What makes an antibiotic the right antibiotic ?

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Disclosures

Industry support for work on investigational compounds from

- Cempra Pharmaceuticals [1]
- GSK
- Melinta Therapeutics [2]
- The Medicine Company [3]
- MerLion Pharmaceuticals
- Trius Therapeutics [4]
- Debiopharm

Non-profit support from

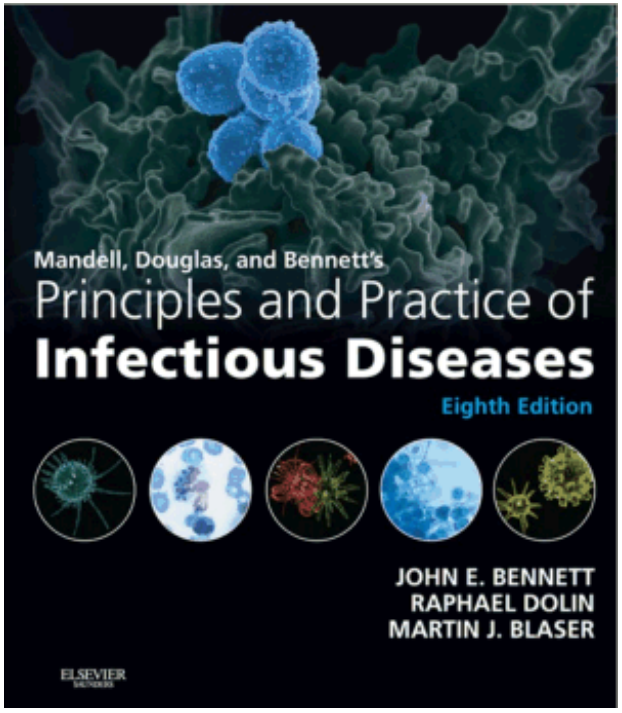
- the *Fond de la Recherche Scientifique* (F.R.S.-FNRS)
- the *Région Wallone*
- the European Union (FP7 programme)

Influenced by my participation to the

- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
- the Governance Body of DRIVE-AB (2014-2017)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

[1] merged in 2017 with and renamed as Melinta Therapeutics
[2] formerly RibX Pharmaceuticals; world rights holder for delafloxacin (with license to Menarini for EU and other countries)
[3] antibiotic portfolio acquired by Melinta Therapeutics in 2018
[4] acquired by Cubist (2014), which was then acquired by Merck (2016)

The right antibiotic ? I always wondered…



https://expertconsult.inkling.com/read/mandell-douglas-bennetts-infectious-diseases-8/mandell-douglas-and-bennetts/cover

Chapter 17:
Principles of Anti-infective Therapy
George M. Eliopoulos
Robert C. Moellering Jr.*

"In choosing the appropriate antimicrobial agent for therapy for a given infection, a number of factors must be considered.

- First, the **identity of the infecting organism must be known** or, at the very least, it must be possible to arrive at a statistically **reasonable guess as to its identity** on the basis of clinical information.
- Second, information about the **susceptibility of the infecting organism**, or **likely susceptibility**, must be as accurate as possible.
- Finally, a series of f**actors specific to the patient who is being treated** *(and his/her disease*) must be considered to arrive at the optimal choice of antimicrobial agent. "

Here are the questions …

When choosing an antibiotic, do we know

1. for the organism
   - its identity and whether it is causal or not
   - its susceptibility to and the main key properties of the proposed antibiotic
2. for the patient
   - the antibiotic effectiveness in the specific disease
   - how to dose the antibiotic appropriately
   - how to prevent / avoid patient- and drug-related side effects
3. for Society
   - how to prevent emergence of resistance
   - how to get "value for money"

Please, think about what YOU would answer !

Possible answers for the organism …

When choosing an antibiotic, do we know

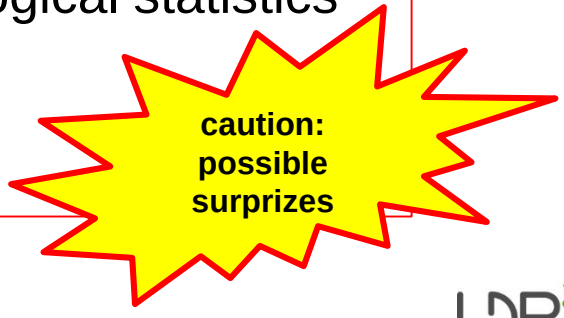
1. for the organism
   - **its identity and whether it is causal or not ?**

If sample(s) is (are) available, use of all "possible" techniques

- Gram stain and direct microscopy examination…
- rapid immunological and molecular techniques…
- culture and identification (galleries / MALDI-TOF)…
- quantitative cultures

If no sample is available… we must use "bacteriological statistics"

- likelihood to cause a specific infection
- endogenous and/or environmental presence



Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - **its susceptibility to the proposed antibiotic**

Susceptibility

- are *in vitro* methods predictive (and which ones to use) ?
- which interpretive criteria ?

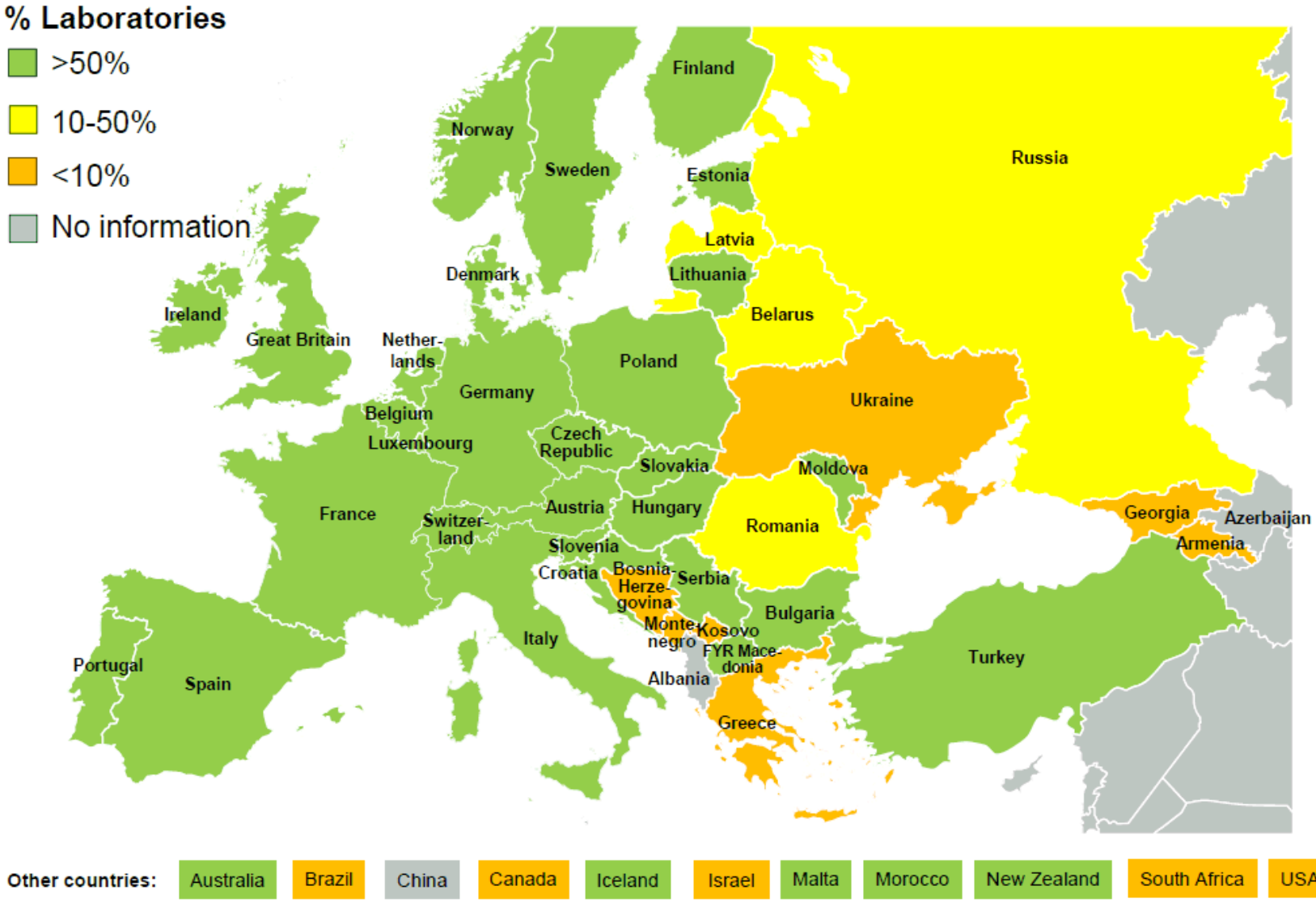
Know the limits of your methods …

EUCAST
European Society of Clinical Microbiology and Infectious Diseases
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

CLSI

FDA U.S. FOOD & DRUG ADMINISTRATION

Implementation of EUCAST breakpoints, January 2018



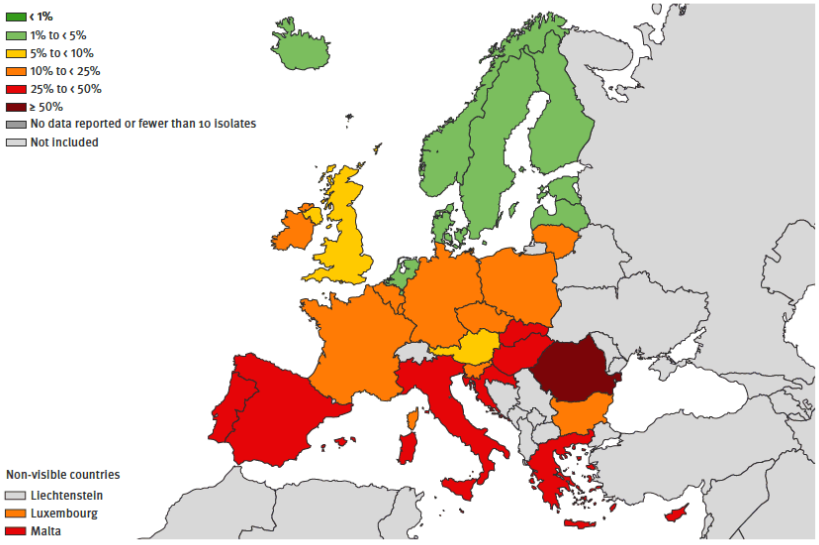
Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - **its susceptibility to the proposed antibiotic**

Epidemiological studies are critical for global antibiotic policy…

Figure 3.25. *Staphylococcus aureus*. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2016



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http://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-Europe-2016.pdf

JCM Journals.ASM.org

Xiao et al. J Clin Microbiol 2013;51:3638-44 - PMID: 23985906

National Surveillance of Methicillin-Resistant *Staphylococcus aureus* in China Highlights a Still-Evolving Epidemiology with 15 Novel Emerging Multilocus Sequence Types

Meng Xiao,[a] He Wang,[a] Ying Zhao,[a] Lei-Li Mao,[a] Mitchell Brown,[b] Yun-Song Yu,[d] Matthew V. N. O'Sullivan,[b,c] Fanrong Kong,[b] Ying-Chun Xu[a]

Department of Clinical Laboratory, Peking Union Medical College Hospital, and Graduate School, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China[a]; Centre for Infectious Diseases and Microbiology Laboratory Services, Westmead Hospital, Westmead, New South Wales, Australia[b]; Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia[c]; Sir RunRun Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China[d]

Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - **the main key properties of the proposed antibiotic against the identified (or likely) target(s)**

Spectrum and mode / extent of action

- narrow or wide spectrum ?
- bactericidal or bacteriostatic (MIC / MBC)…

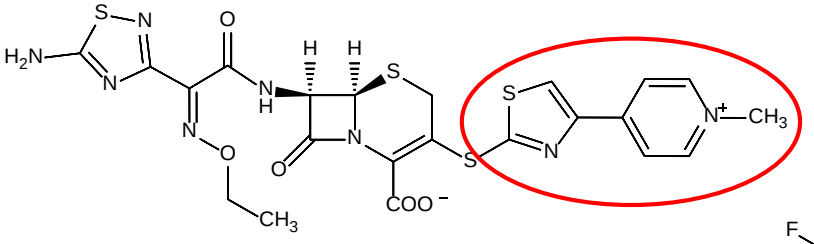
Possible answers for the organism …

When choosing an antibiotic, do we know

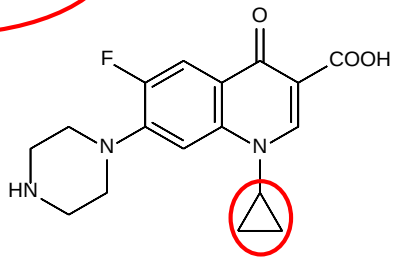
1. for the organism
   - **the main key properties of the proposed antibiotic against the identified (or likely) target(s)**

Spectrum and mode / extent of action

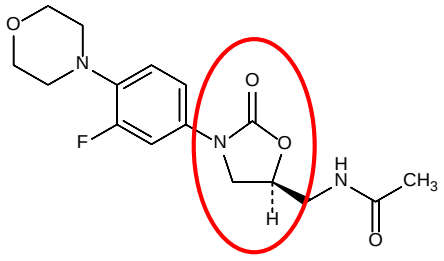
- the molecular parameters that differentiate drugs …



ceftaroline
an anti-MRSA cephalosporin

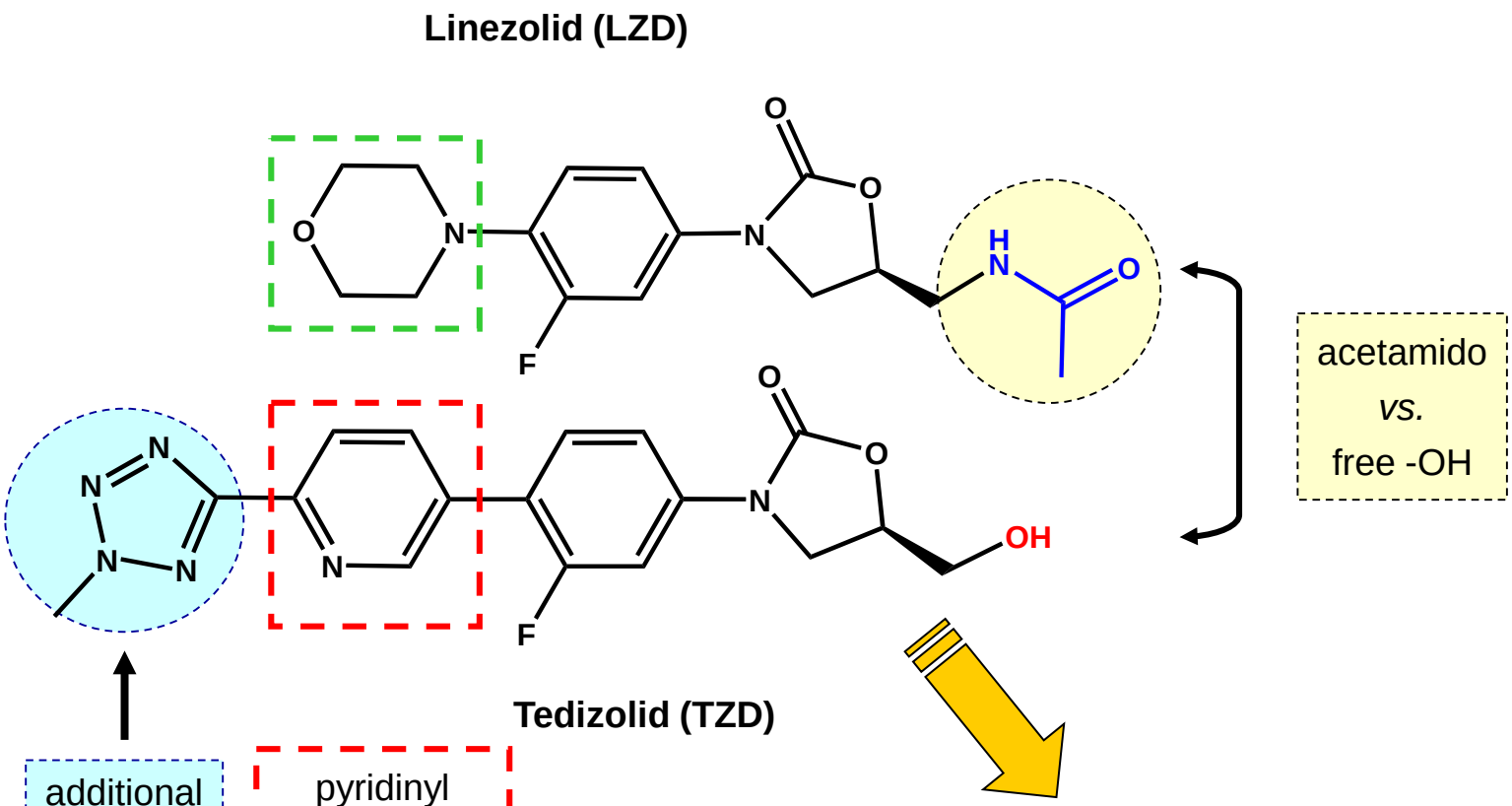


ciprofloxacin
a potent fluoroquinolones



linezolid
the first oxazolidinone

From linezolid to tedizolid: what the structure tells us



Substantial differences that DO impact on

- **intrinsic activity** *(more potent)*
- **activity against LZD-resistant strains**
- **half-life** *(longer)*

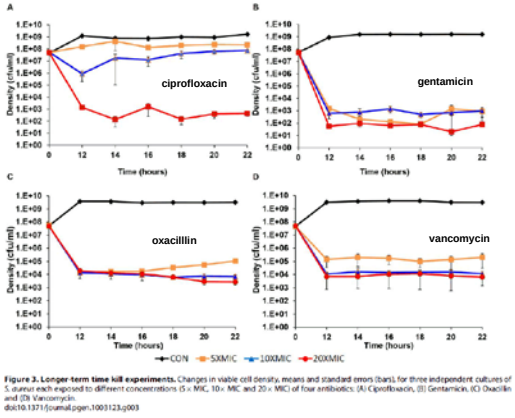
Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - **the main key properties of the proposed antibiotic against the identified (or likely) target(s)**

Spectrum and mode / extent of action

- activity against persisters, small colony variants, intracellulars, biofilms …



Johnson & Levin. PLoS Genet. 13;9:e1003123. - PMID: 23300474;

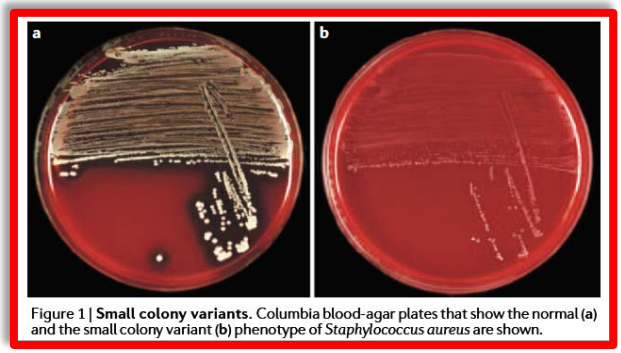
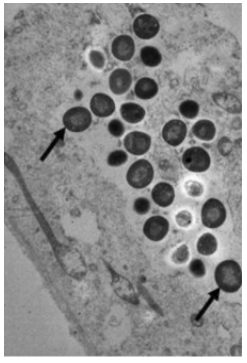


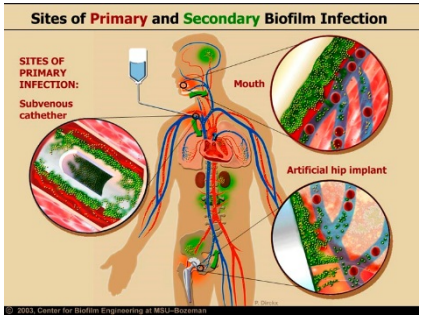
Figure 1 | **Small colony variants.** Columbia blood-agar plates that show the normal (a) and the small colony variant (b) phenotype of *Staphylococcus aureus* are shown.

Proctor et al. Nat Rev Microbiol 2006;4:295–305 - PMID: 16541137

***S. aureus* in human osteoblasts**



Kalinka *et al*., Int J Med Microbiol. 2014; 304:1038-49 - PMID: 25129555



Lewis et al, Nat Rev Microbiol. 2007; 5:48-56

Possible answers …

When choosing an antibiotic, do we know

1. for the organism
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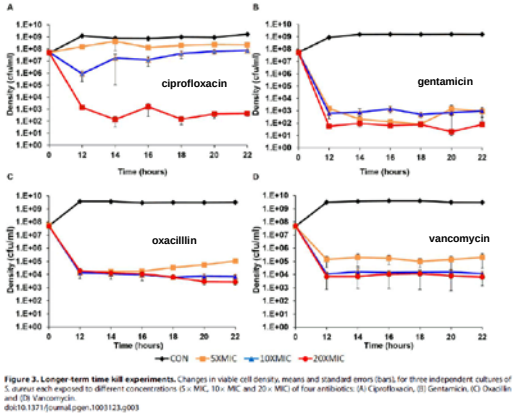
Spectrum and mode / extent of action

- activity against persisters, small colony variants, intrace…
  …

a new frontier ?



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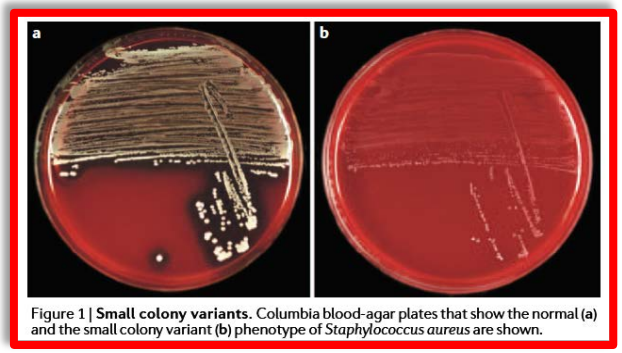

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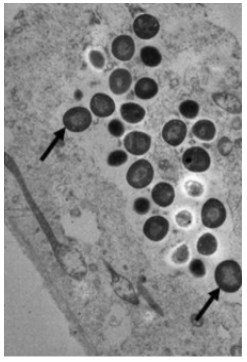

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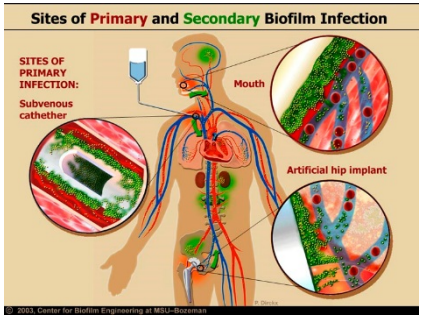


Lewis et al, Nat Rev Microbiol. 2007; 5:48-56

Possible answers for the patient …

When choosing an antibiotic, do we know

2. for the patient
   - **the antibiotic effectiveness in the specific disease ?**

Are potent *in vitro* antibiotics always potent *in vivo* ? …

The daptomycin story…

Inhibition of Daptomycin by Pulmonary Surfactant: In Vitro Modeling and Clinical Impact

Jared A. Silverman, Lawrence I. Mortin, Andrew D. G. VanPraagh, Tongchuan Li, and Jeff Alder

Cubist Pharmaceuticals, Lexington, Massachusetts

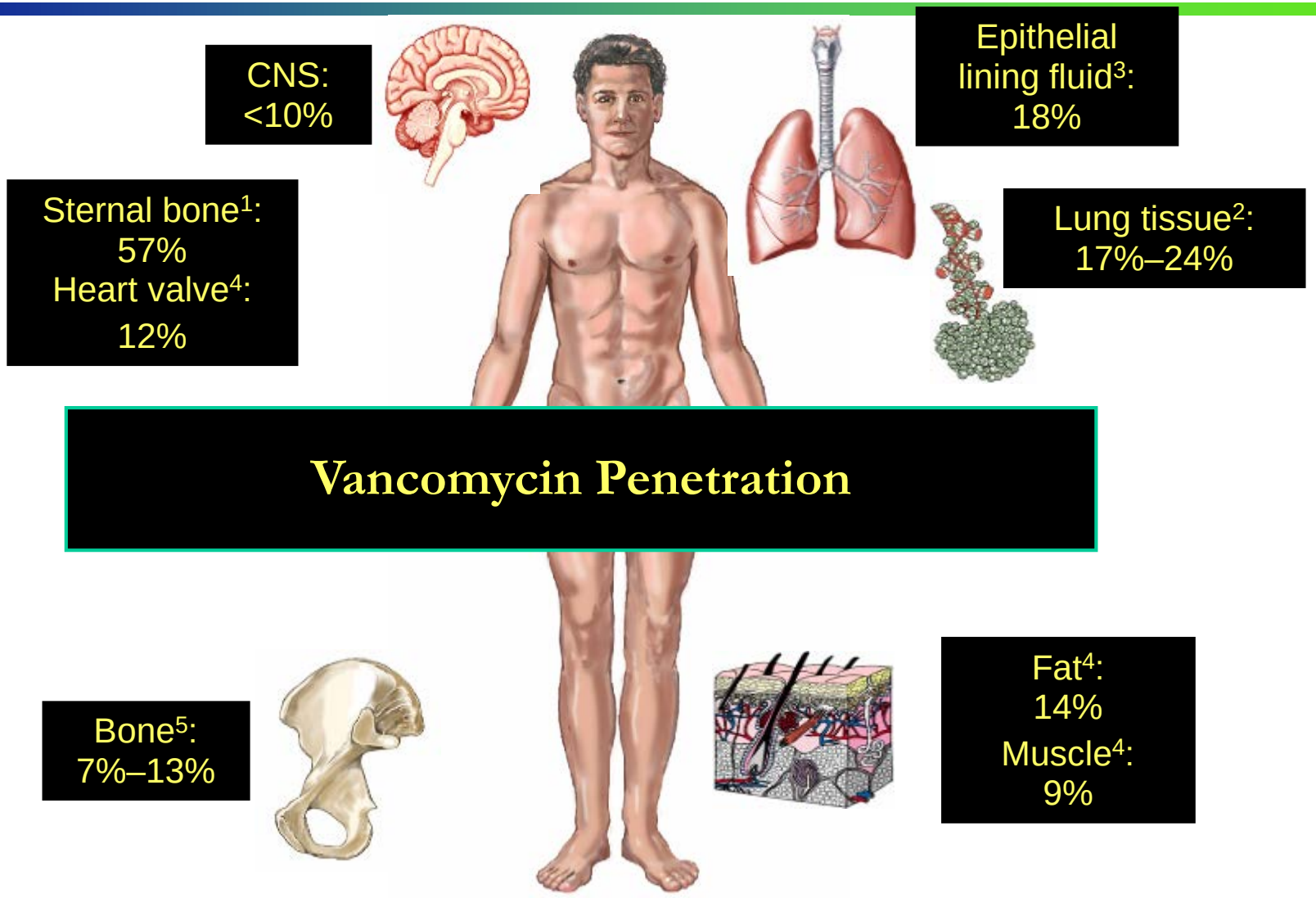
clinical demonstration is essential !

The lipopeptide daptomycin has been approved for use in skin and skin-structure infections but has failed to meet statistical noninferiority criteria in a clinical trial for severe community-acquired pneumonia. Daptomycin exhibited an unusual pattern of activity in pulmonary animal models: efficacy in *Staphylococcus aureus* hematogenous pneumonia and inhalation anthrax but no activity against *Streptococcus pneumoniae* in simple bronchial-alveolar pneumonia. Daptomycin was shown to interact in vitro with pulmonary surfactant, resulting in inhibition of antibacterial activity. This effect was specific to daptomycin and consistent with its known mechanism of action. This represents the first example of organ-specific inhibition of an antibiotic.

caution with off-label use …

Silverman et al. J Infect Dis2005;191:2149-52 - PMID: 15898002

Antibiotic poor penetration can explain many difficulties…



1. Massias L, et al. *Antimicrob Agents Chemother* 1992;36:2539–2541.
2. Cruciani M, et al. *J Antimicrob Chemother* 1996;38:865–869.
3. Lamer C. et al. *Antimicrob Agents Chemother* 1993;37:281–286.
4. Daschner FD et al. *J Antimicrob Chemother* 1987;19:359–362.
5. Graziani AL, et al. *Antimicrob Agents Chemother* 1988;32:1320–1322.

Possible answers for the patient …

When choosing an antibiotic, do we know

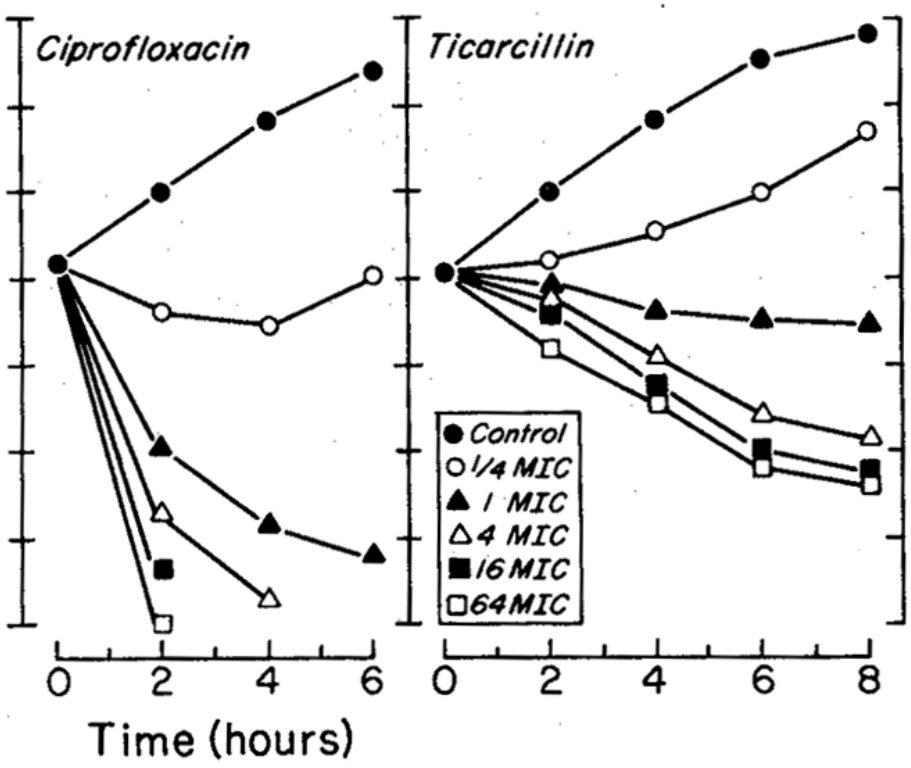
2. for the patient
   - **how to dose the antibiotic appropriately ?**

This is where the PK/PD guys came in (Stockholm, 1989)

A simple *in vitro comparison*

- bacteria in broth
- increasing concentrations (multiples of MIC)
- measure of the change in CFUs over time

quinolone … **β-lactam …**

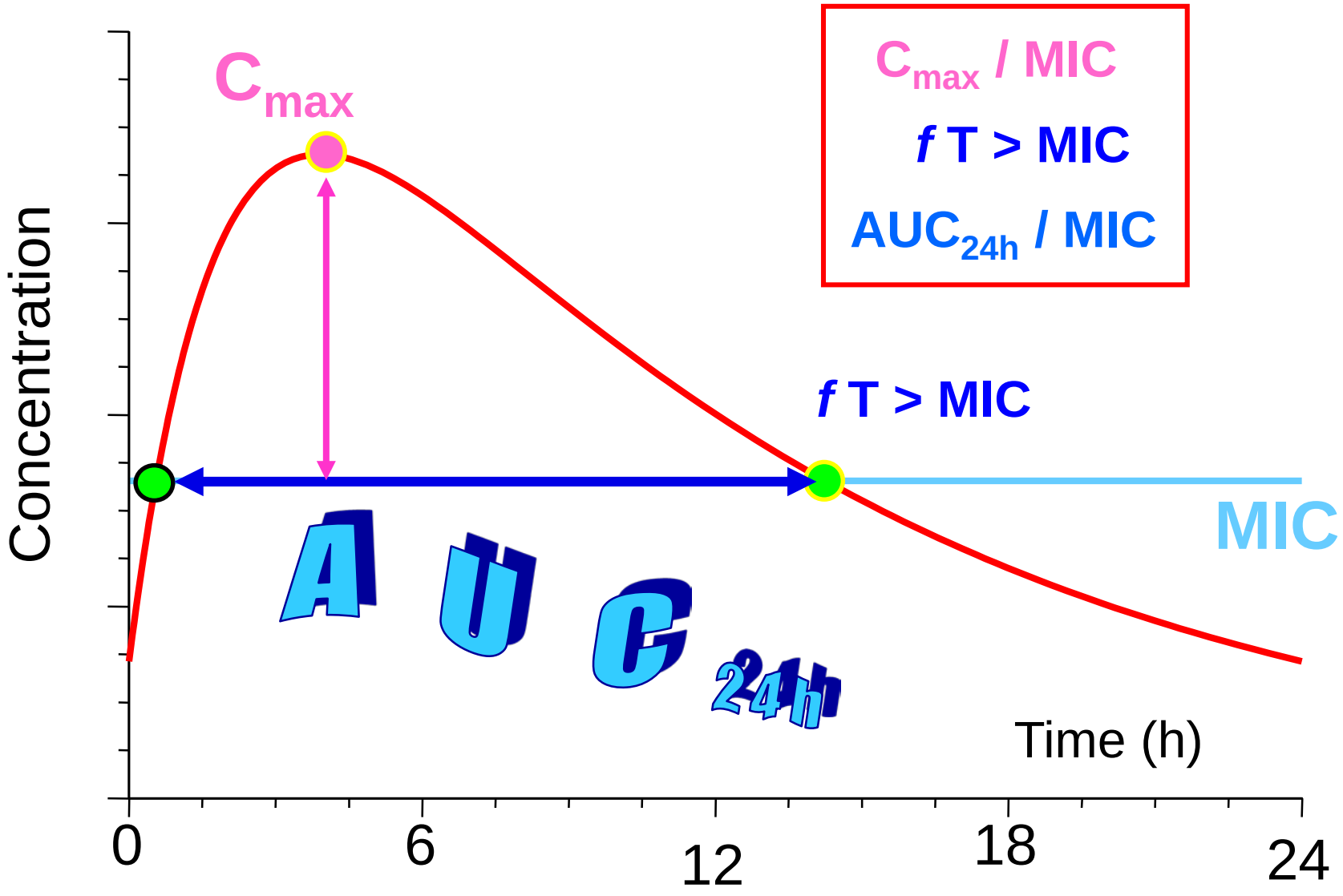


Fast and **concentration**-dependent

Slow and **time**-dependent

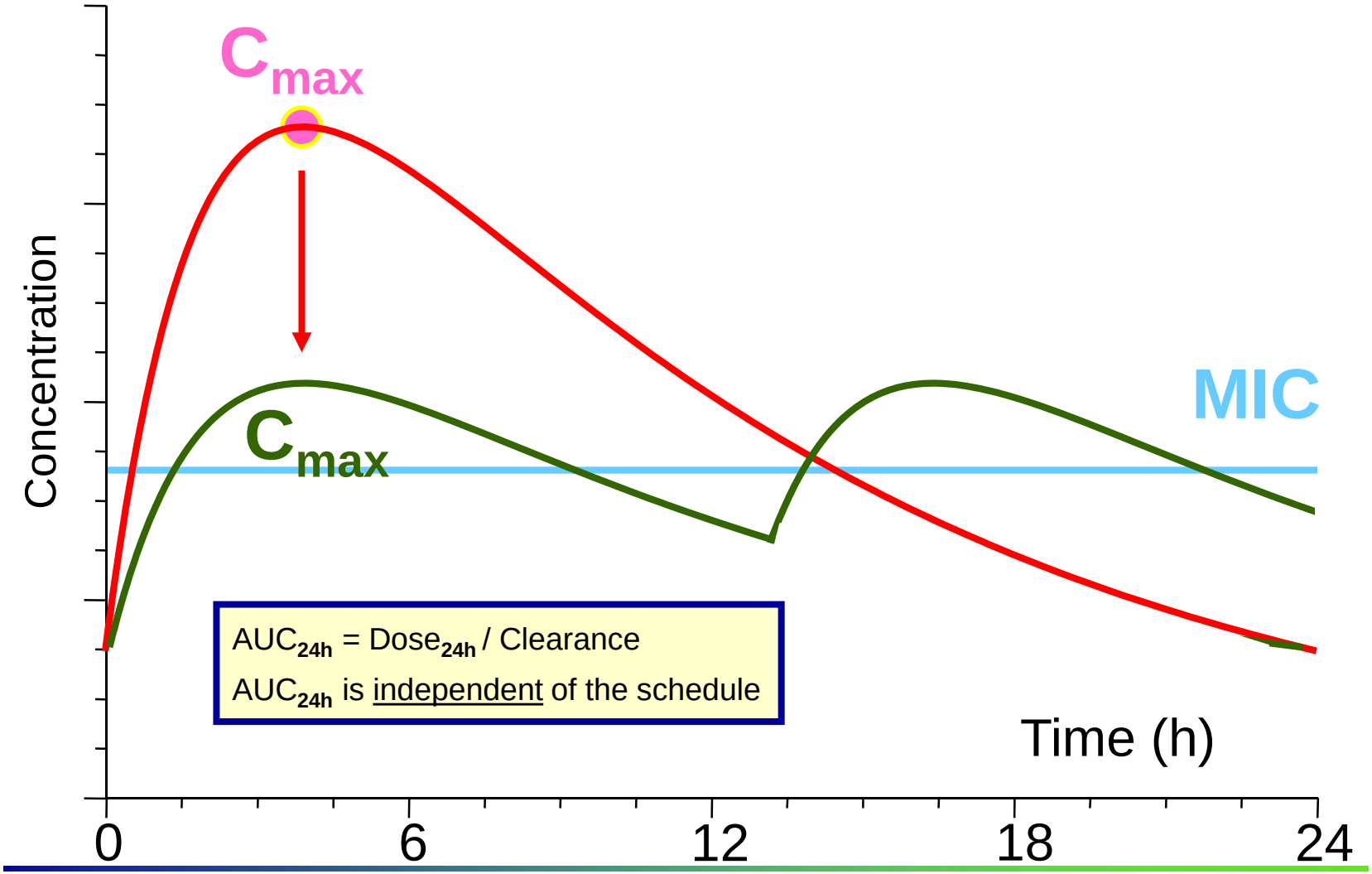
Vogelman & Craig (1986) Jounal of Pediatrics 108:835-840

PK parameters governing the activity of antibiotics



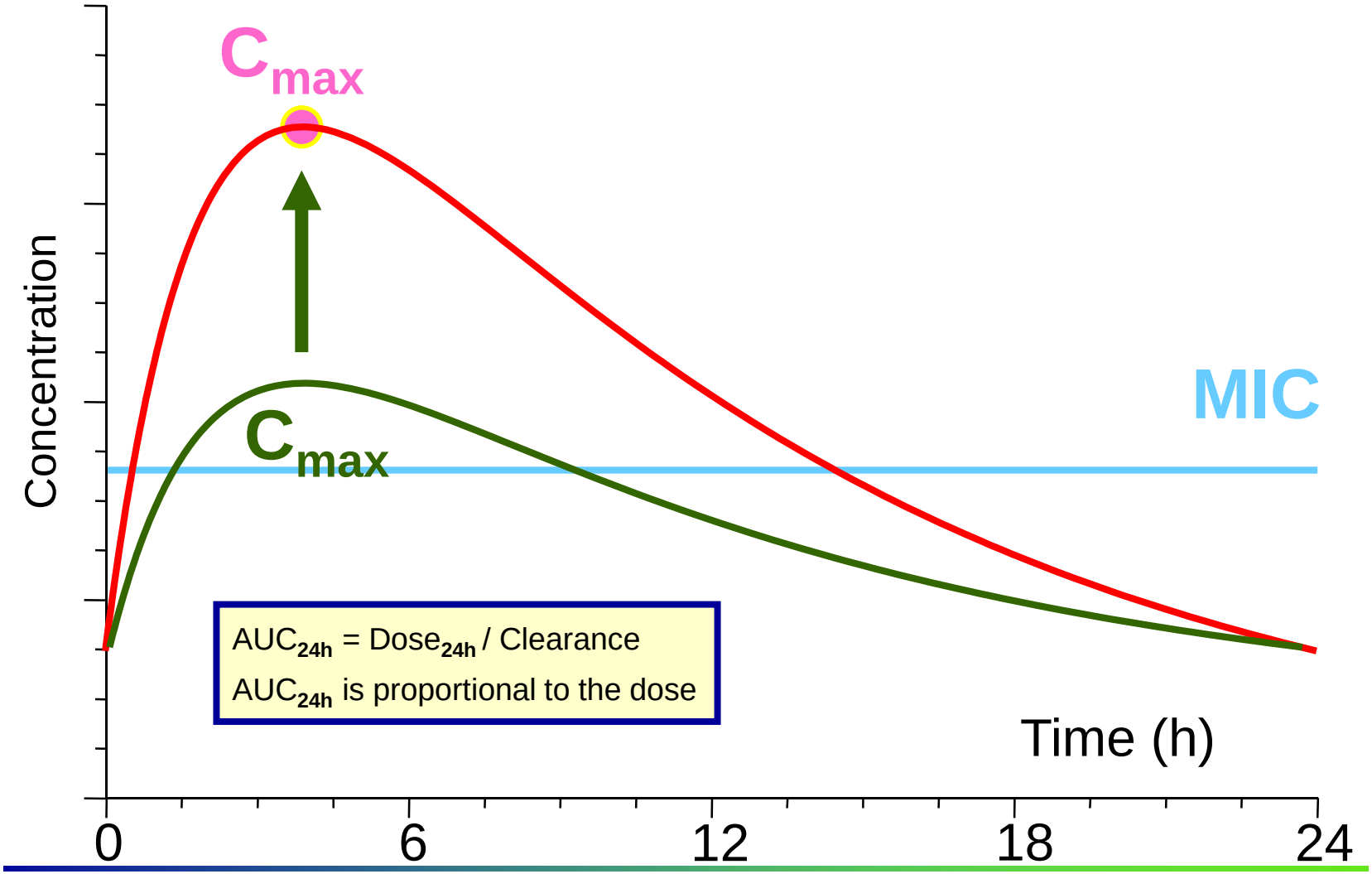
How to determine which PK parameter is critical ?

- If you fractionate the daily dose, you change C_{max} without changing AUC_{24h}



How to determine which PK parameter is critical ?

- If you increase the dose without change of schedule, you increase BOTH C_{max} and AUC_{24h}



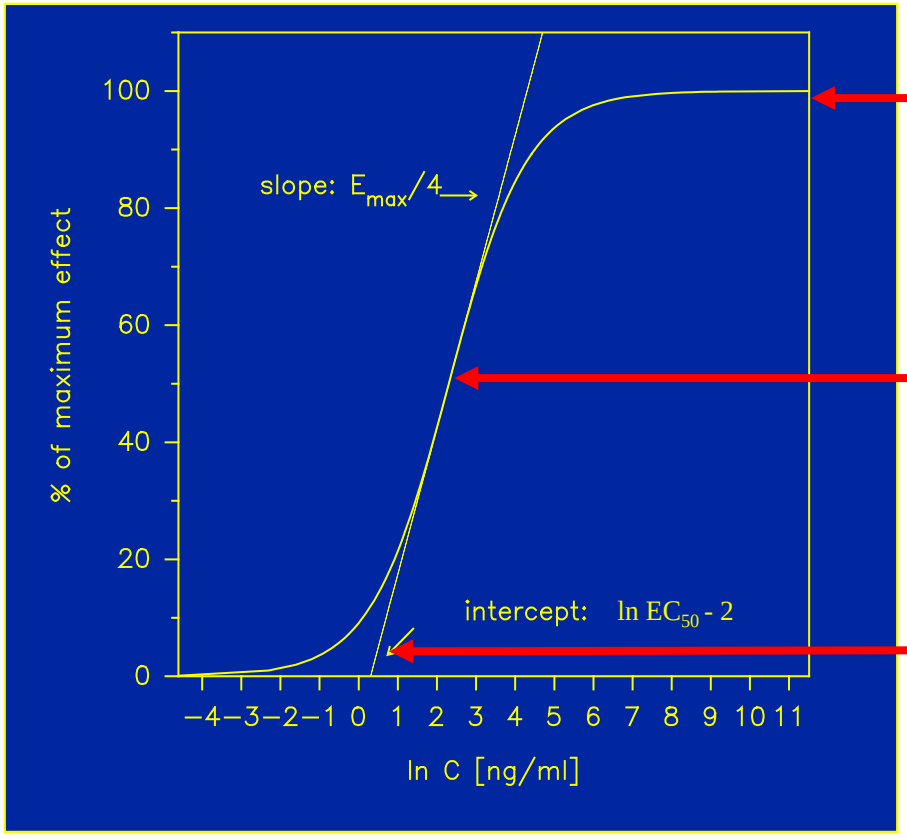
The 3 main patterns of antibiotic PK/PD properties

(W.A. Craig, 2000; revised in 2003)

antibiotic	PK/PD parameter	What to do ?
β-lactams	time > MIC	stay > MIC as needed
macrolides, oxazolidinones, vancomycin…	AUC_{24h} / MIC	give a sufficient total daily dose
quinolones aminoglycosides	peak / MIC and AUC_{24h} / MIC	obtain a peak and aim for a sufficient total daily dose

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003

What should you strive for ?



concentration

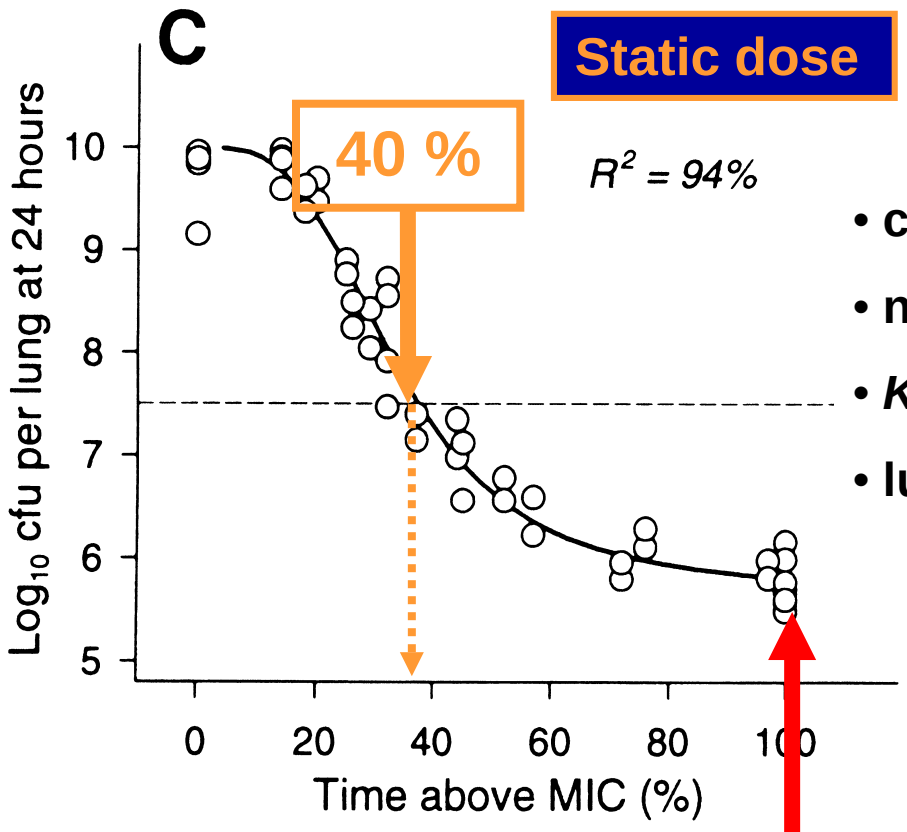
E_{max} — **Maximal effect**

$E_{50\%}$

E_{min} — **Minimal effect**

How to be optimal ?

If you select a β-lactam …

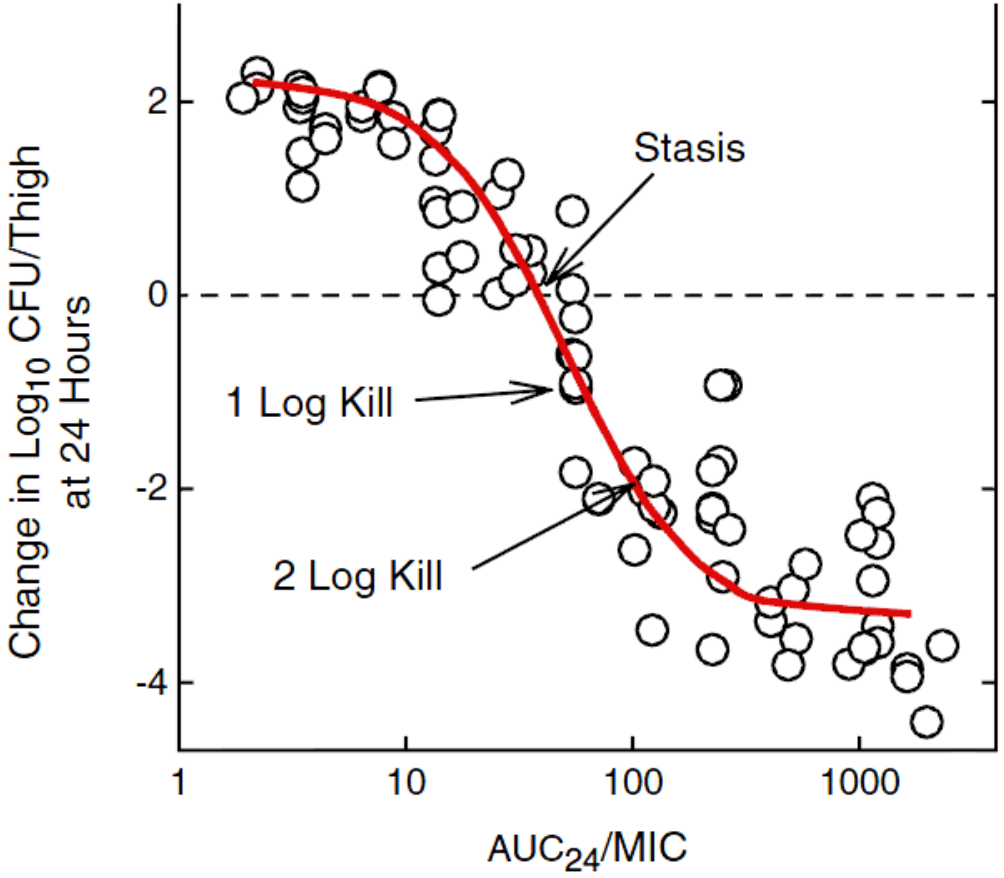


- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

100 % - Maximal effect

Breakpoint setting…

Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



Breakpoint setting: the EUCAST way

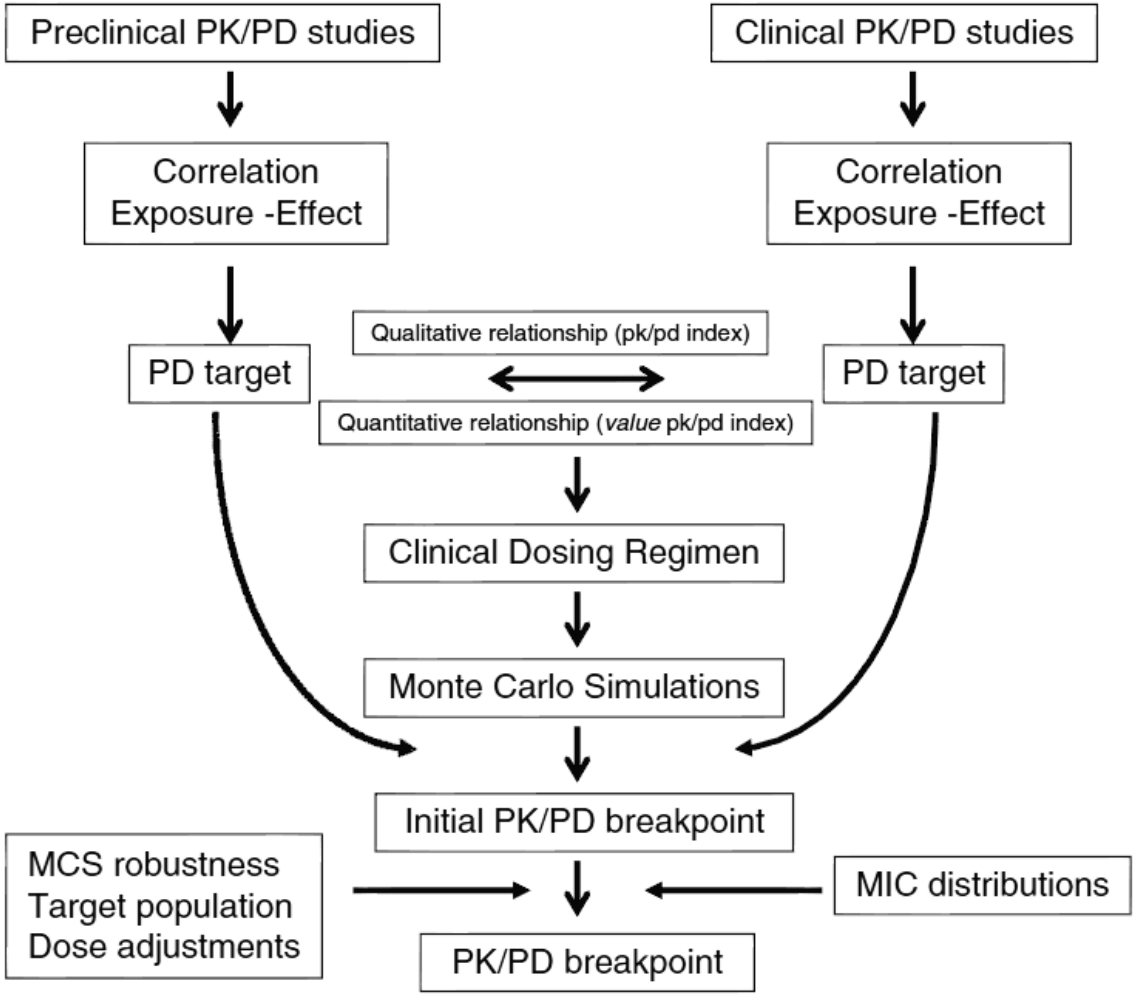


Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

Toxicodynamics: what drives linezolid toxicity…

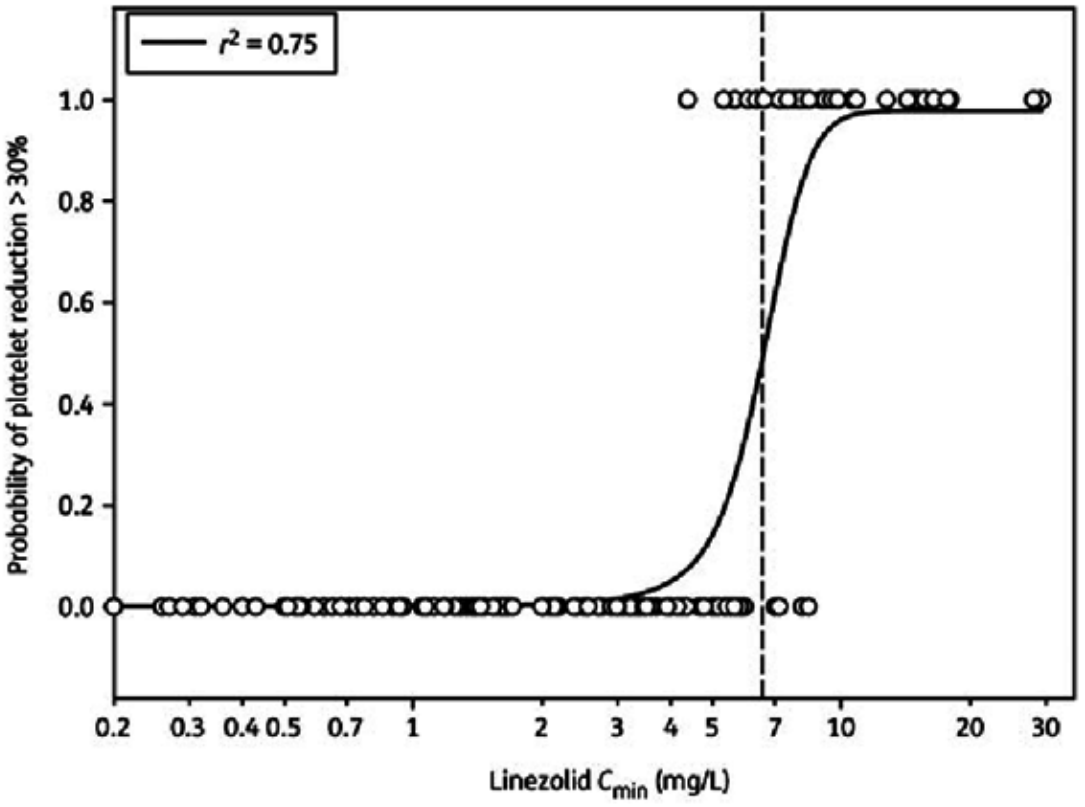


Fig. 16.13 Linezolid C_{min} and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the C_{min} observed over time in each patient with (*top*) or without (*bottom*) thrombocytopenia. The *continuous line* represents the result of the logistic regression model. The *vertical broken line* identifies the C_{min} value predicting 50 % probability of thrombocytopenia

Theuretzbacher U, PK/PD of Oxazolidinones In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinvk, H. Derendorf & JW Mouton eds, Springer, 2014, p 401-443

Answers for the patient …

When choosing an antibiotic, do we know

2. for the specific patient
   - how to prevent / avoid patient- and drug-related side effects

Aminoglycosides are concentration-dependent and need to be given **once-daily** both for increased efficacy and possible reduction of toxicity

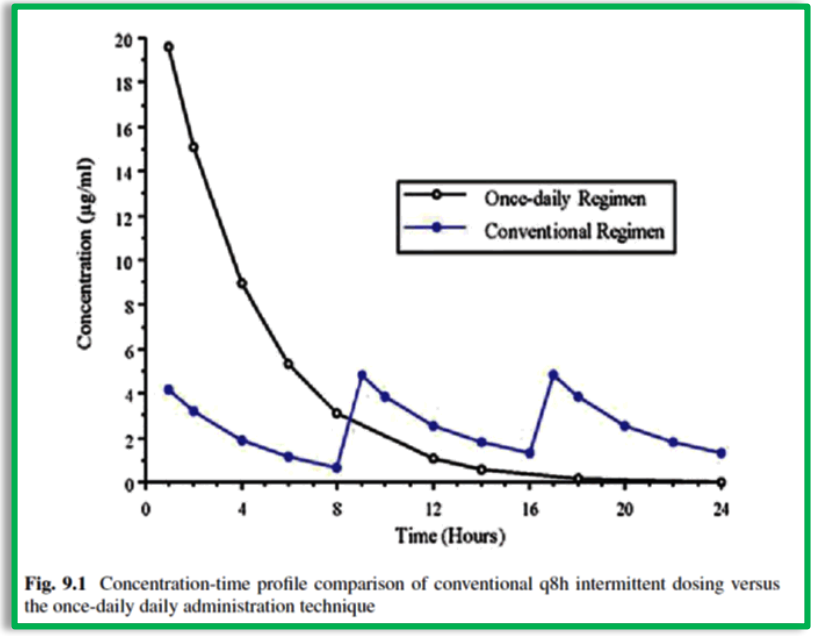


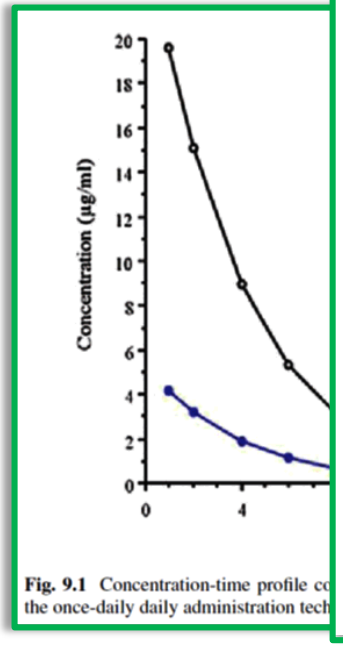
Fig. 9.1 Concentration-time profile comparison of conventional q8h intermittent dosing versus the once-daily daily administration technique

Answers for the patient …

When choosing an antibiotic, do we know

2. for the specific patient
   - how to prevent / avoid patient- and drug-related side effects

aminoglycos
once-daily b



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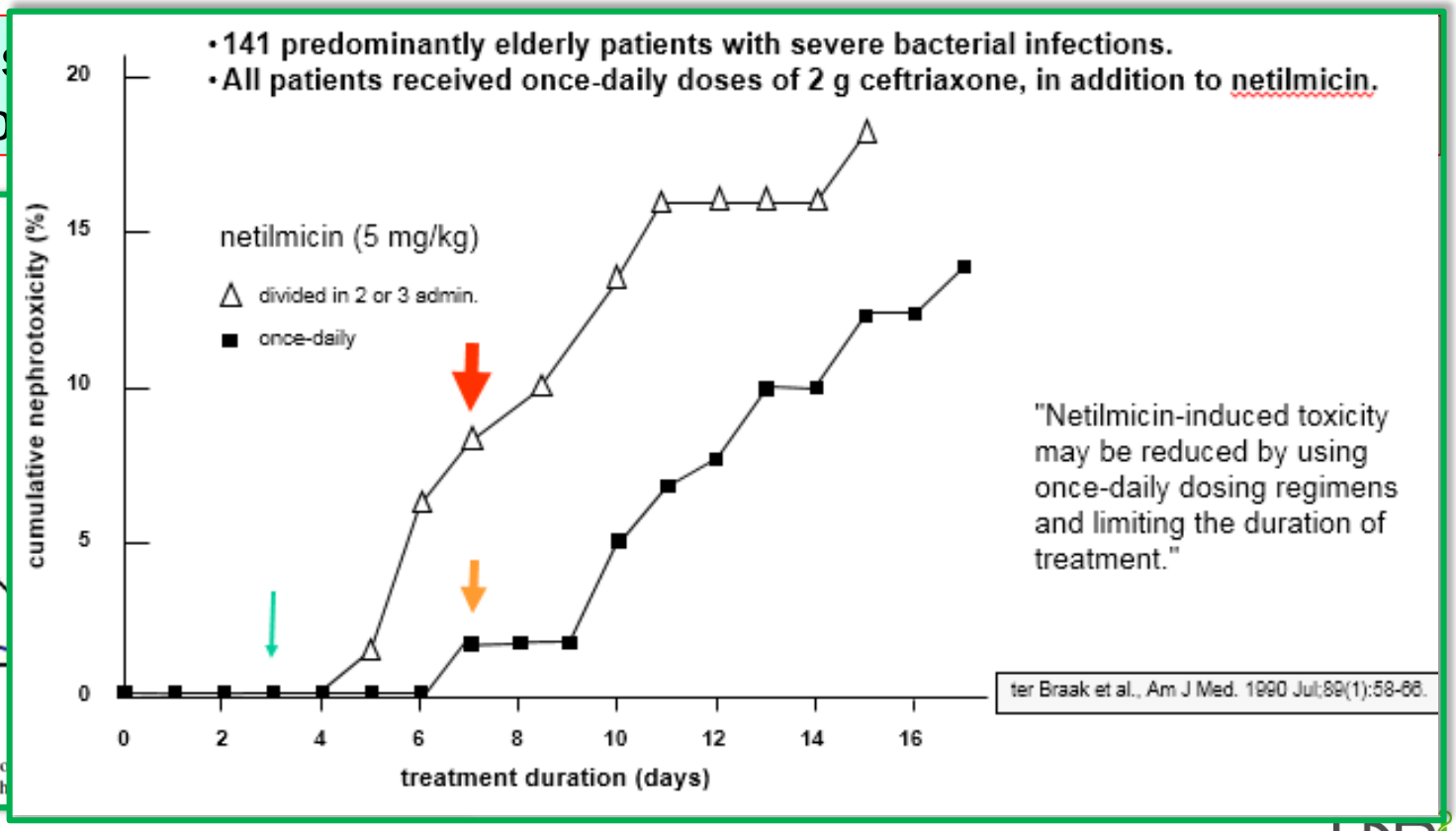


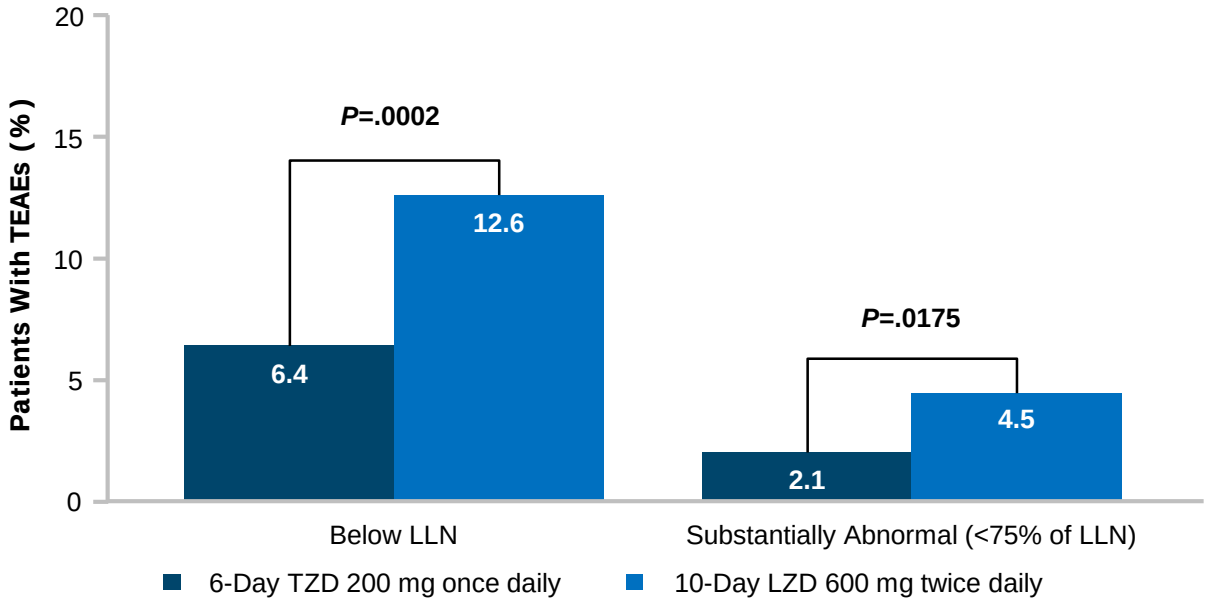
Answers for the patient …

When choosing an antibiotic, do we know

2. for the specific patient
   - how to prevent / avoid patient- and drug-related side effects

Choosing the **appropriate drug derivative** can be rewarding…

Tedizolid (TZD) *vs*. linezolid (LZD) safety: Platelet counts Pooled Phase 3 Studies



DeAnda *et al*. Integrated results from 2 phase 3 studies comparing tedizolid phosphate 6 days vs. linezolid 10 days in patients with ABSSSI. Poster presented at: 53rd Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC); September 10-13, 2013; Denver, CO. (L-203).

Here are the questions …

When choosing an antibiotic, do we know

3. for the society
   - how to prevent emergence of resistance ?

Answers for Society …

When choosing an antibiotic, do we know

3. for the society
   - **how to prevent emergence of resistance ?**

This is probably a **most difficult challenge** because

- resistance genes are already present in nature (**resistome**)
- bacteria quickly adapt to new environments (**mutation/selection**)

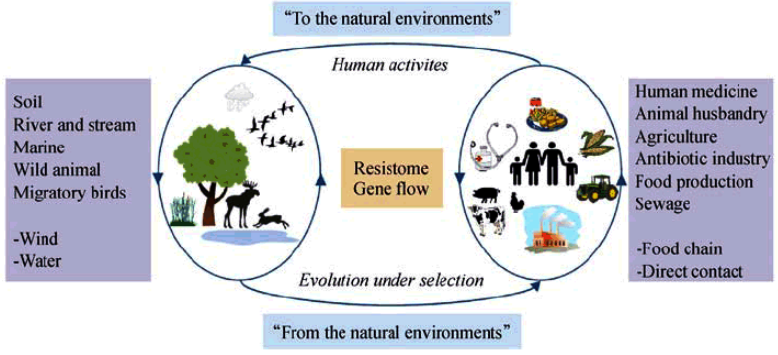


Fig. 1 The antibiotic resistome gene flow in environments, human, and animals. We propose that the antibiotic resistome gene flow is "form the natural environments" and "to the natural environments." The natural environments are the reservoirs for antibiotic resistome. The original ARGs in environmental bacteria can be captured by human or animal pathogens and gradually evolved under the antibiotic selection pressure and become qualified. These ARGs or ARG-bearing bacteria are then disseminated back to the natural environments due to the human activities on producing and using antibiotics. In most cases, the ARGs are more easily transferred within respective ecological niches (the natural environments, and the human- and animal-associated environments). This resistance gene flow scenario is not very applicable to antibiotic resistance caused by chromosomal mutation.

Hu et al. Front Med 2017;11:161-168 - PMID: 28500429

Answers for the Society …

When choosing an antibiotic, do we know

3. for the society
   - **how to prevent emergence of resistance ?**

This is probably a **most difficult challenge** becaus
- resistance genes are already present in nature (**re**
- bacteria quickly adapt to new environments (**muta**

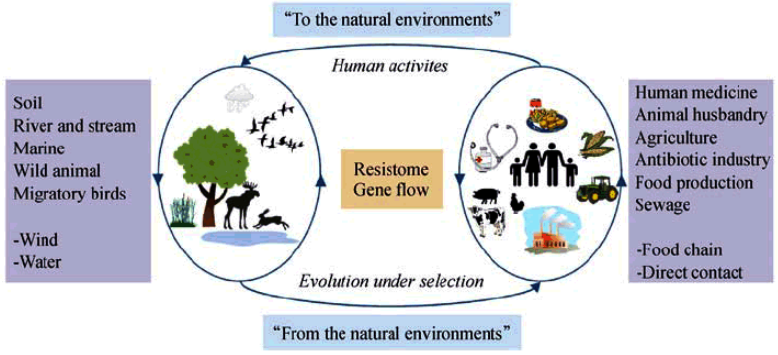
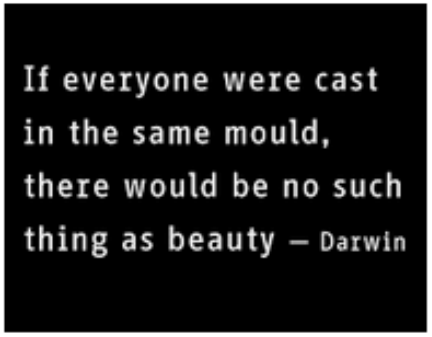
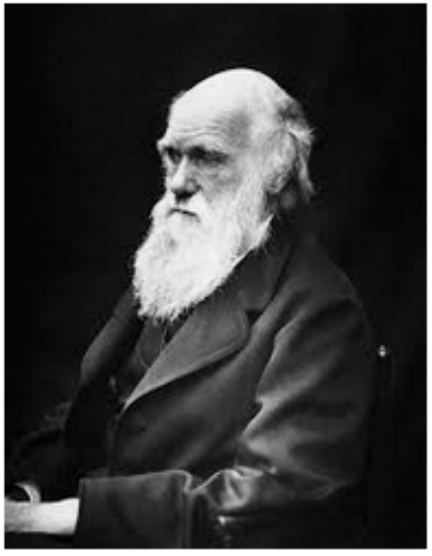


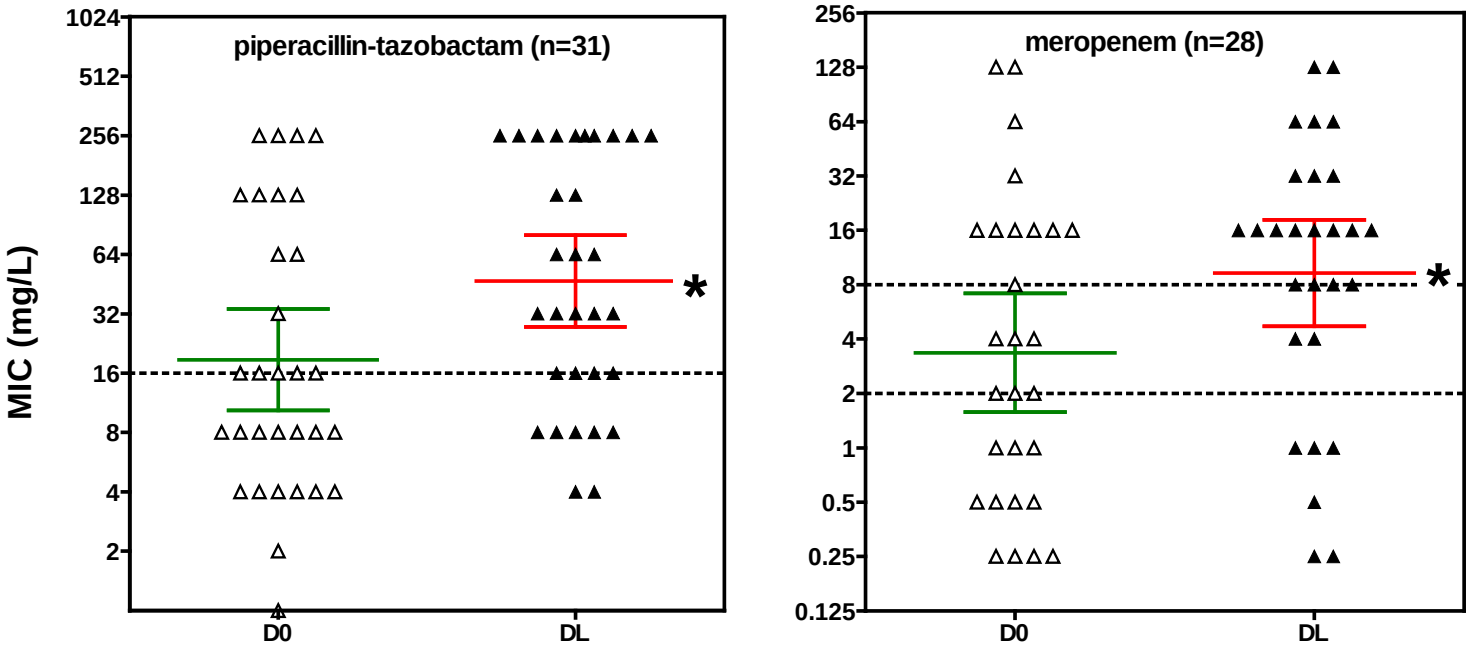
Fig. 1 The antibiotic resistome gene flow in environments, human, and animals. We propose that the antibiotic resistome gene flow is "form the natural environments" and "to the natural environments." The natural environments are the reservoirs for antibiotic resistome. The original ARGs in environmental bacteria can be captured by human or animal pathogens and gradually evolved under the antibiotic selection pressure and become qualified. These ARGs or ARG-bearing bacteria are then disseminated back to the natural environments due to the human activities on producing and using antibiotics. In most cases, the ARGs are more easily transferred within respective ecological niches (the natural environments, and the human- and animal-associated environments). This resistance gene flow scenario is not very applicable to antibiotic resistance caused by chromosomal mutation.

Hu et al. Front Med 2017;11:161-168 - PMID: 28500429





MIC may increase during treatment !



Change in MIC of antibiotics used in empiric antipseudomonal therapy (nosocomial pneumonia; intensive care units) towards the isolate identified before onset of therapy (D0) *vs*. the last isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and $\log_2$ transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

Riou et al. Int J Antimicrob Agents. 2010 Dec;36(6):513-22.

Optimization may prevent emergence of resistance

J Antimicrob Chemother 2017; **72**: 1421–1428
doi:10.1093/jac/dkx001 Advance Access publication 31 January 2017

Journal of Antimicrobial Chemotherapy

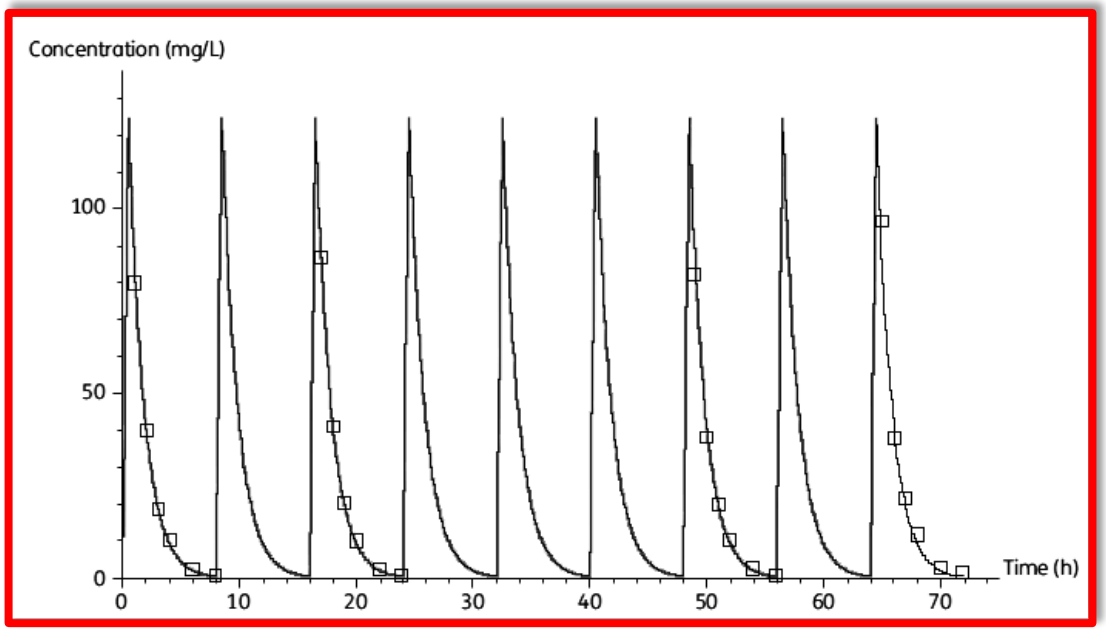
Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam[1]*, Kai-Tai Chang[1], Jian Zhou[1], Kimberly R. Ledesma[1], Kady Phe[1], Song Gao[1], Françoise Van Bambeke[2], Ana María Sánchez-Díaz[3], Laura Zamorano[4], Antonio Oliver[4] and Rafael Cantón[3]

[1]University of Houston, Houston, TX, USA; [2]Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; [3]Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [4]University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain

Tam *et al.* J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Simulation of serum concentration levels (hollow fibers model)



Optimization may prevent emergence of resistance

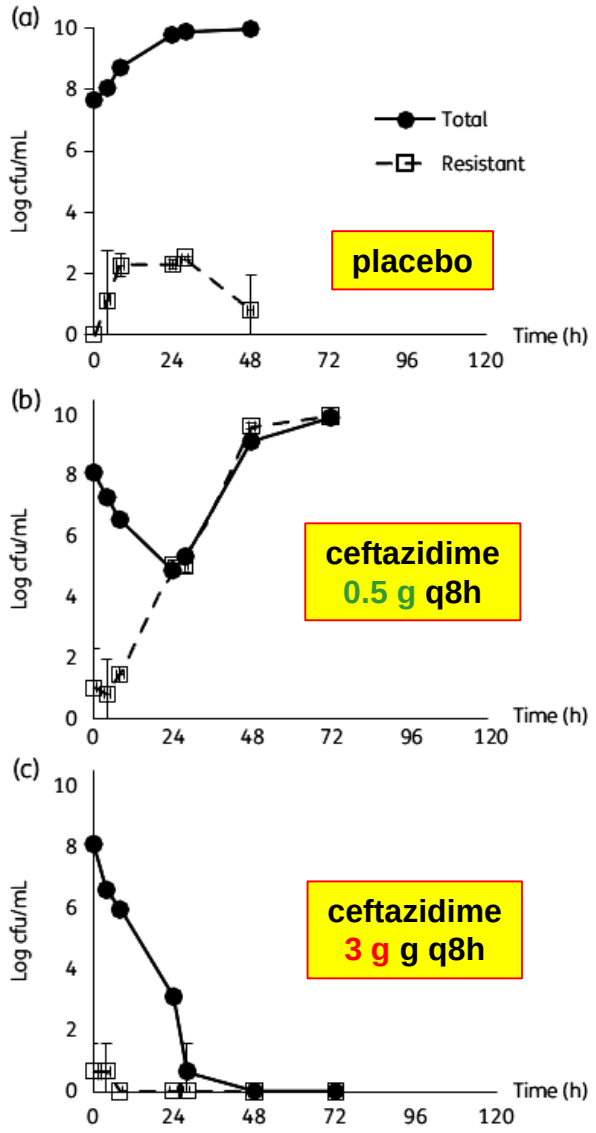


Figure 2. Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h (C_{min}/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h (C_{min}/MIC = 7.7) (c). Data are shown as mean ± SD.

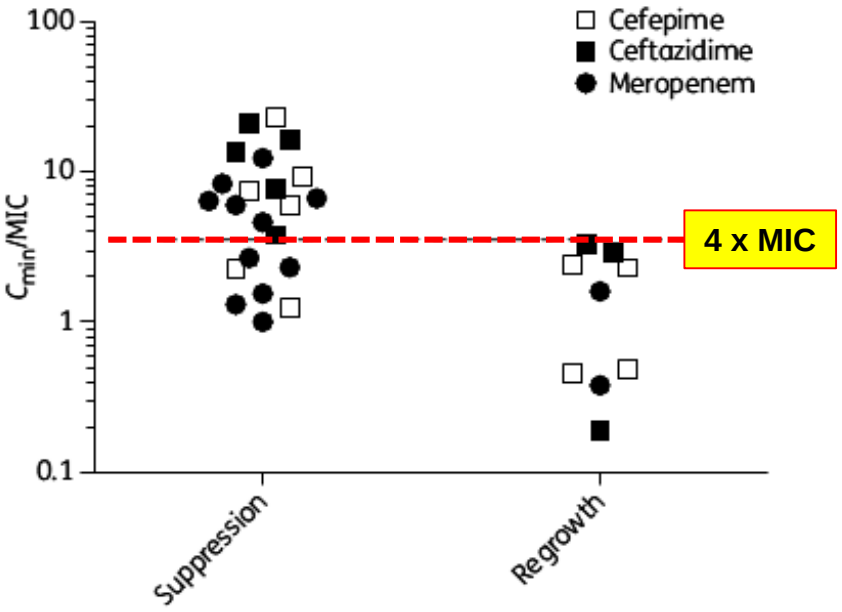
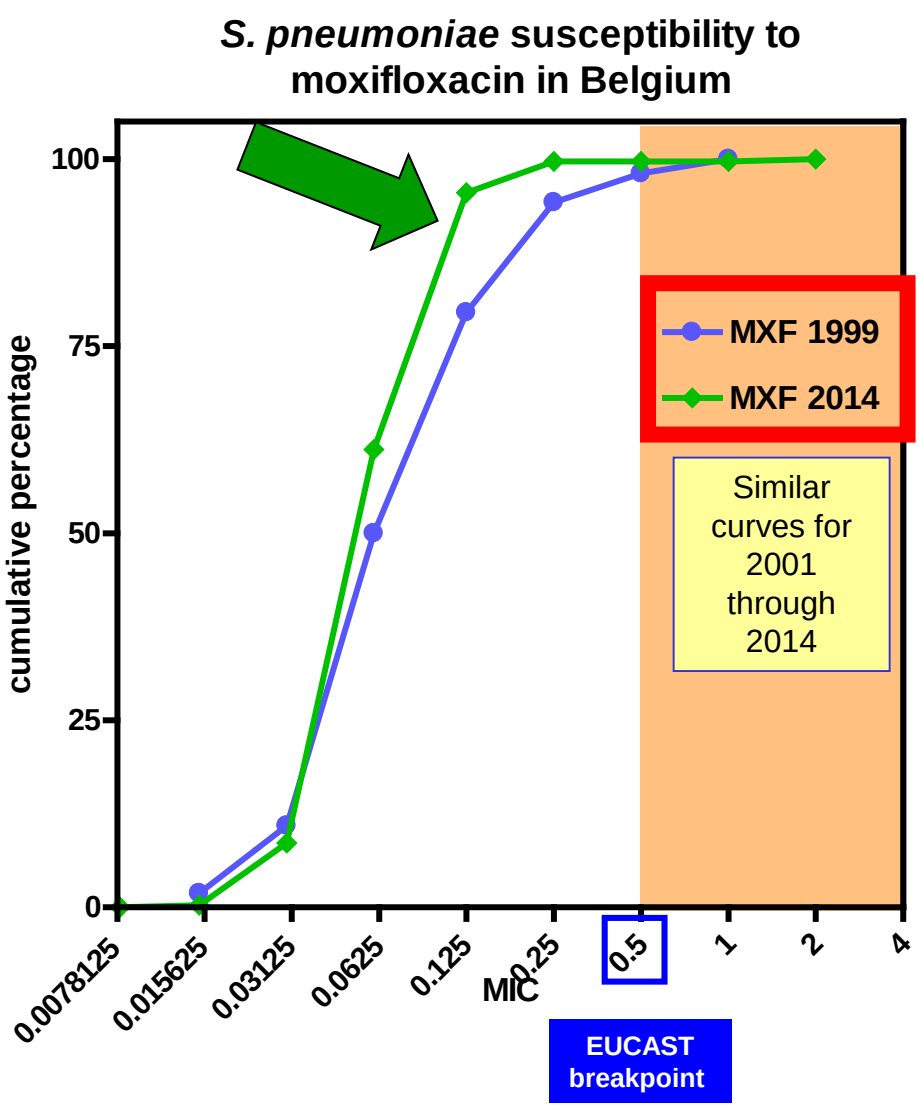


Figure 3. Drug exposures (C_{min}/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold (C_{min}/MIC ≥3.8) is depicted by the horizontal broken line.

To prevent emergence of resistance, C_{min} of β-lactams must stay > 4 x MIC (mean), which commands higher dosages…

Tam et al. J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Appropriately dosed antibiotics may avoid resistance creep



*** Moxifloxacin was introduced in Belgium in 2001 and became the almost only fluoroquinolone used for RTI since 2004**

From data of a national collection

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S. pneumoniae* from clinically-confirmed CAP (n=132)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)
- Data available yearly for 1999 through 2014 at http://www.iph.fgov.be

Vanhoof *et al*. 19th ECCMID, Helsinki, 2009

Ceyssens *et al*. 35th RICAI, Paris, 2015

Ceyssens *et al.* PLoS One 2016;11:e0154816 (17 pages) - PMID 27227336

Why no resistance of *S. pneumoniae* to moxifloxacin ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2007, p. 1315–1320 Vol. 51, No. 4
0066-4804/07/$08.00+0 doi:10.1128/AAC.00646-06

Fluoroquinolone Resistance in *Streptococcus pneumoniae*: Area Under the Concentration-Time Curve/MIC Ratio and Resistance Development with Gatifloxacin, Gemifloxacin, Levofloxacin, and Moxifloxacin[▽]

Kerry L. LaPlante,[1,2,4]† Michael J. Rybak,[1,2,3,4]* Brian Tsuji,[1,2,4]‡ Thomas P. Lodise,[6] and Glenn W. Kaatz[1,3,5]

Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy,[1] Department of Pharmacy Practice,[2] and School of Medicine,[3] Wayne State University, Detroit Receiving Hospital and University Health Center,[4] and John D. Dingell Veterans Affairs Medical Center,[5] Detroit, Michigan, and Department of Pharmacy Practice, Albany College of Pharmacy, Albany, New York[6]

LaPlante et al. Antimicrob Agents Chemother 2007;51:1315-20 - PMID: 17296740

it's all a problem of PK/PD

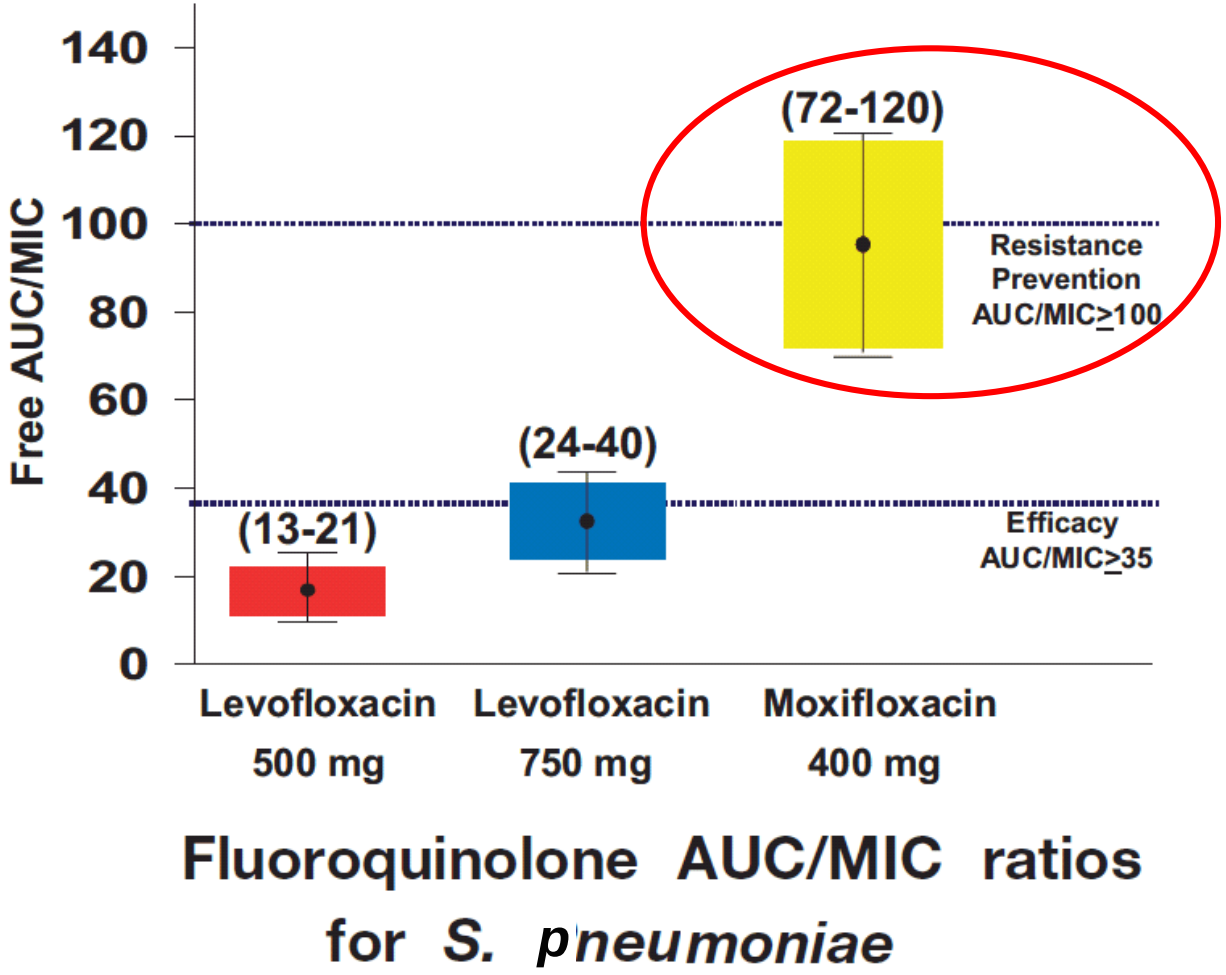
Clinical doses of moxifloxacin exceeded the *f*AUC/MIC resistance breakpoint against wild-type *S. pneumoniae*, whereas those of levofloxacin (500 and 750 mg) were associated with first- and second-step mutations.

Additionally, moxifloxacin breakpoints were significantly lower ($P < 0.002$) than those of gatifloxacin.

The order of resistance development determined from *f*AUC/MIC breakpoints was levofloxacin > moxifloxacin = gemifloxacin, which may be related to structural differences within the class.

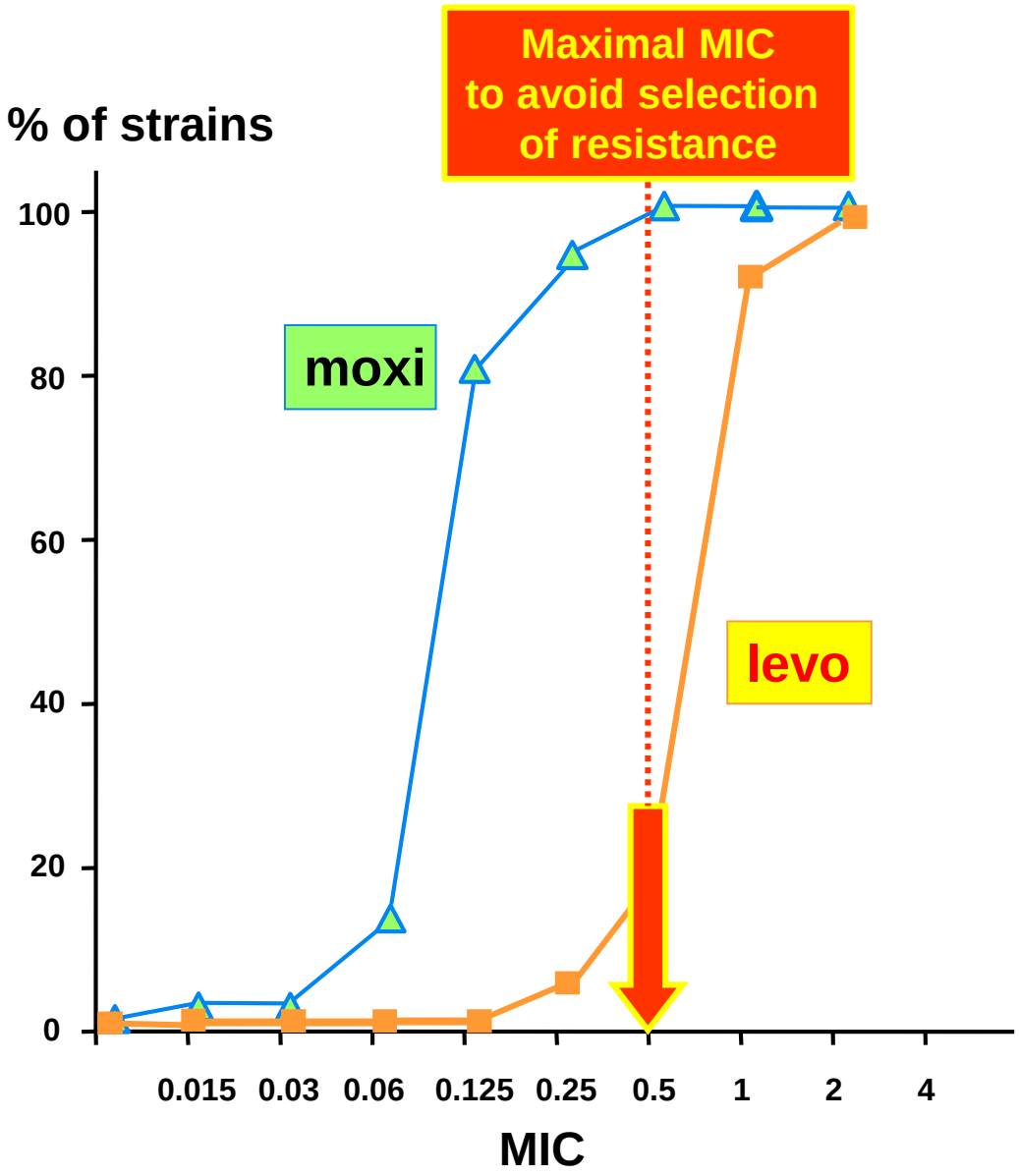
What differentiates fluoroquinolones ?

Results with *S. pneumoniae*



Would this cause less emergence of resistance ?

Pharmacokinetics and “resistance” breakpoint *vs.* MIC



resistance breakpoint
- **AUC/MIC = 100**
- **peak/MIC = 10**

Levofloxacin 500 mg 1X / day
- **AUC [(mg/l)xh] 47**
- **peak [mg/l] 5**

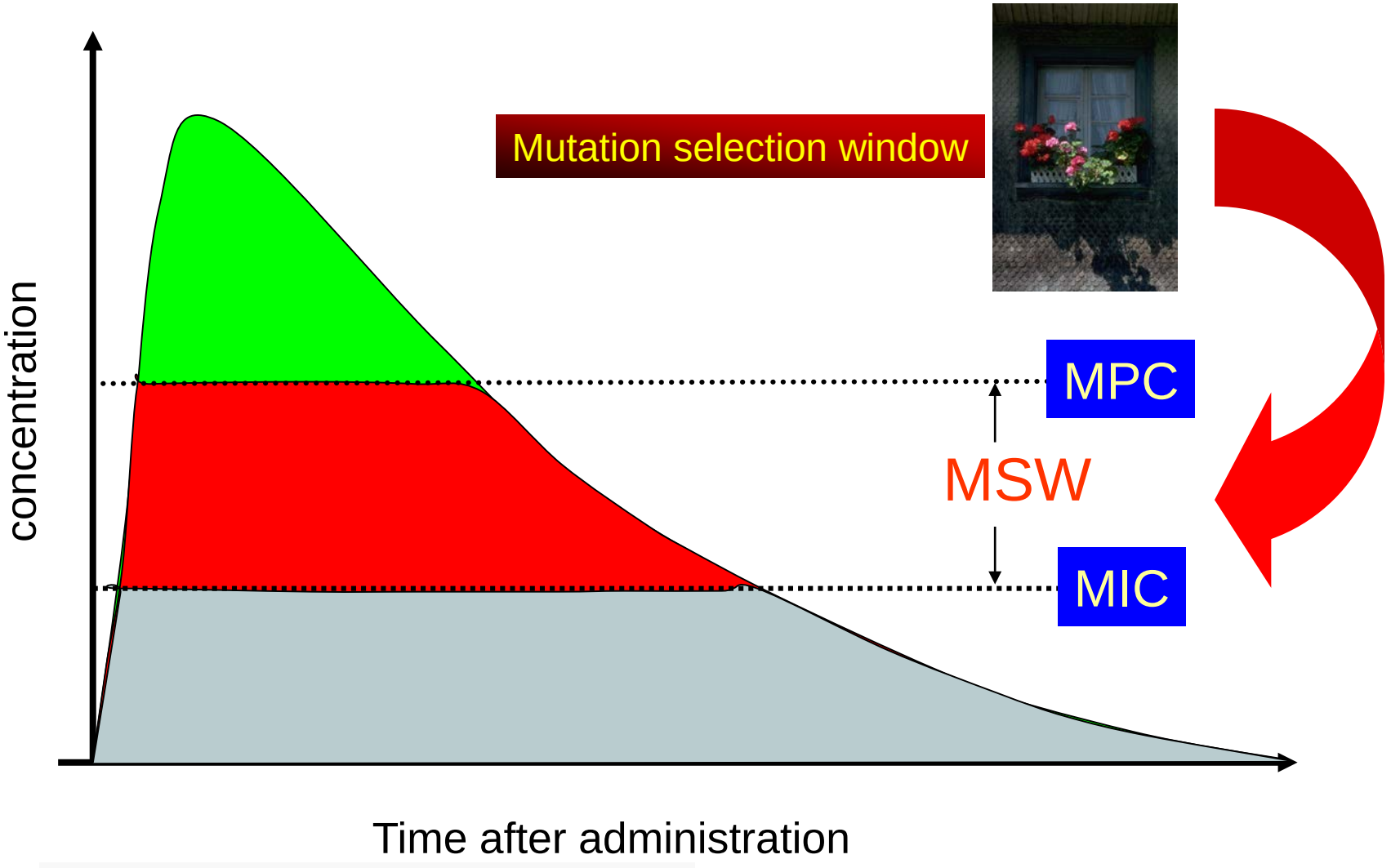
➔ **MIC_{max} ~ 0.5**

Moxifloxacin 400 mg 1X / day
- **AUC [(mg/l)xh] 48**
- **peak [mg/l] 4.5**

➔ **MIC_{max} ~ 0.5**

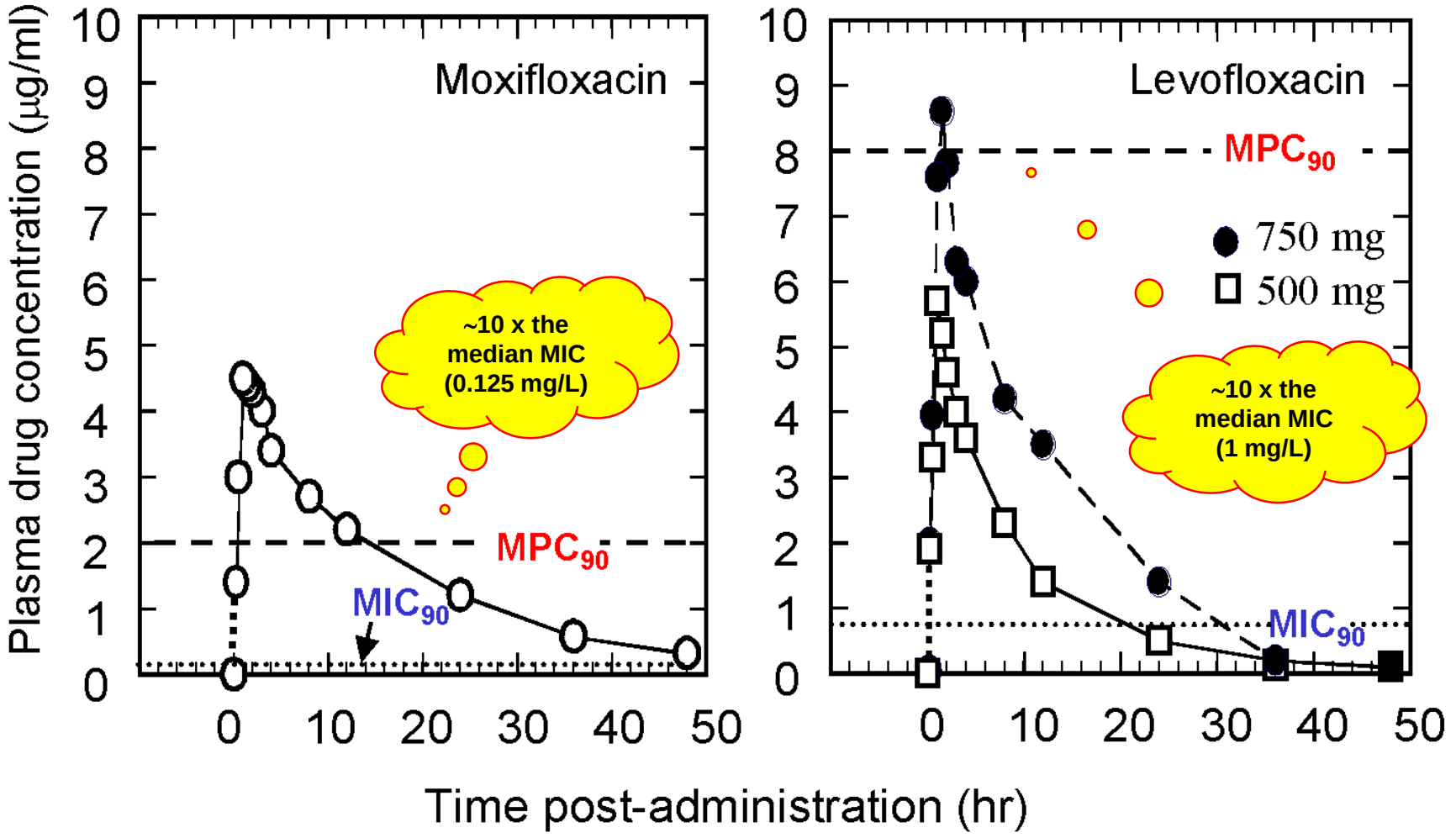
MIC data: EUCAST MIC distributions (wild type)
PK data: US and EU labelling (typical values)

The risk for resistance to fluoroquinolones … the MPC !



concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

MPC: moxifloxacin *vs* levofloxacin



What about the recommendations for CAP ?

ORIGINAL ARTICLE 10.1111/j.1469-0691.2011.03672.x

Guidelines for the management of adult lower respiratory tract infections - Full version

M. Woodhead[1], F. Blasi[2], S. Ewig[3], J. Garau[4], G. Huchon[5], M. Ieven[6], A. Ortqvist[7], T. Schaberg[8], A. Torres[9], G. van der Heijden[10], R. Read[11] and T. J. M. Verheij[12] Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases

Recommendation:

Aminopenicillin ± macrolide[a,b]
Aminopenicillin/β-lactamase inhibitor[a] ± macrolide[b]
Non-antipseudomonal cephalosporin
Cefotaxime or ceftriaxone ± macrolide[b]
Levofloxacin[a]
Moxifloxacin[a,c]
Penicillin G ± macrolide

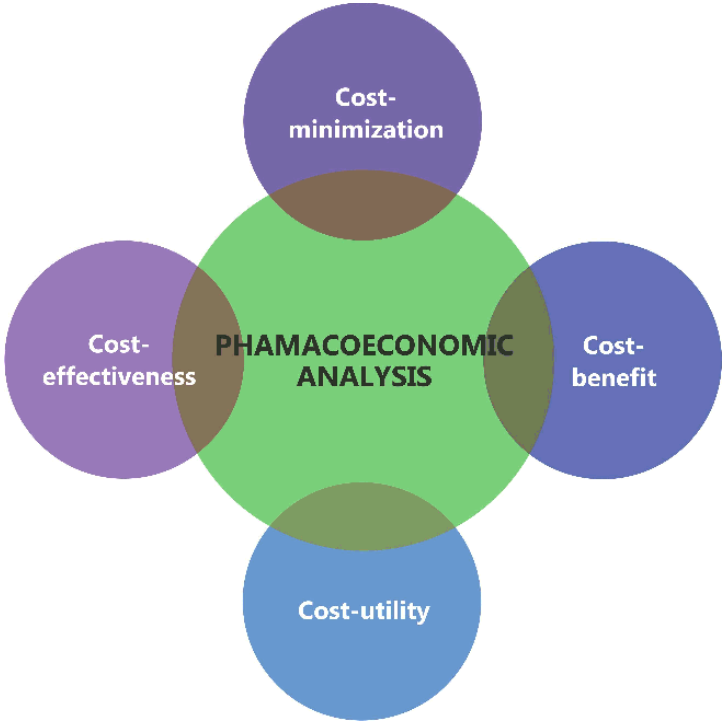
[a]Can be applied as sequential treatment using the same drug.
[b]New macrolides preferred to erythromycin.
[c]Within the fluoroquinolones, moxifloxacin has the highest antipneumococcal activity.
In patients at risk of GNEB, particularly strains with ESBL, but without risk (or after exclusion of) of *P. aeruginosa*, ertapenem may be used.

Woodhead et al. Clin Microbiol Infect 2011;17 Suppl 6:E1-59 - PMID: 21951385

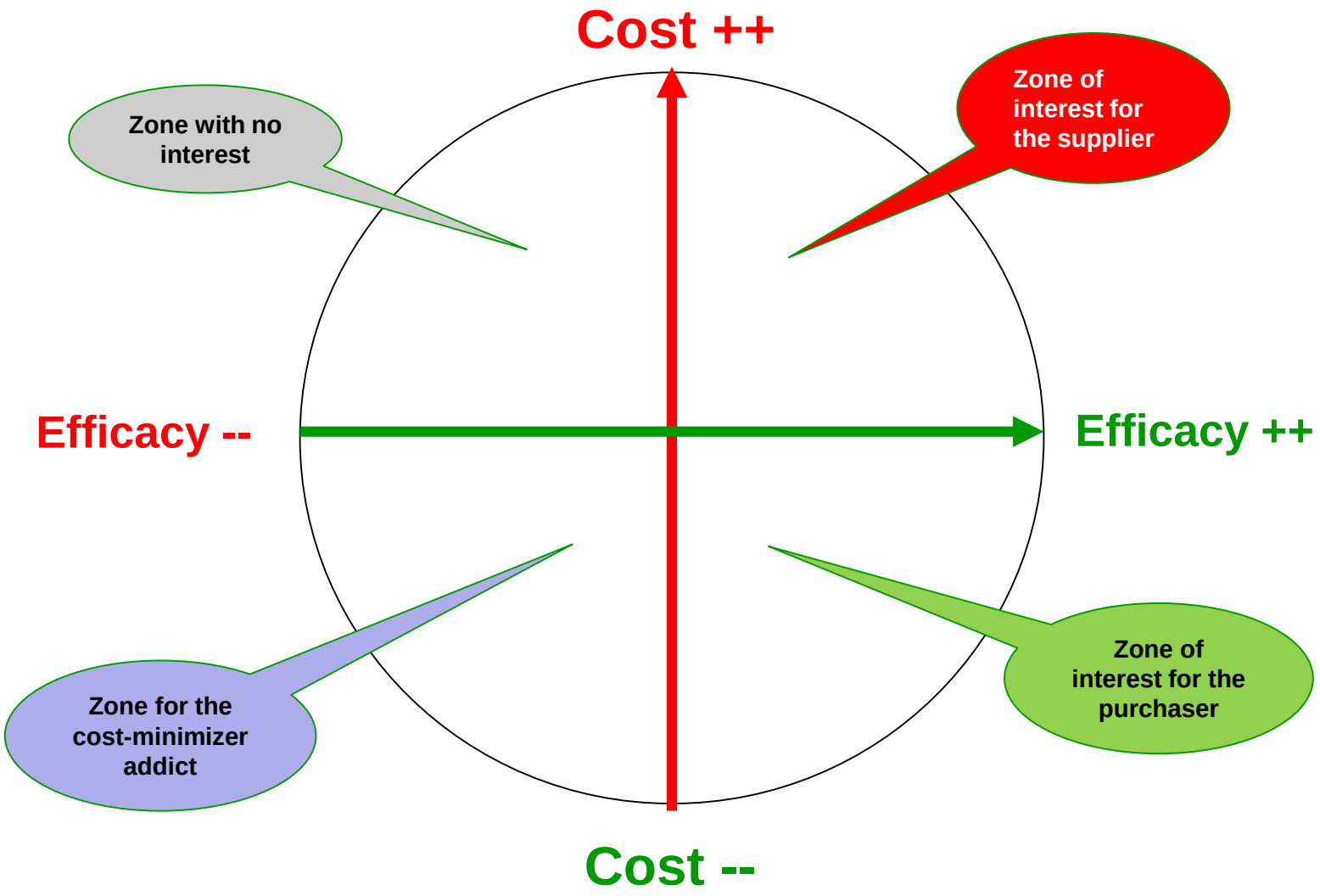
Here are the questions …

When choosing an antibiotic, do we know

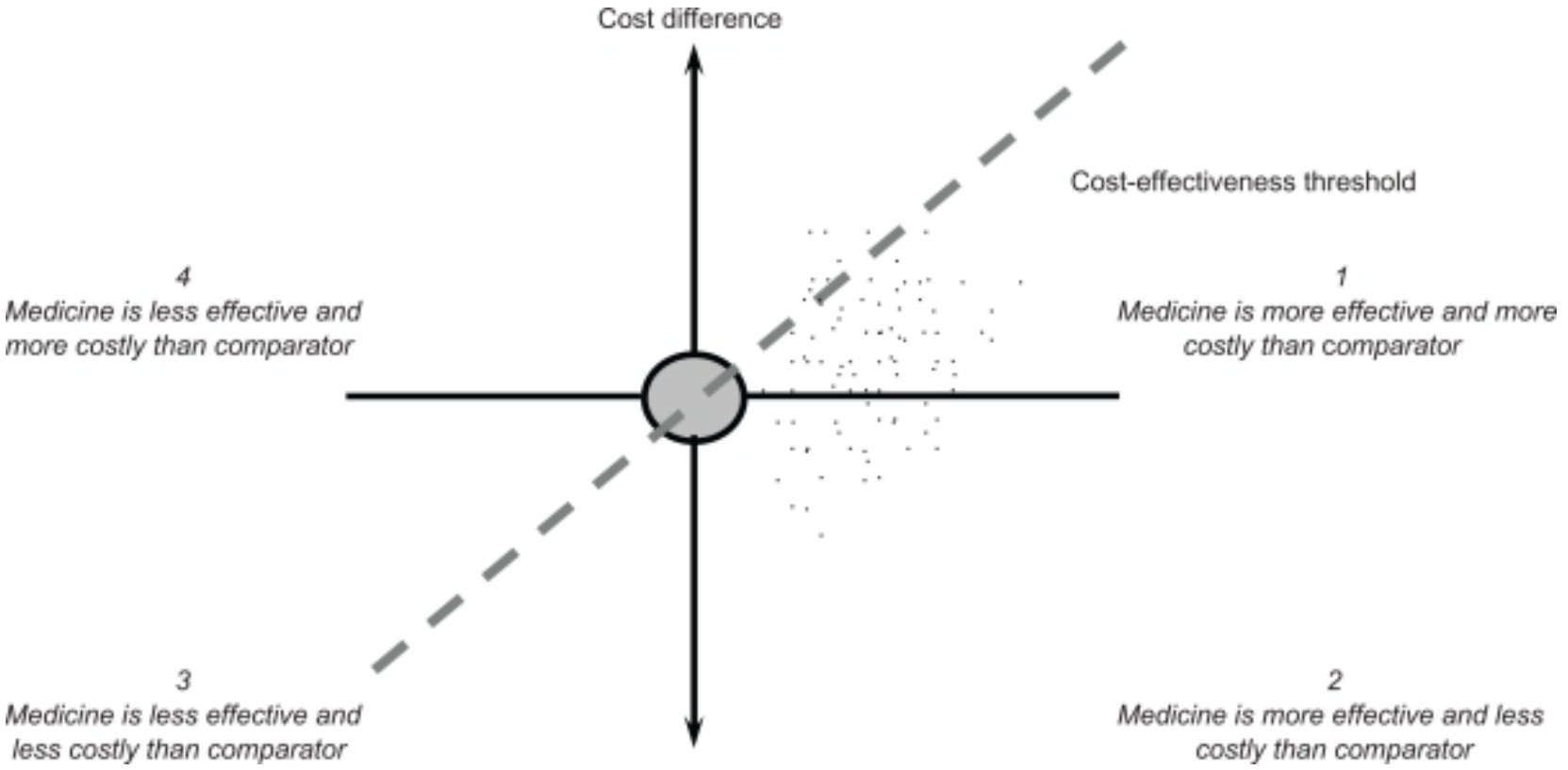
3. for Society
   - **how to get "value for money" ?**



How do you score the cost of a treatment ?



Scoring the cost of treatments



Simoens S. Biosimilar medicines and cost-effectiveness. Clinicoecon Outcomes. Res. 2011;3:29-36.

Costs: an example for vancomycin (always intravenous)

- Medical costs
  - **ordering and acquiring the drug (generic)**
  - storage in the hospital pharmacy
  - preparing the infusion (nurse's time and material)
  - infusion to the patient (twice daily) (nurse's time and material)
  - collecting and handling blood samples for monitoring (nurse's time)
  - laboratory serum level assay (cost and time)
  - maintaining the patient in the hospital for at least 10 days (daily cost)
  - managing nephrotoxicity (~ 5-10% of all patients)

- Non-medical costs
  - patient's absence from home for at least 10 days (need of external help)
  - patient's absence from work for at least 10 days (productivity loss)

The drug acquisition price of the generic vancomycin is only a small part of the total treatment cost !!!

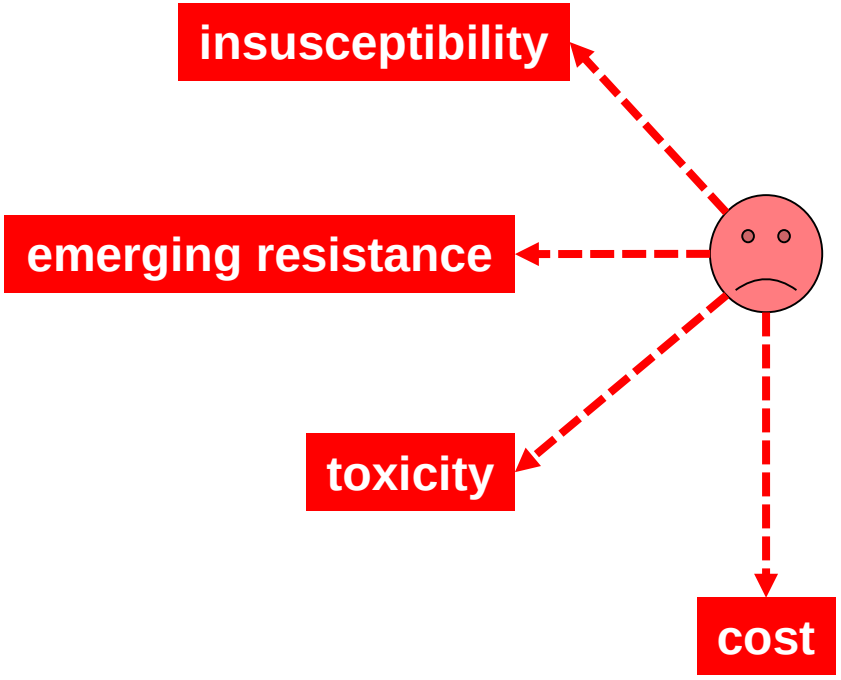
Switching to a short course with an oral form with similar efficacy ?

- Medical costs
  - **ordering and acquiring the drug (branded drug)** ↗
  - storage in the hospital pharmacy
  - ~~preparing the infusion (nurse's time and material)~~
  - ~~infusion to the patient (twice daily) (nurse's time and material)~~
  - ~~collecting and handling blood samples for monitoring (nurse's time)~~
  - ~~laboratory serum level assay (cost and time)~~
  - maintaining the patient in the hospital for at least 10 days (daily cost) ↘
  - ~~managing nephrotoxicity (~ 5-10% of all patients)~~

- Non-medical costs
  - patient's absence from home for at least 10 days(need of external help) ↘
  - patient's absence from work for at least 10 days (productivity loss) ↘

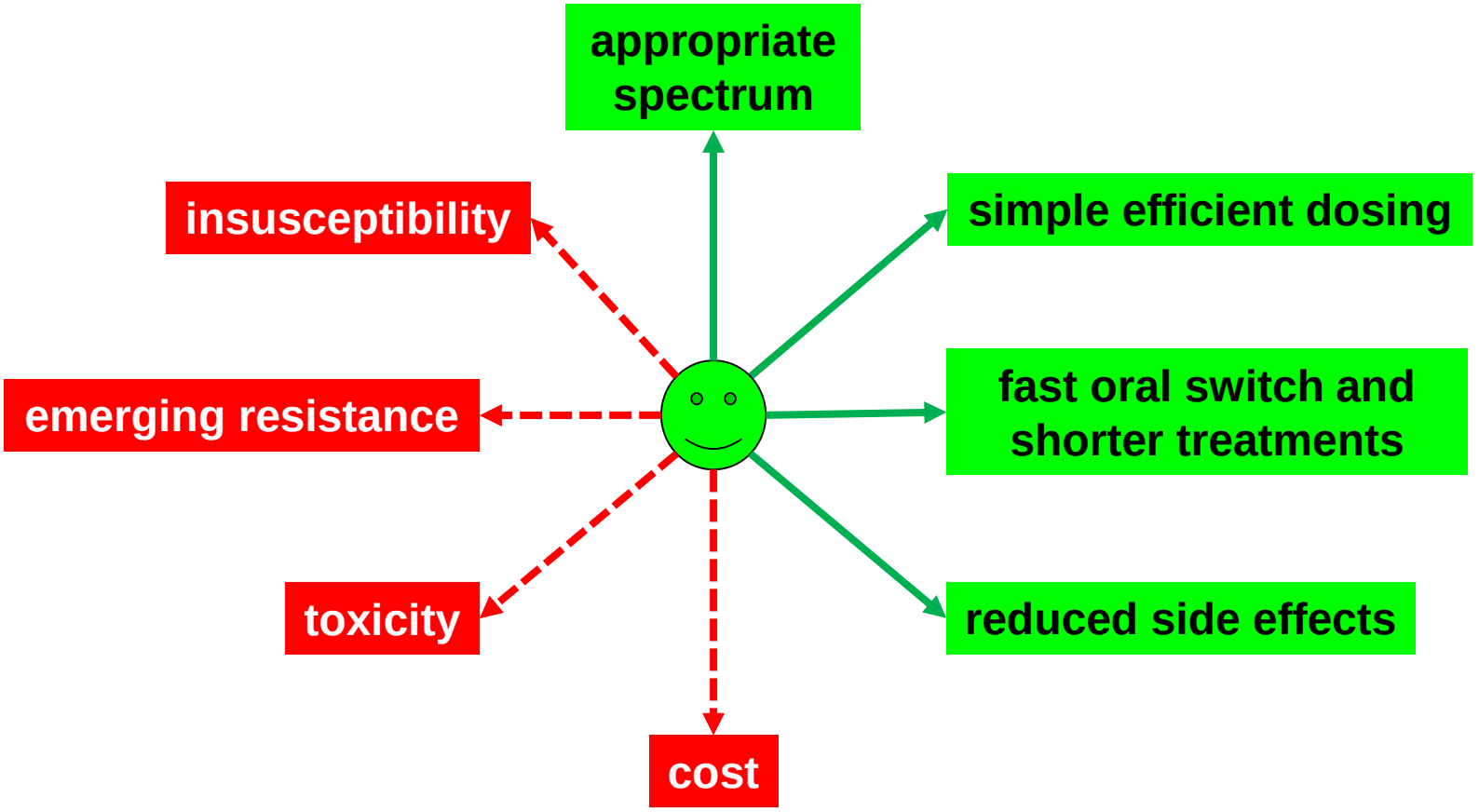
The <u>treatment</u> cost can be substantially reduced with an oral drug…
offsetting the increased drug acquisition cost (branded)

What you wish to avoid …



A short personal view…

and what you may be looking for …



A short personal view…

Last words: strive for quality *

Many antibiotics are available as generics !

For the patient

- lower cost
- availability

For Society

- Social Security savings

For the patient

- API purity ?
- excipients ?
- PK equivalence ?
- PD equivalence ?
- fake drugs !

For Society

- cost of analysis !
- innovation loss ?

API: Active Pharmaceutical Ingredient
PK: Pharmacokinetic
PD: Pharmacodynamic

* based on previous presentations: see http://www.facm.ucl.ac.be/facm-conferences.htm

Its all a problem of balance and compass

平衡

BALANCE