Antibiotic agents, Antimicrobial resistance & Spread of resistant bacteria

Gabriele Arcari
Research Fellow RTD A
Dec 15, 2023

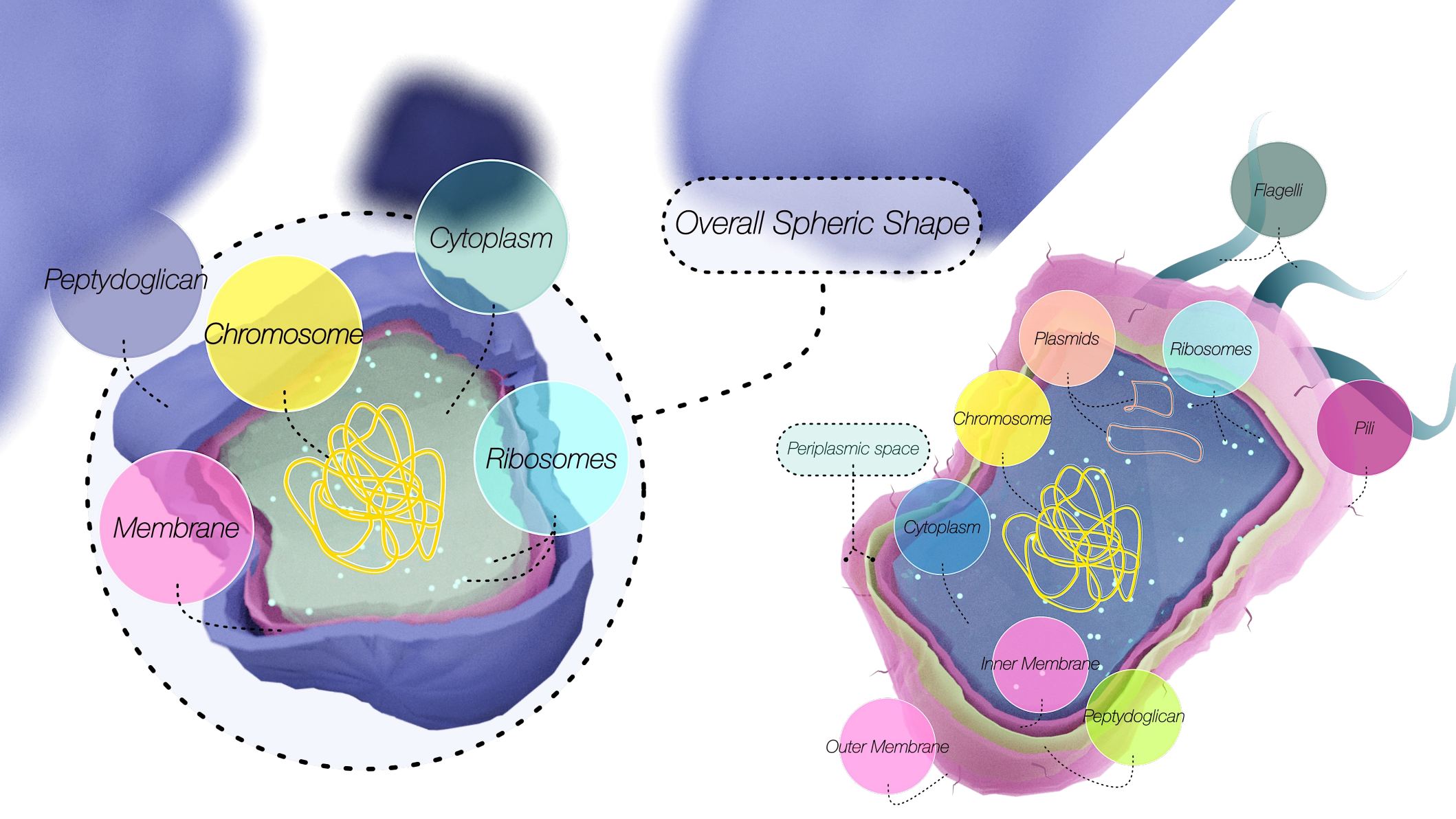
Antibiotics

Molecules that interact with **bacterial** biochemical pathways and:

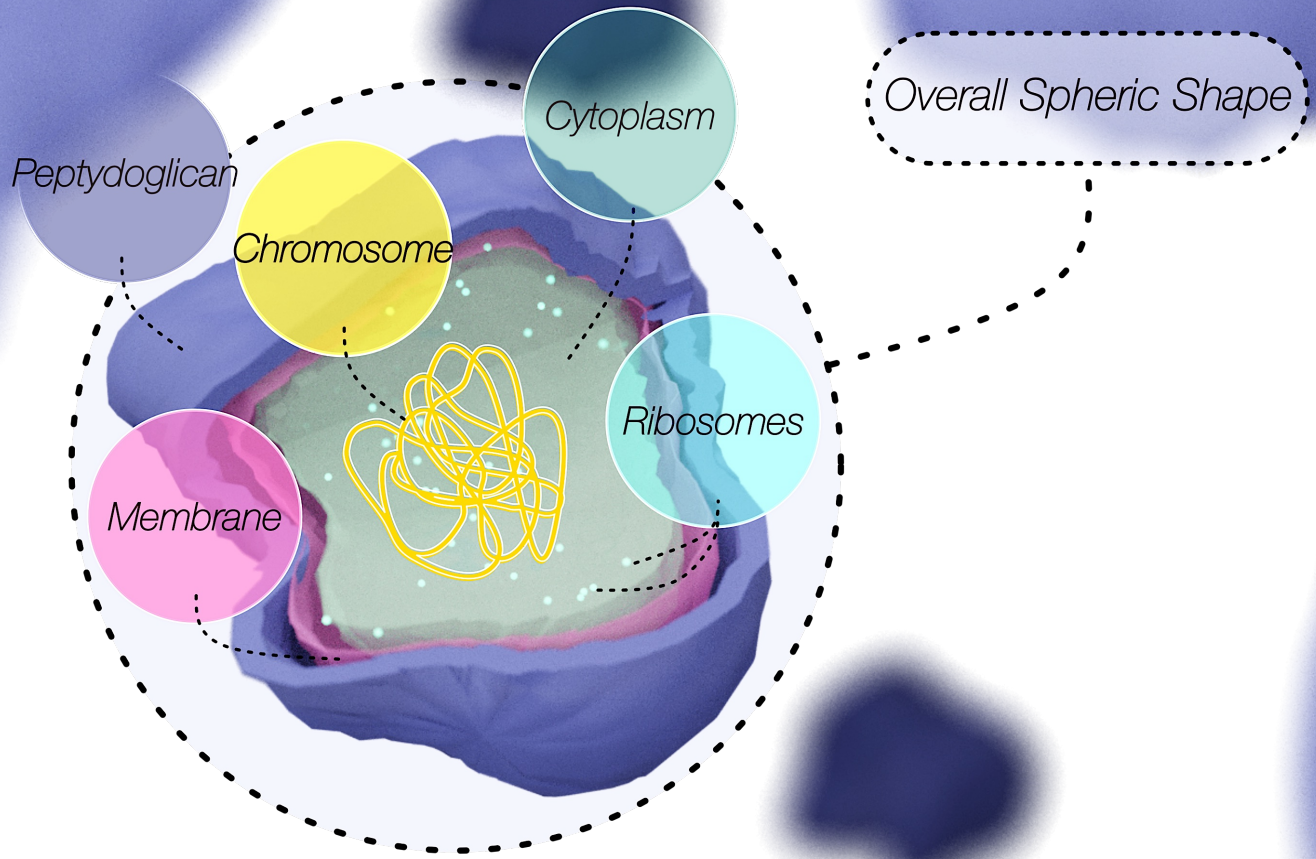
- Kill the microorganism (**bactericidal** agents)
- Stop the microorganism growth (**bacteriostatic** agents)

Based on the targeted species can be divided in:

- **Broad spectrum** antibiotics
- **Narrow spectrum** antibiotics

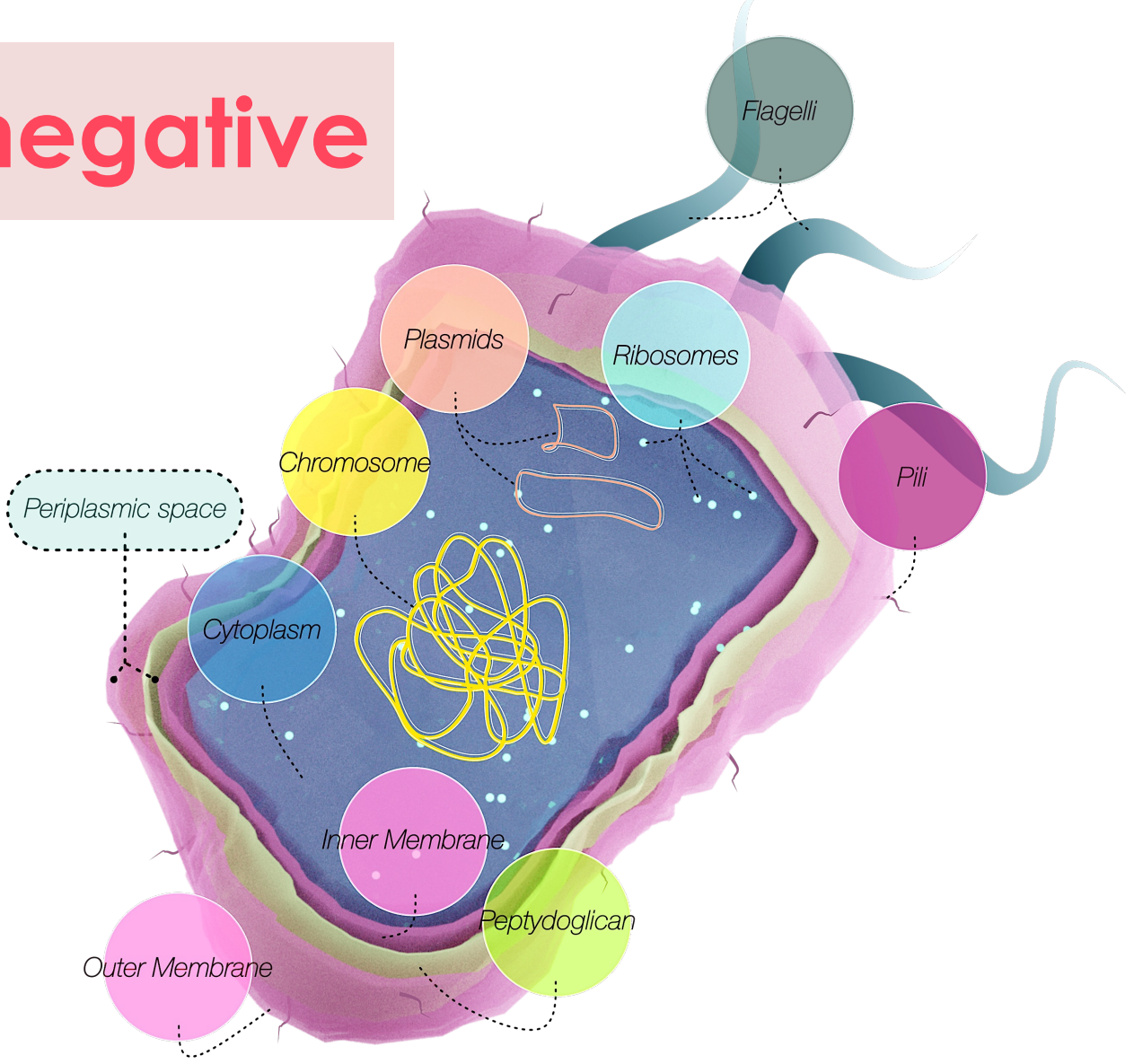

Peptydoglican
Cytoplasm
Chromosome
Ribosomes
Membrane
Overall Spheric Shape
Flagelli
Plasmids
Ribosomes
Chromosome
Pili
Periplasmic space
Cytoplasm
Inner Membrane
Peptydoglican
Outer Membrane

Gram positive

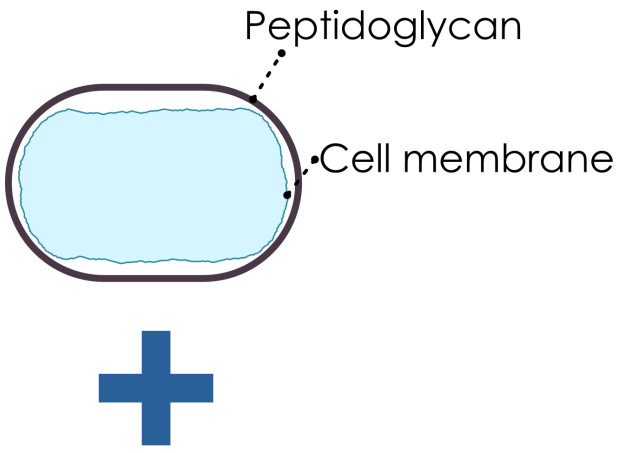


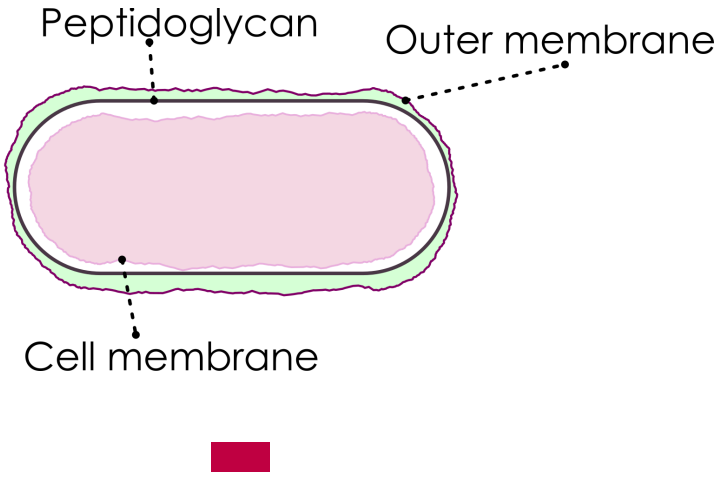
Overall Spheric Shape

Gram negative



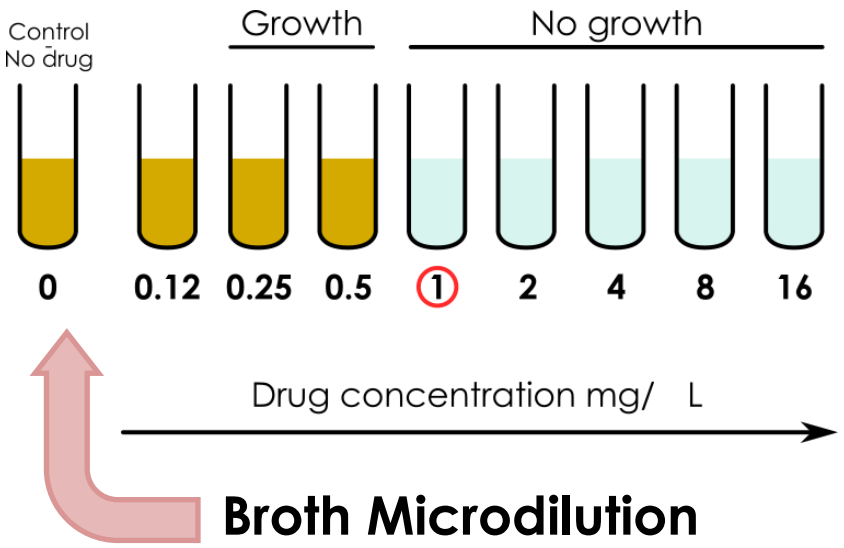
Gram stain


Peptidoglycan
Cell membrane

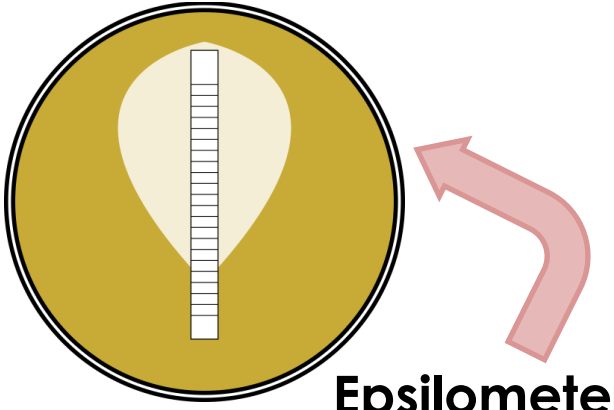

Peptidoglycan
Outer membrane
Cell membrane

Minimum Inhibitory Concentration

"The lowest concentration of an antimicrobial that will **inhibit the visible growth** of a microorganism after overnight incubation"



Broth Microdilution



Epsilometer Test

PROTOCOL

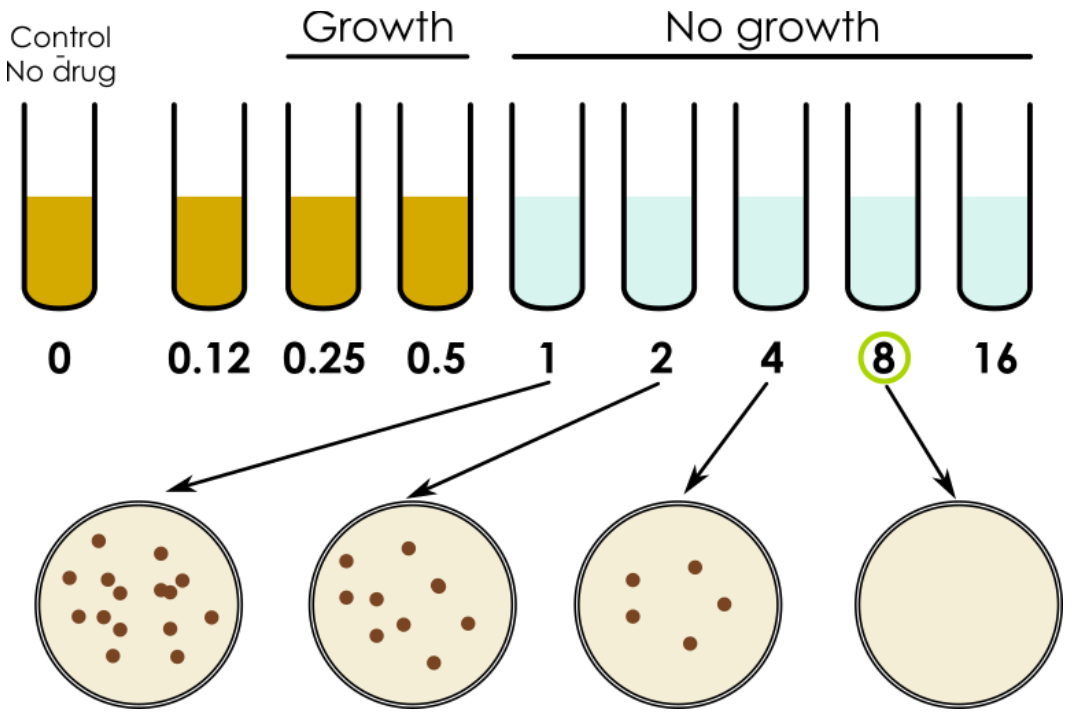
Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances

Irith Wiegand, Kai Hilpert & Robert E W Hancock

Centre for Microbial Diseases and Immunity Research, University of British Columbia, 2259 Lower Mall Research Station, Vancouver, British Columbia, V6T 1Z4, Canada. Correspondence should be addressed to R.E.W.H. (bob@cmdr.ubc.ca).

Minimum Bactericidal Concentration

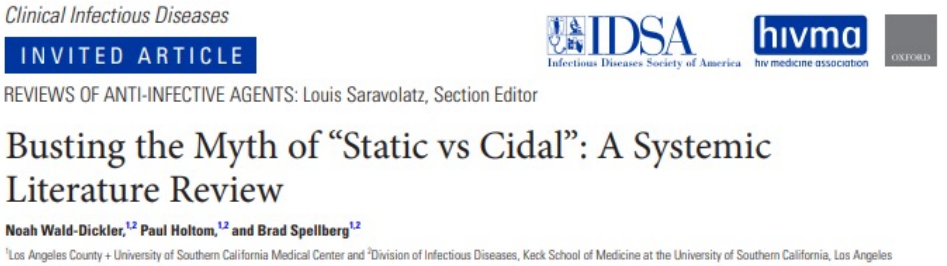
"The lowest concentration of an antimicrobial that **results in bacterial death**"



“-static” versus “-cidal” antibiotics

The closer the MIC is to the MBC, the more “bactericidal” the compound

1



Clinical Infectious Diseases

INVITED ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

REVIEWS OF ANTI-INFECTIVE AGENTS: Louis Saravolatz, Section Editor

Busting the Myth of “Static vs Cidal”: A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

[1]Los Angeles County + University of Southern California Medical Center and [2]Division of Infectious Diseases, Keck School of Medicine at the University of Southern California, Los Angeles

J Antimicrob Chemother 2015; **70**: 382–395
doi:10.1093/jac/dku379 Advance Access publication 28 September 2014

Journal of Antimicrobial Chemotherapy

2

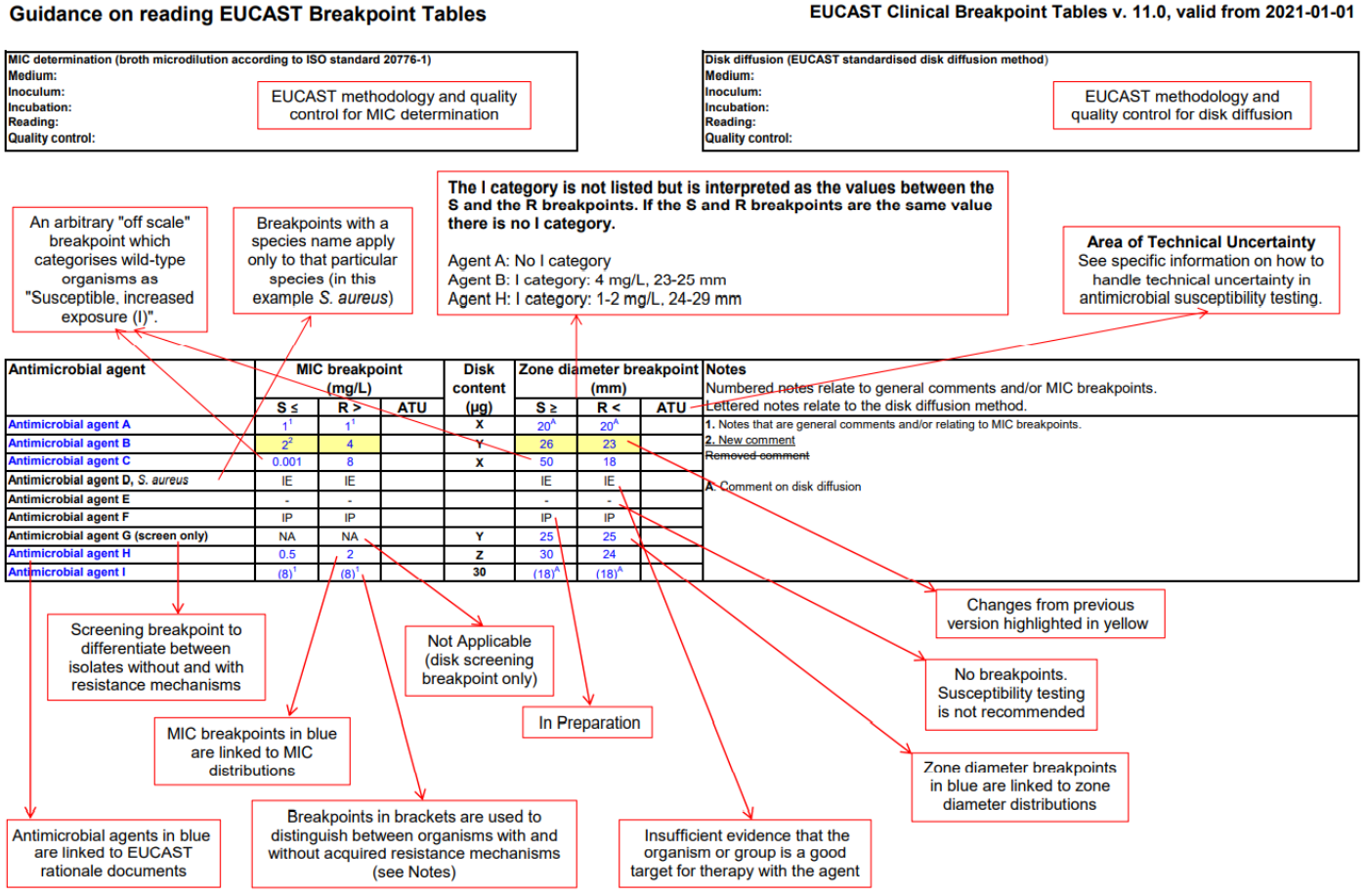
Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis

Johannes Nemeth[1]*†, Gabriela Oesch[2]† and Stefan P. Kuster[1]†

Breakpoints

"[…]*For **clinical purposes susceptibility signifies treatability**, which is based on the toxicological, pharmacodynamic, and pharmacokinetic properties of the antibiotic in question and on the clinical information from clinical trials and the cumulative experience of antibiotic success in treating particular infections* […]"

Bug-drug combination table



How to interpret breakpoints

The S-I-R system

S **Susceptible** at a standard dosage

I **Susceptible** at increased exposure

R **Resistant**

Resistance

Low chances of success when treating an infection caused by this organism with a specific antibiotic

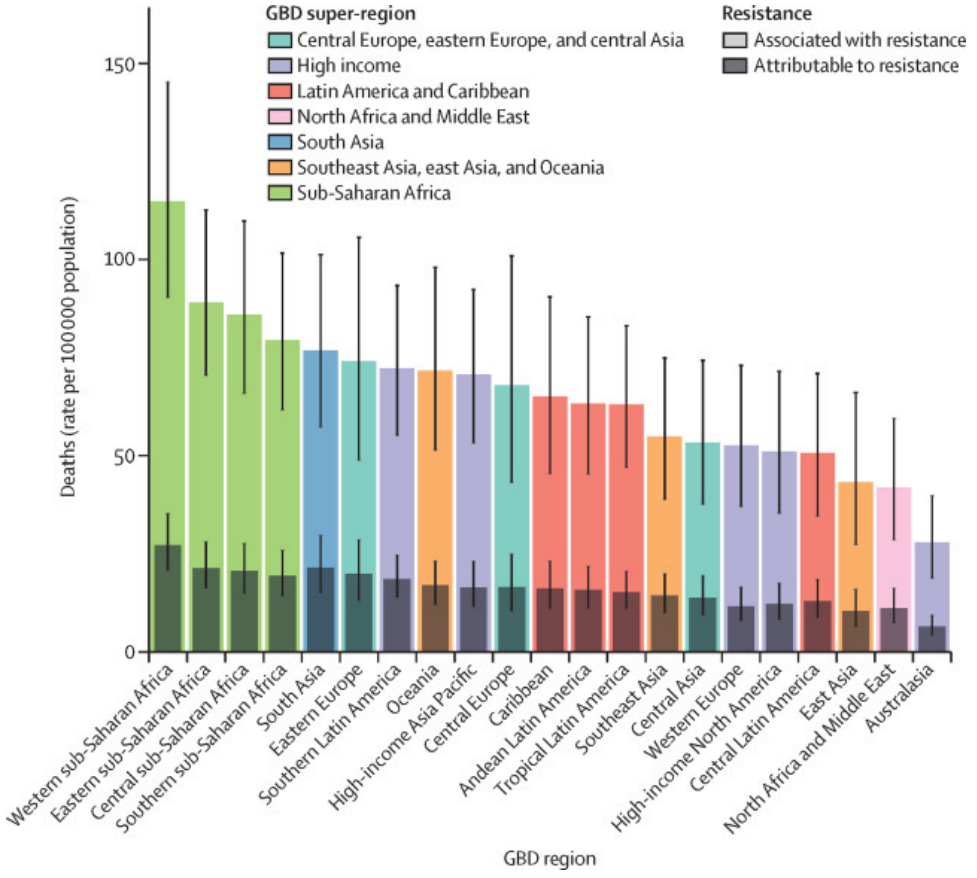
Predictions on the AMR issue …

"[…] *We estimate that by 2050,* ***10 million lives a year*** *and a cumulative 100 trillion USD of economic output* ***are at risk due to the rise of drug resistant infections*** *if we do not find proactive solutions now to slow down the rise of drug resistance.* [...]"

… an unpredictable phenomenon

"Current global estimates of the burden of AMR are not very informative; ***we need detailed, reliable data to be able to improve AMR control measures****, preferably based on comprehensive, population-based surveillance data from low-, middle-, and high-income countries."*

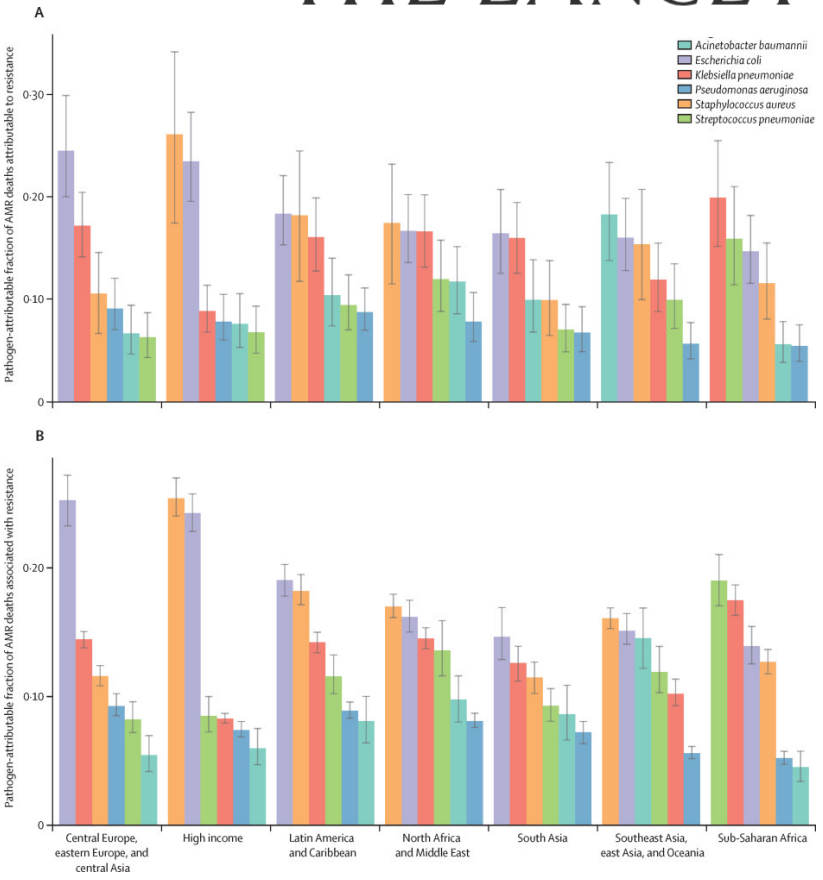
What do data say?



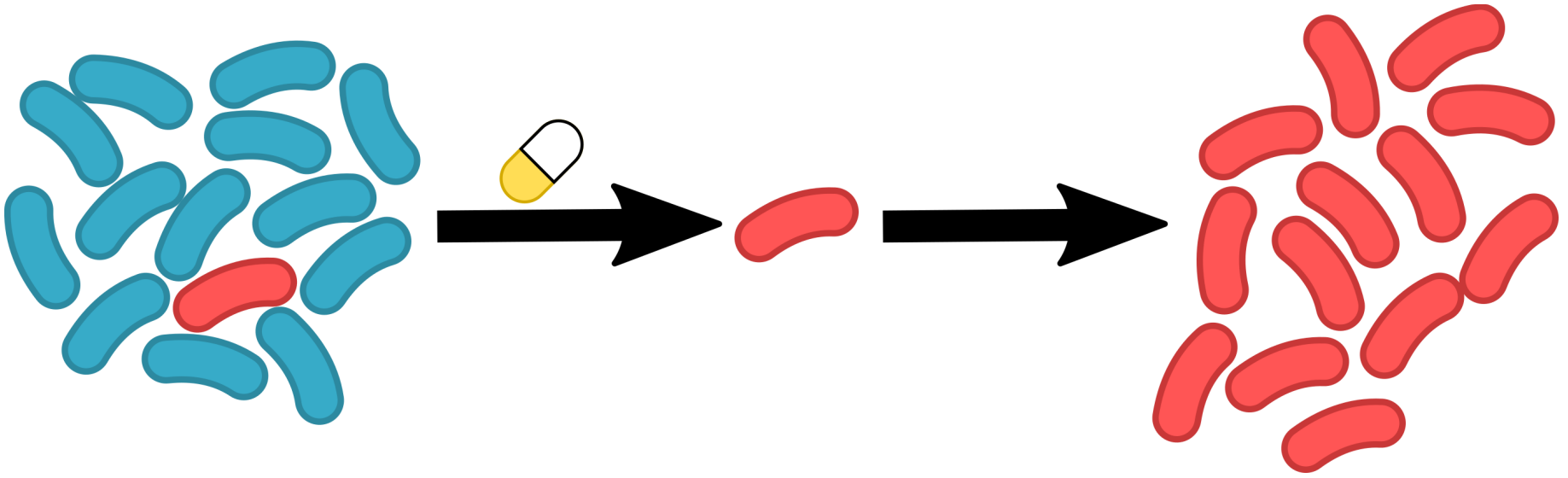
Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators†

THE LANCET



What happens during treatment?



How does resistance happen?

Resistance mechanisms can be:

- **Innate:**

Species/genus-specific and linked to a certain antibiotic agent/class (e.g., Gram-negative bacteria and glycopeptides or Gram-positive bacteria and polymixins)

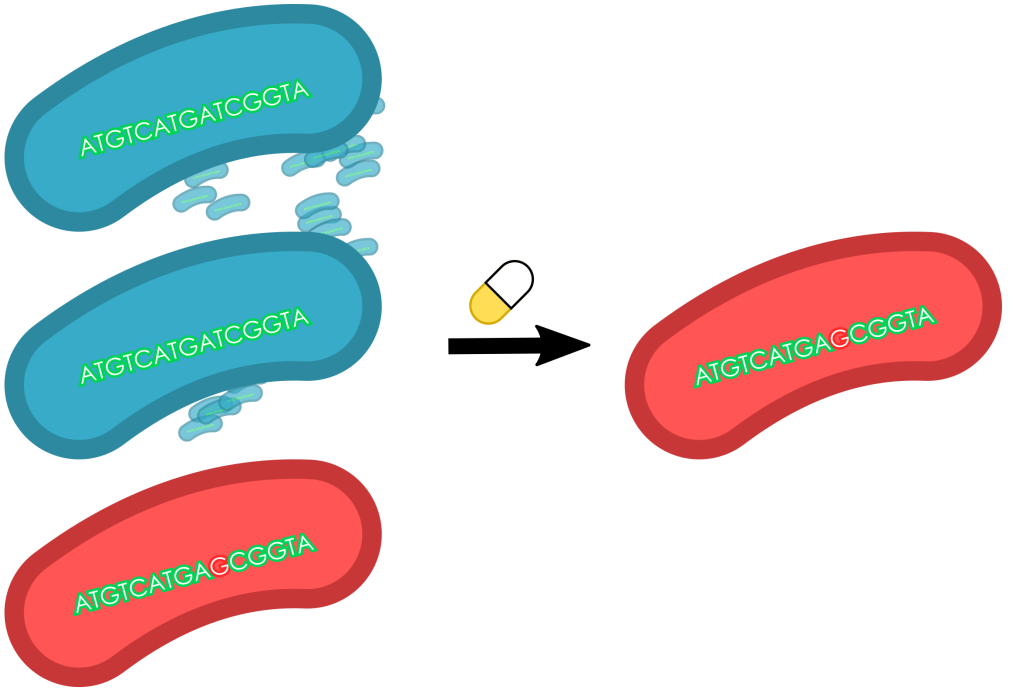
- **Acquired**:

  1) Mutations
  2) Horizontal transmission (i.e. conjugation, transformation and transduction)
  3) Vertical transmission

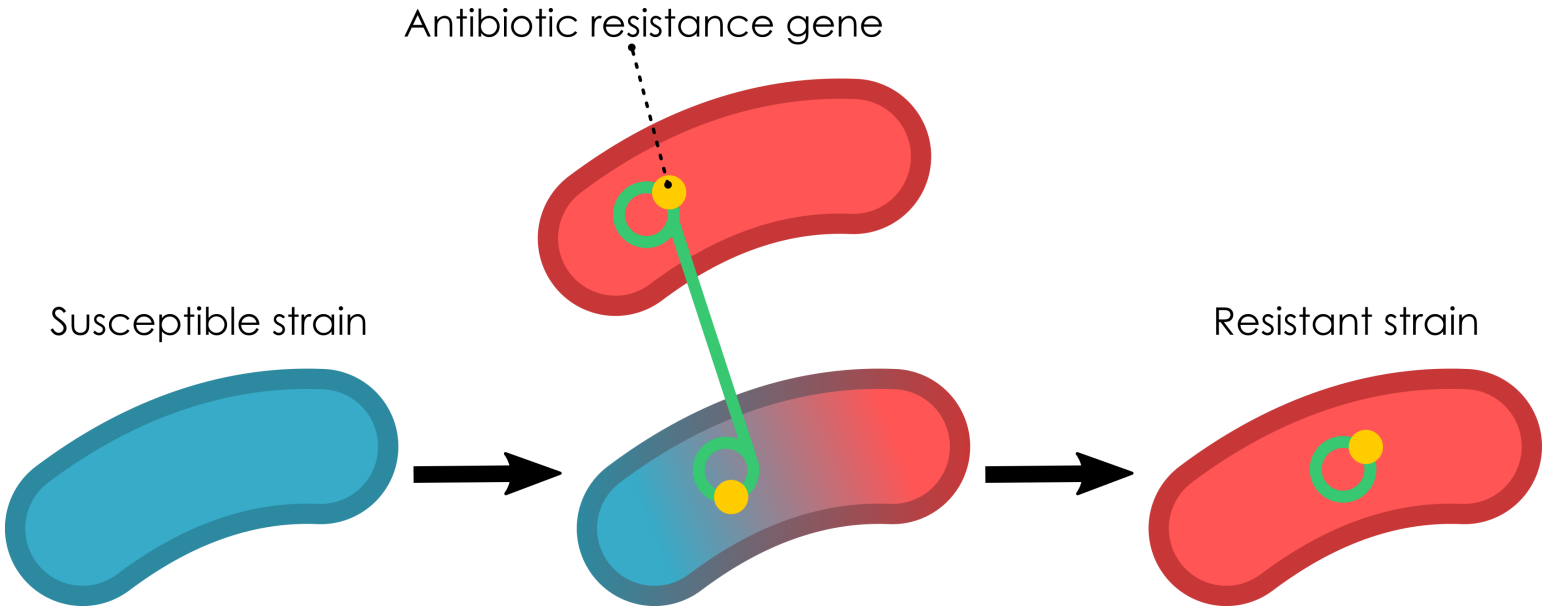
Mutations

Strains carrying a wild-type allele

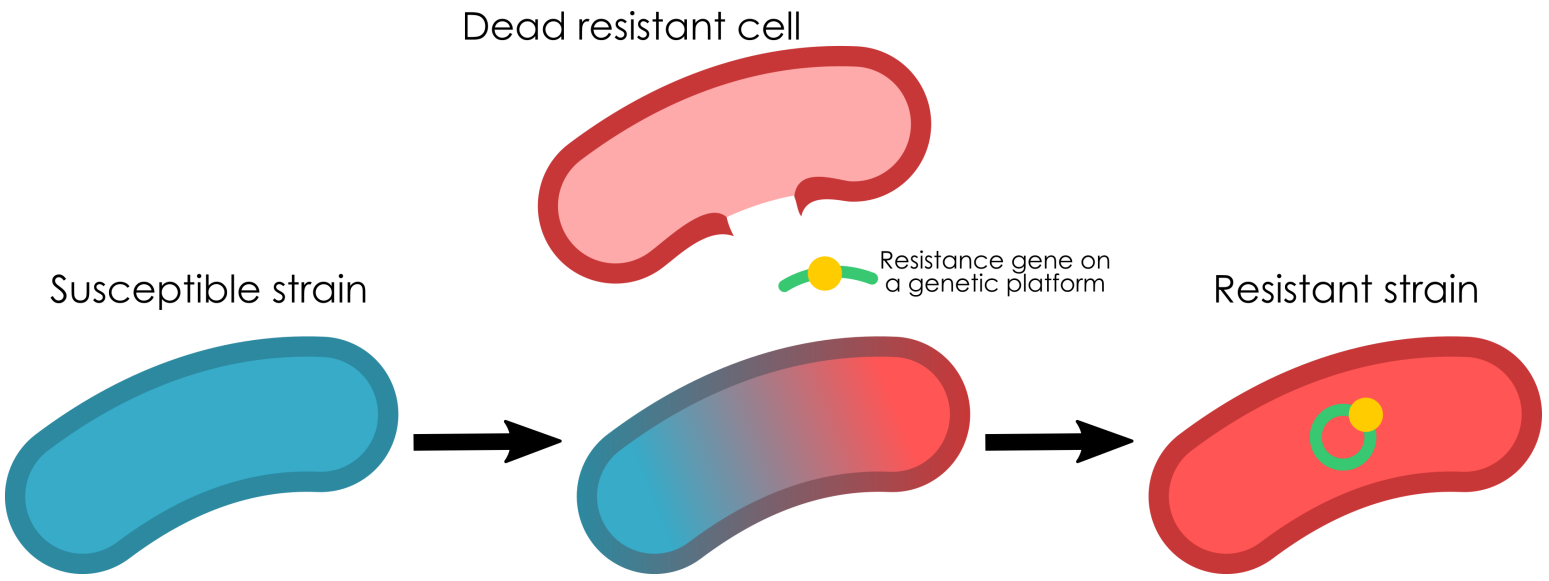
Strain carrying a mutated allele



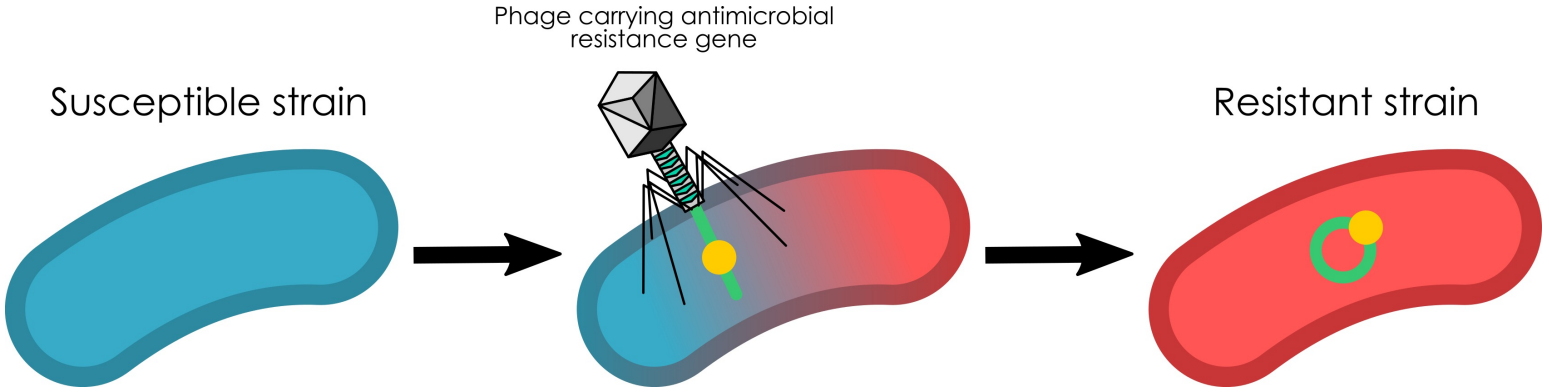
Horizontal transmission - Conjugation



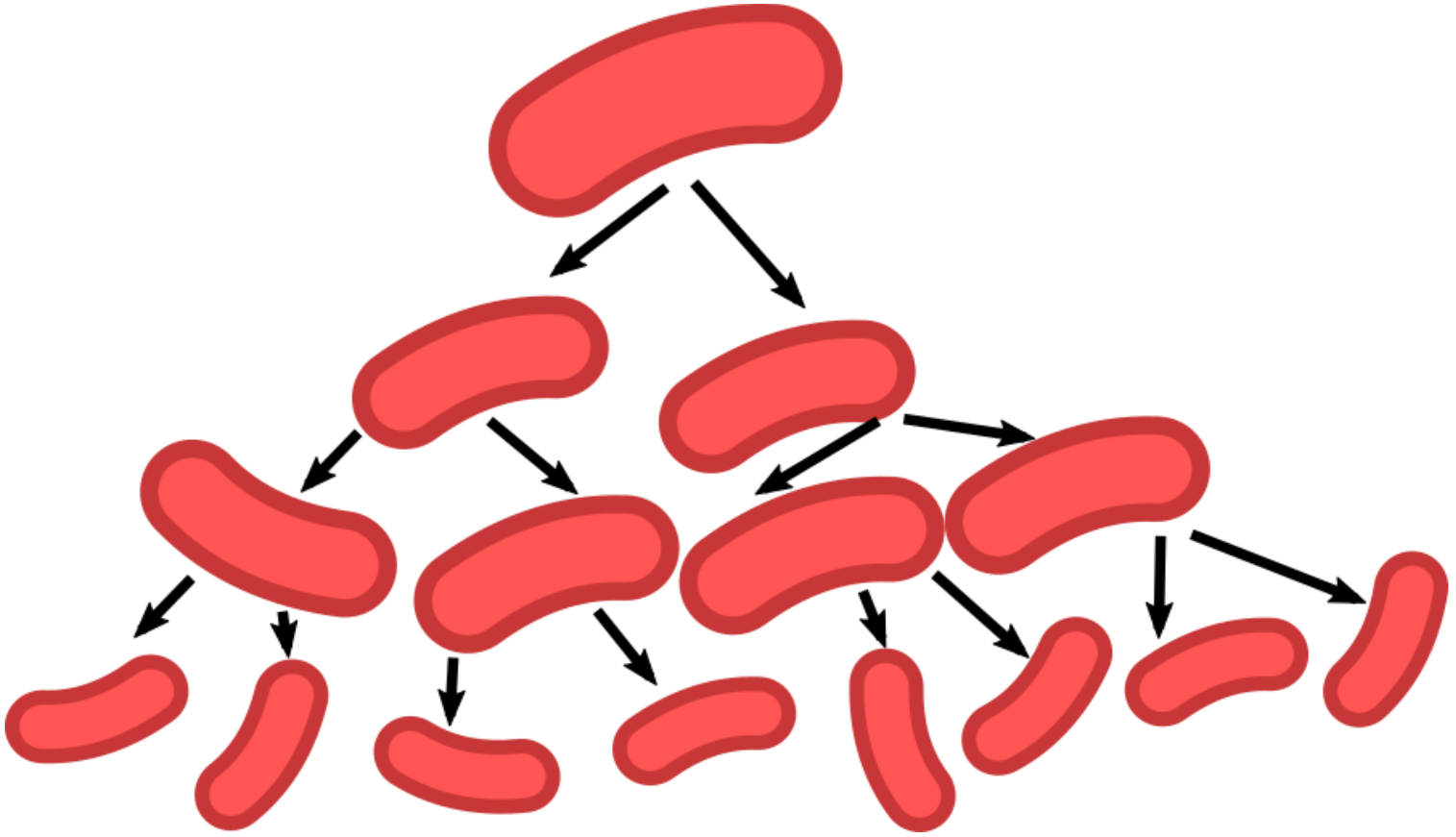
Horizontal transmission - Transformation



Horizontal transmission - Transduction

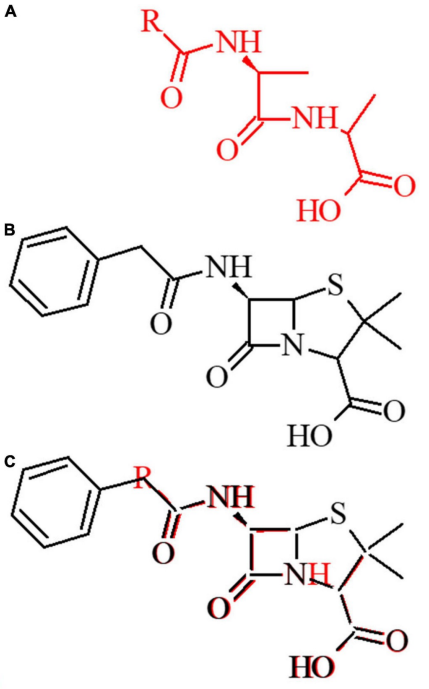


Vertical transmission



β-lactams - +

- Characterized by a four-membered ring
- They **inhibit peptidoglycan synthesis** by binding to several DD-transpeptidases (penicillin-binding proteins, **PBPs**)

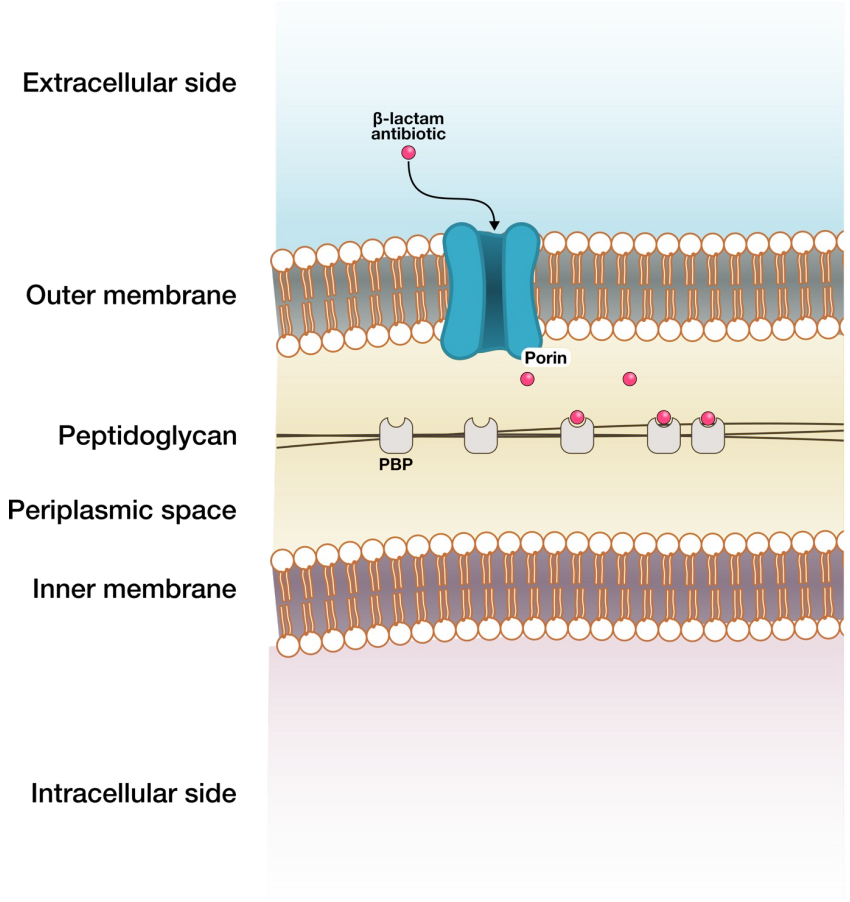


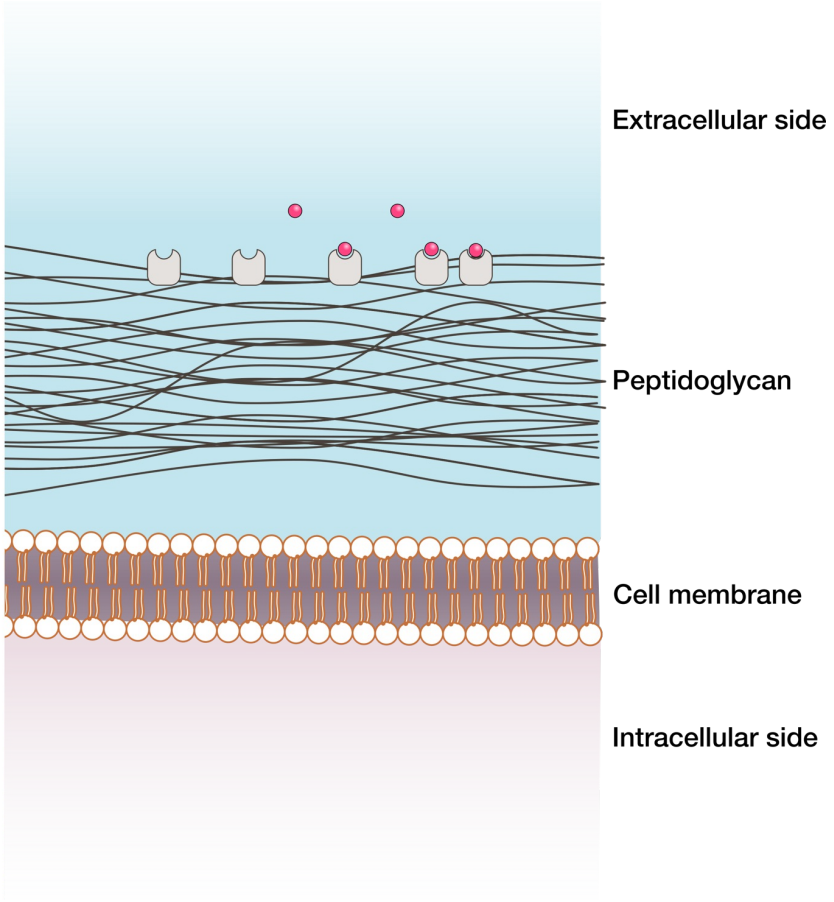
The Chemical Relationship Among Beta-Lactam Antibiotics and Potential Impacts on Reactivity and Decomposition

Jonathan Turner[1,2], Alyssa Muraoka[2], Michael Bedenbaugh[3], Blaine Childress[4], Lauren Pernot[5], Mark Wiencek[5] and Yuri K. Peterson[2*]

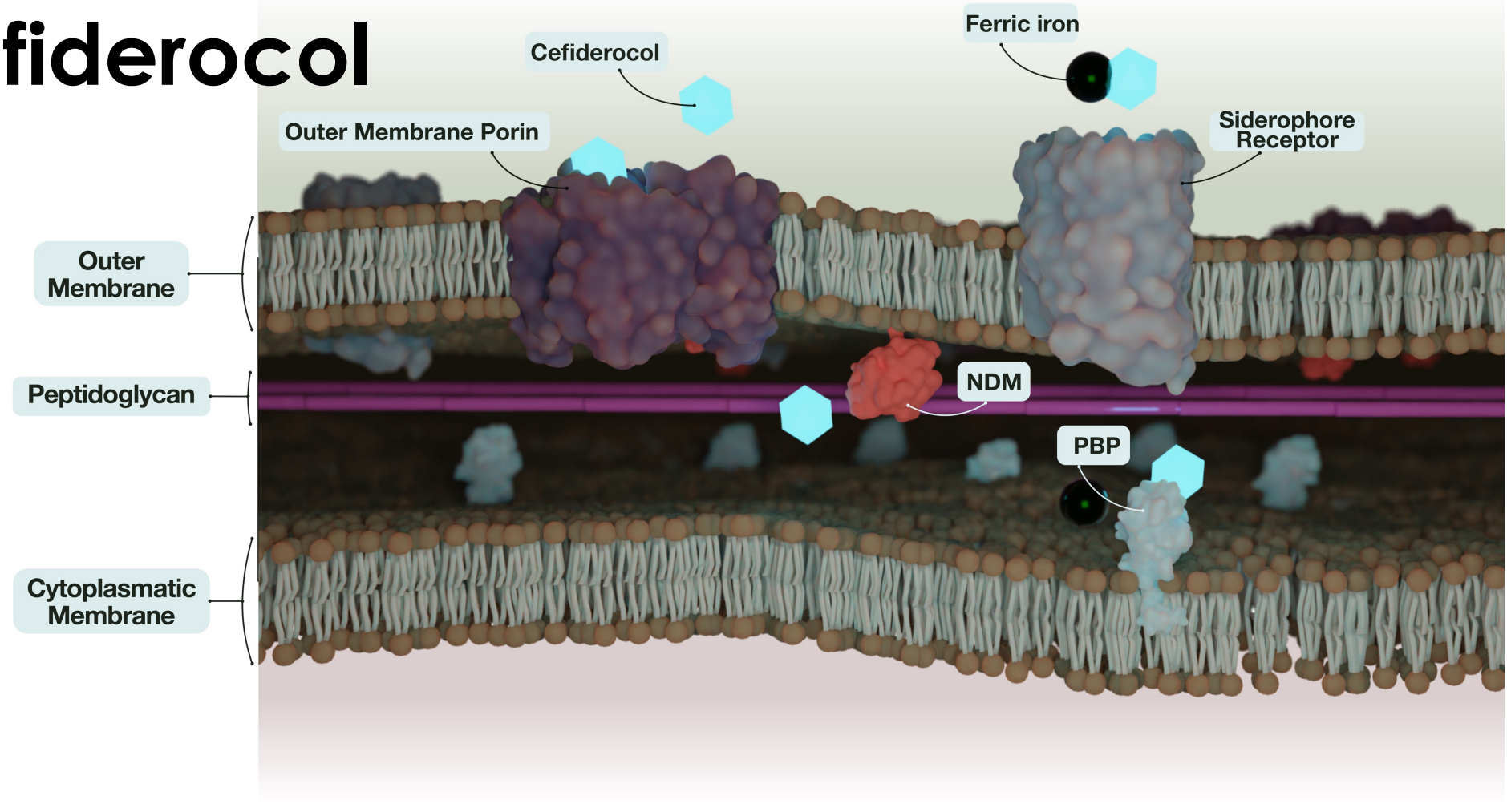
frontiers in Microbiology

β-lactams - action - +





A peculiar β-lactam - cefiderocol



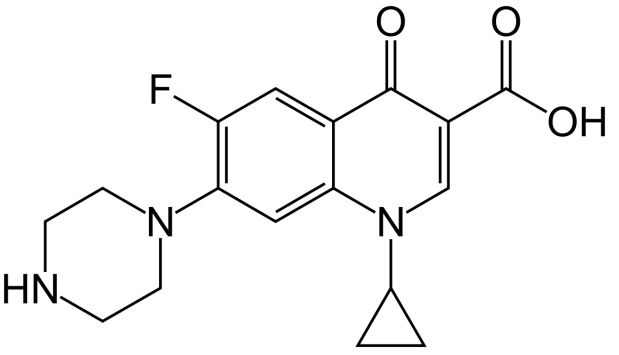
(fluoro)Quinolones + -

- Characterized by a quinoline ring
- They **inhibit DNA gyrase** in Gram-negative **and DNA topoisomerase IV** in Gram-positive bateria, nicking the DNA

BIOCHEMISTRY
including biophysical chemistry & molecular biology

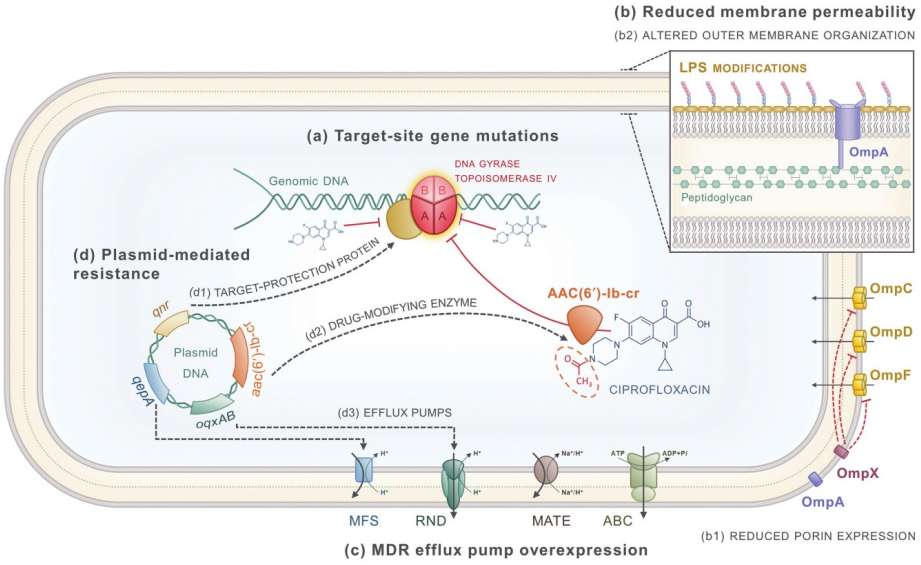
Mechanism of Quinolone Action and Resistance

Katie J. Aldred,[†] Robert J. Kerns,[§] and Neil Osheroff*[,†,‡]



(fluoro)Quinolones - resistance

1. Mutation in target site (***gyrA*** and ***parC***)
2. Gyrase protection (***qnr***)
3. Reduced antibiotic uptake
4. Increased antibiotic efflux
5. Enzymatic antibiotic modification



JOURNAL OF MEDICAL MICROBIOLOGY

REVIEW

Correia *et al.*, *Journal of Medical Microbiology* 2017;66:551–559
DOI 10.1099/jmm.0.000475

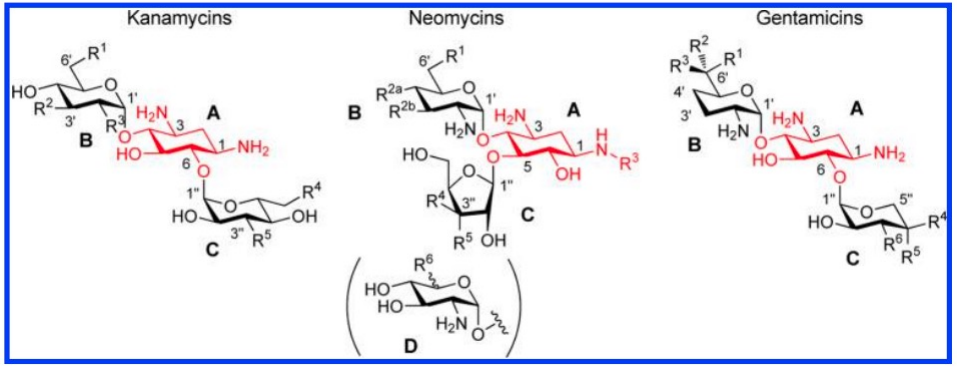
MICROBIOLOGY SOCIETY

Mechanisms of quinolone action and resistance: where do we stand?

Susana Correia,[1,2,3,4] Patrícia Poeta,[3,4] Michel Hébraud,[5,6] José Luis Capelo[4,7] and Gilberto Igrejas[1,2,4,*]

Aminoglycosides + -

- Molecules containing amino-sugar structures
- They **block protein synthesis** by binding the bacterial 16S rRNA



ACS chemical biology

Aminoglycoside Antibiotics in the 21st Century

Bernd Becker and Matthew A. Cooper*

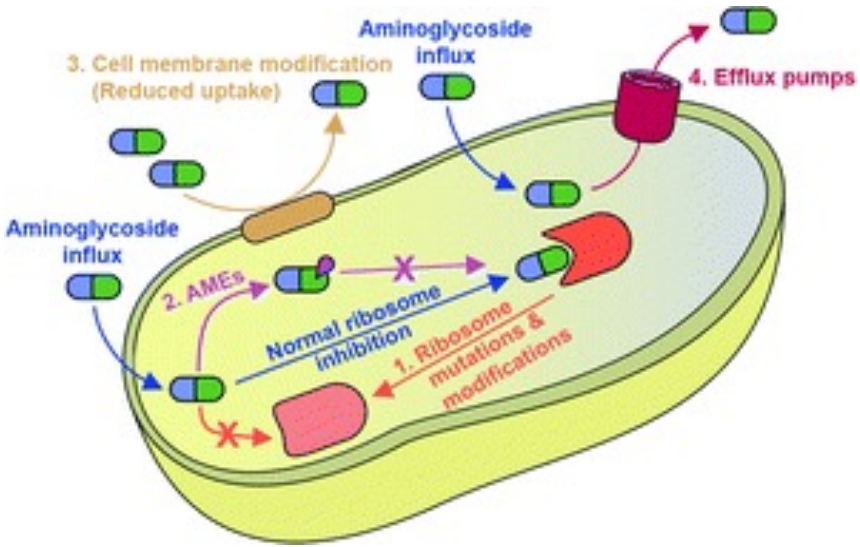
Aminoglycosides - resistance

1. Reduced antibiotic uptake
2. Increased antibiotic efflux
3. Enzymatic antibiotic modification
4. Enzymatic target site (16S) modification

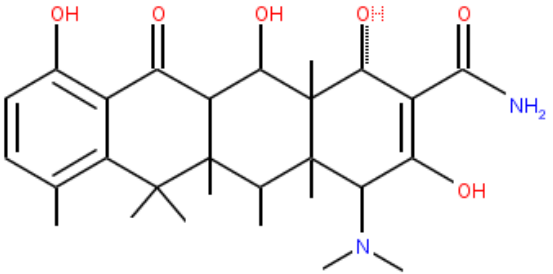
Aminoglycoside Resistance

Updates with a Focus on Acquired 16S Ribosomal RNA Methyltransferases

Jun-Ichi Wachino, PhD[a,*], Yohei Doi, MD, PhD[b,c,d], Yoshichika Arakawa, MD, PhD[a,e]



Tetracyclines + -



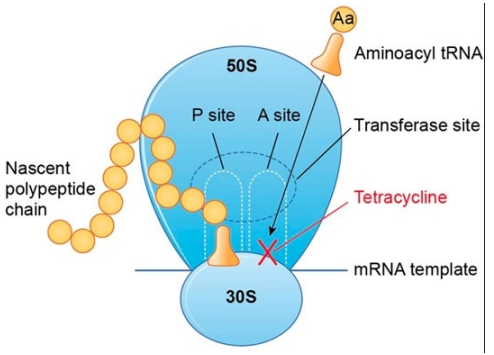
- Characterized by a four rings skeleton (designated as A, B, C and D) with various side-chains
- They **block protein synthesis** by binding the 30S ribosomal subunit (16S rRNA and 21 proteins), they inhibit the entrance of the aminoacyl-tRNA to the mRNA translation complex

INVITED REVIEW

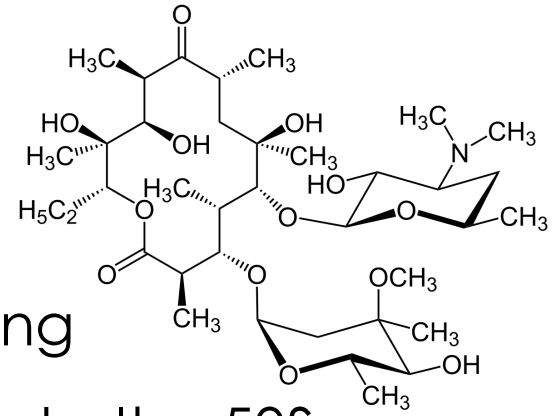
Dermatological Reviews WILEY

Treating acne with the tetracycline class of antibiotics: A review

Emmy M. Graber MD, MBA[1,2]



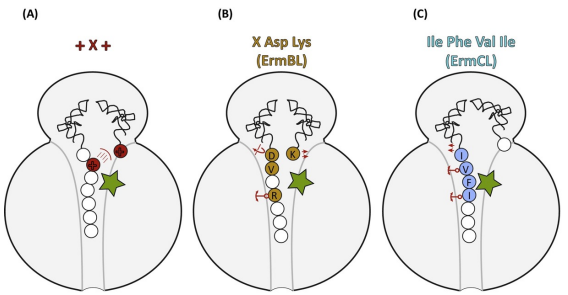
Macrolides + -



- Characterized by a large macrocyclic lactone ring
- They **inhibit protein synthesis** by binding reversibly to the 50S subunit of the bacterial ribosome. When specific aminoacids are translated, this prevents the addition of the next amino acid to the growing peptide

Trends in Biochemical Sciences

CellPress REVIEWS



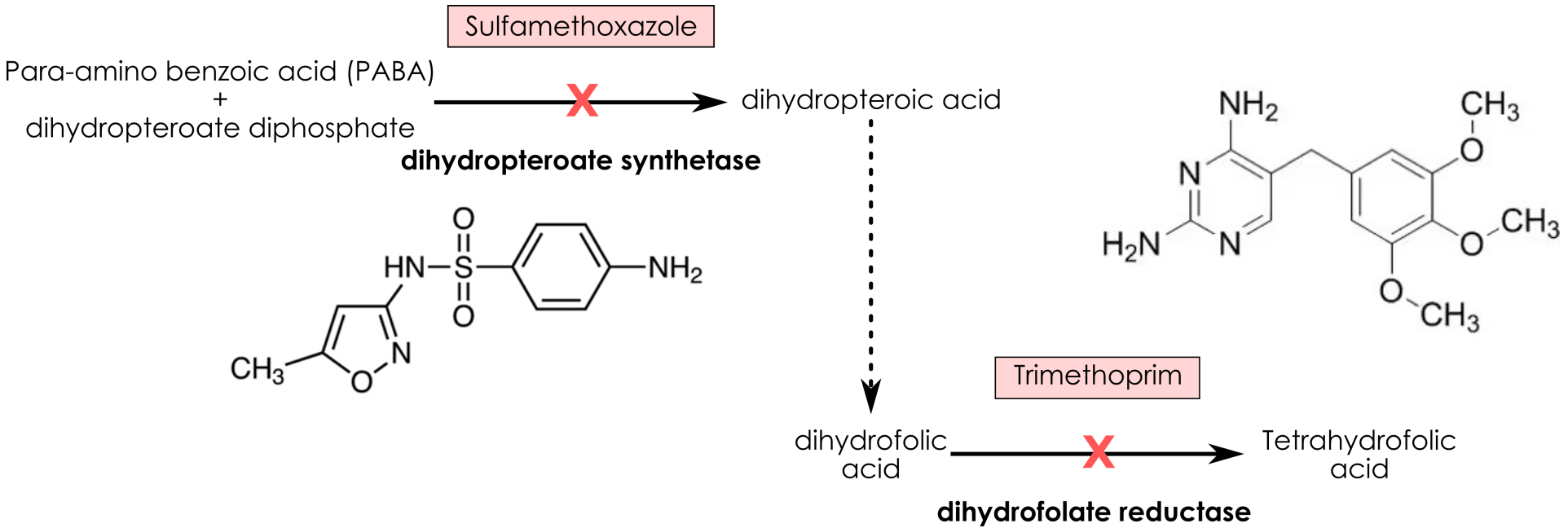
Review

How Macrolide Antibiotics Work

Nora Vázquez-Laslop[1,*] and Alexander S. Mankin[1,*]

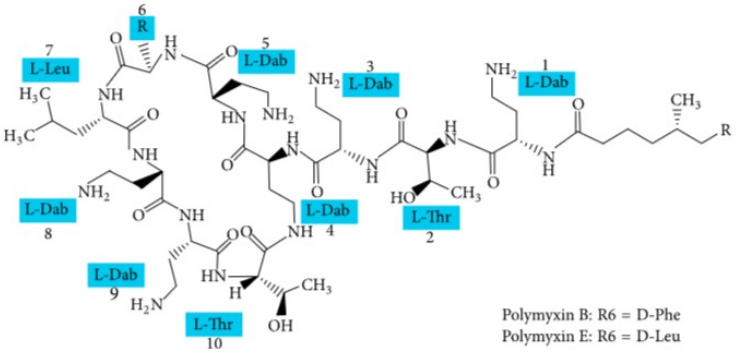
Pholate pathway inhibitors + -

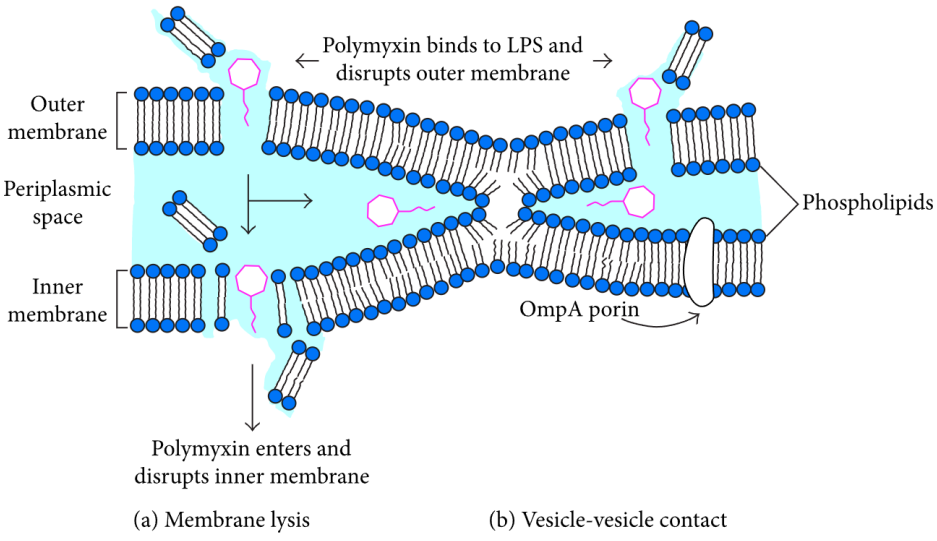
- Two molecules inhibiting the same biochemical pathway



Polymyxins

- Cyclic non-ribosomal polypeptides
- They **bind the lipopolysaccharide of Gram-negative bacteria disrupting both membranes**, with a detergent-like mode of action.



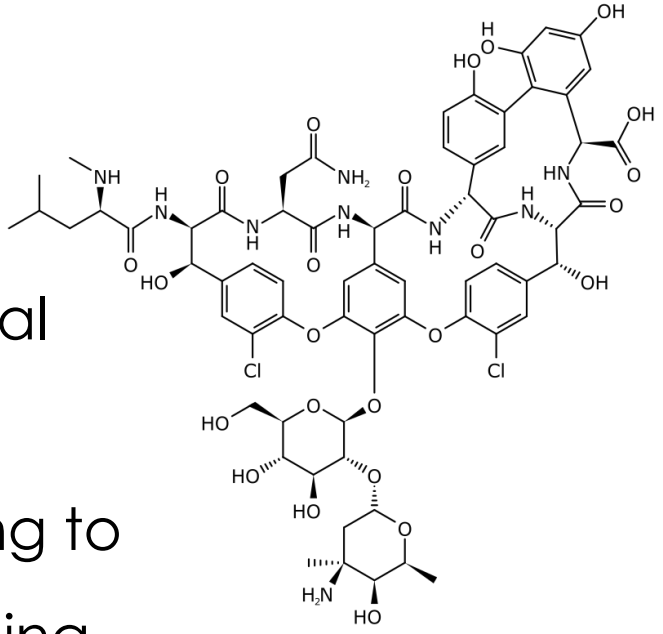


Review Article

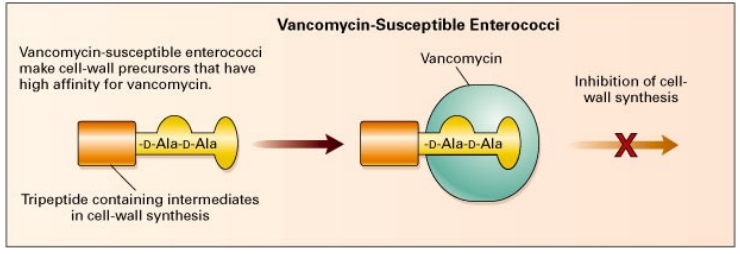
Antibacterial Mechanisms of Polymyxin and Bacterial Resistance

Zhiliang Yu,[1] Wangrong Qin,[1] Jianxun Lin,[2] Shisong Fang,[3] and Juanping Qiu[1]

Glycopeptides



- Glycosylated cyclic or polycyclic nonribosomal peptides
- They **inhibit peptidoglycan synthesis** by binding to the acyl-D-Ala-D-Ala during the cell-wall building, preventing the addition of new units



REVIEW ARTICLE DRUG THERAPY

Vancomycin-Resistant Enterococcal Infections

Barbara E. Murray, M.D.

The ESKAPE pathogens

Enterococcus faecium

Staphylococcus aureus

Klebsiella pneumoniae

Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacter/Escherichia species

Clinical Infectious Diseases

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher ✉, George H. Talbot, John S. Bradley, John E. Edwards, David Gilbert, Louis B. Rice, Michael Scheld, Brad Spellberg, John Bartlett

Enterococcus spp

Gram positive cocci

Occur in pair / short chains

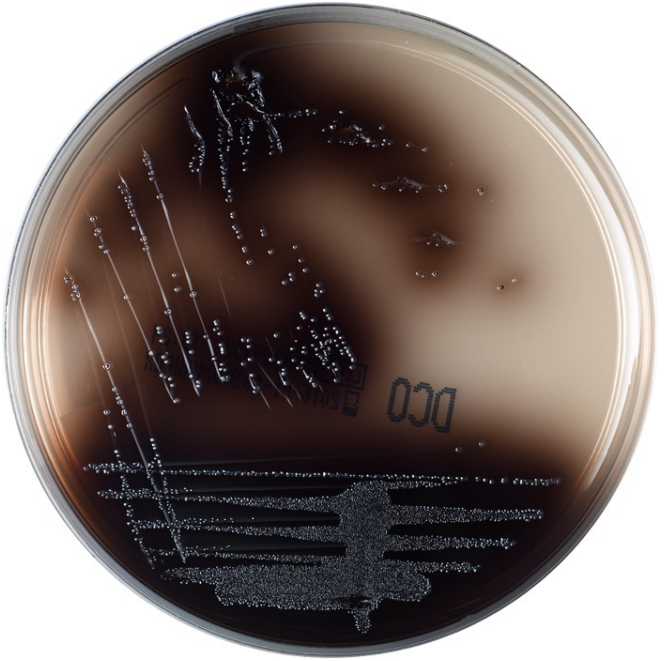
Once classificated as "group D" of the *Streptococcus* genus

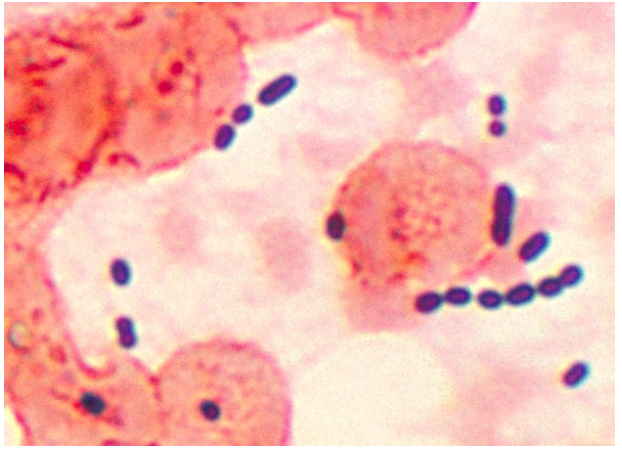
Facultative anaerobic

Non-hemolytic

Typical gut commensal (95**% *E. faecalis***, 5% ***E. faecium***)

Low-moderate pathogenic potential





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REVIEW

Check for updates

The Enterococcus: a Model of Adaptability to Its Environment

Mónica García-Solache,[a] Louis B. Rice[a]

Enterococcus spp

"*The enterococci* ***are not highly virulent organisms****, and the success of E. faecalis and E. faecium as pathogens in the hospital setting is primarily related to their survival capabilities in a hostile antimicrobial-rich environment.* […] ***Virulence factors are more evident in E. faecalis****, perhaps explaining its still leading role in enterococcal infections.*"

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REVIEW

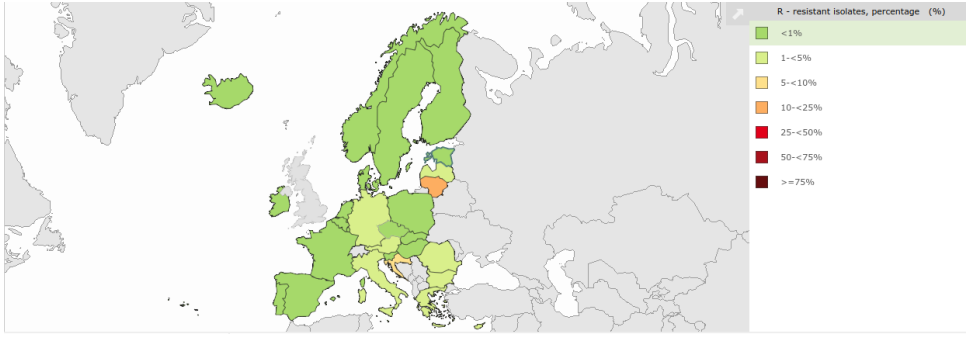
Check for updates

The Enterococcus: a Model of Adaptability to Its Environment

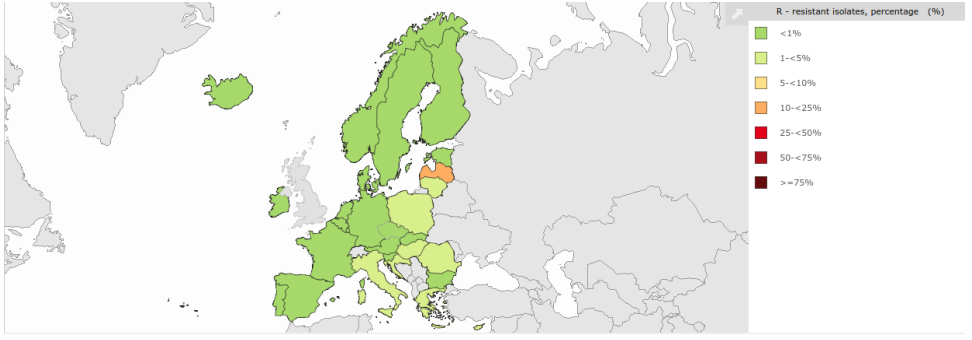
Mónica García-Solache,[a] Louis B. Rice[a]

Enterococcus faecalis

Ampicillin resistance



Vancomycin resistance

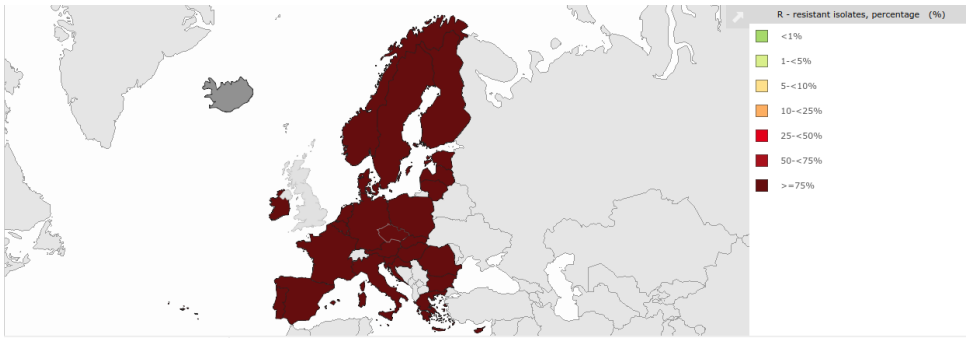


ecdc

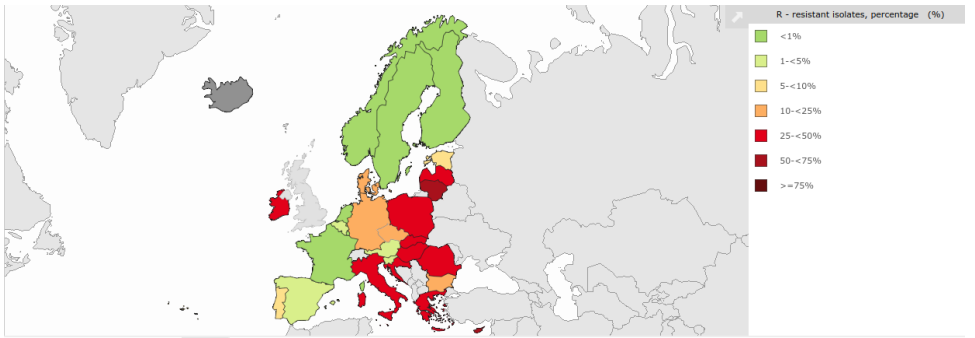
Surveillance Atlas of Infectious Diseases

Enterococcus faecium

Ampicillin resistance (low affinity PBP)



Vancomycin resistance (*van* operons)



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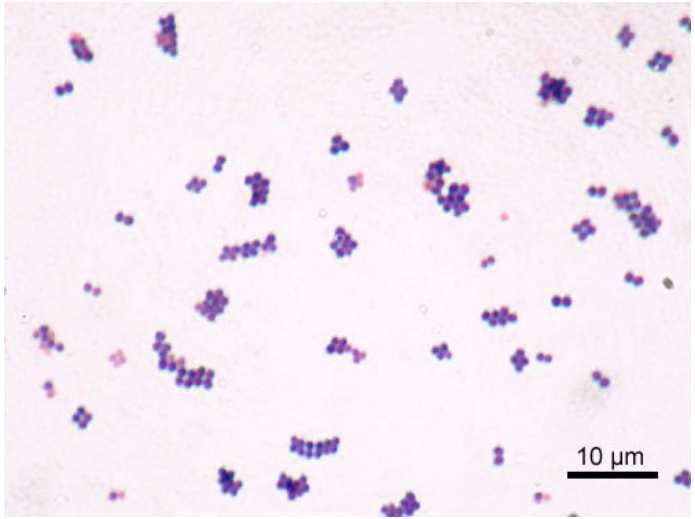
Surveillance Atlas of Infectious Diseases

Staphylococcus aureus



Gram positive cocci

Occurs in irregular grape-like clusters

Nonmotile

Facultative anaerobic

Hemolytic

Coagulase-positive and catalase-positive

High pathogenic potential

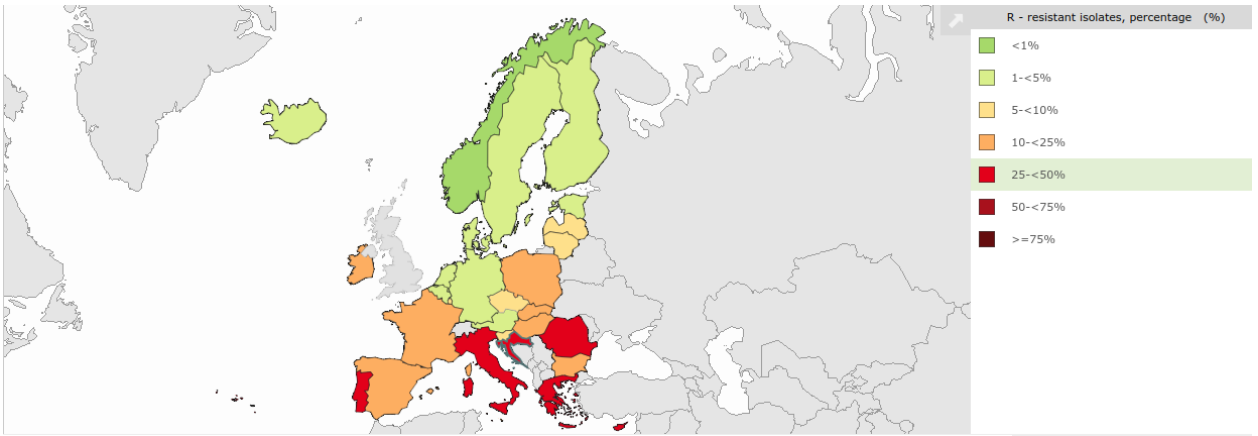
nature reviews microbiology

Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research

Nicholas A. Turner, Batu K. Sharma-Kuinkel, Stacey A. Maskarinec, Emily M. Eichenberger, Pratik P. Shah, Manuela Carugati, Thomas L. Holland & Vance G. Fowler Jr

Staphylococcus aureus

"***Methicillin resistance*** *is mediated by* mecA *and acquired by horizontal transfer of a mobile genetic element designated staphylococcal cassette chromosome* mec *(SCCmec)* […] *the horizontal acquisition of SCCmec has occurred on a limited number of occasions among relatively few predominant strain types* […]



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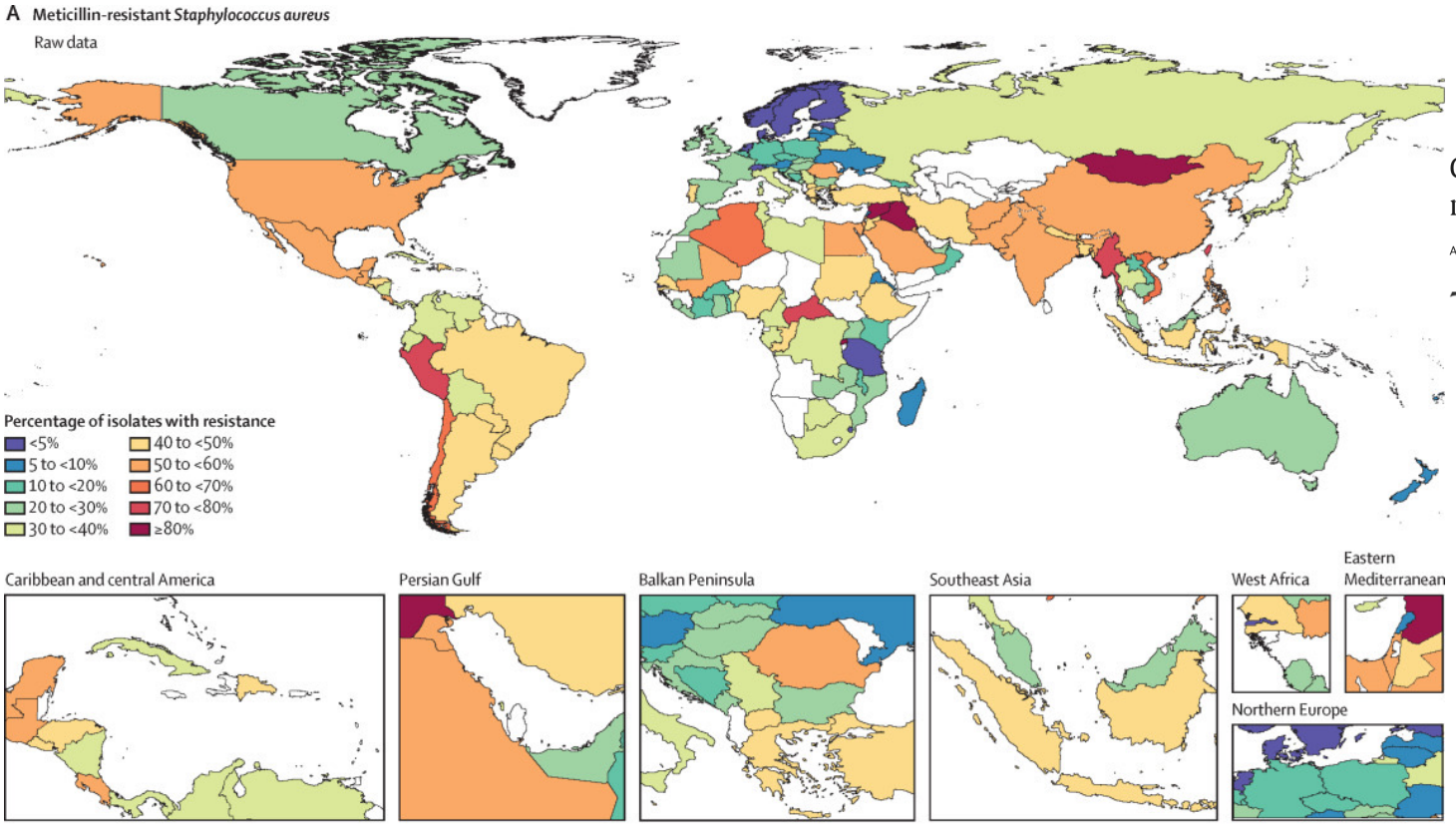
Surveillance Atlas of Infectious Diseases

Meticillin-resistant *S. aureus*

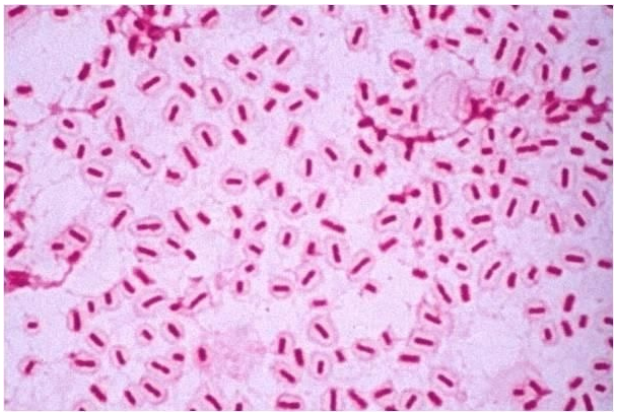


Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators†

THE LANCET

Klebsiella pneumoniae



Gram negative bacilli

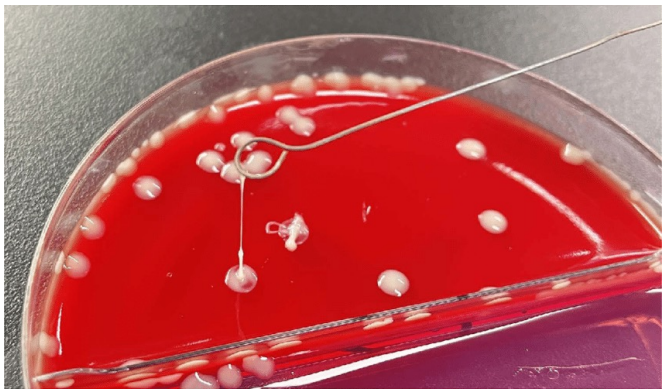
Commonly encapsulated

Glucose fermentative

Oxidase-negative

Nonmotile, and usually nitrate-negative

Opportunistic pathogen/High pathogenic potential



Population genomics of *Klebsiella pneumoniae*

Kelly L. Wyres[1], *Margaret M. C. Lam*[1] *and Kathryn E. Holt*[1,2] ✉

NATURE REVIEWS | MICROBIOLOGY

Klebsiella pneumoniae

- Production of antibiotic degradation/modification enzymes (e.g., β-lactamases)
- High expression of efflux pumps
- Production of modified porins
- Modification of antibiotic targets (e.g. DNA gyrase or LPS biosynthesis)

Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance

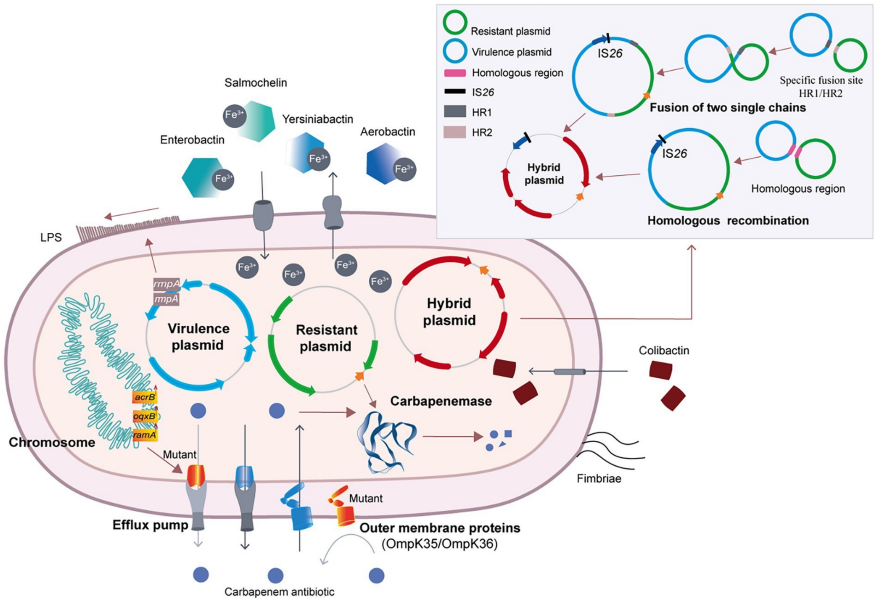
Shiri Navon-Venezia[1,*], Kira Kondratyeva[1] and Alessandra Carattoli[2]

FEDERATION OF EUROPEAN MICROBIOLOGICAL SOCIETIES FEMS JOURNALS investing in science

Klebsiella pneumoniae

Acquisition of

- resistance genes in hypervirulent strains
- virulence plasmids in multi-drug resistant strains
- hybrid plasmids



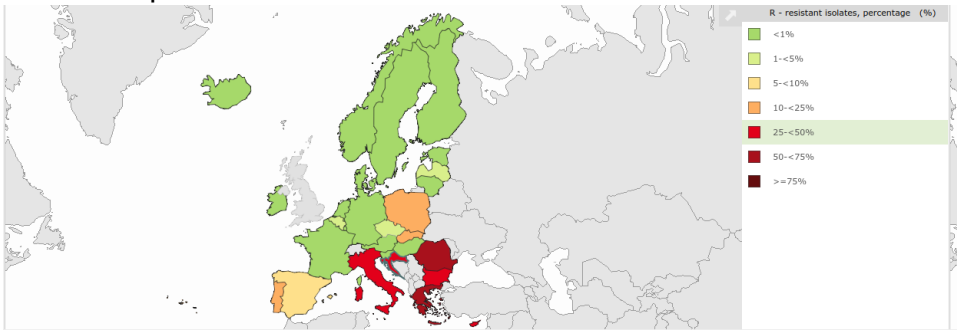
Epidemiological characteristics and molecular evolution mechanisms of carbapenem-resistant hypervirulent *Klebsiella pneumoniae*

Yu-Ling Han[1,2], Xu-Hui Wen[1,2], Wen Zhao[1], Xi-Shan Cao[1], Jian-Xun Wen[3], Jun-Rui Wang[1], Zhi-De Hu[1] and Wen-Qi Zheng[1,2*]

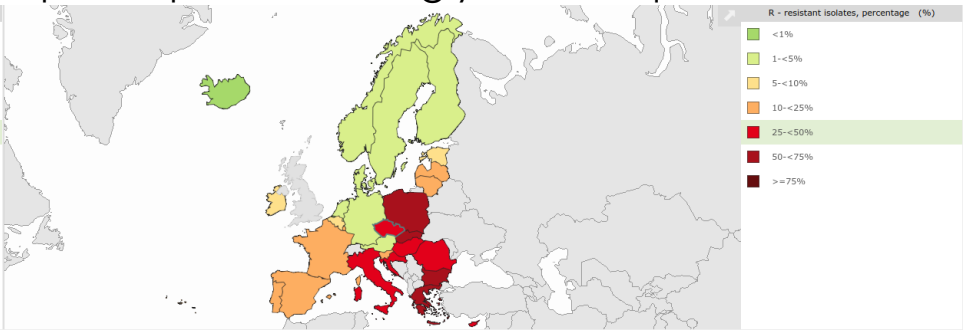
frontiers in Microbiology

Klebsiella pneumoniae

Carbapenems resistance



cephalosporins-aminoglycosides-quinolones resistance



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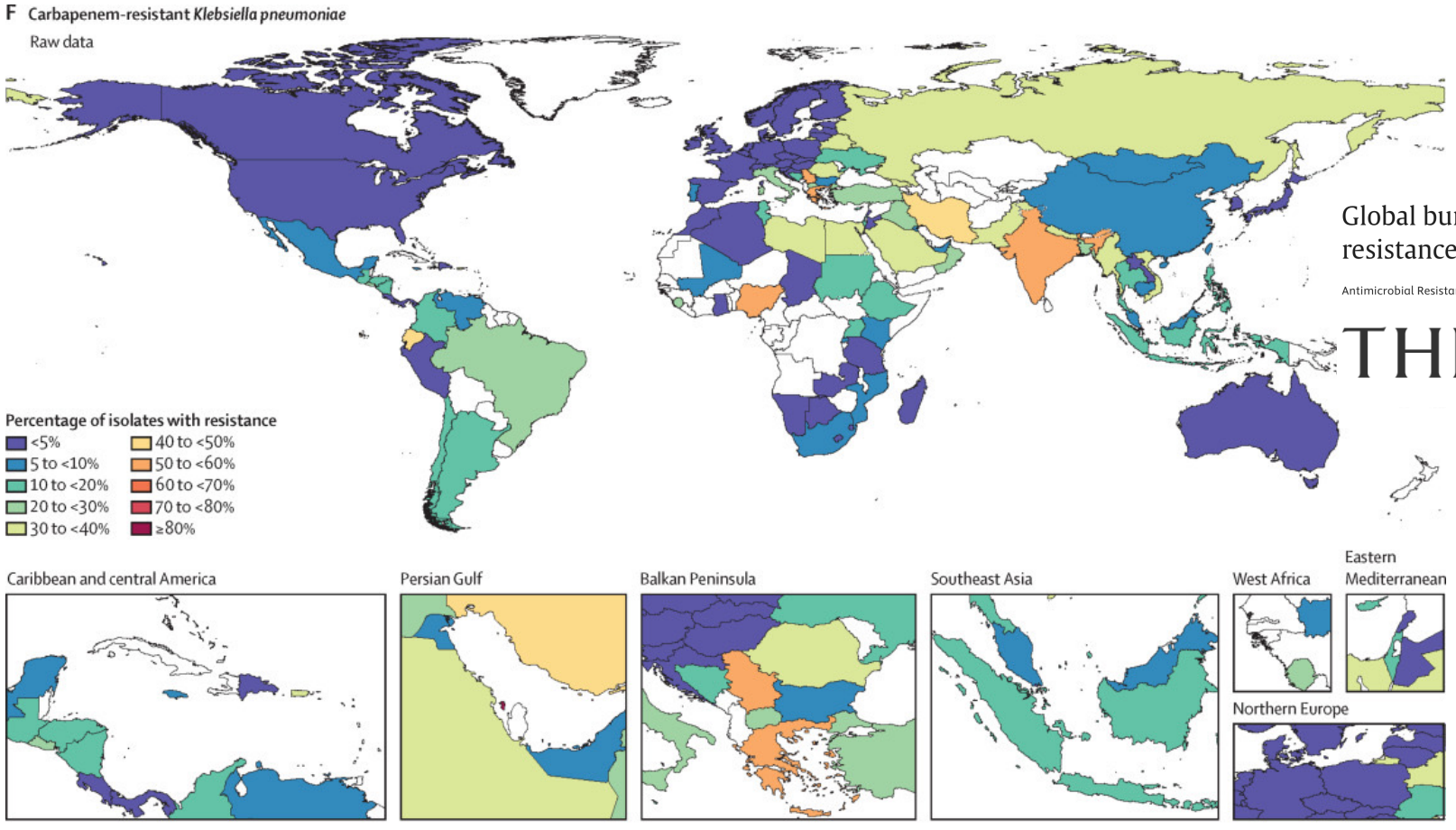
Surveillance Atlas of Infectious Diseases

Carbapenem resistant *K. pneumoniae*



Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

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Acinetobacter baumannii

Gram negative cocco-bacilli

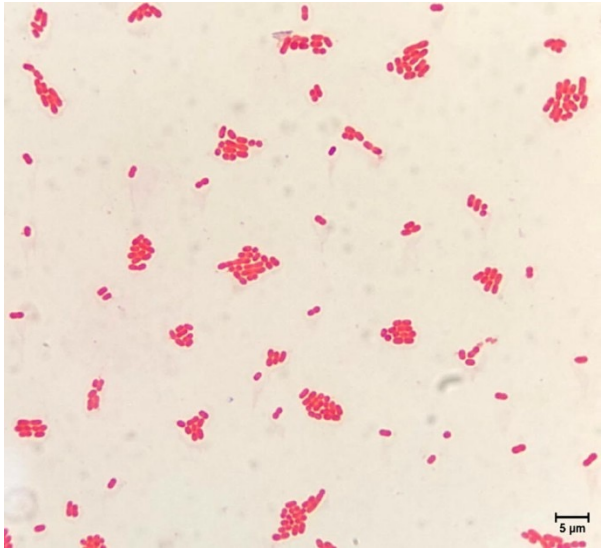
Strictly aerobic

Nonfermentative

Oxidase-negative, catalase-positive

Nonmotile, and usually nitrate-negative

Opportunistic pathogen



Biology of *Acinetobacter baumannii*: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options

Chang-Ro Lee[1†], Jung Hun Lee[1†], Moonhee Park[1,2†], Kwang Seung Park[1], Il Kwon Bae[3], Young Bae Kim[4], Chang-Jun Cha[5], Byeong Chul Jeong[1] and Sang Hee Lee[1*]

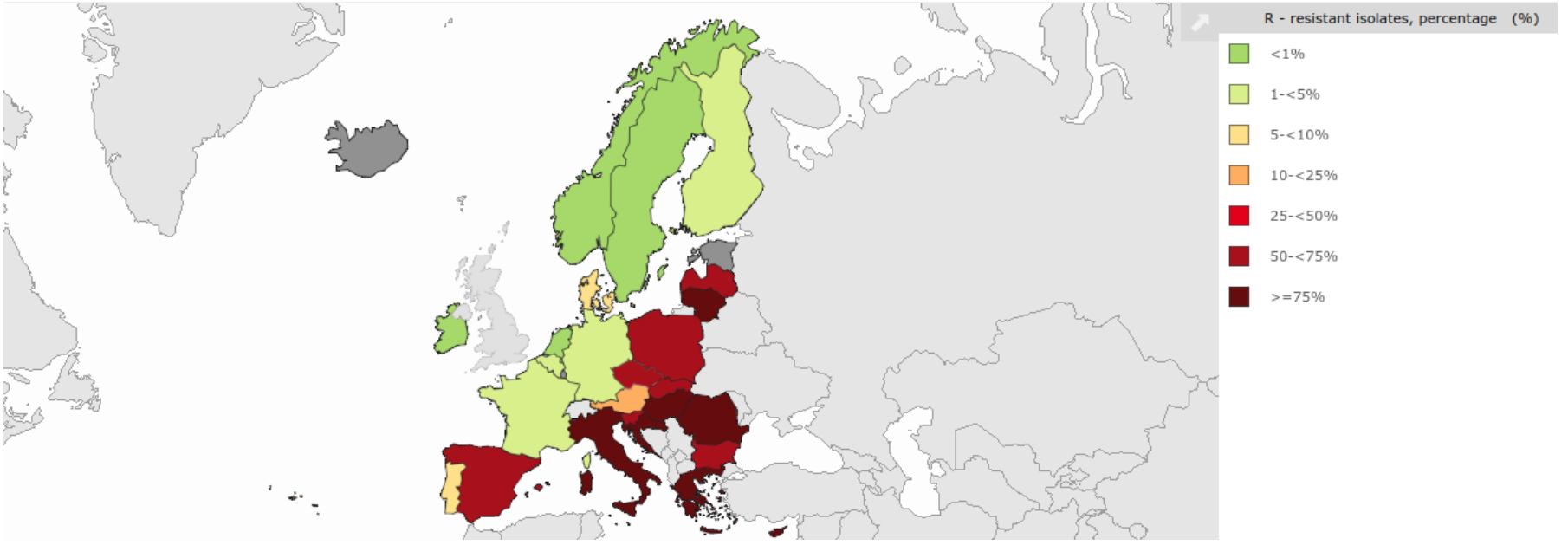
frontiers in Microbiology

Acinetobacter baumannii

- Production of antibiotic degradation/modification enzymes (e.g. β-lactamases)
- High expression of efflux pumps
- Production of modified porins
- Modification of antibiotic targets (e.g. DNA gyrase or LPS biosynthesis)

Acinetobacter baumannii

Carbapenems/quinolones/aminoglycosides-resistance



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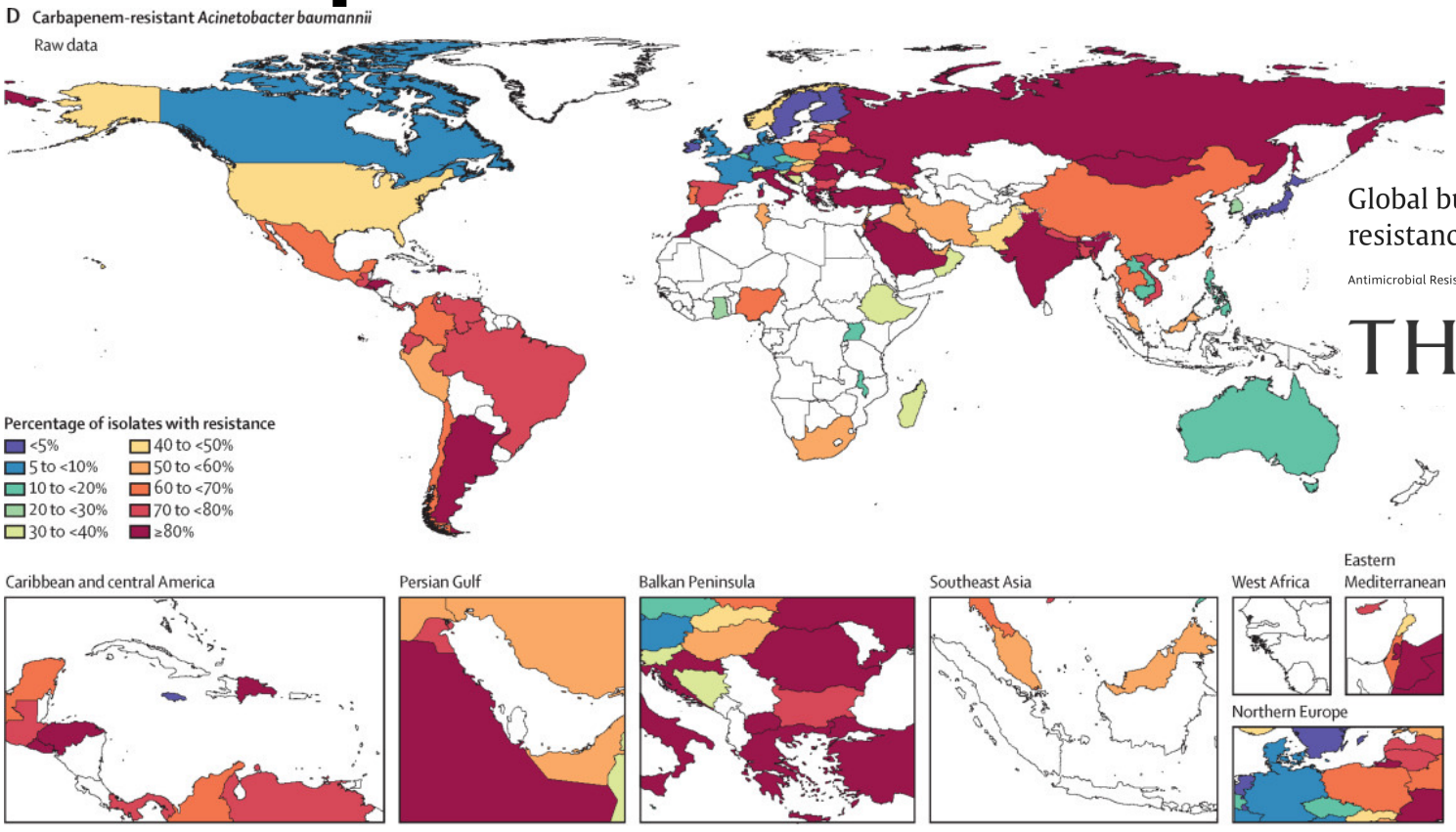
Surveillance Atlas of Infectious Diseases

Carbapenem resistant *A. baumannii*



Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

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Pseudomonas aeruginosa

Gram negative bacilli

Environmental origin

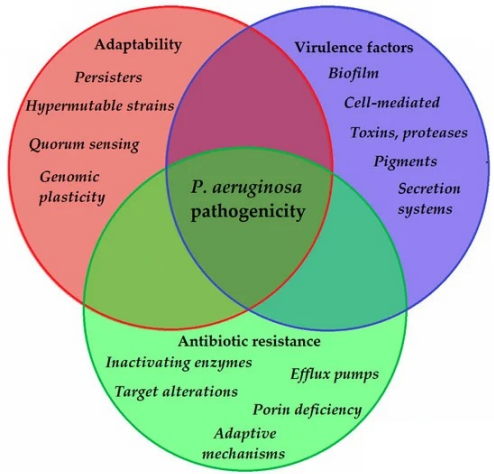
Nonfermentative

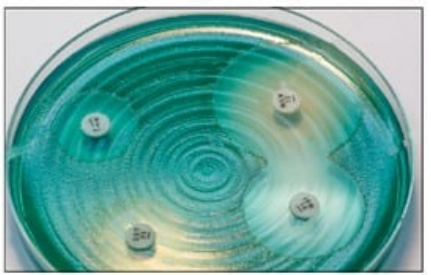
Oxidase-positive

Hemolytic

Pigment-producers (pyoverdine/pyocyanin/pyorubin/pyomelanin)

Moderate/high pathogenic potential



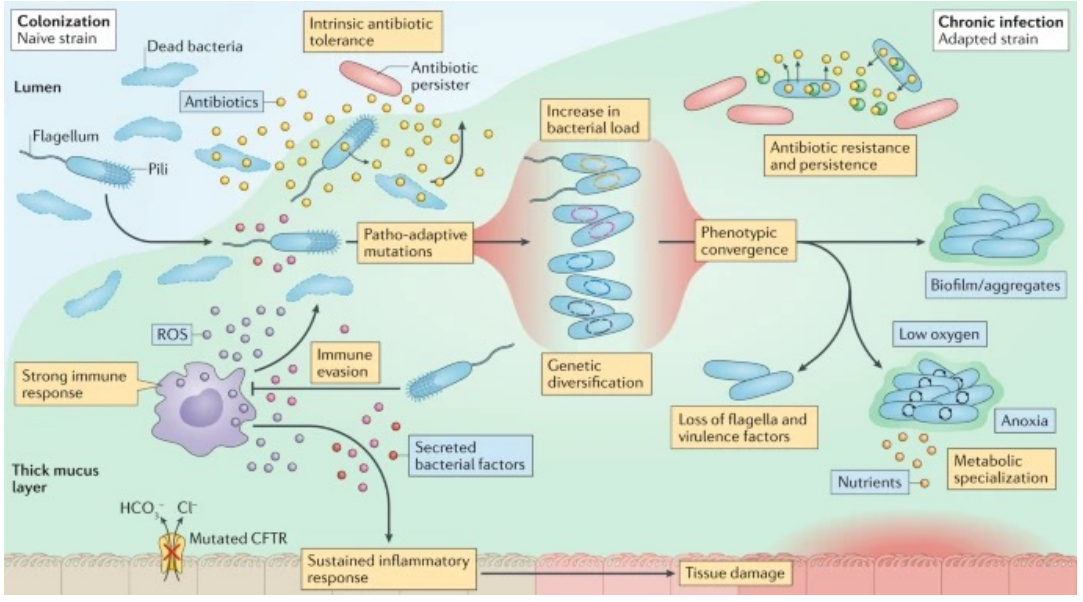


It's Not Easy Being Green: A Narrative Review on the Microbiology, Virulence and Therapeutic Prospects of Multidrug-Resistant *Pseudomonas aeruginosa*

by Payam Behzadi [1], Zoltán Baráth [2,†] and Márió Gajdács [3,4,*,†]

antibiotics

Pseudomonas aeruginosa



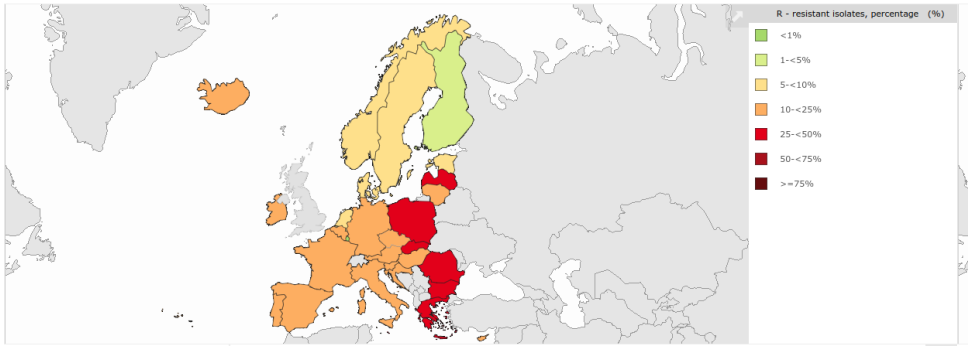
Pseudomonas aeruginosa adaptation and evolution in patients with cystic fibrosis

nature reviews microbiology

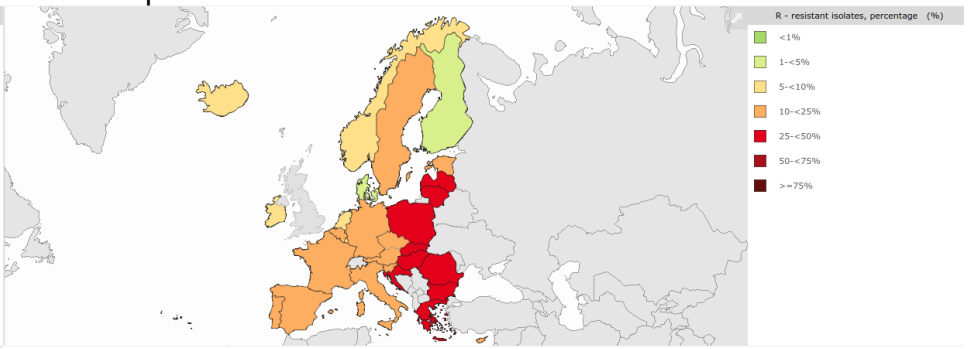
Elio Rossi, Ruggero La Rosa, Jennifer A. Bartell, Rasmus L. Marvig, Janus A. J. Haagensen, Lea M. Sommer, Søren Molin & Helle Krogh Johansen ✉

Pseudomonas aeruginosa

Piperacillin/tazobactam resistance



Carbapenems resistance



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Surveillance Atlas of Infectious Diseases

Escherichia coli

Gram negative bacilli

Rarely encapsulated

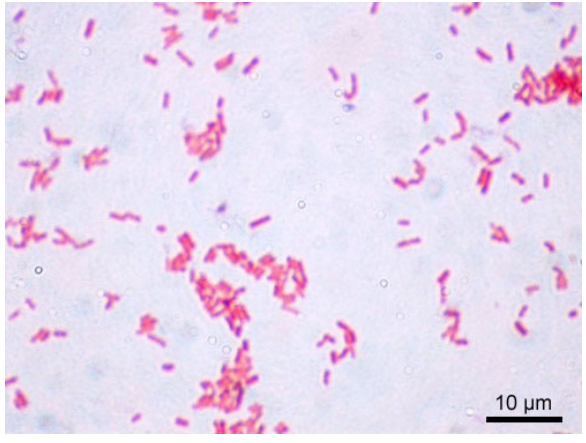
Glucose fermentative

Oxidase-negative

Motile

Wide spectrum of pathogenic potential

(Commensal/diarrhoeagenic/ExPEc)



nature reviews microbiology

The population genetics of pathogenic *Escherichia coli*

Erick Denamur ✉, Olivier Clermont, Stéphane Bonacorsi & David Gordon

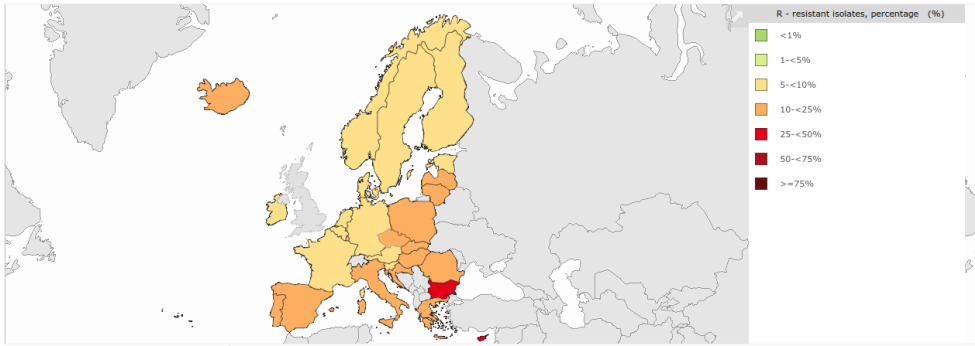
Escherichia coli

"*Due to its particular ecology,* E. coli *can be considered as a sensor of the current situation of antimicrobial resistance* [...] *Some of the newer resistance mechanisms have emerged in the so-called high-risk clones, which facilitate persistence and further dissemination of resistance traits around the world*"

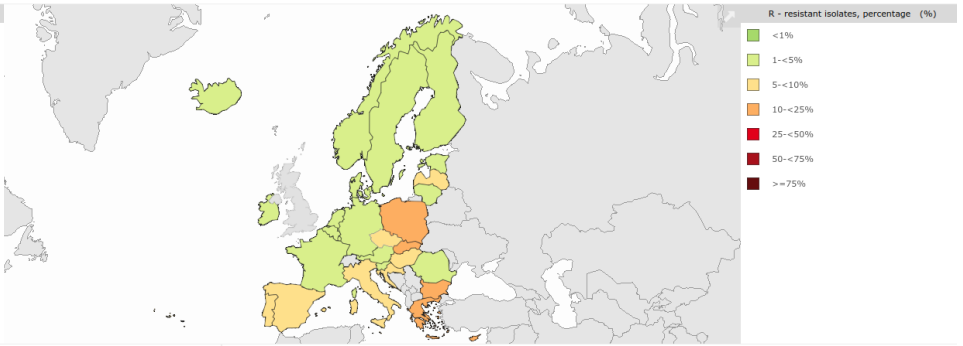
"*By contrast, untreated hospital wastewater strongly selected for multiresistant* E. coli *in different controlled exposure experiments with individual isolates and communities*"

Escherichia coli

Cephalosporins resistance



Cephalosporins/aminoglycosides/quinolones resistance



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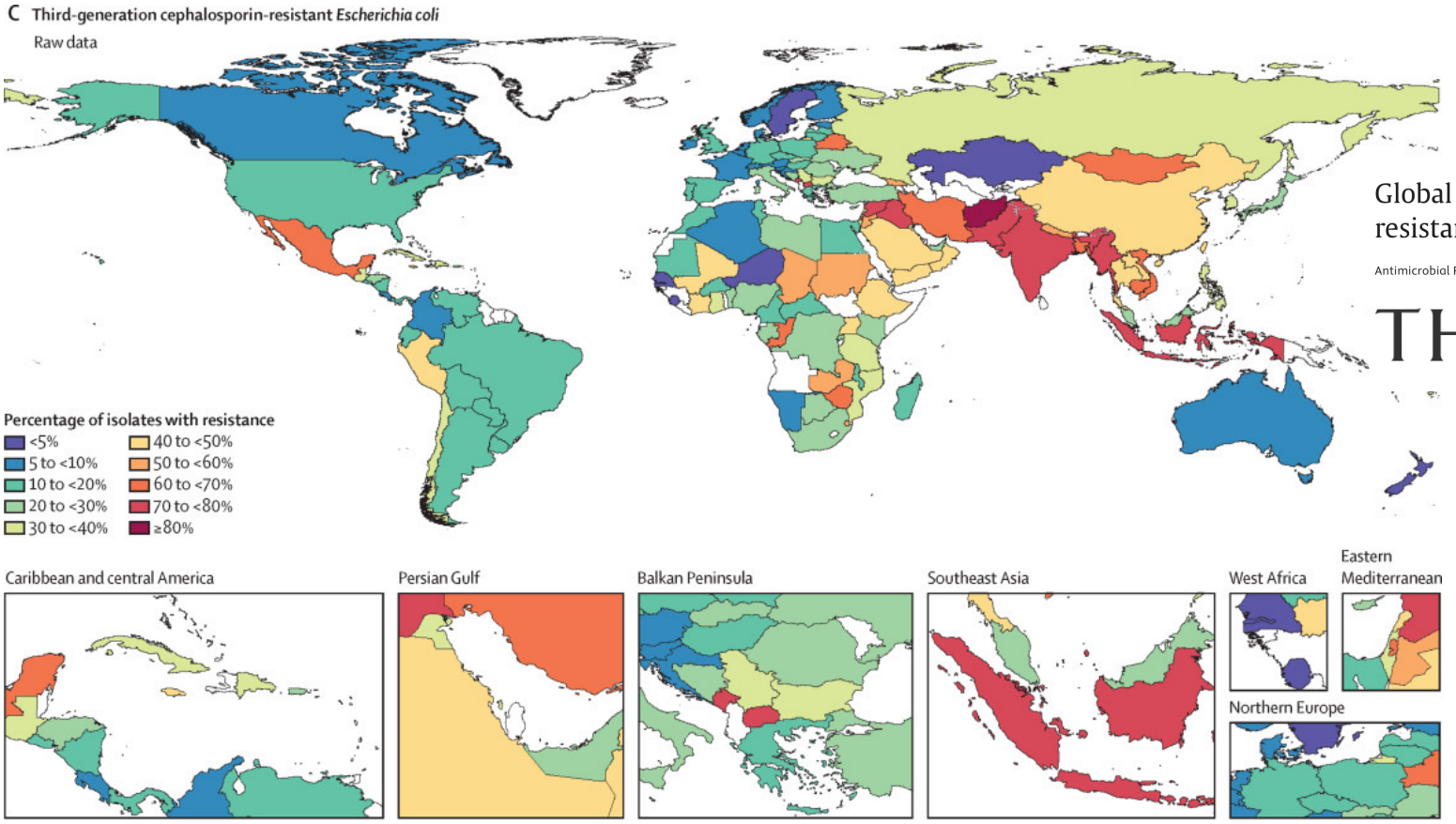
Surveillance Atlas of Infectious Diseases

3GC Resistant *E. coli*



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Take home messages

- **Antimicrobial resistance is a complex phenomenon**, emerging from the juxtaposition of several determinants (e.g., species, mobile genetic elements, resistance genes), and it is going to be one of the biggest challenges for the medical doctors of the XXI century
- There are **few solutions**, difficult to carry out
- **Every bug-drug combination has some resistance issues**, which should be accounted for when considering an antimicrobial treatment

Questions?