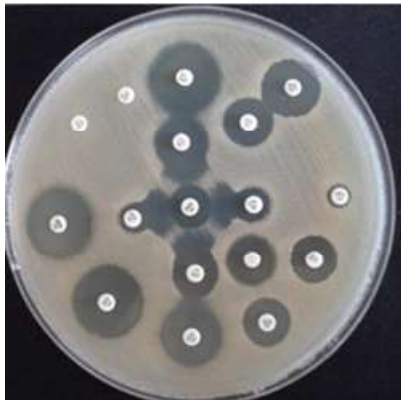
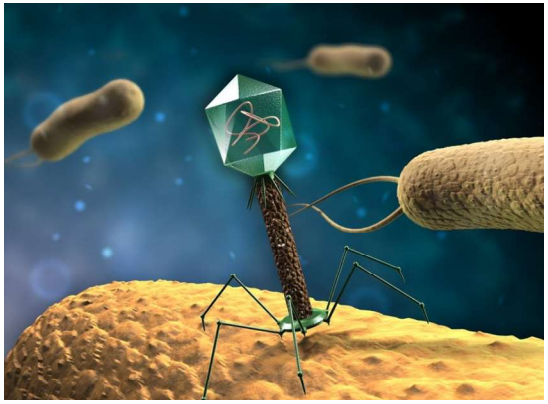
BMM0413 – Aula 4: Mecanismos de resistência aos antimicrobianos


Nilton Lincopan, PhD

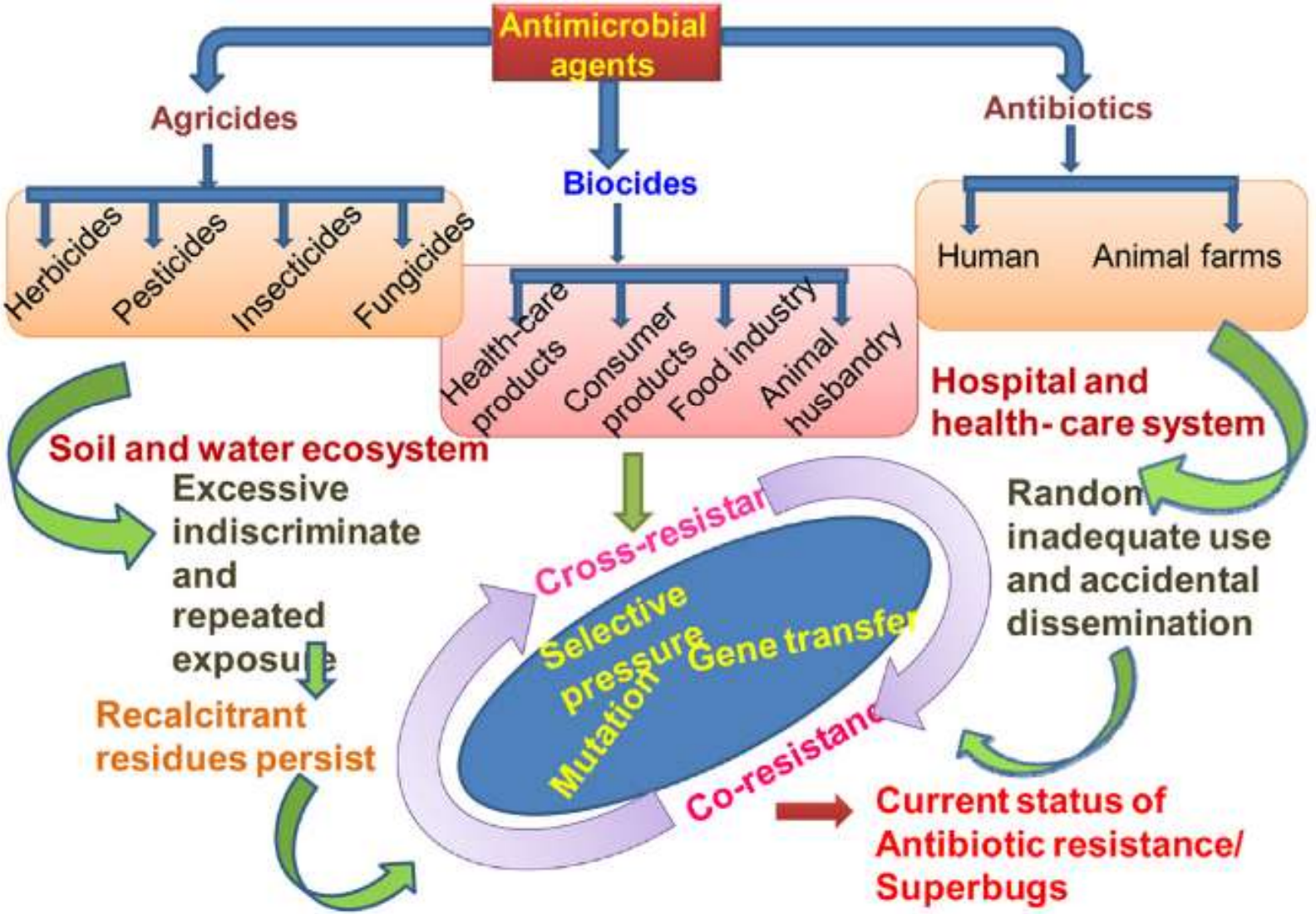
lincopan@usp.br

http://www.onehealthbr.com/

Departamento de Microbiologia – Instituto de Ciências Biomédicas

Universidade de São Paulo, Brasil

Antimicrobianos



Paul *et al*., 2019. *Ecotoxicol Environ Saf*. 174:601-610.

ATB: Uso Clínico versus Resistência

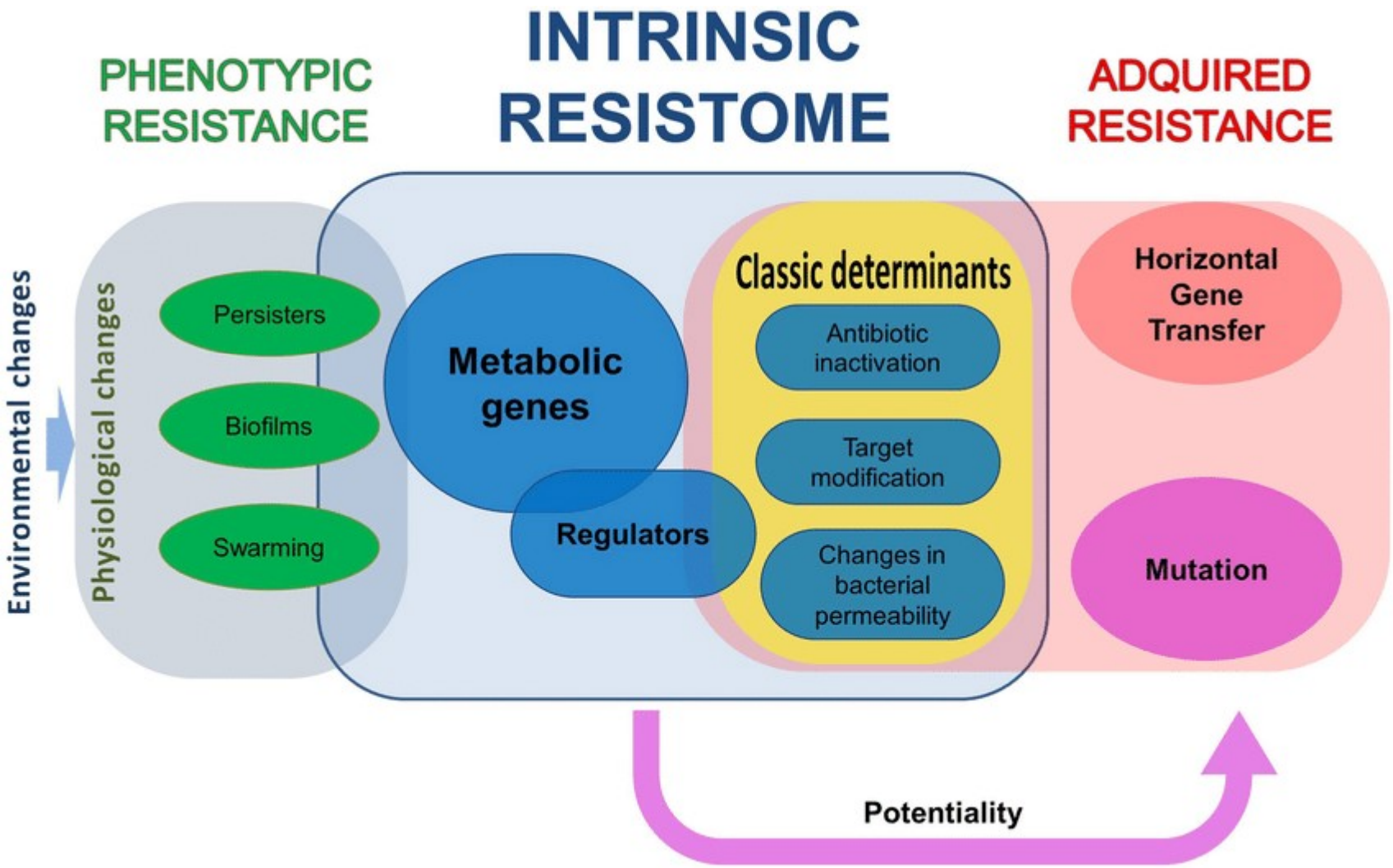
Antibacteriano	Uso clínico	Resistência
Sulfonamidas	1935	1940
Penicilinas	1942	1945
Estreptomicina	1944	1958
Tetraciclína	1948	1954
Cloranfenicol	1949	1956
Colistina	**1949**	**2015***
Vancomicina	1955	1982
Cefalosporinas	**1964**	**1969**
Quinolonas	1967	1969
Carbapenems	**1985**	**1998**
Ciprofloxacina	1987	1990
Linezolida	2000	2003
Caz/Avibactam	**2015**	**2015**

* Mediada por plasmídeos

Weinstein A.J., *Drugs* 1980, 20:137-154.

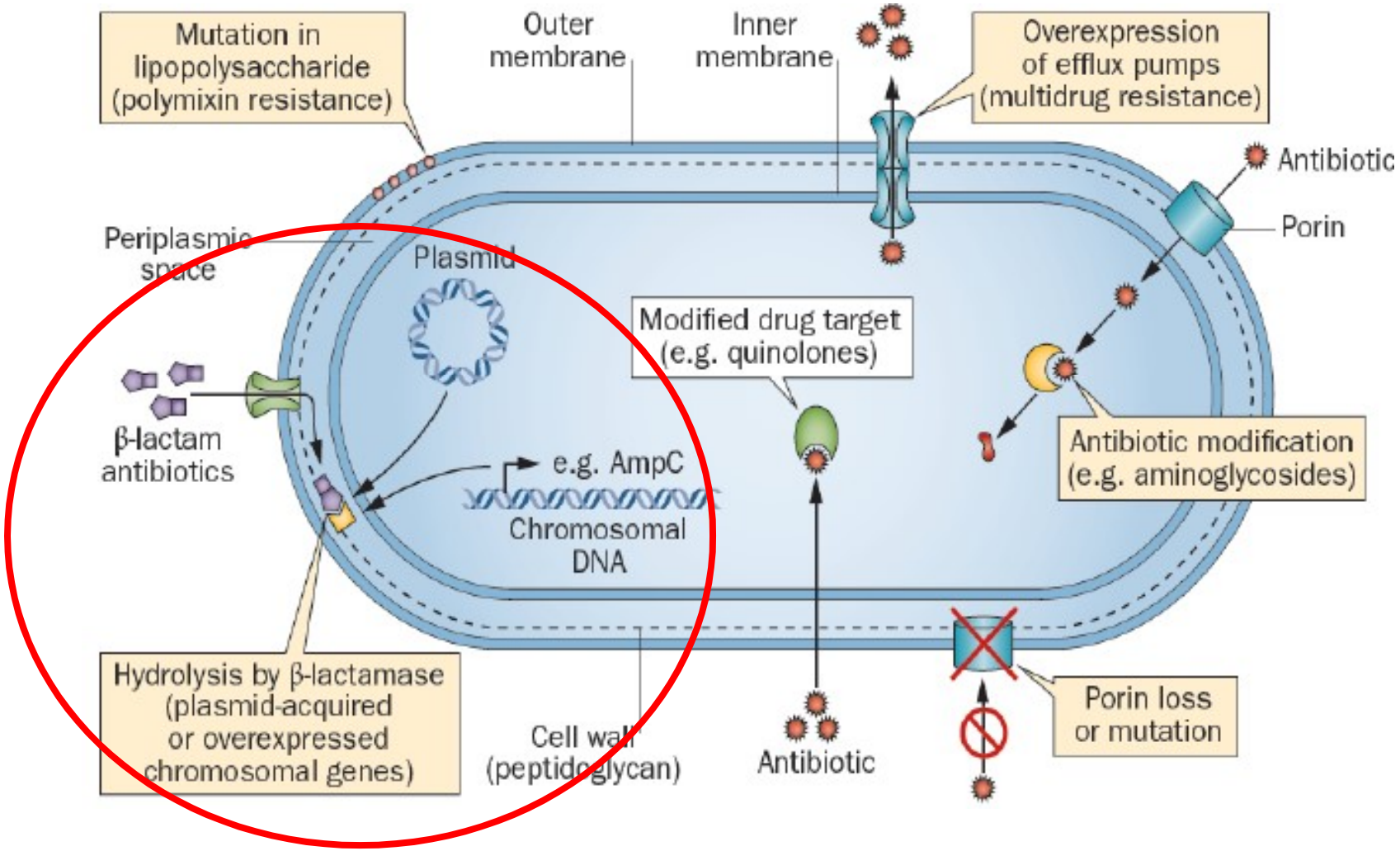
Winkler M.L., *Antimicrob Agents Chemother*, 2015, 59:1020-1029.

Origem da RAM



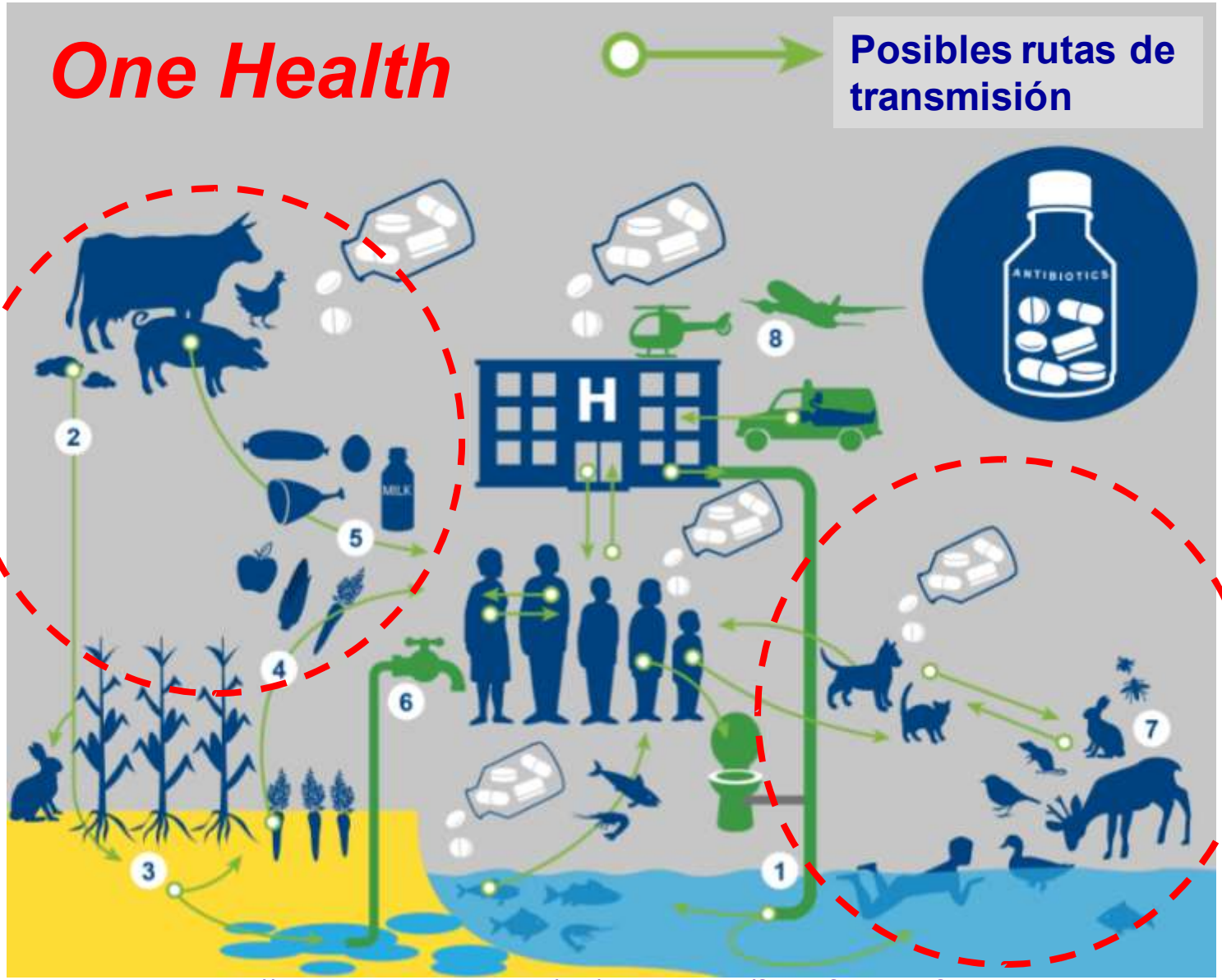
Front Microbiol. 2013 Apr 30;4:103.

Mecanismos de resistência



Zowawi, et al. (2015). *The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nature Reviews Urology, 12(10), 570–584.*

Antimicrobianos e saúde única



https://amr.biomerieux.com/en/challenges/from-farm-to-food-to-people-one-health/

Como produzir bacteria resistêntes?

Pressão seletiva *in vivo*

Alta densidade de pacientes (superlotação)

+

Fácil circulação de patógenos

+

Condições de higiene deficientes

+

Amplo uso de antimicrobianos e desinfetantes

Antimicrobianos: promotor, profilático, terapêutico

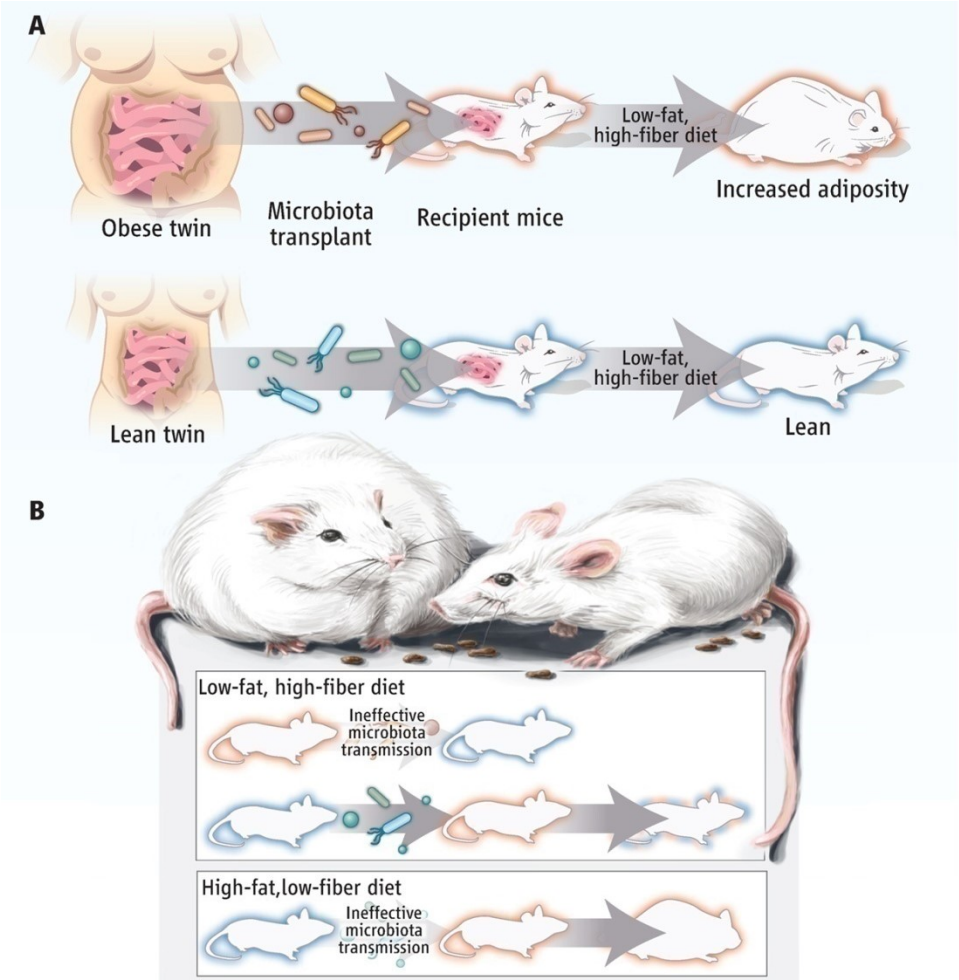
Lancet Infect Dis. 2015, 15:1243

MICROBIOLOGY

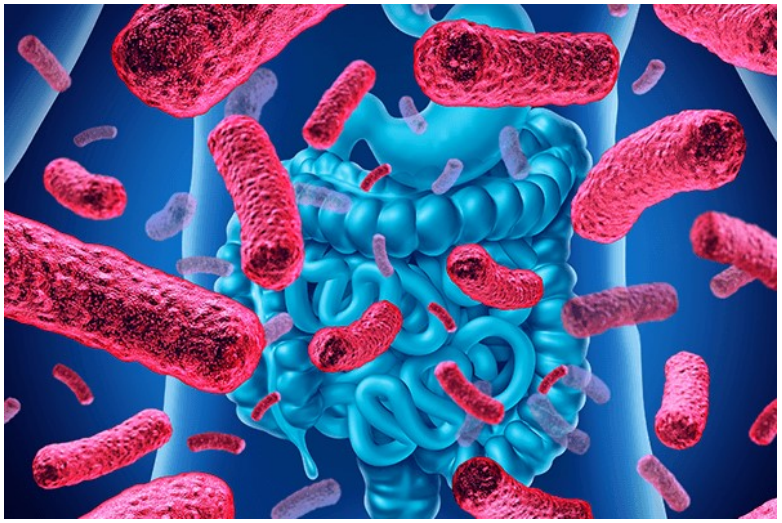
Fighting Obesity with Bacteria

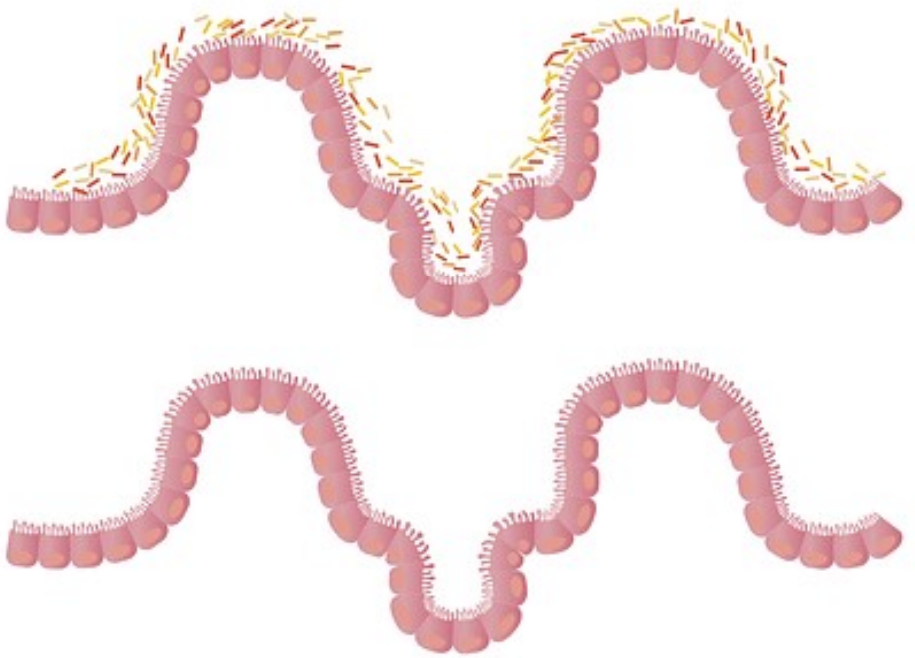
Alan W. Walker and Julian Parkhill

Intestinal bacteria from lean humans can confer protection against fat gain in experimental mice.

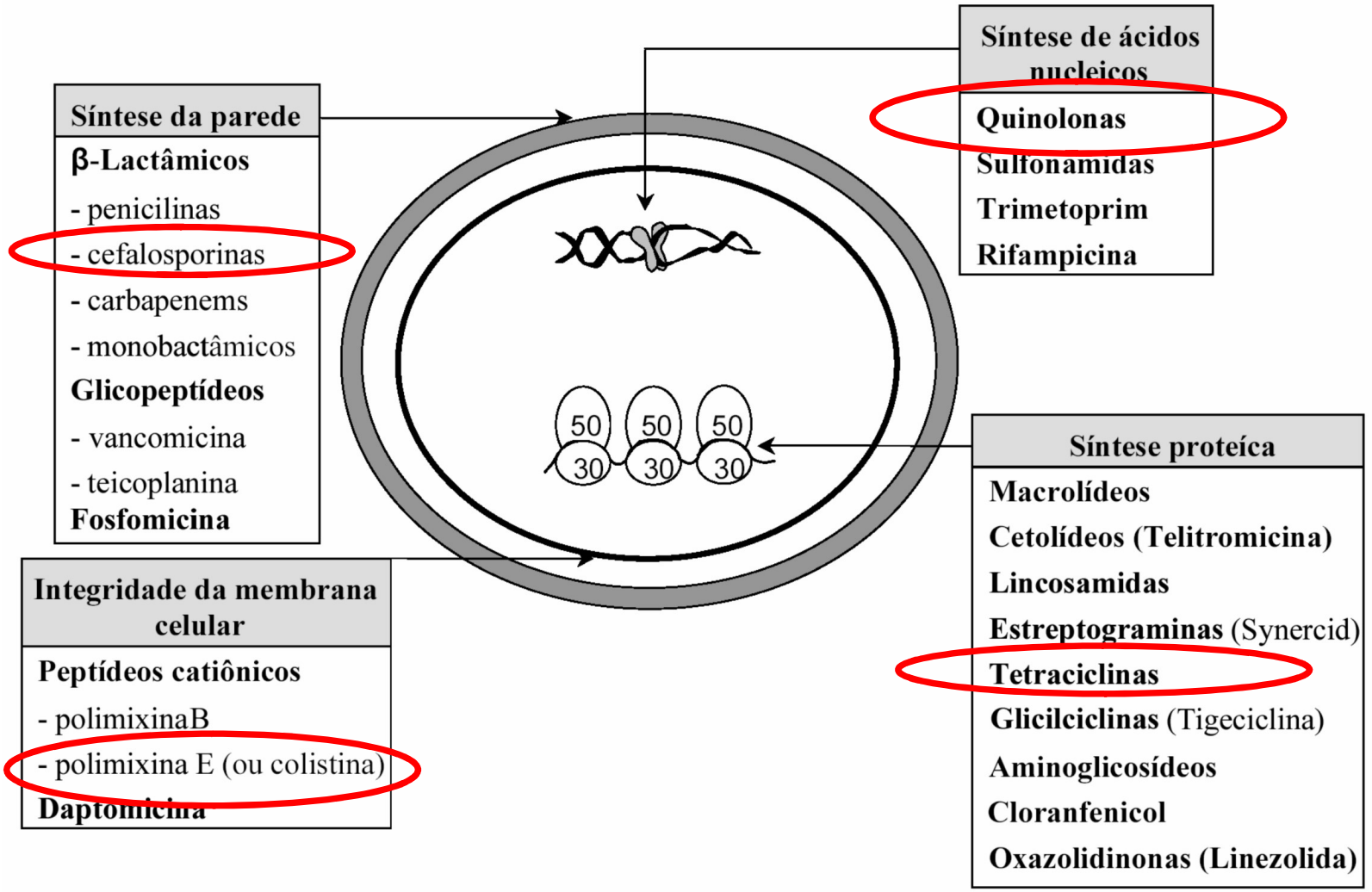


Transplante fecal: probióticos, prebióticos, fagos





Antibacterianos em animais de produção



Antibacterianos em animais de produção

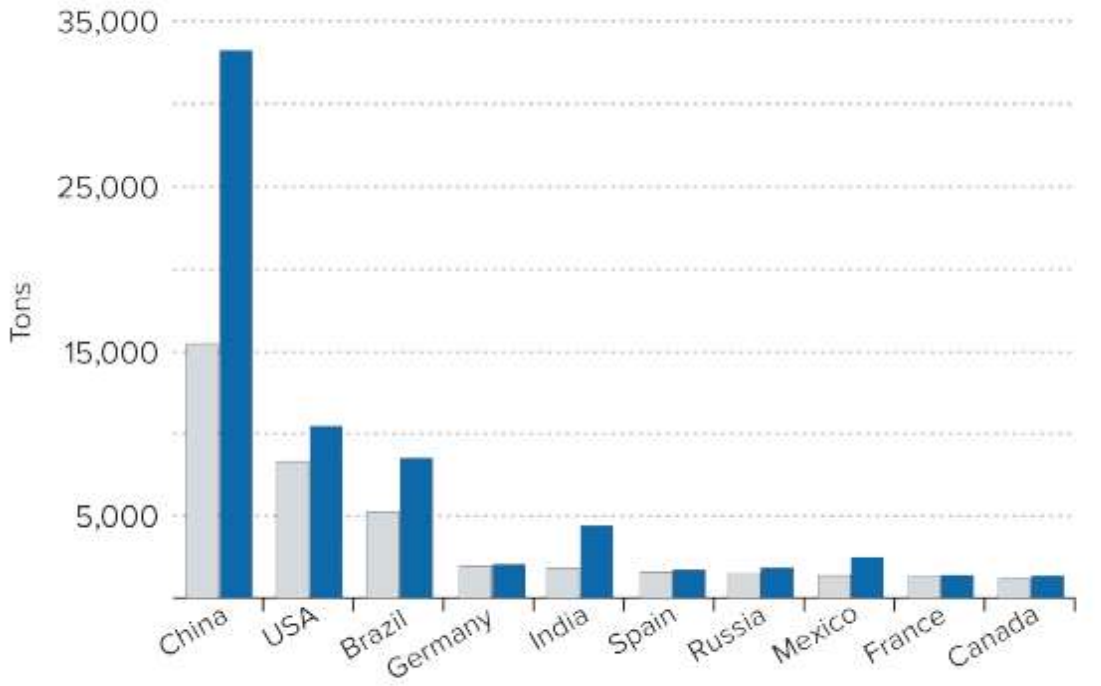


FIGURE ES-3: Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)

Source: Van Boeckel et al. 2015

PNAS 2015, 112: 5649-5654.

Impacto da RAM no agronegócio e saúde única

RESEARCH

RESEARCH ARTICLE

ONE HEALTH

Global trends in antimi resistance in animals ir middle-income countri

nature

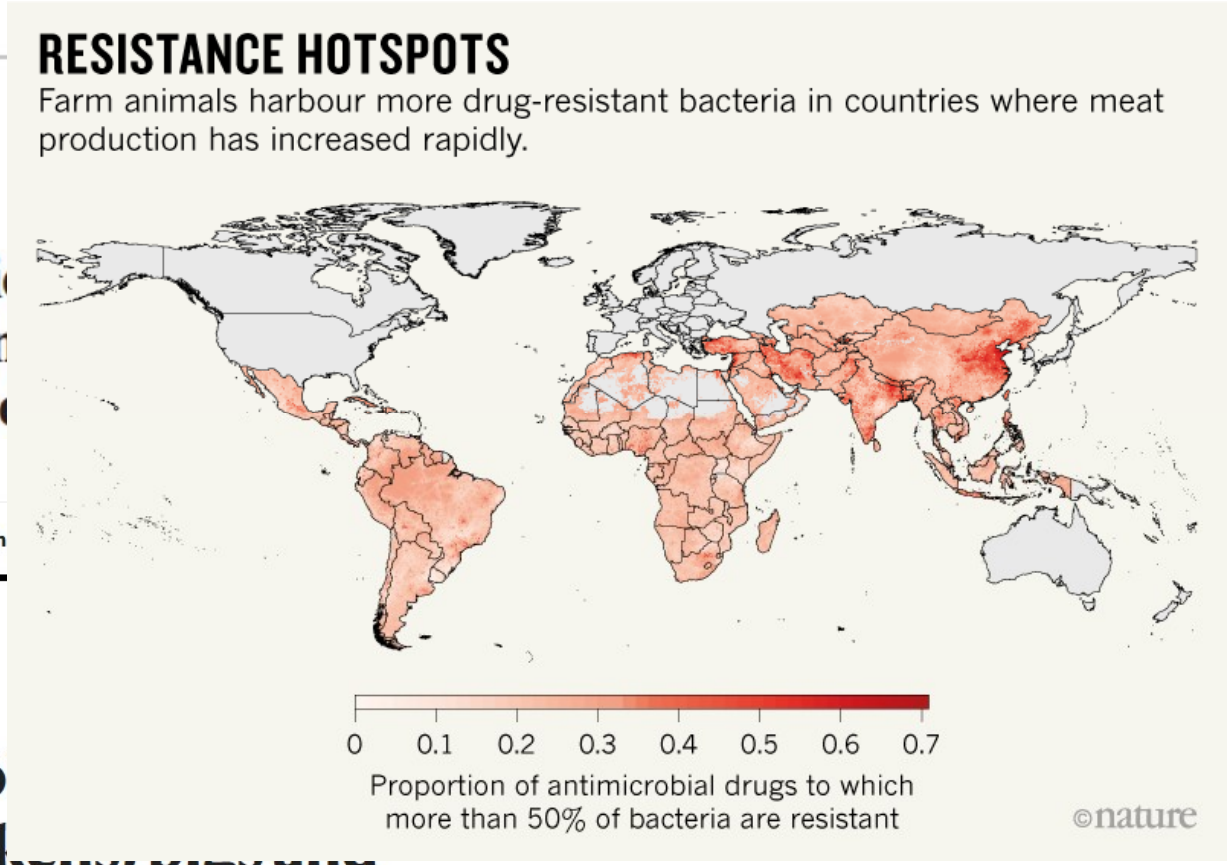
Explore content ⌄ About the journal ⌄ Publish

nature › news › article

NEWS | 20 September 2019

Alarm as antimicro surges among chick cattle

Drug-resistant bacteria are gaining a stronghold in developing countries where meat production has soared.



Van Boeckel et al. 2019. Science. 365(6459). pii: eaaw1944.
https://www.nature.com/articles/d41586-019-02861-5

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

First Characterization of CTX-M-15-Producing *Escherichia coli* Strains Belonging to Sequence Type (ST) 410, ST224, and ST1284 from Commercial Swine in South America

Ketrin C. Silva,[a] Marina Moreno,[a] Carlos Cabrera,[a] Beny Spira,[b] Louise Cerdeira,[b,c] Nilton Lincopan,[b,c] Andrea M. Moreno[a]

Department of Preventive Medicine and Animal Health, School of Veterinary Medicine, University of São Paulo, São Paulo, Brazil[a]; Department of Microbiology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil[b]; Department of Clinical Analysis, School of Pharmacy, University of São Paulo, São Paulo, Brazil[c]

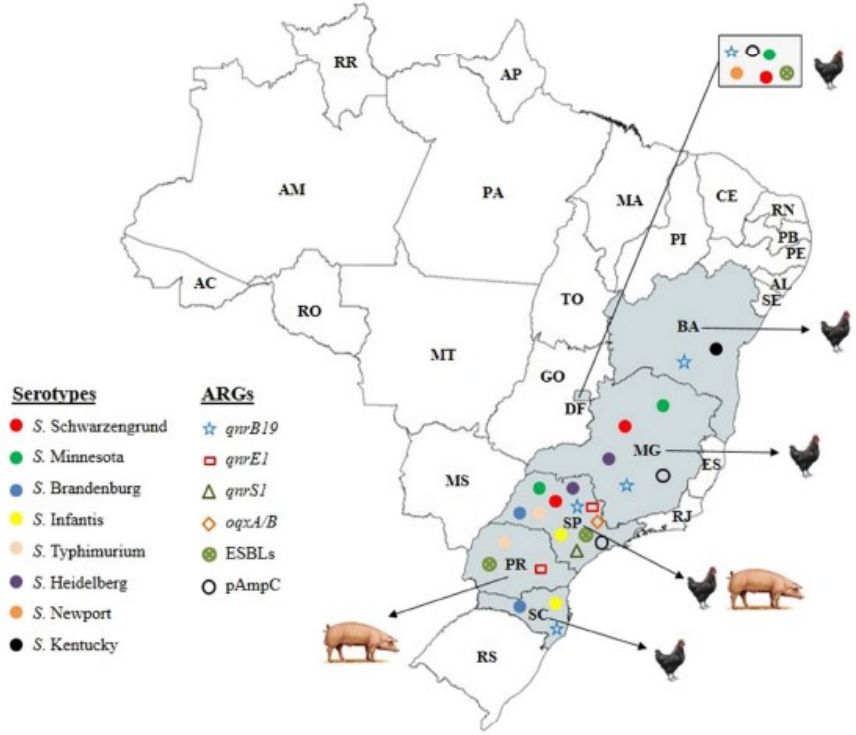
SCIENTIFIC REPORTS
nature research

OPEN

Genomic Features of High-Priority *Salmonella enterica* Serovars Circulating in the Food Production Chain, Brazil, 2000–2016

Received: 29 January 2019
Accepted: 11 June 2019
Published online: 30 July 2019

Daniel F. Monte[1,4], Nilton Lincopan[2,3], Hanna Berman[4], Louise Cerdeira[3], Shivaramu Keelara[4], Siddhartha Thakur[4], Paula J. Fedorka-Cray[4] & Mariza Landgraf[1]

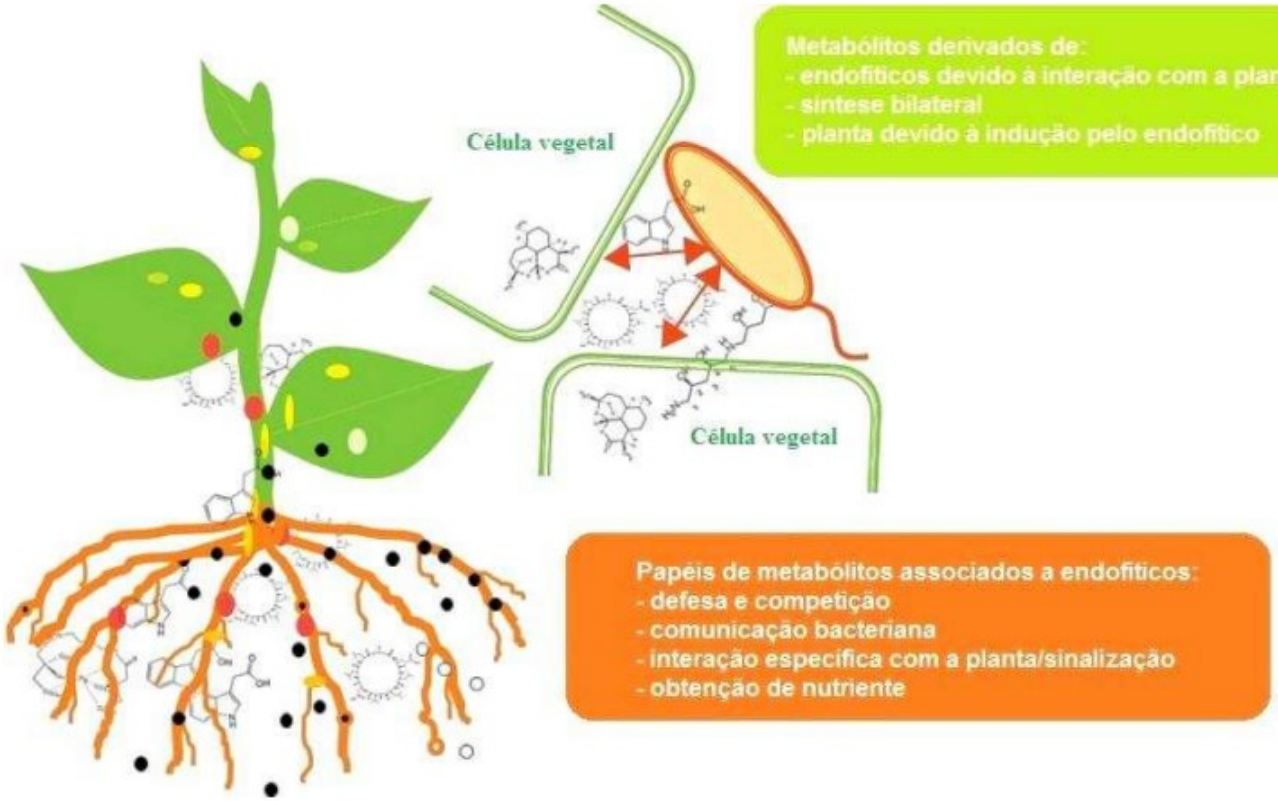


AMERICAN SOCIETY FOR MICROBIOLOGY | mSystems®

RESEARCH ARTICLE
Clinical Science and Epidemiology

Endophytic Lifestyle of Global Clones of Extended-Spectrum β-Lactamase-Producing Priority Pathogens in Fresh Vegetables: a Trojan Horse Strategy Favoring Human Colonization?

Ralf Lopes,[a] Danny Fuentes-Castillo,[b,c] Herrison Fontana,[c,d] Larissa Rodrigues,[c,d] Karine Dantas,[a] Louise Cerdeira,[e] Isabel Henriques,[f,g] Nilton Lincopan[a,c,d]



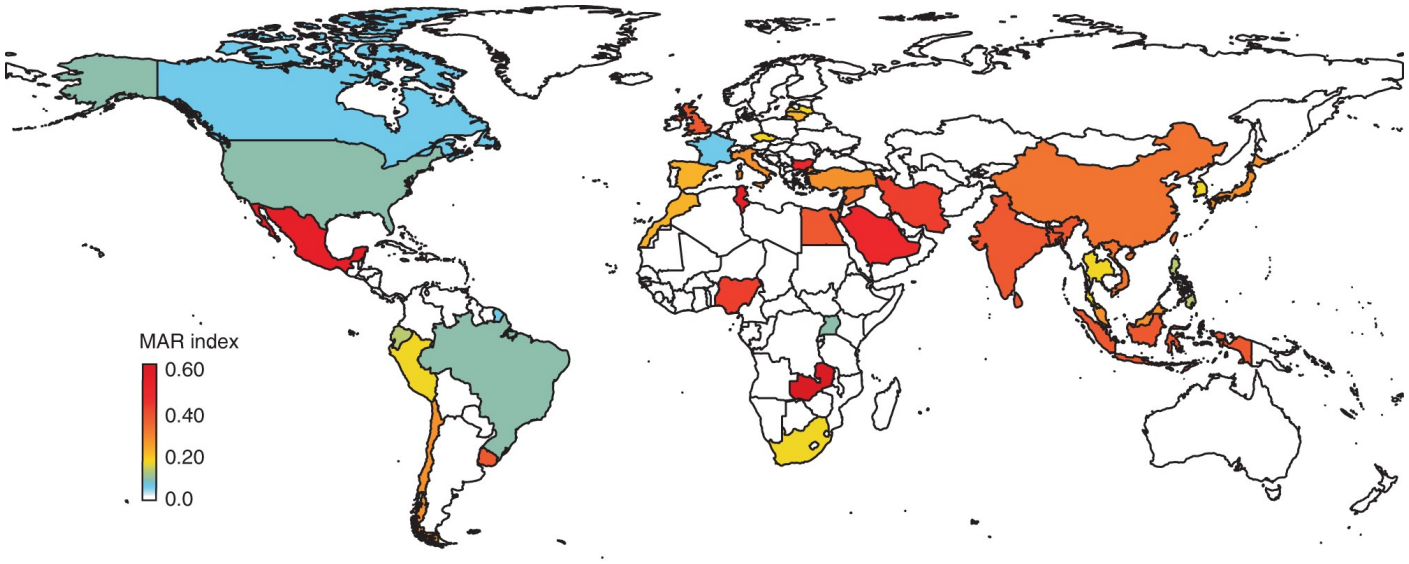
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-15735-6 OPEN

Aquaculture at the crossroads of global warming and antimicrobial resistance

Miriam Reverter[1,2✉], Samira Sarter[1,3], Domenico Caruso[1], Jean-Christophe Avarre[1], Marine Combe[1], Elodie Pepey[1,3], Laurent Pouyaud[1], Sarahi Vega-Heredía[1], Hugues de Verdal[1,3] & Rodolphe E. Gozlan[1✉]



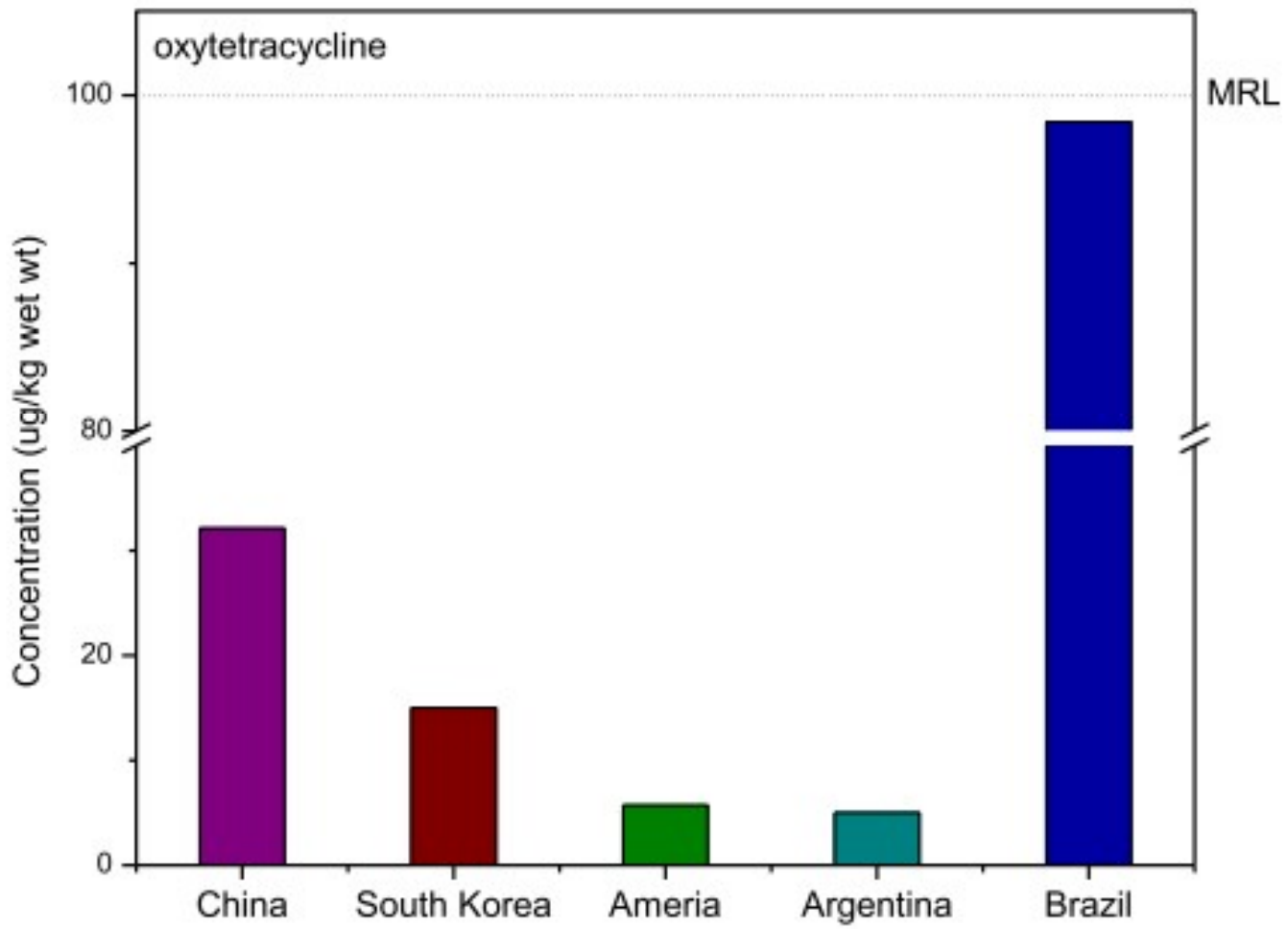
Nat Commun. 2020 Apr 20;11(1):1870.

Origen de la RAM em ambientes acuáticos

Corriente pluvial
Plantas de tratamiento de aguas residuales
Alcantarillado
Acuicultura

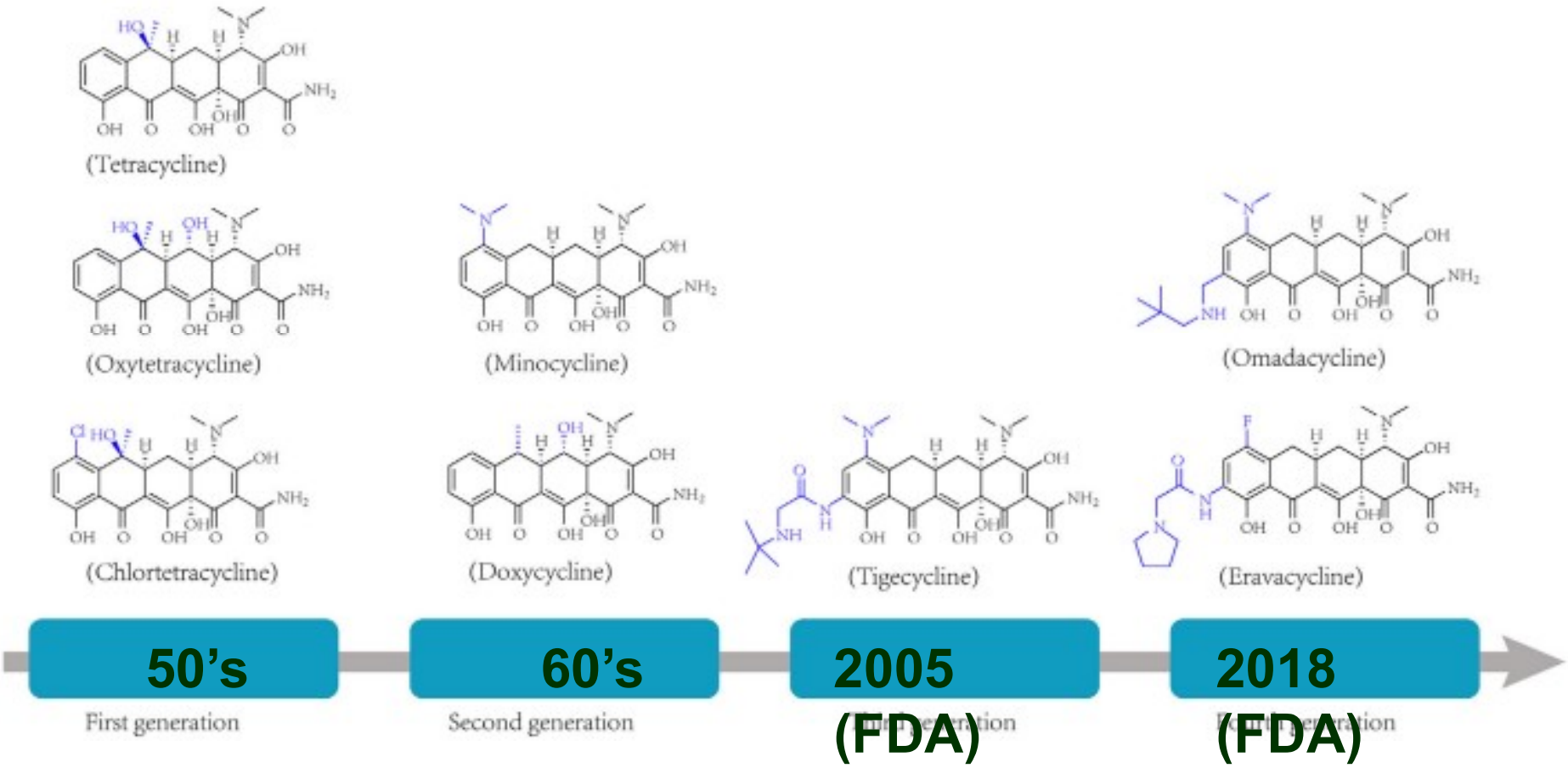
Sci Total Environ. 2021 Jul 10;777:146009

Oxitetraciclina en productos de acuicultura



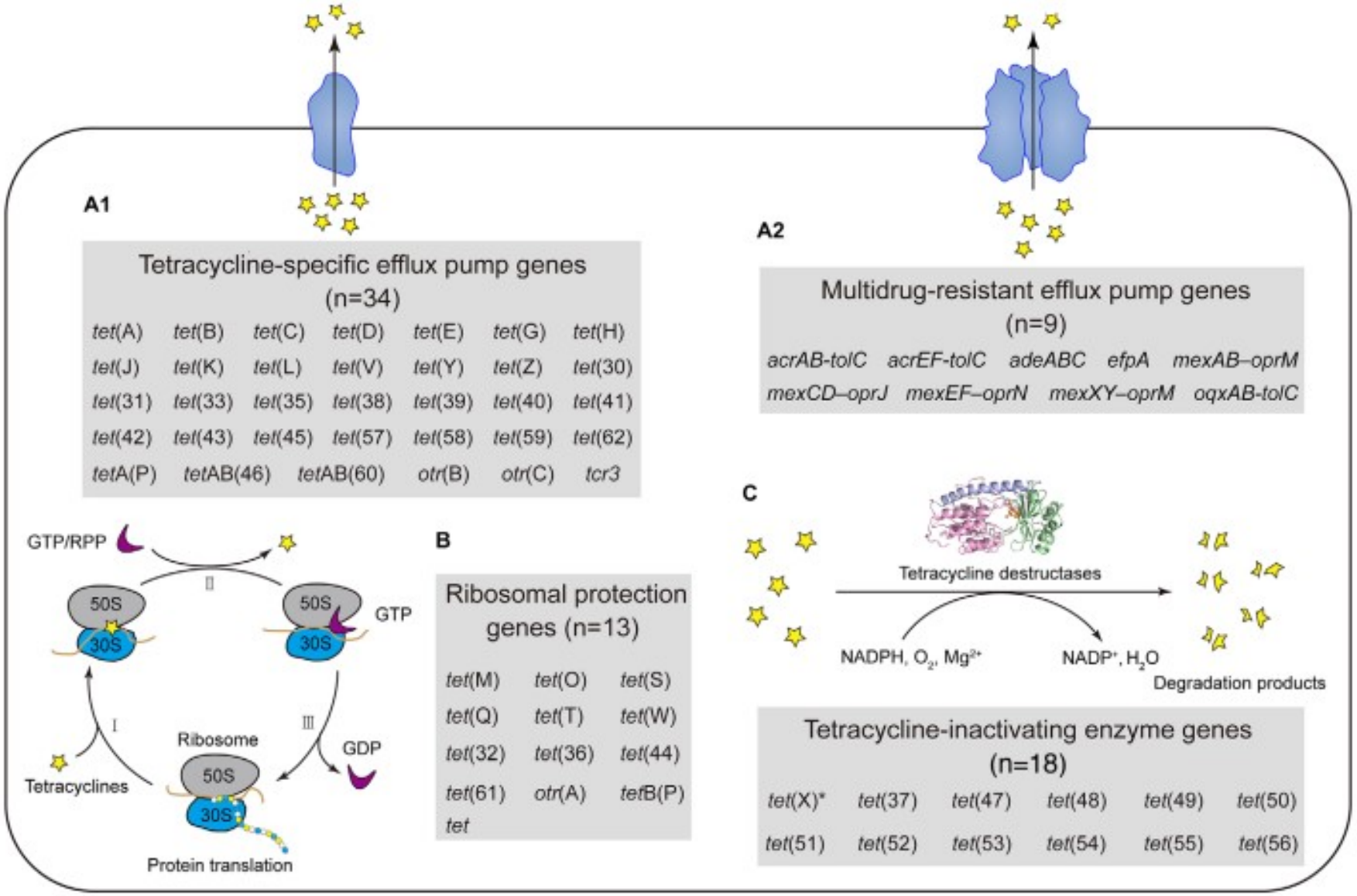
J Agric Food Chem 2020 Oct 28;68(43):11908-11919.

Tetraciclinas



Bioessays. 2020 Aug;42(8):e2000014.

Resistência ás tetraciclinas



Bioessays. 2020 Aug;42(8):e2000014.

Bombas de efluxo

antibiotics

MDPI

Article

Genetic Characterization of the Tetracycline-Resistance Gene *tet*(X) Carried by Two *Epilithonimonas* Strains Isolated from Farmed Diseased Rainbow Trout, *Oncorhynchus mykiss* in Chile

Christopher Concha [1], Claudio D. Miranda [1,2,*], Javier Santander [3] and Marilyn C. Roberts [4]

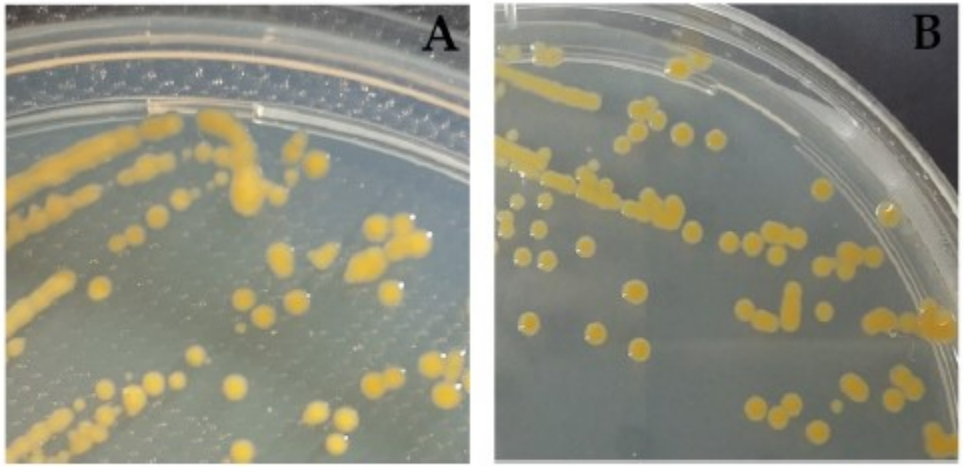
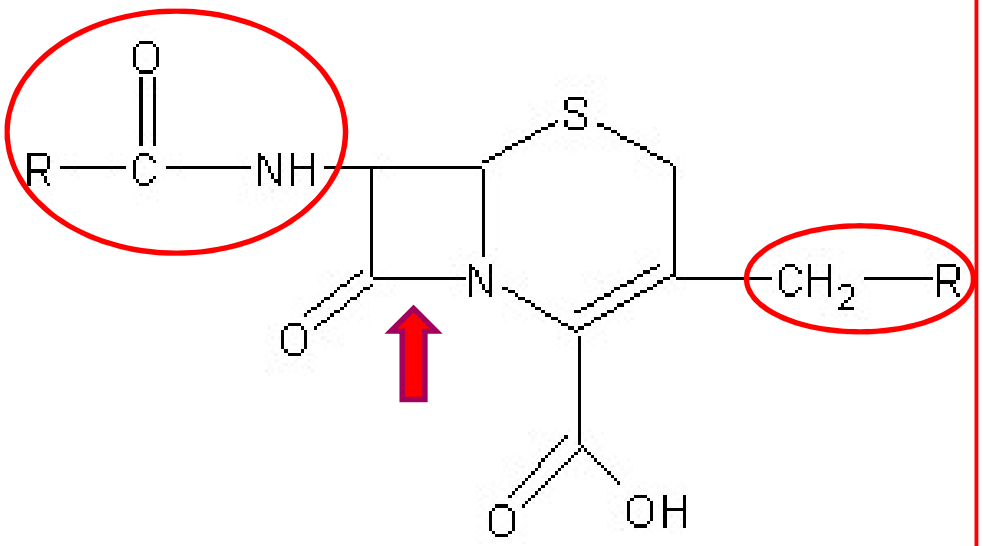


Figure 1. Colony morphotypes of the *Epilithonimonas* strains recovered from diseased rainbow trout from Chilean farms grown on TYES agar: (**A**) FP105; (**B**) FP211-J200.

β-lactâmicos

Cefalosporinas



1G: Cefalotina (Keflin), Cefazolina

2G: Cefaclor

3G: **Cefotaxima (Claforan)**

Ceftriaxona (Rocephin)

Ceftazidima (Fortaz)

+ Avibactam (KPC)

Ceftiofur (Veterinário)

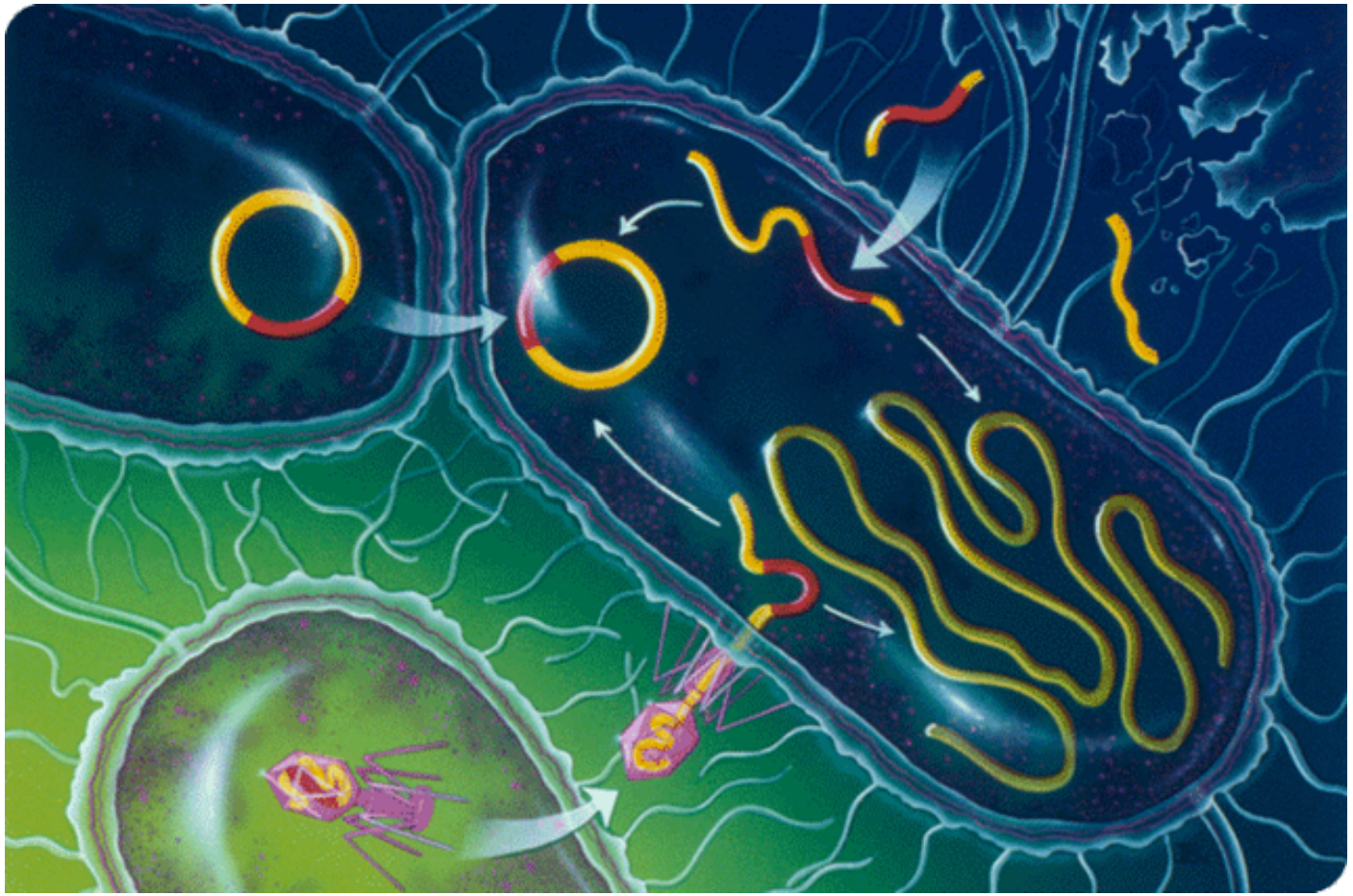
Cefovecina (Veterinário)

4G: Cefepime (Maxipime)

5G: Ceftarolina (MRSA)

Ceftobiprole (MRSA)

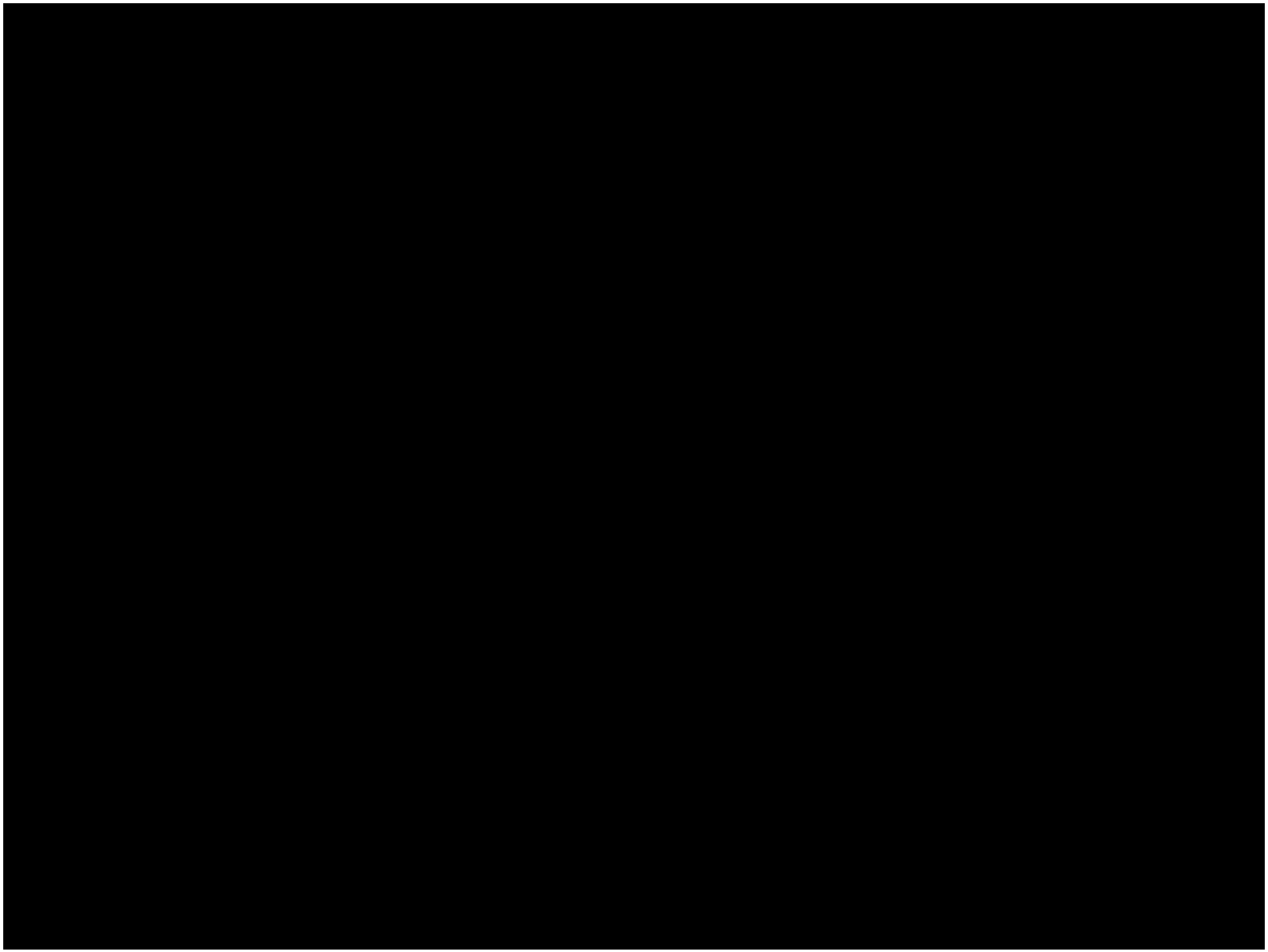
Resistência por recombinação e β-lactamases



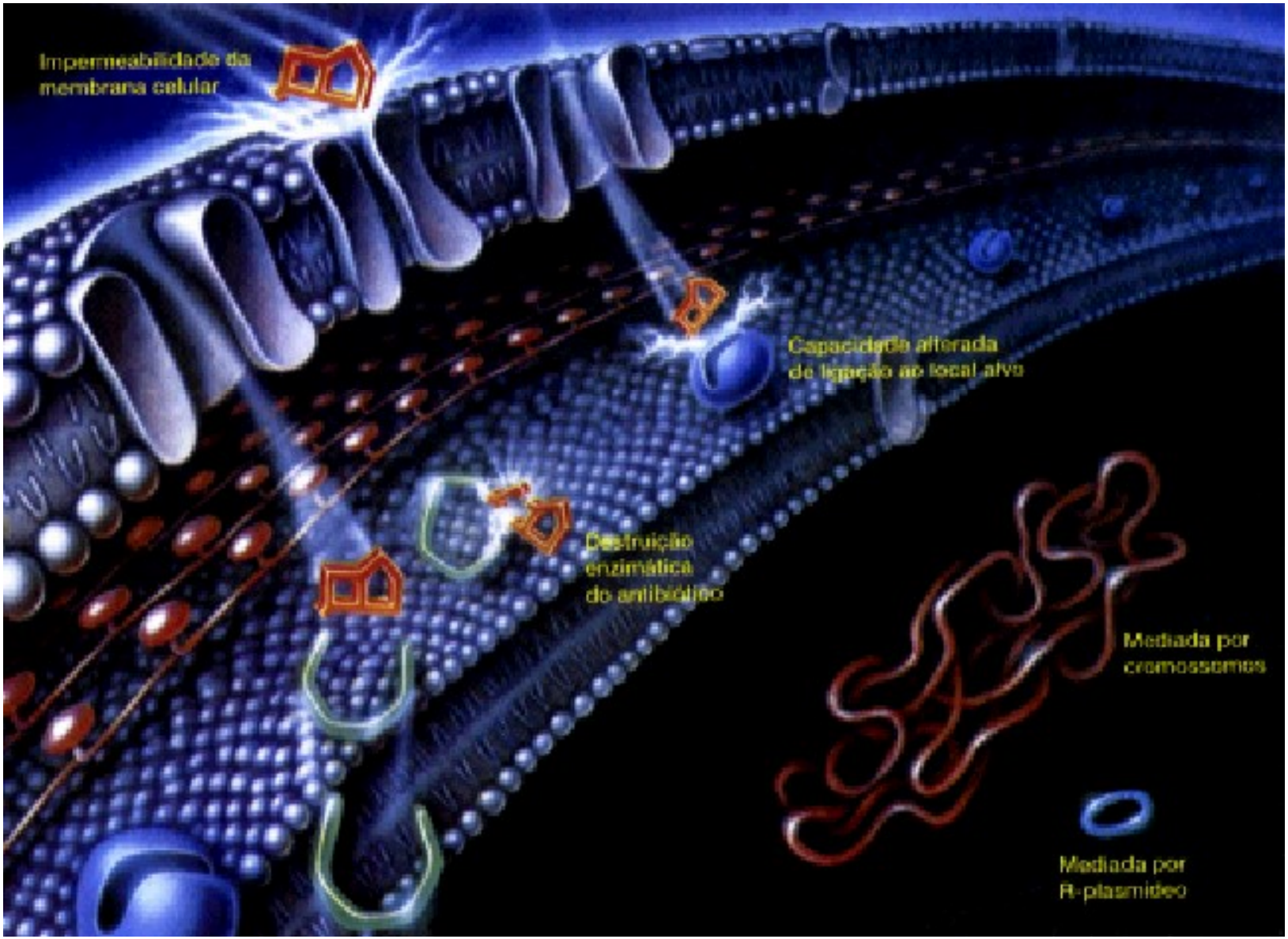
1. Conjugação (plasmídeos)
2. Transformação
3. Transdução

Nature Rev Microbiol 2015, 13:42–51.

Conjugação

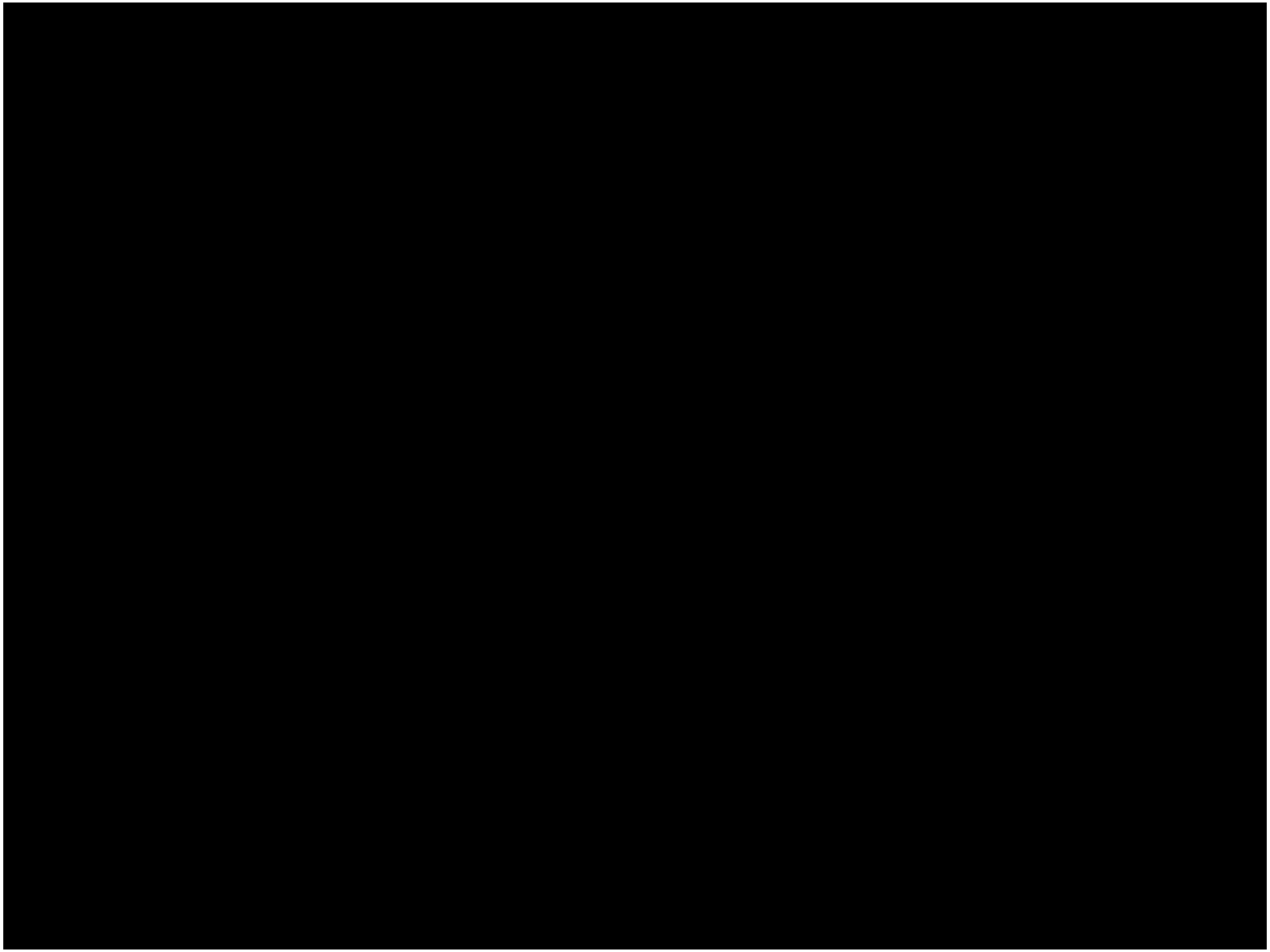


Resistencia por recombinación y β-lactamasas



β-lactâmicos

β-lactamases



Genes de R na natureza

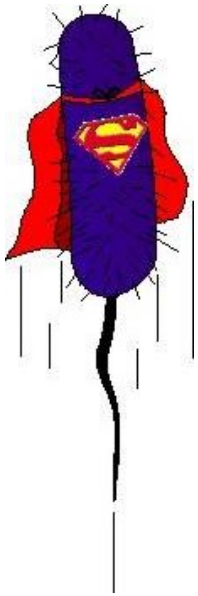
Fuente de nuevos mecanismos en species ambientales

CTX-M-	--------	***Kluyvera sp***
Qnr	--------	***Shewanella sp***
OXA-23	--------	***Acinetobacter radioresistens***
NDM	--------	***Erythrobacter litoralis***
OXA-48	--------	***Shewanella sp***

Gene *bla*$_{\text{CTX-M}}$ → β-lactamase CTX-M → Resistência:
β-lactâmicos
Cefalosporinas
Ceftiofur
Cefovecina

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS



Priority 1: Critical

Acinetobacter baumannii; carbapenem
Pseudomonas aeruginosa; carbapenem
*Enterobacteriaceae**; carbapenem, ESBL

Priority 2: High

Enterococcus faecium; vancomycin
Staphylococcus aureus; methicillin and vancomycin
Helicobacter pylori; clarithromycin
Campylobacter spp.; fluoroquinolone
Salmonella; fluoroquinolone
Neisseria gonorrhoeae; cephalosporin and fluoroquinolone

O Problema "*One Health*"

- ✓ **Diseminación de patógenos de prioridad crítica**
- ✓ **Realización de antibiograma en menor proporción em MV**
- ✓ **Tratamento empírico mas frequente en MV**
- ✓ **Menos opciones terapéuticas para MDR en MV**
- ✓ **Infección hospitalar en MH y MV**

Review on antimicrobial resistance: https://amr-review.org/home.html

Journal of Global Antimicrobial Resistance

Available online 4 November 2018

In Press, Accepted Manuscript

Genome Note

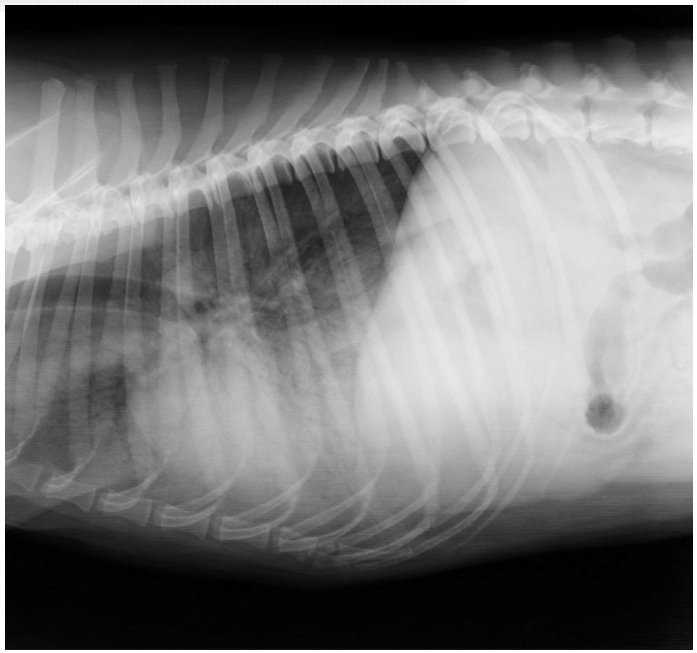
Genomic features of a highly virulent ceftiofur-resistant CTX-M-8-producing *Escherichia coli* ST224 causing fatal infection in a domestic cat

Meire M. Silva [a], Fábio P. Sellera [b], Miriam R. Fernandes [c], Quézia Moura [d], Felício Garino [a], Sérgio S. Azevedo [a], Nilton Lincopan [c, d]

Resistome: β-lactams ($bla_{CTX-M-8}$), sulphonamides (*sul2*), tetracycline (*tetA*), trimethoprim (*dfrA14*), chromosomal point mutations in ParC (S80I), GyrA (S83L), and GyrB (D87N).

Virulome:

cba, *gad*, *ipfA*, *iroN*, *iss*, *mchF* and *tsh.*



Thoracic radiography of the cat infected by CTX-M-8-producing *E. coli*. Diffuse pulmonary opacification with air bronchograms in the ventral lung regions suggesting pneumonia.

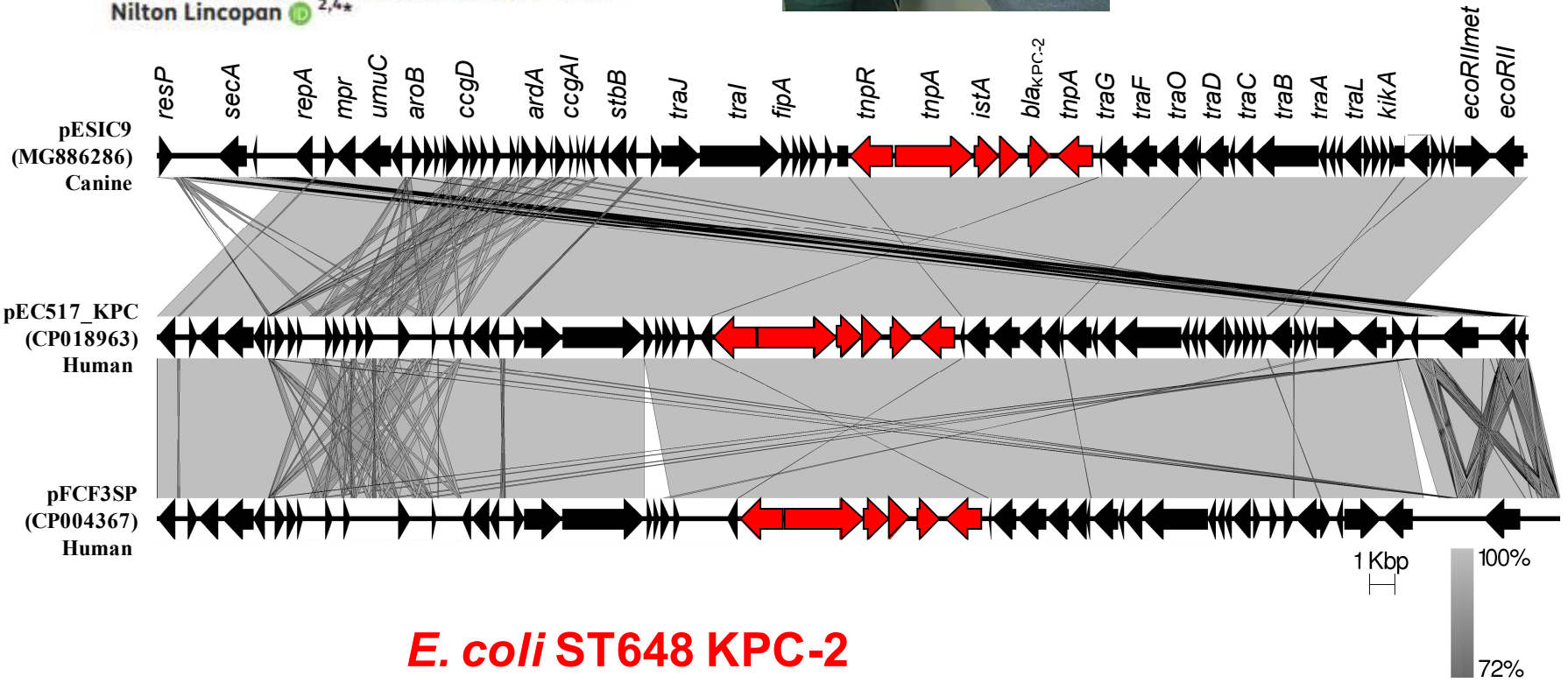
ESBL (CTX-M) em Animais de Companhia

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dky173

Identification of KPC-2-producing *Escherichia coli* in a companion animal: a new challenge for veterinary clinicians

Fábio P. Sellera[1]†, Miriam R. Fernandes[2]†, Regina Ruiz[3], Ana C. M. Falleiros[3], Fernanda P. Rodrigues[3], Louise Cerdeira[2] and Nilton Lincopan[2,4]*



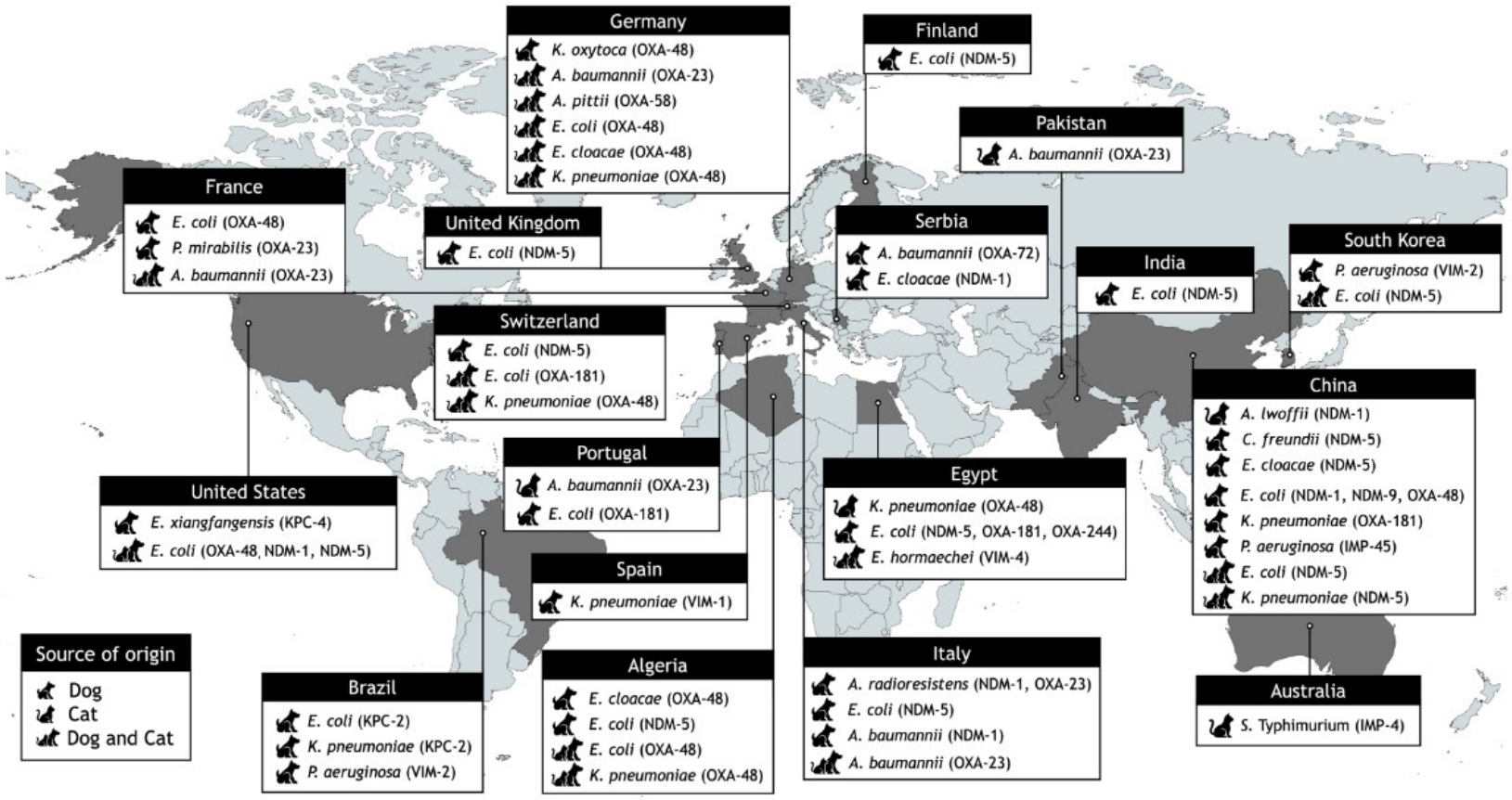
***E. coli* ST648 KPC-2**

J Antimicrob Chemother 2021; **76**: 2225–2229
doi:10.1093/jac/dkab169 Advance Access publication 10 June 2021

Journal of Antimicrobial Chemotherapy

Rapid spread of critical priority carbapenemase-producing pathogens in companion animals: a One Health challenge for a post-pandemic world

Fábio P. Sellera[1,2]†, Luciano C. B. A. Da Silva[2]† and Nilton Lincopan[3,4]*



COVID-19 triggers exposure of endangered wildlife to WHO critical priority pathogens co-producing NDM and KPC carbapenemases

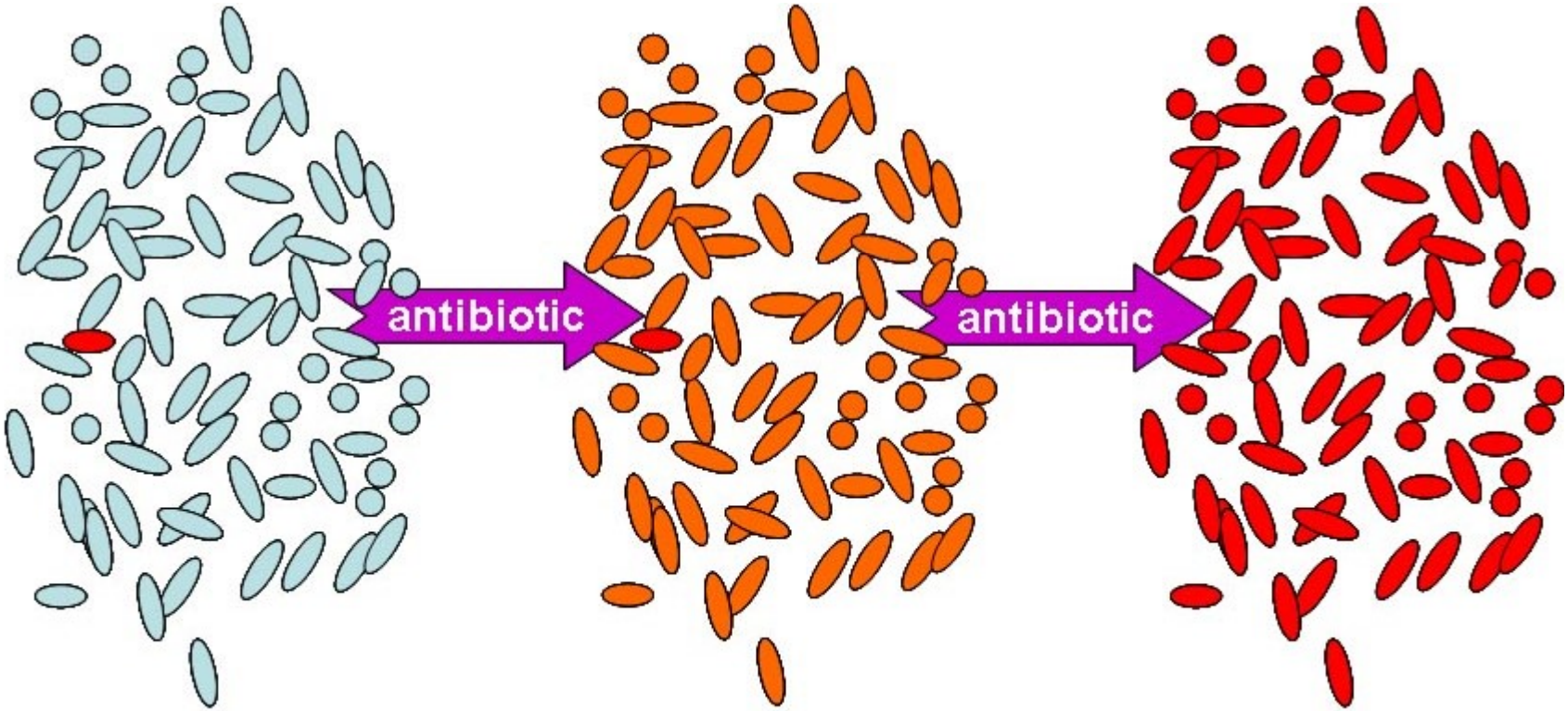
Fábio P. Sellera[1,2,3], Brenda Cardoso[1,4], Danny Fuentes-Castillo[1,5], Bruna Fuga[1,4,6], Fernanda

	Carbapenemase (ESBL)*	ST‡	Wildlife§	State¶	Isolation site	Diagnosis	Outcome
K. pneumoniae, 883b	NDM-1, KPC-2, (CTX-M-15)	1308	Magnificent frigatebird	RJ	Skin	Sepsis	Died
K. pneumoniae, 868	NDM-1, KPC-2, (CTX-M-15)	1308	Magnificent frigatebird	RJ	Skeletal muscle	Myositis	Died
K. pneumoniae, 795b	NDM-1, KPC-2, (CTX-M-15)	1308	Magnificent frigatebird	RJ	Skeletal muscle	Myositis	Died
K. pneumoniae, FAI130	NDM-1, KPC-2, (CTX-M-15)	1308	Green turtle	RJ	Bone	Osteomyelitis	Died
K. pneumoniae, FAI131	NDM-1, KPC-2, (CTX-M-15)	1308	Neotropic Cormorant	RJ	Lung	Pneumonia	Died
K. pneumoniae, PG2	NDM-1, (CTX-M-15)	1308	Magellanic penguin	SP	Cloacae	Cachexia	Died
K. pneumoniae, PG10A	NDM-1, (CTX-M-15)	1308	Magellanic penguin	SP	Cloacae	Cachexia	Died
K. pneumoniae, PG11	NDM-1, (CTX-M-15)	1308	Magellanic penguin	SP	Cloacae	Cachexia	Died
E. coli, 795a	(CTX-M-15)	10	Magnificent frigatebird	RJ	Cloacae	Sepsis	Died
E. coli, PG1	NDM-1	91	Magellanic penguin	SP	Cloacae	Cachexia	Died
E. coli, BA01	NDM-1	162	Pygmy sperm whale	SC	Lymph node	Cardiomyopathy	Died
E. cloacae, FAI128	NDM-1	244	Green turtle	RJ	Bone	Osteomyelitis	Died
C. freundii, 883c	NDM-1	1	Magnificent frigatebird	RJ	Skin	Sepsis	Died
C. freundii, FAI129	NDM-1	22	Green turtle	RJ	Bone	Osteomyelitis	Died
C. freundii, PG4	NDM-1	214	Magellanic penguin	SP	Cloacae	Cachexia	Died
C. freundii, FAI193	NDM-1	328	Magnificent frigatebird	RJ	Cloacae	Acute hepatitis	Died
P. putida, FAI194	IMP-16	128	Magnificent frigatebird	RJ	Cloacae	Sepsis	Died
P. putida, FAI191	IMP-16	128	Magnificent frigatebird	RJ	Cloacae	Sepsis	Survival
A. baumannii, FAI132	OXA-23	15	Green turtle	RJ	Bone	Osteomyelitis	Died

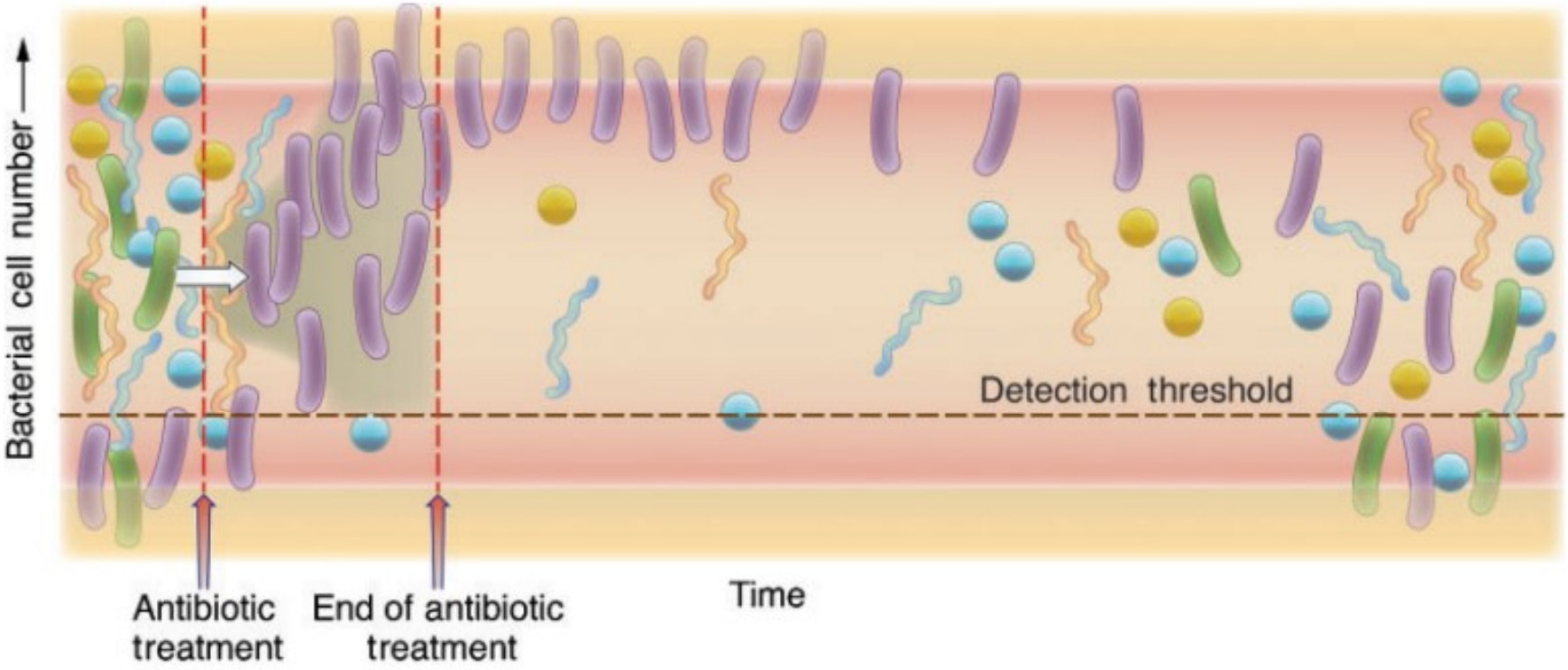

R3
ANIMAL
FOTO | NILSON COELHO/R3 ANIMAL

Mutações

Pressão seletiva *in vitro*



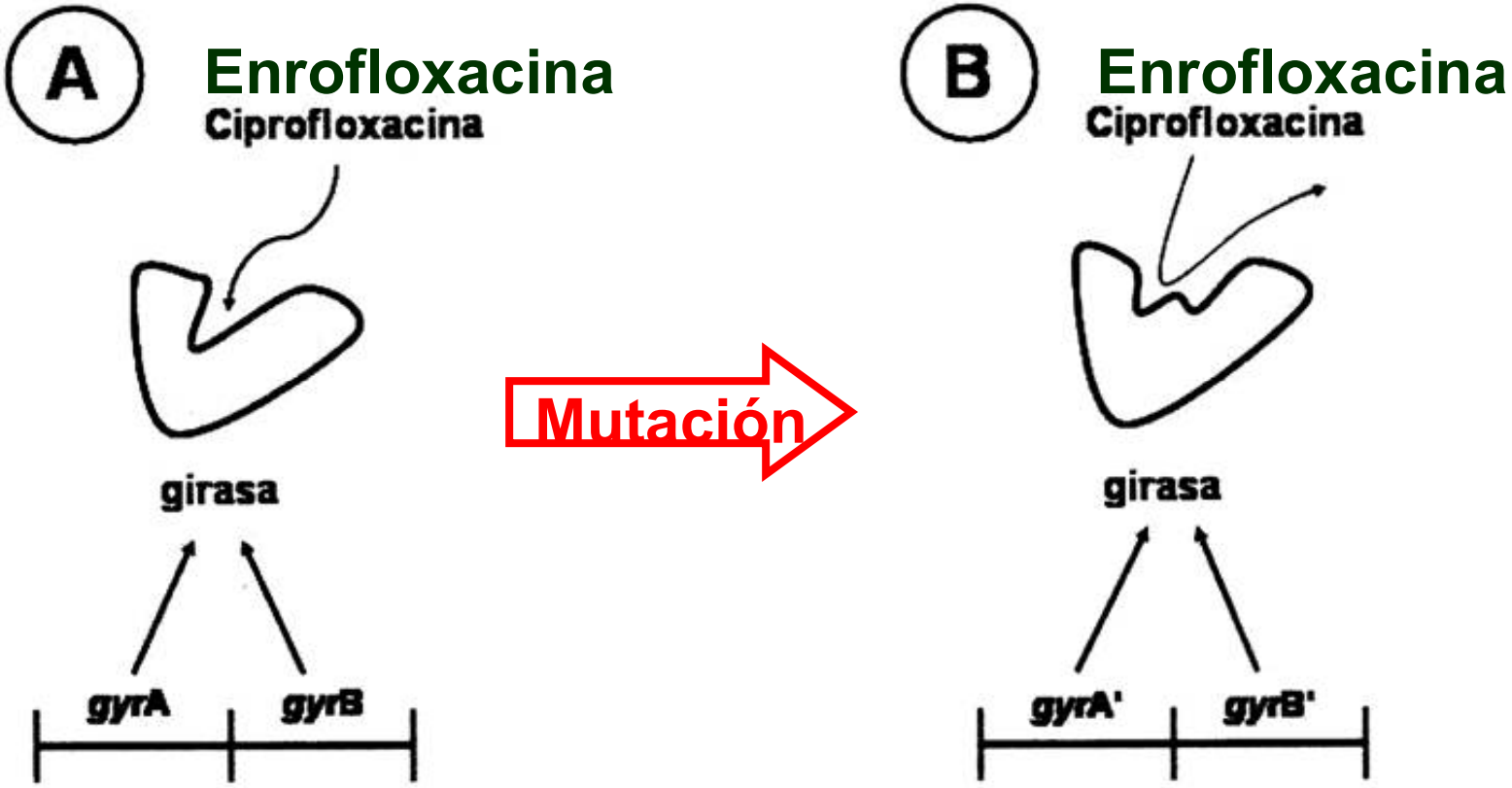
Qué se disemina?



Cepas, clones, genes, plasmídeos?

Jernberg C, et al. *Microbiology.* 2010; 56: 3216-3223.

Resistência às fluoroquinolonas



Suscetível **Bactéria Resistente**

Nature Rev Microbiol 2015, 13:42–51.

Qué se disemina?

Sumatoria de eventos genéticos

Genes	IS/Tn	Plásmidos	Linajes
KPC-2	Tn*125*	IncP	ST2
OXA-48	Tn4401	IncA/C	ST258
NDM	Tn*1999*	Gr2	ST101
OXA-23	Tn*3*	IncL/M	ST131
VIM	Tn*2006*	Gr6	ST25
OXA-24	Tn*2009*	IncF	ST235
IMP	IS*Ecp1*	IncH	ST111
CTX-M	IS*26*	IncX3	ST15

4 momentos decisivos na prescrição de antibioticos

O PACIENTE TEM UMA INFECÇAO QUE REQUER ANTIBIÓTICOS?

Leva a uma síntese das informações relevantes sobre o paciente.

ALGUNS DIAS DEPOIS... É POSSÍVEL TORNAR A PRESCRIÇÃO MAIS ESPECÍFICA? POSSO TROCAR A VIA DE ADMINISTRAÇÃO OU PARAR COM O ANTIBIÓTICO?

Deve ser uma reflexão diária do prescritor. Pode ser feita entre a equipe durante a ronda.

SOLICITEI AS CULTURAS APROPRIADAS ANTES DE COMEÇAR O ANTIBIÓTICO? QUAL ANTIBIOTICOTERAPIA EMPÍRICA DEVO COMEÇAR?

Análise dos fatores de risco específicos ao paciente e das prováveis causas de infecção. Garante que a administração do tratamento seja feita no tempo adequado.

QUAL É A DURAÇÃO DA ANTIBIOTICOTERAPIA NECESSÁRIA PARA A CONDIÇÃO DIAGNOSTICADA NESTE PACIENTE?

Um lembrete de que duração deve ser baseada em literatura cientifica e não na verificação de se o paciente teve ou não resposta clinica adequada.