One Health approach for antimicrobial resistance

II Encontro de Estudantes de Doutoramento em Ambiente e Agricultura

16 e 17 de Novembro

Universidade de Évora

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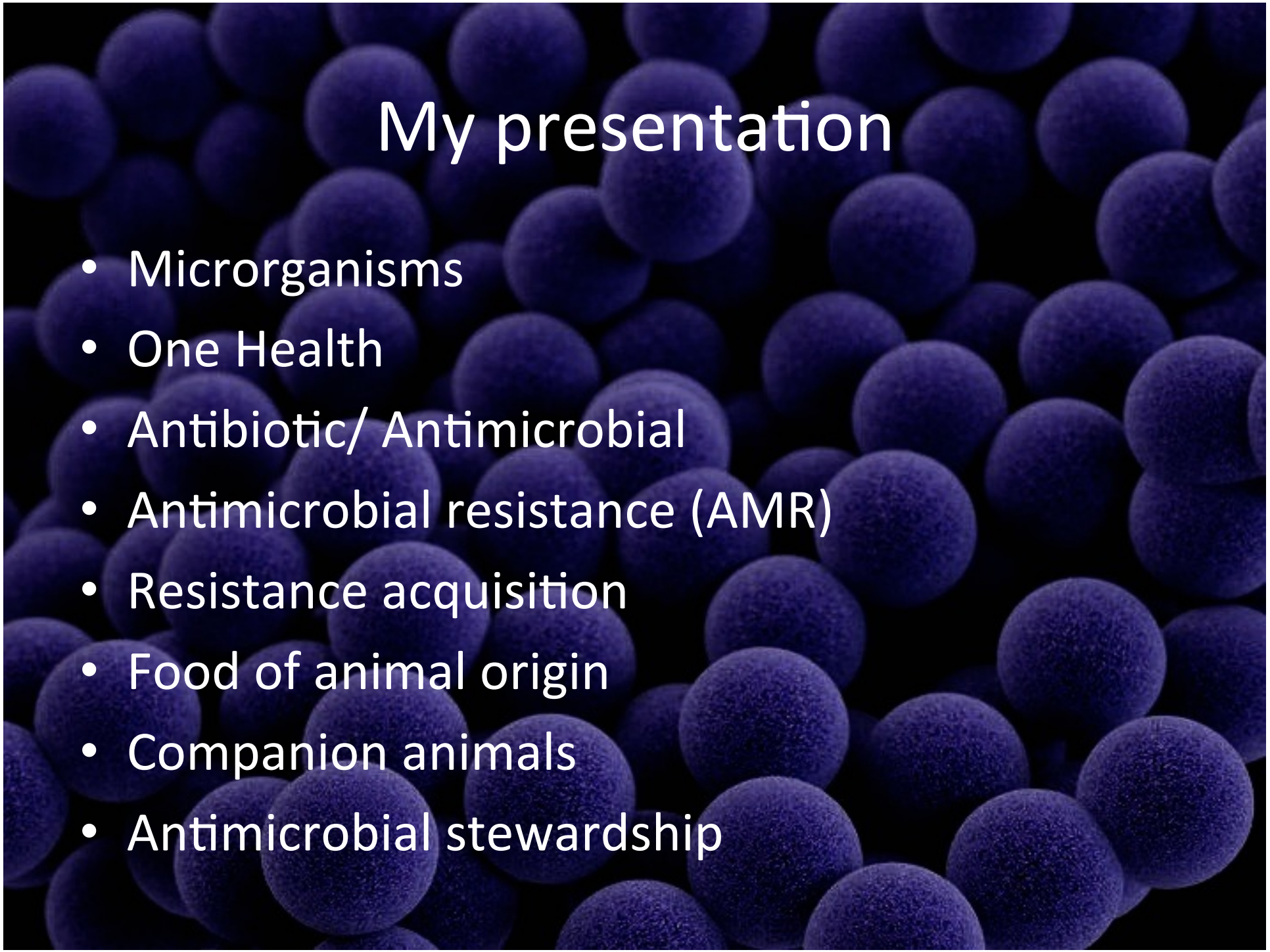

My presentation
• Microrganisms
• One Health
• Antibiotic/ Antimicrobial
• Antimicrobial resistance (AMR)
• Resistance acquisition
• Food of animal origin
• Companion animals
• Antimicrobial stewardship

Microrganisms

- Most abundant living beings on Earth
- Humans and other animals - colonized on surfaces exposed to the environment
- In the gastrointestinal tract - commensal bacteria are 10 times more numerous than host cells
- Indigenous microbiota is responsible for several vital functions for the host: vitamin synthesis, complex polysaccharide digestion, maintenance of intestinal epithelial barrier, prevent colonization by pathogens, stimulation of immune system development → host health depends on its microbiota → microbioma → HEALTH/ DISEASE

Microrganisms

- Microbiota - symbiotic bacteria (commensalism/ mutualism)
- Opportunistic pathogens → acute infections (from environment or other parts of the body)
- Patobionts – symbionts of indigenous microbiota with pathogenic potential → chronic inflammation
- Pathogens - cause disease even in healthy individuals

One Health

Concept - worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment

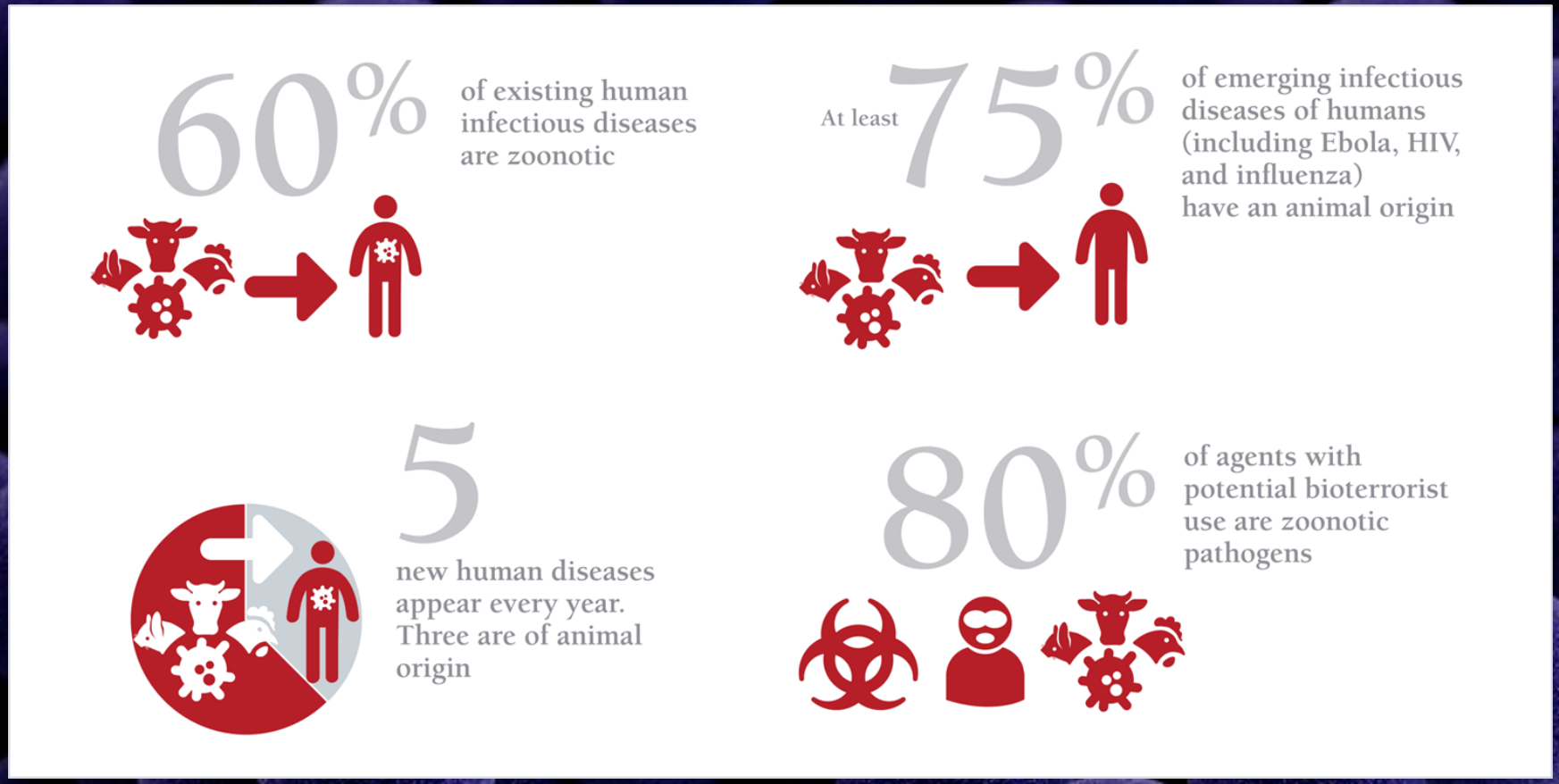
The synergism achieved will advance health care for the 21st century and beyond by:

- accelerating biomedical research discoveries
- enhancing public health efficacy
- expeditiously expanding the scientific knowledge base
- improving medical education and clinical care

When properly implemented, it will help protect and save untold millions of lives in our present and future generations


SAFER ENVIRONMENT
HEALTHY ANIMALS
ONE HEALTH
HEALTHY HUMANS

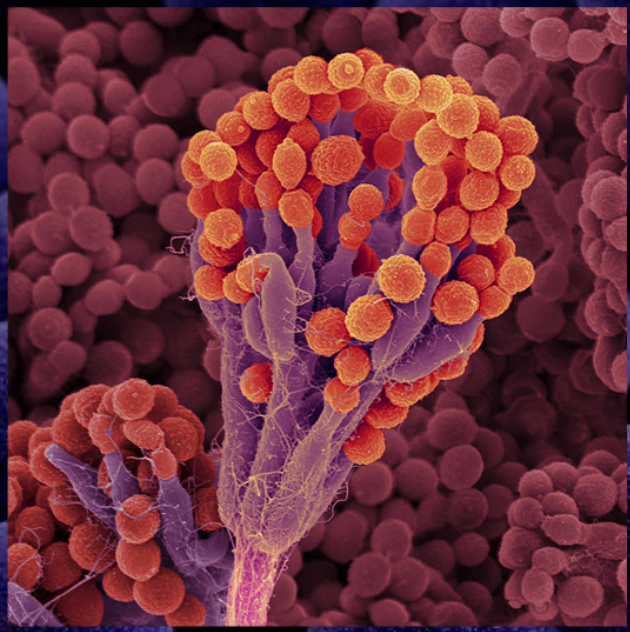
- ZOONOSIS - Infectious disease transmissible, in natural conditions, from vertebrates - both domestic and wild - to man and *vice-versa*



Antibiotic/ Antimicrobial

- Antibiotic - Chemical substances produced by microorganisms which in very low concentrations kill or selectively inhibit other micro-organisms

  - Bactérias
    - *Streptomyces* spp
    - *Micromonospora* spp
    - *Bacillus* spp
  - Fungos
    - *Penicillium* spp
    - *Cephalosporium* spp



Penicilium notatum

Antibiotic/ Antimicrobial

- Antimicrobials – various chemical substances that inhibit microorganisms including antibiotics

Exemples of nonantibiotic antimicrobials

- Sulfamides
- Quinolones

Both may be applied internally unlike disinfectants and antiseptics, which are applied to inert materials or to external tissues

Antibiotic/ Antimicrobial
Mechanism of action

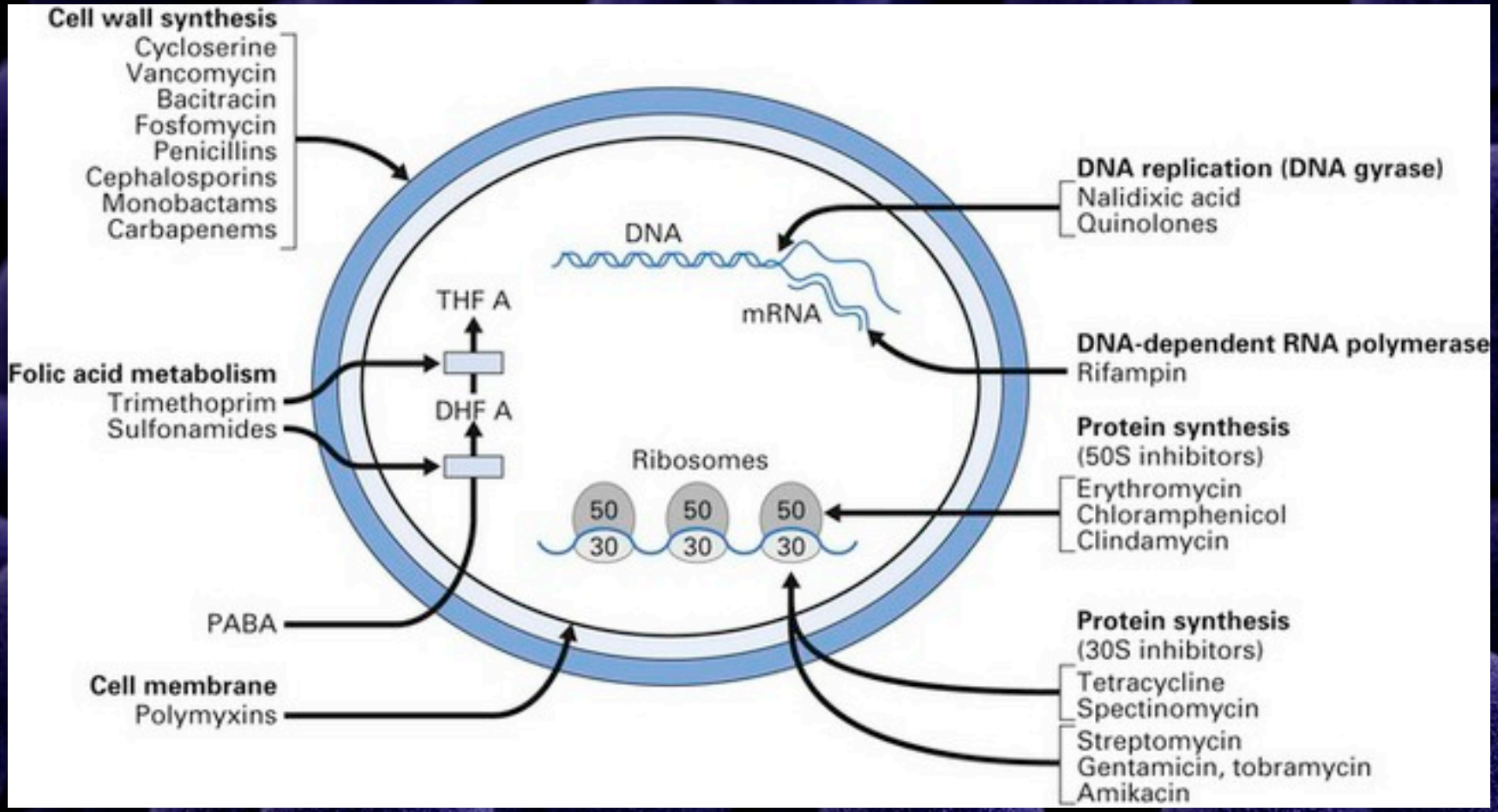
- Acting on the bacterial cell wall
  - β-Lactams
  - Glycopeptides
  - Phosphonopeptides
- Acting on the cytoplasmic membrane
  - Gramicidins
  - Polymyxins
- Acting on protein synthesis
  - Aminoglycosides – 30S
  - Tetracyclins – 30S
  - Macrolides, lincosamides, streptogramins, ketolides (MLSK) – 50S
  - Chloramphenicol – 50S

Antibiotic/ Antimicrobial
Mechanism of action

- Acting on nucleic acid synthesis
  - Quinolones
  - Metronidazole
  - Nitrofurans
  - Rifampicin
- Acting as folate pathway inhibitors
  - Sulfamides
  - Trimethoprim

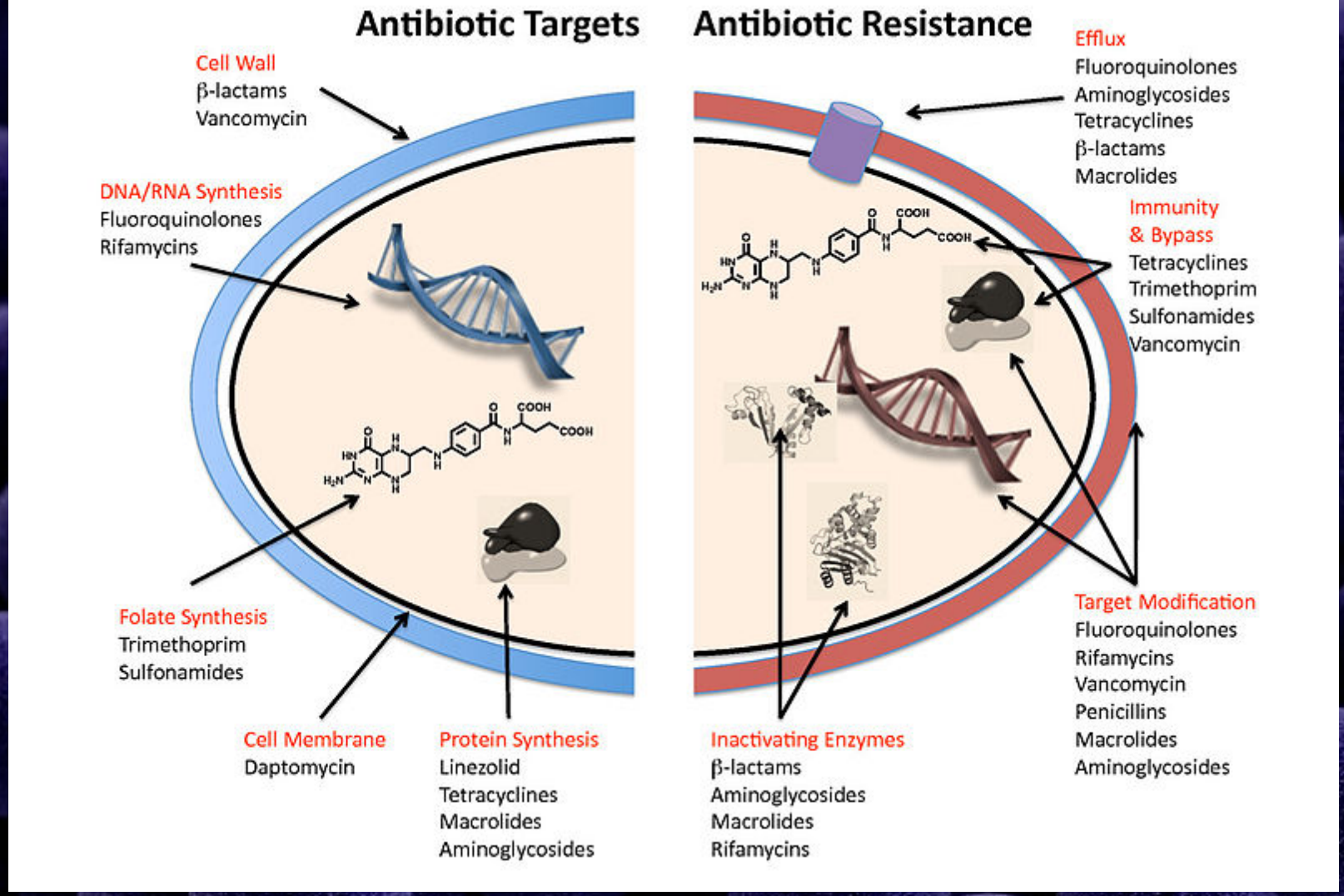
Antibiotic/ Antimicrobial

Mechanism of action



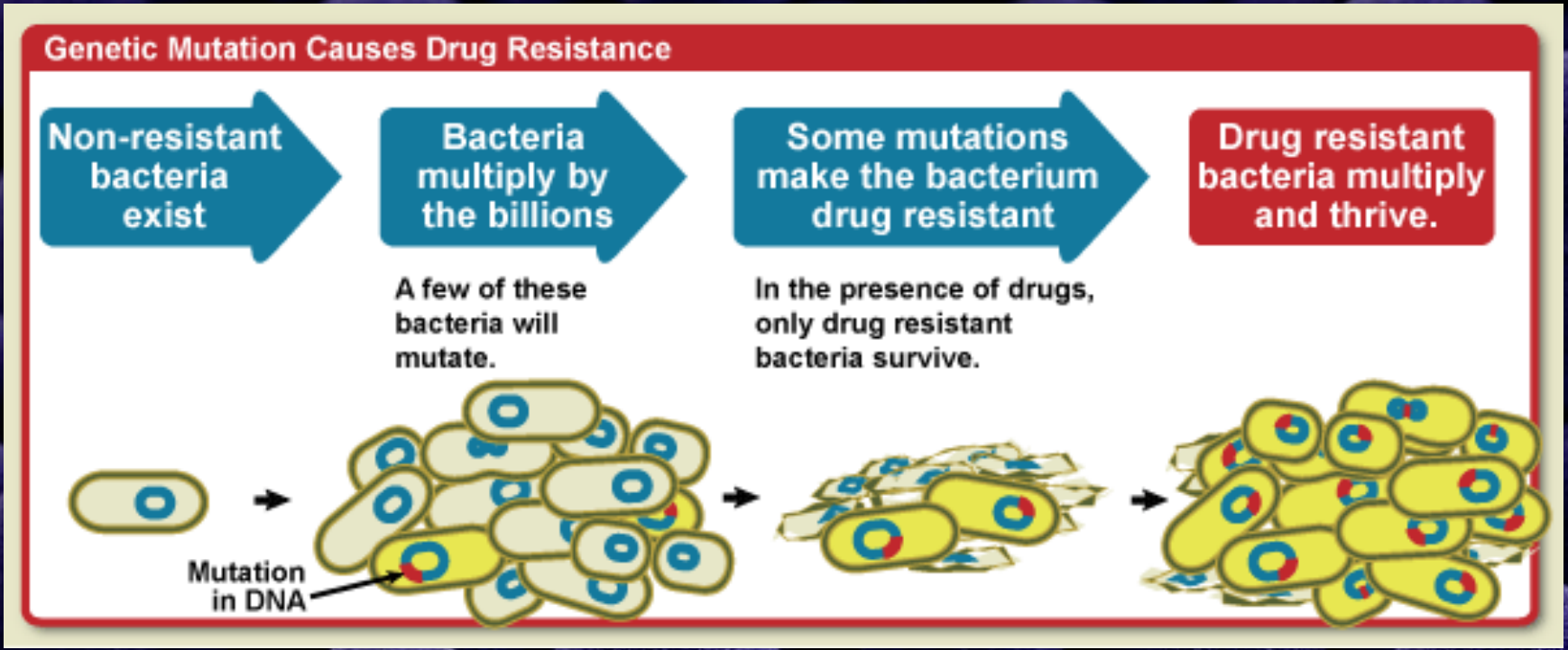
Antimicrobial resistance (AMR)

- Reduction in the drug quantity reaching the target
  - Impermiability
  - Up-regulated efflux systems
- Target modification
  - Mutation (conferring target resistance)
  - Target bypassed (acquisition of external genes allowing targets to be bypassed)
- Antimicrobial inactivation


Antibiotic Targets
Antibiotic Resistance
Cell Wall
β-lactams
Vancomycin
DNA/RNA Synthesis
Fluoroquinolones
Rifamycins
Folate Synthesis
Trimethoprim
Sulfonamides
Cell Membrane
Daptomycin
Protein Synthesis
Linezolid
Tetracyclines
Macrolides
Aminoglycosides
Efflux
Fluoroquinolones
Aminoglycosides
Tetracyclines
β-lactams
Macrolides
Immunity
& Bypass
Tetracyclines
Trimethoprim
Sulfonamides
Vancomycin
Target Modification
Fluoroquinolones
Rifamycins
Vancomycin
Penicillins
Macrolides
Aminoglycosides
Inactivating Enzymes
β-lactams
Aminoglycosides
Macrolides
Rifamycins

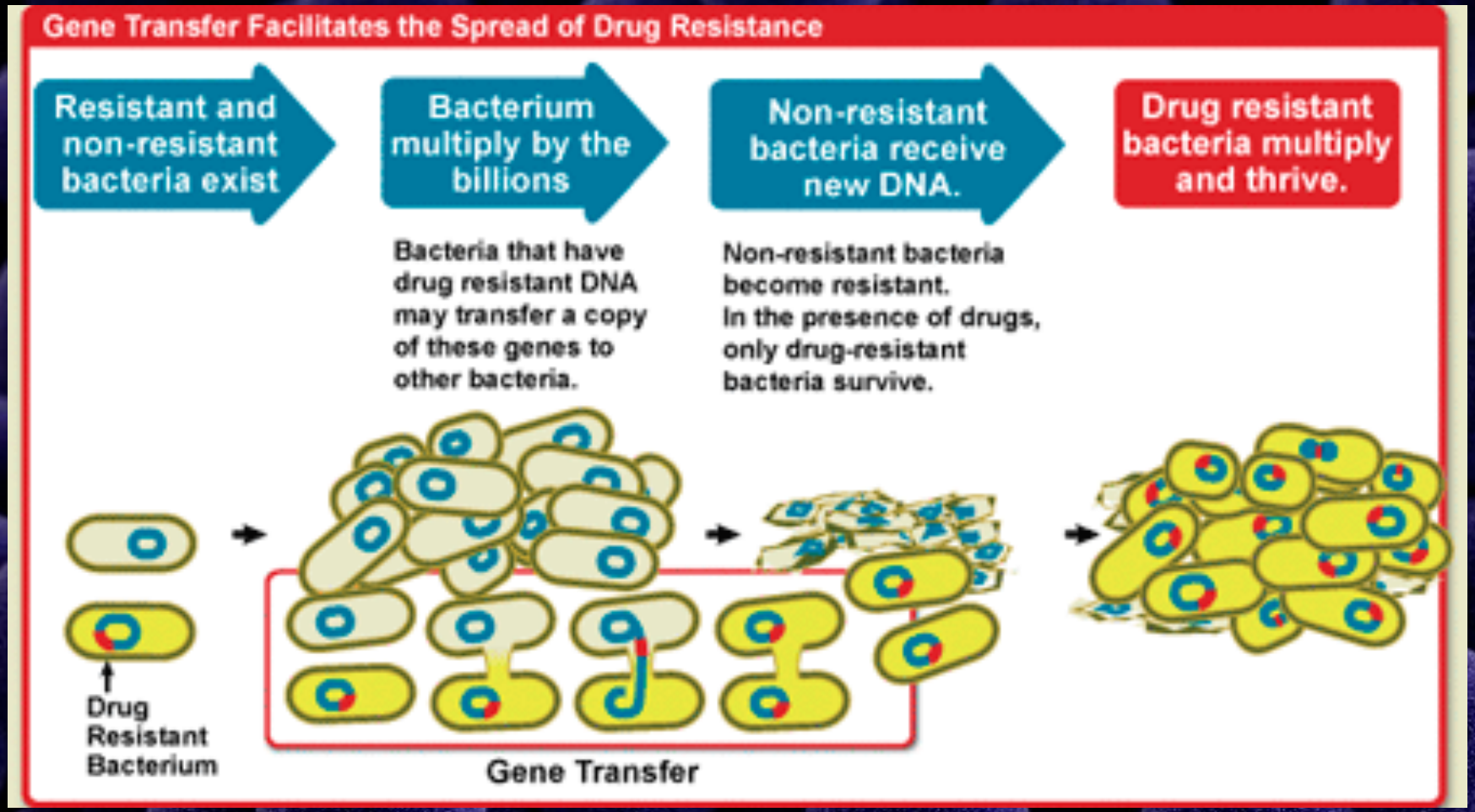
Resistance acquisition

Mutation



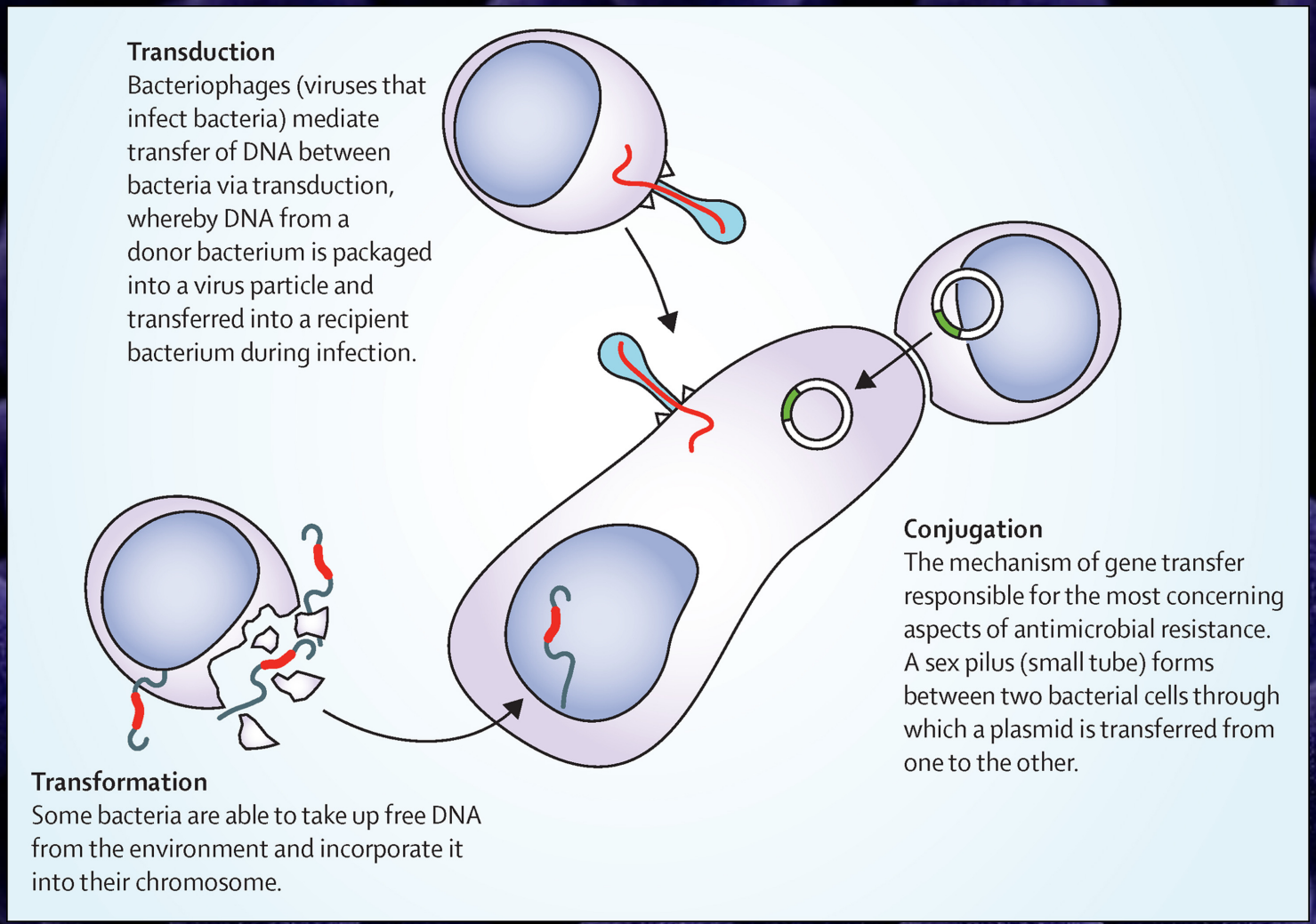
Resistance acquisition

Gene transfer



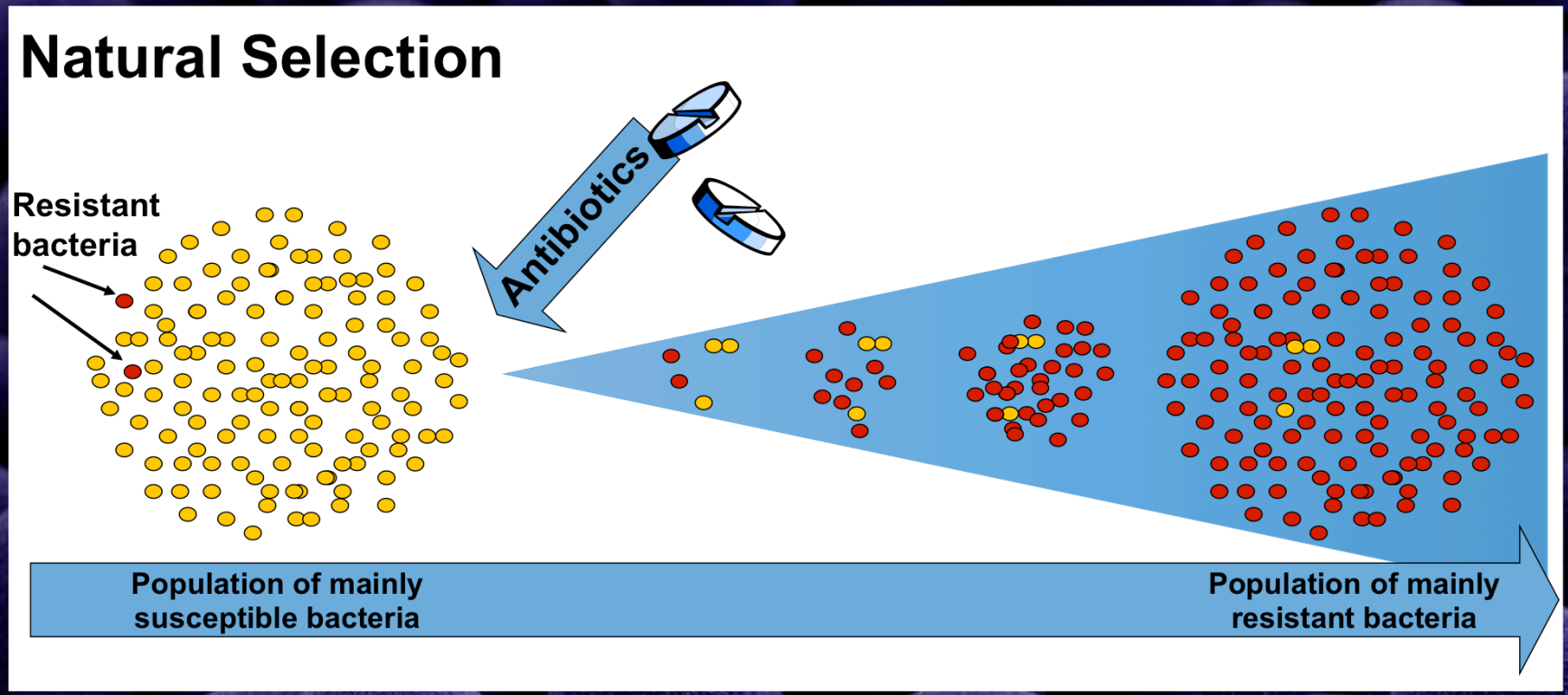
Resistance acquisition

Gene transfer

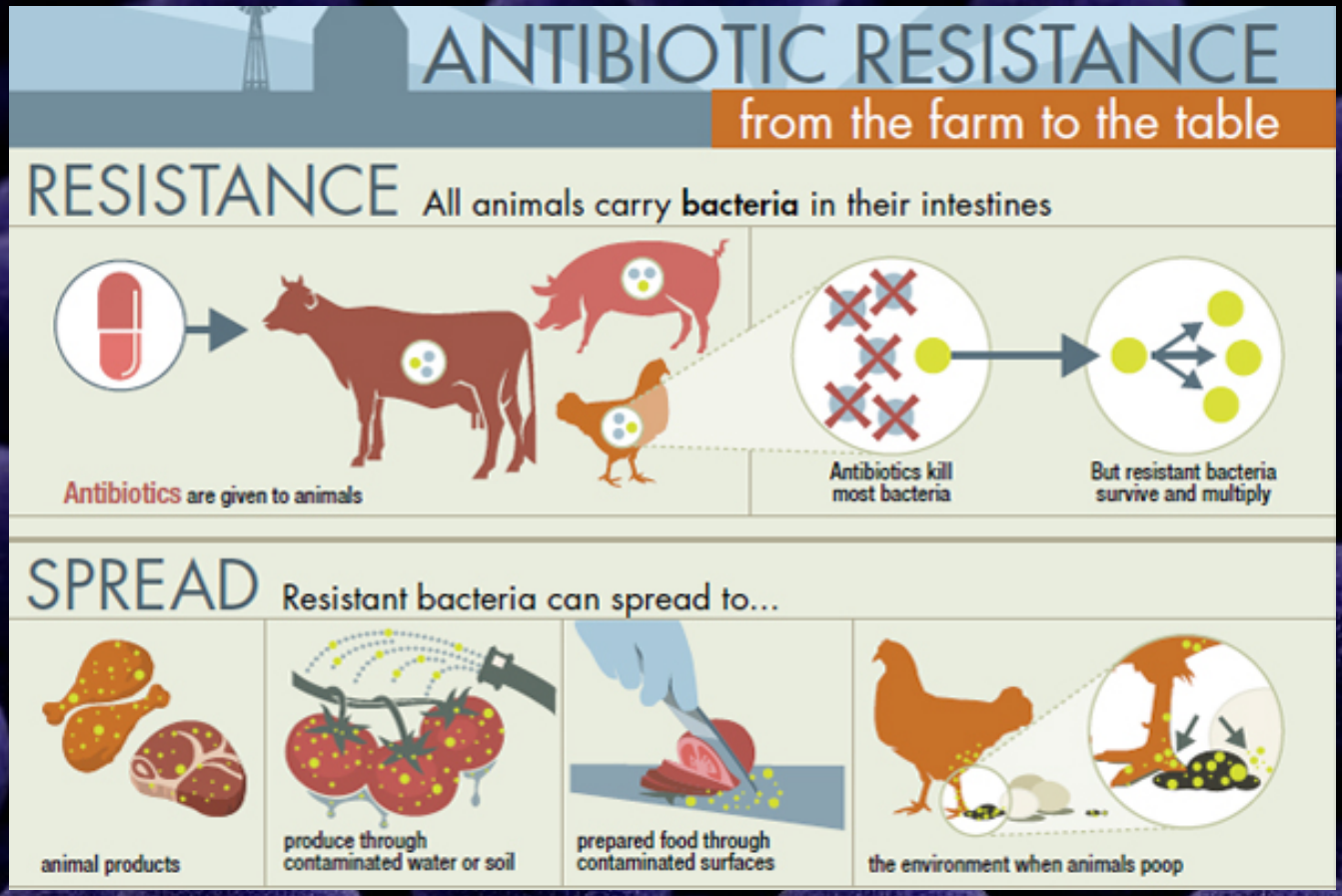


Resistance acquisition

Selection pressure

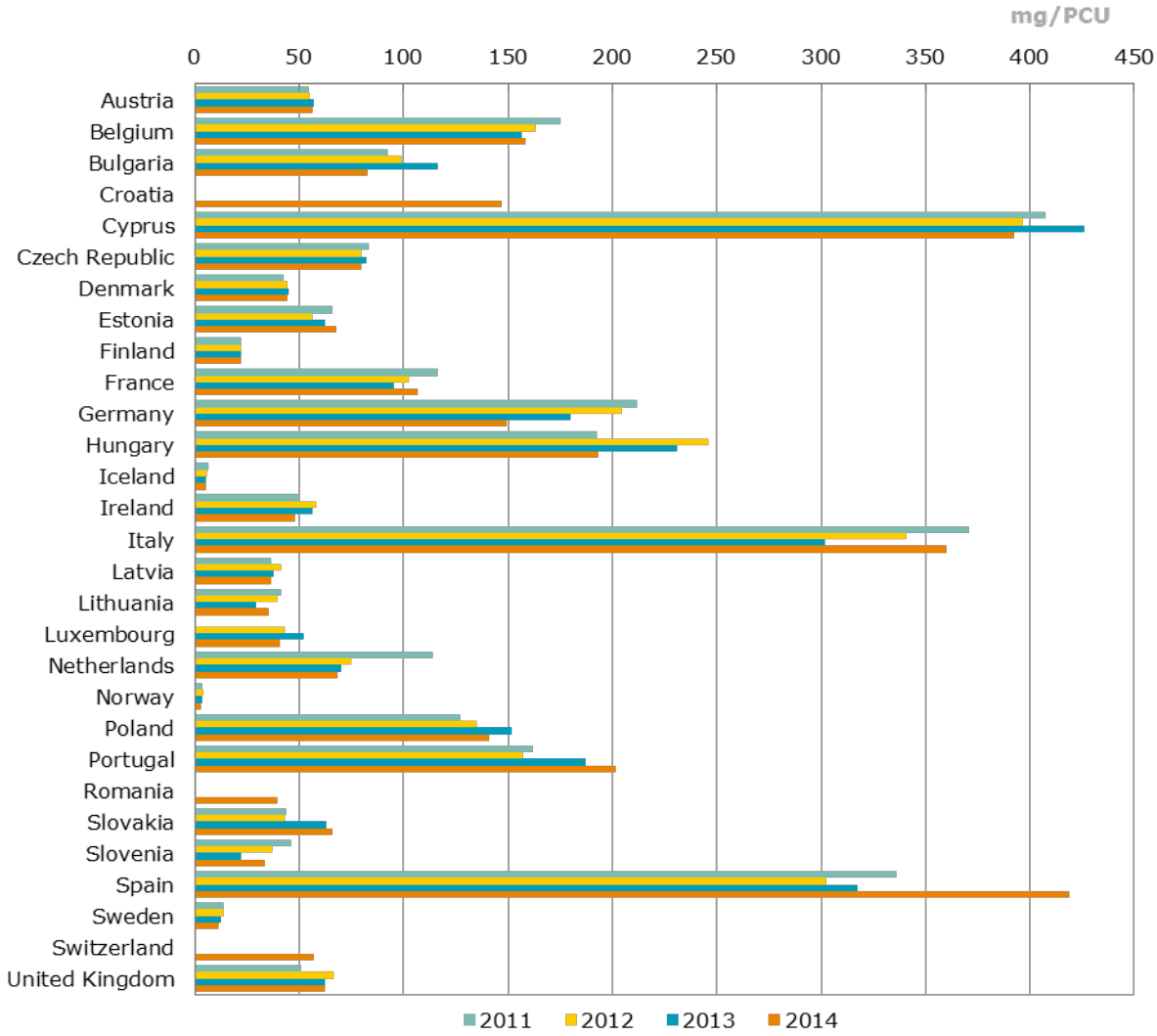


Food of animal origin

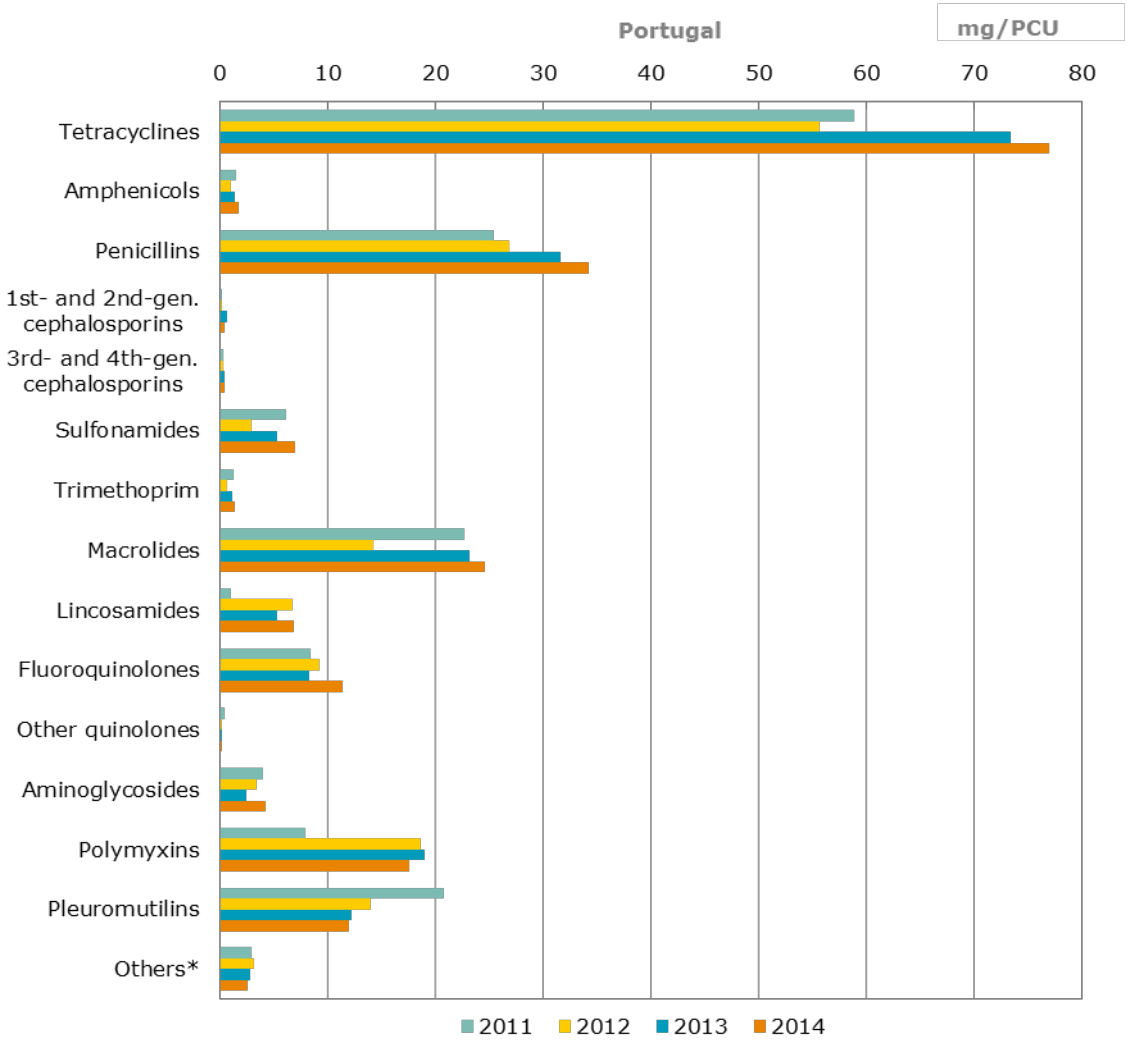


Consumption of food products
microorganisms from the animal's microbiome ➔ consumer

Figure 55. Total sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, from 2011 to 2014, for 29 European countries1-7

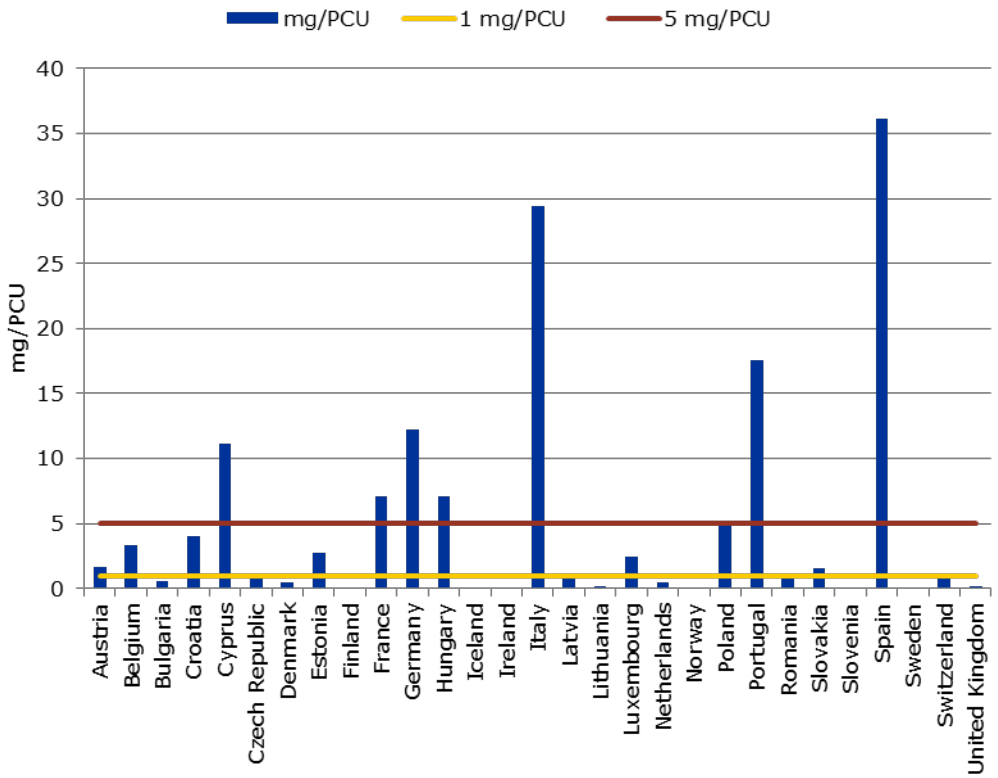


Portugal

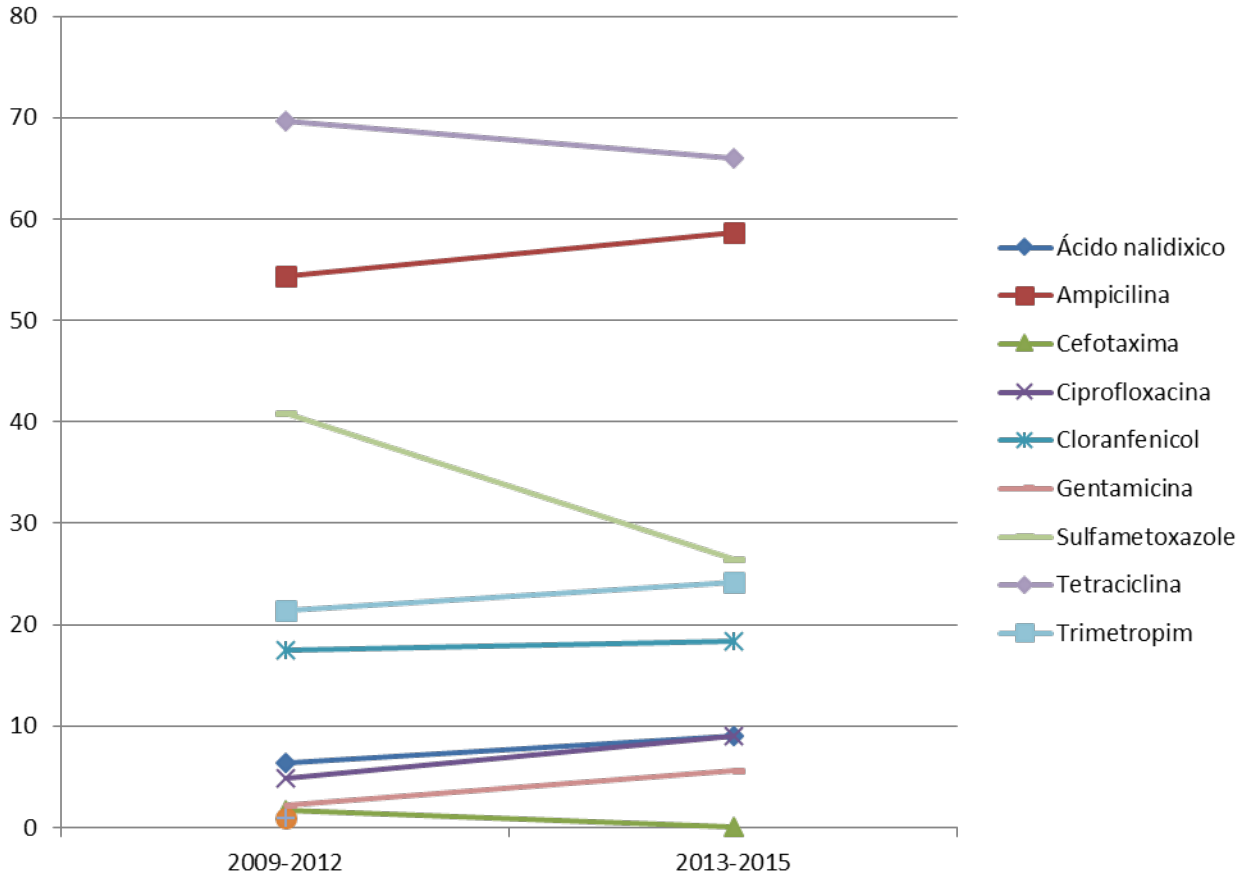


www.dgav.pt

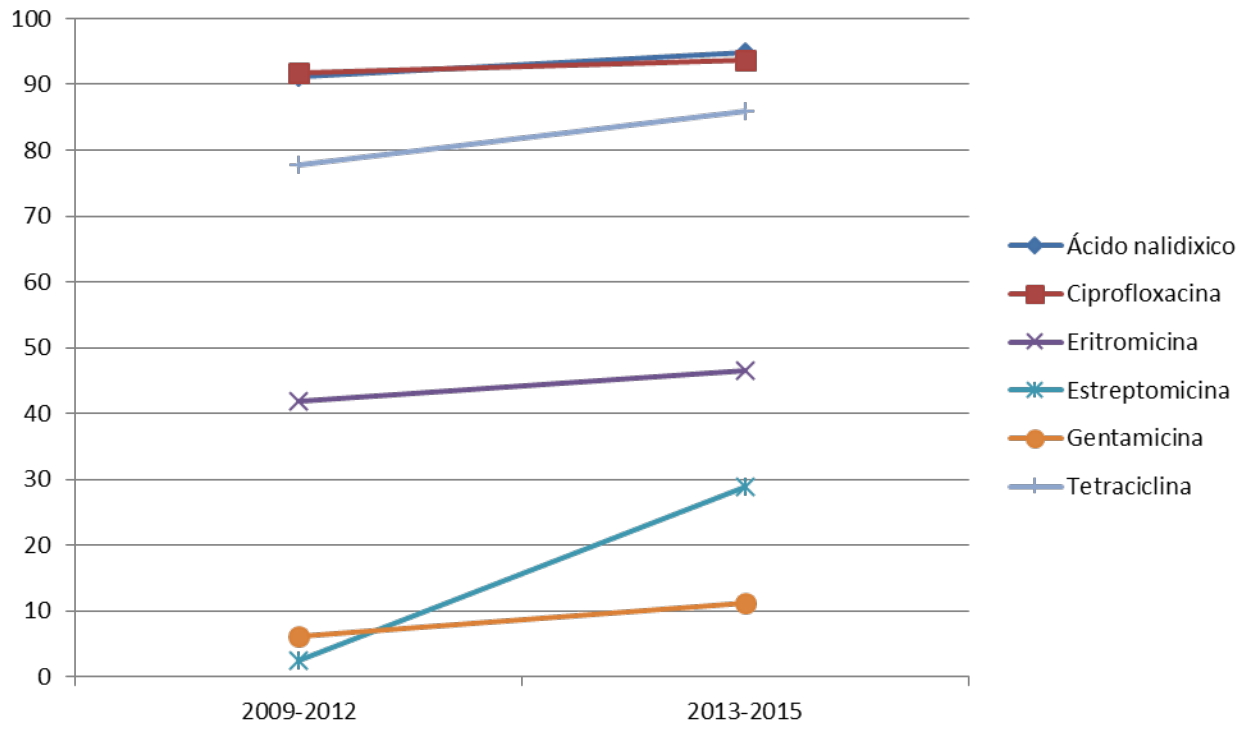
Figure A1. Sales of colistin for use in food-producing animals, in mg/PCU, in 2014, including the 5 and 1 mg/PCU levels1



Resultados obtidos em isolados de *Salmonella* em alimentos 2009-2012/ 12013-2015



Resultados obtidos em isolados de *Campylobacter* em alimentos 2009-2012/ 12013-2015

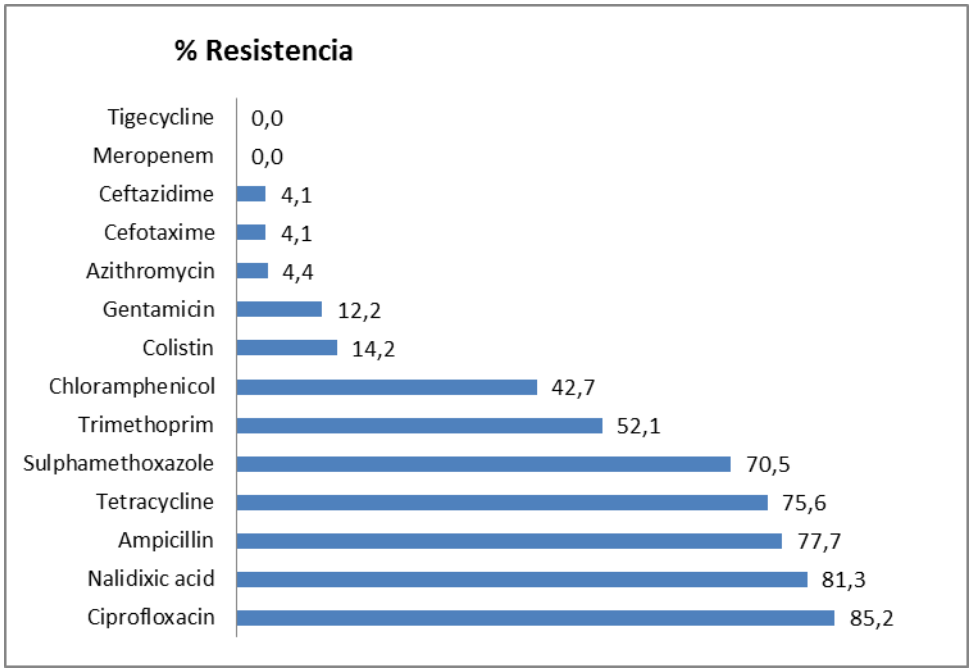


PVRAM de 2014

E. coli - isolada em amostras de aves

Antimicrobiano	R	S	% Resistencia
Ciprofloxacin	329	57	85,2
Nalidixic acid	314	72	81,3
Ampicillin	300	86	77,7
Tetracycline	292	94	75,6
Sulphamethoxazol	272	114	70,5
Trimethoprim	201	185	52,1
Chloramphenicol	165	221	42,7
Colistin	55	331	14,2
Gentamicin	47	339	12,2
Azithromycin	17	369	4,4
Cefotaxime	16	370	4,1
Ceftazidime	16	370	4,1
Meropenem	0	386	0,0
Tigecycline	0	386	0,0

386 isolados de *E.coli* provenientes de amostras cecais de frangos e perus



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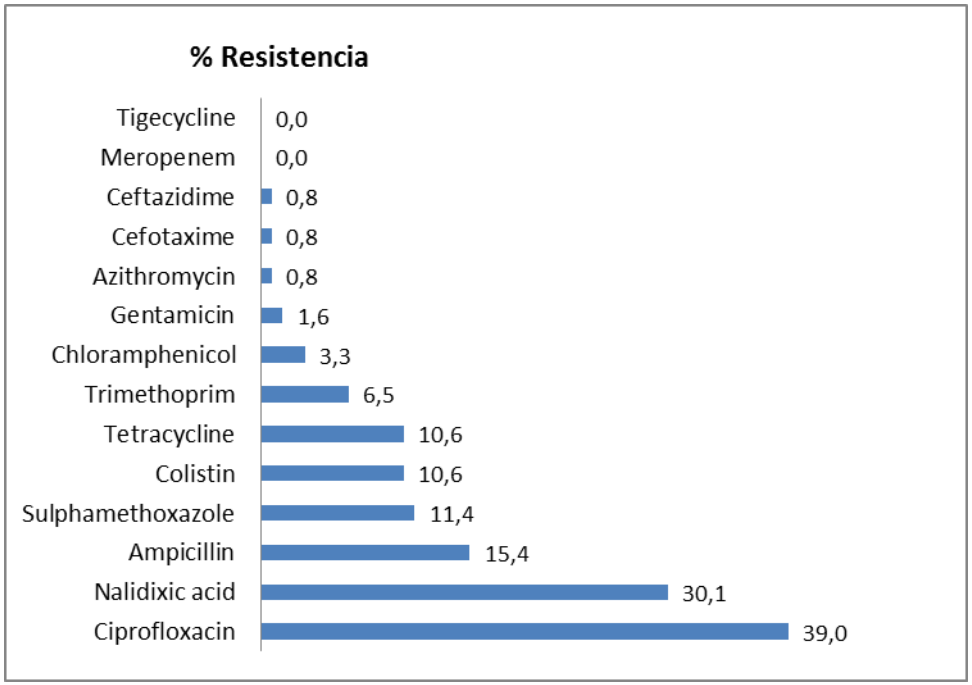
PVRAM de 2014

Salmonella spp - isolada em amostras de aves

Antimicrobiano	R	S	% Resistencia
Ciprofloxacin	48	75	39,0
Nalidixic acid	37	86	30,1
Ampicillin	19	104	15,4
Sulphamethoxazole	14	109	11,4
Colistin	13	110	10,6
Tetracycline	13	110	10,6
Trimethoprim	8	115	6,5
Chloramphenicol	4	119	3,3
Gentamicin	2	121	1,6
Azithromycin	1	122	0,8
Cefotaxime	1	122	0,8
Ceftazidime	1	122	0,8
Meropenem	0	123	0,0
Tigecycline	0	123	0,0

123 isolados de *Salmonella* provenientes de amostras de aves (PIGA e PNCS)



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PVRAM de 2015

E. coli ESBL isolado em amostras de **carne** de suínos

Antimicrobiano (1º painel)	R	S	% Resistência	
Ampicillin	39		100,0	⇦
Azithromycin	8	31	20,5	
Cefotaxime	39		100,0	⇦
Ceftazidime	34	5	87,2	
Chloramphenicol	10	29	25,6	
Ciprofloxacin	20	19	51,3	
Colistin	3	36	7,7	
Gentamicin	7	32	17,9	
Meropenem		39	0,0	
Nalidixic acid	19	20	48,7	
Sulphamethoxazole	31	8	79,5	⇦
Tetracycline	35	4	89,7	⇦
Tigecycline		39	0,0	
Trimethoprim	27	12	69,2	

39 isolados de *E.coli* ESBL provenientes de amostras de carne de suino

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PVRAM de 2015

E. coli *ESBL* isolado em amostras **carne** de suíno

Antimicrobiano (2º painel)	R	S	% Resistência	
Cefepime	37	2	94,9	⇦
Cefotaxime	39		100,0	⇦
Cefotaxime/clavulanic acid	7	32	17,9	
Cefoxitin	8	31	20,5	
Ceftazidime	36	3	92,3	⇦
Ceftazidime/clavulanic acid	7	32	17,9	
Ertapenem		39	0,0	
Imipenem	1	38	2,6	
Meropenem		39	0,0	
Temociline		39	0,0	

39 isolados de *E.coli* provenientes de amostras de carne de suino

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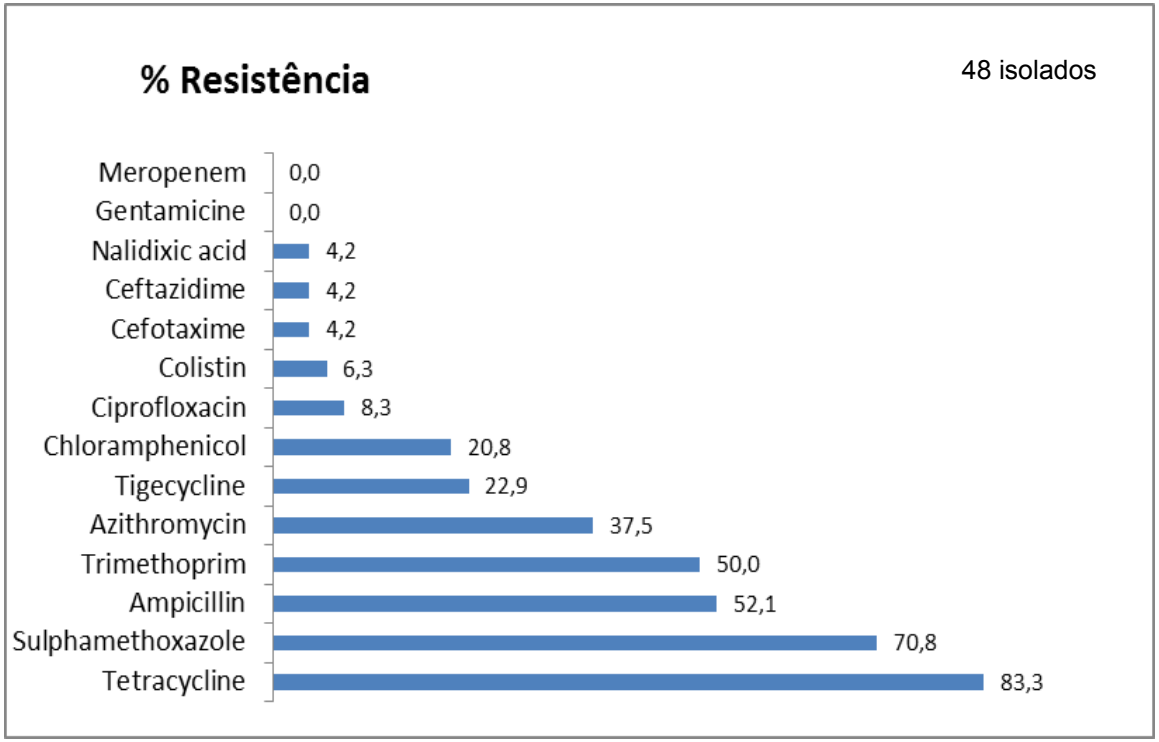
PVRAM de 2015

Salmonella em carcaças de suínos



PVRAM de 2015

E. coli ESBL - isolado em amostras de carne de bovino

Antimicrobiano (1º painel)	R	S	% Resistência	
Ampicillin	12		100,0	⇦
Azithromycin	1	11	8,3	
Cefotaxime	12		100,0	⇦
Ceftazidime	11	1	91,7	⇦
Chloramphenicol	5	7	41,7	
Ciprofloxacin	6	6	50,0	
Colistin		12	0,0	
Gentamicin	2	10	16,7	
Meropenem		12	0,0	
Nalidixic acid	9	3	75,0	
Sulphamethoxazole	10	2	83,3	
Tetracycline	12		100,0	⇦
Tigecycline		12	0,0	
Trimethoprim	8	4	66,7	

12 isolados de *E.coli* ESBL provenientes de amostras de carne de bovino

PVRAM de 2015

E. coli ESBL - isolado em amostras de carne de bovino

Antimicrobiano (2º painel)	R	S	% Resistência	
Cefepime	12		100,0	⇦
Cefotaxime	12		100,0	⇦
Cefotaxime/clavulanic acid	2	10	16,7	
Cefoxitin	1	11	8,3	
Ceftazidime	11	1	91,7	⇦
Ceftazidime/clavulanic acid	2	10	16,7	
Ertapenem		12	0,0	
Imipenem		12	0,0	
Meropenem		12	0,0	
Temociline		12	0,0	

12 isolados de *E.coli* ESBL provenientes de amostras de carne de bovino

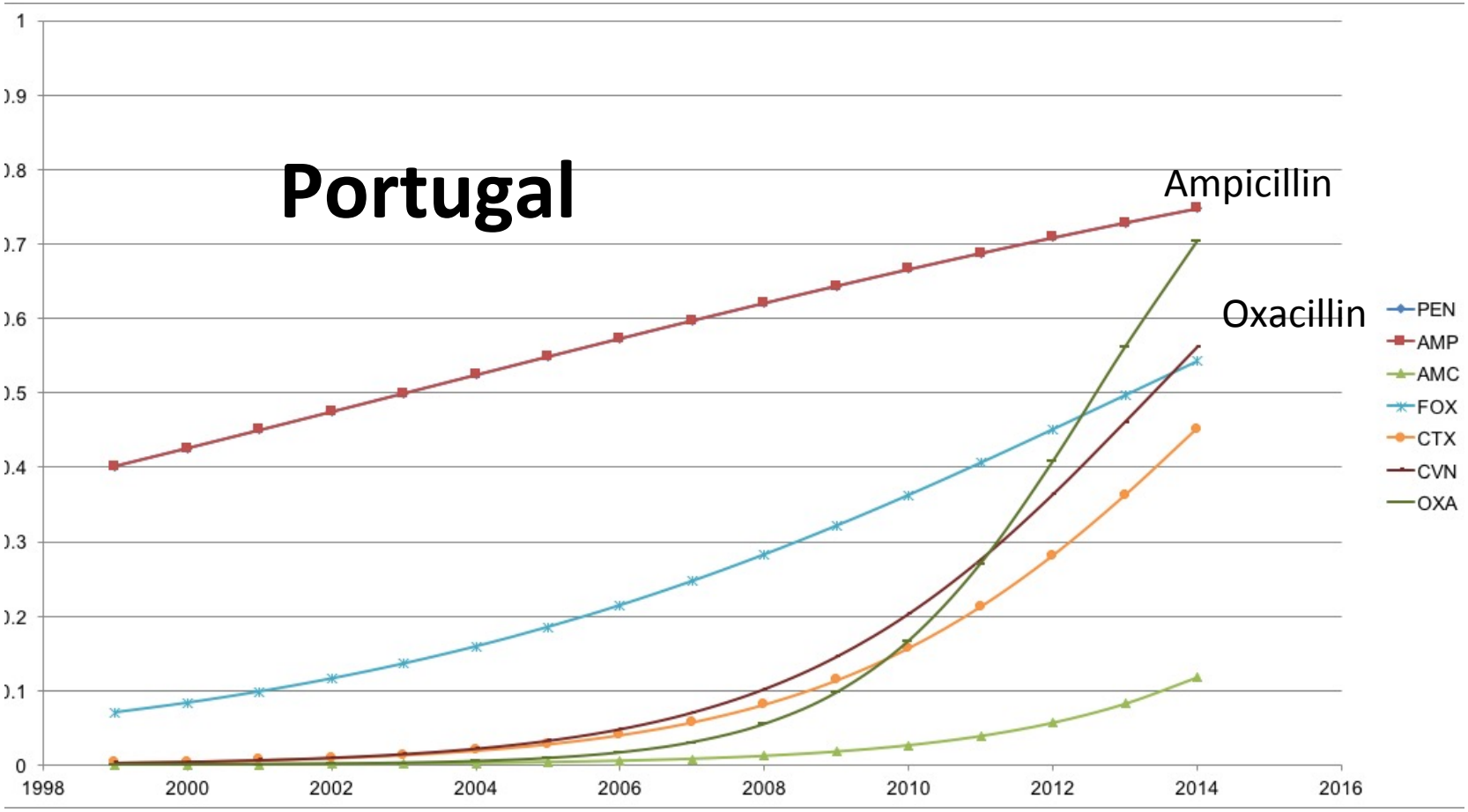
Pet animals

Pet animals

Microorganism exchange:

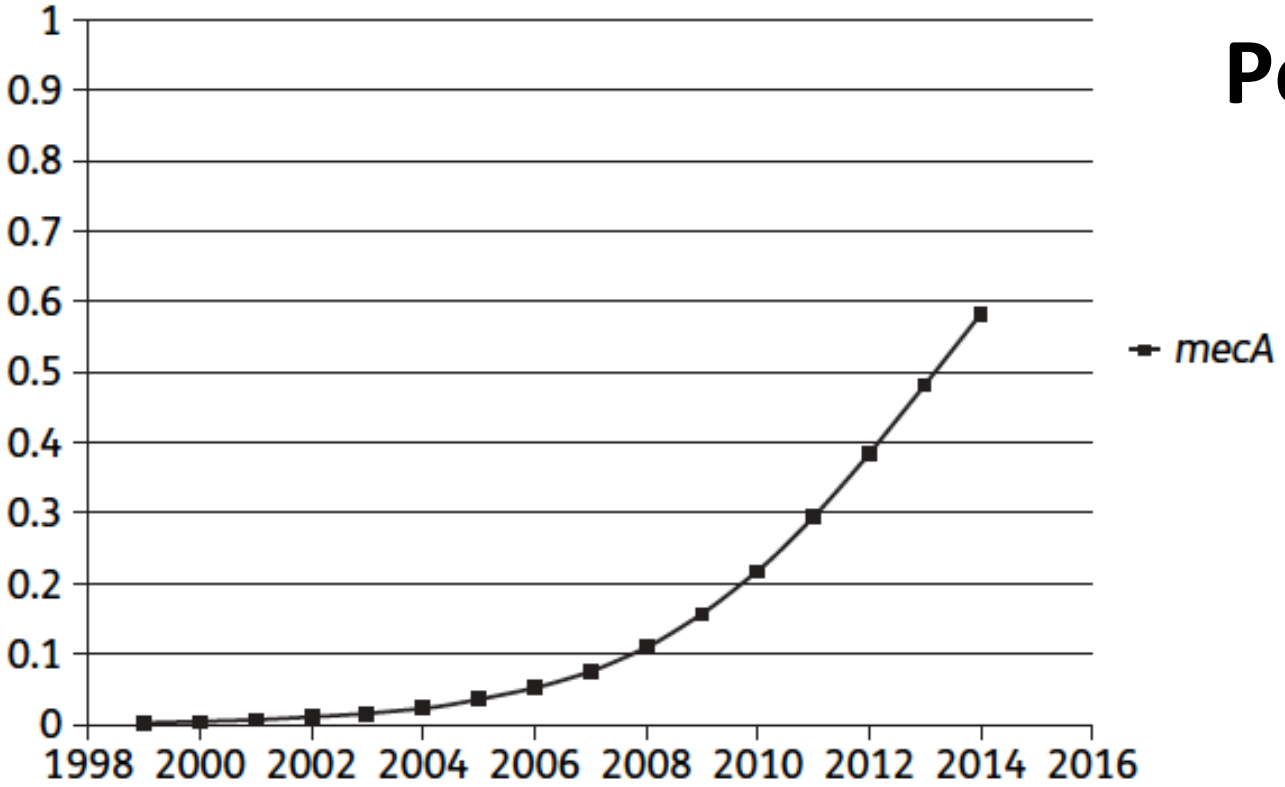
- between people and
- between animals and people living in the same environment

Evolution of antimicrobial resistance over the 16 years – Staphyloccoci isolated from companion animals



Couto et al, 2016, J Antimicrob Chemother. Jun;71(6):1479-87

mecA is increasing…

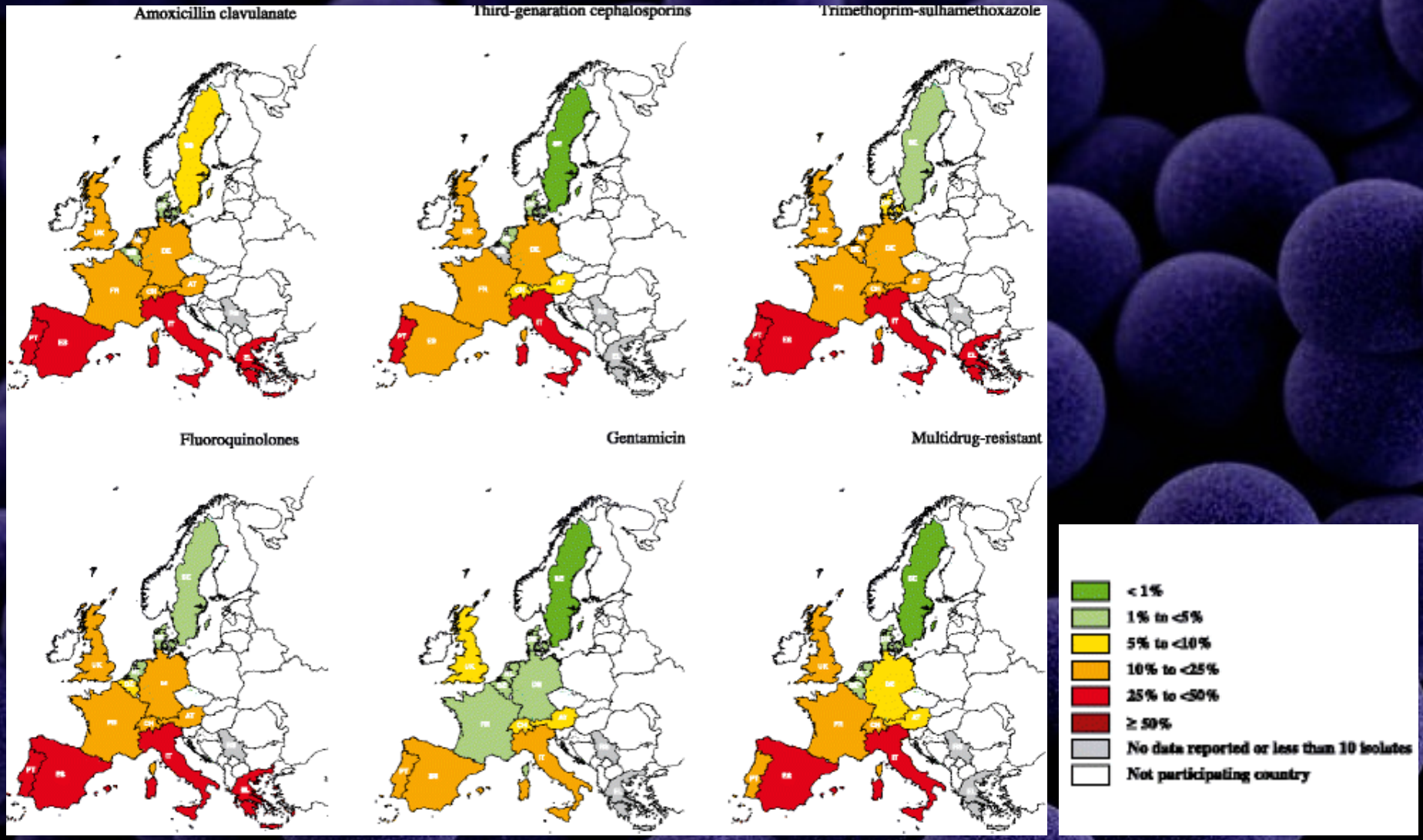


Portugal

Figure 2. Proportion of *mecA*-positive isolates over the 16 years studied ($P < 0.05$).

Escherichia coli antimicrobial resistance

isolated from companion animal urinary tract infections (Marques *et al.*, 2016)



Escherichia coli antimicrobial resistance

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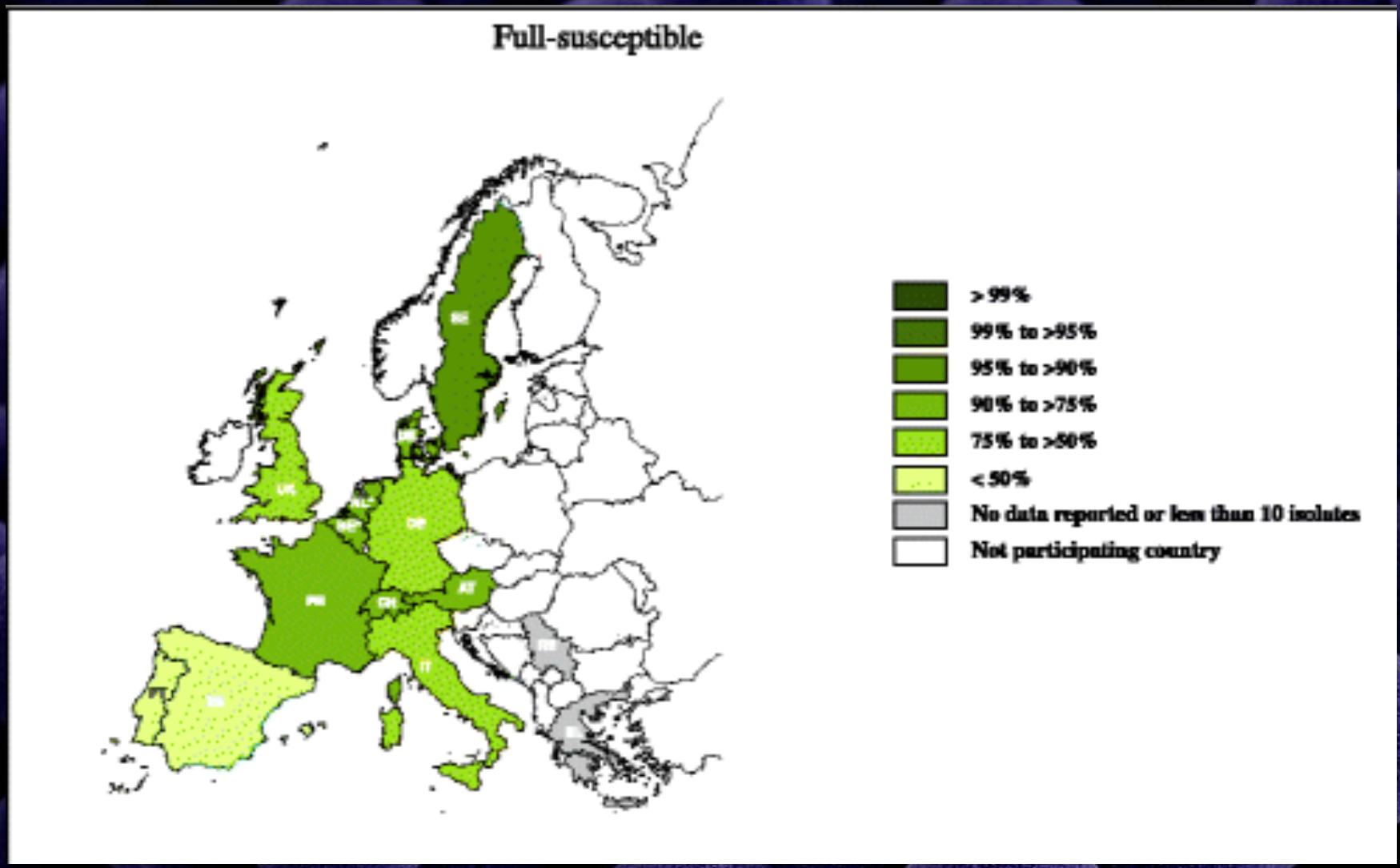
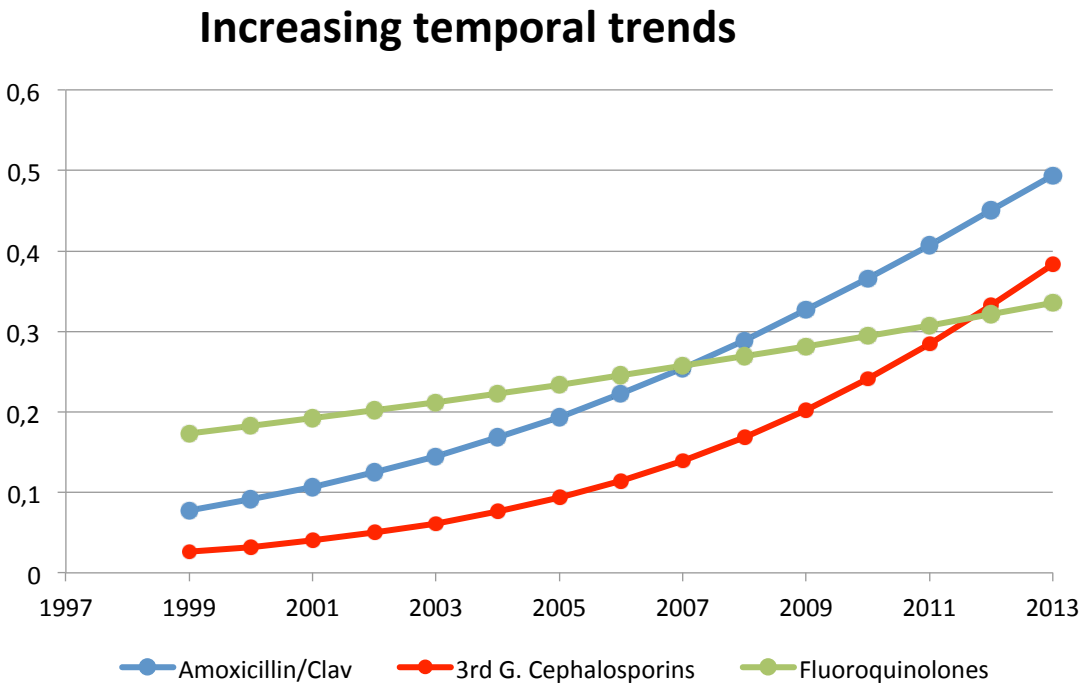


Escherichia coli

- Significant increase detected, AMC p<0.0001, 3GC p<0.0001, FLU p=0.0396

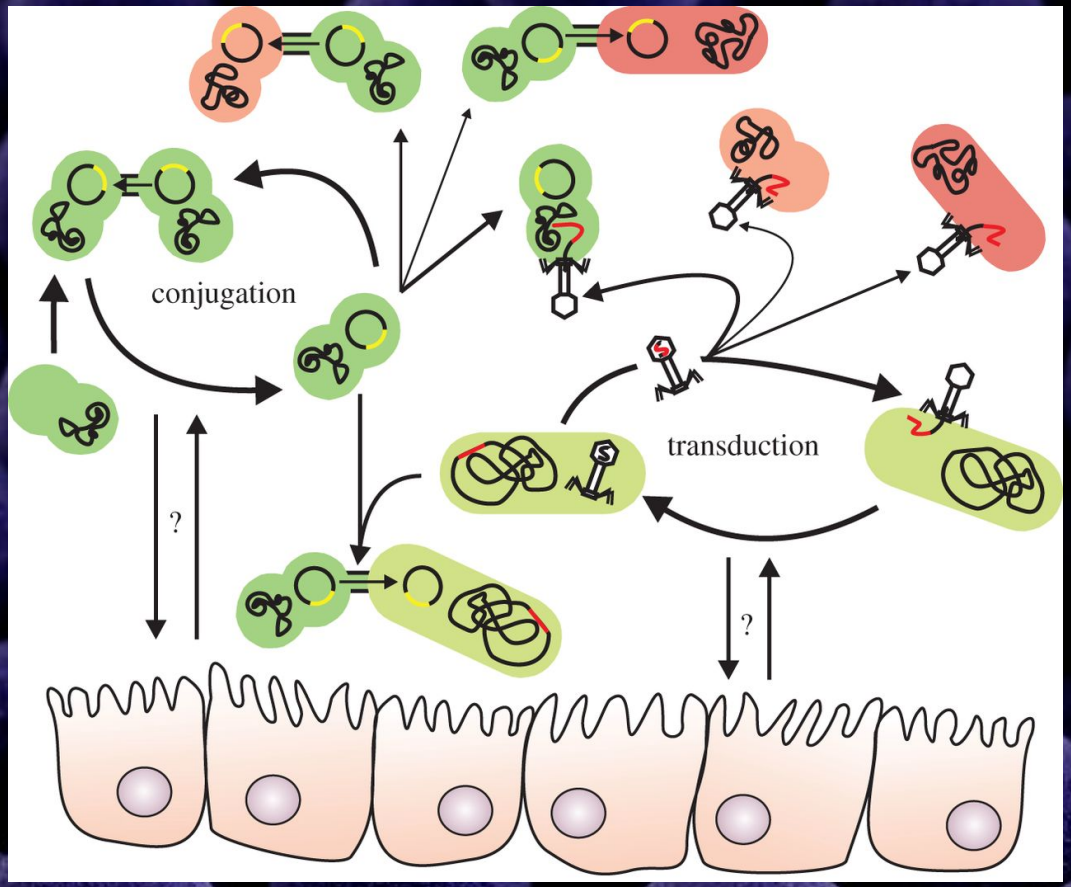


Antimicrobial category	Antimicrobial agents
Penicillins + β-lactamase inhibitors	Amoxicillin/ clavulanate
Third generation Cephalosporins	Cefotaxime Ceftazidime
Fluoroquinolones	Enrofloxacin Ciprofloxacin
Aminoglycoside	Gentamicin
Folate pathway inhibitors	Trimetropim/ Sulfametoxazole

(Magiorakos *et al*, 2011)

Resistance acquisition

Gene transfer



Horizontal transfer of genetic material, including antibiotic resistance genes, through conjugation and transduction is a frequent event in the gut microbiota

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European Society of Clinical Microbiology and Infectious Diseases

Which bacteria maybe a risk of transfer from pets to humans?

Antimicrobial resistant bacteria in companion animals	Type of hazard	Sources
Methicillin-resistant *Staphylococcus aureus*	Direct hazard	Dogs, cats, horses
Methicillin-resistant *Staphylococcus pseudintermedius*	Direct hazard[a]	Dogs, cats, horses
Vancomycin-resistant enterococci	Indirect hazard[b]	Dogs, horses
ESBL-producing Enterobacteriaceae	Indirect hazard	Dogs, cats, horses
Carbapenem-resistant Gram-negative bacteria	Indirect hazard[b]	Dogs, cats
Colistin-resistant *Escherichia coli*	Indirect hazard	Dogs, cats

[a]low number of cases of human infections originating from companion animals
[b]no human infections originating from companion animals have been reported

Public health risk of antimicrobial resistance transfer from companion animals
Pomba et al, 2017, Journal of Antimicrobial Chemotherapy, 2017 72 (4): 957–968

EMERGING INFECTIOUS DISEASES®

Volume 22, Number 9—September 2016

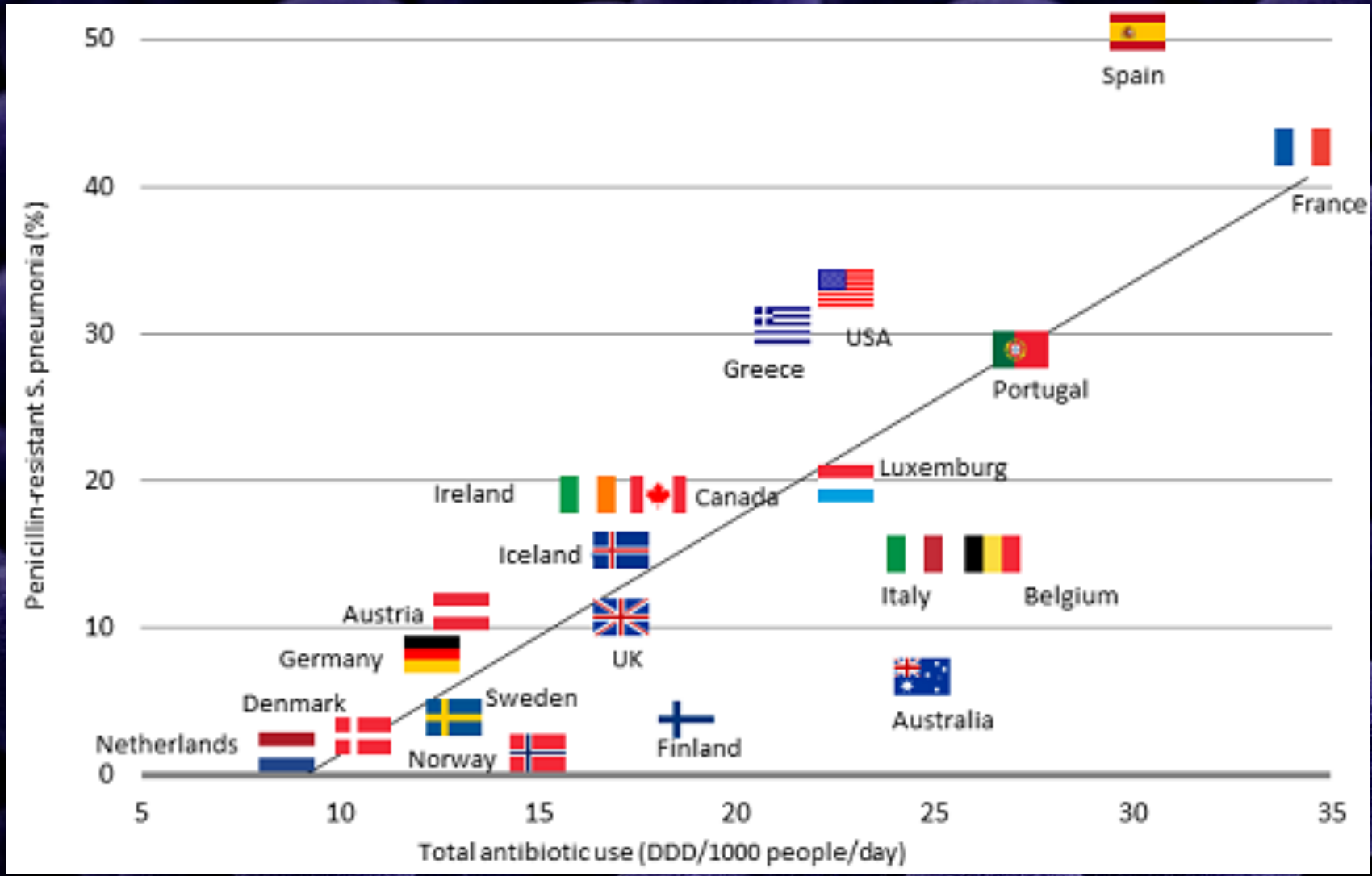
Letter

Possible Transmission of *mcr-1*–Harboring *Escherichia coli* between Companion Animals and Human

Problem

- Superbugs → untreatable
- 700 000 people are already dying of resistant bacteria infections every year
- 10 million deaths a year by 2050?

Problem


Penicillin-resistant S. pneumonia (%)
50
40
30
20
10
0
5
10
15
20
25
30
35
Total antibiotic use (DDD/1000 people/day)
Spain
France
USA
Greece
Portugal
Luxemburg
Ireland
Canada
Iceland
Italy
Belgium
Austria
Germany
UK
Australia
Denmark
Sweden
Netherlands
Norway
Finland

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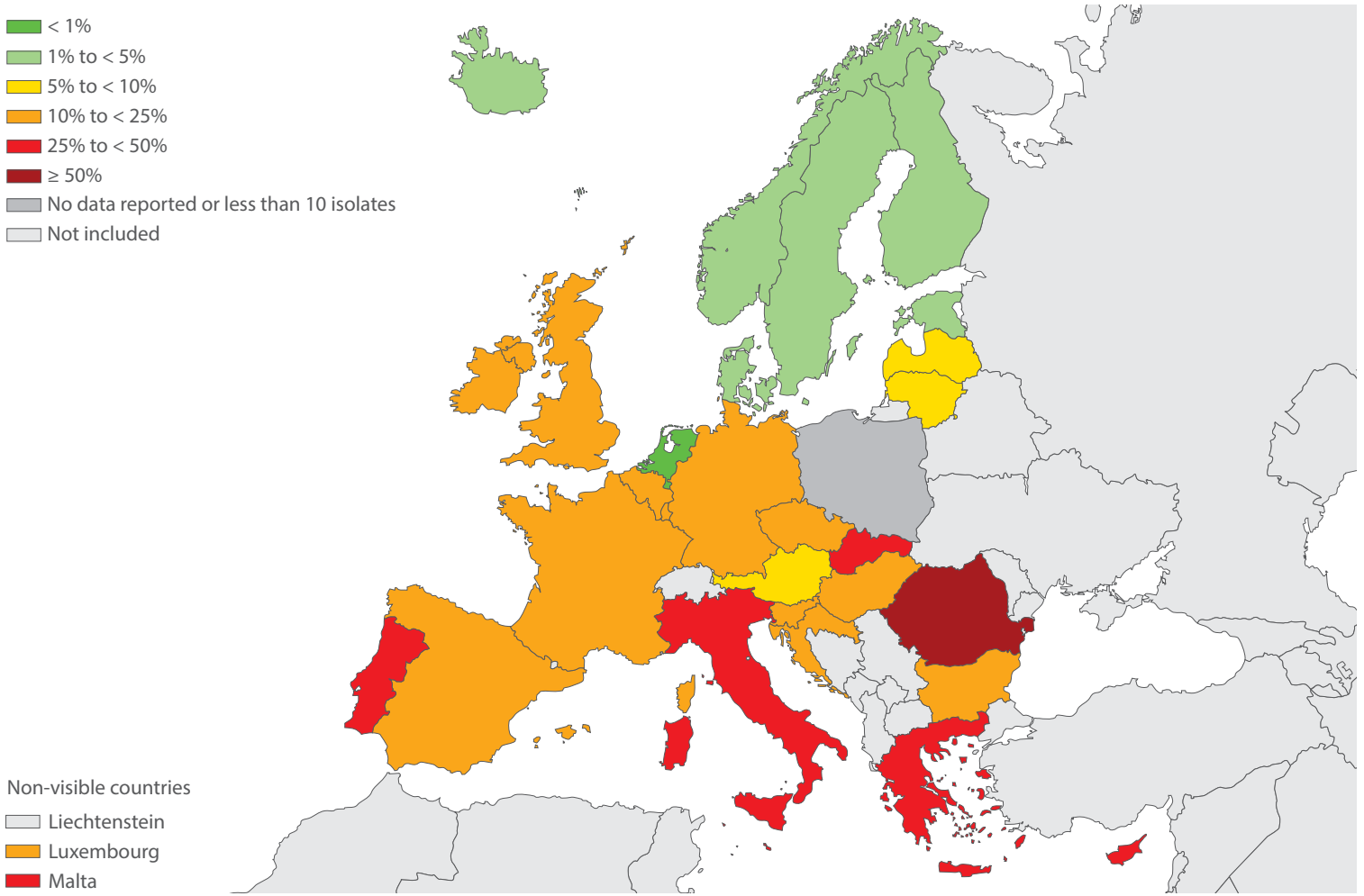
EARSS MRSA in humans in Europe 2014

Figure 3.23. ***Staphylococcus aureus*****. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2014**



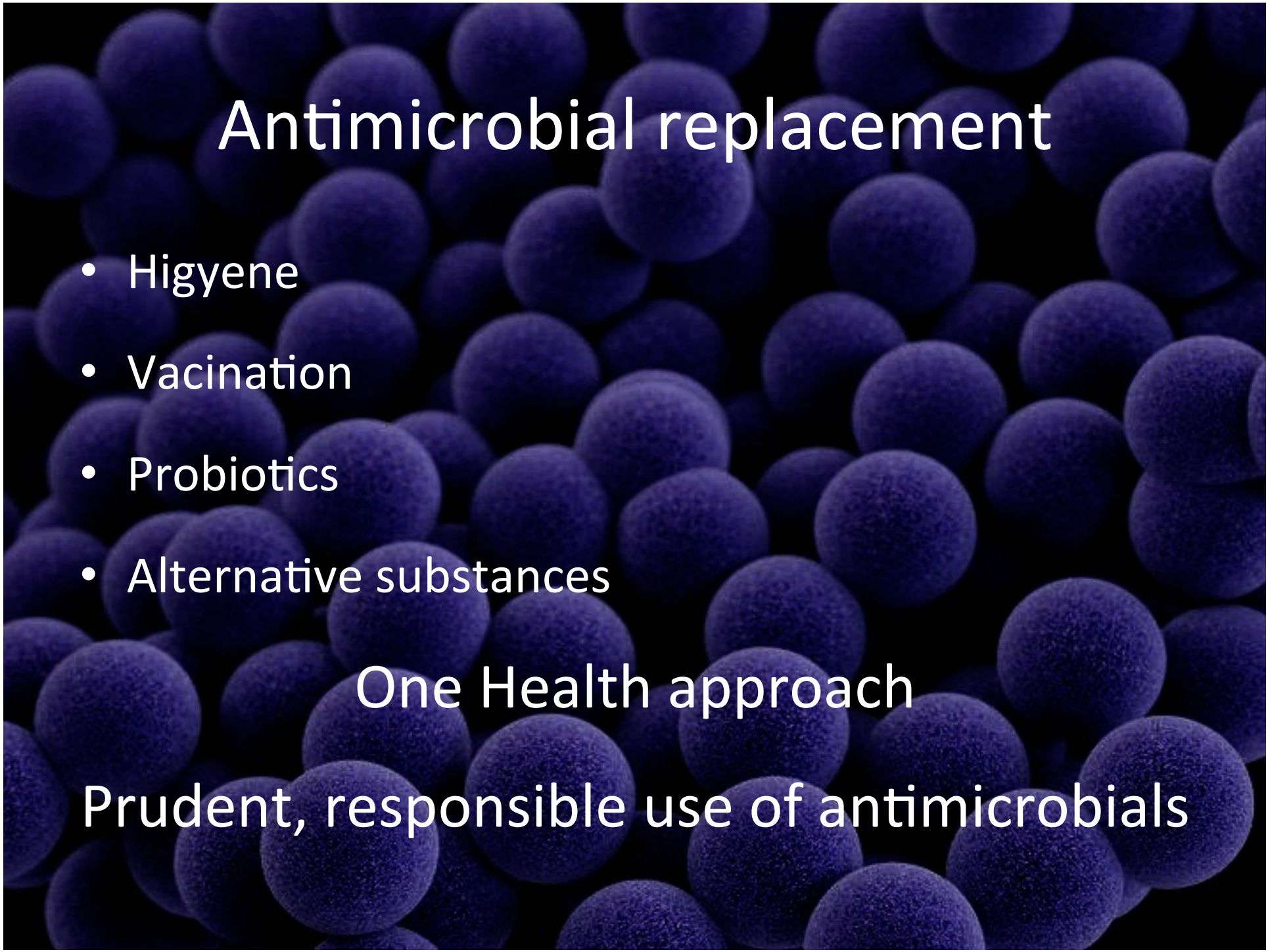
Mail Online

New potentially lethal superbug resistant to ALL antibiotics is found in the UK - and 12 people have been infected

- All 12 have been treated for infections linked to virulent strains of salmonella and E.coli carrying a deadly resistance gene, scientists say
- Plus bugs carrying the gene have been found on three pig farms in the UK and chicken meat imported from Europe
- Now this same resistance gene – MCR-1 - has been found on bugs in people, farm animals and meat in Britain

Antimicrobial stewardship

- Coordinated interventions designed to improve and measure the appropriate use of antimicrobials
- Selection of the optimal antimicrobial drug regimen: dose, duration of therapy, route of administration
- Achieve optimal clinical outcomes
- Minimize toxicity and other adverse events
- Reduce the costs of health care for infections
- Limit the selection for antimicrobial resistant strains


Antimicrobial replacement
• Higyene
• Vacination
• Probiotics
• Alternative substances
One Health approach
Prudent, responsible use of antimicrobials

Official actions adopted

- PANRUAA - «Plano de Ação Nacional para a Redução do Uso de Antibióticos nos Animais»
- Regulamento "Saúde Animal" (Publicado –2016)
  - general prevention / behavior measures - to contribute to the reduction of antibiotics use
  - biosafety, some rules on the use of veterinary drugs (vaccines, prudent use) etc.
  - responsibilities, knowledge, awareness of operators, veterinarians, etc.
  - monitoring of pathogens AMR
  - other disease prevention and control measures

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dgav Direção Geral de Alimentação e Veterinária

Sistema de Vigilância de Antibioresistências

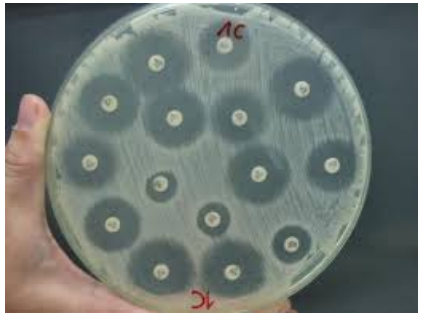
Diretiva 2003/99
Decisão 2013/652

PIGA

Monitorização dos perigos microbiológicos nos géneros alimentícios

PVRAM

Vigilância das resistências antimicrobianas em bactérias zoonóticas e comensais



European Union approach to the critical list *

dgav Direção Geral de Alimentação e Veterinária

* Answers to requests for scientific advice on the impact of public health and animal health on the use of antibiotic in animals, EMA 381884/2014 18 December 2014 **Future assessments could result in a change of the categorisation.

European Union approach to the critical list * **Category**	**Classes**	**Management**
1 Low or Limited Risk	Macrolides, Penicillins, Rifamycins, Tetracyclins	Responsible use
2 Higher Risk	Cephalosporins, Fluorochinolones, **Polymyxins,** *Aminoglycosides*** *Aminopenicillins **	Use only if no alternatives
3 Not approved for veterinary medicine	Carbapenems, Cyclic Esters, Glycopeptides, Glycylcyclines, Lipopeptides, Monobactams, Oxazolidinones, Carboxy and Ureidopenicillins, Sulfones, etc…	Use by exception, according to national rules, only in companion animals

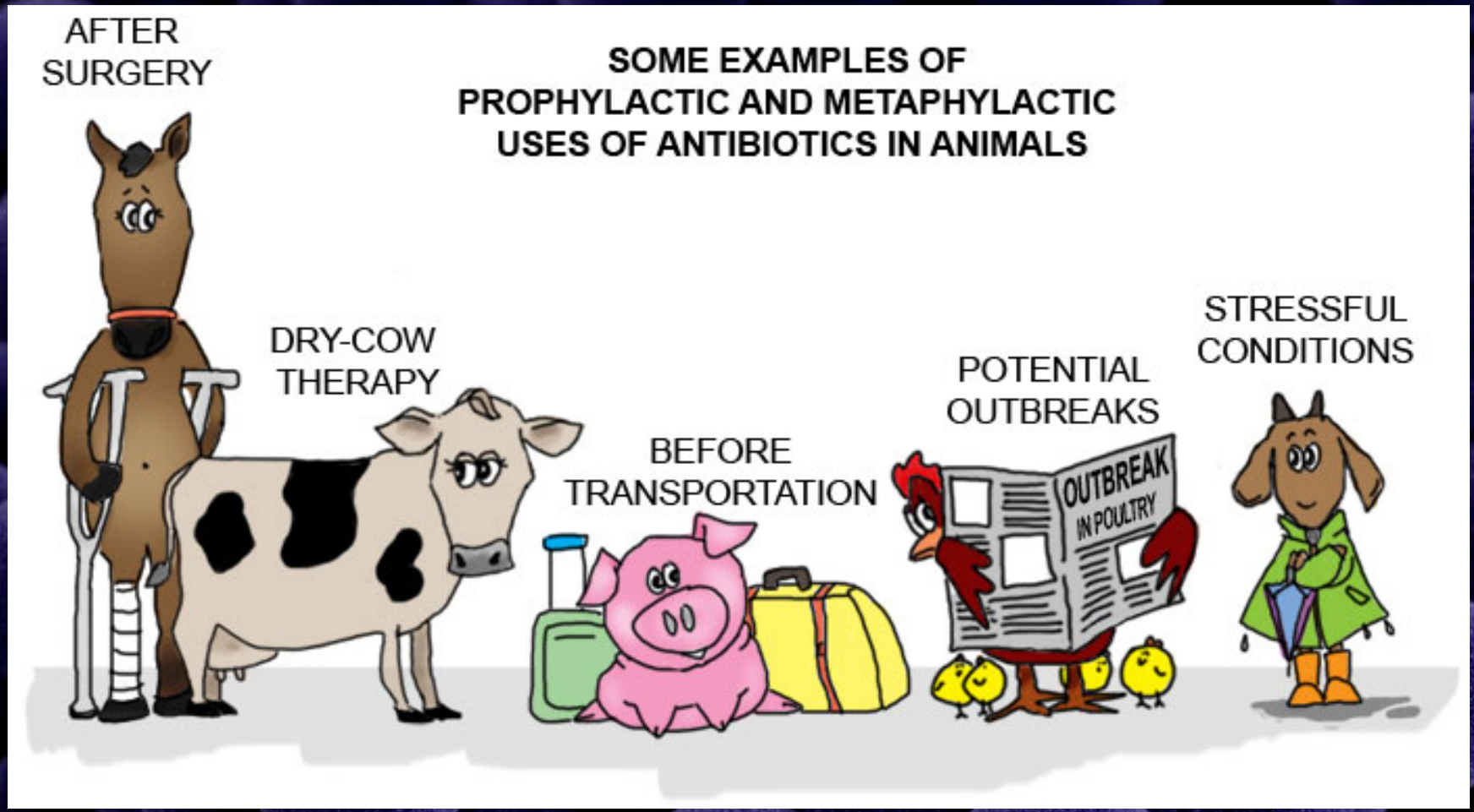
WHO - list of critically important antimicrobials for human medicine

These antimicrobials are essential as last-resort treatments for multidrug-resistant infections in humans

5th revision of the list published in April 2017, the antibiotics considered highest priority:

- Quinolones
- 3rd and higher generation Cephalosporins
- Macrolides and ketolides
- Glycopeptides and polymyxins (colistin)

WHO is recommending that farmers and the food industry stop using antibiotics routinely to promote growth and prevent disease in healthy animals



Approach


ONE
HEALTH
HUMANS · ENVIRONMENT · ANIMALS · LIVING · TOGETHER · HARMONIOUSLY

OIE organizes awareness week for proper use of antimicrobials

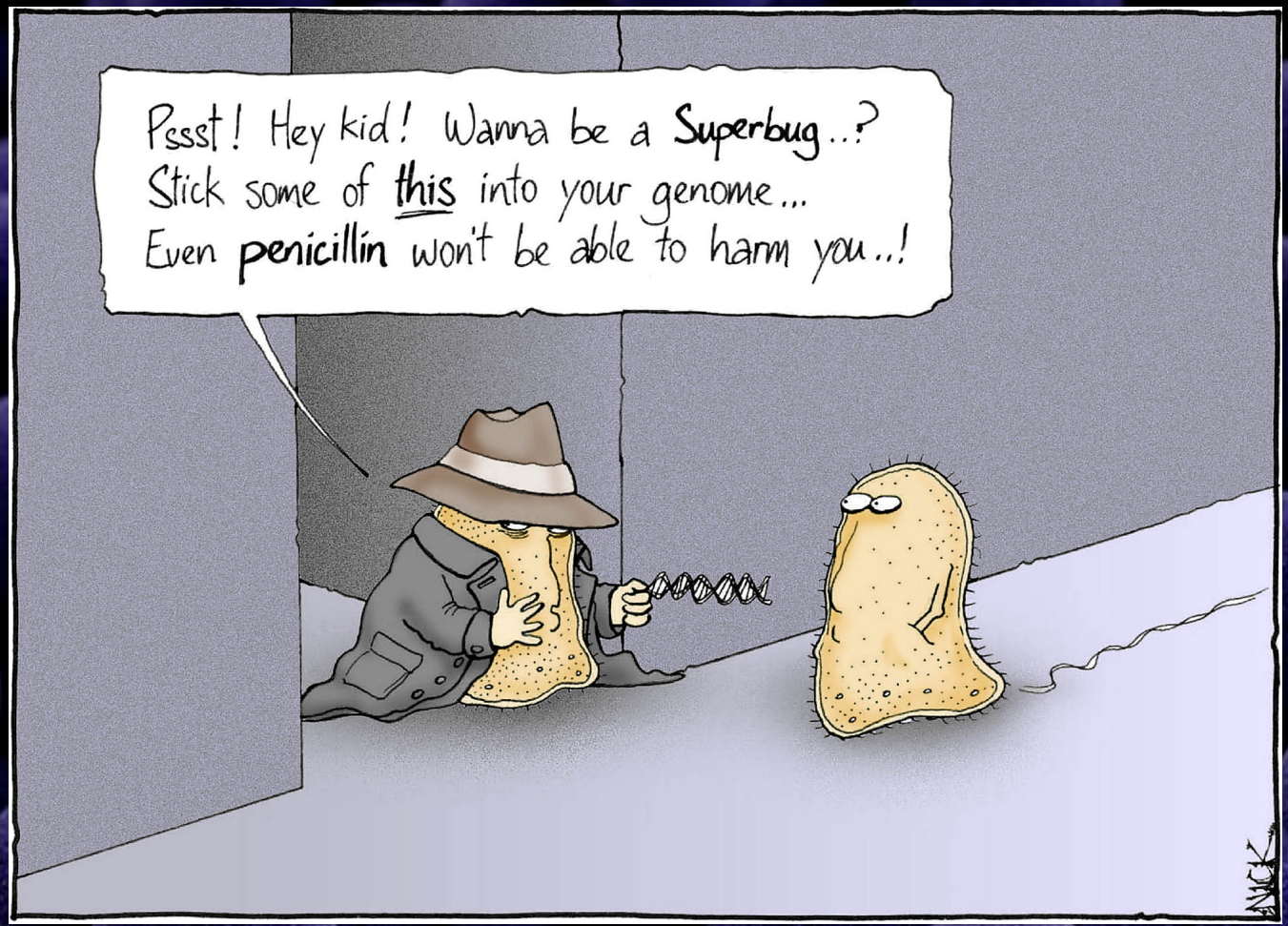
- OIE (Office International des Epizooties)
- WHO (World Health Organization)
- FAO (Food and Agriculture Organization of the United Nations)

are jointly combating antimicrobial resistance

"Each of us has a role to play in the fight against antimicrobial resistance, in doing so, to protect the effectiveness of these vital treatments and at the same time our future"

https://www.youtube.com/embed/QoUqO5dNhDw?rel=0&autoplay=1

Thank you


Pssst! Hey kid! Wanna be a Superbug..?
Stick some of this into your genome...
Even penicillin won't be able to harm you..!