Antibiotic resistance: are we heading for failures ?

Paul M. Tulkens, MD, PhD
Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Université catholique de Louvain
Brussels, Belgium

Wednesday June 29th, 2011 12h30 – 13h30 Auditorium 3-4, Lisbon Congress Center

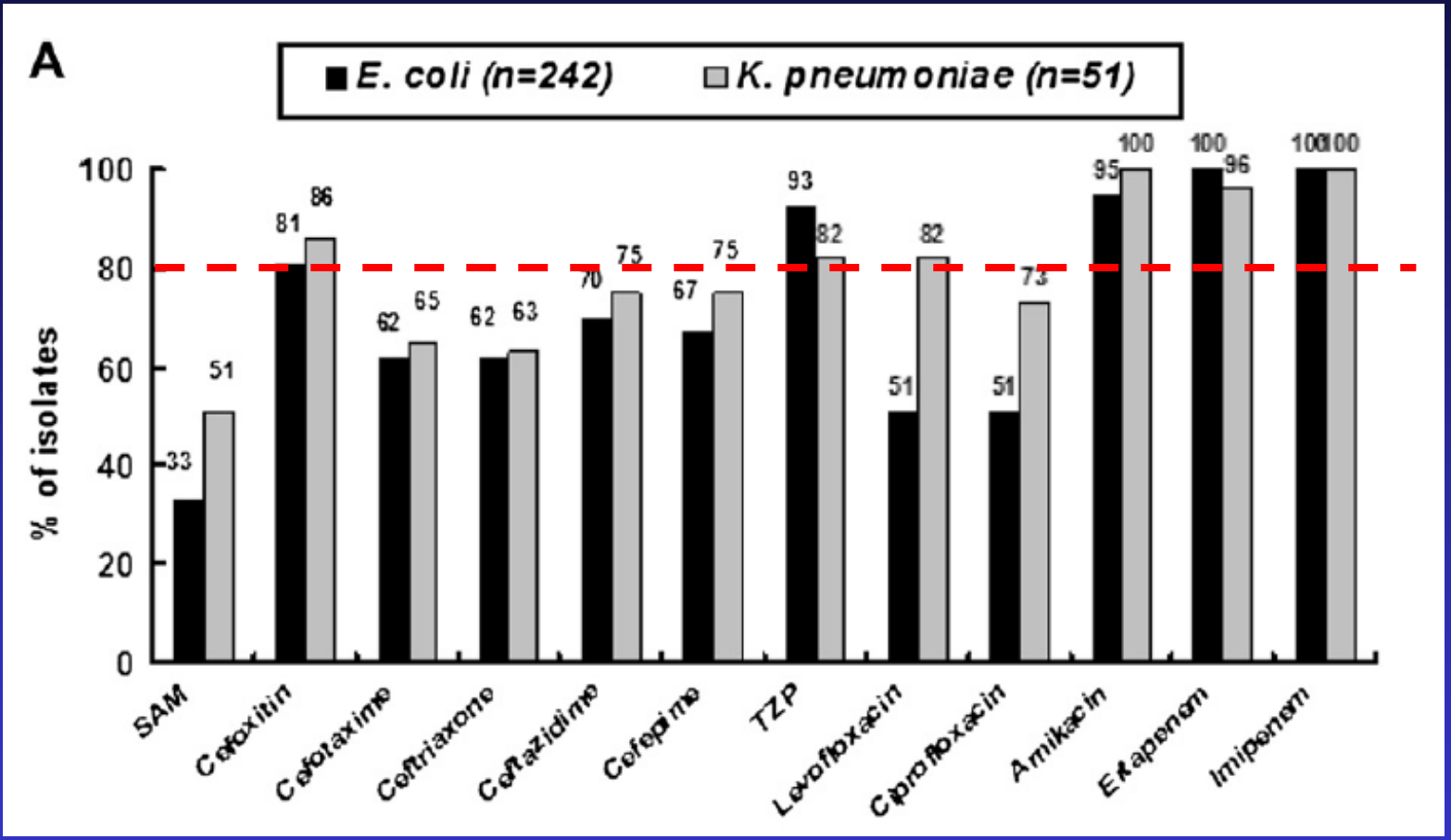
THE GUIDELINES OFFER MORE THAN ANTIBIOTICS TO MANAGE RECURRENT URINARY TRACT INFECTIONS

Chairman: Prof. K. Naber

slides: http://www.facm.ucl.ac.be

Antibiotic resistance: what ?

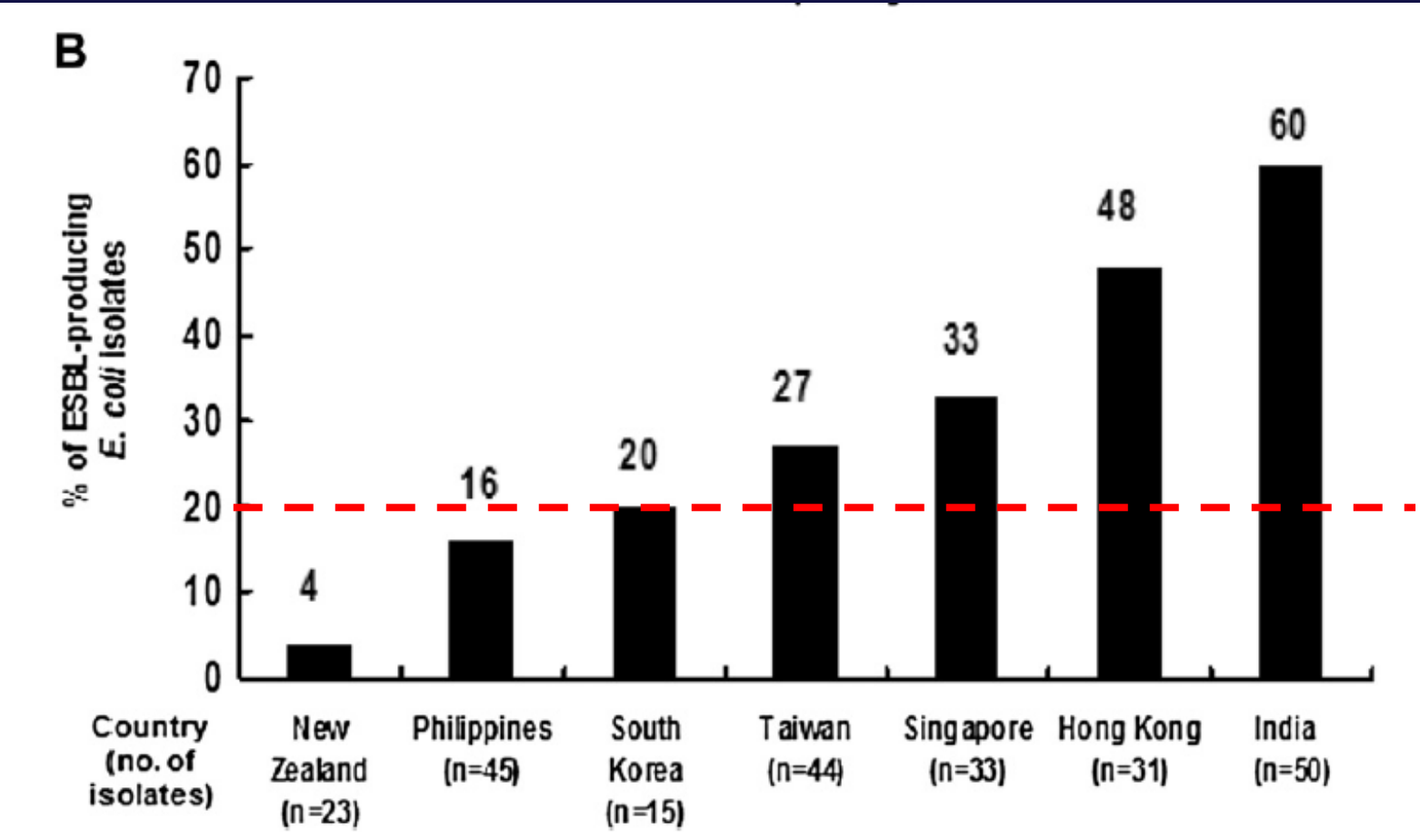
% of susceptible isolates in complicated UTI…



Hsueh P-R, et al., Consensus review of the epidemiology and appropriate antimicrobial therapy of **complicated** urinary tract infections in Asia-Pacific region, J Infect (2011), doi:10.1016/j.jinf.2011.05.015

Antibiotic resistance: what ?

% ESBL producers in complicated UTI …



Hsueh P-R, et al., Consensus review of the epidemiology and appropriate antimicrobial therapy of **complicated** urinary tract infections in Asia-Pacific region, J Infect (2011), doi:10.1016/j.jinf.2011.05.015

Antibiotic resistance: what ?

Resistance also exists in uncomplicated UTI …

Int Urol Nephrol (2011) 43:461–466

Table 2 Percentage of isolates from women resistant to selected antimicrobial agents

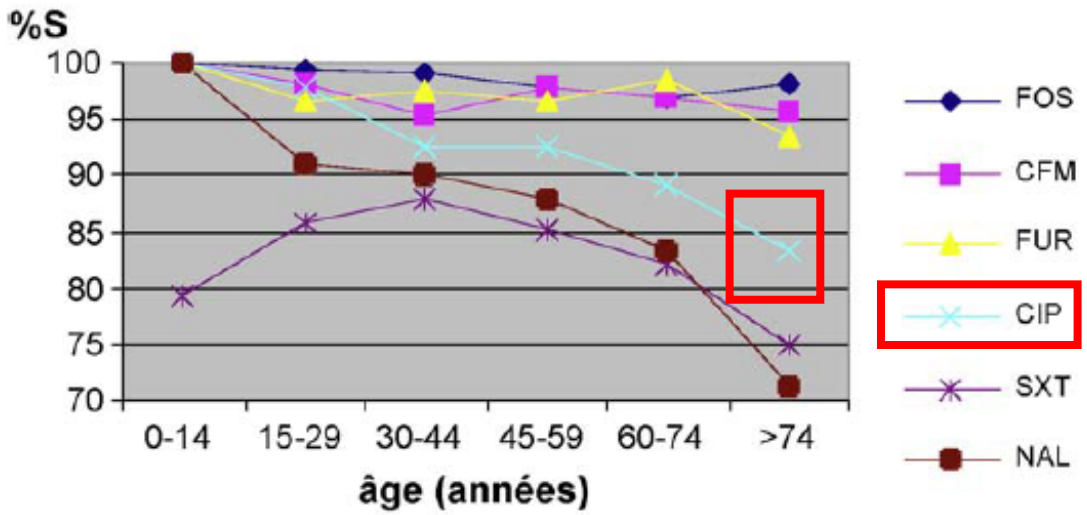
	Overall (%)	*E. coli* (%)	*Klebsiella* (%)	*Enterobacter* (%)	Coagulase negative staphylococcus (%)[a]	*Proteus* (%)
AMX	17.4	11.9	14.4	52.4	–	18.9
AMP	63.7	52.8	96.1	92.5	–	51.1
CEF	4.9	2.0	5.9	13.1	–	9.7
CIP	10.2	9.2	12.7	28.6	4.9	12.9
GEN	3.5	3.5	2.4	1.5	4.8	0.0
LEV	18.2	18.0	20.6	44.4	0.0	8.3
NIT	15.7	9.4	16.3	23.1	0.0	92.3
NOR	7.5	7.4	7.1	7.4	0.0	9.1
SMZ	39.8	43.6	29.9	39.7	100.0	22.2
NAL	14.1	14.0	11.8	14.3	–	16.1

Sonia et al. Antimicrobial resistance of uropathogens in women with acute **uncomplicated** cystitis from primary care settings. Int. Urol. Nephrol., 2011; 43:461-466

Antibiotic resistance: what ?

Age is a risk in uncomplicated UTI

R. Fabre et al. / Médecine et maladies infectieuses 40 (2010) 555–559



FOS : fosfomycine ; CFM : céfixime ; FUR : furadantine ; CIP : ciprofloxacine ; SXT : cotrimoxazole ; NAL : acide nalidixique

Fig. 1. Sensibilité de 1359 souches de *Escherichia coli* à six antibiotiques isolées d'infections urinaires communautaires chez la femme en fonction de l'âge. *Susceptibility to six antibiotics of 1359 Escherichia coli strains isolated from female community acquired urinary tract infections (UTIs) according to age.*

Antibiotic resistance: relation to consumption

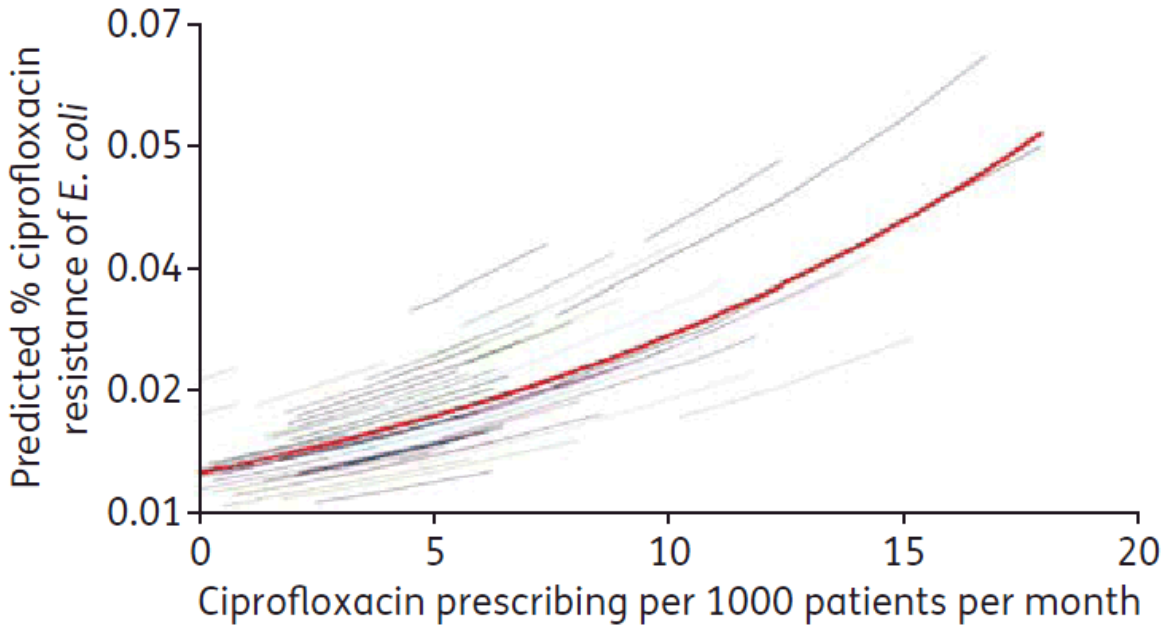


Figure 2. Predicted practice and overall (thick line) correlation between ciprofloxacin prescribing and resistance.

J Antimicrob Chemother 2010; **65**: 1514–1520
doi:10.1093/jac/dkq149 Advance Access publication 10 May 2010

A multilevel analysis of trimethoprim and ciprofloxacin prescribing and resistance of uropathogenic *Escherichia coli* in general practice

Akke Vellinga[1]*, Andrew W. Murphy[1], Belinda Hanahoe[2], Kathleen Bennett[3] and Martin Cormican[2,4]

Antibiotic resistance: which consequences ?

Journal of Infection (2011) 62, 159–164

Impact of discordant empirical therapy on outcome of community-acquired bacteremic acute pyelonephritis

Seung Soon Lee [a], Youngsu Kim [b], Doo Ryeon Chung [c,*]

Table 2 Comparison of clinical outcomes for bacteremic acute pyelonephritis between the groups of patients who received concordant and discordant therapy.

Clinical outcome	Concordant empirical therapy (n = 135)	Discordant empirical therapy (n = 29)	P value
Early clinical response	111 (82.2)	10 (34.5)	<0.001
Length of hospital stay, mean (SD), days	8.7 (6.8)	13.3 (14.0)	0.002
Length of ICU stay, mean (SD), days	0.4 (1.6)	0.2 (0.8)	0.61
Duration of antibiotic therapy, mean (SD), days	14.6 (4.3)	18.3 (5.1)	<0.001
Overall mortality	2 (1.5)	0 (0)	0.51
Infection-related mortality	1 (0.7)	0 (0)	0.64
Clinical cure	132 (97.8)	29 (100)	0.42

Abbreviations: SD = standard deviation Note. Data are shown as number (%) unless specified.

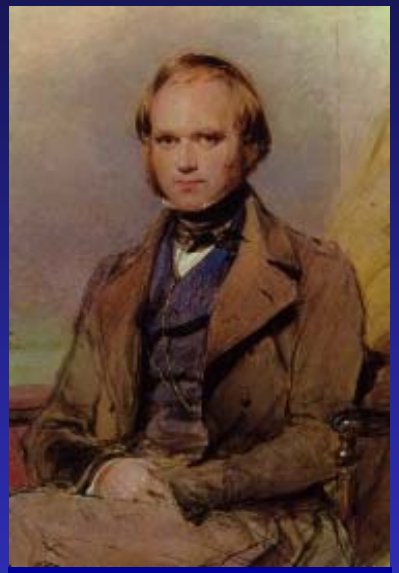
Antibiotic resistance: why ?

A simple application of Darwin's concepts ...

gene

enzyme / nucleoprotein

function



Detail of watercolor by George Richmond, 1840. Darwin Museum at Down House

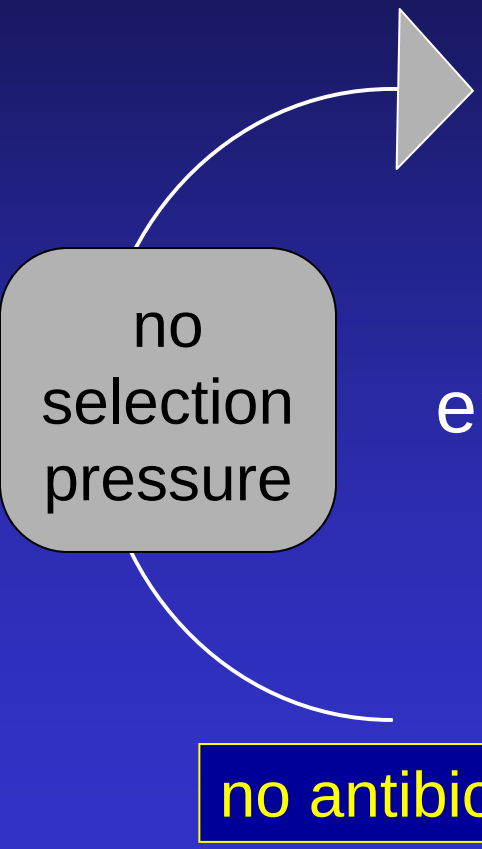
Antibiotic resistance: why ?

A simple application of Darwin's concepts …
to a highly changeable material

- typical infectious foci contain as much as 10^6 - 10^9 organisms
- most bacteria are VERY quickly (20 min…) multiplying with a high level of errors (10^{-6} – 10^{-8})
- pathogenic bacteria easily exchange genetic material

Rapid acquisition and dissemination of resistance determinants

Antibiotic resistance: why ?



gene

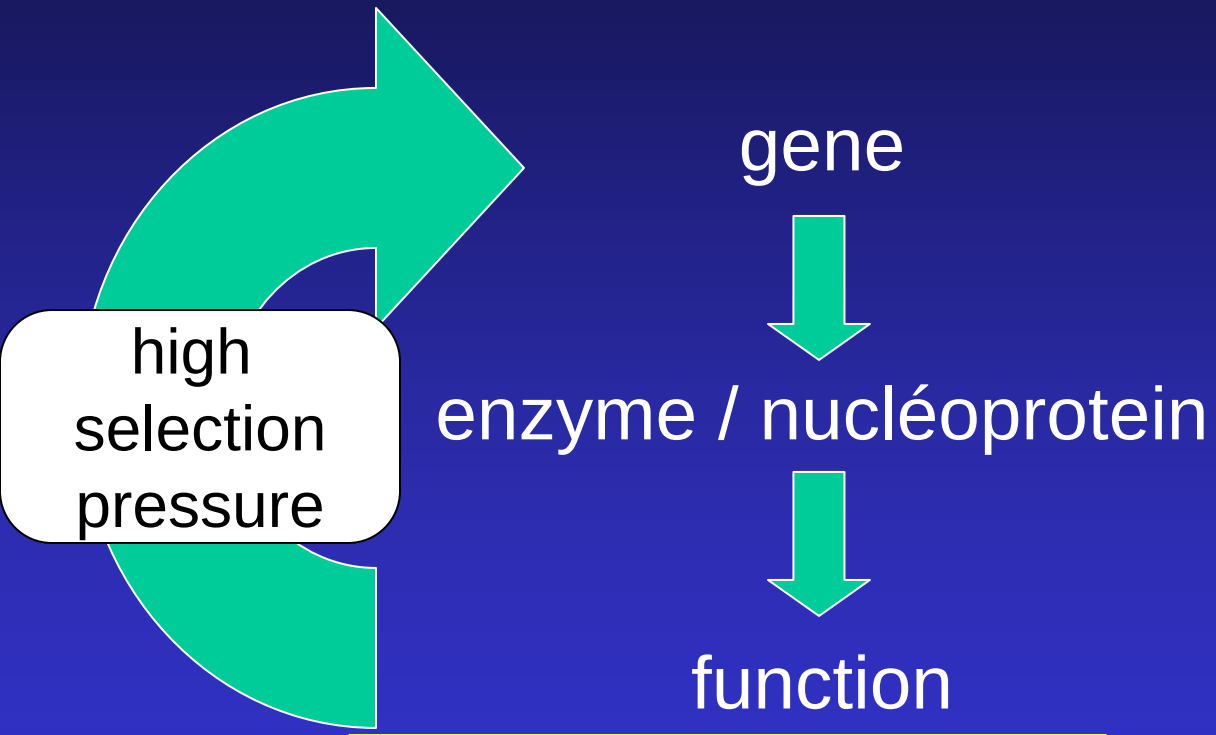
enzyme / nucleoprotein

function

Resistance ↗ if

- High consumption **and**
- Inappropriate use

Antibiotic resistance: why ?



High and inappropriate antibiotic consumption;
A lot of surviving bacteria

Resistance ↗ if

- High consumption **and**
- Inappropriate use

A simple experiment …

Exposure of E. aerogenes to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC détermination

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 8 April 2011

A simple experiment …

Exposure of E. aerogenes to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC détermination

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 6 April 2011

sub-MIC concentrations create resistance !

We were not alone …

MICROBIAL DRUG RESISTANCE
Volume 17, Number 2, 2011

DOI: 10.1089/mdr.2010.0101

De Novo Acquisition of Resistance to Three Antibiotics by *Escherichia coli*

Michael A. van der Horst,[1] Jasper M. Schuurmans,[1,2] Marja C. Smid,[1] Belinda B. Koenders,[1,2] and Benno H. ter Kuile[1,2]

We were not alone …

MICROBIAL DRUG RESISTANCE
Volume 17, Number 2, 2011

DOI: 10.1089/mdr.2010.0101

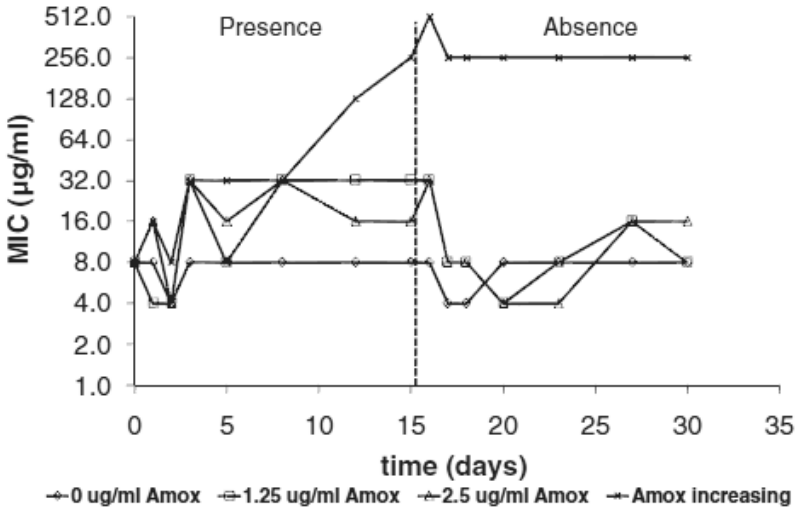


FIG. 1. Increase of the MIC during growth of *Escherichia coli* at various amoxicillin regimes. MIC, minimal inhibitory concentration.

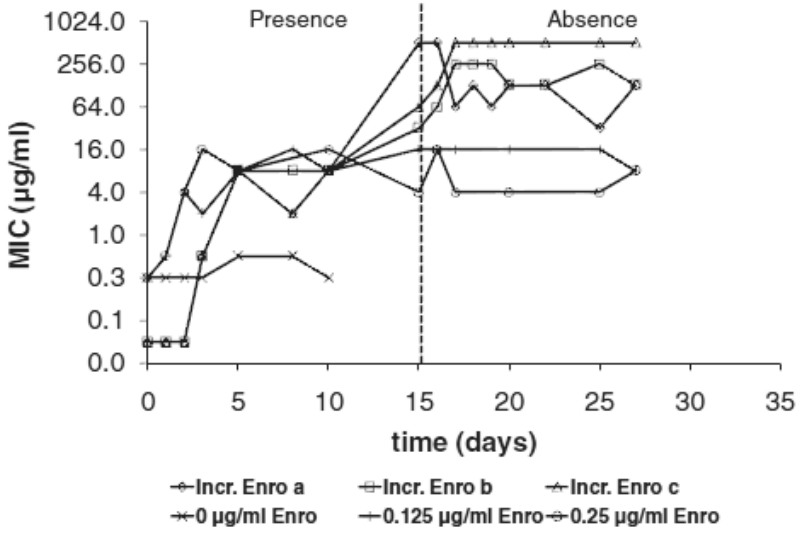


FIG. 3. Increase of the MIC during growth of *E. coli* at various enrofloxacin regimes.

We were not alone …

MICROBIAL DRUG RESISTANCE
Volume 17, Number 2, 2011

DOI: 10.1089/mdr.2010.0101

TABLE 1. CROSS RESISTANCE OF *ESCHERICHIA COLI* ADAPTED TO DIFFERENT ANTIBIOTICS

	MIC for (μg/ml)		
Adapted to	*Amoxicillin*	*Tetracycline*	*Enrofloxacin*
Wild type (not adapted)	4	2	0.25
Amoxicillin	128	8	1
Tetracycline	8	32	0.5
Enrofloxacin	4	4	512

MIC, minimal inhibitory concentration.

Thus, you need to do something …

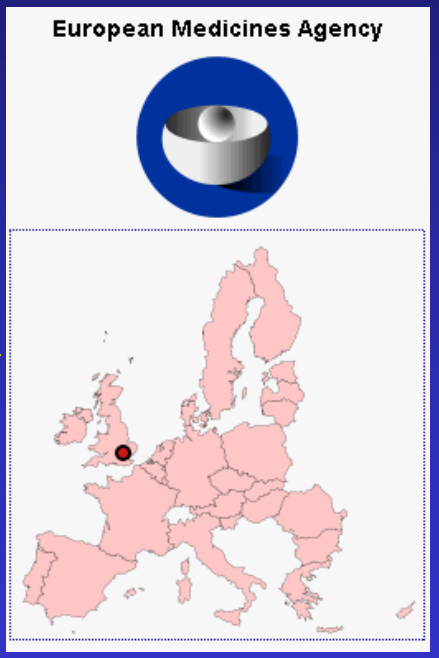
- "HIT HARD & HIT FAST ?"

Paul Ehrlich:

‚Frapper fort et frapper vite' (Hit hard and early) –

Address to the 17th International Congress of Medicine, 1913

Ehrlich P, Lancet 1913; 2:445–51.



PK /PD and resistance in Europe in 1999

" Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

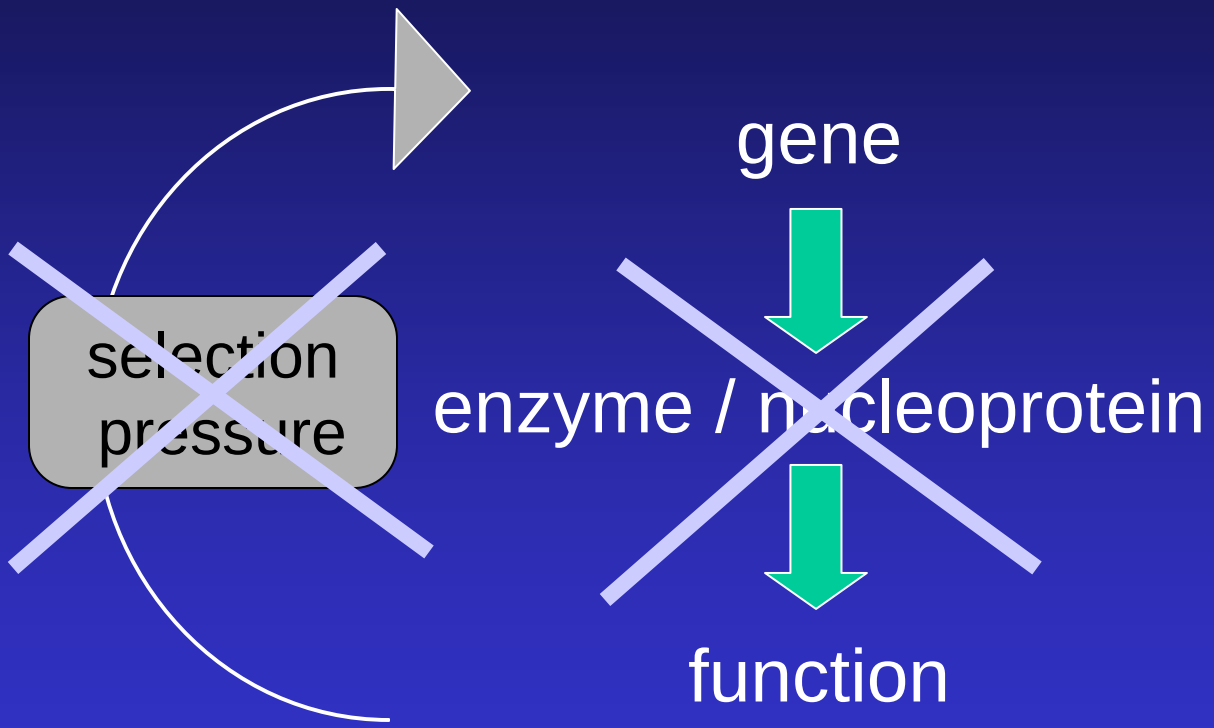
A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties… "

---

* Committee for Proprietary Medicinal Products – European Medicines Agency

Antibiotic resistance: the PK/PD way



Resistance ↗ if

- High consumption **and**
- Inappropriate use

Appropriate dose of antibiotic;
No surviving bacteria

Can we help ?

- Avoiding risk factors ?
- Guidelines ?
- Eradicate ?
- Breakpoints ?
- Mutation-Preventing Concentration ?
- Or a more subtle approach ?

Avoiding risk factors ?

J Antimicrob Chemother 2011; **66**: 650–656
doi:10.1093/jac/dkq465 Advance Access publication 1 December 2010

Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection

Willize E. van der Starre[1]†, Cees van Nieuwkoop[1]*†, Sunita Paltansing[2], Jan W. van't Wout[1,3], Geert H. Groeneveld[1], Martin J. Becker[4], Ted Koster[5], G. Hanke Wattel-Louis[6], Nathalie M. Delfos[7], Hans C. Ablij[8], Eliane M.S. Leyten[9], Jeanet W. Blom[10] and Jaap T. van Dissel[1]

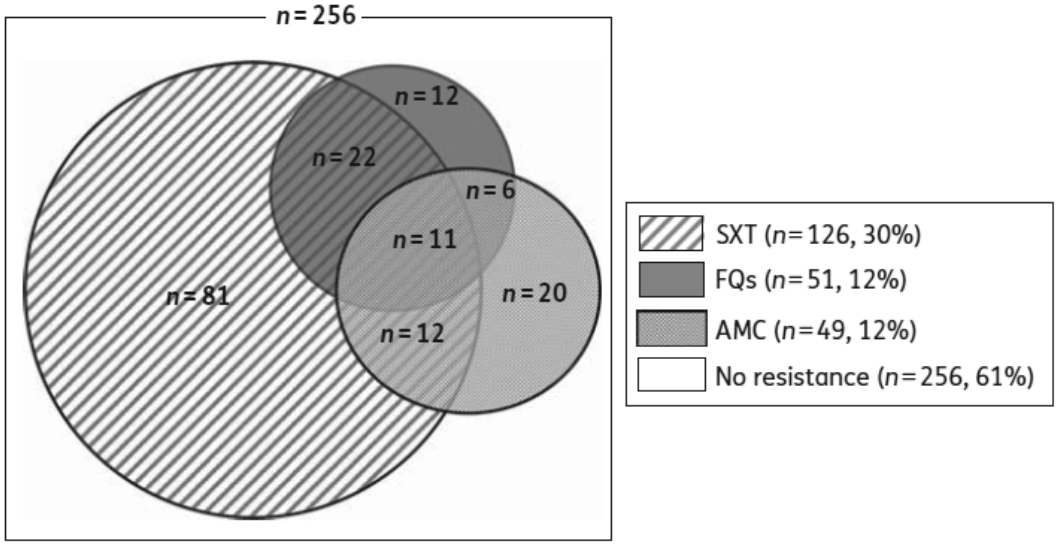


Figure 2. Distribution of resistance to oral antibiotics in 420 patients with febrile *E. coli* UTI. SXT, trimethoprim/sulfamethoxazole; FQs, fluoroquinolones; AMC, amoxicillin/clavulanate.

Avoiding risk factors ?

J Antimicrob Chemother 2011; **66**: 650–656
doi:10.1093/jac/dkq465 Advance Access publication 1 December 2010

Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection

Willize E. van der Starre[1]†, Cees van Nieuwkoop[1]*†, Sunita Paltansing[2], Jan W. van't Wout[1,3], Geert H. Groeneveld[1], Martin J. Becker[4], Ted Koster[5], G. Hanke Wattel-Louis[6], Nathalie M. Delfos[7], Hans C. Ablij[8], Eliane M.S. Leyten[9], Jeanet W. Blom[10] and Jaap T. van Dissel[1]

Conclusions: Recent hospitalization, urinary catheter and fluoroquinolone use in the past 6 months were independent risk factors for fluoroquinolone resistance in community-onset febrile *E. coli* UTI. Contact with animals or hospitalized household members was not associated with fluoroquinolone resistance. Fluoroquinolone resistance may be a marker of broader resistance, including ESBL positivity.

Are guidelines always good ?

International Journal of Infectious Diseases 14 (2010) e770–e774

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Increasing resistance in community-acquired urinary tract infections in Latin America, five years after the implementation of national therapeutic guidelines

P.H.A. Bours [a,1,*], R. Polak [a,1], A.I.M. Hoepelman [a], E. Delgado [b], A. Jarquin [b], A.J. Matute [b]

Conclusions: Resistance rates in community-acquired UTIs in Nicaragua are increasing. The introduction of therapeutic guidelines with ceftriaxone recommended for upper UTIs and nitrofurantoin for lower UTIs, has led to increasing resistance against both antibiotics. The emergence of ESBL-producing *E. coli* is worrisome, along with the appearance of *Serratia spp* in the population.

Eradicate …

The most effective strategy against antibiotic resistance is:

- “to unequivocally destroy microbes”
- “thereby defeating resistance before it starts”

WHO Overcoming Antimicrobial Resistance, 2000

Why would you like to eradicate …

- Killed bacteria do not mutate anymore …
  (simple application of Darwin's concepts…)
- If they are killed, they cannot contaminate their neighbors …
  (basic principle for epidemiology actions …)
- After all, if Pasteur is right (and he is…), don't we need to eliminate the pathogen to cure ?
  (physiopathological basis of infectious diseases…)
- Don't you wish that you patient recovers more quickly and definitely ?
  (a satisfied patient will be faithfully)

Why would you like to eradicate …

- Killed bacteria do not mutate anymore …
  (simple application of Darwin's concepts…)

- If they are killed, they cannot contaminate their neighbors …
  (basic principle for epidemiology actions …)

- After all, if Pasteur is right ([illegible]), [illegible] have need to eliminate [illegible] to cure ?
  (physiopathological basis of infectious diseases…)

But, can you really do that ?

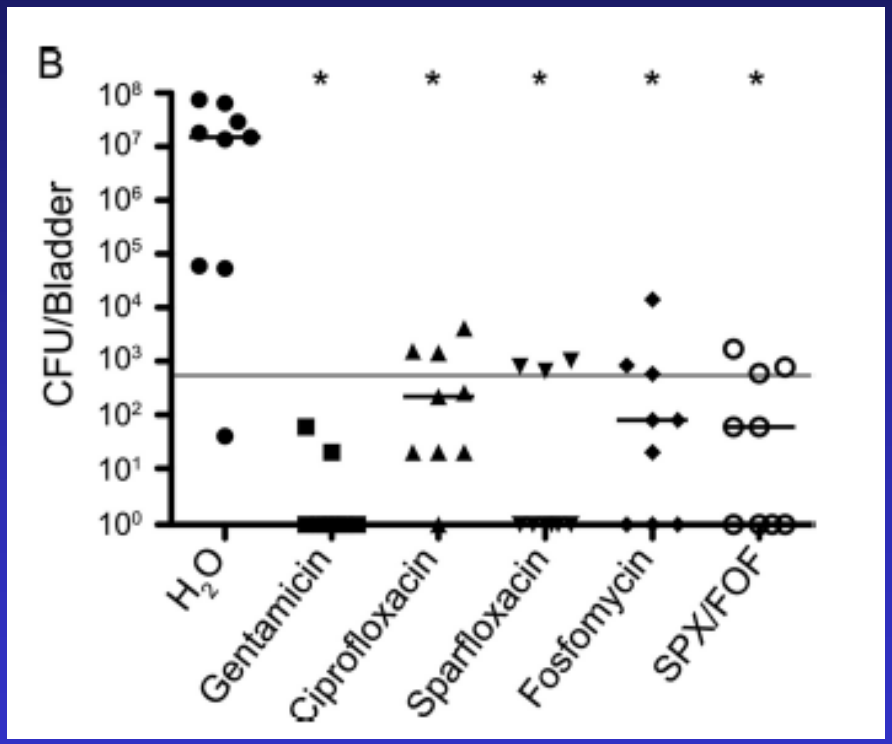
- Don't you wish that you patient recovers more quickly and defenitely ?
  (a satisfied patient will be faithfully)

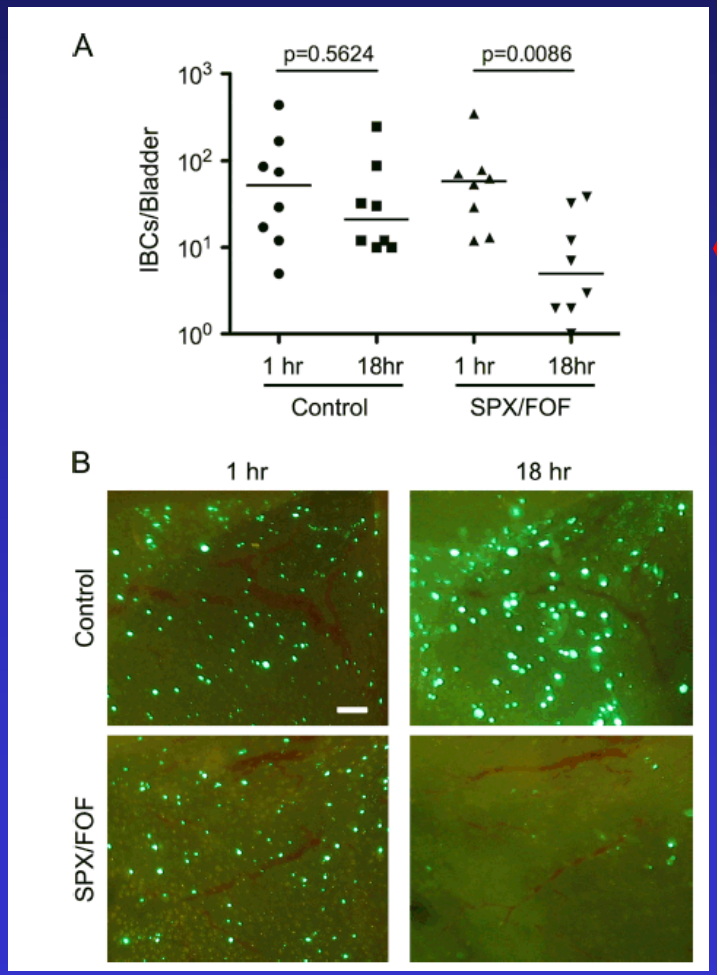
Eradicate even the intracellular bacteria ?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1855–1863 Vol. 54, No. 5

Persistence of Uropathogenic *Escherichia coli* in the Face of Multiple Antibiotics[▽]

Matthew G. Blango and Matthew A. Mulvey*





Better breakpoints ? ...

Journal of Chemotherapy Vol. 22 - n. 5 (345-355) - 2010

Do Different Susceptibility Breakpoints Affect the Selection of Antimicrobials for Treatment of Uncomplicated Cystitis?

G.C. SCHITO [1] - L. GUALCO [1] - K.G. NABER [2] - H. BOTTO [3] - J. PALOU [4] - T. MAZZEI [5] - A. MARCHESE [1]

[1] Institute of Microbiology, University of Genoa, Genoa, Italy. [2] Technical University of Munich, Munich, Germany. [3] Department of Urology, Hôpital Foch, Suresnes, France. [4] Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain. [5] Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, Italy.

Corresponding author: Anna Marchese, Di.S.C.M.I.T., Microbiology Unit, University of Genoa, Largo R. Benzi, 10, 16132 Genoa, Italy. Tel.: +39-010-3537502; Fax: +39-010-3537651; e-mail: anna.marchese@unige.it

In conclusion, fosfomycin, mecillinam, and nitrofurantoin have preserved their *in vitro* activity in all countries investigated, regardless of the criteria adopted. They continue to represent effective options for the empiric therapy of female patients with uncomplicated cystitis. The use of different interpretative criteria for *E. coli* responsible for UTIs therefore has no influence on the decision to be taken by the physicians managing the patients.

Can we be so optimist ? …

MIC distributions of fosfomycin in commonly encountered isolates in Taiwan (n=960)

TABLE 2: Minimum inhibitory concentration (MIC) distributions, epidemiological cutoff values and susceptibility rates of the species examined

Species	Subgroup[a]	N	MIC (µg/mL)													ECV[b] (µg/mL)	CLSI BP %S[c]	EUCAST BP %S[d]
			0.25	0.5	1	2	4	8	16	32	64	128	256	512	>512			
Escherichia coli		100	15	70	6	5	2		2							1	100	100
Klebsiella pneumoniae		100			1		12	45	19	8	7	2	5		1	16	92	85
Enterobacter cloacae		100		6	6	3	6	16	18	17	13	8	6	1		512	85	72
Enterococcus faecalis	Van-S	50							7	37	5	1				64	99	94
	Van-R	30							1	28	1					64	100	96.7
	Combined	80							8	65	6	1				64	98.8	91.3
Enterococcus faecium	Van-S	50							1	11	33	5				128	95	62
	Van-R	30								8	18	4				128	86.7	26.7
	Combined	80							1	19	51	9				128	88.8	25.0
Staphylococcus aureus	Meth-S	100		20	46	20	8		4	2						4	100	100
	Meth-R	100		12	32	5	27	9	2	2		1			10	2	89	89
	Combined	200		32	78	25	35	9	6	4		1			10	2	94.5	94.5
Acinetobacter baumannii		100									3	68	29			256	3	0
Pseudomonas aeruginosa		100				4	4	1	4	16	51	15	2		3	256	80	29
Stenotrophomonas maltophilia		100					1			1	58	32	7		1	128	59	1

Lu et al. AAC Accepts, E-pub 13 June 2011

Can we be so optimist ? …

Fosfomycin yesterday … and today in MIC surveys

Table 1 $MICs_{90}$ for clinically relevant isolates

Bacteria	Older studies MIC_{90} (µg/ml)	More contemporary studies MIC_{90} (µg/ml)
S. aureus	1–8	8–64
S. epidermidis	32–64	na
Enterococcus faecalis	8–64	64
Streptococcus group A	32–64	≥64
Streptococcus group B	32–64	≥64
Streptococcus pneumoniae	8–16	na
Escherichia coli	0.5–4	≤64
Klebsiella	32–256	32–128
Enterobacter	16–256	128
P. mirabilis	16–64	≥128
Proteus spp. (indole pos.)	512–1024	128
Pseudomonas aeruginosa	16–128	128

Eur J Clin Microbiol Infect Dis (2010) 29:127–142

Fosfomycin: an old, new friend?

M. Popovic · D. Steinort · S. Pillai · C. Joukhadar

Can we be so optimist ? ...

Fosfomycin and ESBL

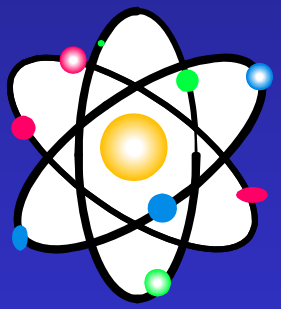
Table 1 Comparison of antimicrobial susceptibilities between ESBL-producing *E coli* and ESBL-producing *K pneumoniae*

Antibiotic	ESBL-EC ($n = 134$)		ESBL-KP ($n = 66$)		p
	S (%)	MIC_{90} (mg/L)	S(%)	MIC_{90} (mg/L)	
Fosfomycin	95.5		57.6		<0.001
Nitrofurantoin	79.1	>128	13.6	>128	<0.001
Ciprofloxacin	29.1	>4	37.9	>4	0.276
Gentamicin	44.8	>16	30.3	>16	0.049
Trimethoprim-sulfamethoxazole	22.4	>4	18.2	>4	0.492
Amikacin	97.0	8	57.6	>64	<0.001
Imipenem	99.3	1	90.9	4	0.003

ESBL-*EC* = extended-spectrum β-lactamase producing *Escherichia coli*; ESBL-*KP* = extended-spectrum β-lactamase producing *Klebsiella pneumoniae*; MIC = minimal inhibition concentration; S = susceptibility.
Significantly different if $p < 0.05$.

Liu H-Y, et al., Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan, Journal of Microbiology, Immunology and Infection (2011), doi:10.1016/j.jmii.2010.08.012

Lisbon, we have a problem …



Can Science offer a better solution for our patients ?

slides: http://www.facm.ucl.ac.be

Disclosures …

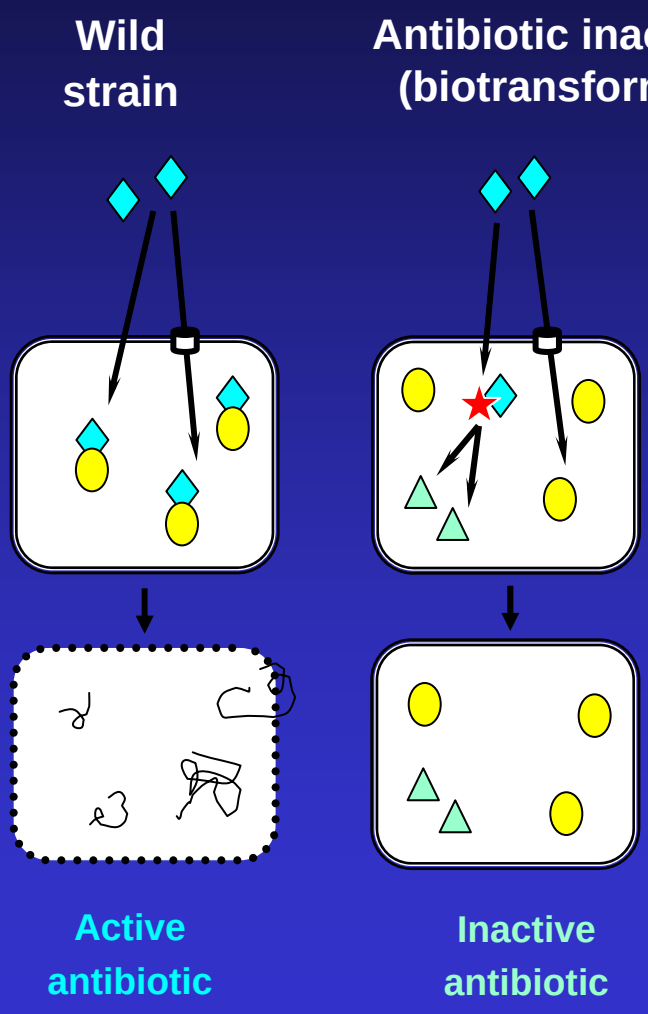
- Research grants from Bayer, Sanofi-Aventis, The Medicines Company, Trius Pharmaceuticals, Cerexa Inc., …
- Speaker's honoraria from GSK, AstraZeneca, Vifor Pharma, …
- Ex-Member of the European Committee for Antibiotic Susceptibility Testing (EUCAST)
- Ex-Member of the Belgian Antibiotic Policy Coordination Committee and the Belgian Drug Reimbursement Committee

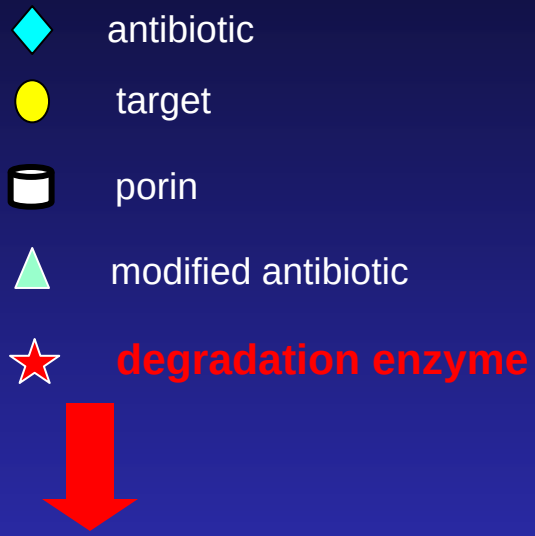
All slides are available on http://www.facm.ucl.ac.be

Back-up slides

Antibiotic resistance: mechanisms

1. « fighting » strategy

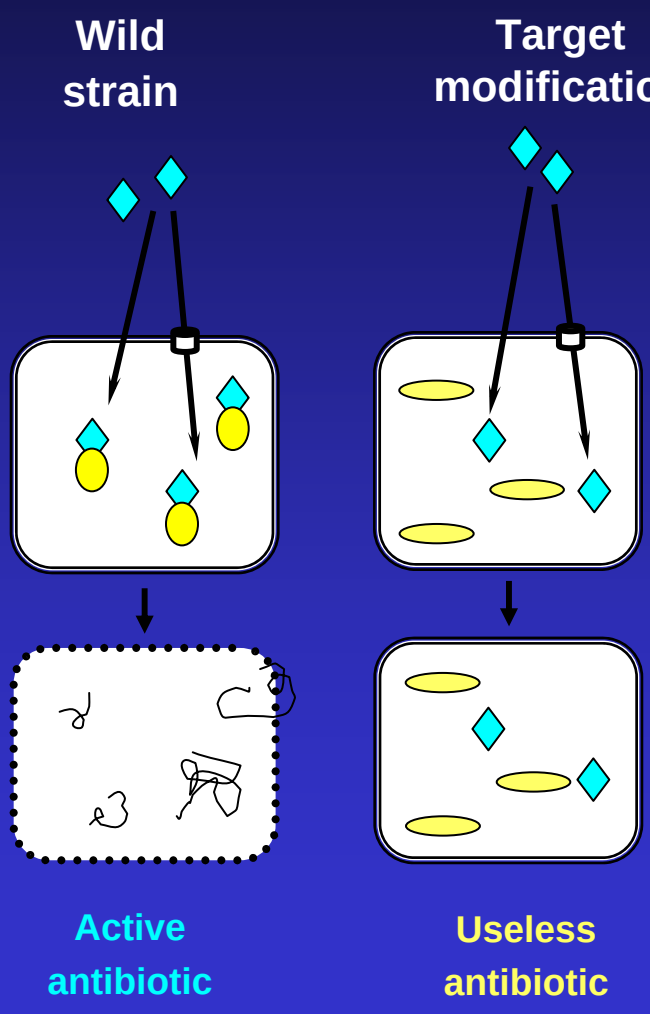




- **β-lactamases**
  (*S. aureus, H. influenzae, E. coli, P. aeruginosa, …*)
- **aminoglycoside-inactivating enzymes**
  (enterobacteriaceae)
- **macrolide-inactivating enzymes**
  (*E. coli*)

Antibiotic resistance: mechanisms

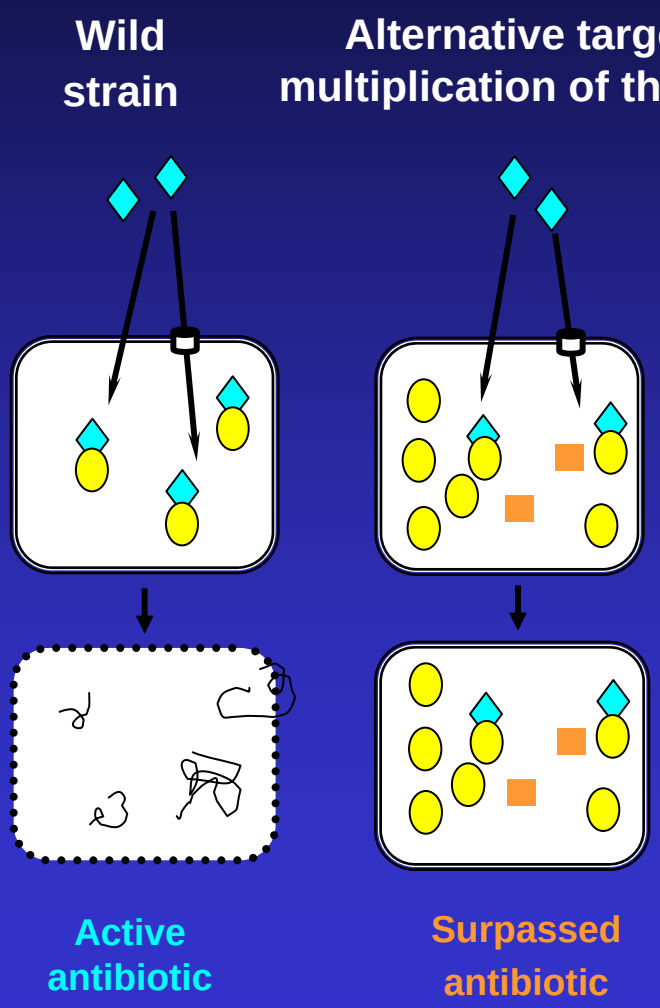
2. « escaping » strategy

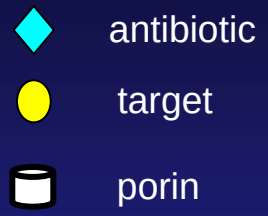


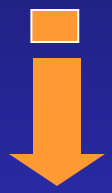
- **quinolone target mutation (GyrA et ParC subunits of the enzymes responsible for ADN supercoiling/decoiling)** (*S. aureus, S. pneumoniae, P. aeruginosa, …*)
- **ribosome methylation at the site of macrolides binding** (*S. aureus, S. pneumoniae*)
- **mutation of PBP (target for β-lactams)** (*S. aureus* [= MRSA !], *S. pneumoniae*)

Antibiotic resistance: mechanisms

3. « avoiding » strategy



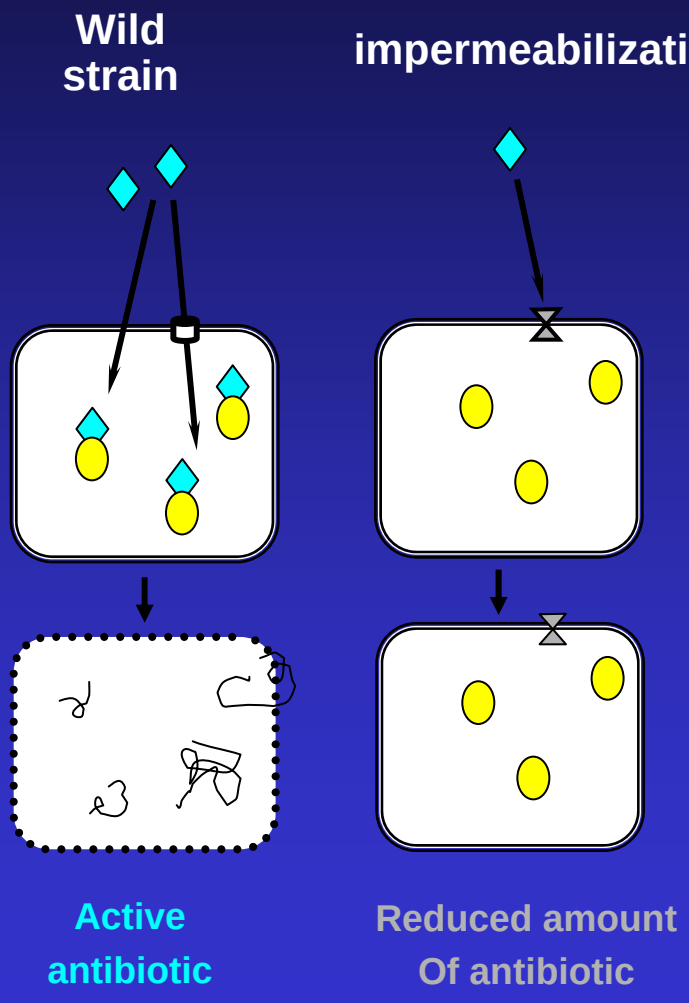




- **production of an altered peptidoglycan not recognized by glycopeptides**
  (enterococci, …)
- **production of a thicker cell wall, saturating glycopeptide binding**
  (*S. aureus* [VISA])

Antibiotic resistance: mechanisms

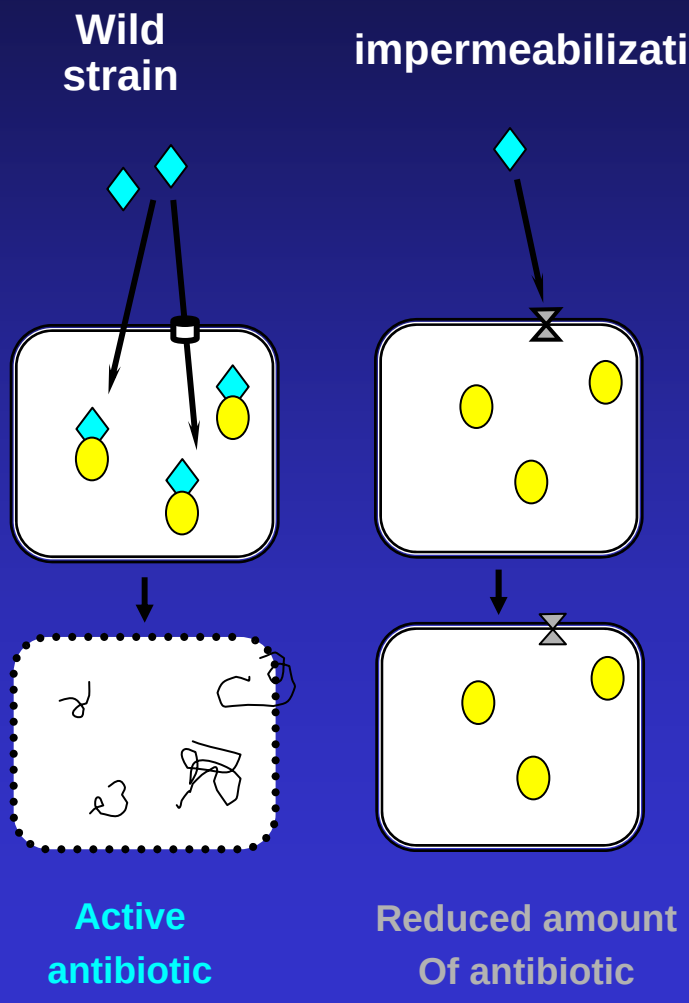
4. « elimination » strategy



- **mutation of the OprD porine reducing the penetration of various antibiotics in *Pseudomonas aeruginosa***

Antibiotic resistance: mechanisms

4. « elimination » strategy



antibiotic

target

porin

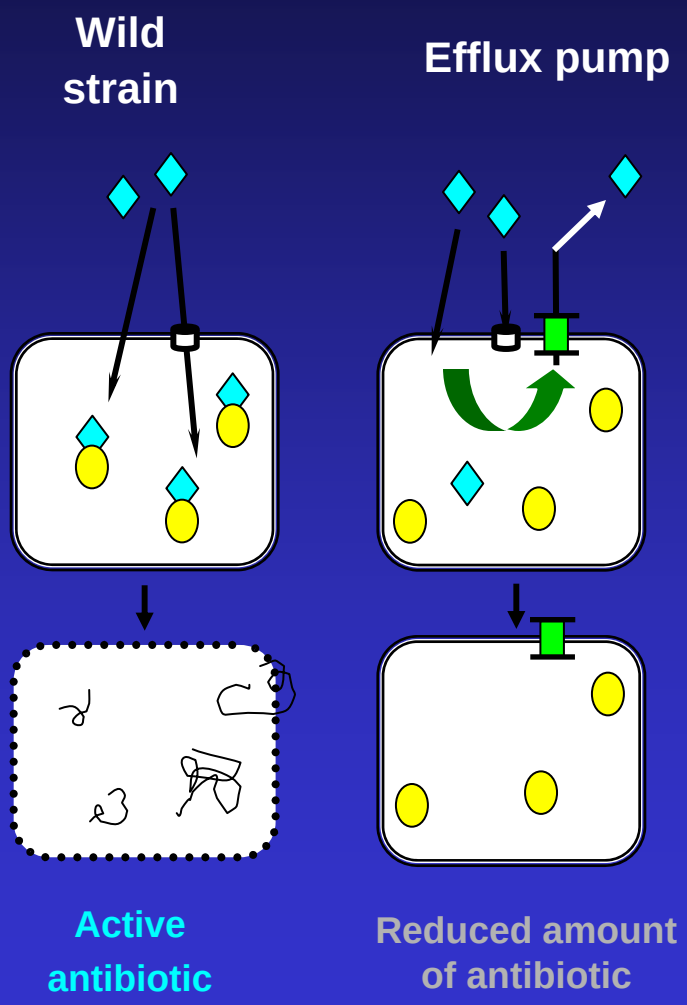
Modified porine

- **mutation of the OprD porine reducing the penetration of various antibiotics in *Pseudomonas aeruginosa***

responsible for « intrinsic » resistance of *P.aeruginosa* to a large number of antibiotics

Antibiotic resistance: mechanisms

4. « elimination » strategy

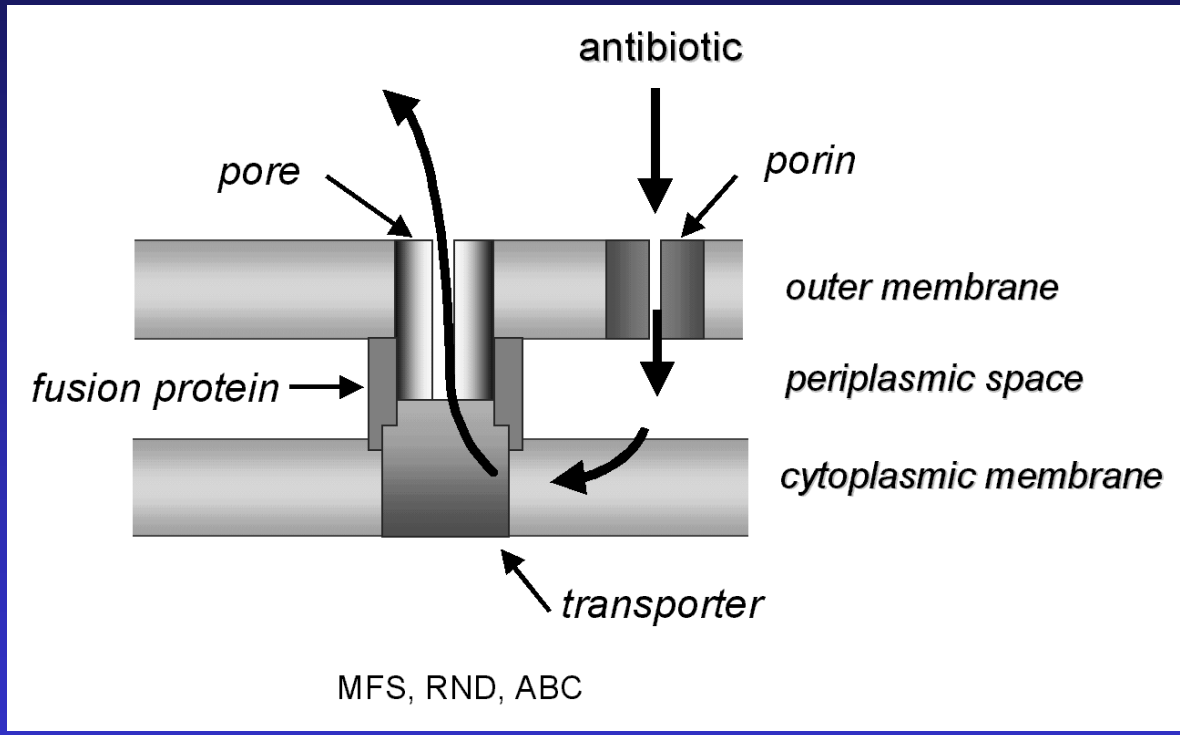


- overexpression of … pumps conferring … large number of … *Pseudomonas* …
- overexpression of narrow … conferring resistance to a given class … antibiotics in *S. aureus* and *S. pneumoniae*

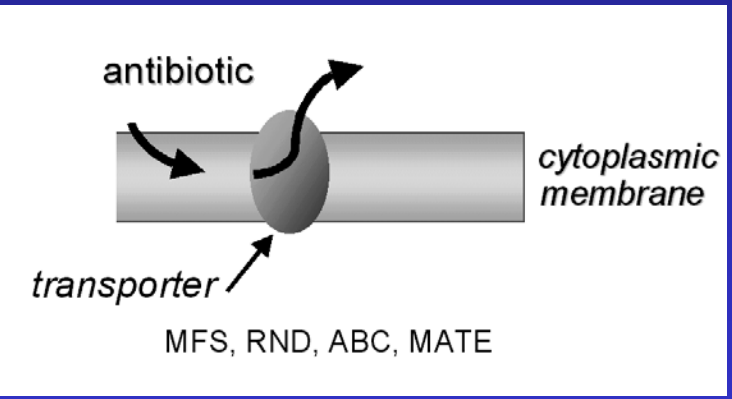
Responsible for « intrinsic » resistance of *P.aeruginosa* to a large number of antibiotics

Antibiotic transport through bacterial membranes

Gram(-)



Gram(+)



Van Bambeke *et al* JAC (2003) 51:1067-1077

Antibiotic efflux in Gram (-)

organism	famiy	pump	antibiotic						
			β-lactams	Aminoglycosides	Fluoroquinolones	Macrolides	Tetracyclines	Trimetoprim	Sulfamides
E. coli	ABC	MacAB-TolC				■			
	MFS	ErmAB-TolC			■		■		
		TetA-E					■		
	RND	AcrAB-TolC	■		■	■	■	■	
		AcrCD-TolC		■					
		AcrEF-TolC	■		■	■	■	■	
	SMR	ErmE				■	■		■

…and the list is much longer

Antibiotic efflux in Gram (-)

organism	family	pump	antibiotic						
			β-lactams	Aminoglycosides	Fluoroquinolones	Macrolides	etracyclines	Trimetoprim	Sulfamides
P. aeruginosa	MFS	TetA,C,E					■		
	RND	MexAB-OprM	■		■	■	■	■	■
		MexCD-OprJ	■		■		■	■	
		MexEF-OprN			■			■	
		MexJK-OprM				■	■		
		MexXY-OprM		■		■	■		

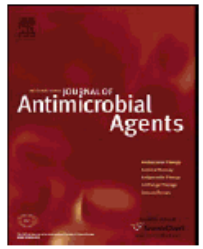
Is this real ?

International Journal of Antimicrobial Agents 36 (2010) 513–522

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

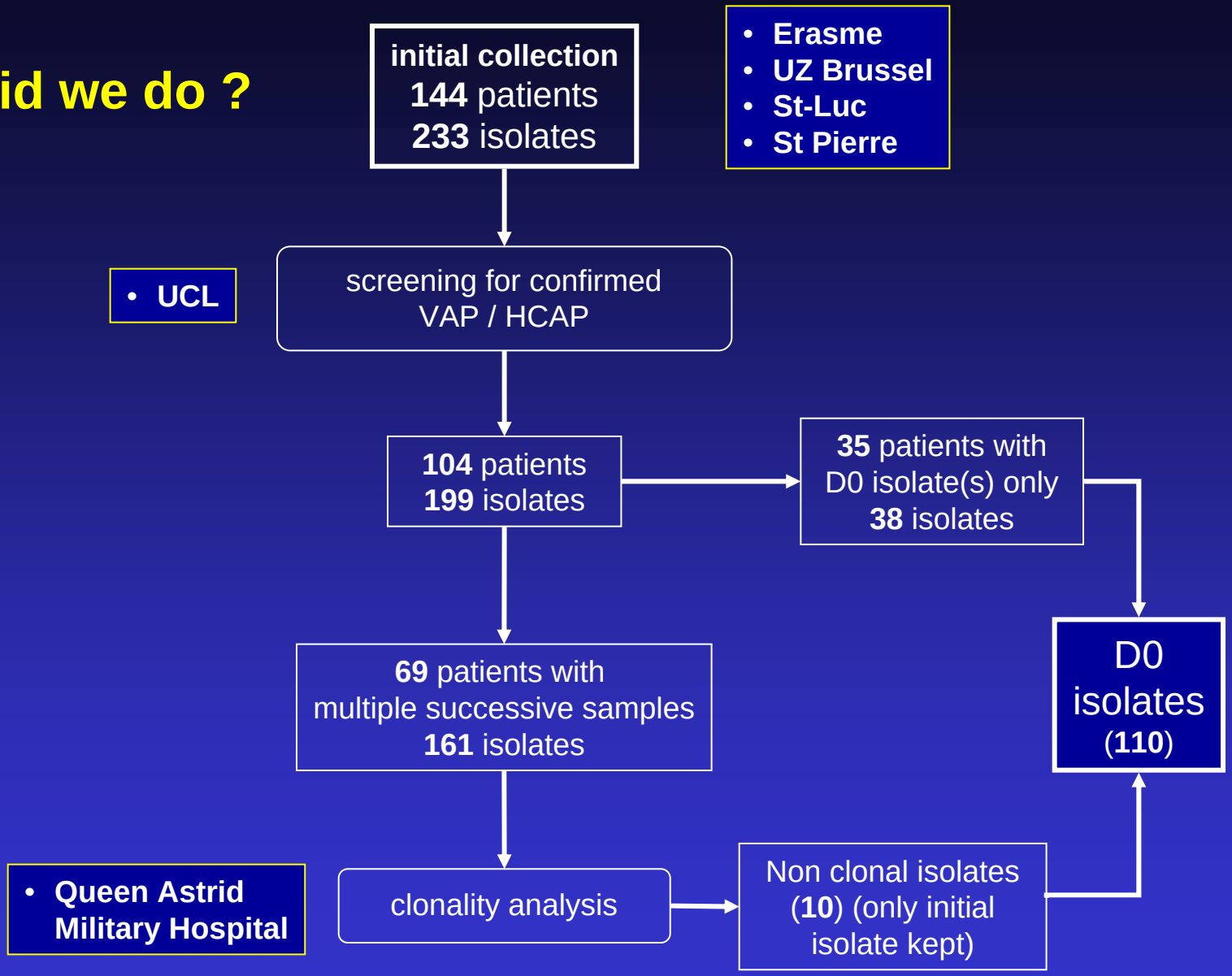
journal homepage: http://www.elsevier.com/locate/ijantimicag



In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

What did we do ?



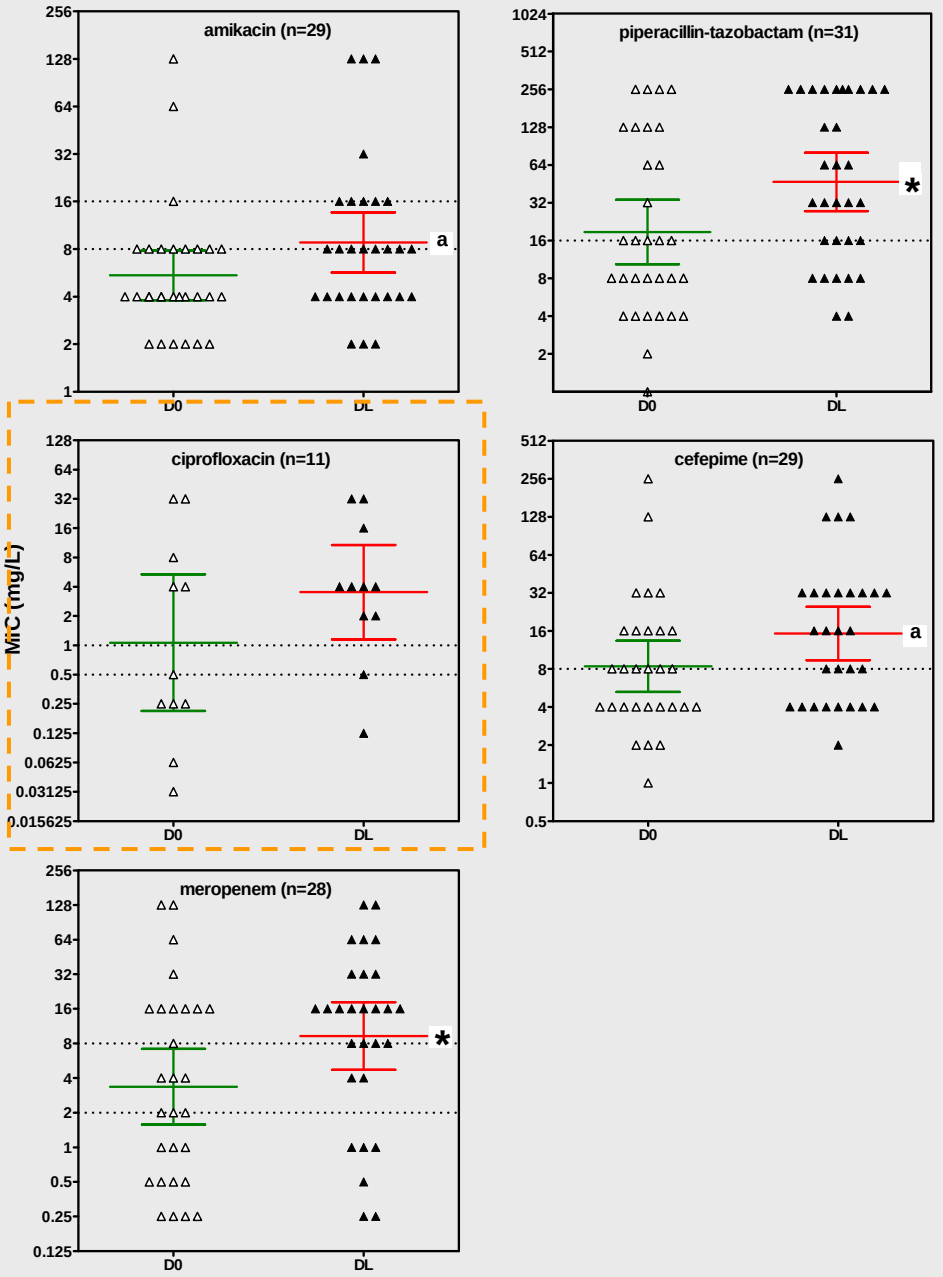
This is what happens…

- D0: initial isolate
  DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

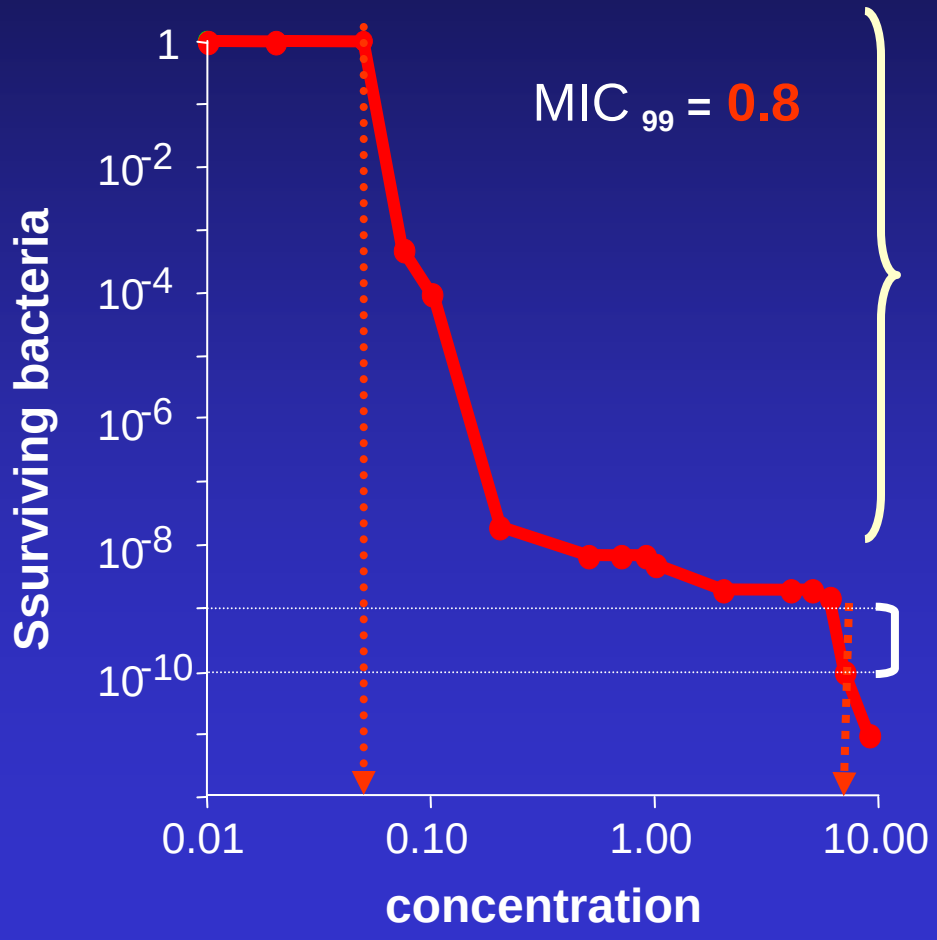
[a] $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)



Mutation-Preventing Concentration (MPC)...

Example: bactericidal activity of FQs vs *Mycobacterium bovis*

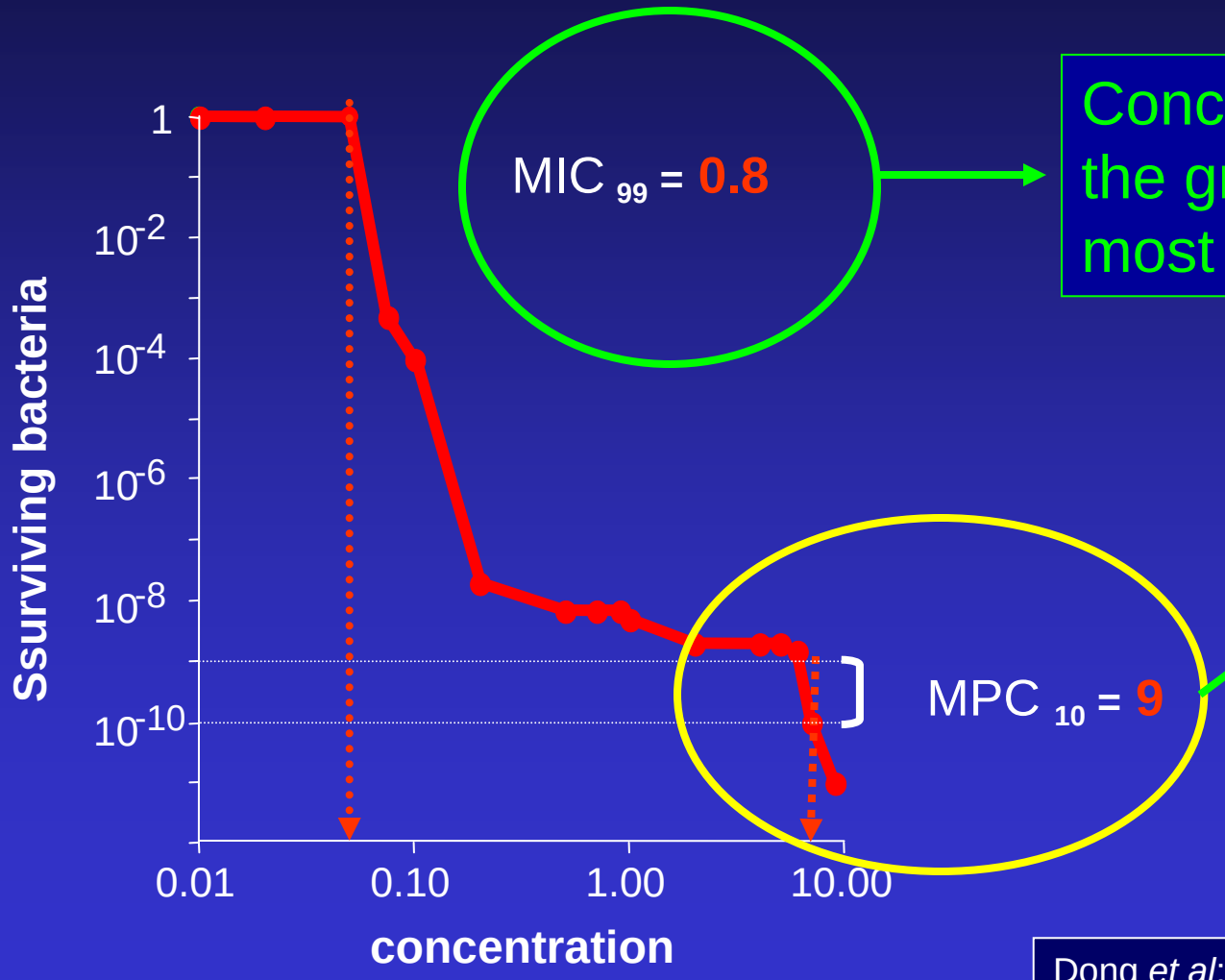


« classical » bactericidal activity

Elimination of first-step mutants

Dong *et al*; AAC 43:1756-1758

Mutation-Preventing Concentration (MPC)...

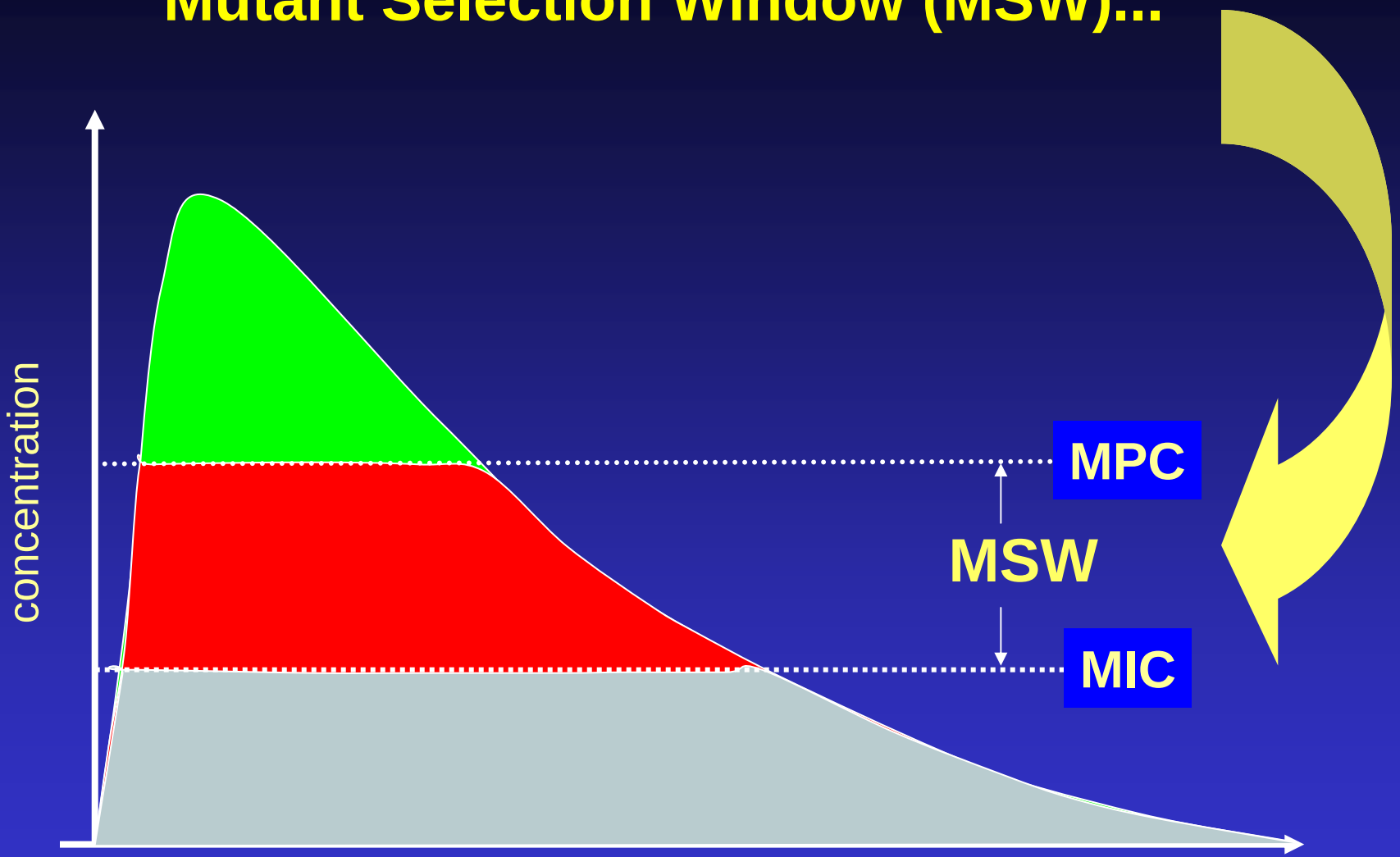


Concentration inhibiting the growth of most organisms

concentration required to prevent thea selection of first-step mutants

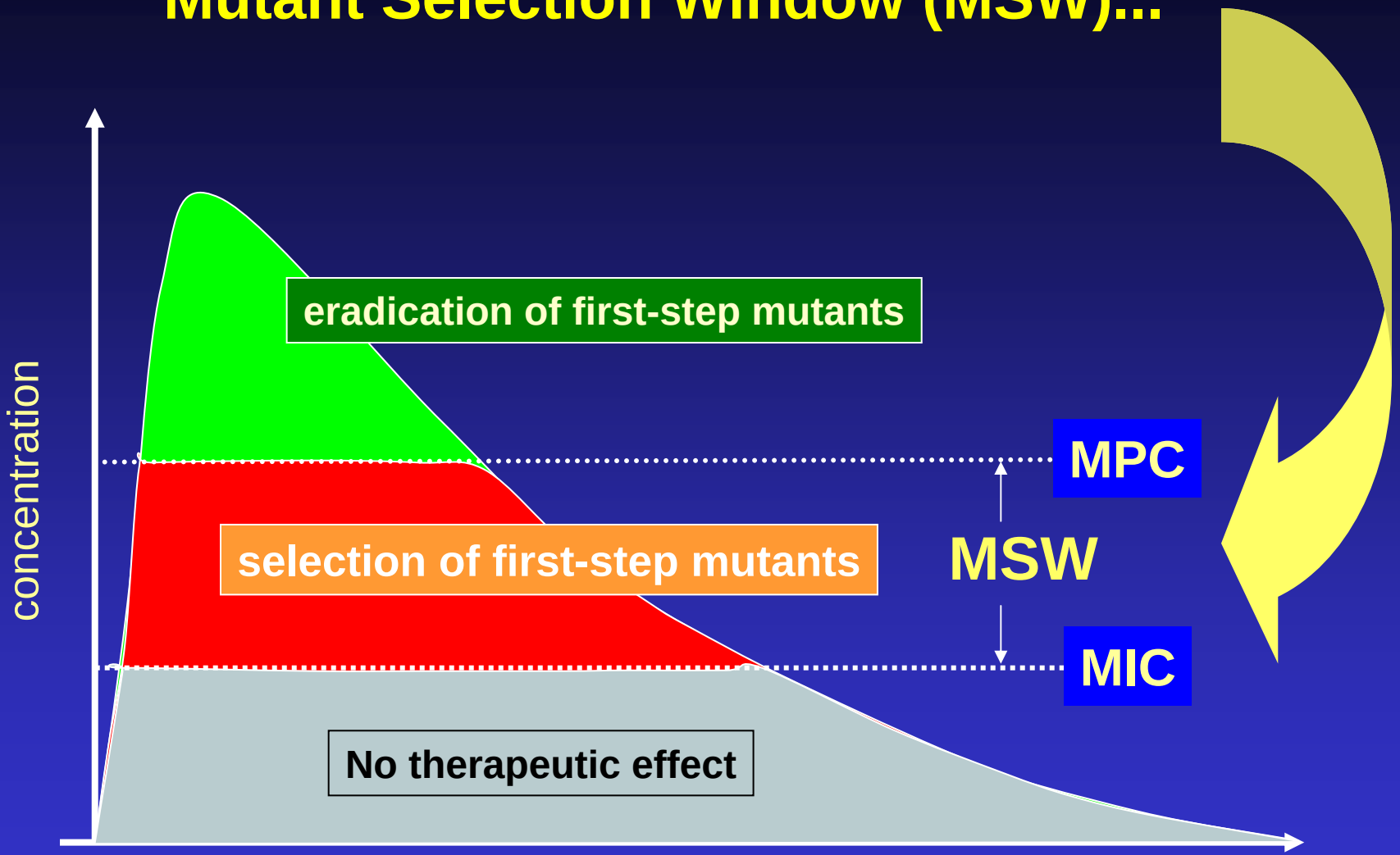
Dong *et al*; AAC 43:1756-1758

Mutant Selection Window (MSW)...



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

Mutant Selection Window (MSW)...



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

Exercise with fluoroquinolones...

Prevention of resistance and efficacy:

- peak / MIC > 12

  and/or > MPC

- AUC / MIC > 100
  (non fully immunocompetent patients)

Why do you **REALLY** need a peak with fluoroquinolones ?

Low concentrations increase the frequency of resistant mutants

Table 1: Frequency of mutation at plasma antimicrobial concentrations in *E. coli* and *Klebsiella spp.*

Drug		Frequency of mutation			
		E. coli (n = 20)		Klebsiella spp. (n = 20)	
		Cmax	Cmin *	Cmax	Cmin*
LVX 500 mg	Range	$<10^{-11}$	$< 10^{-11}$ - 1.0×10^{-7}	$<10^{-11}$	$<10^{-11}$ - 7.4×10^{-5}
LVX 750 mg	Range	$<10^{-11}$	$<10^{-11}$ - 2.7×10^{-5}	$<10^{-11}$	$<10^{-11}$ - 7.7×10^{-6}
CIP 500 mg	Range	$<10^{-11}$	$<10^{-11}$ - 6.3×10^{-6}	$<10^{-11}$	3.2×10^{-8} - 8.5×10^{-5}

* Frequency of mutations was calculated only for strains with MIC < Cmin.

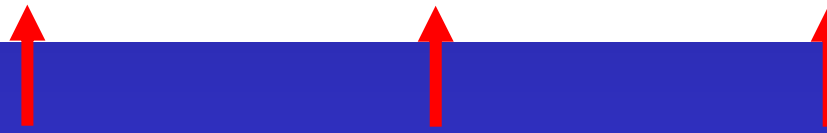
Drago *et al. BMC Microbiology* 2010, **10**:119 **(edited)**

Do NOT divide the dose of levofloxacin !

Divided doses may yield the same microbiological outcome (AUC_{24h}/MIC related), but greatly <u>decreases</u> the target attainment rate for resistance (C_{max}/MIC-dependent)

Table 2 Probabilities of achieving the AUC_{0-24}/MIC target (≥31.5) and the C_{max}/MIC target (≥2.7) for prediction of microbiological outcome and the C_{max}/MIC target (≥8) for prevention of selection of fluoroquinolone resistance in 10000 cases of complicated UTIs with *P. aeruginosa*

Target	Probability of achieving target in complicated UTIs by *P. aeruginosa* with the following treatment regimens			
	500 mg × 1/day	100 mg × 3/day	200 mg × 2/day	200 mg × 3/day
For prediction of microbiological outcome				
AUC_{0-24}/MIC	55.5	48.9	52.2	57.5
C_{max}/MIC	55.1	44.1	48.2	51.1
For prevention of selection of fluoroquinolone resistance				
C_{max}/MIC	44.2	10.8	21.7	31.7



Takashi Deguchi · Kensaku Seike · Mitsuru Yasuda · Tetsuro Matsumoto

J Infect Chemother Published online: 17 March 2011

Evaluation by Monte Carlo simulation of levofloxacin dosing for complicated urinary tract infections caused by *Escherichia coli* or *Pseudomonas aeruginosa*

Exercise with fluoroquinolones...

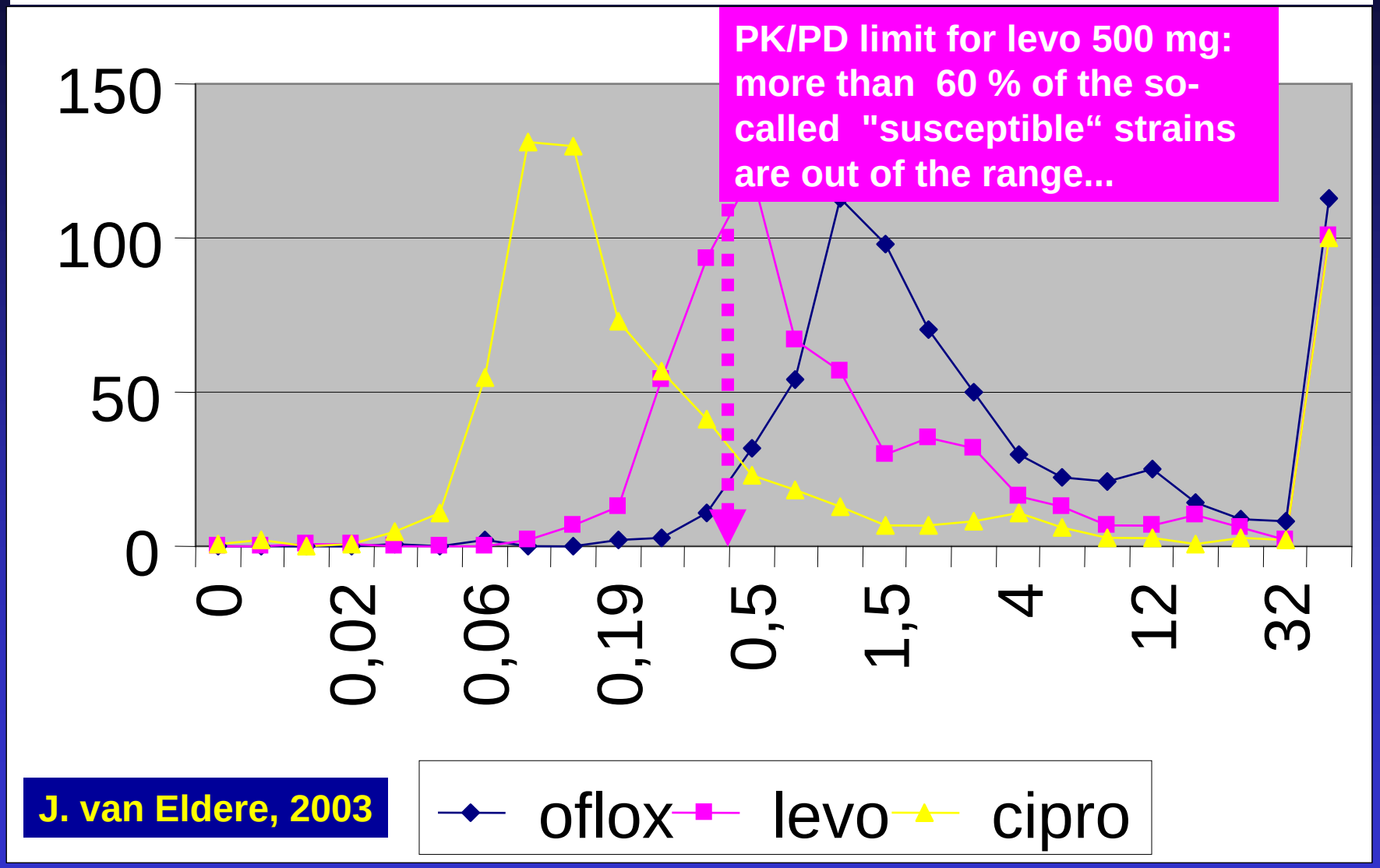
Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free	Proposed PK/PD upper limit of sensitivity (μg/ml) for: Efficacy[b]	Proposed PK/PD upper limit of sensitivity (μg/ml) for: Prevention of resistance[c]	
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	0.5-1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	0.5-1
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	0.5-1
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	1-2
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	0.5-1

EUCAST breakpoints

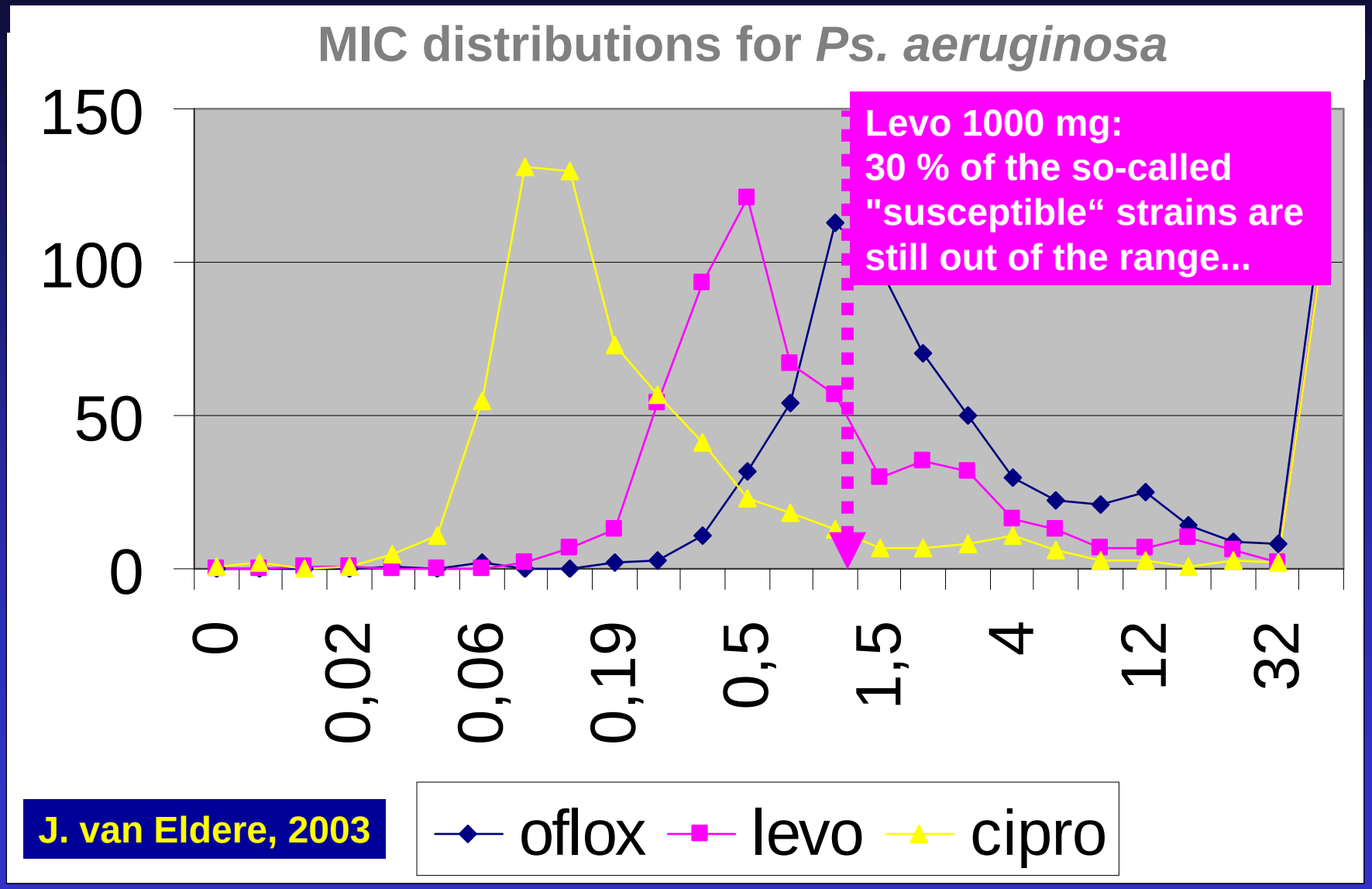
Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Can we do the exercise in Belgium ?

MIC distributions for *P. aeruginosa*



Can we do the exercise in Belgium ?



Can we do the exercise in Belgium ?