



CATÓLICA
FACULTY
OF BIOTECHNOLOGY

PORTO

Resistência a antibióticos: da natureza a contaminante ambiental

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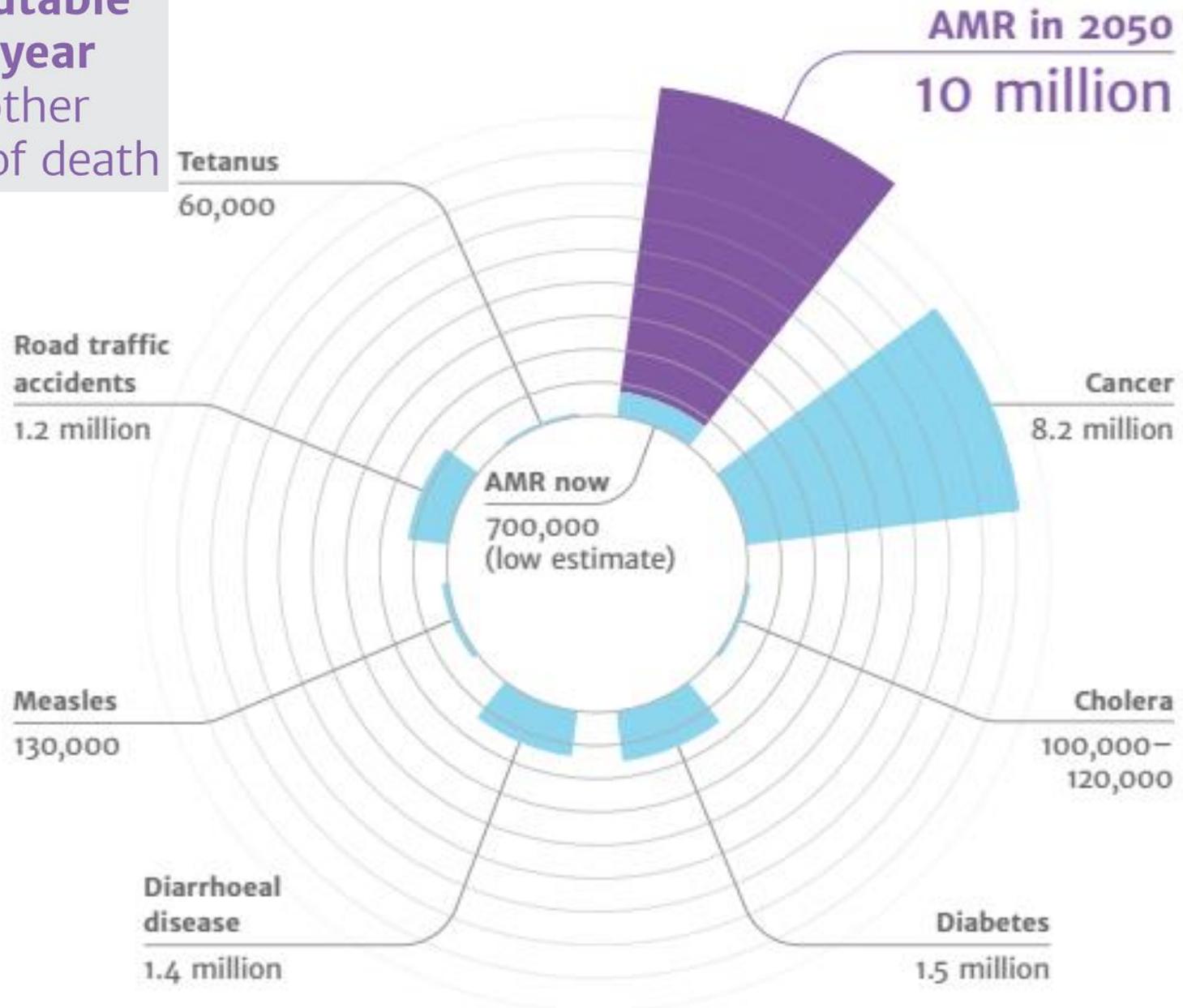
Rede Galega de Riscos
Emerxentes en
Seguridade Alimentaria

www.risegal.csic.es



Vigo, June 20th, 2018

Deaths attributable to AMR every year compared to other major causes of death



Human and economic impact of antimicrobial resistance

Human and economic impact of antimicrobial resistance*



Each year, in EU countries...

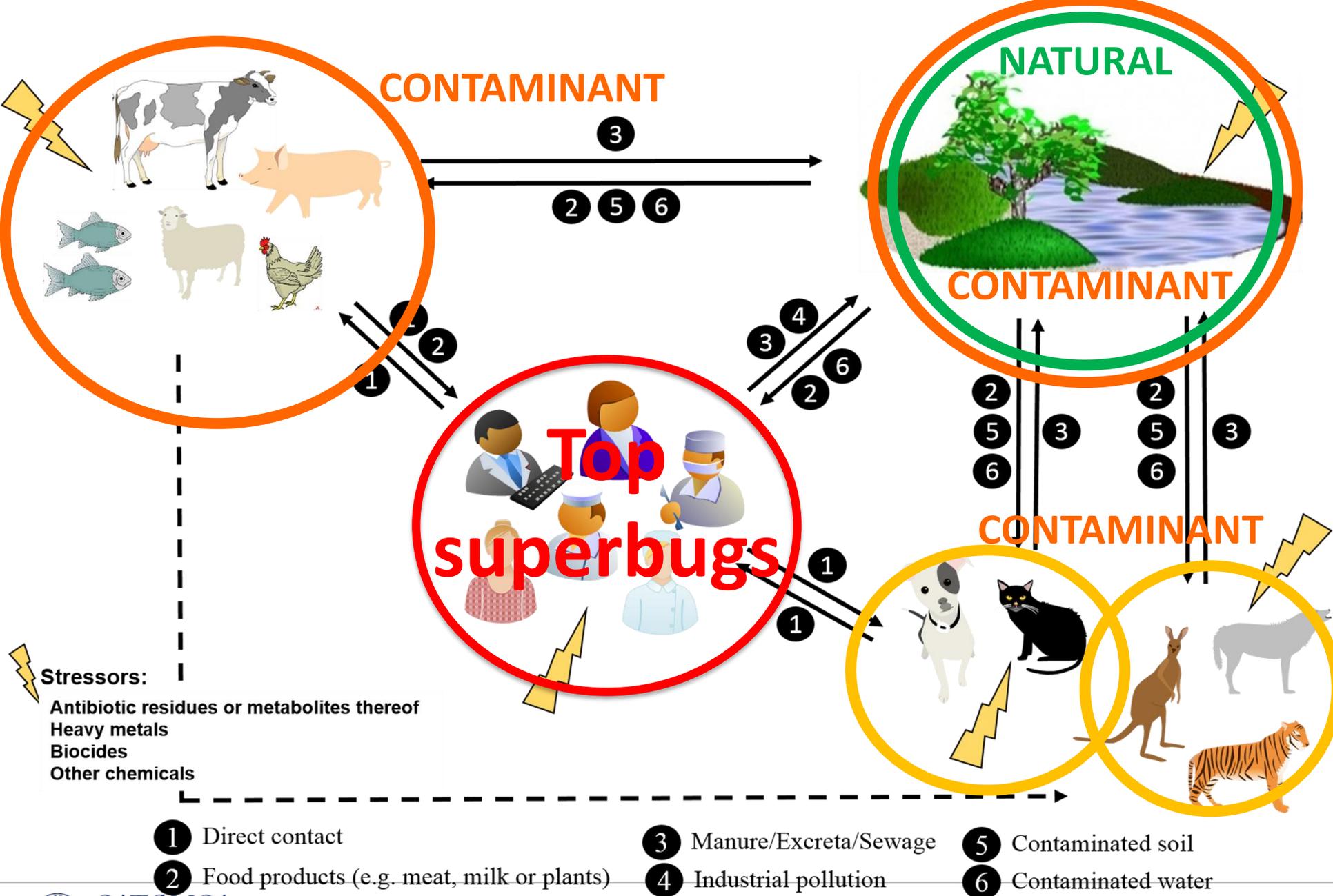
25,000 deaths directly attributable to multidrug-resistant infections

Extra in-hospital costs	Extra outpatient costs	Productivity losses due to absence from work	Productivity losses due to patients who died from their infection	TOTAL
€ 927.8 million	€ 10 million	€ 150.4 million	€ 445.9 million	€ 1.5 billion

Source – *The bacterial challenge: time to react*, Joint Technical Report from ECDC and EMA, Stockholm, September 2009. Available online at:
http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=444

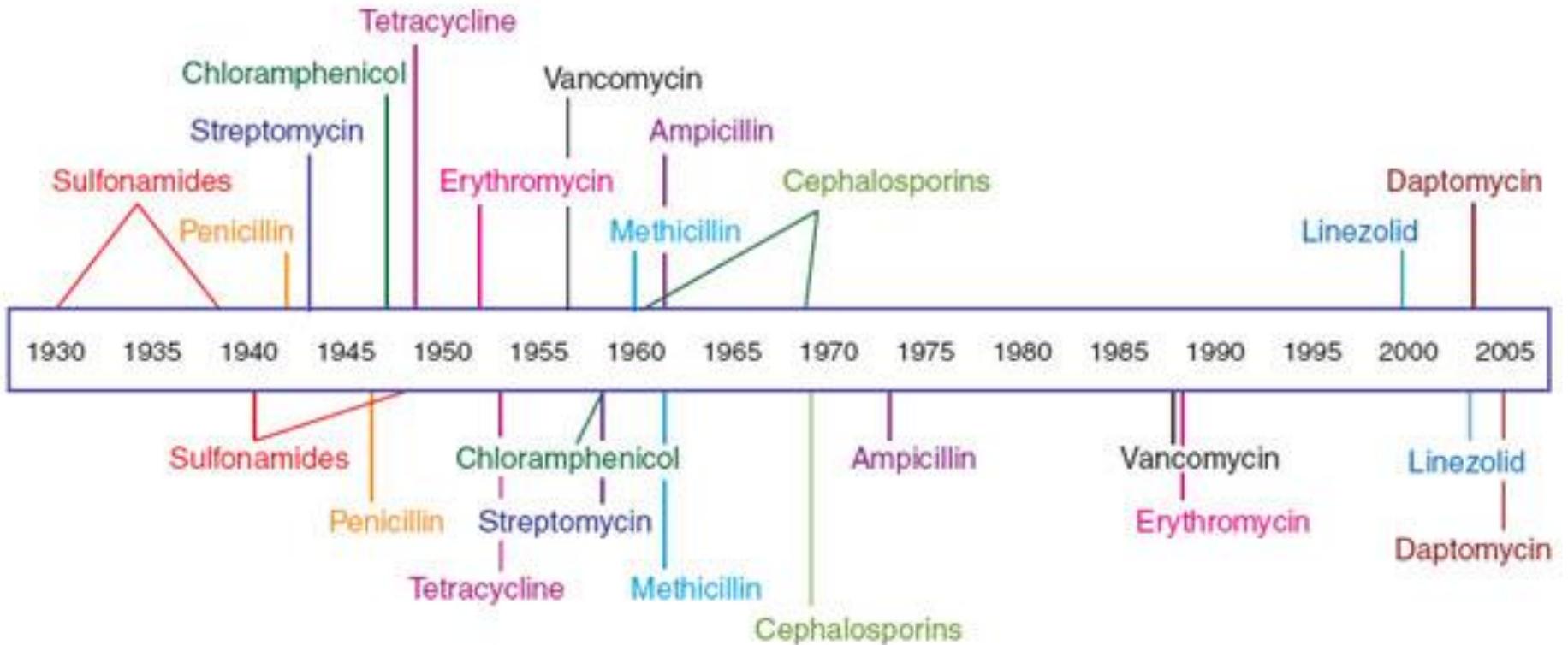
**Estimates for 5 common multidrug-resistant bacteria (EU Member States, Norway and Iceland, 2007)*





NEW ANTIBIOTICS ...

Antibiotic deployment



Antibiotic resistance observed

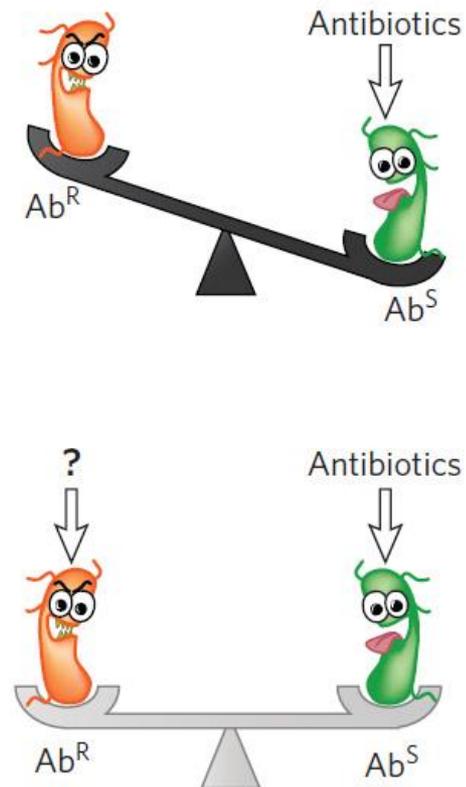
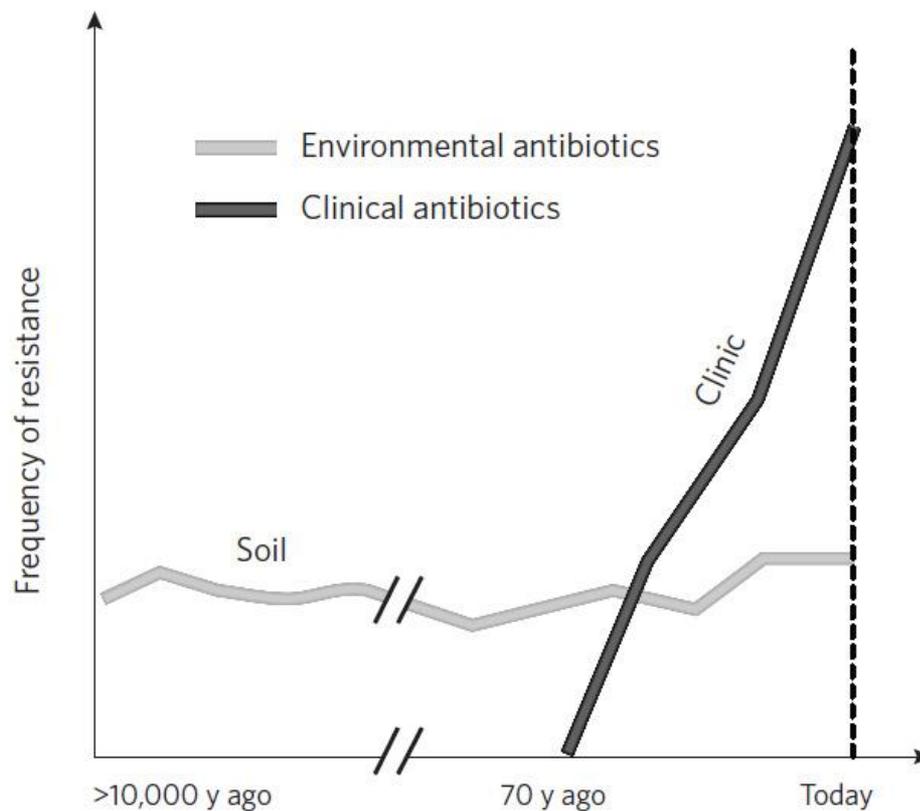
NOVEL RESISTANCE TYPES ...



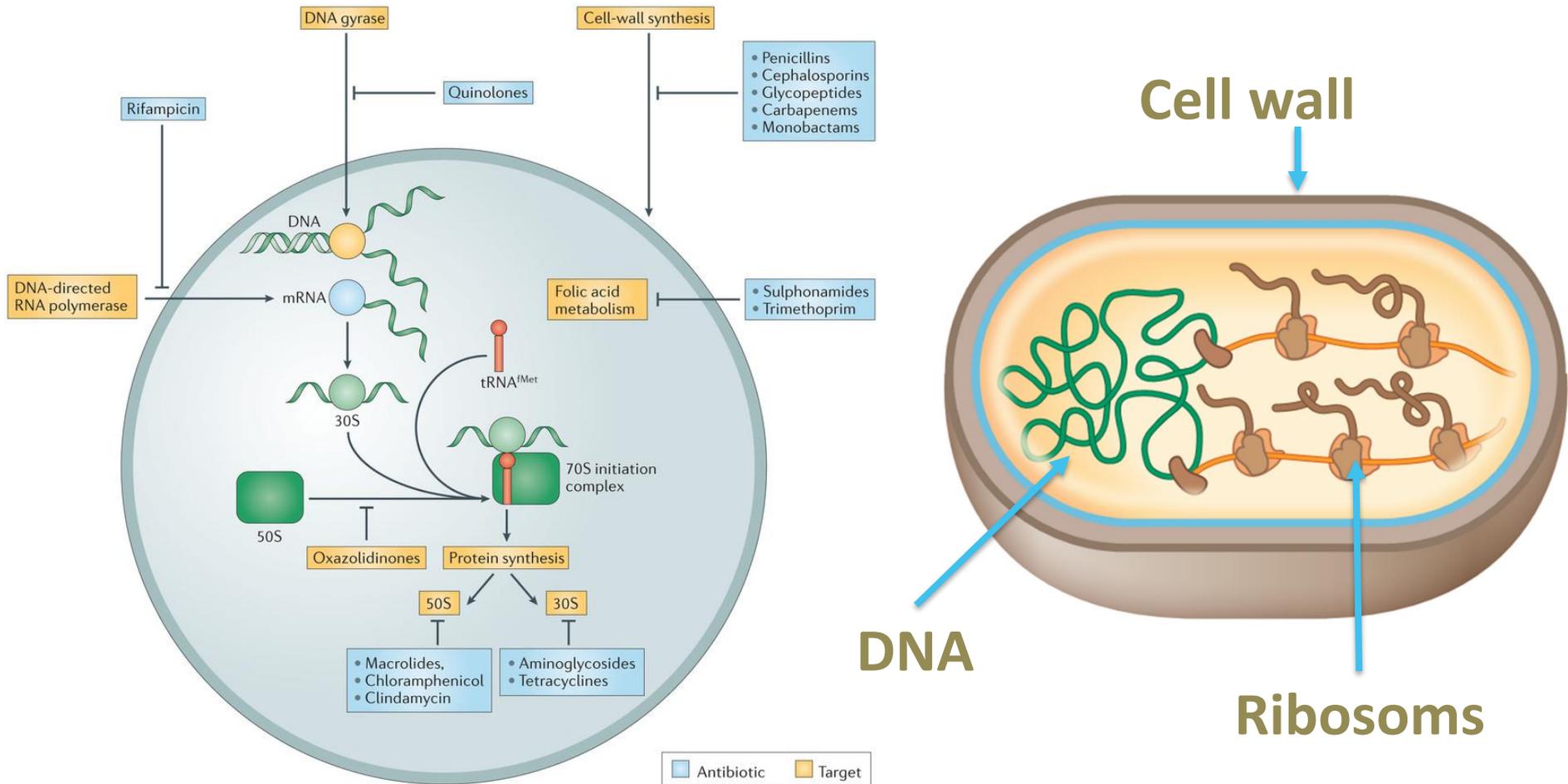
REVIEWS

Call of the wild: antibiotic resistance genes in natural environments

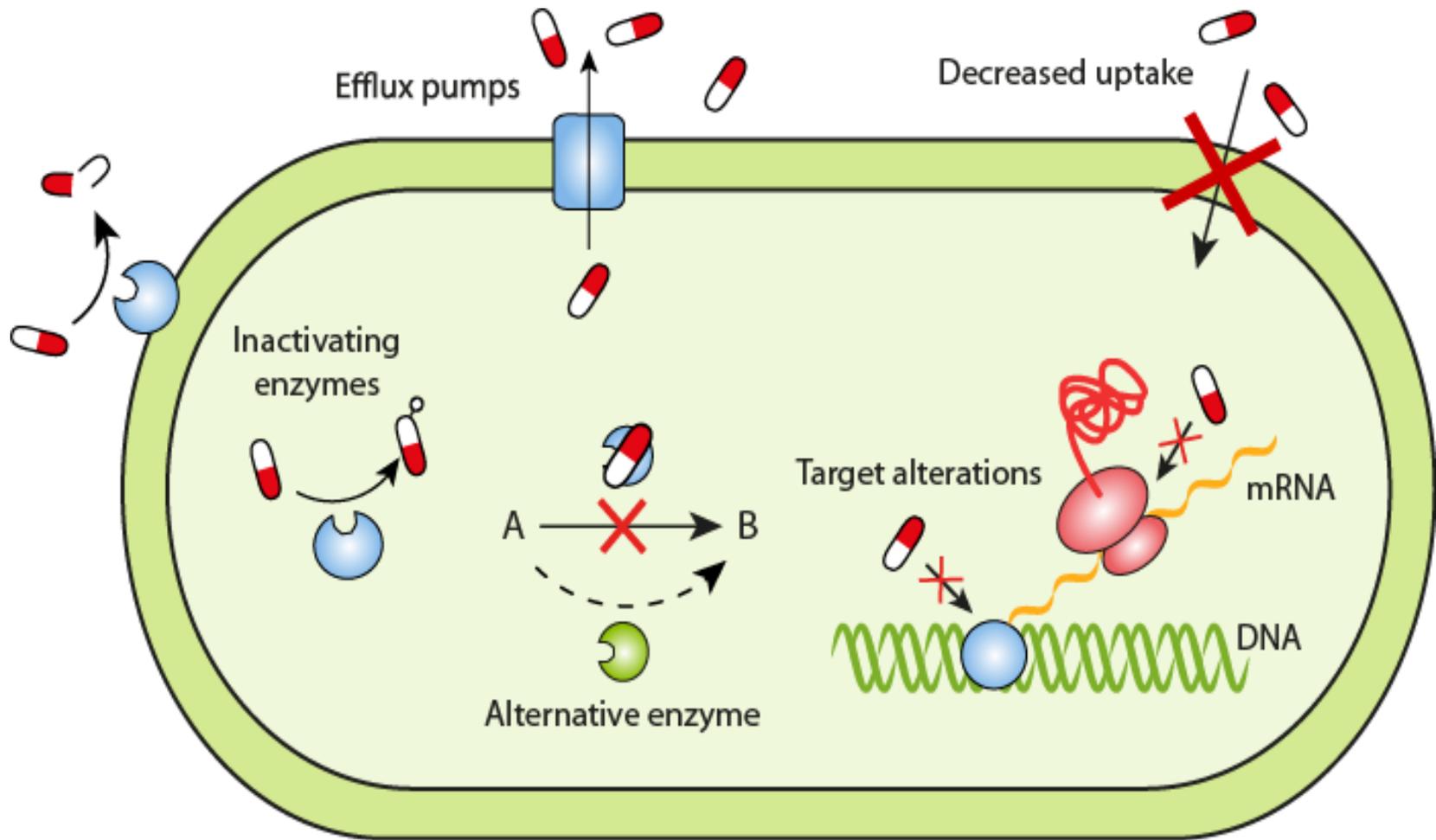
Heather K. Allen^{1*}, Justin Donato², Helena Huimi Wang³, Karen A. Cloud-Hansen⁴, Julian Davies⁵ and Jo Handelsman^{1||}



ANTIBIOTICS HAVE THREE MAJOR HIGHLY SPECIFIC TARGETS IN BACTERIAL CELLS



FIVE GENERAL RESISTANCE MECHANISMS



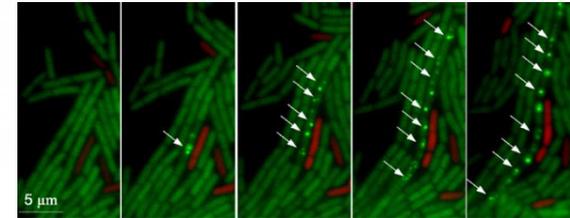
HUNDREDS OF RESISTANCE GENES...



HUNDREDS OF RESISTANCE GENES THAT CAN BE PROPAGATED

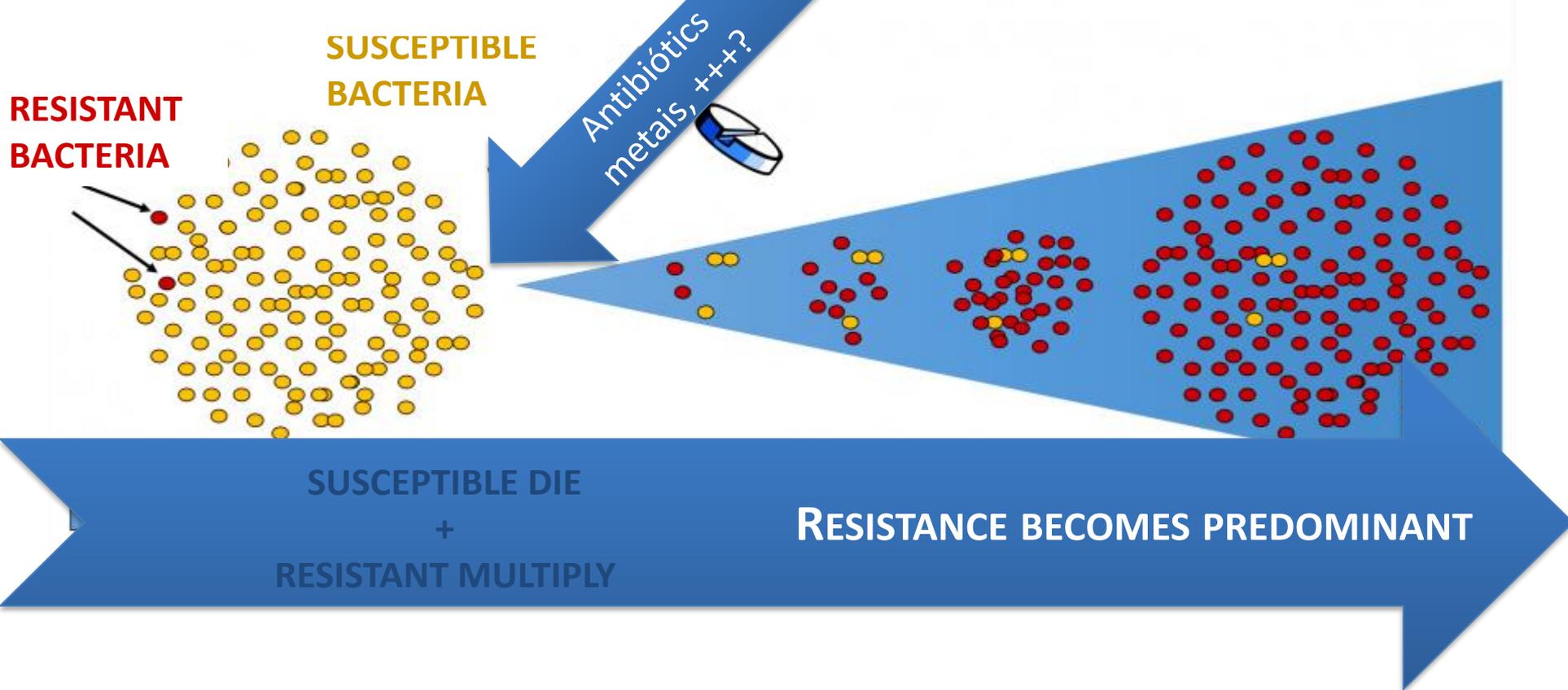


HORIZONTAL GENE TRANSFER



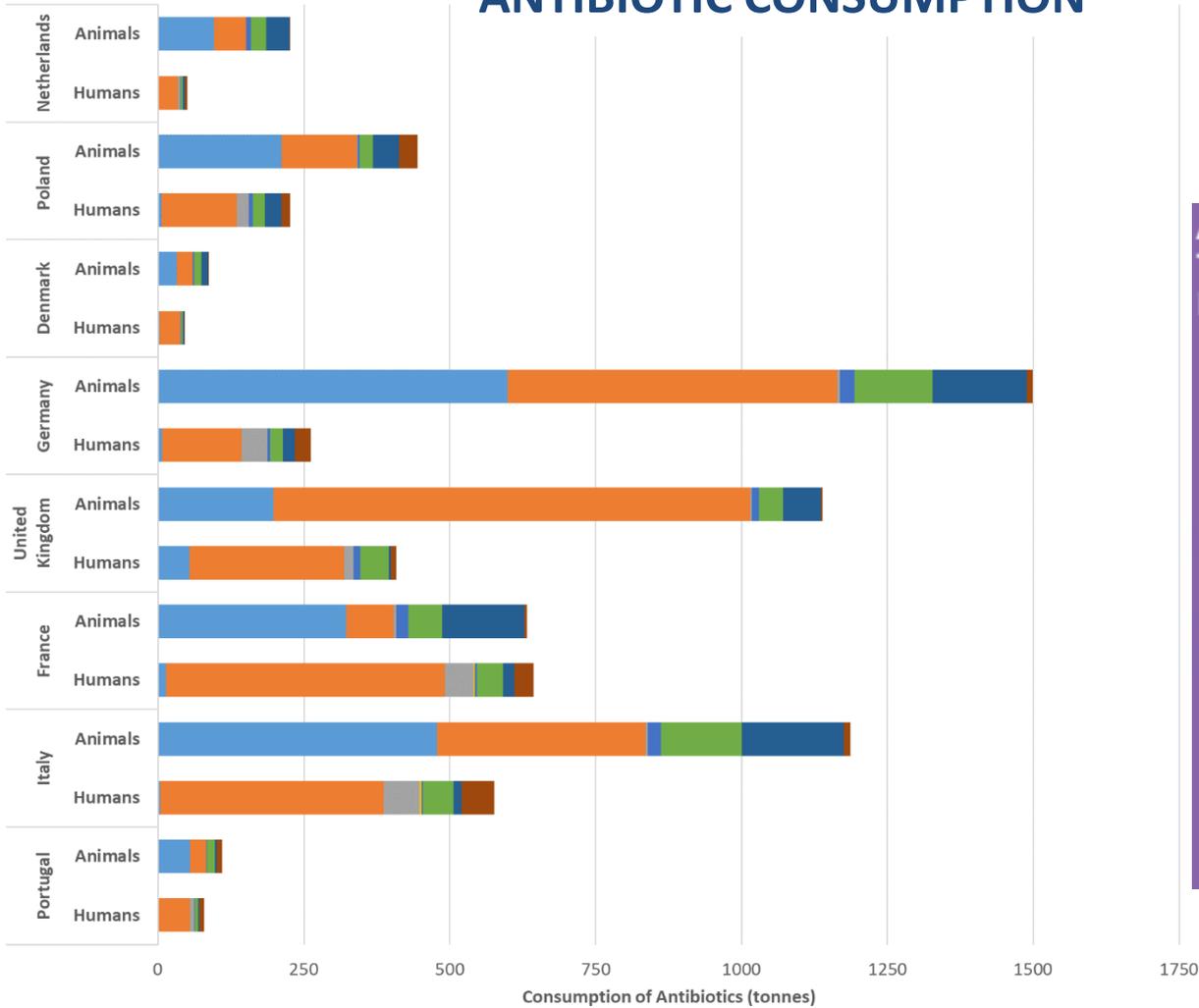
HUNDREDS OF RESISTANCE GENES THAT CAN BE PROPAGATED UNDER THE EFFECT OF...

SELECTIVE PRESSURES

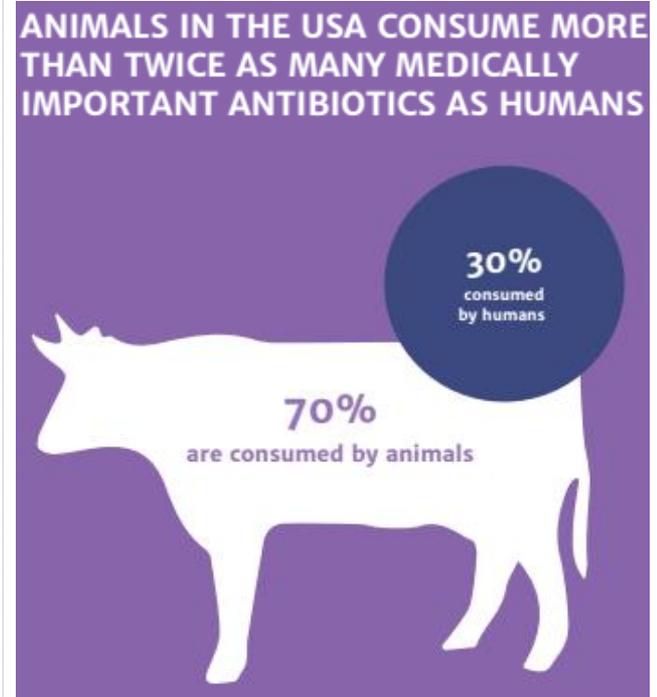


SELECTIVE PRESSURE

ANTIBIOTIC CONSUMPTION

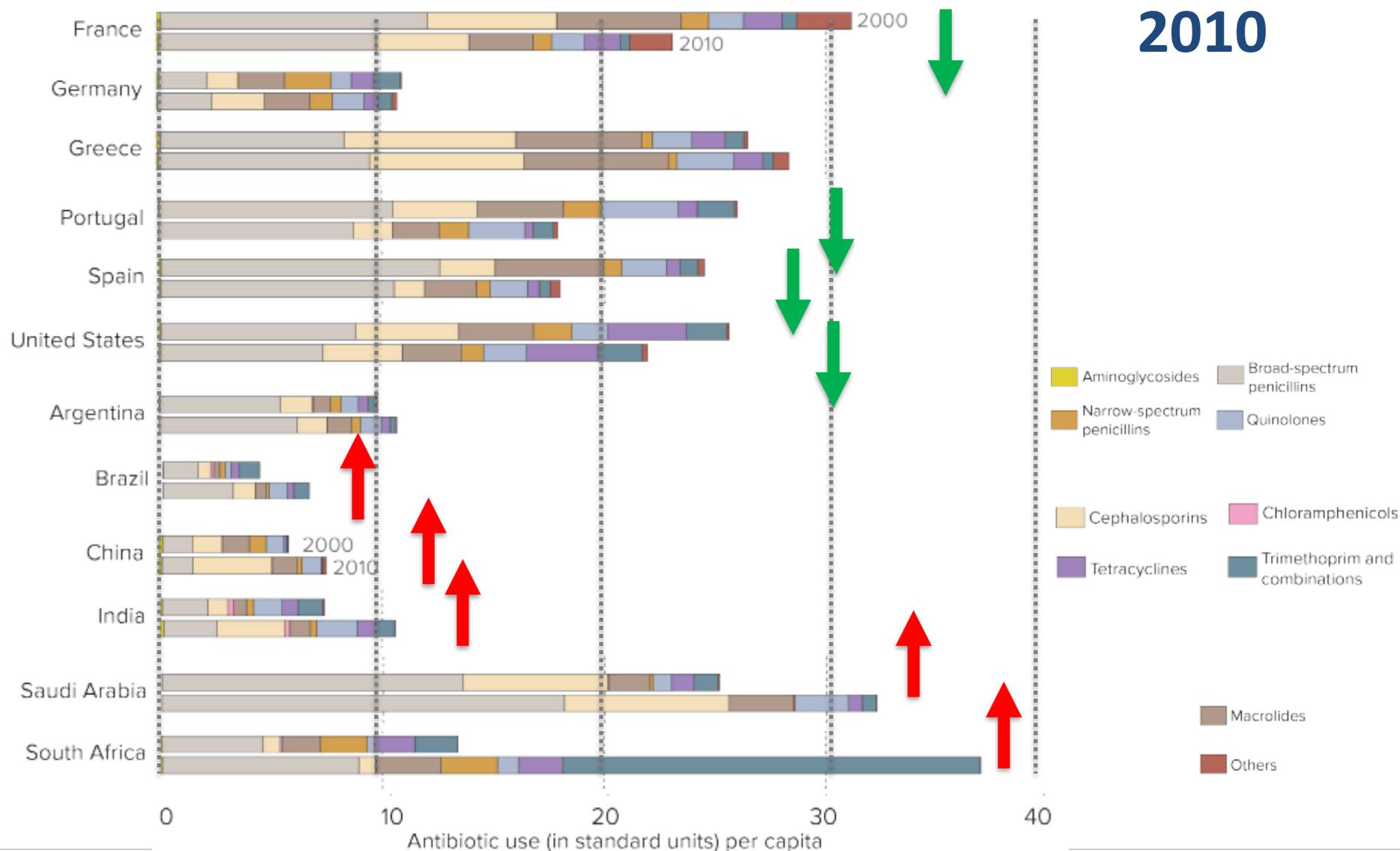


■ Tetracyclines ■ Penicillins ■ Cephalosporins ■ Carbapenems ■ Trimethoprim ■ Macrolides ■ Sulfonamides ■ Fluoroquinolones

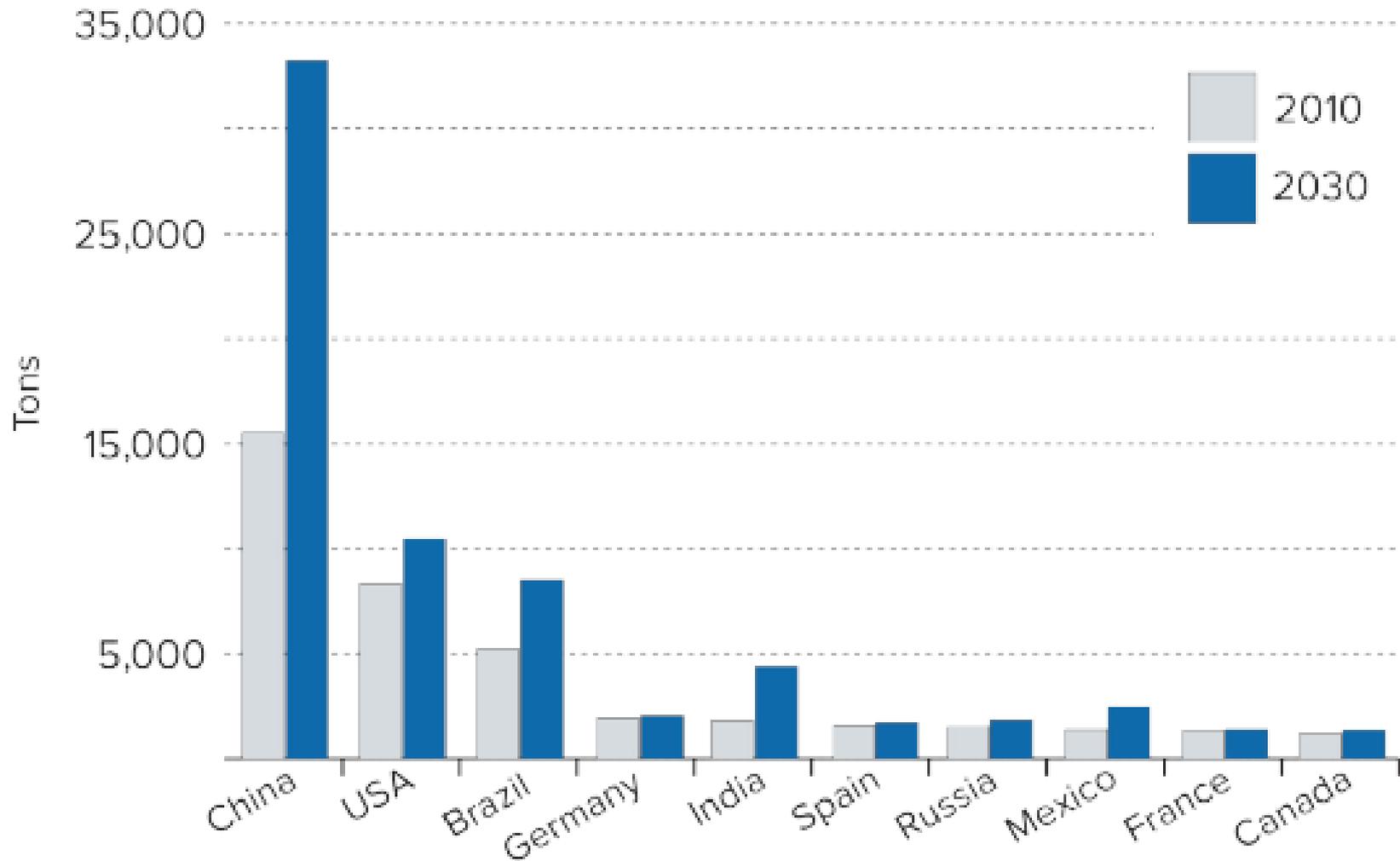


ANTIBIOTIC CONSUMPTION PER CAPITA

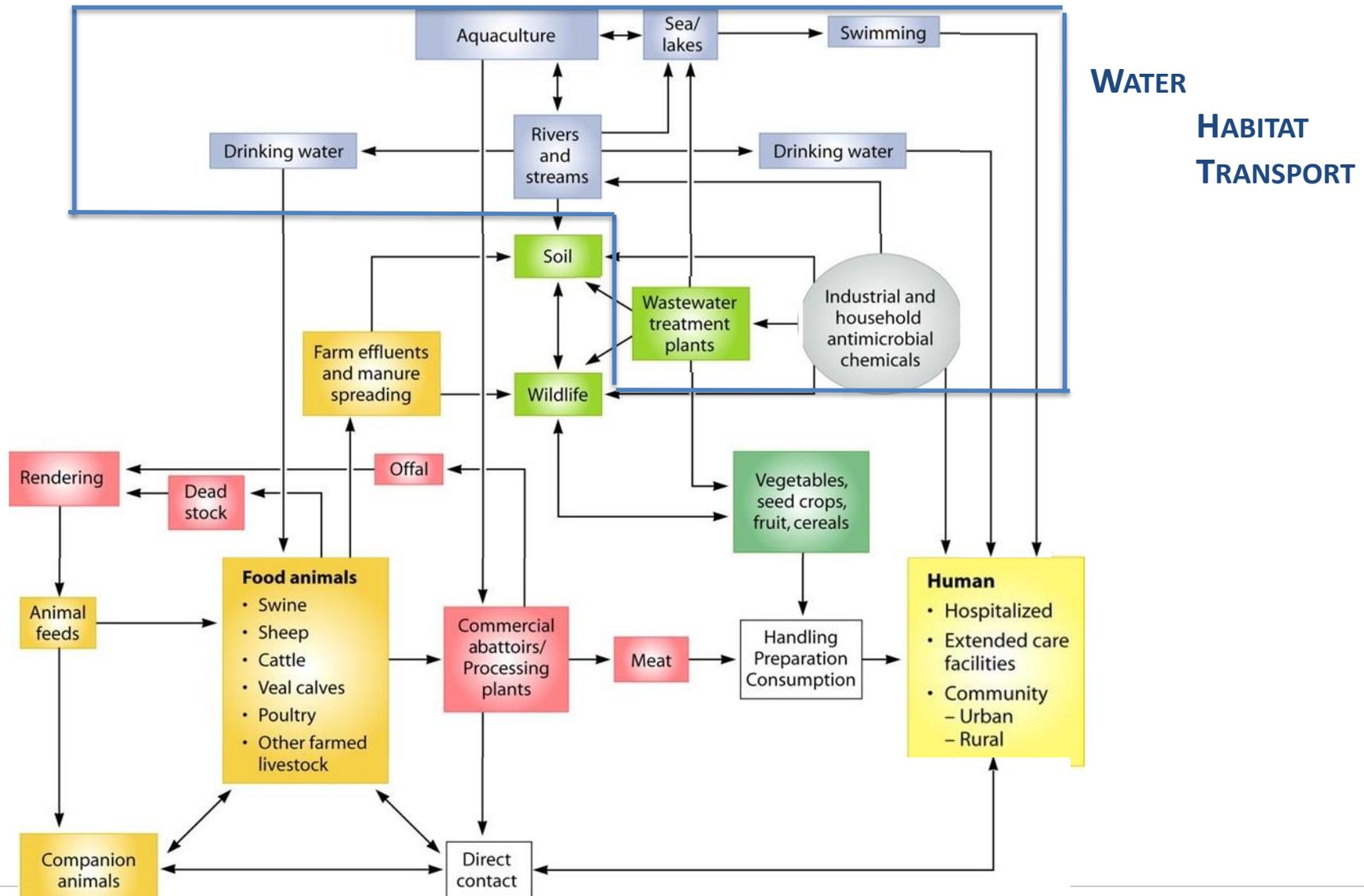
2000
2010



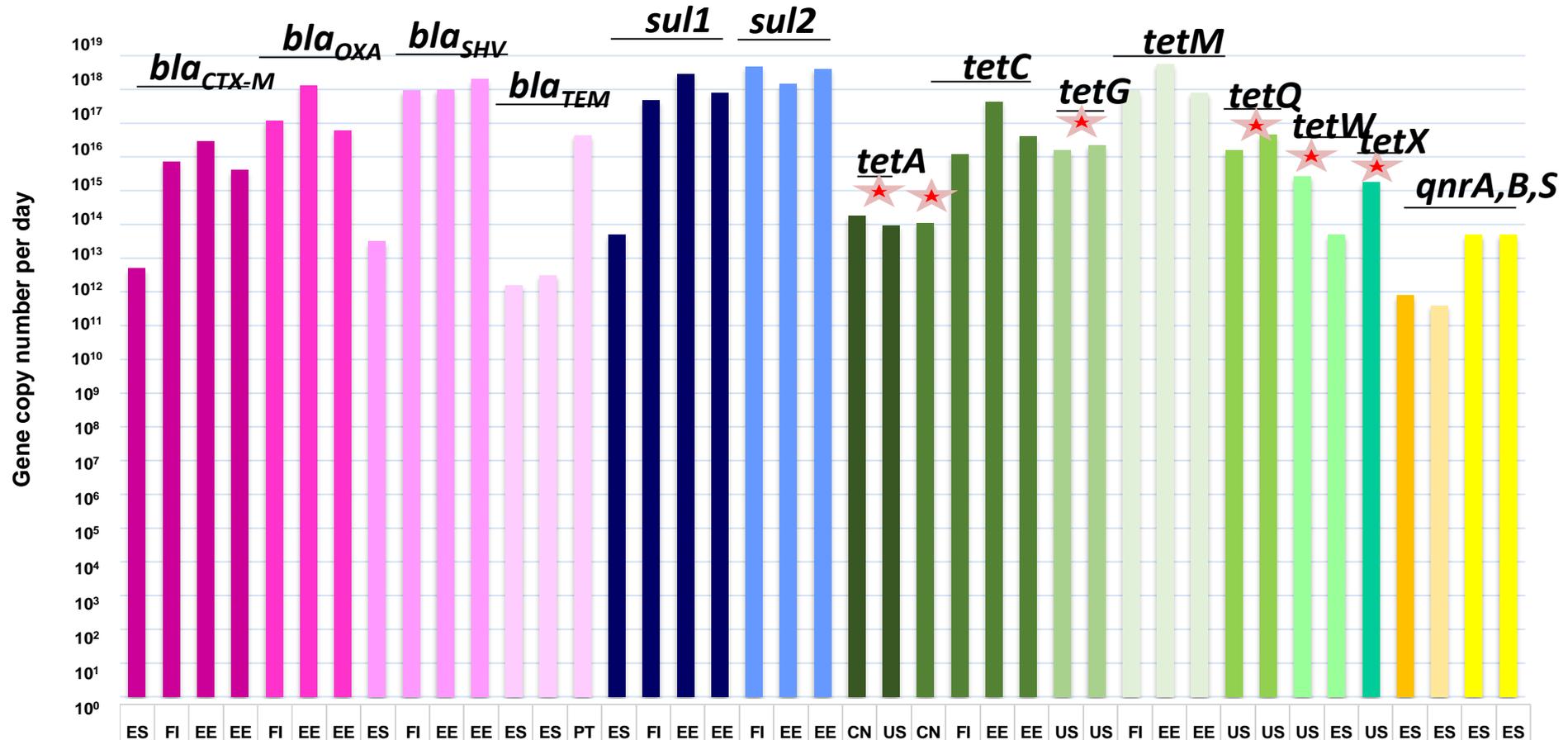
ANTIBIOTIC CONSUMPTION FOR ANIMAL PRODUCTION BY 2030



THE COMPLEX NETWORK OF RESISTANCE PROPAGATION...



It is estimated that more than 10^{10} to 10^{14} copies of genes encoding for tetracycline or beta-lactam resistance are released per minute to the surrounding environment

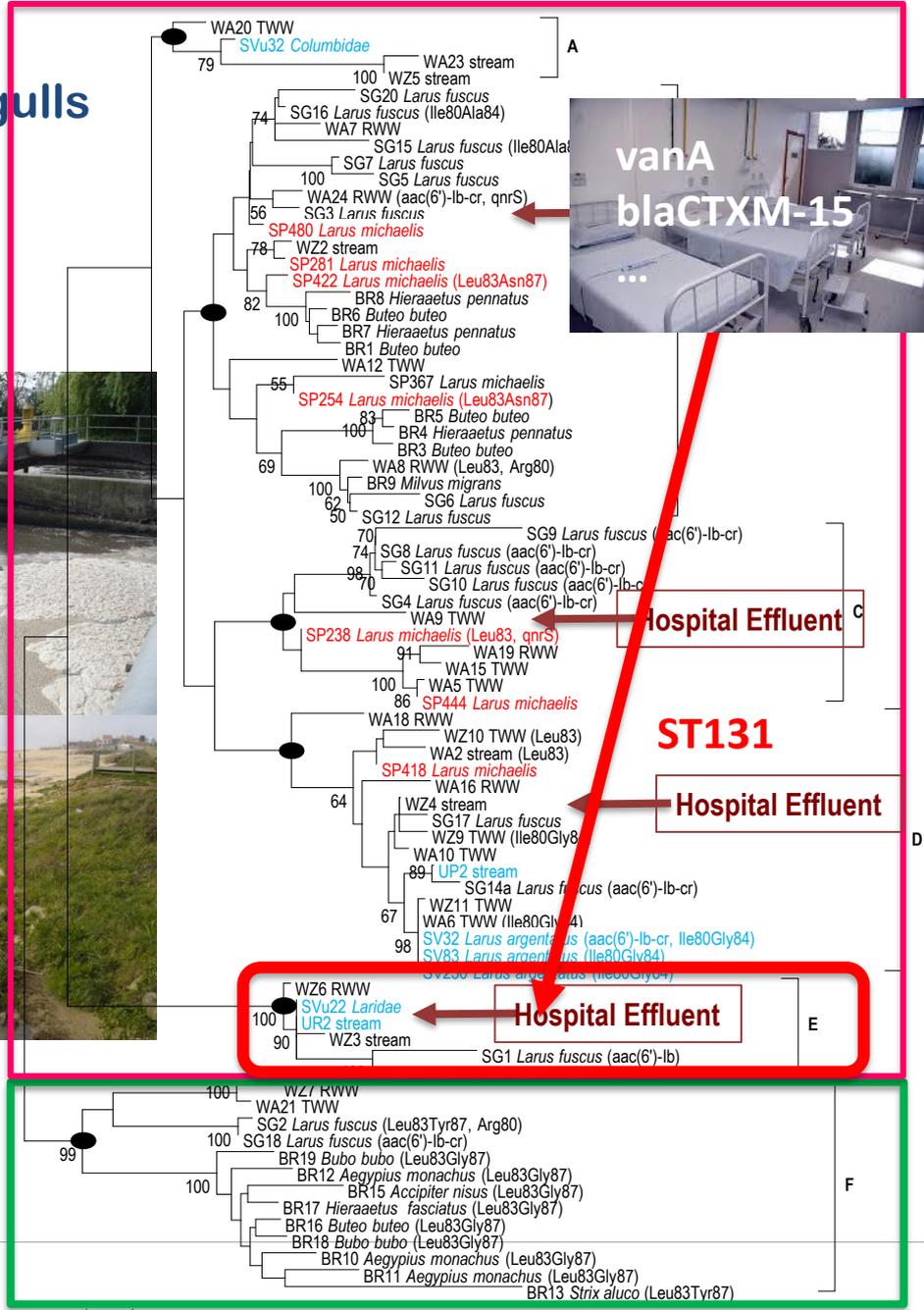


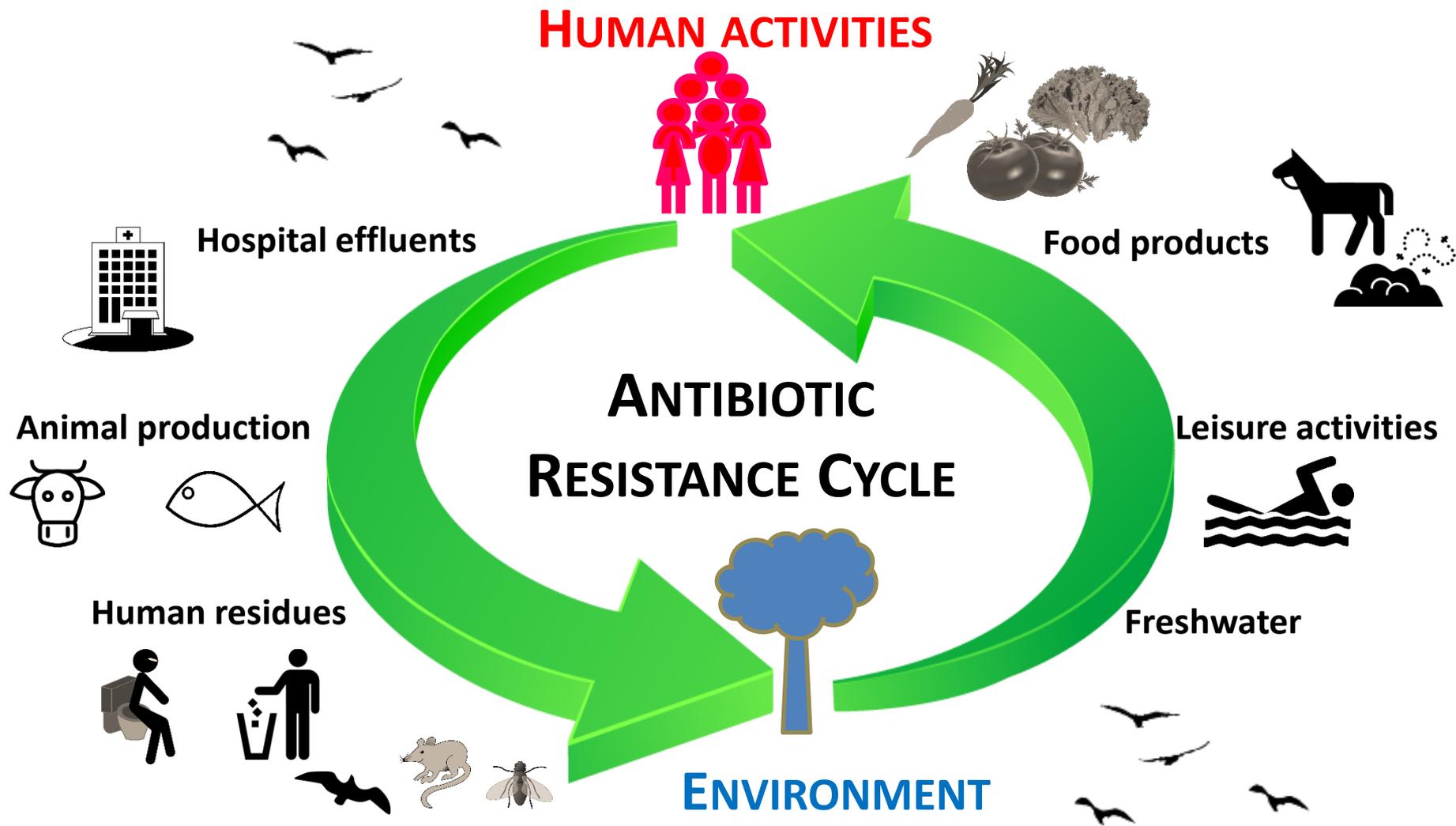
Quinolone resistant *Escherichia coli* birds of prey, water environments and gulls Portugal, Spain and Sweden

Gulls →
Wastewater →
Surface water →



Birds of prey →
Natural reserve →





Mitigation measures



GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE



**World Health
Organization**

Objective 2: Strengthen the knowledge and evidence base through surveillance and research

Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training

Objective 3: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

Objective 4: Optimize the use of antimicrobial medicines in human and animal health

Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

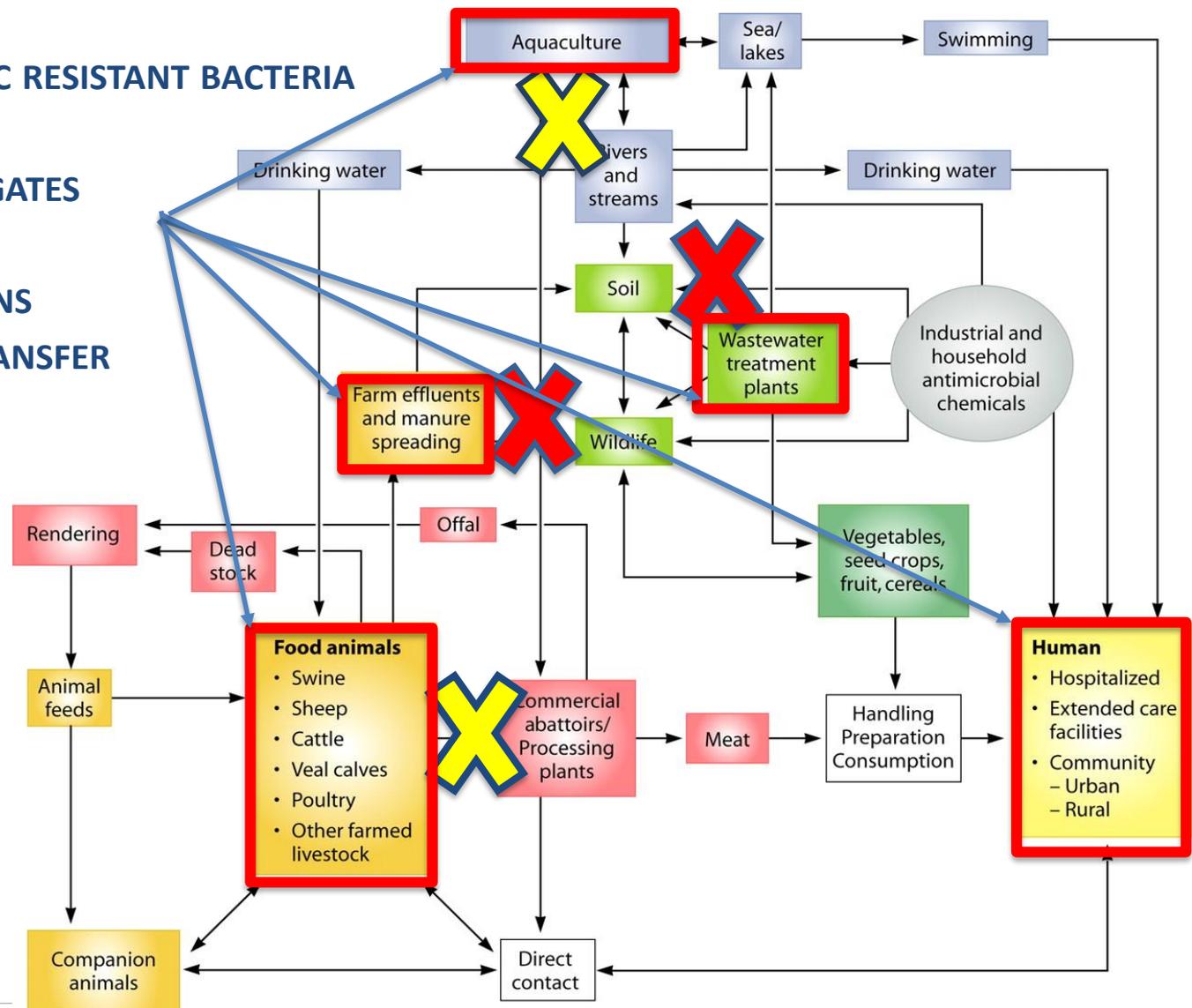


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PORTO

I. IDENTIFICATION OF CRITICAL CONTROL POINTS

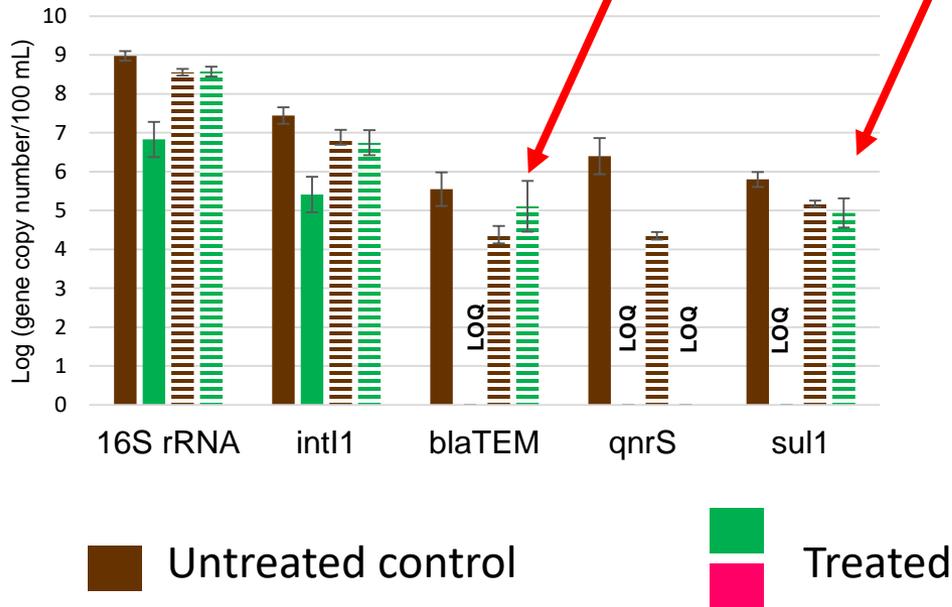
- INCOME OF ANTIBIOTIC RESISTANT BACTERIA
- BACTERIAL GROWTH
- BIOFILM/CELL AGGREGATES
- SELECTIVE PRESSURES
- ADAPTATIVE MUTATIONS
- HORIZONTAL GENE TRANSFER



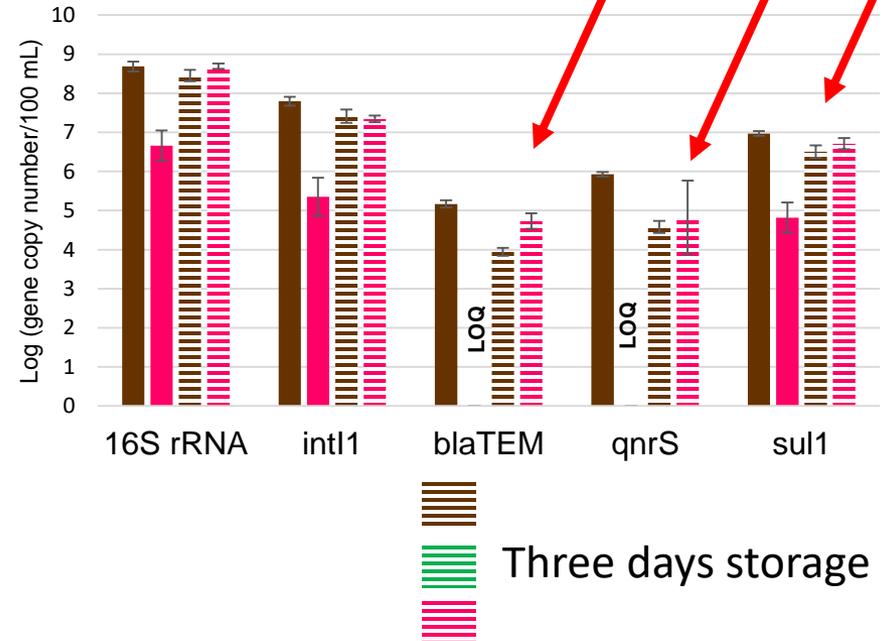
WASTEWATER DISINFECTION

Antibiotic resistance genes

Ozonation



UV



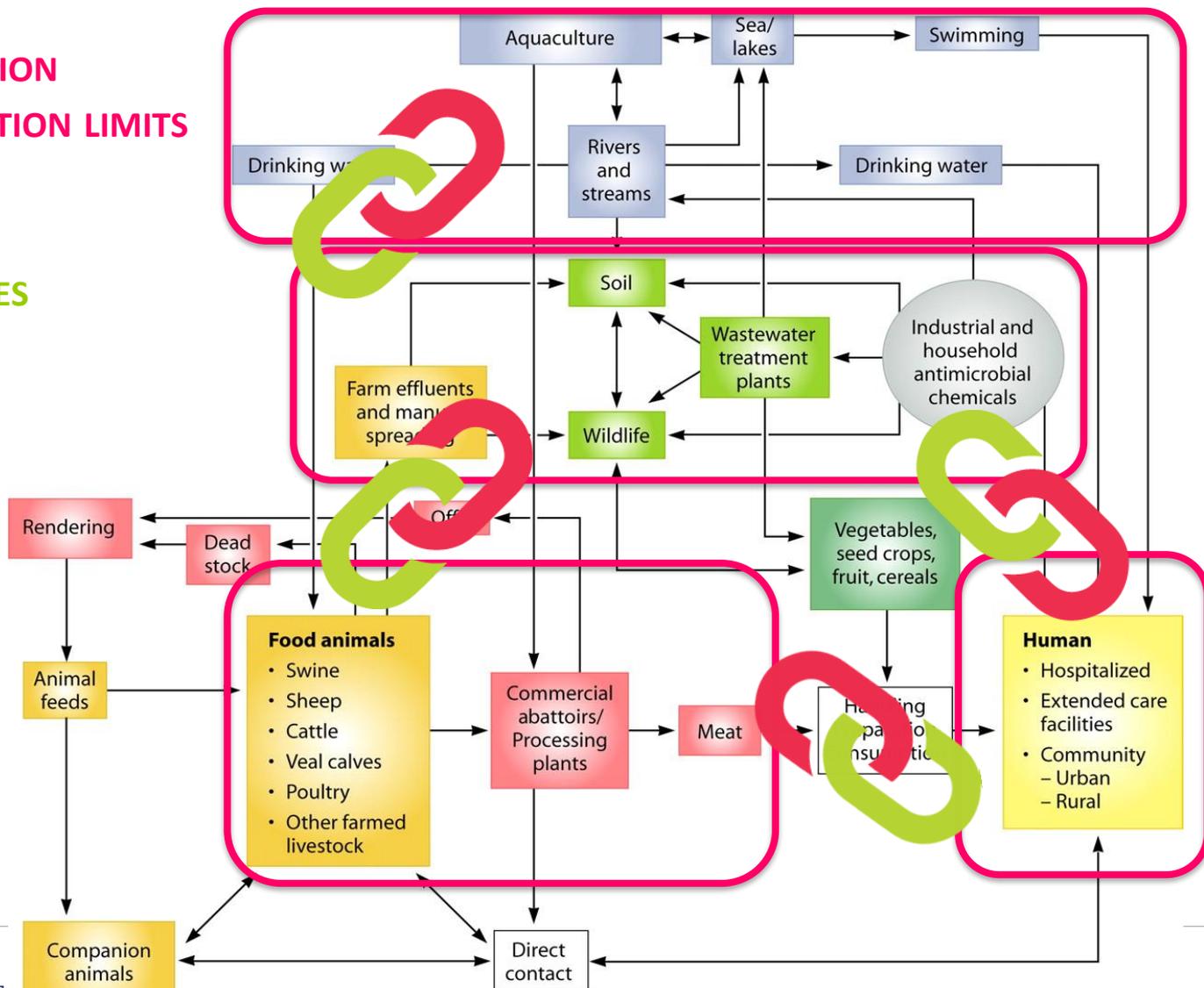
II. ONE SURVEILLANCE FOR ONE HEALTH

METHODS HARMONIZATION
LOWER THE QUANTIFICATION LIMITS

EXPAND ARG DATABASES

ENVIRONMENT

+ ANIMAL
+ HUMAN



Risks of transmission from the environment to humans



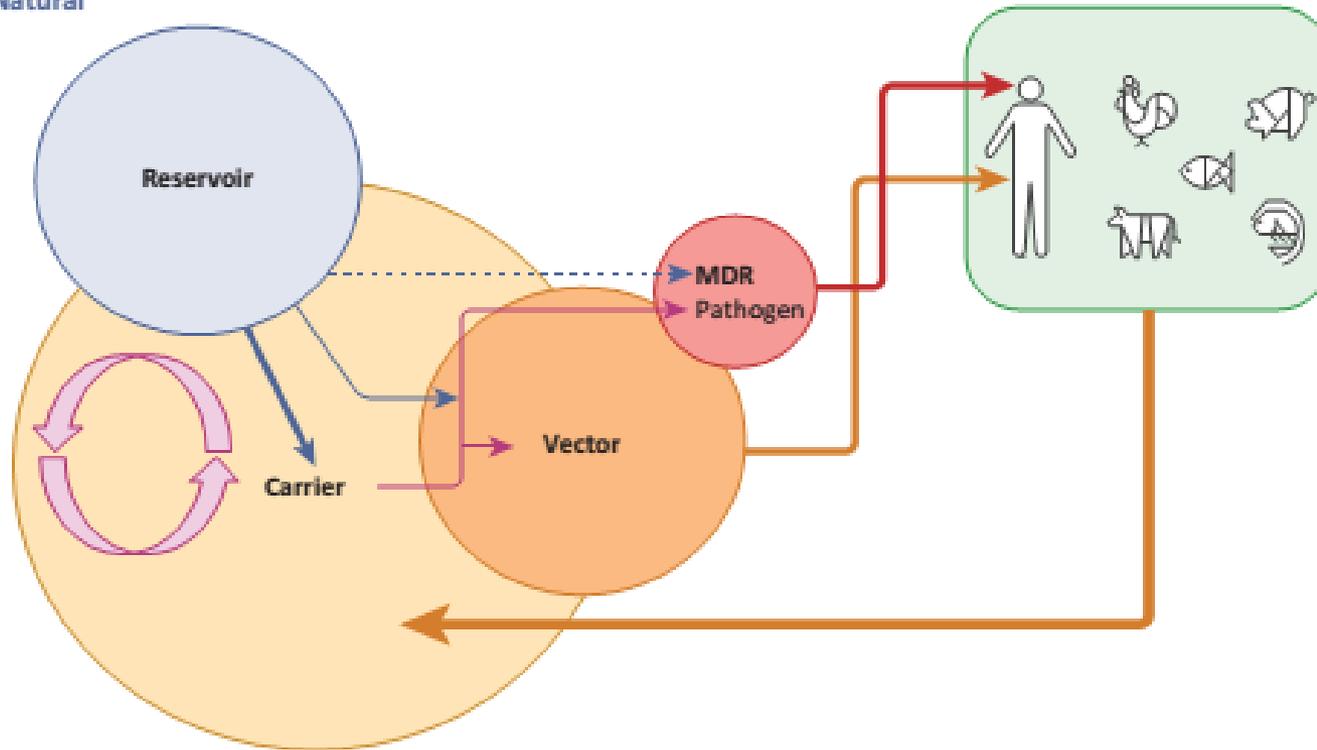
ASSESS THE RISKS OF TRANSMISSION FROM ENVIRONMENT TO HUMANS

Step of risk assessment	Description of the step
<p>✓ Hazard identification (A)</p> <p><i>Is a given environmental compartment a potential source of ARB&ARG?</i></p>	<p><u>Identification of ARB&ARG</u> belonging to the contaminant resistome i.e. that resultant from human activities</p>
<p>➤ Hazard characterization (B)</p> <p><i>The potential environmental source identified in A harbours ARB able to colonize humans, ie vectors?</i></p>	<p>The <u>qualitative and/or quantitative</u> evaluation of the occurrence of <u>ARB able to colonize humans</u> and assessment of the potential adverse associated effects</p>
<p>➤ Exposure assessment (C)</p> <p><i>How probable is the colonization by the vectors identified in B?</i></p>	<p>The <u>qualitative and/or quantitative evaluation</u> of the <u>probability that vectors</u> from environmental sources can affect somebody</p>
<p>☐ Risk characterization (D)</p> <p><i>How dangerous is it?</i></p> <p>$D = A \times B \times C$</p>	<p><u>Estimation of the adverse effects</u> likely to occur, based on the combination of hazard <u>identification</u>, hazard <u>characterization</u> and <u>exposure</u> assessment</p>

VECTOR BACTERIA ARE KEY ELEMENTS ON THE TRANSMISSION TO HUMANS

Relationship between the Natural and the Contaminant Environment Antibiotic Resistence

Natural



Contaminant

Reservoirs	Mainly strictly environmental, harbour ARG that occasionally may be transferred, directly or indirectly, to clinically relevant bacteria
Carriers	Mainly environmental, with high capacity to acquire and transfer by horizontal gene transfer clinically relevant ARG
Vectors	Ubiquitous human-commensal and clinically relevant bacteria with high capacity to receive clinically relevant ARG by horizontal gene transfer
MDR pathogens	Vectors that may combine ARGs with virulence factors and that have a high capacity to infect and cause disease

POSSIBLE VECTORS?

WASTEWATER



HUMANS

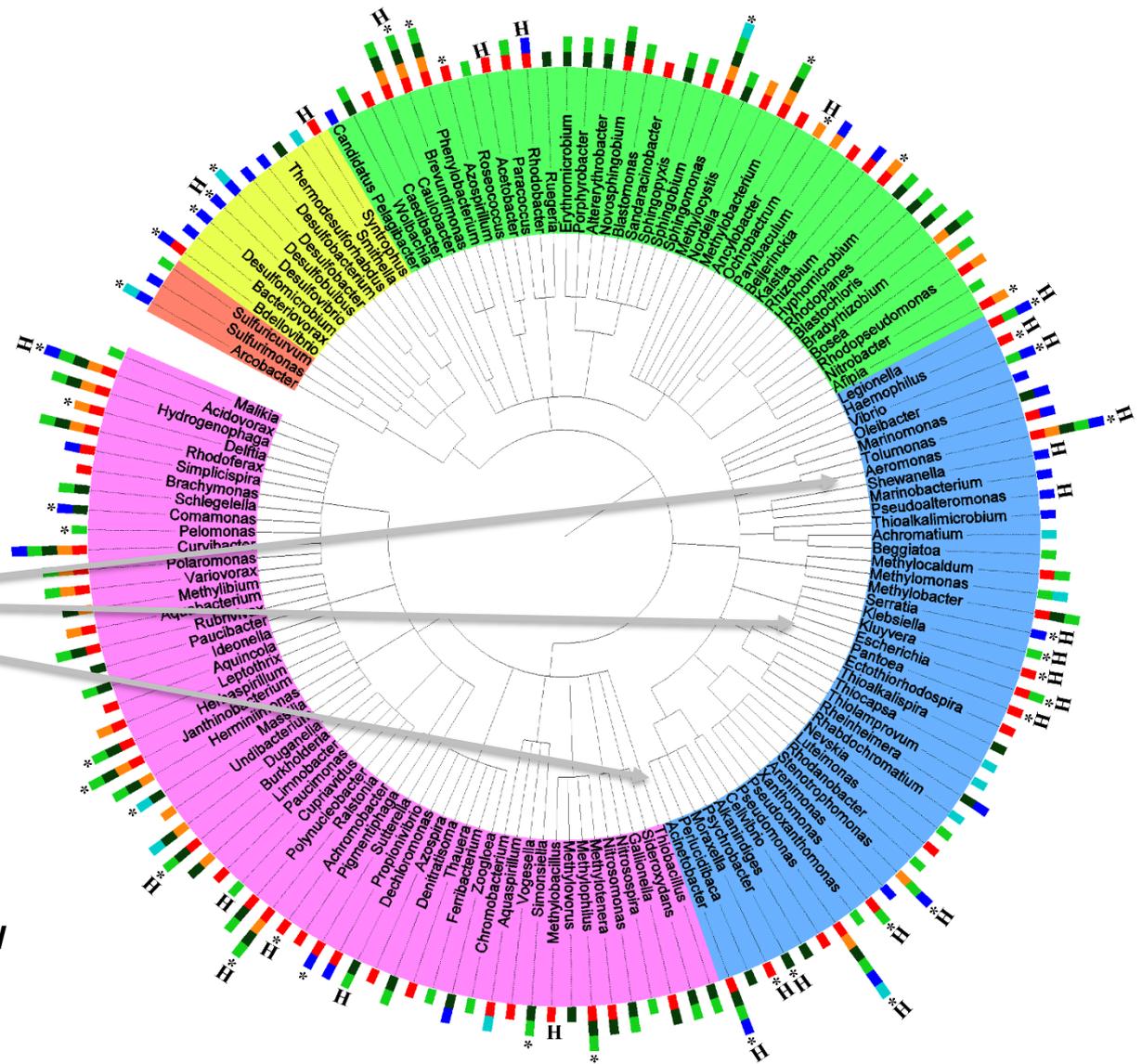
- Escherichia/Shigella*
- Pseudomonas*
- Acinetobacter*
- Klesbsiella*
- Enterococcus*
- Aeromonas*

Type of water (outer bars)

- SW (red)
- MW (orange)
- U-DW (dark green)
- T-DW (light green)
- Ur-WW (blue)
- A-WW (cyan)

Phylum (inner circle)

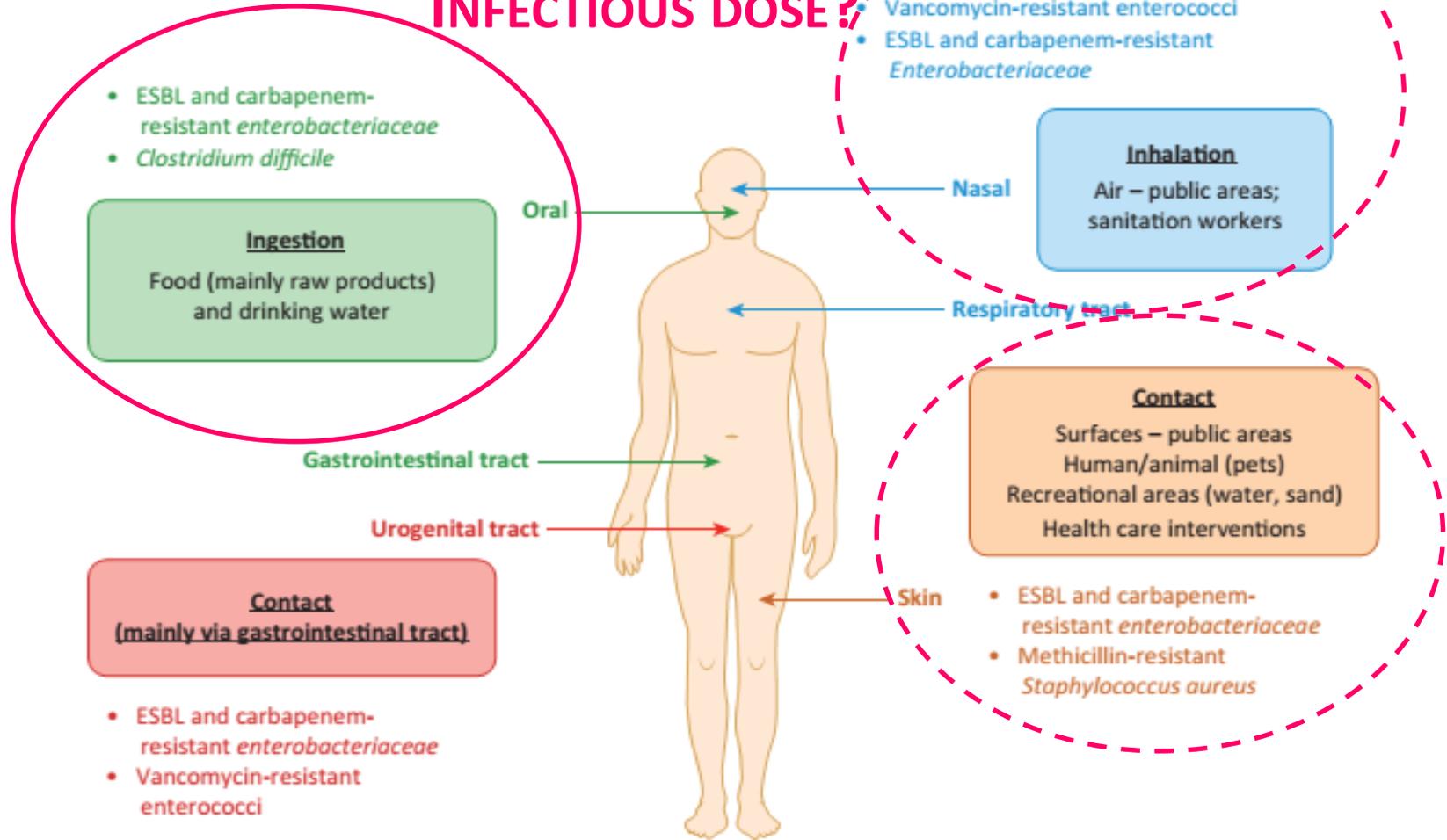
- Epsilonproteobacteria* (orange)
- Deltaproteobacteria* (yellow-green)
- Alphaproteobacteria* (light green)
- Gammaproteobacteria* (blue)
- Betaproteobacteria* (pink)



POSSIBLE ROUTES OF TRANSMISSION?

Portals of entry/ paths/ sources of arb from environmental sources

INFECTIOUS DOSE?



Trends in Microbiology



Take home messages

- ❖ Antibiotic Resistance is spread over Humans, Animals and the Environment
- ❖ Mitigation measures include
 - An integrated surveillance of AR in the HUMAN-ANIMAL-ENVIRONMENT nexus – ONE HEALTH PERSPECTIVE
 - Improved antibiotic use
 - Improved effluents management and treatment
- ❖ The development of risk assessment frameworks is urgently needed
 - Identification and characterization of exposure pathways
 - Identification of vector bacteria and evaluation of infectious doses



**Because antibiotic
resistance is a global
issue...**



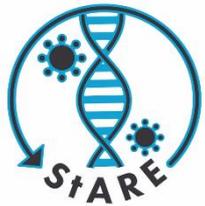
On-going projects on antibiotic resistance in wastewater (and its reuse)



EU



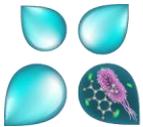
US
EU
Asia



EU



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PARA O DESENVOLVIMENTO



ANSWER

EU



EU
US
Australia
Asia



Bacterial diversity group

ESB-UCP, Porto, Portugal

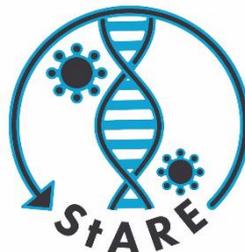


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FCT Fundação para a Ciência e a Tecnologia

MINISTÉRIO DA EDUCAÇÃO E CIÊNCIA



UID/Multi/50016/2013-CBQF

Stopping Antibiotic Resistance Evolution

<https://stareurope.wordpress.com/>



COST-European Cooperation in Science and Technology, to the COST Action ES1403: New and emerging challenges and opportunities in wastewater reuse (NEREUS) - <http://www.nereus->



Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances - <http://www.norman-network.net/?q=node/19>



ANTibioticS and mobile resistance elements in WastEwater Reuse applications: risks and innovative solutions – ANSWERS. European Commission Horizon 2020 - MSCA-ITN-2015-ETN: Marie Skłodowska-Curie Innovative Training Networks (ITN-ETN)



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OVERSEAS (FLAD 298/2015)

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