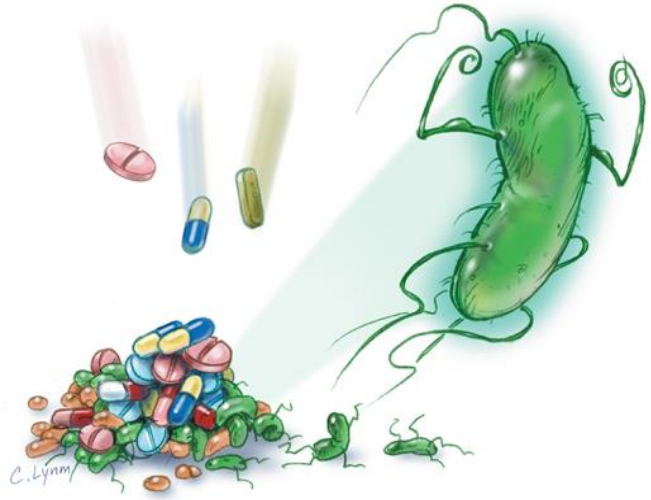

Antibiotic Resistance

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Overview

- **ANTIBIOTICS**
- Antibiotic use in **LIVESTOCK** and **RISKS FOR HUMANS**
- **ANTIBIOTIC RESISTANCE**

  definition, origin, evolution, causes and consequences
- **MECHANISMS** of resistance

  strategies that bacteria use to resist antibiotics
- **TRANSFER** of resistant bacteria and genes

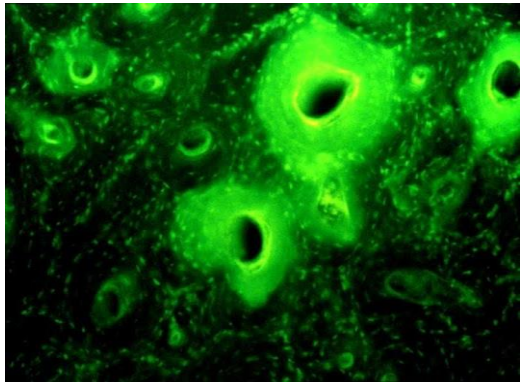
What is antibiotic?

Anti = “against” and bios = “life”

antibiosis – life is used to destroy another life

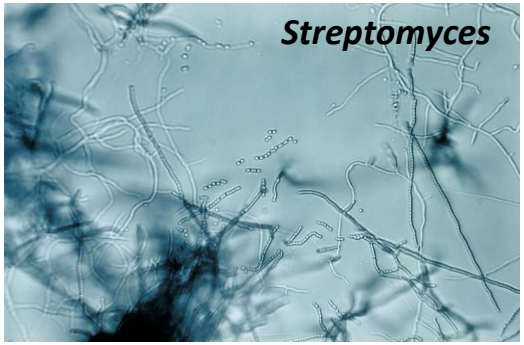
History of antibiotics

"Natural, synthetic/semisynthetic compound that can inhibit or kill sensitive microbes"



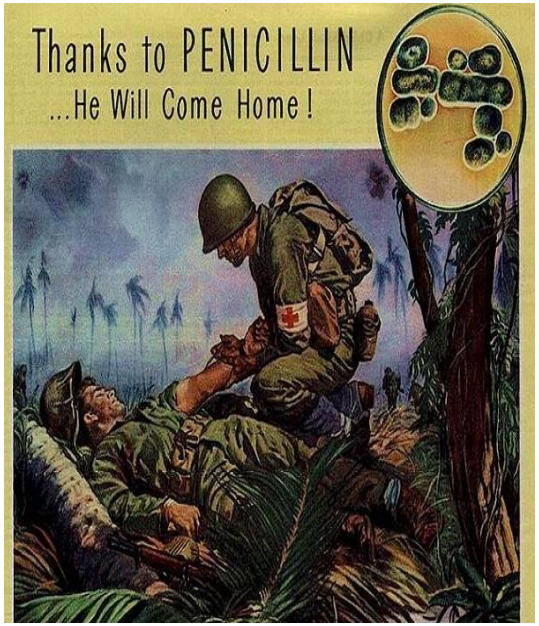
Antibiotics and egyptian mummies
(1980, tetracycline, Nubia 550 years B.C.)

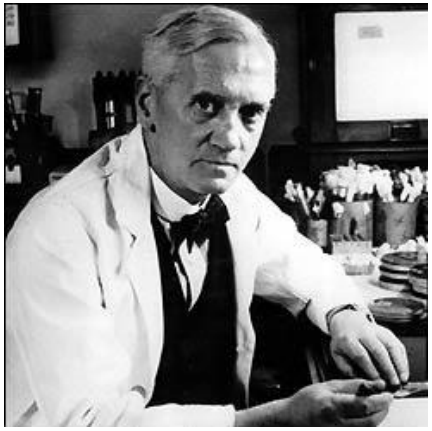
"beer" with *Streptomycetes* and tetracycline



History of antibiotics

- Penicillin in 1929 - Alexander Fleming
- 2nd World War
- Golden era of antibiotics
- 150 types used today



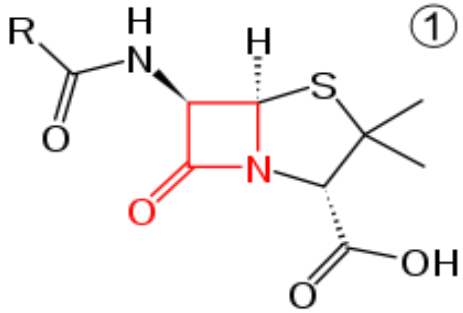


Alexander Fleming
(1881-1955)

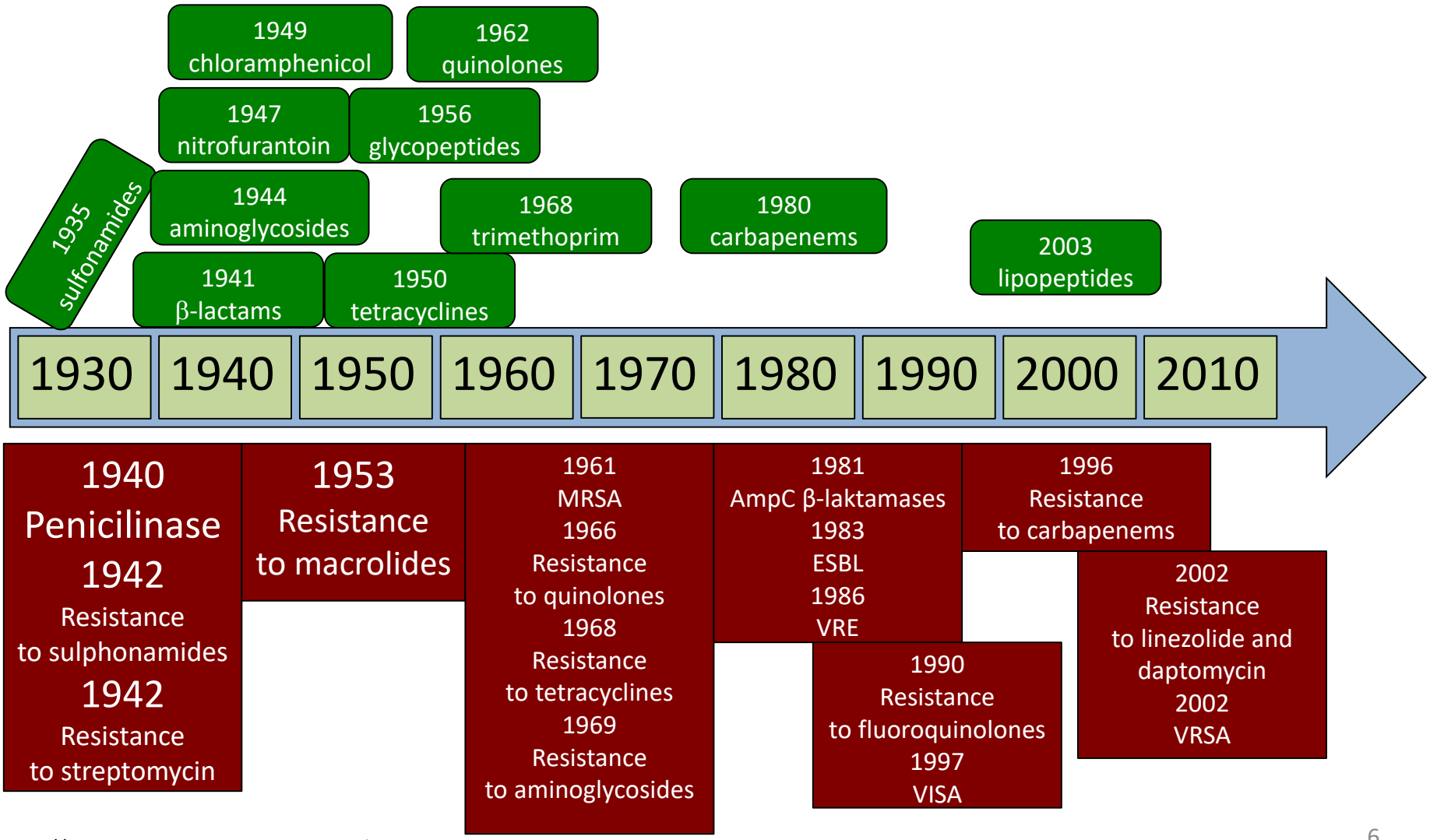
Penicillium notatum

Inhibited colonies of
Staphylococcus aureus

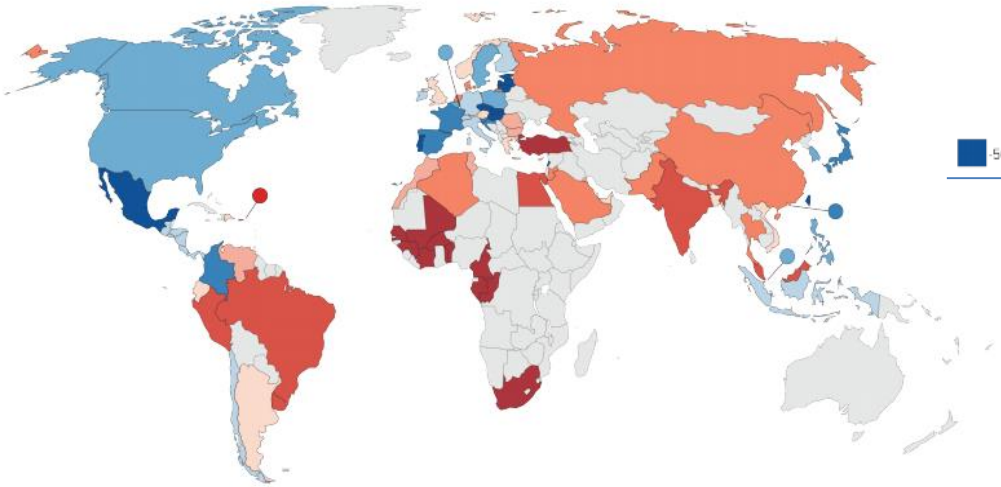
Staphylococcus aureus



Antibiotics and resistance – Timeline



Inscreasing antibiotic use



Human medicine

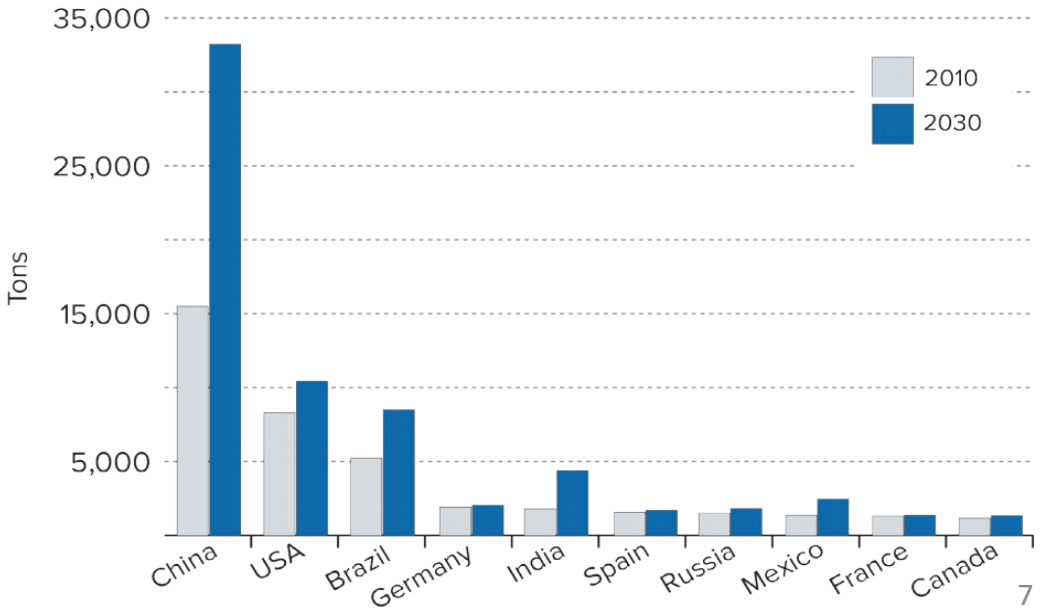
decrease

increase

30% increase of global consumption of ATB between 2000 and 2010

Farm animals

2010-2030: 67% increase



https://www.cddep.org/

Antibiotic resistance

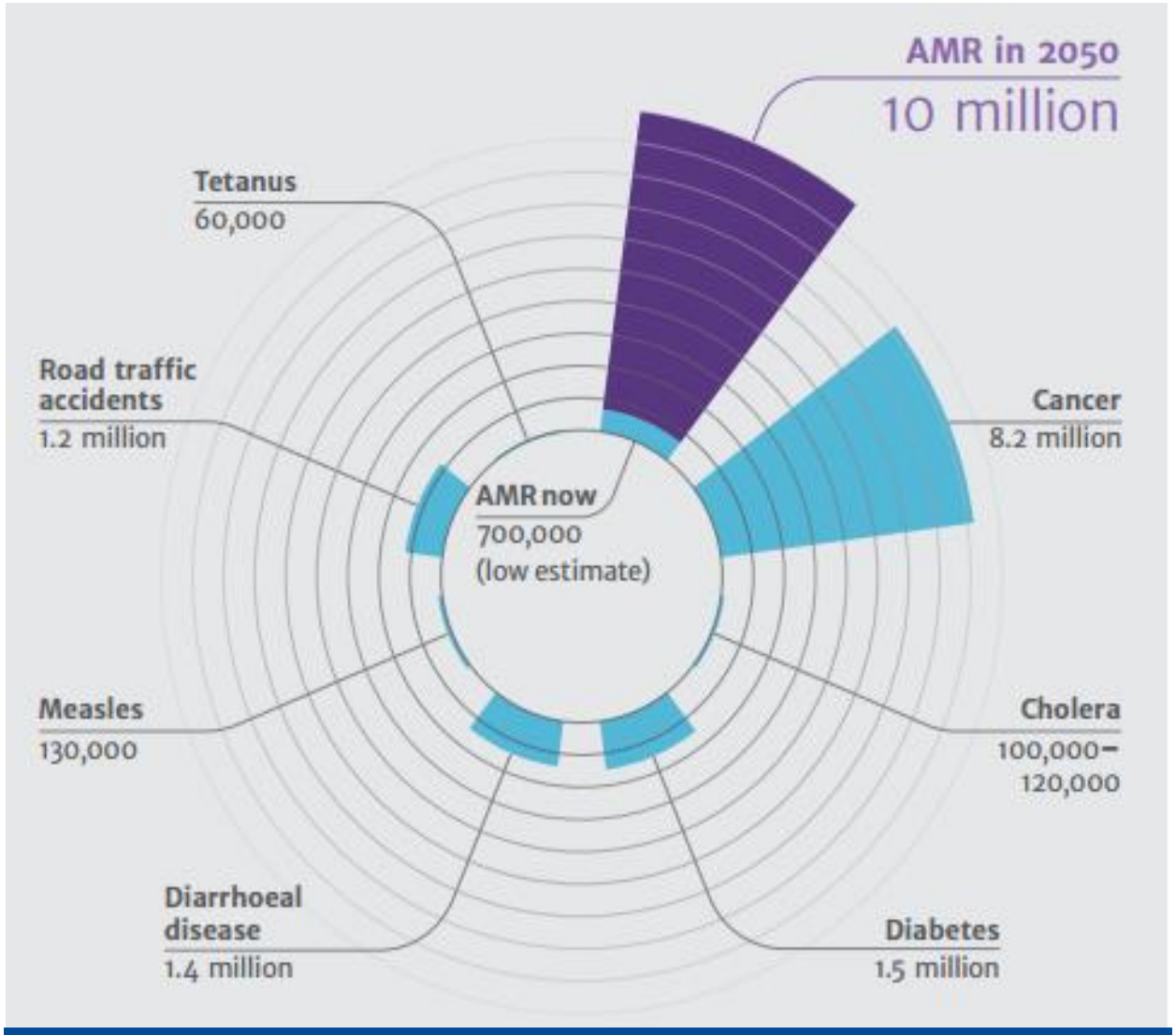
Resistance to antibiotics is the ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive

- Worldwide problem
- Misuse and overuse of antibiotics
- Threatens effective prevention and treatment of infectious diseases
- Increased mortality and morbidity
- Persistence of infections and increased risk of transfer to other individuals
- Economic costs
- Threat for modern society

EUROPE

25 000 death/year from MDR hospital infections

€1.5 billion / year - costs of extra health-care costs and productivity losses



Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

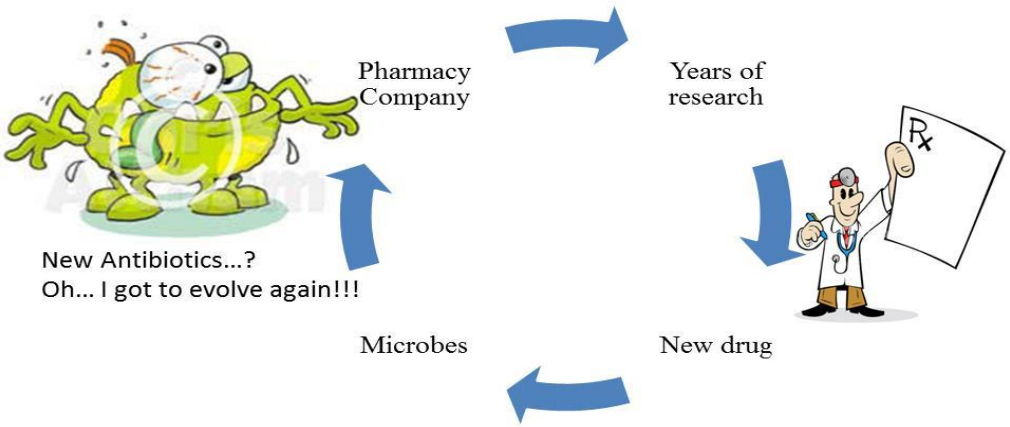
HM Government

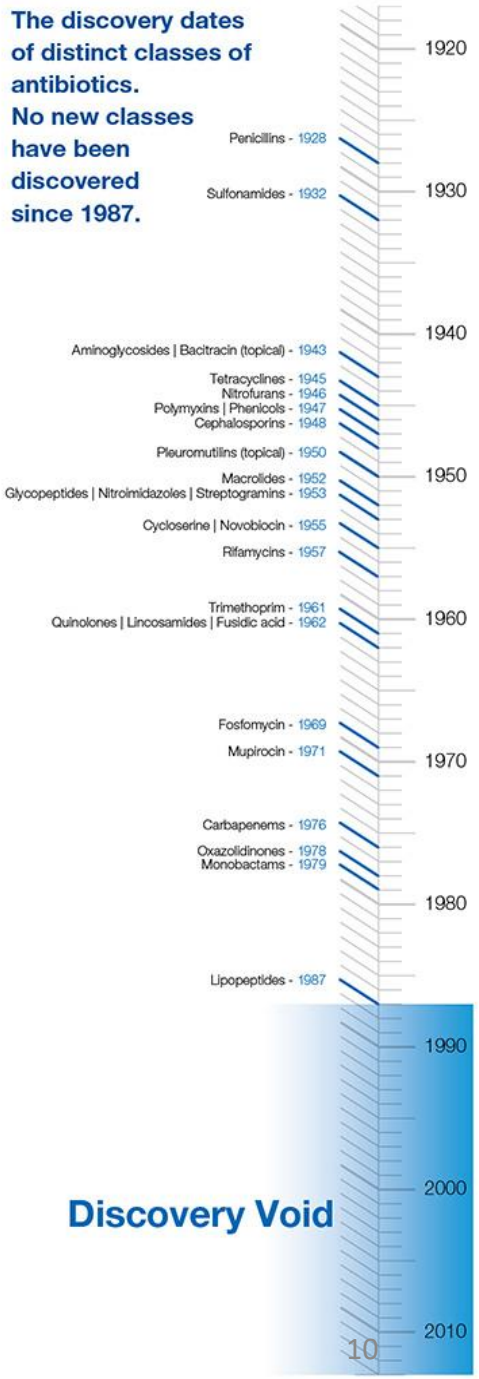
wellcome trust

Antibiotic resistance

- Increasing, multiresistance, novel mechanisms
- Absence of effective antibiotics and limited development of novel drugs

  teixobactin
- Predictions of a medical catastrophe and return to pre-antibiotic era

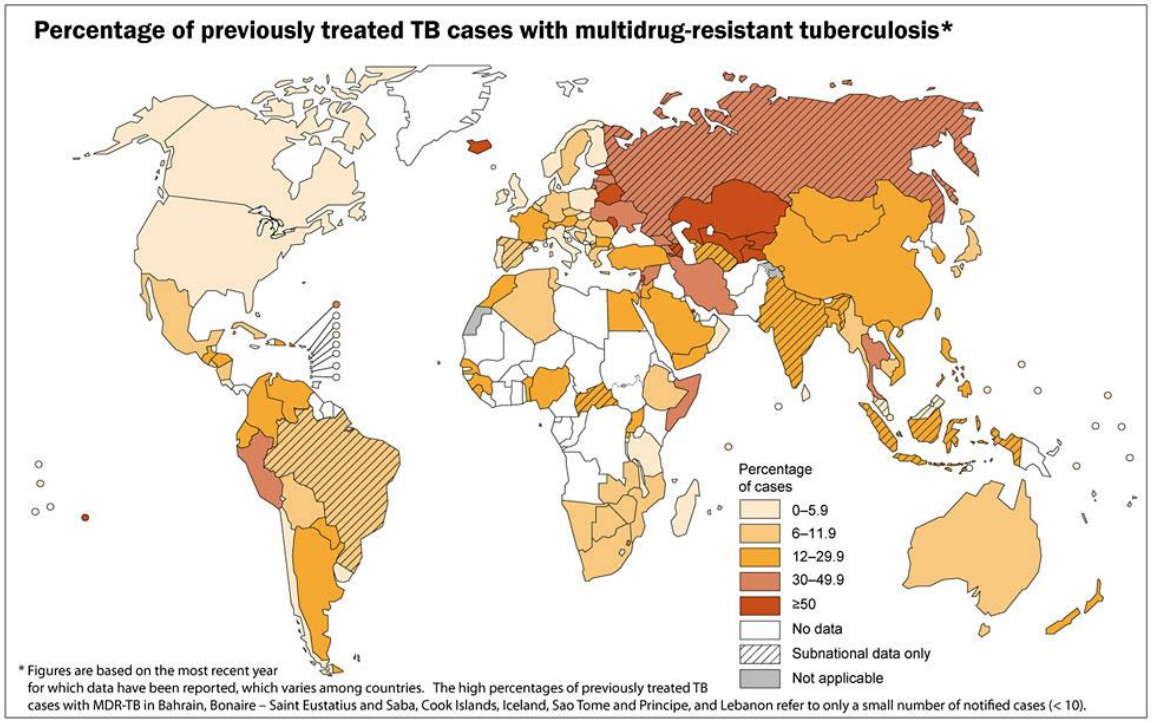


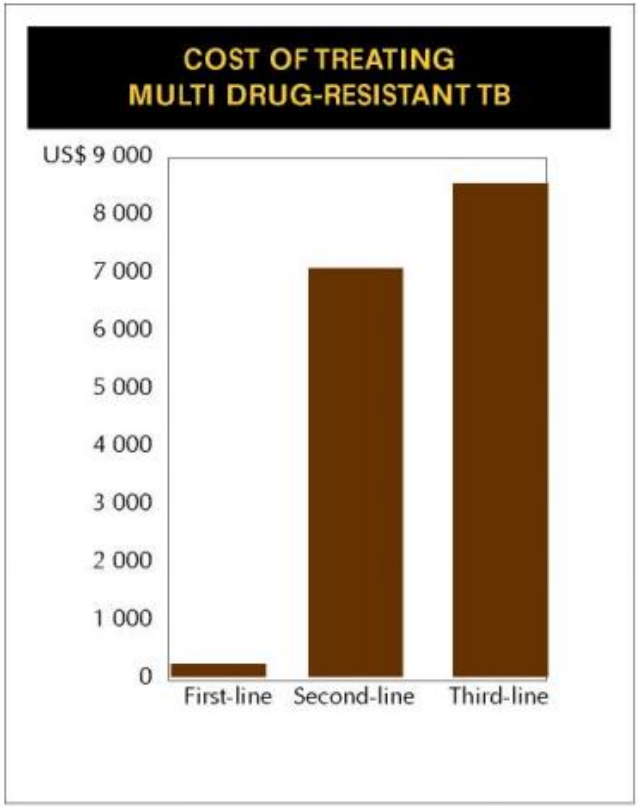


Antibiotic resistance - economic burden

Multiresistant *Mycobacterium tuberculosis*

penicilin $0.24
linezolid $86.90
360 x as much





Source: Farmer et al. The Global Impact of Drug Resistant Tuberculosis, Harvard Medical School and Open Society Institute: pp. 168,1999

Hot issues in antimicrobial resistance

Bacteria

HIV

malaria

influenza

WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

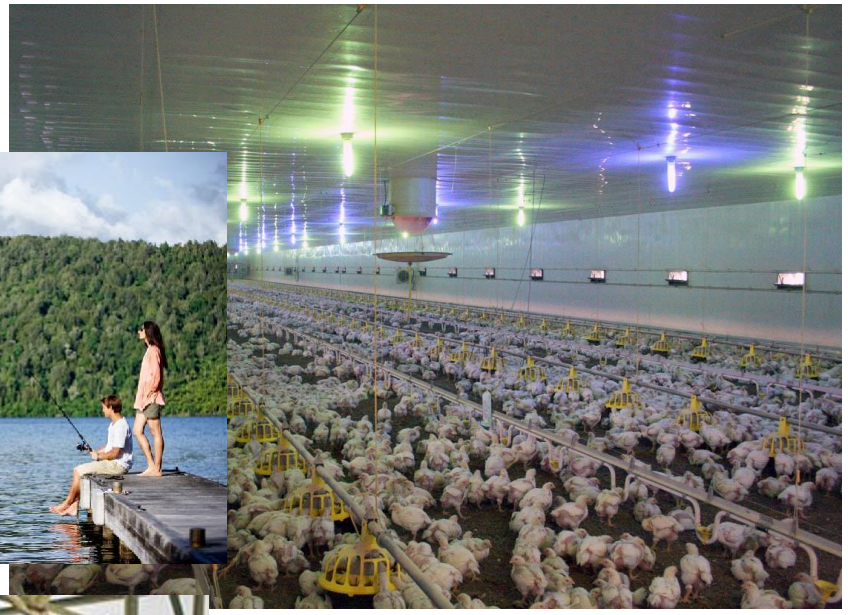
Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

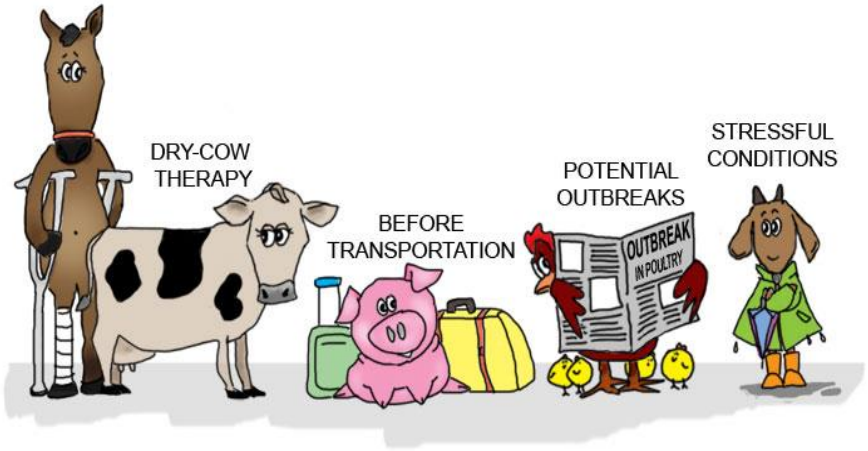
Antibiotics in livestock



Antibiotics in livestock

All veterinary antibiotics have they analogues in human medicine – cross-resistance!

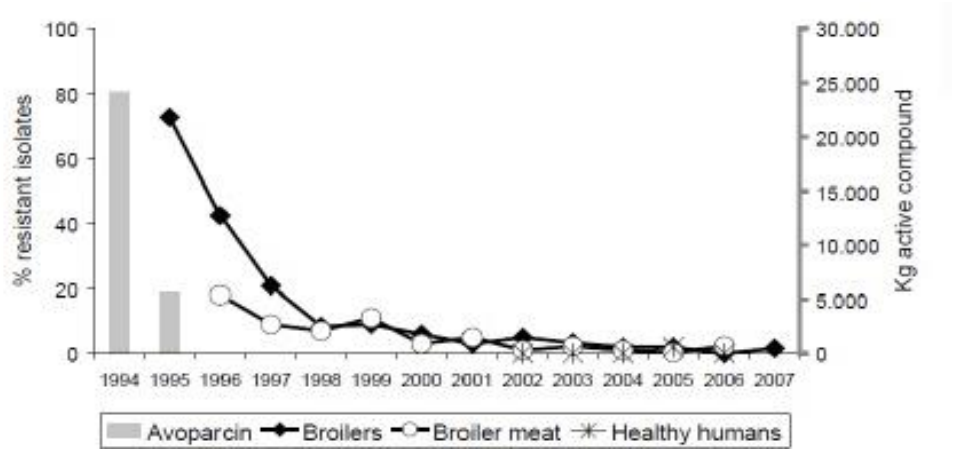
Therapeutic – prophylactic - metaphylactic



Growth promoters

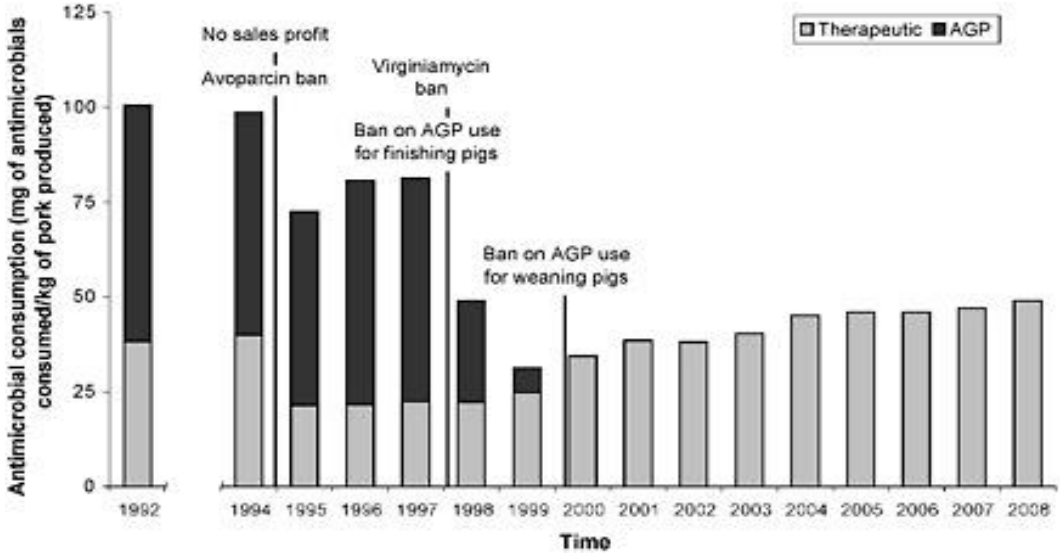
1st January 2006 – no antibiotics as growth promoters in EU

Antibiotics in livestock



Glycopeptide resistance of *Enterococcus faecium* in Denmark

Hammerum A. Emerging Infectious Diseases 2007, 13.



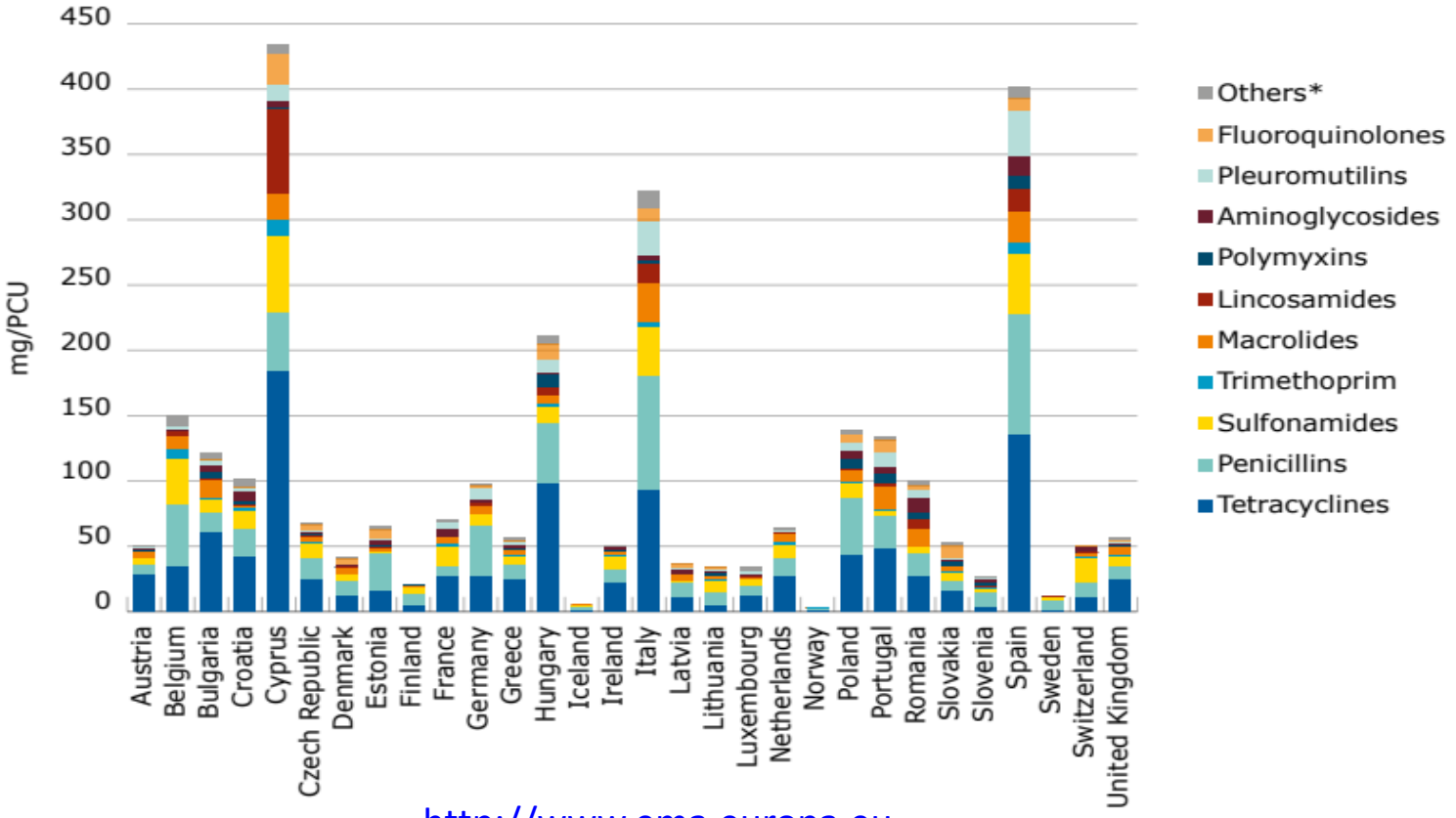
Ban of antibiotic growth promoters and the impact on therapeutic use of antibiotics

Hammerum A. Emerging Infectious Diseases 2007,13.

Antibiotics in livestock

Sales of antibiotics for animal use decrease by 13% in Europe between 2011 and 2015

Figure 3. Sales for food-producing species, in mg/PCU, of the various veterinary antimicrobial classes, for 30 European countries, in 2015[1]

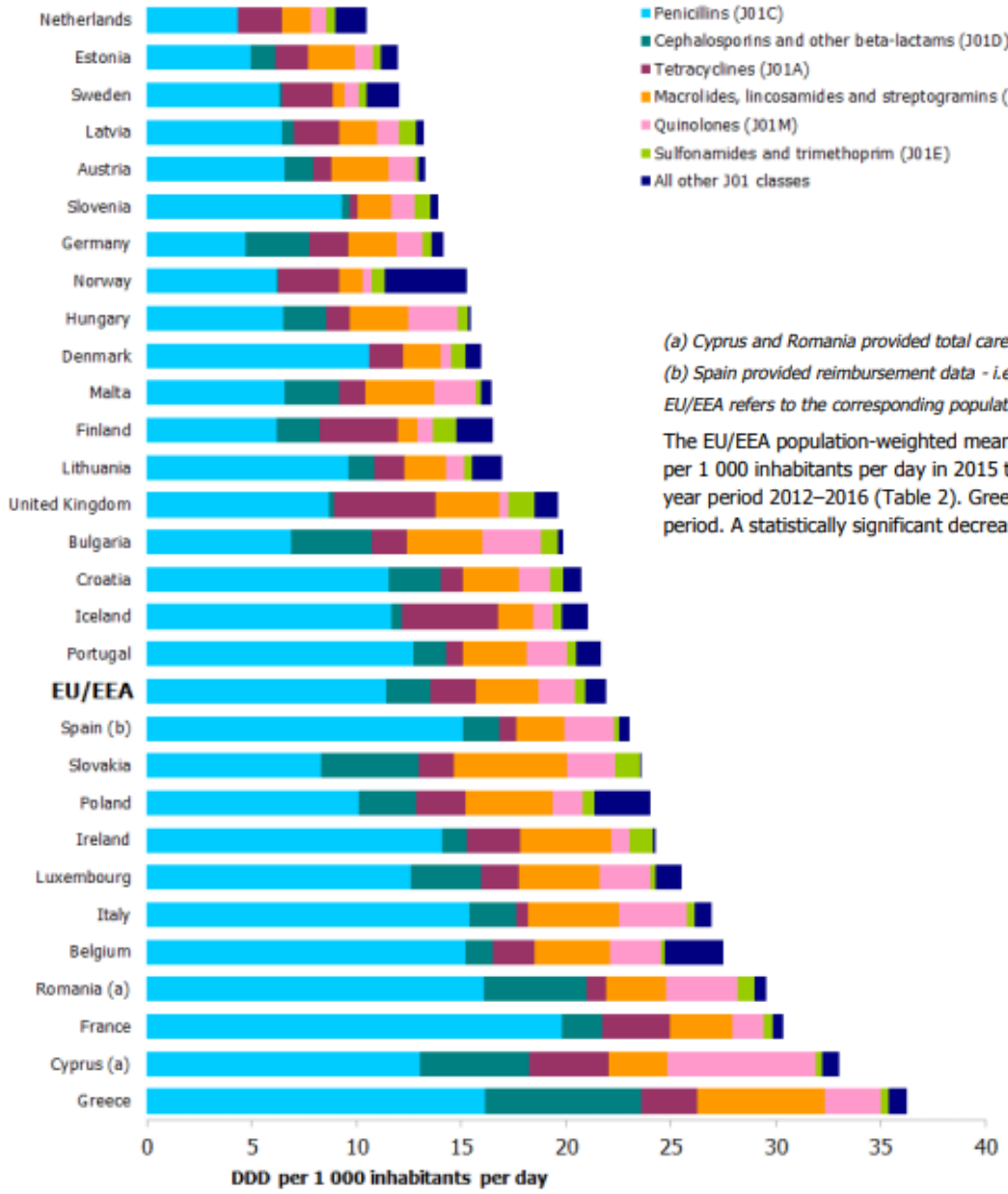


http://www.ema.europa.eu

* Amphenicols, cephalosporins, other quinolones and other antibacterials (classified as such in the ATCvet system).

[1] Differences between countries can be partly explained by differences in animal demographics, in the selection of antimicrobial agents, in dosage regimes, in type of data sources, and veterinarians prescribing habits and prices.

Figure 2. Consumption of antibacterials for systemic use (ATC group J01) and ATC group level 3 in the community, EU/EEA countries, 2016, expressed as DDD per 1 000 inhabitants per day



(a) Cyprus and Romania provided total care data (i.e. including the hospital sector).

(b) Spain provided reimbursement data - i.e. not including consumption without a prescription and other non-reimbursed courses.

EU/EEA refers to the corresponding population-weighted mean consumption.

The EU/EEA population-weighted mean consumption of antibacterials for systemic use decreased from 22.4 DDD per 1 000 inhabitants per day in 2015 to 21.9 in 2016, but there was no statistically significant trend for the five-year period 2012–2016 (Table 2). Greece and Spain showed a statistically significant increasing trend for this period. A statistically significant decreasing trend was observed for Finland, Luxembourg, Norway and Sweden.

Antibiotics in human medicine

Antibiotics in veterinary medicine – risk for humans

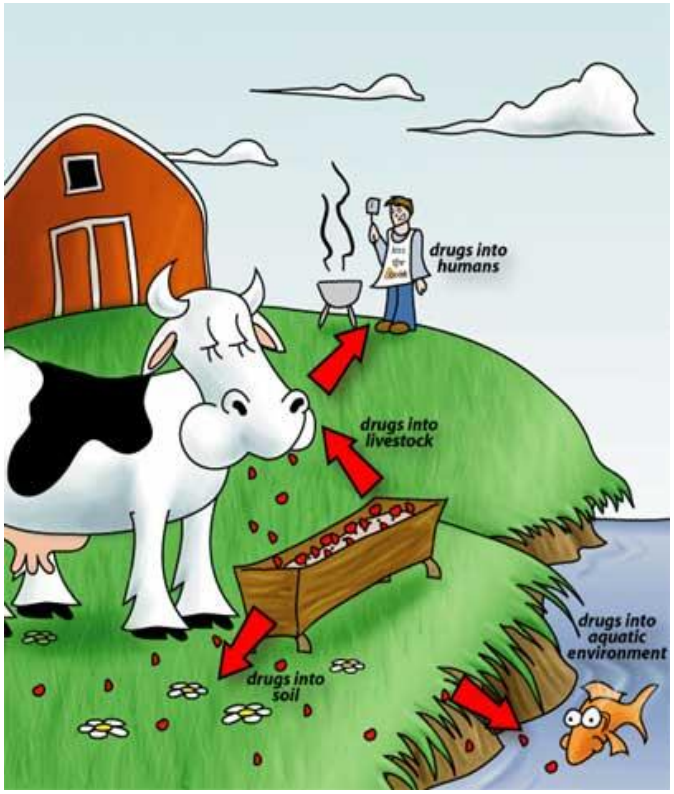
Risk antibiotic groups

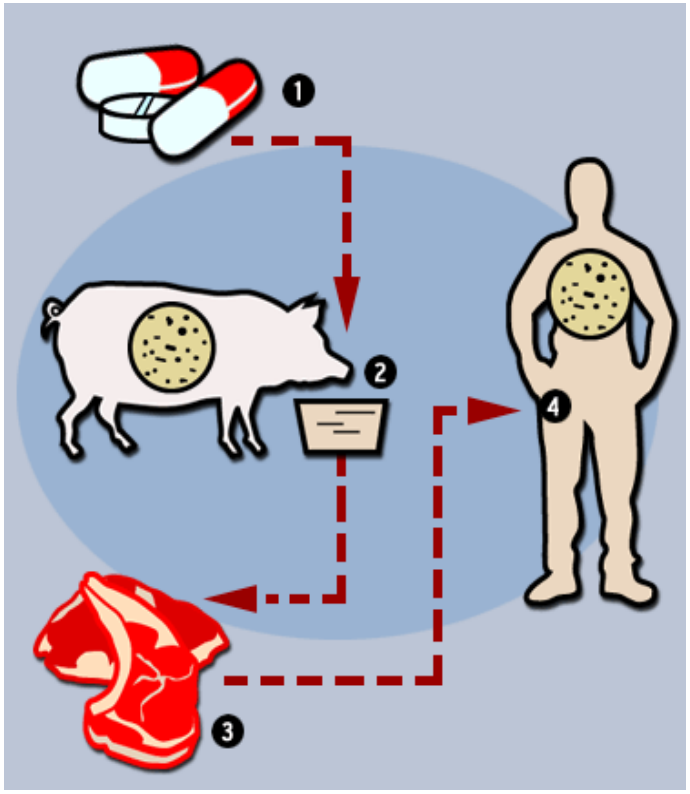
fluoroquinolones

cephalosporins of 3rd and 4th generation

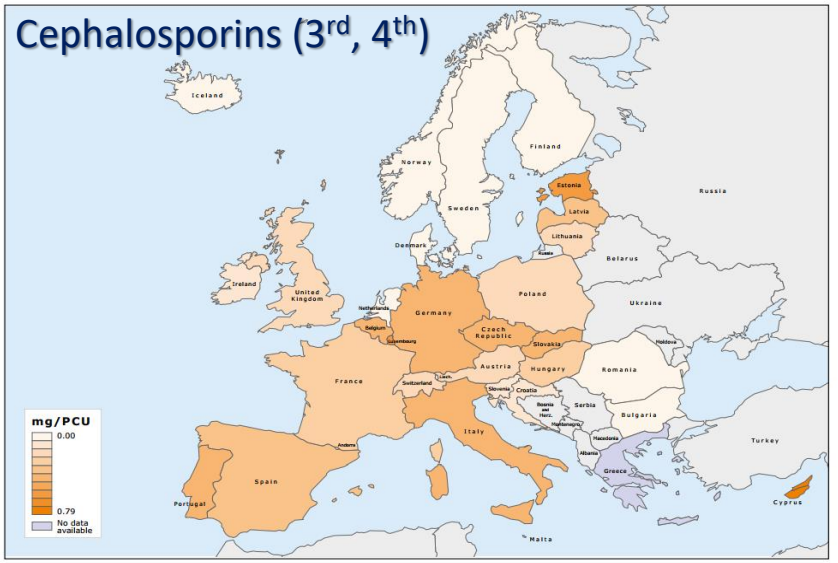
aminoglycosides

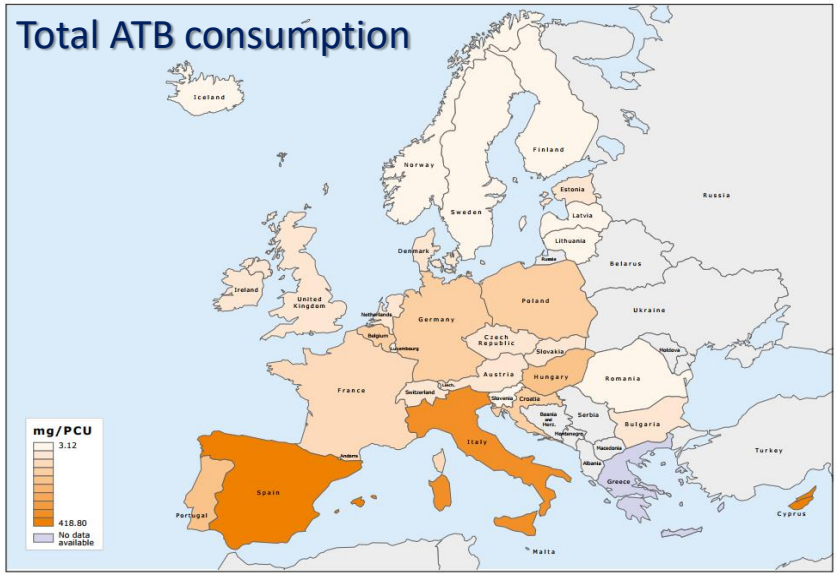
polymyxins

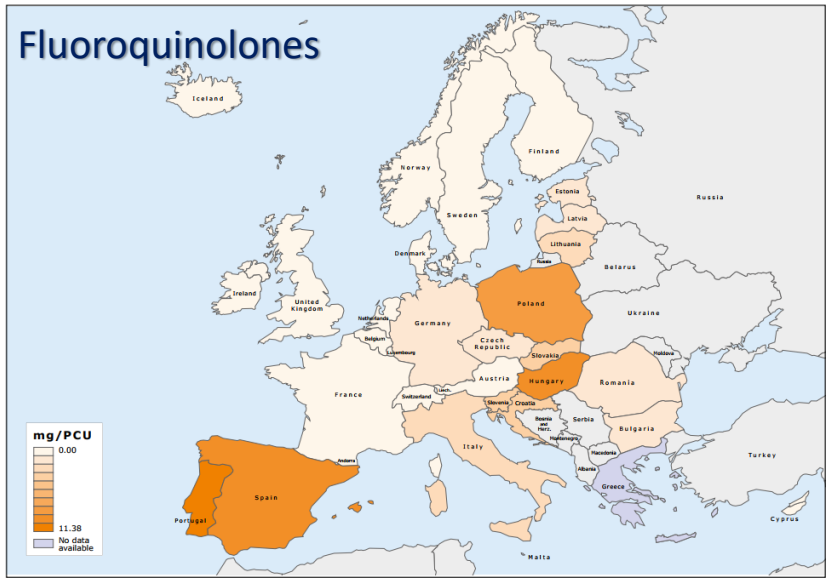




Antibiotics in veterinary medicine





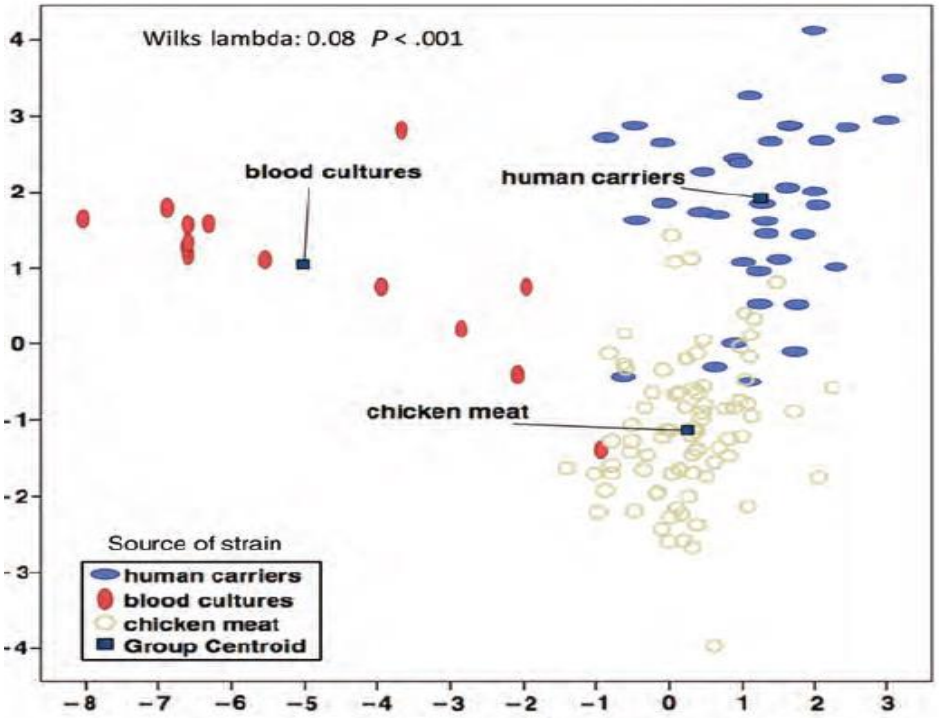


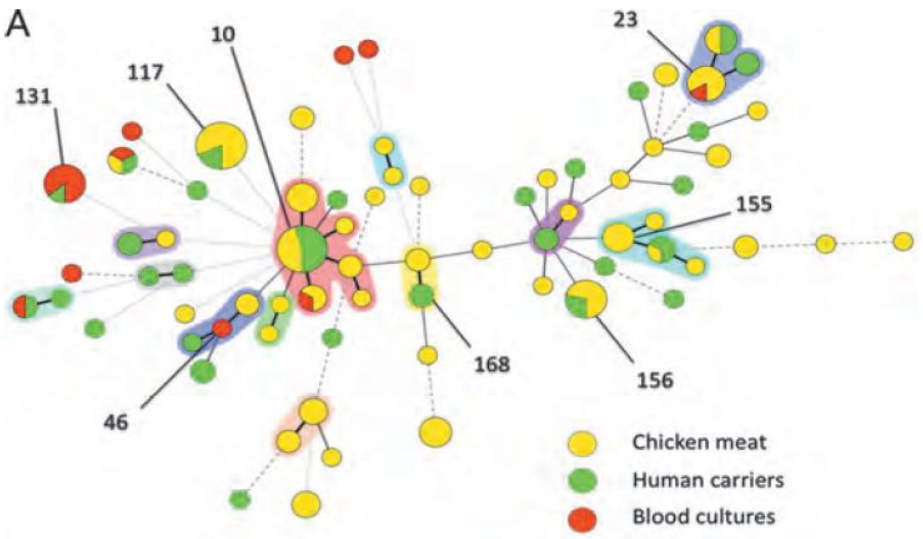
European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) – Report 2014

Antibiotics in veterinary medicine – risk for humans

Extended-Spectrum β-Lactamase–Producing *Escherichia coli* From Retail Chicken Meat and Humans: Comparison of Strains, Plasmids, Resistance Genes, and Virulence Factors

Jan A. J. W. Kluytmans,[1,2,3] Ilse T. M. A. Overdevest,[1,2] Ina Willemsen,[1] Marjolein F. Q. Kluytmans-van den Bergh,[1] Kim van der Zwaluw,[4] Max Heck,[4] Martine Rijnsburger,[3] Christina M. J. E. Vandenbroucke-Grauls,[3] Paul H. M. Savelkoul,[3] Brian D. Johnston,[5] David Gordon,[6] and James R. Johnson[5]





Antibiotics in veterinary medicine – risk for humans

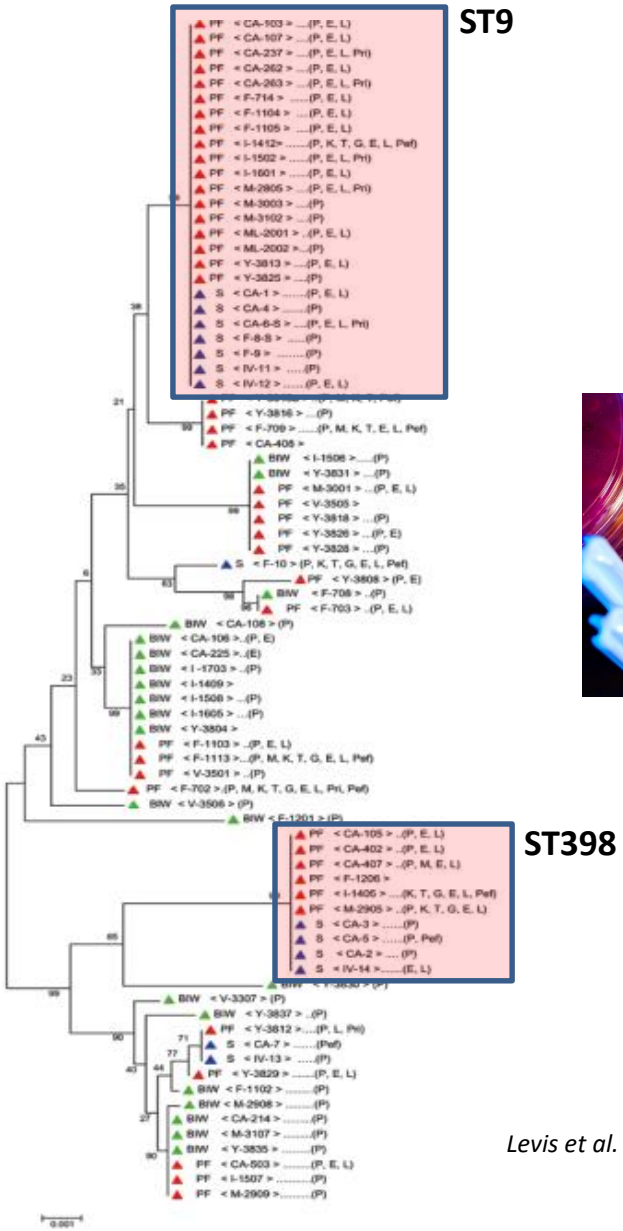
Clonal Comparison of *Staphylococcus aureus* Isolates from Healthy Pig Farmers, Human Controls, and Pigs

Laurence Armand-Lefevre,* Raymond Ruimy,* and Antoine Andremont*

▲ insurance company workers

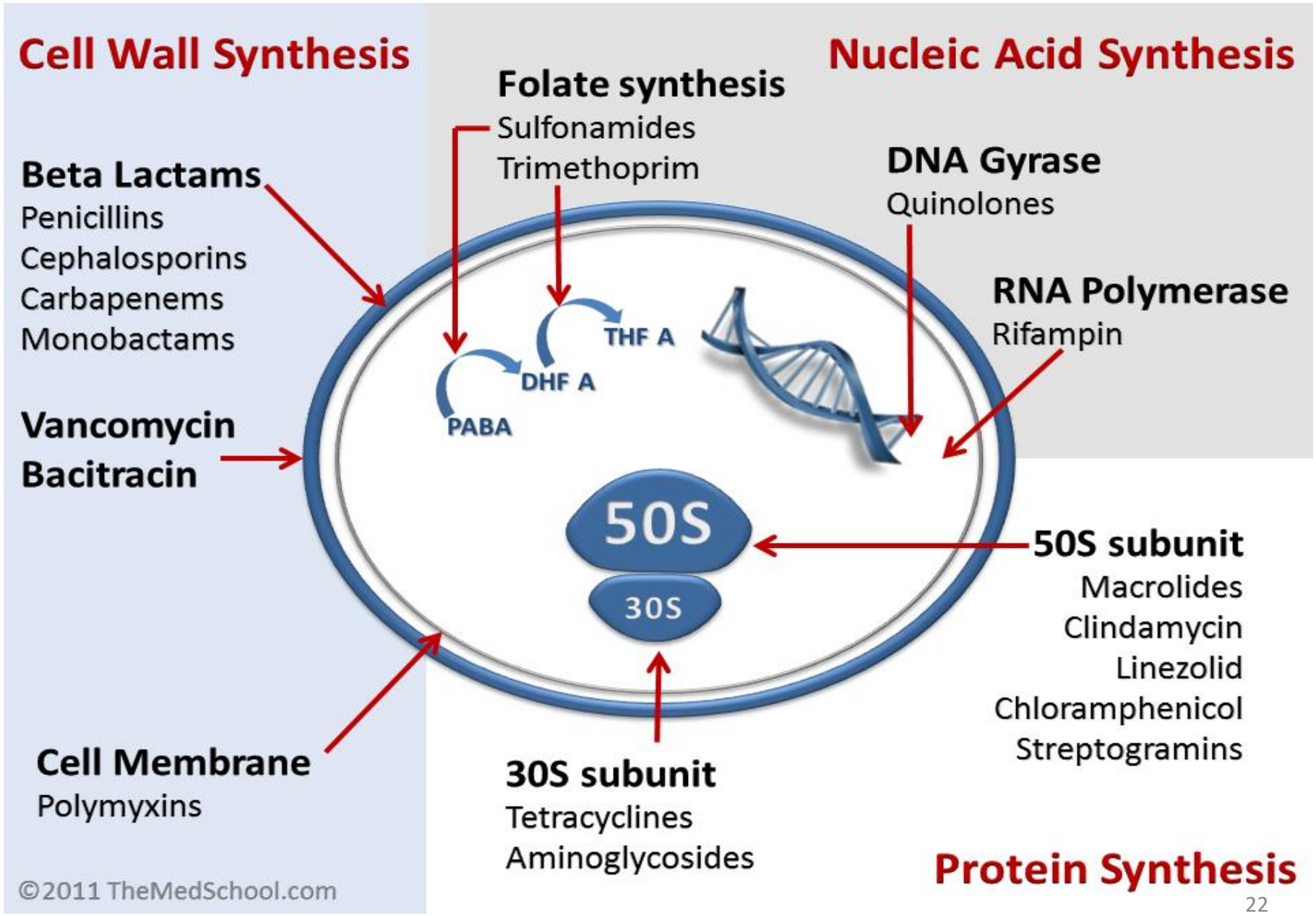
▲ pig farm workers

▲ pigs

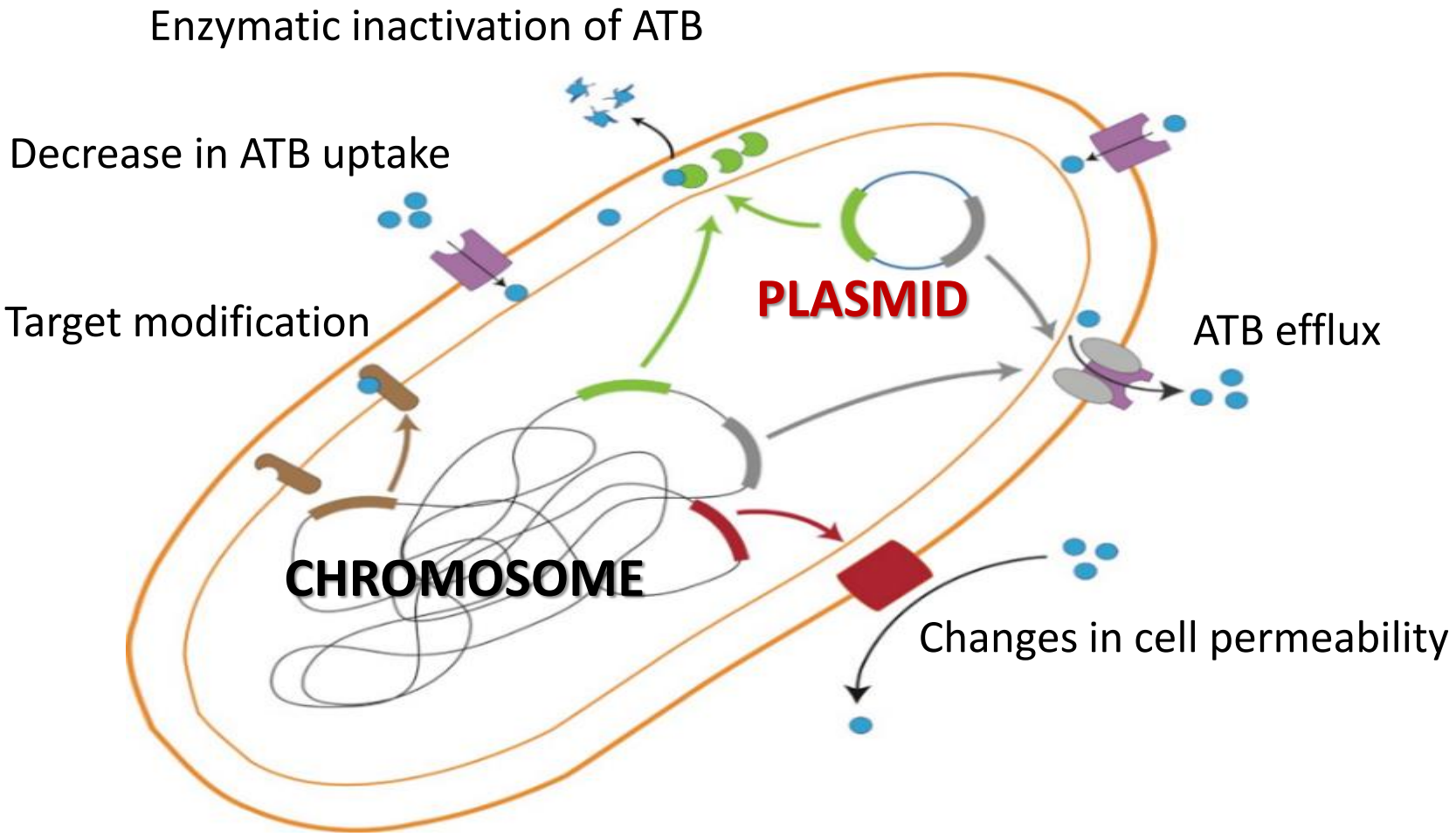


Levis et al. 2005, 2008 Emerging Infectious Diseases

Antibiotics – mode of action

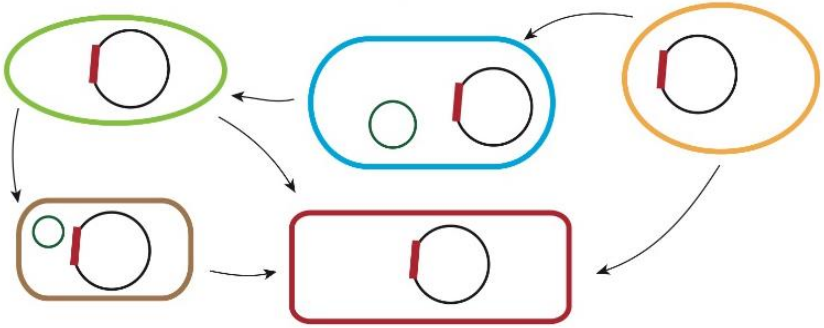


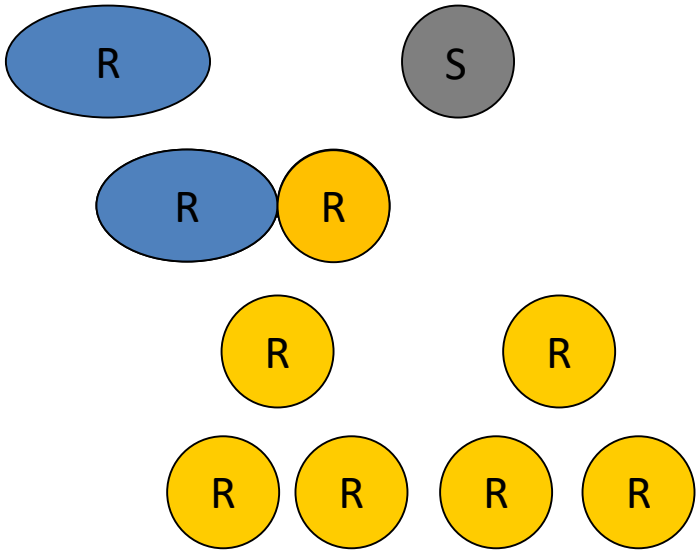
How bacteria become resistant to antibiotics?

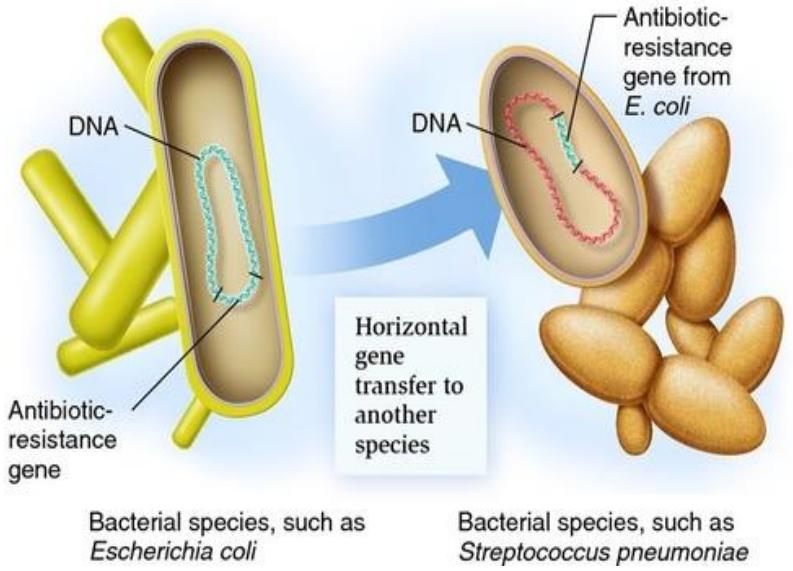


ATB, antibiotic

How is AMR disseminated?



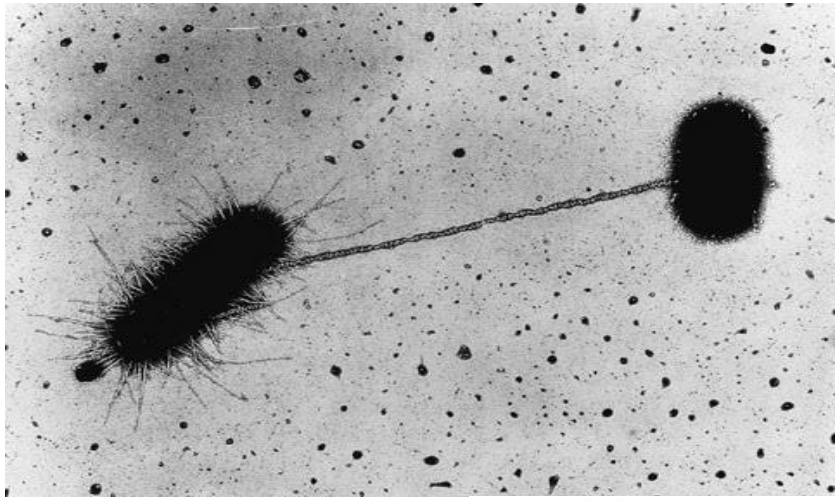


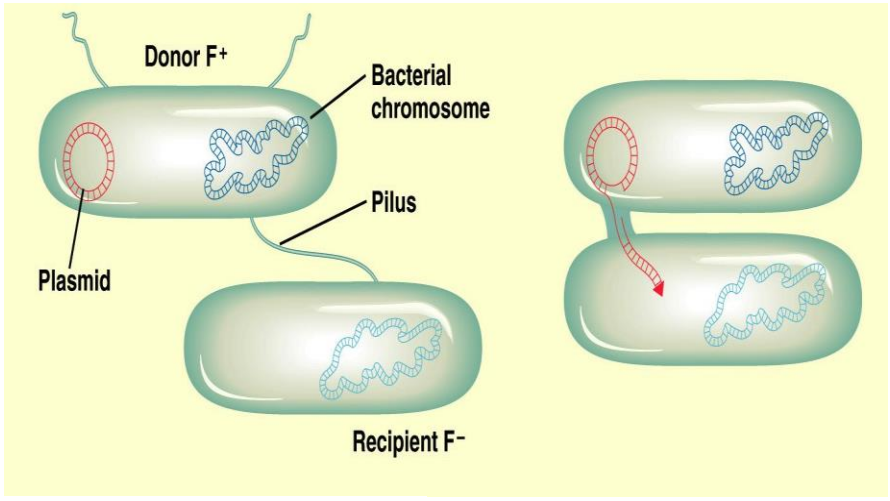


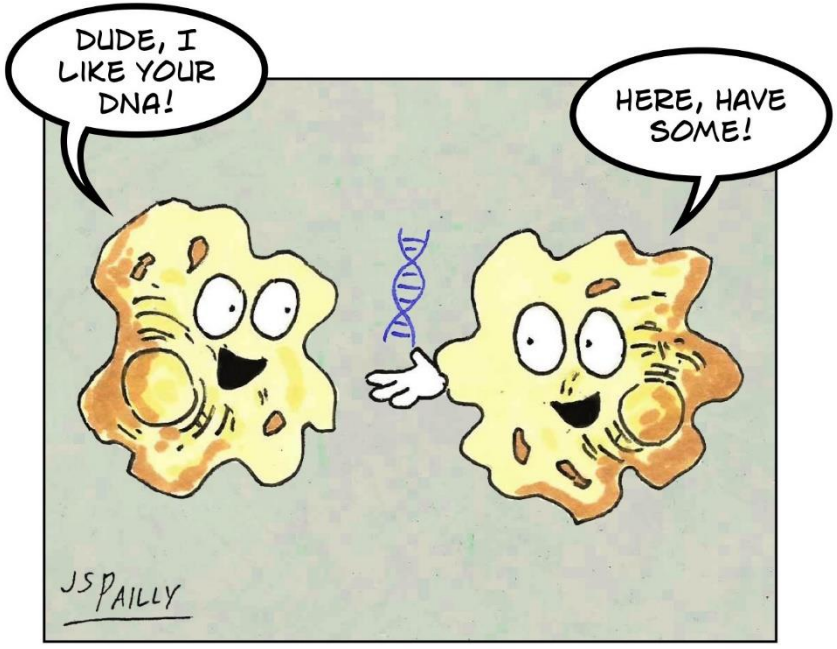
AMR genes are transferred between diverse bacterial strains, species, genera

R, resistant to antibiotic; S , susceptible to antibiotic

How is AMR disseminated?

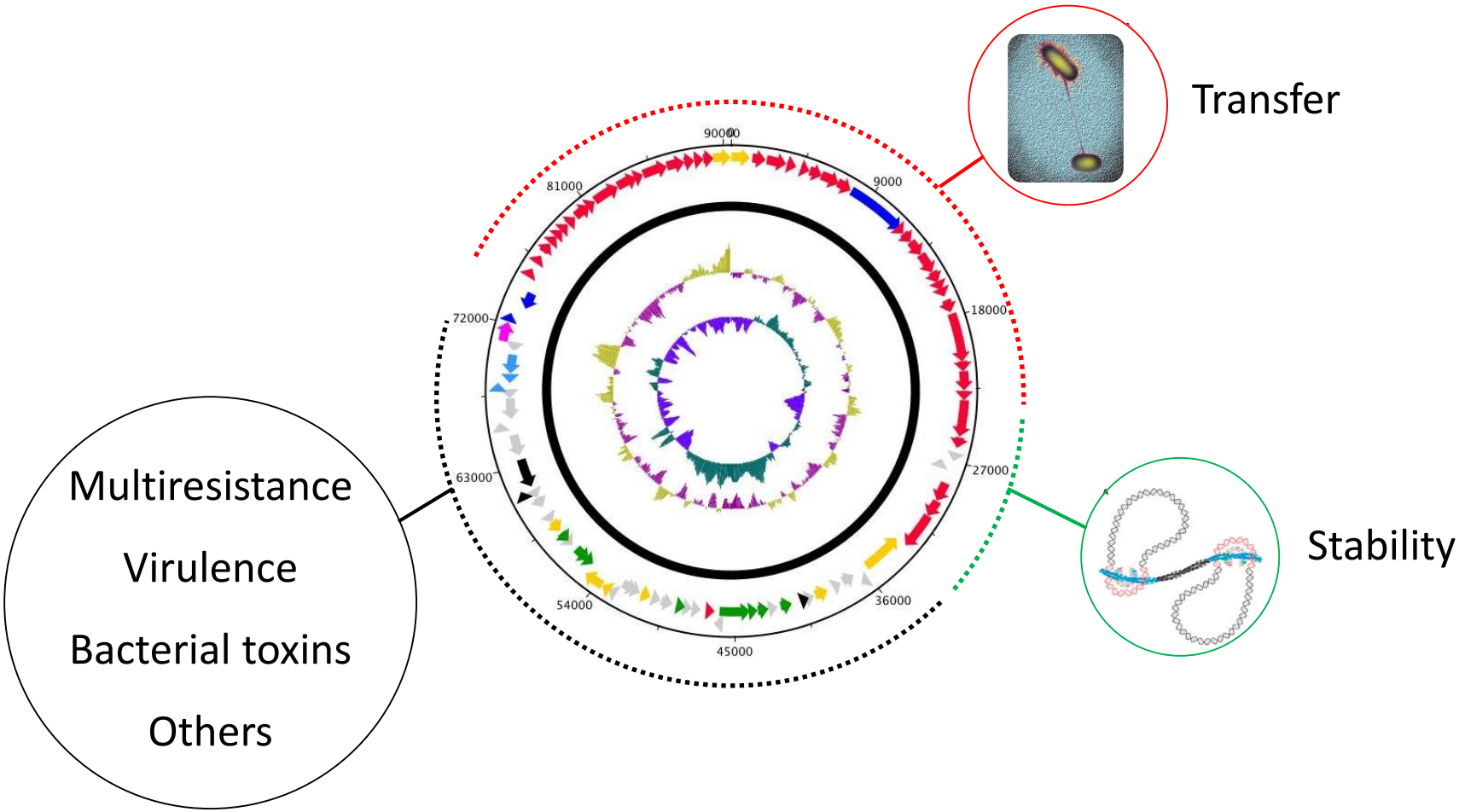






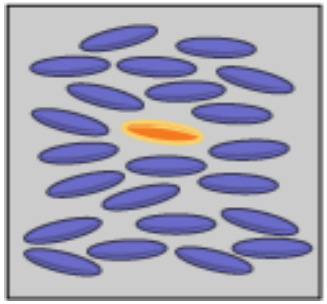
http://leavingbio.net/bacteria/
https://planetpailly.com/2016/03/04/sciency-words-bacterial-conjugation/

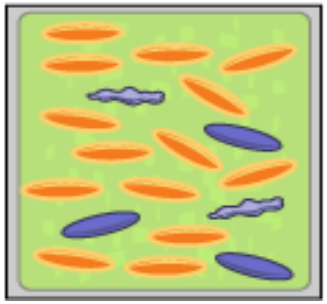
Plasmids in dissemination of AMR

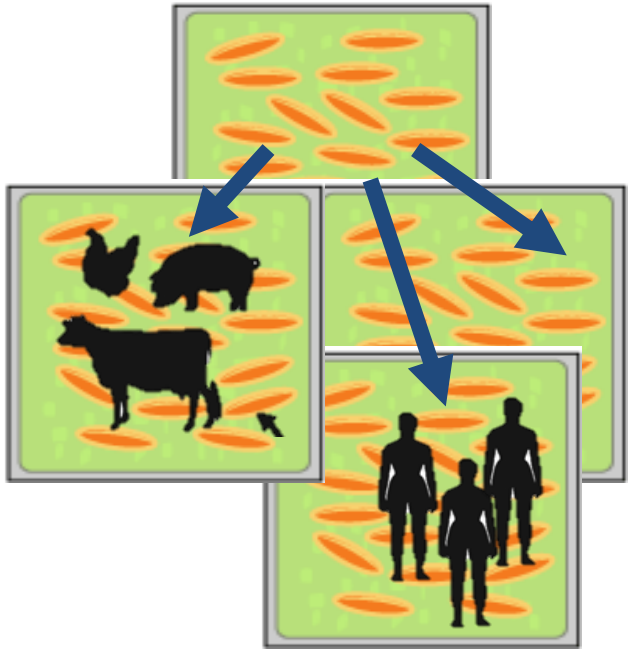


3 Steps in antibiotic resistance

Emergence of resistant bacteria → **Selection** → **Dissemination**







Origin of resistant bacteria

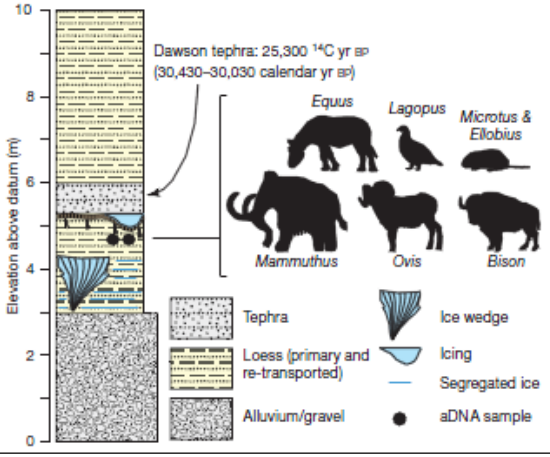
Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

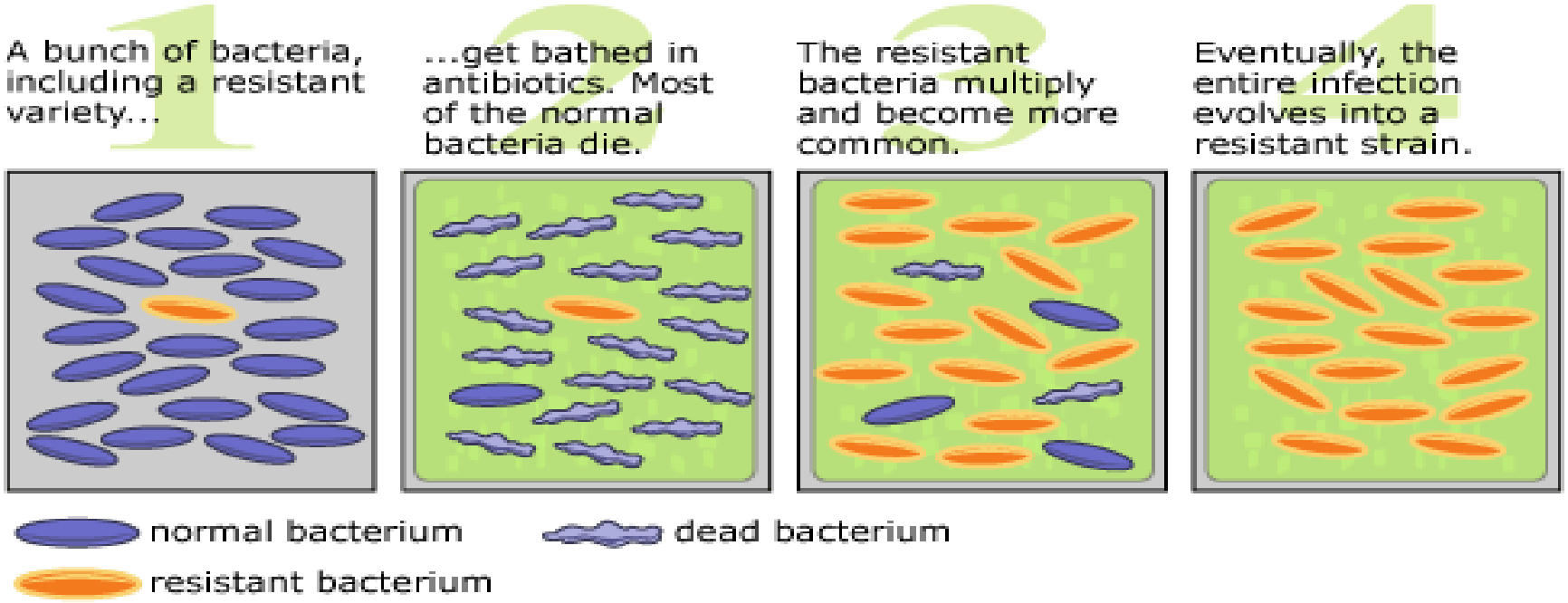
The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes[1,2]. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics[3]. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

with high concentrations of *Escherichia coli* harbouring the *gfp* (green fluorescent protein) gene from *Aequorea victoria* (Supplementary Information).

After fracturing of the samples (Supplementary Fig. 3), total DNA was extracted from a series of five subsamples taken along the radius of each core (Supplementary Information). Quantitative polymerase

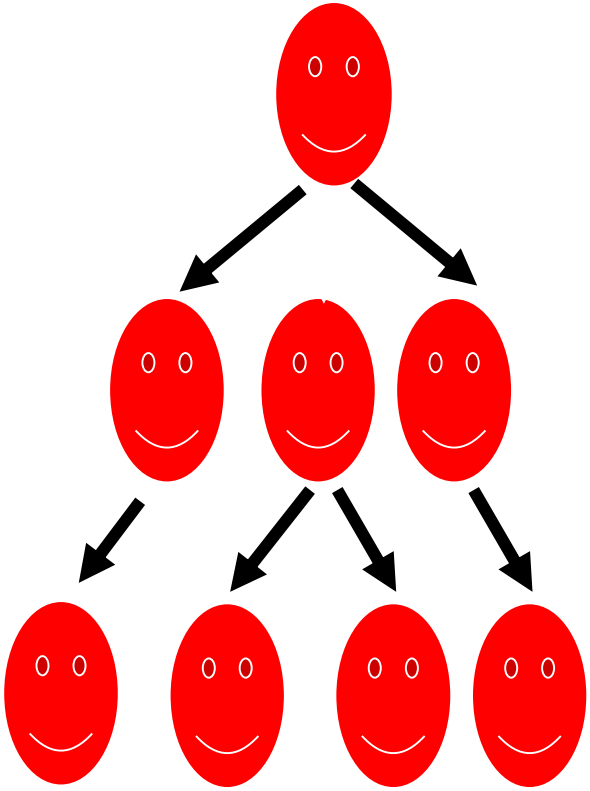


2. Selection of resistant bacteria



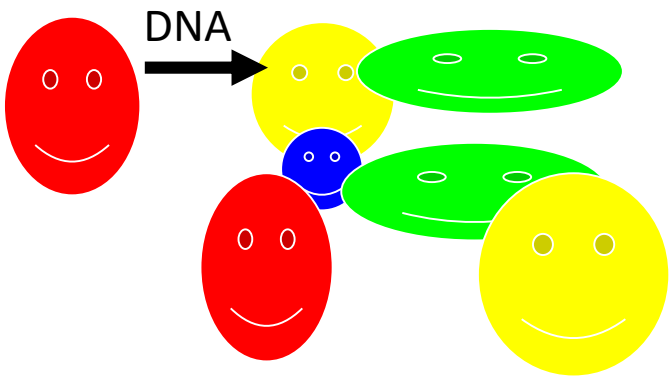
3. Dissemination of resistant bacteria

Clonal dissemination



→ Successful bacterial lineages

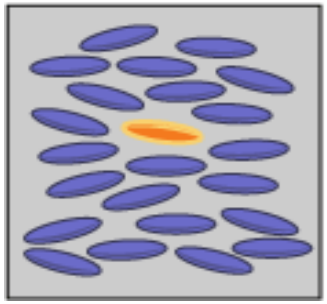
Horizontal transfer of genetic information

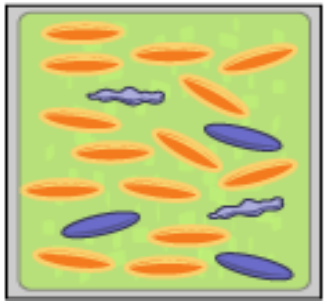


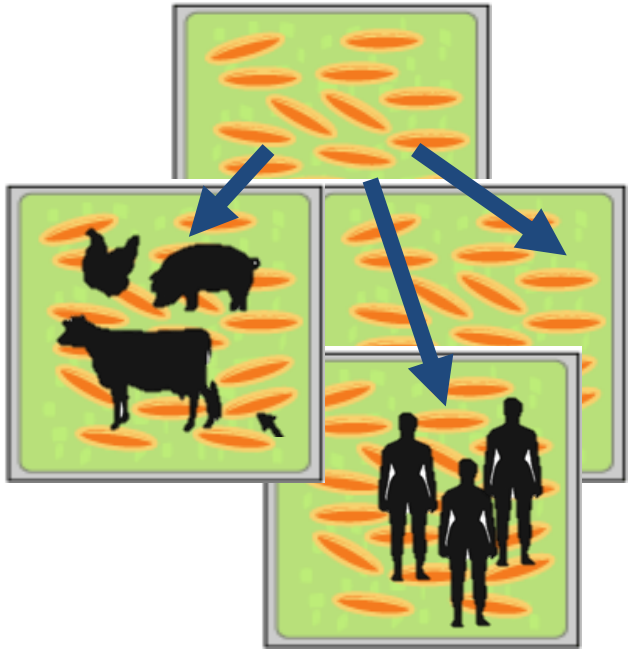
→ Successful resistance genes

3 Steps in antibiotic resistance

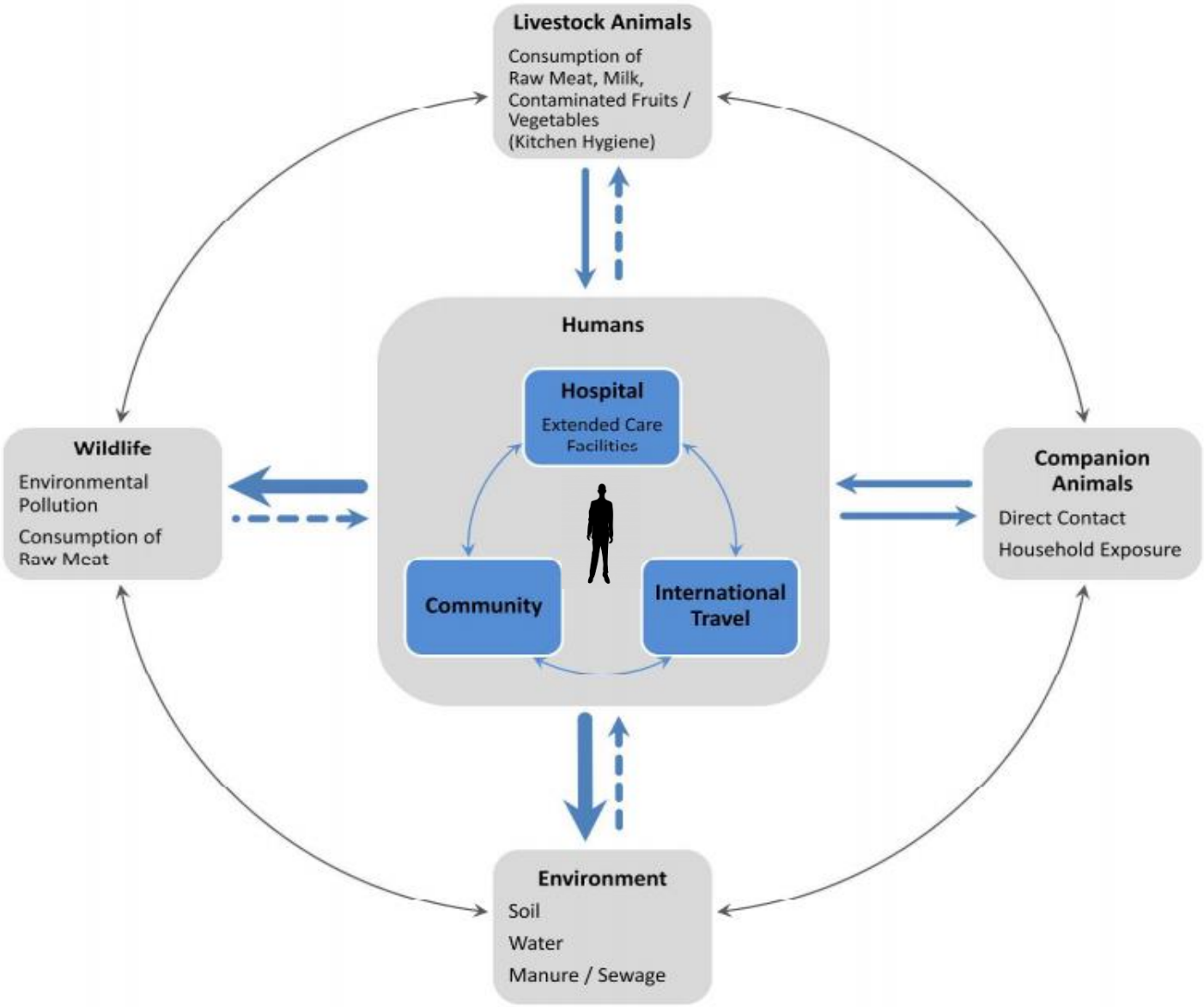
Emergence of resistant bacteria → **Selection** → **Dissemination**





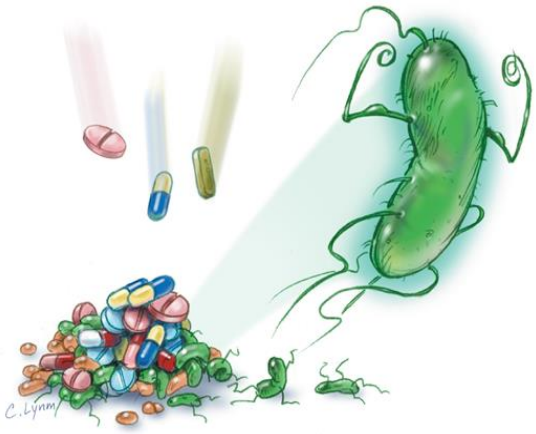


Transfer of resistant bacteria



To conclude…

- Misuse, overuse, under/ inadequate use of antimicrobials
- Costs money and lives
- Threat to global stability and national security
- Antibiotic resistant bacteria are found everywhere
- Increasing resistance and multiresistance
- Emergence and worldwide transmission of multiresistant clones
- Dissemination accelerated by gene transfer



To conclude…

- Antibiotic policy
- National and international programs to combat resistance
- Hygiene and infection control strategies
- Novel antibiotics
- Alternative treatment methods