FOCUS
LOTTA ALLE INFEZIONI CORRELATE ALL'ASSISTENZA

2019 MOTORE SANITÀ
Gestire il Cambiamento

TORINO
GOLDEN PALACE
SALA DIAMANTE
Via Arcivescovado, 18
12 NOVEMBRE 2019

Infezioni Correlate all'Assistenza: Resistenza Batterica e Visioni di Stewardship Antimicrobica

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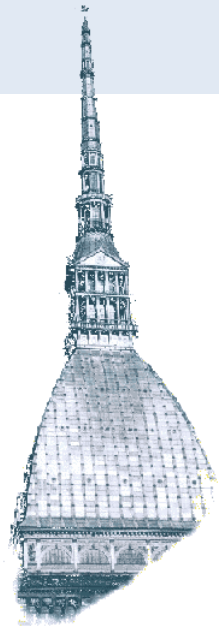
Ospedale Amedeo di Savoia



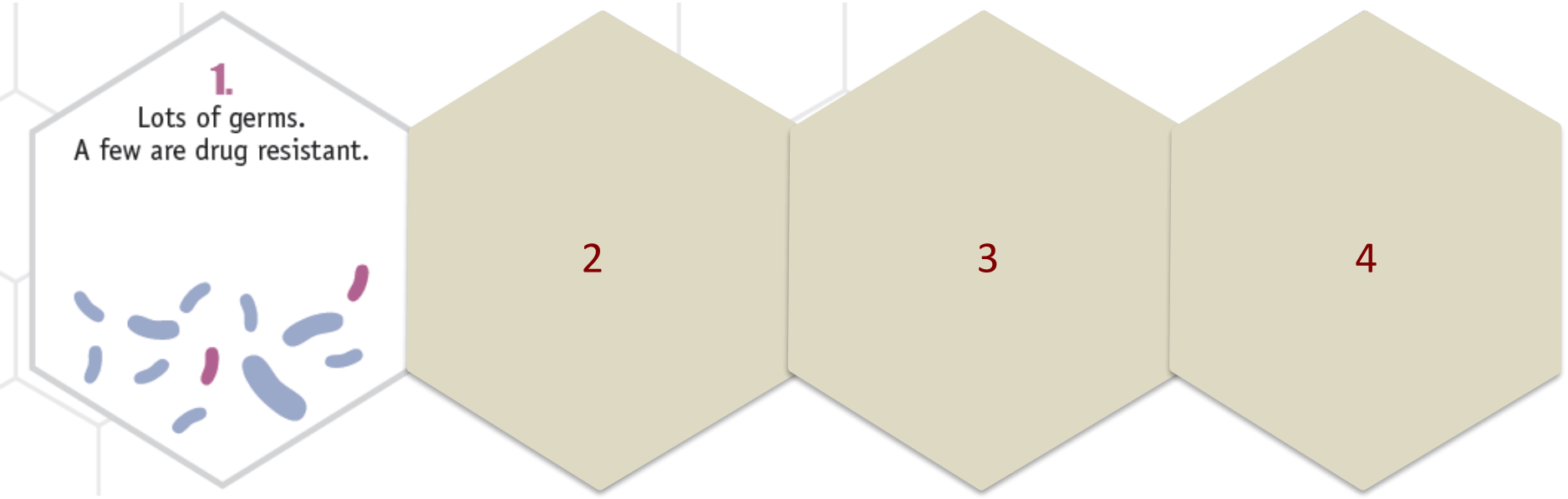
Ospedale Amedeo di Savoia

Financial Disclosures

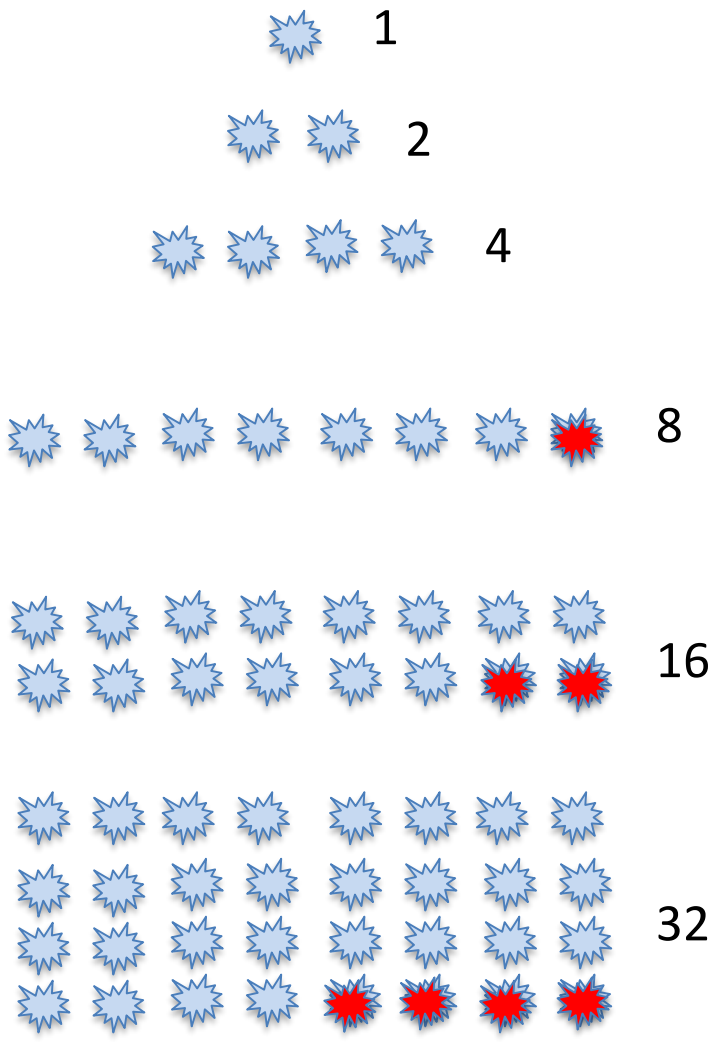
Speaker fees, consultancies, research grants from:

- Abbvie
- BMS
- GS
- MSD
- Janssen
- ViiV
- Pfizer
- Novartis
- Astellas
- Basilea
- Correvio
- Zambon

How Antibiotic Resistance Happens



CDC, Antibiotic resistance threats in the United States, 2013



..e così via....

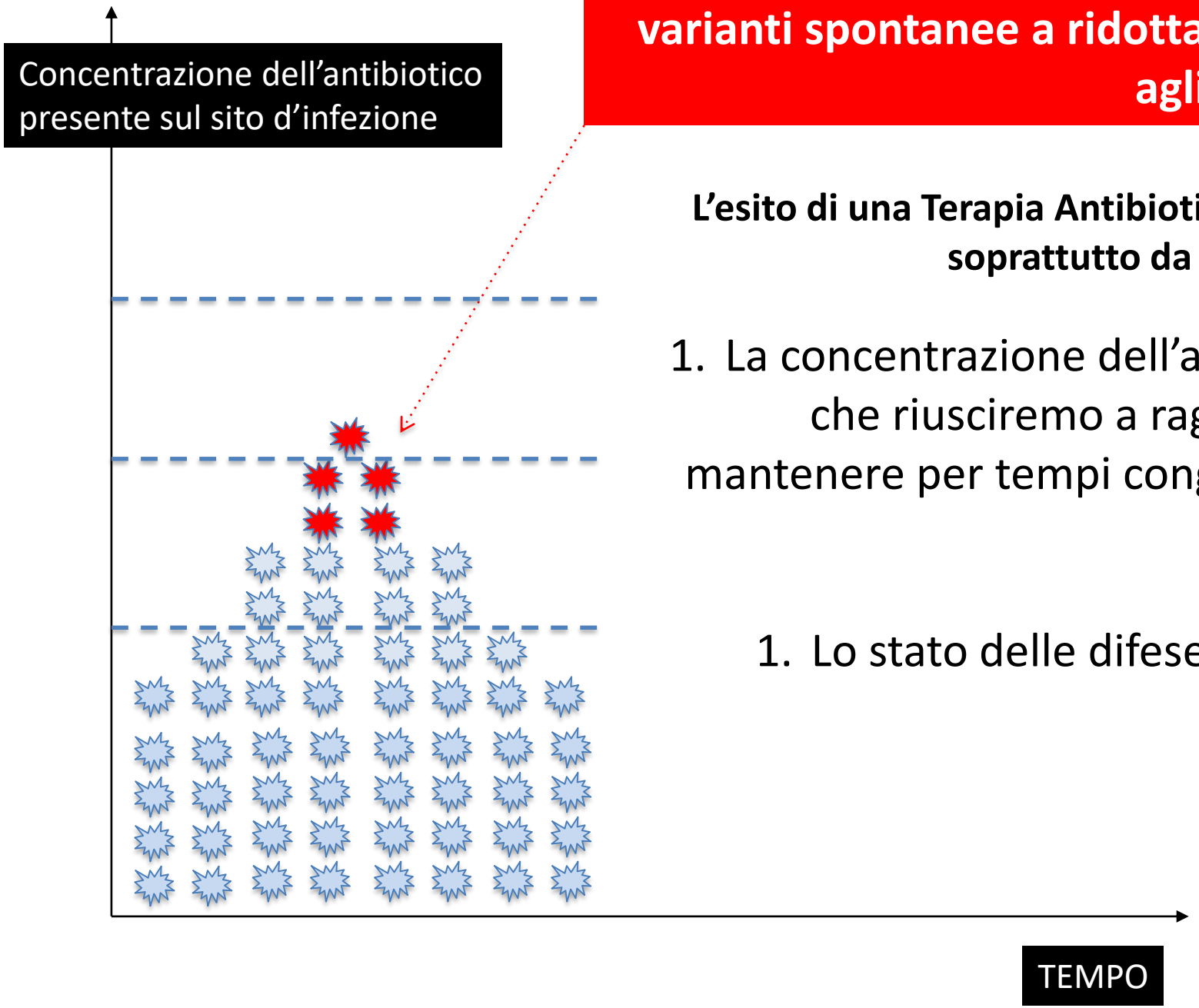
I batteri si moltiplicano per fissione binaria, replicando il proprio DNA:

Nel corso dei processi replicativi avvengono delle mutazioni spontanee, ovvero errori nella copia del DNA

Se questi errori sono compatibili con la vita si trasmettono alla progenie:

Fra i caratteri codificati da queste mutazioni sono comprese le resistenze agli antibiotici

In ogni popolazione batterica esistono varianti spontanee a ridotta sensibilità agli antibiotici



L'esito di una Terapia Antibiotica dipenderà soprattutto da due variabili:

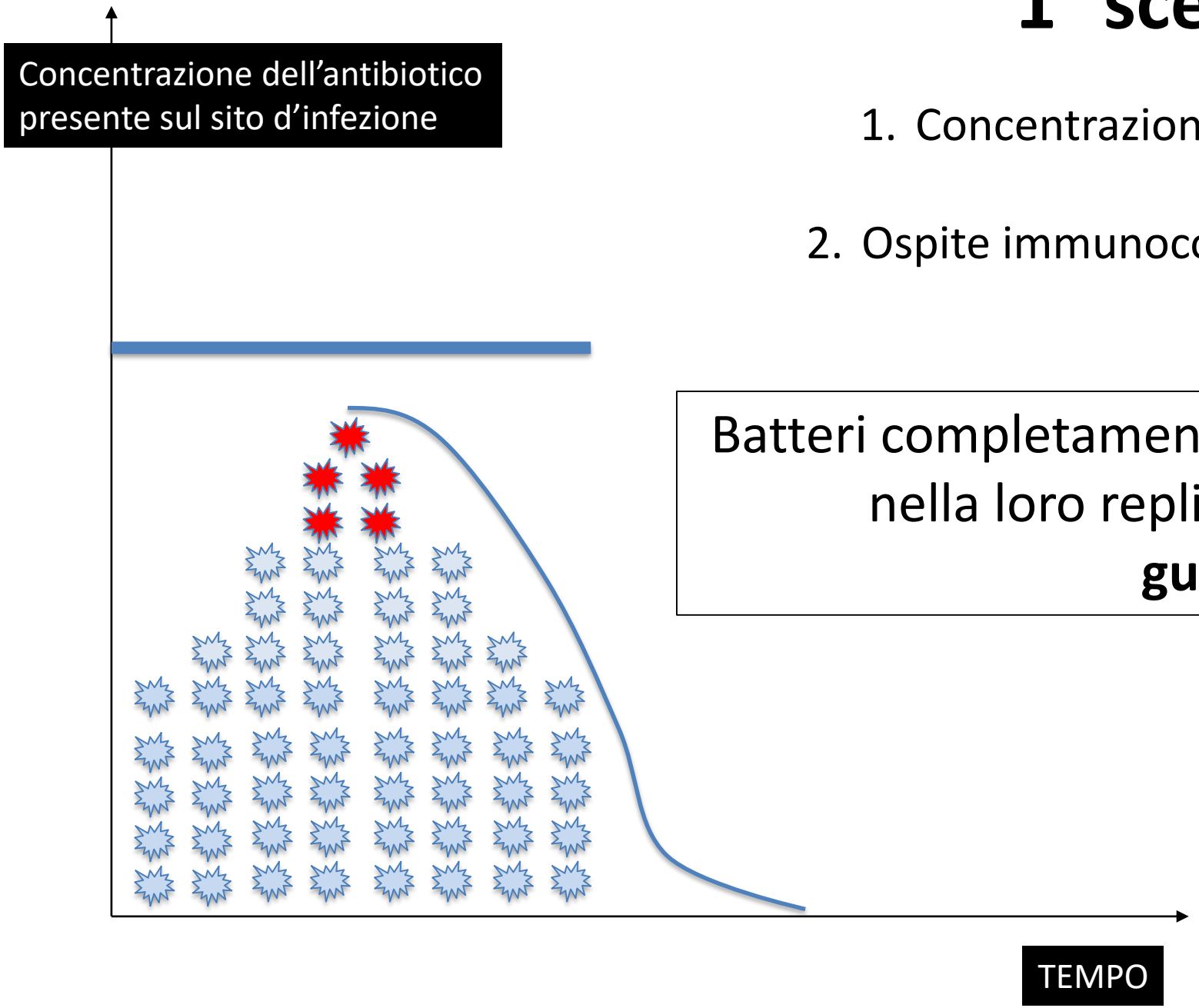
1. La concentrazione dell'antibiotico/i che riusciremo a raggiungere e mantenere per tempi congrui sul sito d'azione

1. Lo stato delle difese dell'ospite

1° scenario:

1. Concentrazioni adeguate

2. Ospite immunocompetente



Batteri completamente inibiti nella loro replicazione, **guarigione**

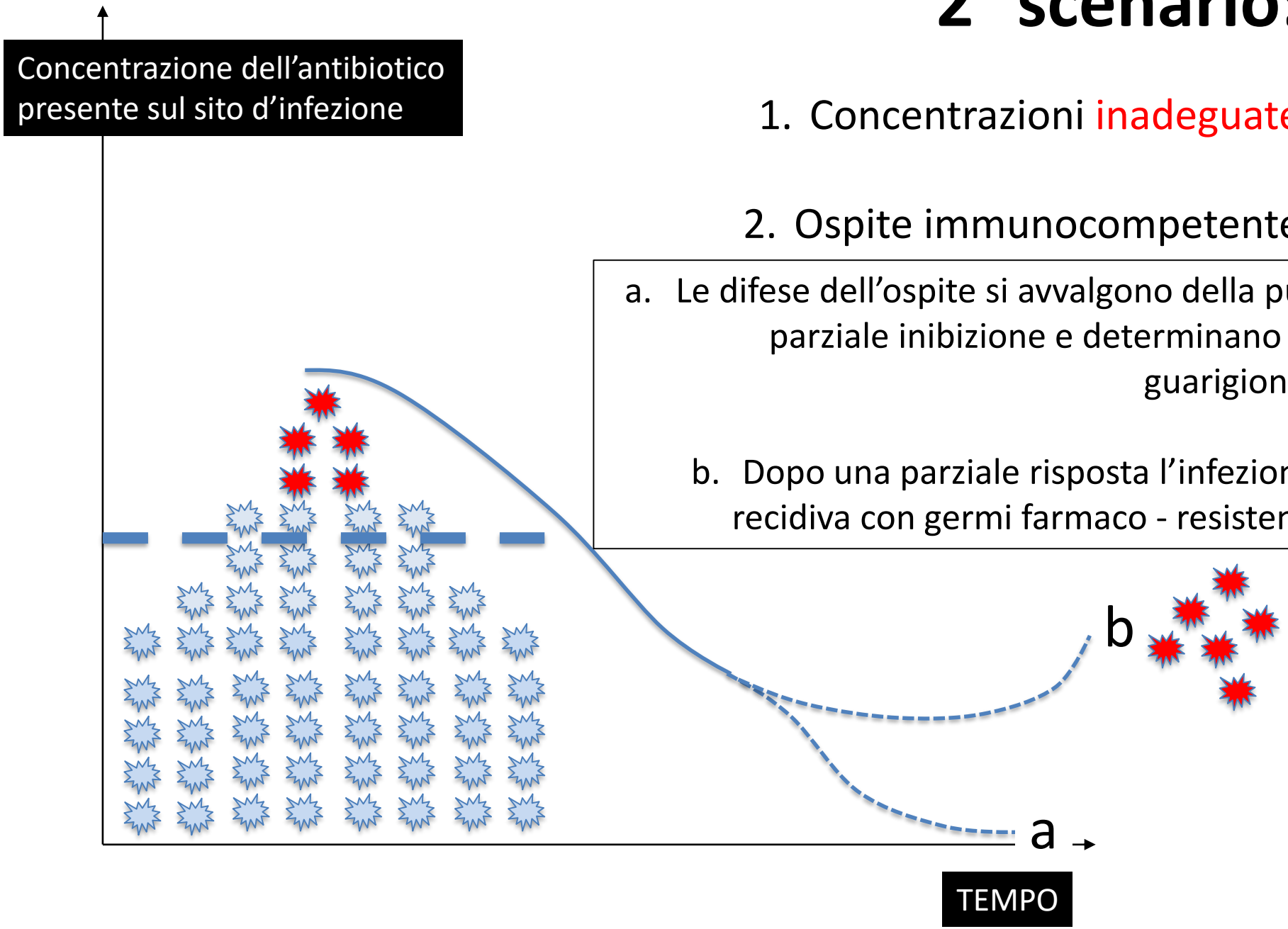
2° scenario:

1. Concentrazioni inadeguate

2. Ospite immunocompetente

   a. Le difese dell'ospite si avvalgono della pur parziale inibizione e determinano la guarigione;

   b. Dopo una parziale risposta l'infezione recidiva con germi farmaco - resistenti

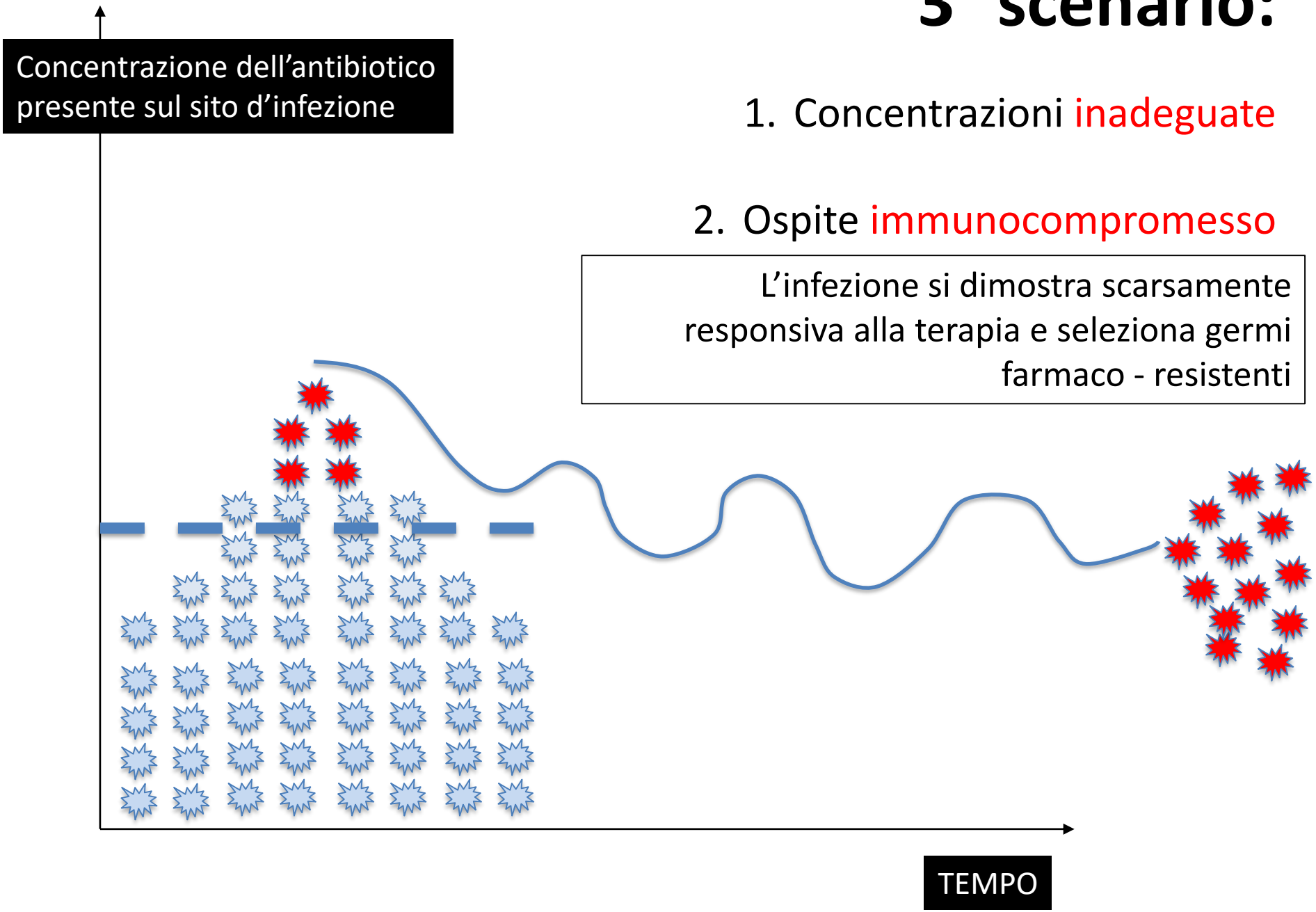


3° scenario:

1. Concentrazioni inadeguate

2. Ospite immunocompromesso

L'infezione si dimostra scarsamente responsiva alla terapia e seleziona germi farmaco - resistenti

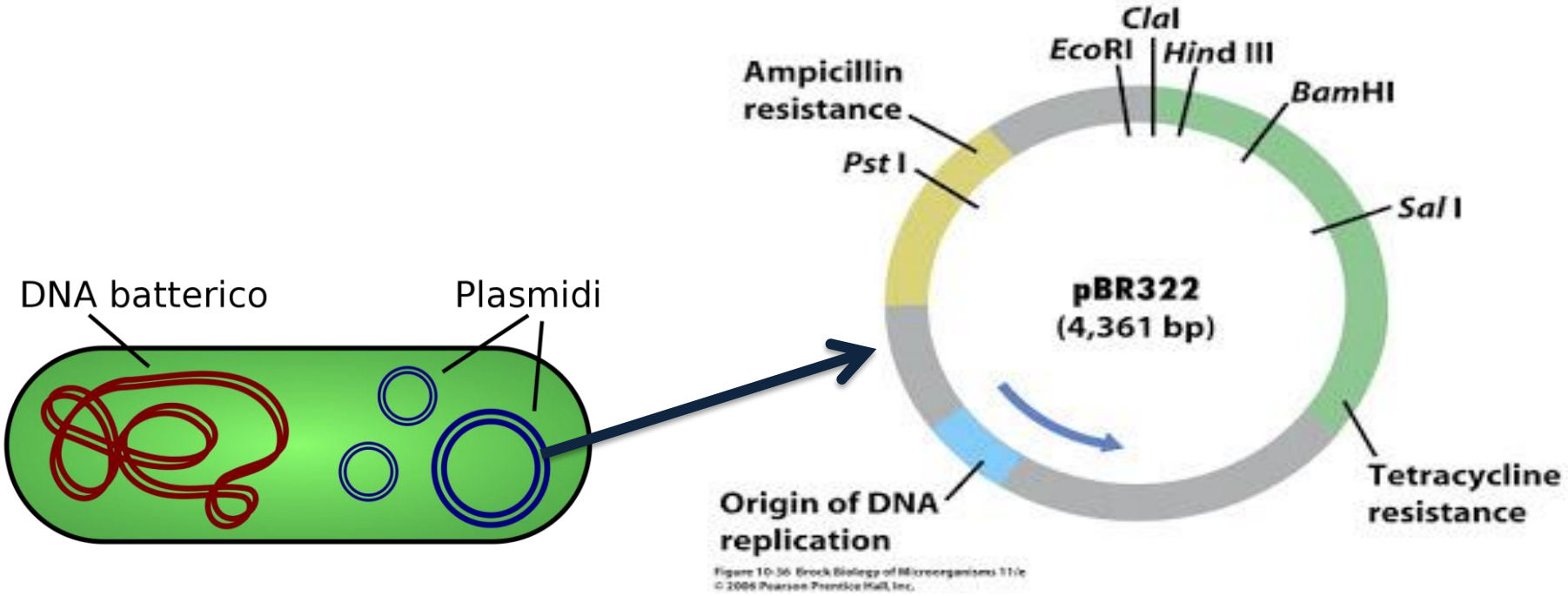


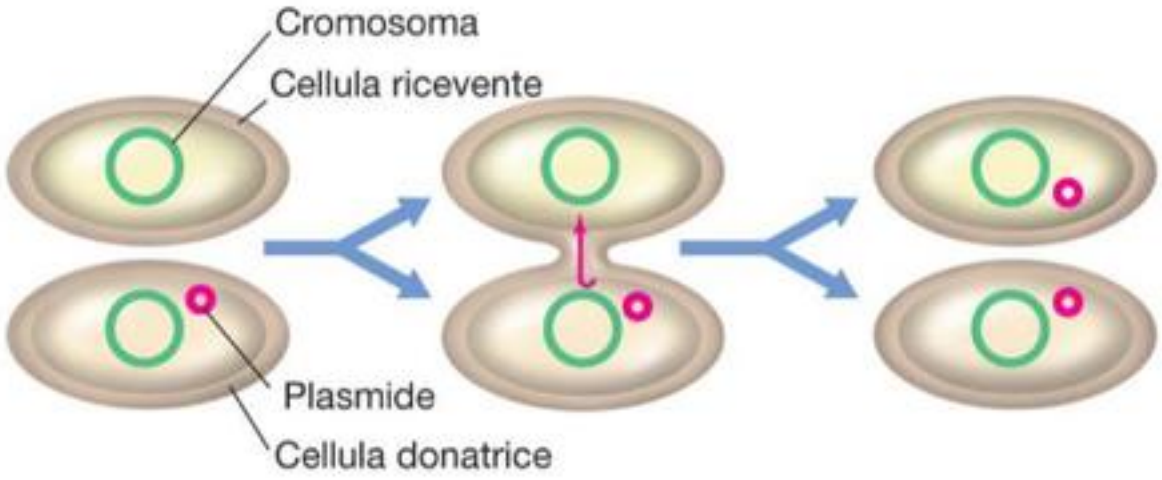
RESISTENZA BATTERICA: alcune semplici definizioni

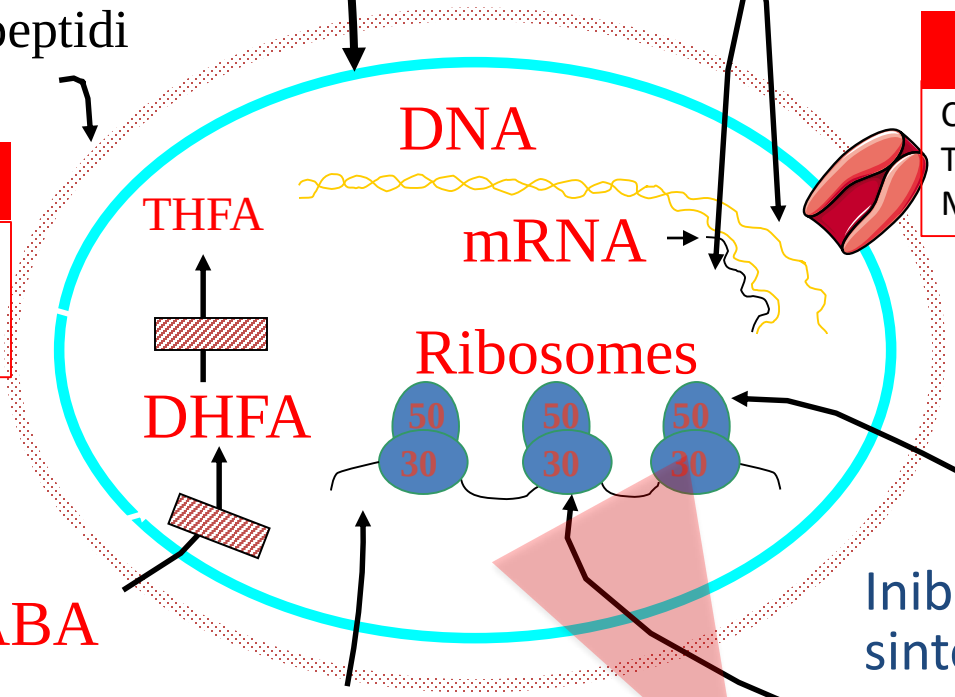
- Resistenza innata, intrinseca o costitutiva (c'è sempre stata….. a nostro sapere)

- Resistenza acquisita
  - Per selezione diretta
  - Per integrazione genica di elementi mobili

- Resistenza trasferibile (plasmidi, trasposoni ed integroni)


DNA batterico
Plasmidi
ClaI
EcoRI
Hind III
BamHI
Ampicillin resistance
Pst I
Sal I
pBR322
(4,361 bp)
Origin of DNA replication
Tetracycline resistance


Cromosoma
Cellula ricevente
Plasmide
Cellula donatrice



Formazione di pori e depolarizzazione della membrana

Daptomicina

Sintesi della parete batterica

ß-lattamici & Glicopeptidi (Vancomicina)

Bersaglio modificato

Chinoloni, Rifamicine, Vancomicina, Penicilline, Macrolidi, Aminoglicosidi

Sintesi dell'Acido folico

Trimethoprim Sulfonamidi

Enzimi inattivanti

B-lattamici, Aminoglicosidi, Macrolidi, Rifamicine

DNA gyrase

Chinoloni

RNA polimerasi DNA-dipendente

Rifampicina

Pompe ad efflusso

Chinoloni, Aminoglicosidi, Tetracicline, β-lattamici, Macrolidi

Macrolidi & Lincomicine

Inibizione della sintesi proteica

Tetracyclines

Errata traduzione nella sintesi proteica

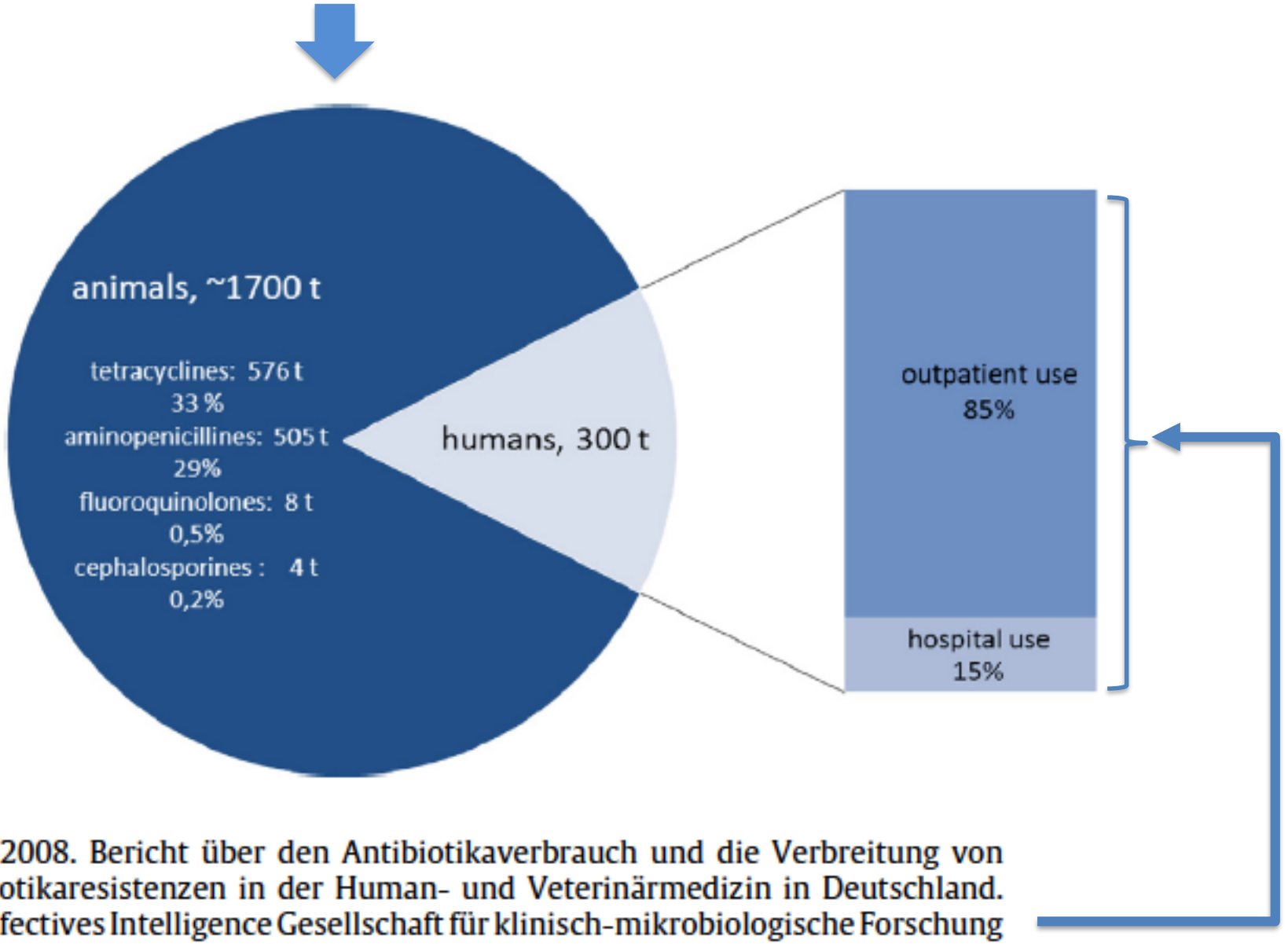
Aminoglicosidi

By-pass metabolico

Tetracicline, Sulfamidici, Vancomicina

Cohen. Science 1992; 257:1064

Fleischatlas, 2013. Fleischatlas – Daten und Fakten über Tiere als Nahrungsmittel. Edited by H.-B.-S. i K. m. B. u. L. M. Diplomatique, Berlin.



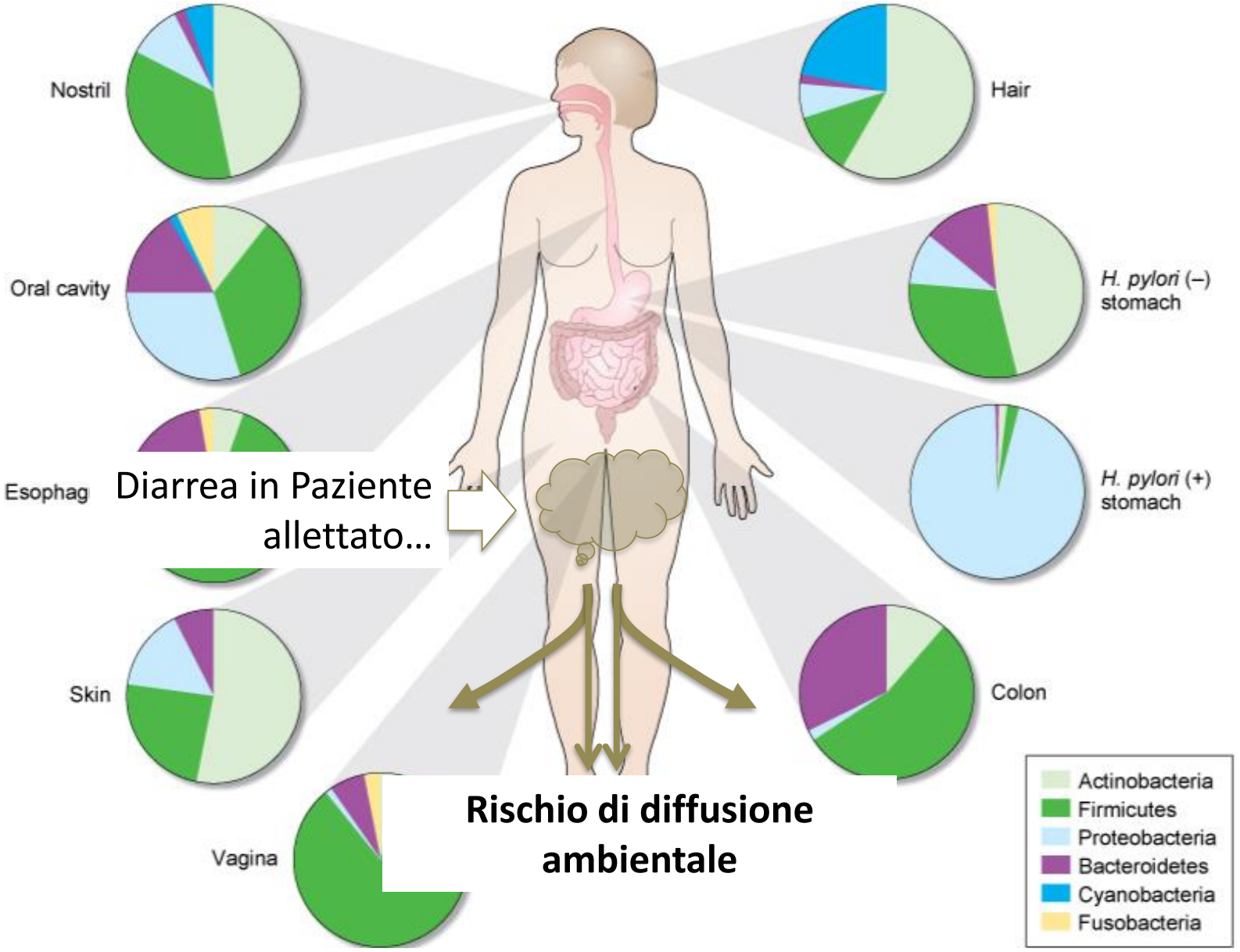
GERMAP, 2008. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland. Antiinfectives Intelligence Gesellschaft für klinisch-mikrobiologische Forschung und Kommunikation mbH, Rheinach, ISBN 978-3-00-0250972.

Accanto agli scenari relativi ad una Terapia Antibiotica somministrata con specifici scopi terapeutici, occorre considerare come lo stesso scenario – **di presenza di varie concentrazioni di antibiotici in presenza di specie batteriche diverse** – si realizza:

Nello stesso individuo in sedi non interessate dall'infezione che vogliamo curare (e.g. intestino)

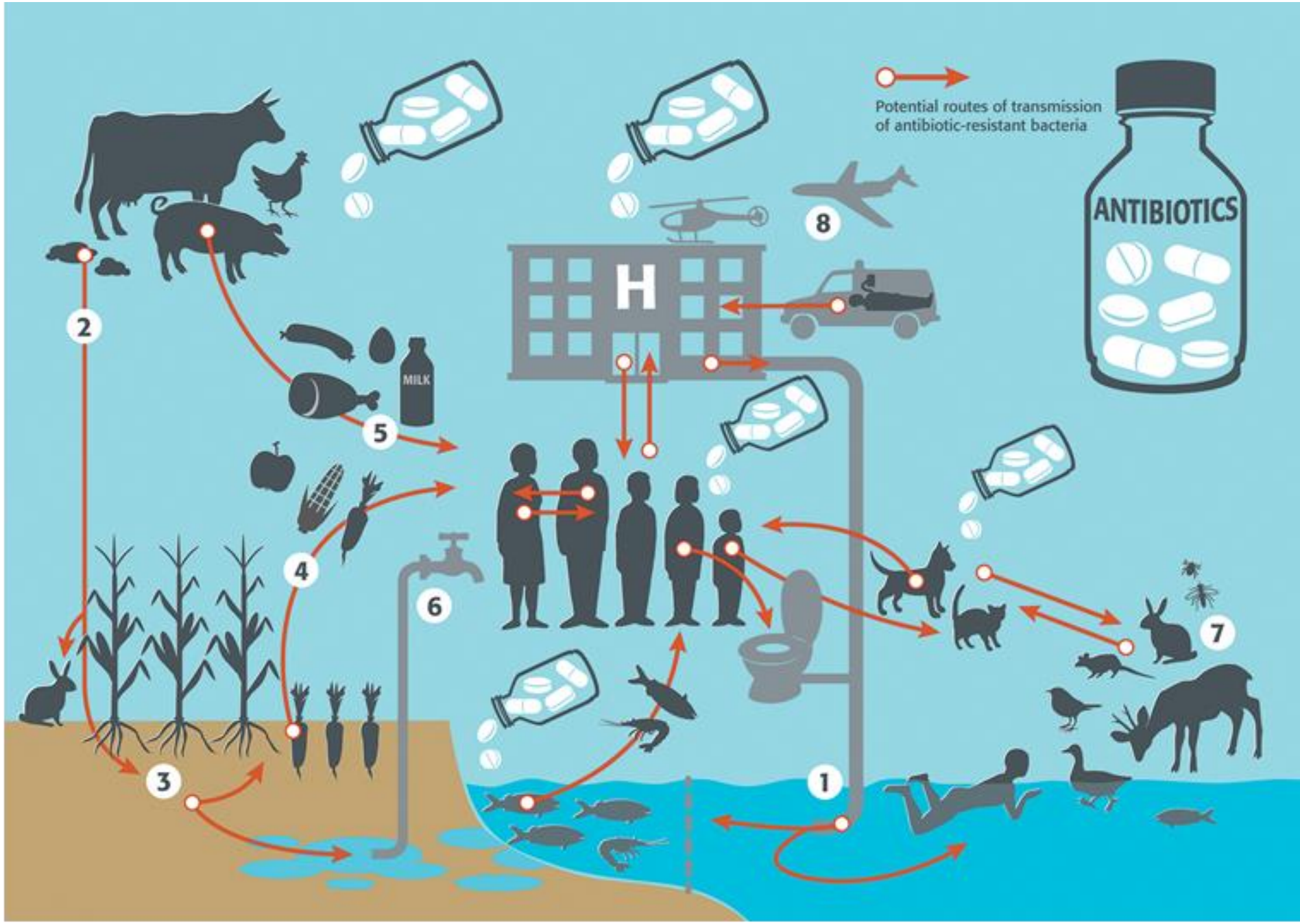
Più indietro nella gerarchia ambientale, nelle acque e nel cibo compresi nelle filiere di preparazione ed erogazione

Diffusione di specie batteriche farmaco - resistenti



Composizione del “Microbioma” umano secondo le diverse sedi anatomiche

L'Agenzia europea per la regolamentazione sui medicinali (EMA) ha fissato una soglia per l'uso agricolo della colistina che dovrebbe essere limitata ad un massimo di 5 mg per chilogrammo per il bestiame, onde evitare la pericolosa diffusione della resistenza batterica al farmaco, verificatasi lo scorso anno.


Potential routes of transmission of antibiotic-resistant bacteria
ANTIBIOTICS
H
MILK
1
2
3
4
5
6
7
8

Possiamo distinguere alcuni "MacroAmbienti" nei quali ed attraverso i quali l'Antibiotico Resistenza viene selezionata e si diffonde…….

Reparti, Procedure ad Alto Rischio

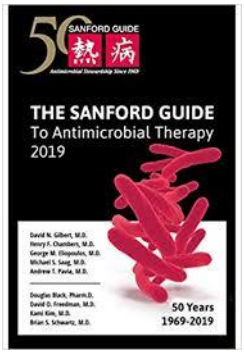
Ospedali, RSA

Medicina di Base e del Territorio

Ambiente Rurale, Filiera del Cibo e delle Acque

Possiamo distinguere alcuni “MacroAmbienti” nei quali ed attraverso i quali l’Antibiotico Resistenza viene selezionata e si diffonde…….

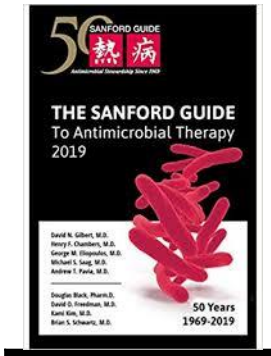
REPARTI AD ALTO RISCHIO



The Sanford Guide to Antimicrobial Therapy 2019

GRAM +

Germe:	Resistente a:
Enterococcus faecium *Enterococcus faecalis*	Vancomicina (VRE), Ampicillina, Penicillina G, Gentamicina (reistenza di alto livello)
Staphylococcus aureus	Vancomicina (VISA o VRSA), β-lattamici (eccetto il Ceftaroline e Ceftobiprole)
Streptococcus pneumoniae	Penicillina G (MIC ≥ 4ug/mL)



The Sanford Guide to Antimicrobial Therapy 2019

GRAM -

Germe:	Resistente a:
Acinetobactercalcoloaceticus-baumanni complex	Tutti i β-lattamici (eccetto sulbactam), Aminoglicosidici, Fluorchinoloni, Trimetoprim-sulfametossazolo
Produttori di β-lattamasi a spettro esteso (ESBL)*:P.aeruginosa, E.coli, K.pneumoniae,* Enterobacteriaceae	Tutte le Cefalosporine, Aminoglicosidici, Fluorchinoloni, Trimetoprim-sulfametossazolo
Enterobacteriaceae produttrici di OXA-48	Tutte la Penicilline, Aminoglicosidici, Fluorchinoloni, Trimetoprim-sulfametossazolo
Enterobacteriaceae produttrici di KPC	Tutte le Penicilline, Cefalosporine, Aztreonam, Carbapenemi, Aminoglicosidici, Fluorchinoloni, Trimetoprim-sulfametossazolo
GRAM – produttori di Metallo-carbapenemasi	Tutti i β-lattamici (eccetto Aztreonam), Aminoglicosidici, Fluorchinoloni, Trimetoprim-sulfametossazolo
Stenotrophomonas maltophilia	Tutti i β-lattamici, Aminoglicosidici, Fluorchinoloni

ECDC country visit to Italy to discuss antimicrobial resistance issu

9-13 January 2017

- The proportion of ***Klebsiella pneu*** carbapenems **increased from 1.3** resistance (third-generation ceph

Klebsiella pneumoniae resistant to Carbapenems

1.3% in 2005 >>> 33.5% in 2015

Escherichia coli resistant to 3rd gen Cephalosporins, Fluorquinolones, Aminoglycosides

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are resistant to
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- The proportion of ***Acin*** carbapenems is **very h** resistance (fluoroquin and 72.6% (2015).

Acinetobacter spp. resistant to 3rd gen Cephalosporins, Fluorquinolones, Aminoglycosides & Carbapenems

72.6% - 83% in 2012 - 2015

Staphylococcus aureus MRSA
44.3% (2000) >> 34.1% (2015)

Enterococcus faecium VancoR
15% (2001) >> 11.2% (2015)

that are resistant to
44.3% in 2000 to **34.1%** in
esistant to vancomyin is
.2% in 2015.

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- One particular observation is that Italy reports the second highest percentage of ***K.pneumoniae*** blood isolates resistant to the last-line group of antibiotics, the carbapenems (33.5%, 2015 data from EARS-Net), and Italian experts have reported an **endemic situation** in the country regarding carbapenemase-producing, carbapenem resistant Enterobacteriacae (expert self-assessment from the European Survey on Carbapenamase-Producing Enterobacteriaceae - EuSCAPE project).

- Moreover, the healthcare system in the country remains at risk of other types of carbapenem-resistant ***K. pneumoniae*** or ***E. coli*** being introduced that could rapidly spread and exacerbate the already endemic situation in the country.

- A recent development highlighted by the EuSCAPE project is the rapid and country-wide dissemination of colistin resistant, **carbapenem-resistant *K. pneumoniae*** and the detection of **pandrug-resistant isolates** - i.e. isolates resistant to all antibiotics.

- For other bacteria, the percentages of resistance reported by Italy to EARS-Net are **generally above the EU/EEA average** and **often among the highest for all EU/EEA Member States.**

Elementi di Stewardship Antimicrobica

Antimicrobial stewardship has been defined as the optimal selection, dose and duration of an antimicrobial that results in the best clinical outcome for the treatment of infection with minimal toxicity to the patient and minimal impact on subsequent resistance development.

McGowan JE, Gerding DN. Does antibiotic restriction prevent resistance? New Horiz 1996; 4: 370-376.

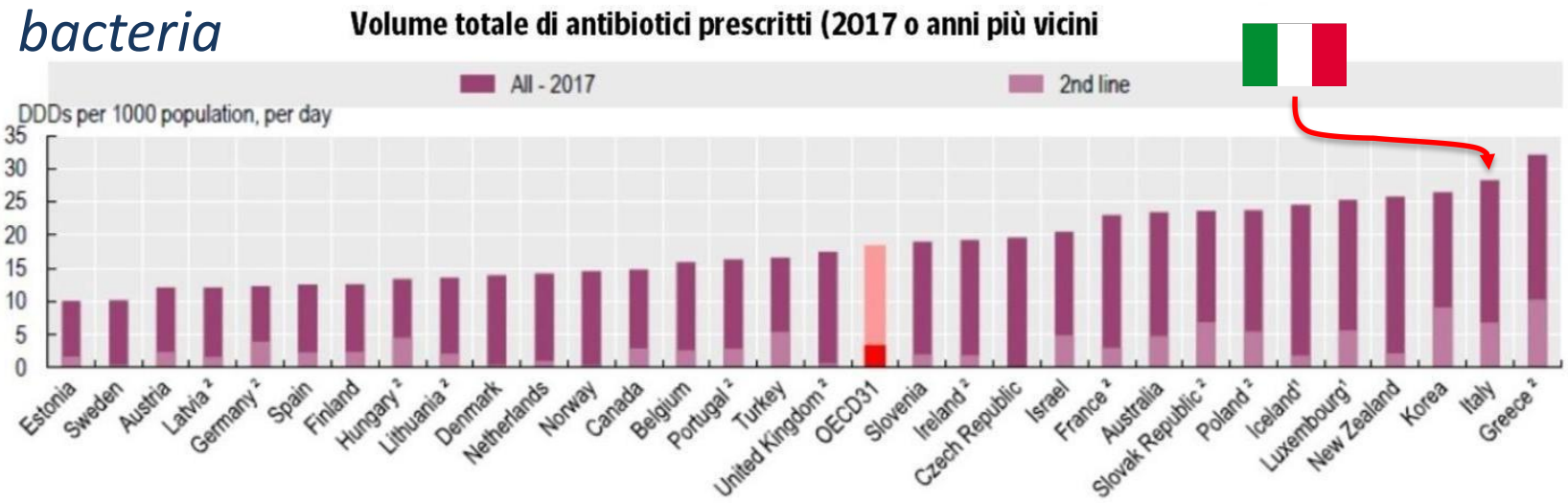
Shlaes DM, Gerding DN, John JF, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance:guidelines for the prevention of antimicrobial resistance in hospitals. Infect Control Hosp Epidemiol 1997; 18: 275-291.

Owens RC, Ambrose PG. Antimicrobial stewardship and the role of pharmacokinetics-pharmacodynamics in the modern antibiotic era. Diagn Microbiol Infect Dis 2007; 57: 77S-83S

Background: Antibiotic Misuse

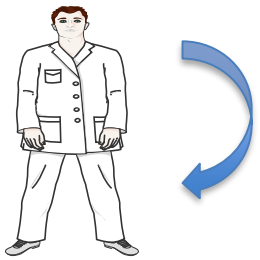
- **Between 20-50% of antibiotic prescriptions are either unnecessary or inappropriate**
  - *Given when they are not needed*
  - *The wrong antibiotic is chosen to treat an infection*
  - *Continued when they are no longer necessary*
  - *Given at the wrong dose*
  - *Broad spectrum agents are used to treat very susceptible bacteria*

Fishman N. Am J Med. 2006 Jun;119(6 Suppl 1):S53-61

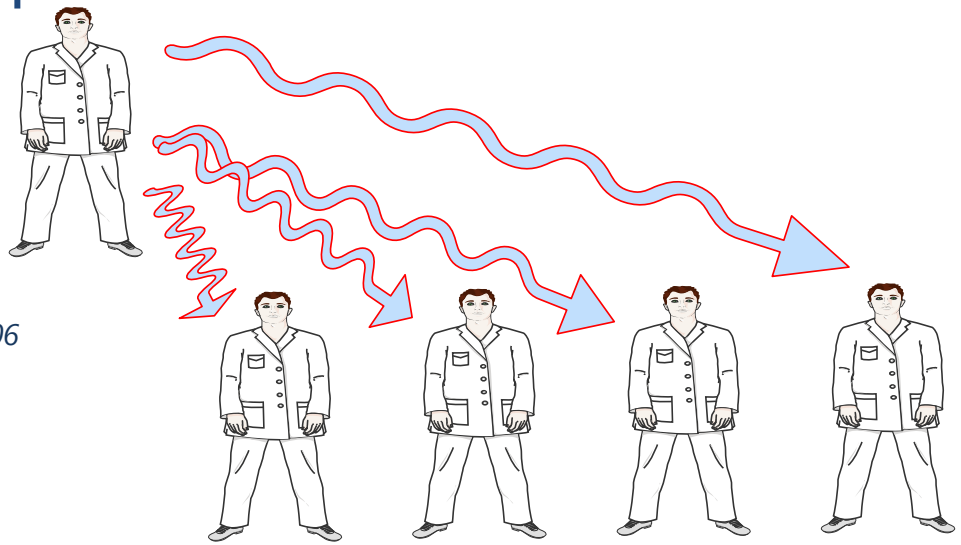


Antibiotic Use Drives Resistance

- For an individual, getting an antibiotic increases a patient's chance of becoming colonized or infected with a resistant organism



- Increasing use of antibiotics in healthcare settings increases the prevalence of resistant bacteria in hospitals

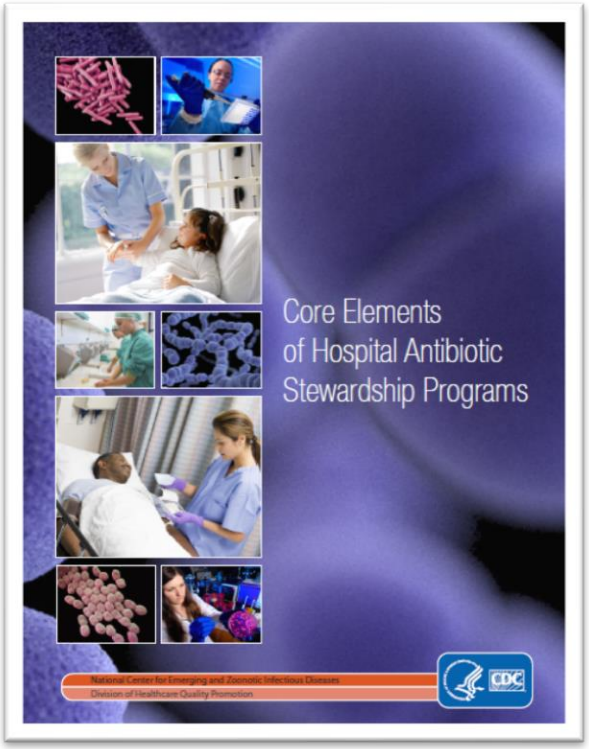


Patel G et al. Infect Control Hosp Epidemiol 2008;29:1099-1106
Zaoutis TE et al. Pediatrics 2005;114:942-9
Talon D et al. Clin Microbiol Infect 2000;6:376-84

Antimicrobial Stewardship

- **Strategic multidisciplinary and facility specific efforts to optimize antimicrobial prescribing**
  - Right drug
  - Right dose
  - Right duration
  - Recognize when not needed

Core Elements of Antimicrobial Stewardship Programs



- Leadership Commitment
- Accountability
- Drug Expertise
- Action
- Tracking
- Reporting
- Education

Leadership Commitment

- Leadership support for efforts to improve and monitor antibiotic prescribing
- Assurance that involved staff has time, authority, and accountability
- Funding can augment efforts
  - Staff time to accomplish goals
  - Training for staff
  - IT support
- Stewardship programs will often pay for themselves

Key Supporters

- Clinician groups
- Infection preventionists
- Quality improvement staff
- Laboratory staff
- Nurses

Drug Expertise

- Identify a pharmacist to be involved
- Formal training in infectious diseases and/or antibiotic stewardship is beneficial
- Pharmacist can assist in
  - Identifying areas for improvement, and
  - Monitoring use

Stewardship Program Functions

- Develop guidelines, policies, and protocols that support optimal prescribing

- Prioritize efforts
  - Specific conditions
  - Particular units or prescriber groups
  - Specific antimicrobial drugs

- Educate
- Monitor and report

Persuasive Antimicrobial Stewardship

Pros	Cons
• Words • Dialogue • Patients • Diseases • News • References • Problem-sharing	• Time-consuming • Few metrics • Outcome • LOS • Audit • Feedback

Restrictive Antimicrobial Stewardship

Pros	Cons
• Numbers • Metrics • Technique • Link to health economy • Pharmaco-economy • Audit • Feedback	• Choice of metrics • Issue of costs • Technical team • Delays in treatment • Breakdown in trust by clinical team • Measurement (i.e. DDD)

Antimicrobial Stewardship: Philosophy versus Practice

Dodds Ashley ES et al Clin Infect Dis 2014; 59(S3): S112-121

- **Impact difficult to measure**
- **Outcome and process measures as metrics**
- **Antimicrobial use & costs are indicators most used**
  - By institutions to justify…. The effectiveness of AS programs
- **Use of more meaningful outcomes has been constrained by:**
  - Difficulties inherent to those measures
  - Lack of funding and resources
  - Inadequate study designs
- **AS programs can be made more credible by:**
  - Refocusing to target specific disease states
  - Reassessing the usefulness of current metrics
  - Integrating AS programs into institutional quality & safety efforts

Bestiario Borges* Classificazione degli animali da UNA CERTA ENCICLOPEDIA CINESE di Borges*

- a) appartenenti all'imperatore,
- b) imbalsamati,
- c) addomesticati,
- d) maialini da latte,
- e) sirene,
- f) favolosi,
- g) cani in libertà,
- h) inclusi nella presente classificazione,
- i) che si agitano follemente,
- j) innumerevoli,
- k) disegnati con un pennello finissimo di peli di cammello,
- l) et cetera,
- m) che fanno l'amore,
- n) che da lontano sembrano mosche

Aspetti talvolta ambigui….

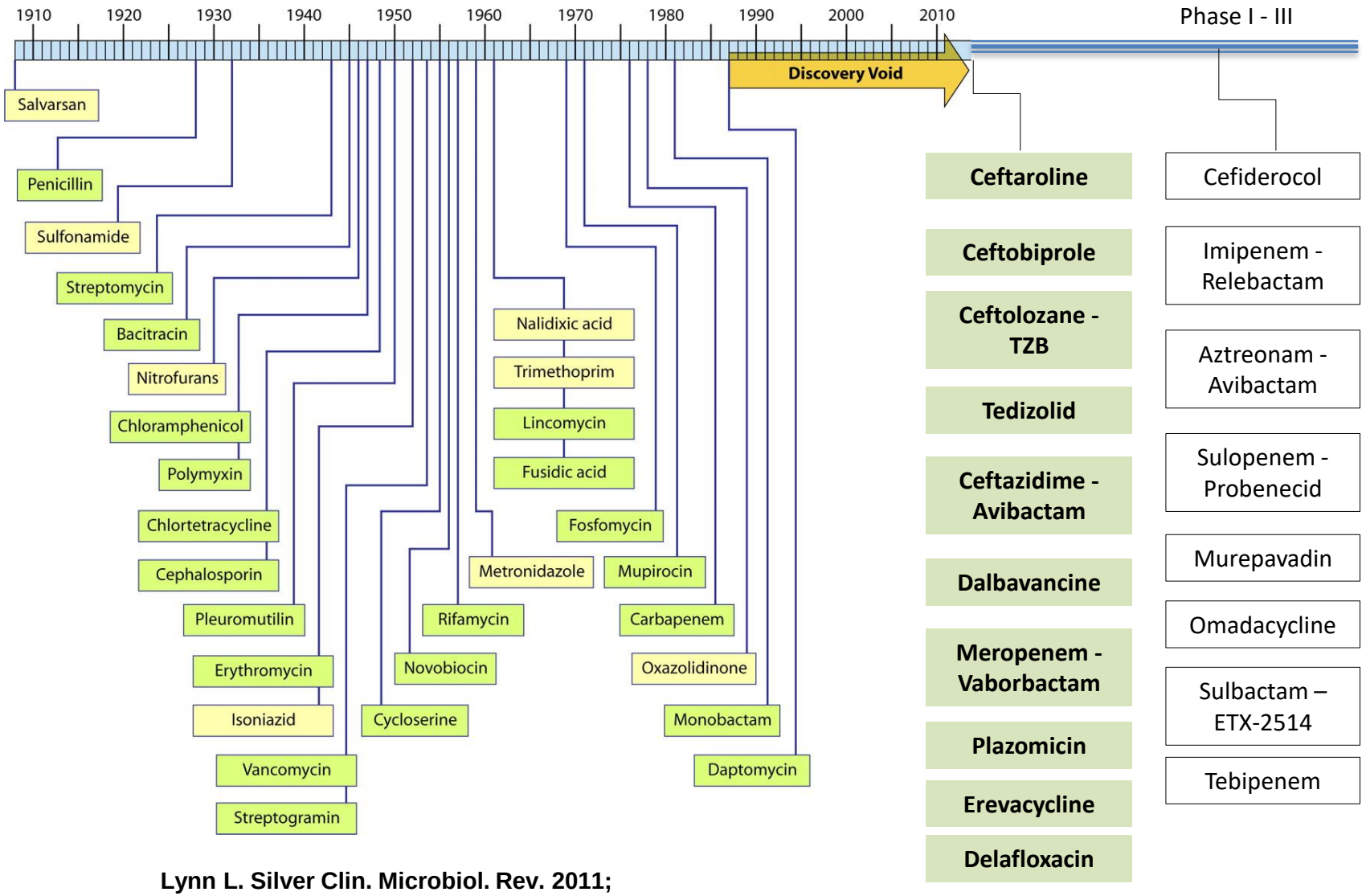
- ✓ Competenza di Chi se ne occupa
- ✓ Individuazione della Leadership in seno al Gruppo o Comitato
- ✓ Impatto geografico (e.g. cittadino, provinciale, sub-regionale, regionale)
- ✓ Individuazione degli obiettivi:

  - Sorveglianza
  - Correzione delle principali “devianze” prescrittive
  - Contenimento della diffusione di specifici fenomeni di Resistenza antimicrobica
  - Gestione oculata delle nuove risorse


Antibiotici nei Reparti ad AR
Antibiotici nei grandi Ospedali
Antibiotici negli Ospedali periferici
Antibiotici nella Medicina del Territorio (MdB)
Antibiotici nell'Industria Alimentare

RICERCA, INNOVAZIONE, SPAZIO CONCESSO AL “DRIVER” FIN QUI PIU’ EFFICACE, IL MERCATO

Illustration of the “discovery void.” Dates indicated are those of reported initial discovery or patent.



Lynn L. Silver Clin. Microbiol. Rev. 2011;
doi:10.1128/CMR.00030-10

E’ facile quindi identificare un “vuoto” produttivo, e qualche spunto interpretativo:

- Mancanza di idee nuove;
- Affollamento di scienziati sulla biologia molecolare a discapito degli studi di fisiologia batterica;
- Crescente complessità normativa dell’iter sperimentale, allungamento dei tempi e riduzione dei margini di guadagno;
- Furto di competenze di vertice verso ambiti maggiormente remunerativi da parte di Industria ed Accademia (e.g. HIV, HCV);
- Scarsa competenza media dello staff regolatorio;
- Discriminazione “elettorale” del personale medico (e.g. Medici di Base vs Medici in Servizo Ospedaliero), calo delle motivazioni

Ma quando l'innovazione, nonostante tutto, arriva, I risultati si possono vedere (se si vuole)….

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Journal of Antimicrobial Chemotherapy (2003) **51**, 1431–1434
DOI: 10.1093/jac/dkg262
Advance Access publication 13 May 2003

JAC

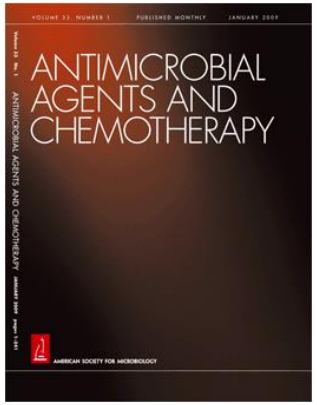
Intrapulmonary penetration of linezolid

David Honeybourne[1]*, Caroline Tobin[2], Gail Jevons[3], Jenny Andrews[3] and Richard Wise[3]

Patient number	Time after dose (h)	Serum (mg/L)	Macrophage (mg/L)	Epithelial lining fluid (mg/L)	Mucosal biopsy (mg/kg)
1	2.90	15.20	3.00	35.60	12.90
2	3.00	17.00	3.70	18.90	12.90
3	3.00	17.40	7.20	23.70	15.00
4	3.60	10.10	14.40	NDL	7.40
5	3.65	19.60	5.90	39.60	17.80
6	6.30	13.10	9.90	21.90	13.10
7	6.70	9.20	3.10	25.70	8.10
8	7.10	9.50	0.50	20.00	5.50
9	7.20	8.60	23.70	13.10	6.40
10	7.50	14.30	9.60	52.40	8.00
Mean	5.10	13.40	8.10	25.09	10.71
S.D.	2.01	3.92	6.85	14.59	4.15
S.E.M.	0.64	1.24	2.17	4.62	1.31

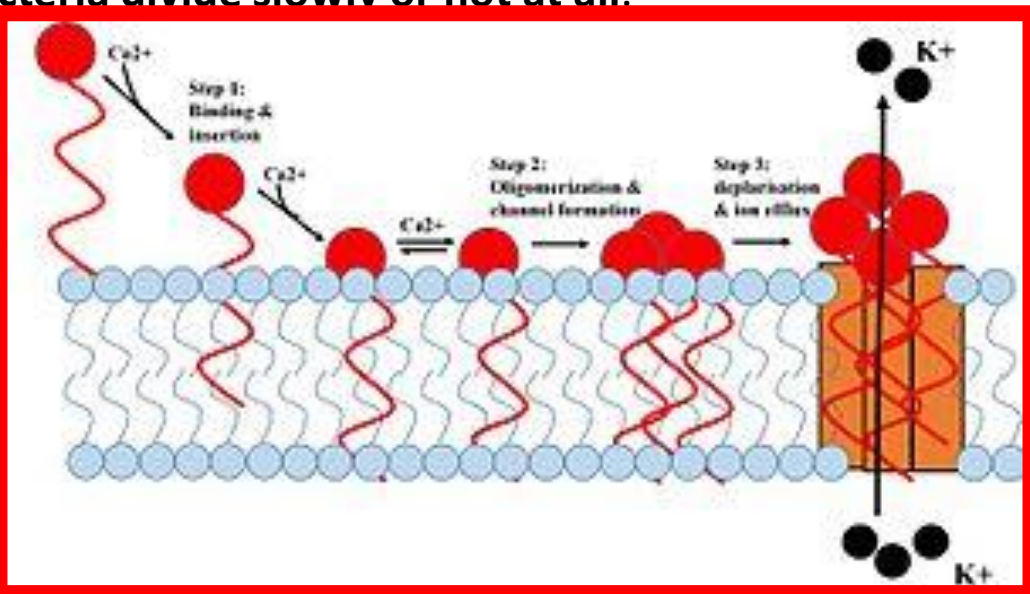
NDL, no detectable level; S.D., standard deviation; S.E.M., standard error of the mean.

Bactericidal Action of Daptomycin against Stationary-Phase and Nondividing *Staphylococcus aureus* Cells.
Mascio TM, et al. AAC 2007; 51: 4255-4260.



Most antibiotics with bactericidal activity require that the bacteria **be actively dividing** to produce rapid killing. However, in many infections, such as endocarditis, prosthetic joint infections, and infected embedded catheters, the **bacteria divide slowly or not at all**.

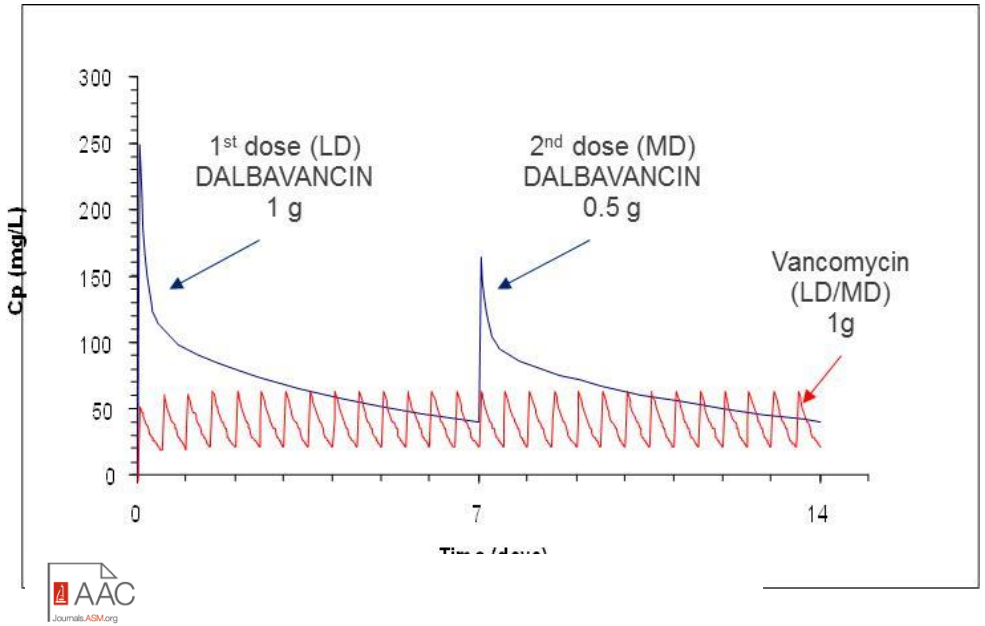
In a study comp cin demonstrated **faster bacterici** cin, and vancomycin. In lted by the metabolic inhib or erythromycin, daptomycin (10 -log reduction) within 2 h. In c bactericidal activity. Daptor ld-arrested *S. aureus*, which v nd nafcillin. The data presented asses of antibiotics, **the quire cell division or active metab** t action on the bacterial memb



1. Daptomycin binds and inserts into the cell membrane.
2. It aggregates in the membrane.
3. It alters the shape of the membrane to form a hole, allowing ions in and out of the cell easily.

Dalbavancin: Unique Pharmacokinetic Profile

Dalbavancin dosed with 1,000 mg IV on Day 1 and 500 mg IV on Day 8



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Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[c]* Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]

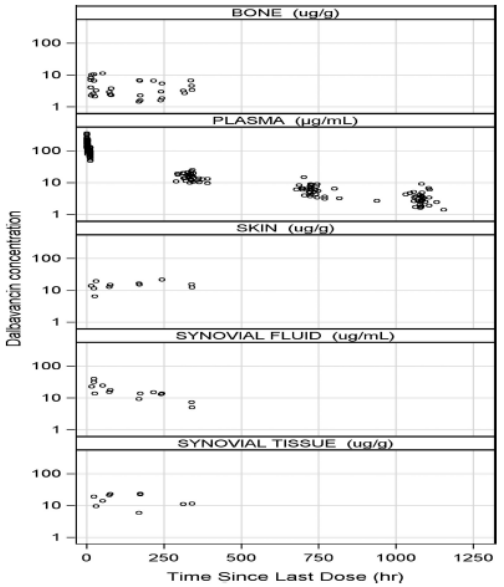
Dalbavancin's pharmacokinetic profile enables:

- Broad tissue distribution
- Continuous cidality
- Once weekly dosing
- Maintenance of high plasma concentration

Dorr, JAC 2005;55 Supp S2:ii25; data on file

Comparative MIC90 (μg/ml) of selected agents and dalbavancin tested against Worldwide clinical isolates (2002)*

	S. aureus (1,815) OX-S	*S. aureus* (1,177) OX-R	β-hemolytic streptococci (234)	viridans group streptococci (30) PCN-R
Dalbavancin	**0.06**	**0.06**	**0.06**	**0.03**
Teicoplanin	1	2		
Vancomycin	1	2	0.5	0.5
Oxacillin	S	R	PCN = 0.06	R
Linezolid	2	2	1	1



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Ilaria Zedda

Alice Ianniello

Elisa De Vivo

Luca Paglietti

Miriam Antonucci

Mattia Trunfio

Elena Salvador

Giulia De Zan

Walter Rugge

Acknowledgments

THE UNIVERSITY *of* LIVERPOOL

LIVERPOOL:

David Back

Saye Khoo

Andy Owen

Marco Siccardi

SSAT ST STEPHEN'S AIDS TRUST

LONDON:

Marta Boffito

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