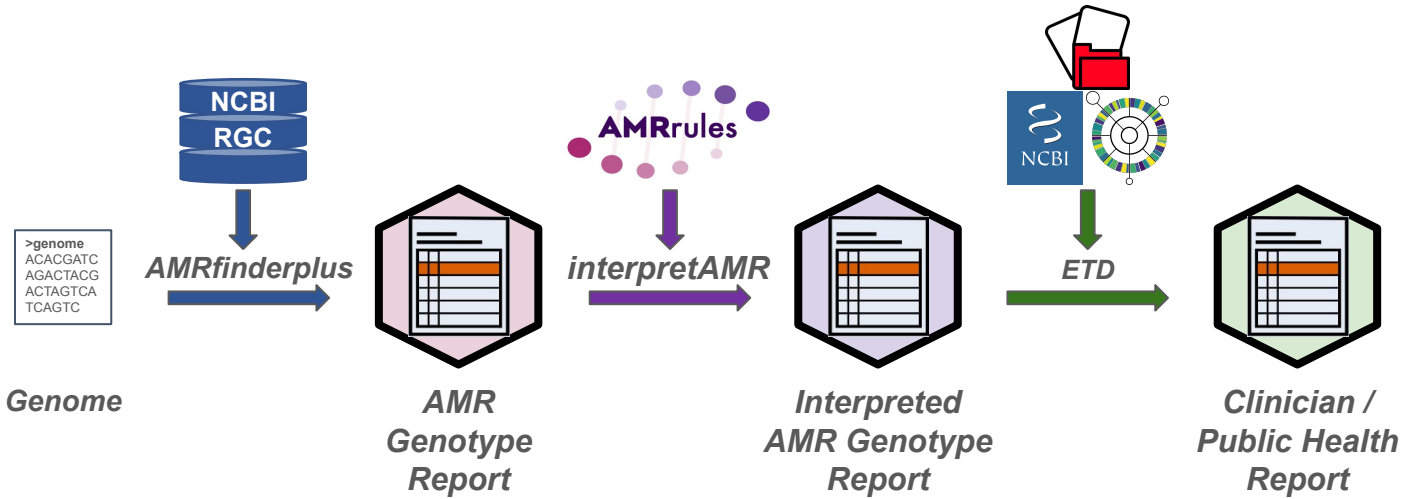
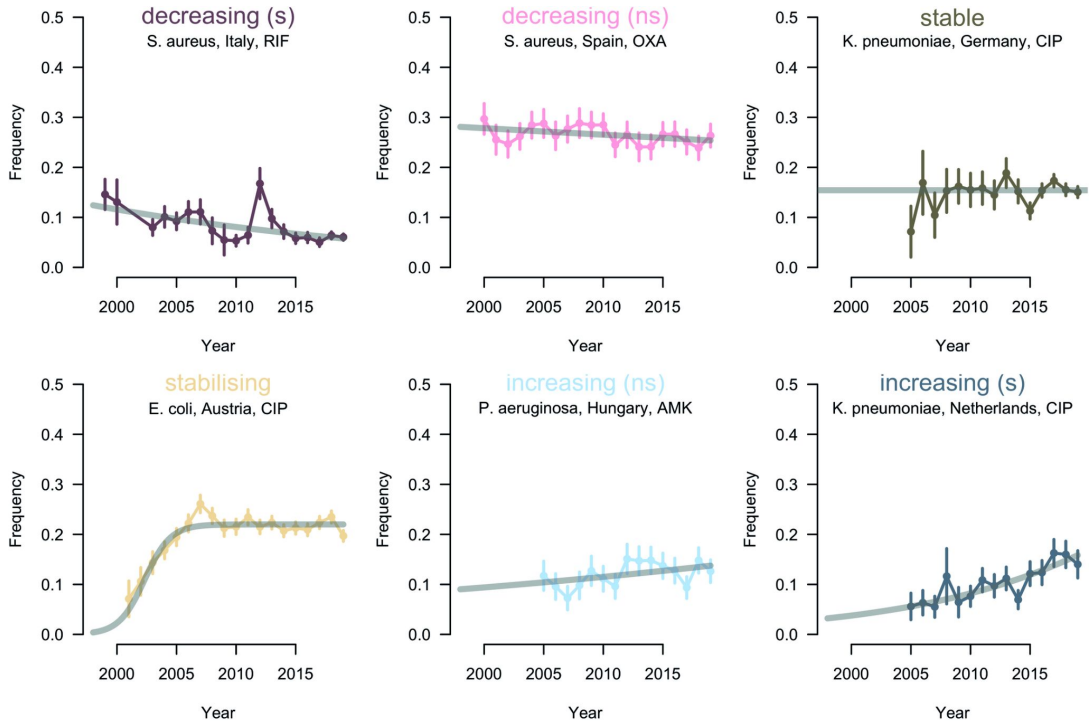


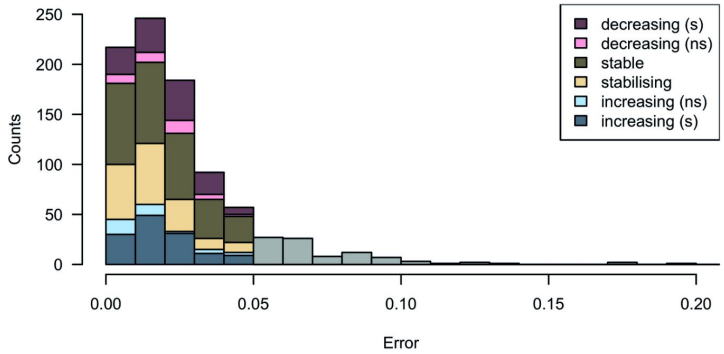
Evolving Threat Detector: Automating contextual analyses



Good news?

AMR not growing everywhere - success of AMR policies?





Summary

1. Antimicrobials

- *Selective action, favourable PK/PD*
- *Antivirals/fungals/parasitics hard to develop due to overlap between host and microbe*
- *Antibiotics have many targets e.g., cell wall (beta-lactams), protein synthesis (macrolides & tetracyclines), and transcription (quinolones)*
- *Antibiotic organised into mechanistic families (or other properties/usage groups)*
- *Antibiotic usage driven by broad-spectrum penicillins in human and tetracyclines in animals*

2. Antimicrobial Resistance

- *Antibiotic Susceptibility Testing measures resistance measured but defining resistance is non-trivial and context dependent (i.e., ECOFFs vs Clinical Breakpoints)*
- *Many mechanisms of AMR (e.g., antibiotic inactivation, target modification, efflux/permeability)*
- *AMR is ancient and can evolves rapidly via mutation and LGT*
- *Surveillance of AMR is complicated and occurs at multiple geographic and technical scales*
- *High global burden of AMR but accurate measurement is difficult*

3. Solutions to Antimicrobial Resistance

- *Surveillance needs improved and capacity needs increased in highest burden areas*
- *Vaccines, IPAC, Public Health reduce infections and need for antimicrobials*
- *Hard to incentivise development of new antimicrobials*
- *Promising alternative treatments being developed like phage therapy, adjuvants, and anti-virulence*
- *Antimicrobial Stewardship key to more effectively using existing antimicrobials*
- *Rapid diagnostics enable targeted therapy but lots of work to do be done to make them effective*