



Otimizando a terapia para minimizar resistência

Alexandre P. Zavascki

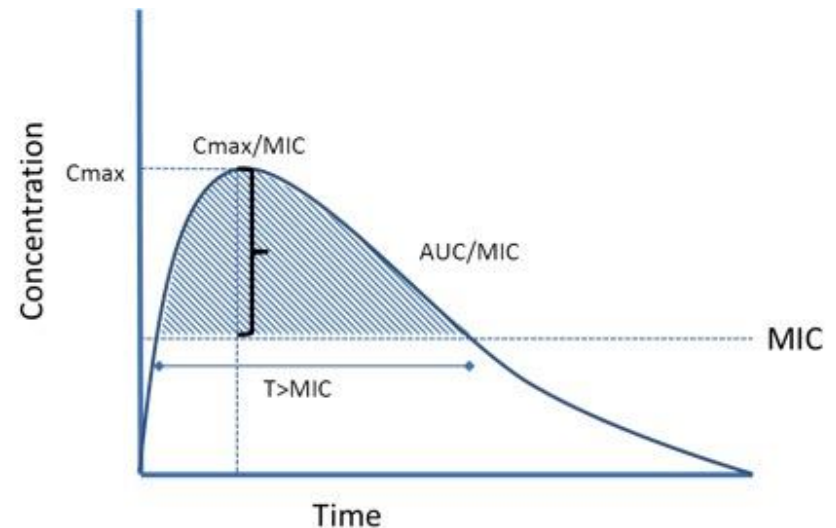
Serviço de Infectologia - HCPA

Faculdade de Medicina - UFRGS

Conflito de Interesse: nenhum

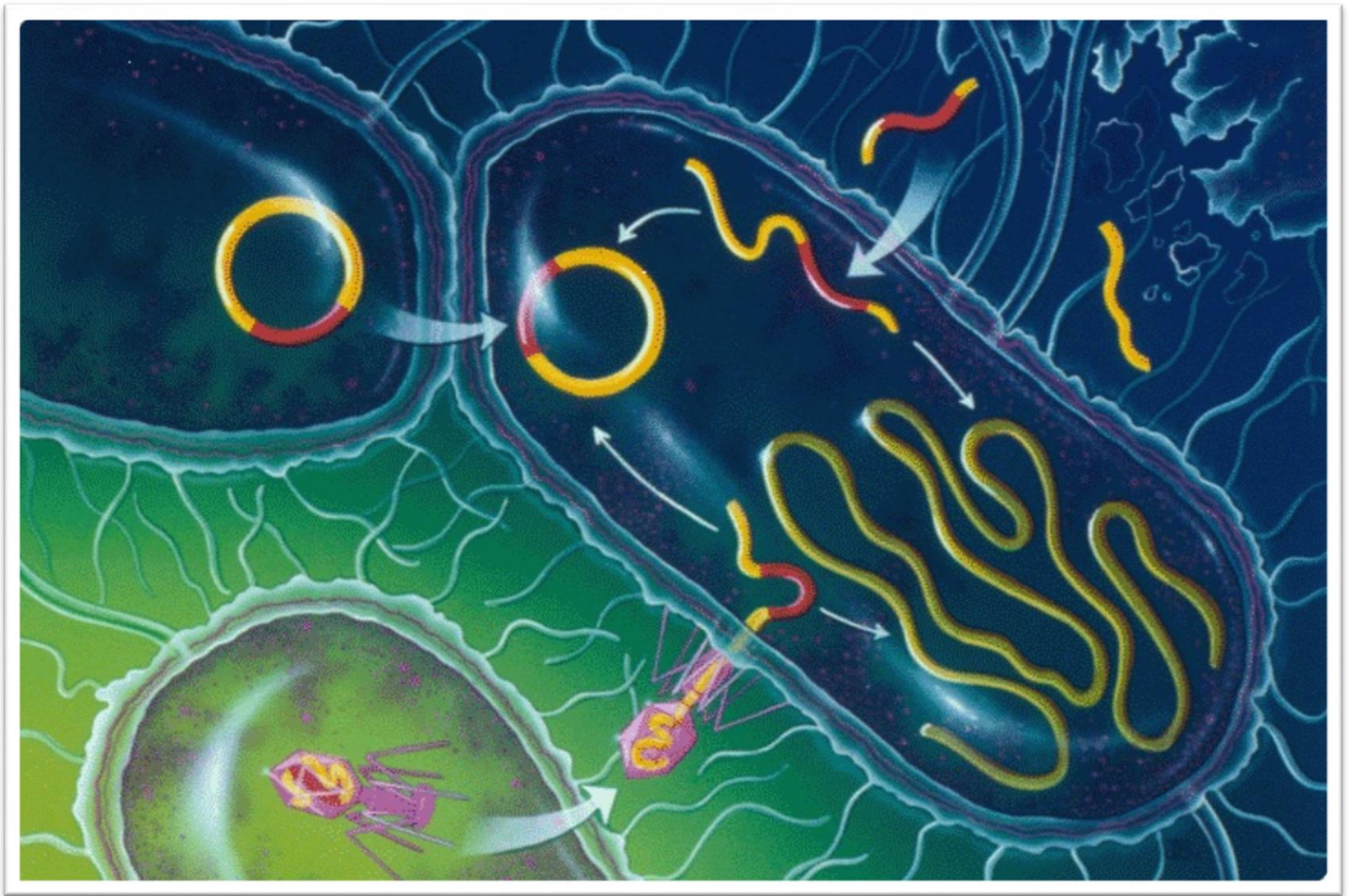
Otimizando a terapia para minimizar resistência

- Aplicação dos parâmetros PK/ PD não para efeito bactericida ou bacteriostático (terapêutico), mas para prevenir aparecimento de resistência
- É possível prevenir a emergência de resistência utilizando PK/PD?
- Como surge a resistência?

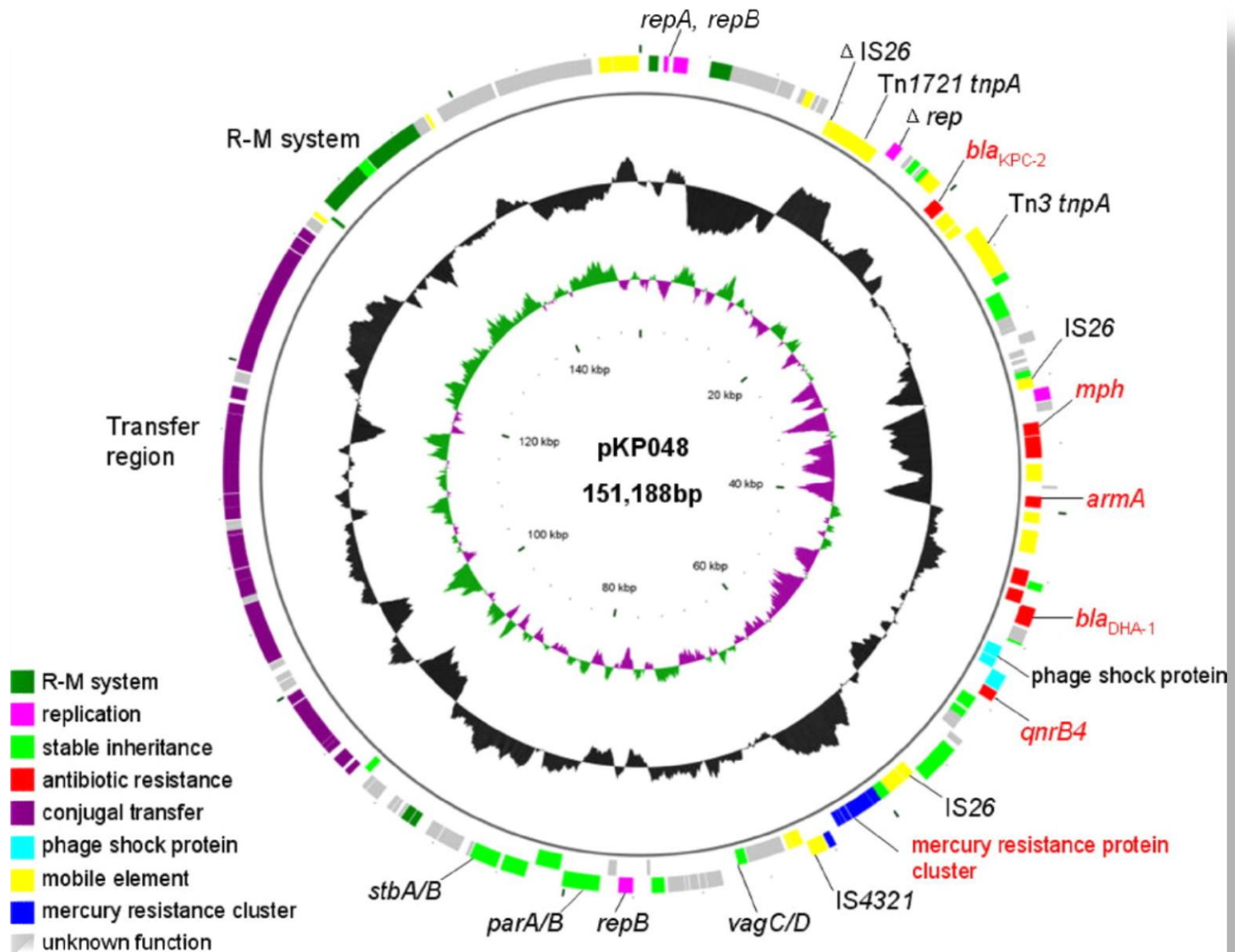


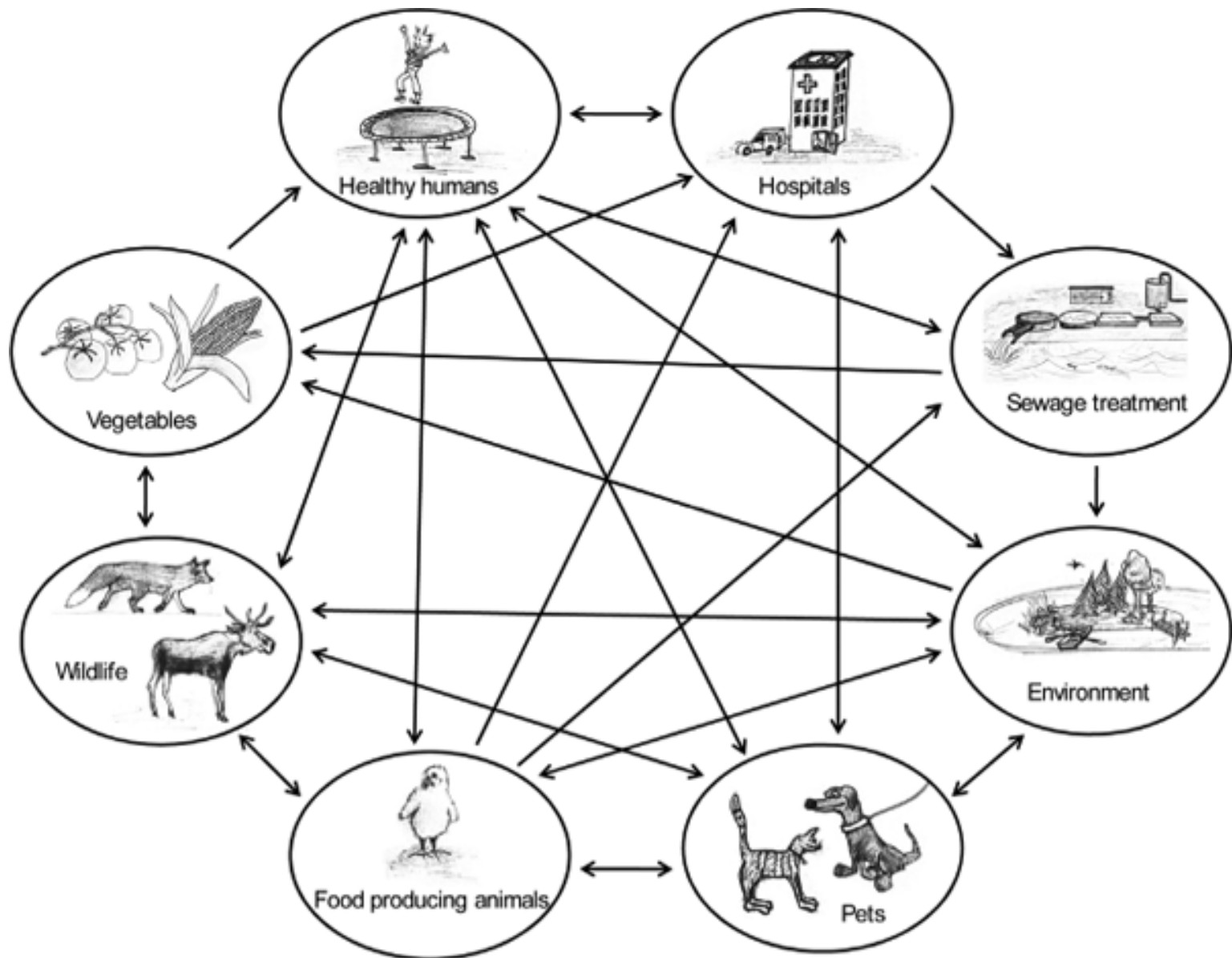
Como surge a resistência?

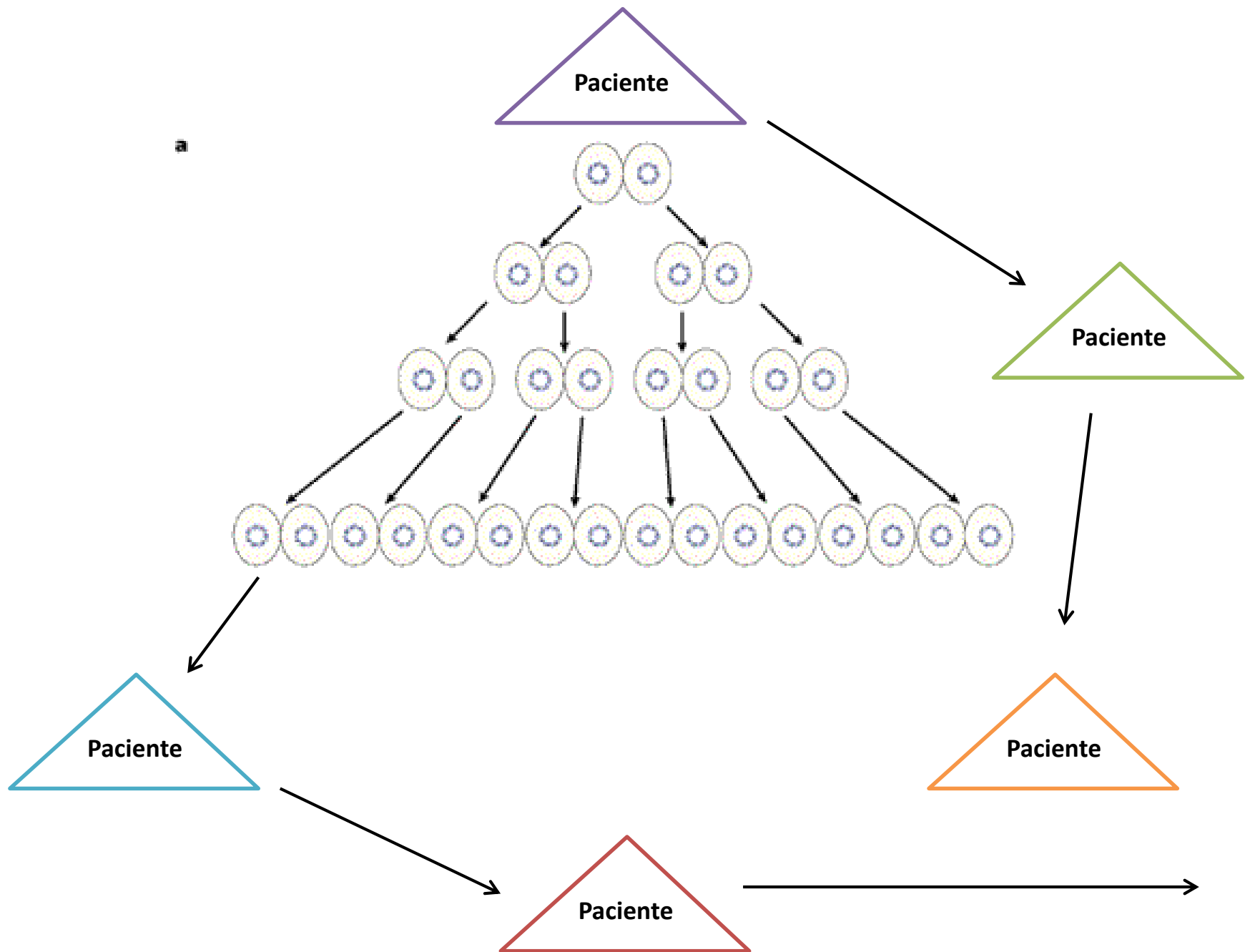
- **Mutação espontânea em gene bacteriano – *De novo***
- **Resistência adquirida**

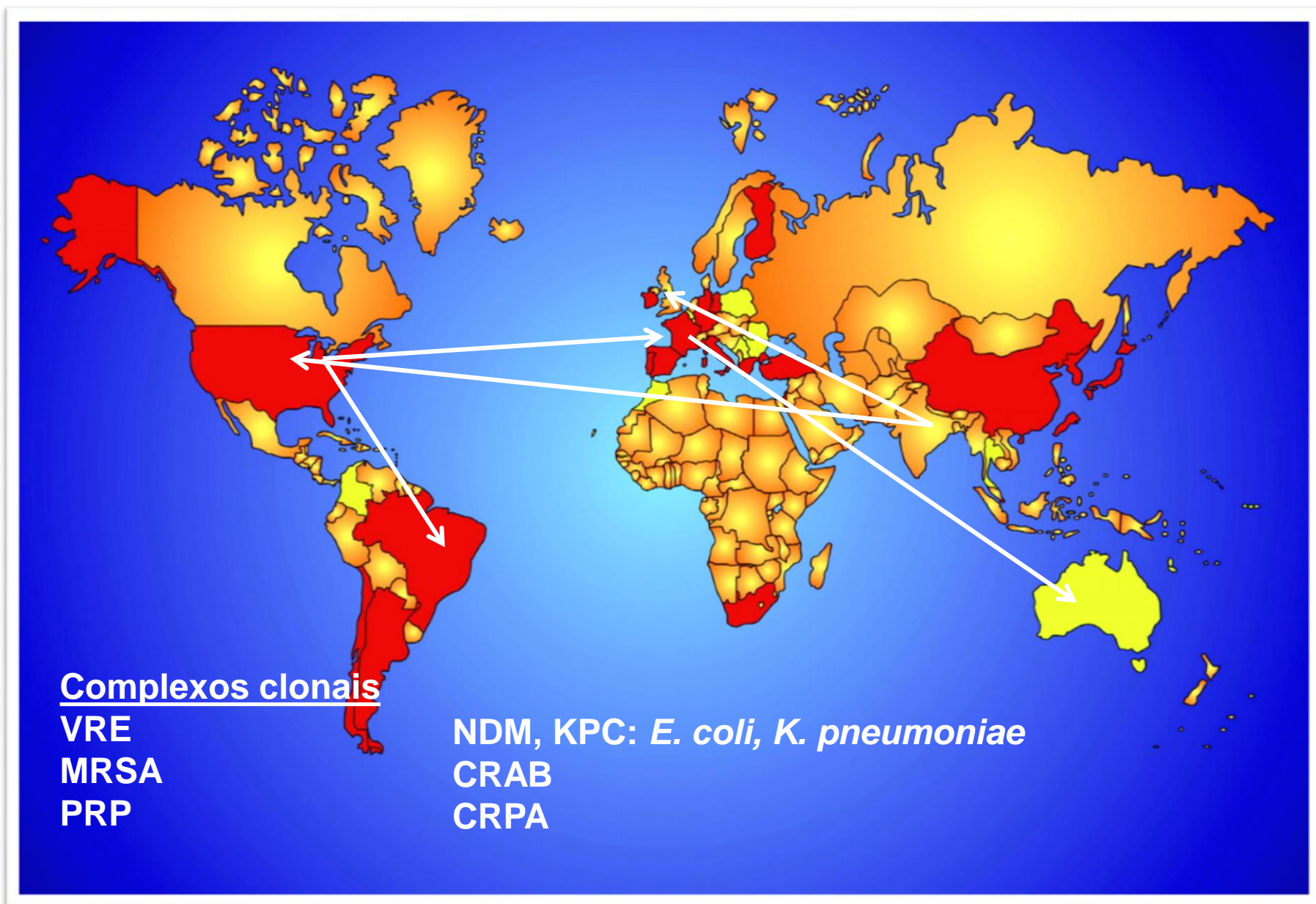


Circular map of plasmid pKP048 of a MDR *K. pneumoniae*.









Otimizando a terapia para minimizar resistência

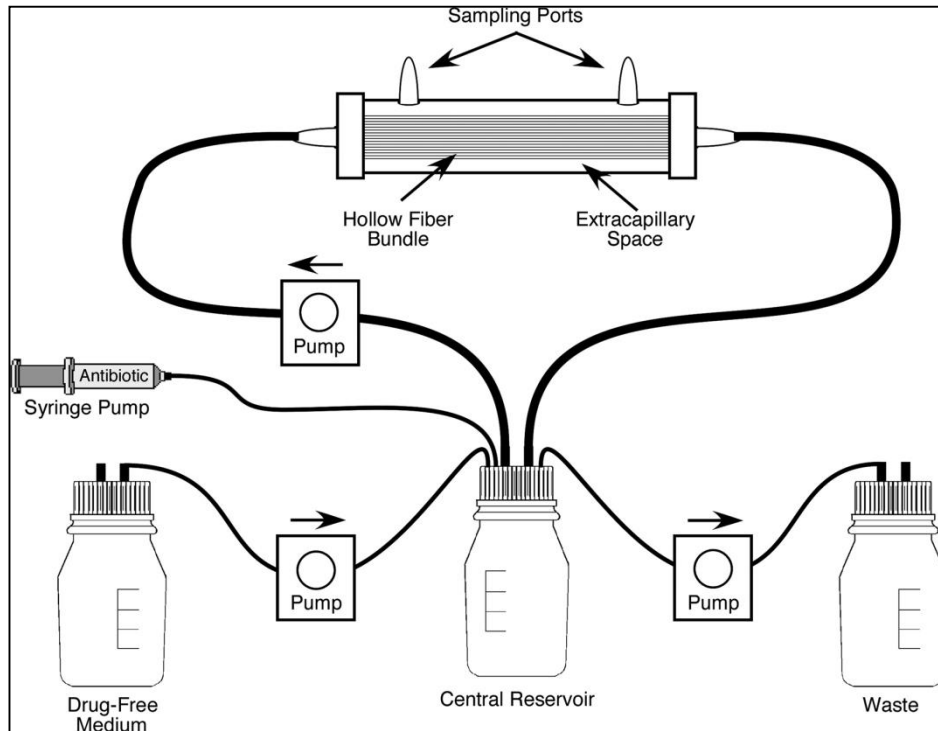
- É possível prevenir a emergência de resistência pela transmissão horizontal de genes de resistência ou disseminação horizontal de clones bacterianos utilizando PK/PD?
- PK/PD → emergência de resistência *de novo*

Princípios gerais de um processo infecciosos

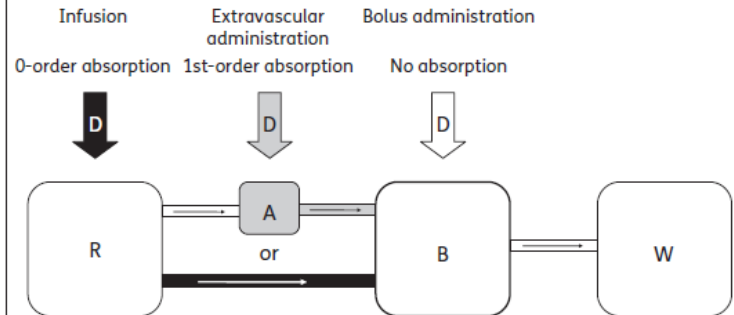
1. Inoculo $\rightarrow 10^6$ a 10^9 UFC/ml
2. Mutação espontânea capazes de determinar resistência $\rightarrow 10^{-6}$ a 10^{-10} dependendo do gene e da bactéria
3. $>$ inóculo $\rightarrow >$ frequência de mutantes (MIC mais elevada)



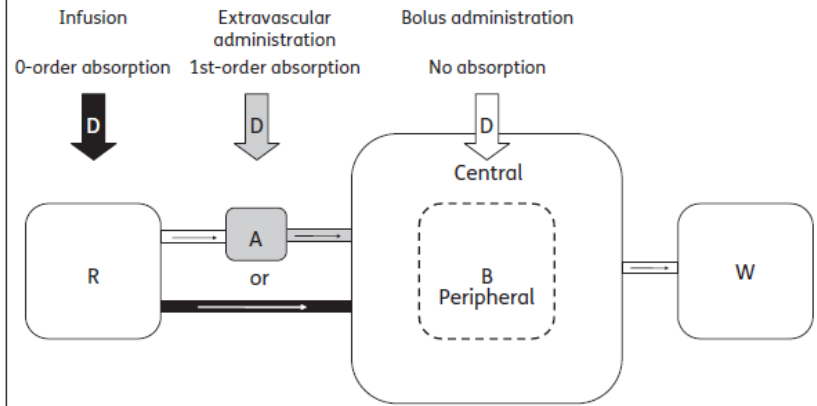
In vitro pharmacodynamic models



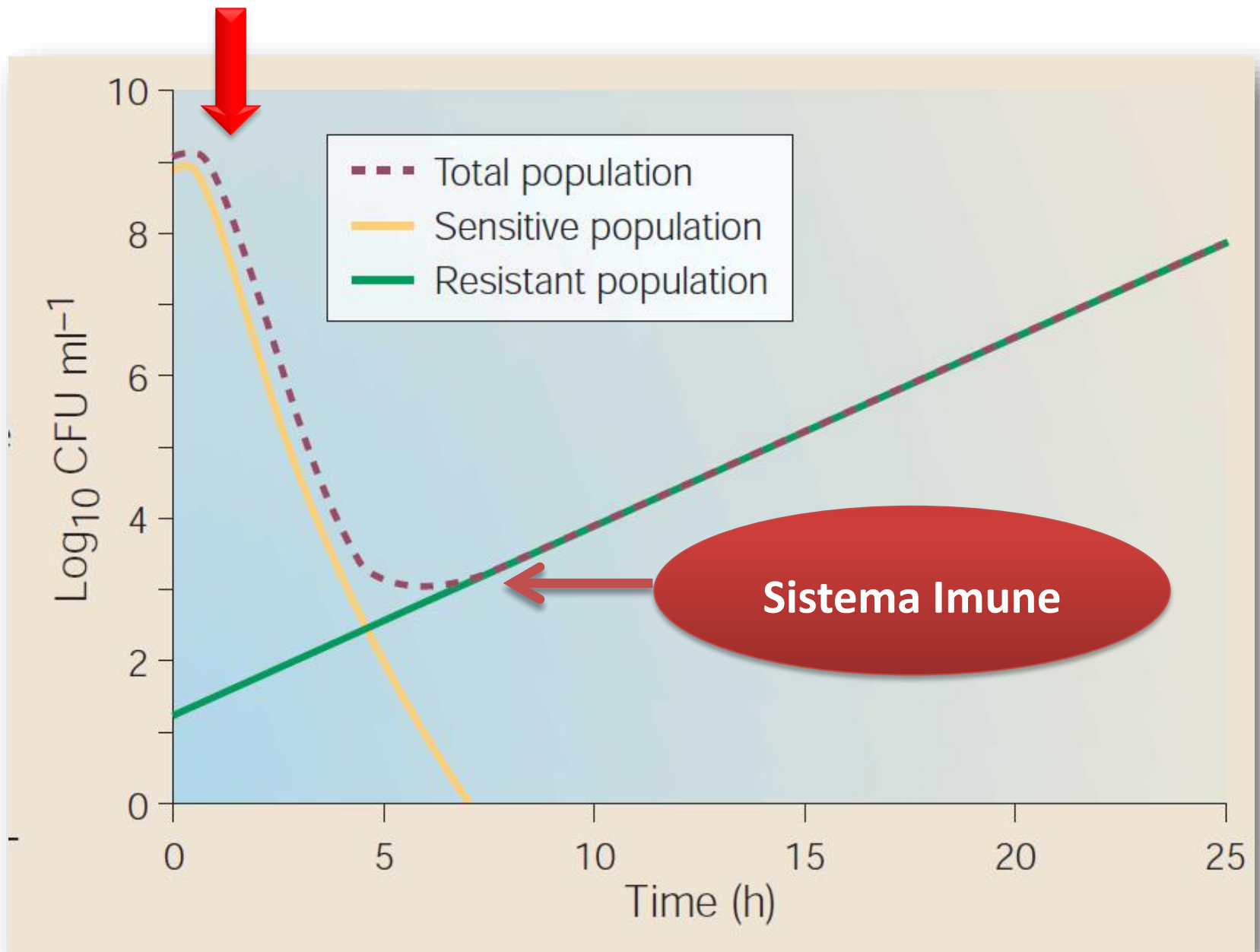
(a) In dilution models with the example of a continuous simple dilution model



(b) In dialysis/diffusion models with the example of an embedded peripheral compartment



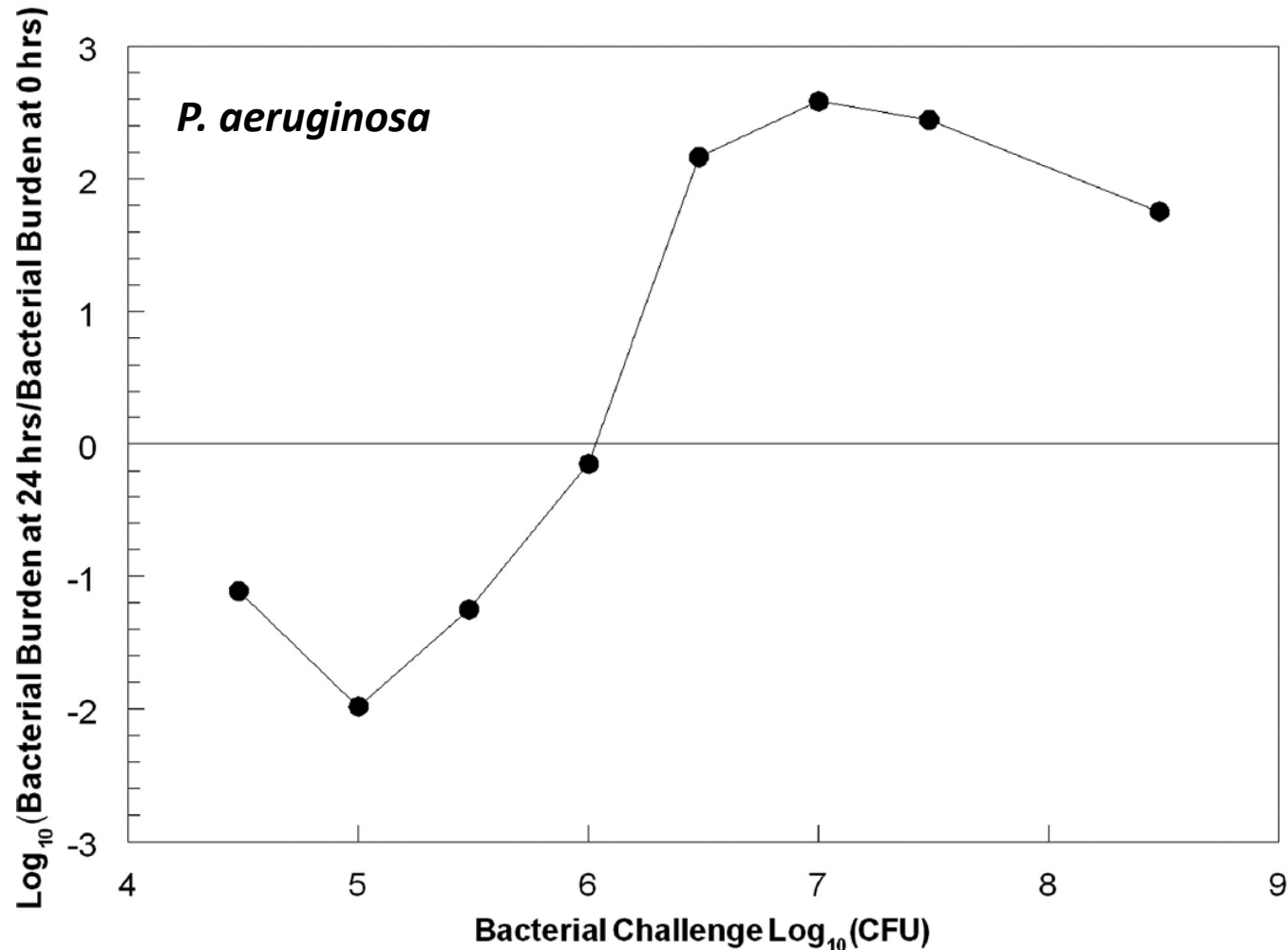
D drug
R reservoir
A additional vessel, mimicking absorption (optional)
B culture vessel with bacteria
W waste



Impact of Burden on Granulocyte Clearance of Bacteria in a Mouse Thigh Infection Model[▽]

G. L. Drusano,* Christine Fregeau, Weiguo Liu, D. L. Brown, and Arnold Louie

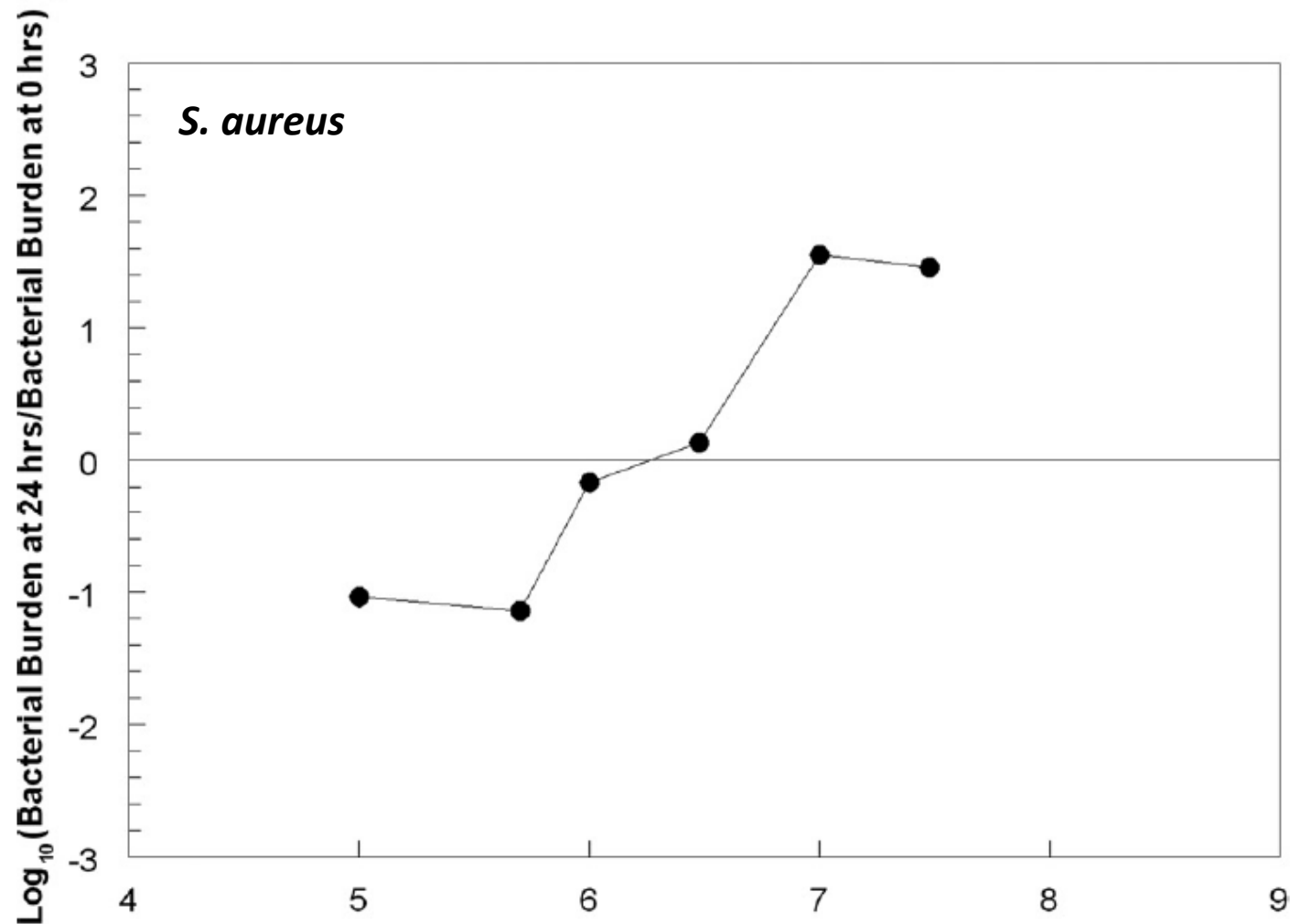
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2010,

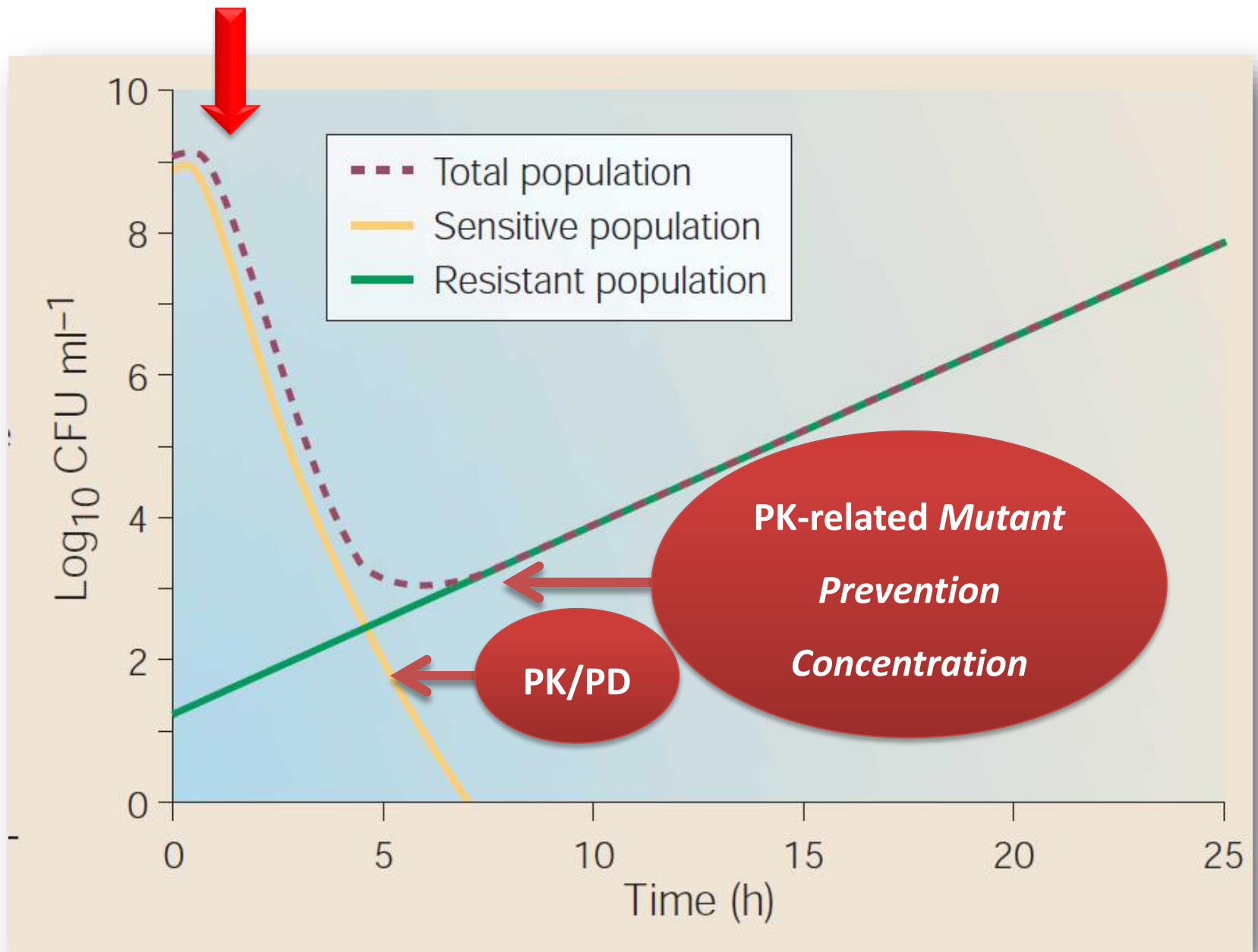


Impact of Burden on Granulocyte Clearance of Bacteria in a Mouse Thigh Infection Model[∇]

G. L. Drusano,* Christine Fregeau, Weiguo Liu, D. L. Brown, and Arnold Louie

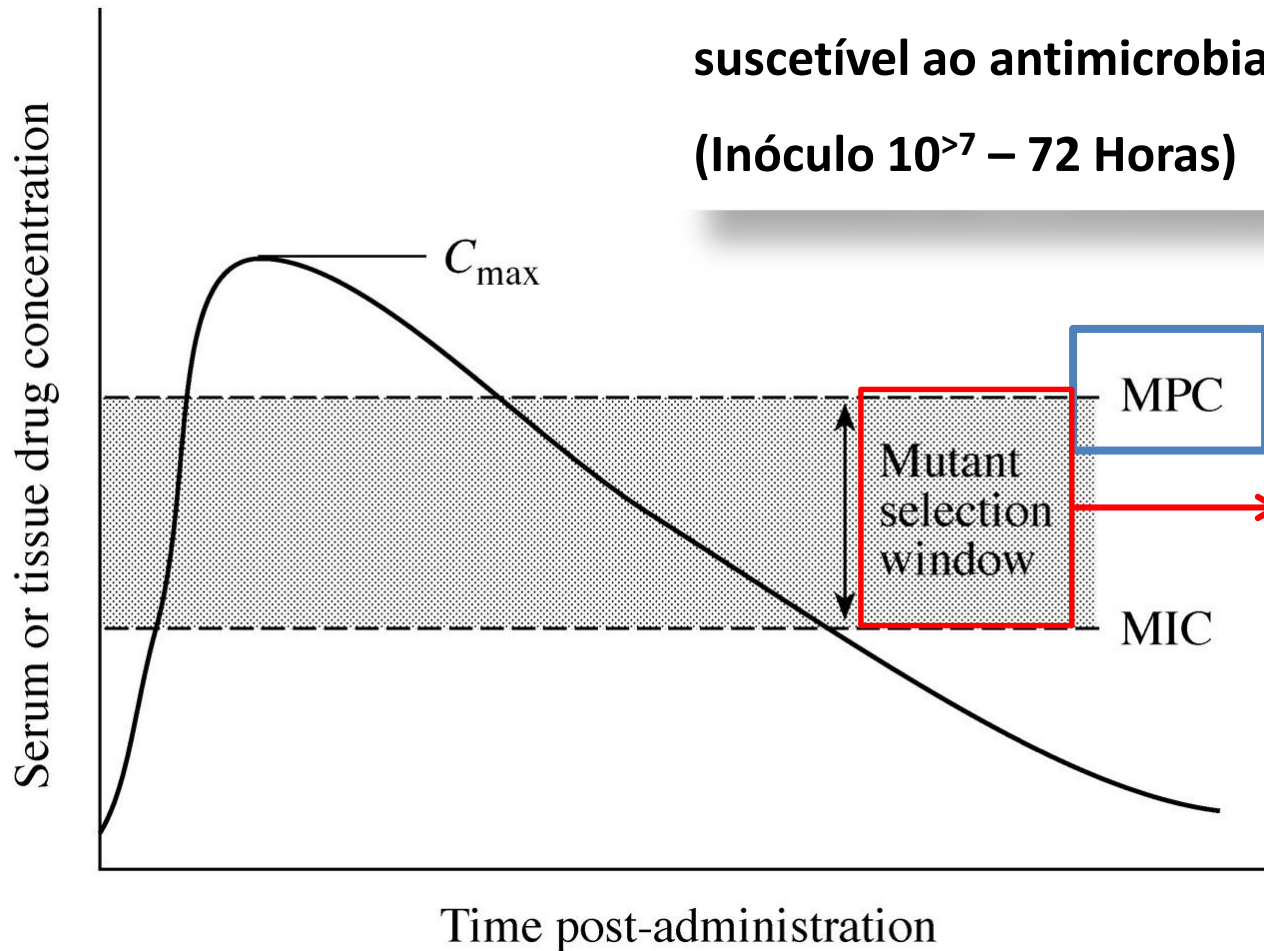
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2010.





MPC (Concentração de Prevenção de Mutações)= A concentração mais baixa capaz de inibir o crescimento do mutante menos suscetível ao antimicrobiano.

(Inóculo 10^{10} – 72 Horas)



Janela de seleção de mutação = MPC – MIC

PK-related Mutant Prevention

Concentration

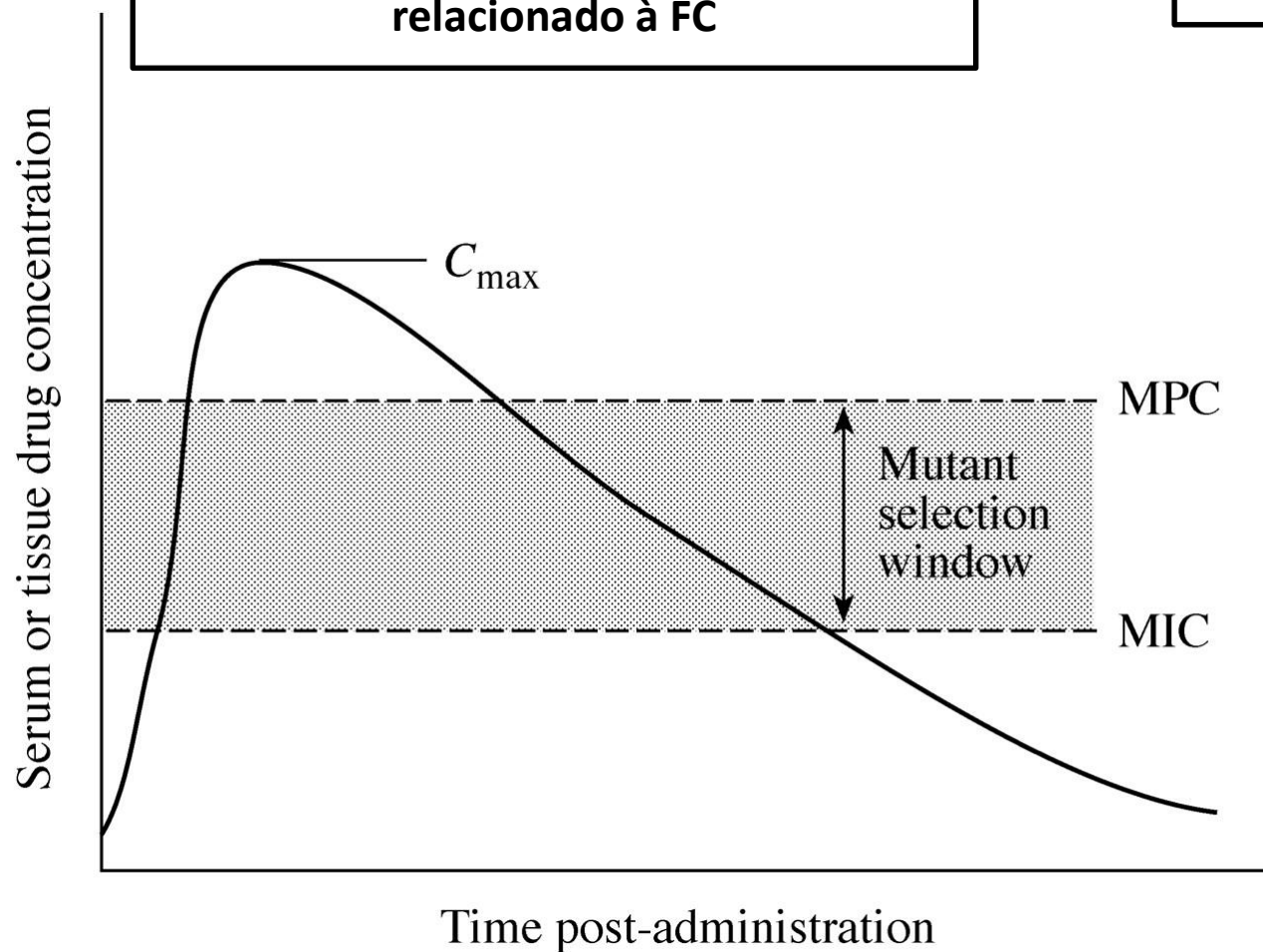
**Concentração de Prevenção de Mutação
relacionado à FC**



C_{max}/MPC

AUC_{24h}/MPC

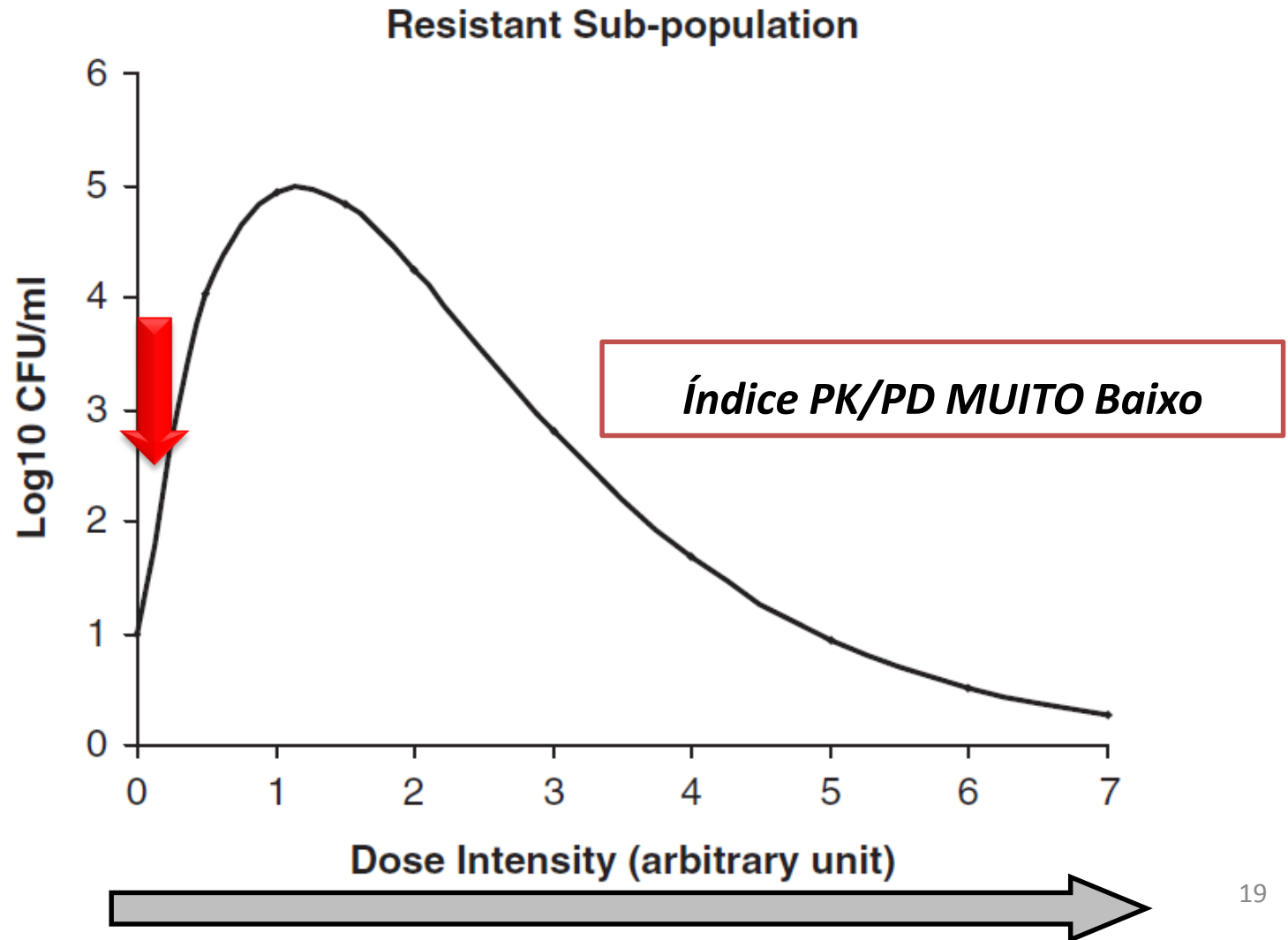
T%>MPC



The Relationship between Quinolone Exposures and Resistance Amplification Is Characterized by an Inverted U: a New Paradigm for Optimizing Pharmacodynamics To Counterselect Resistance[▽]

Vincent H. Tam,* Arnold Louie, Mark R. Deziel,† Weiguo Liu, and George L. Drusano

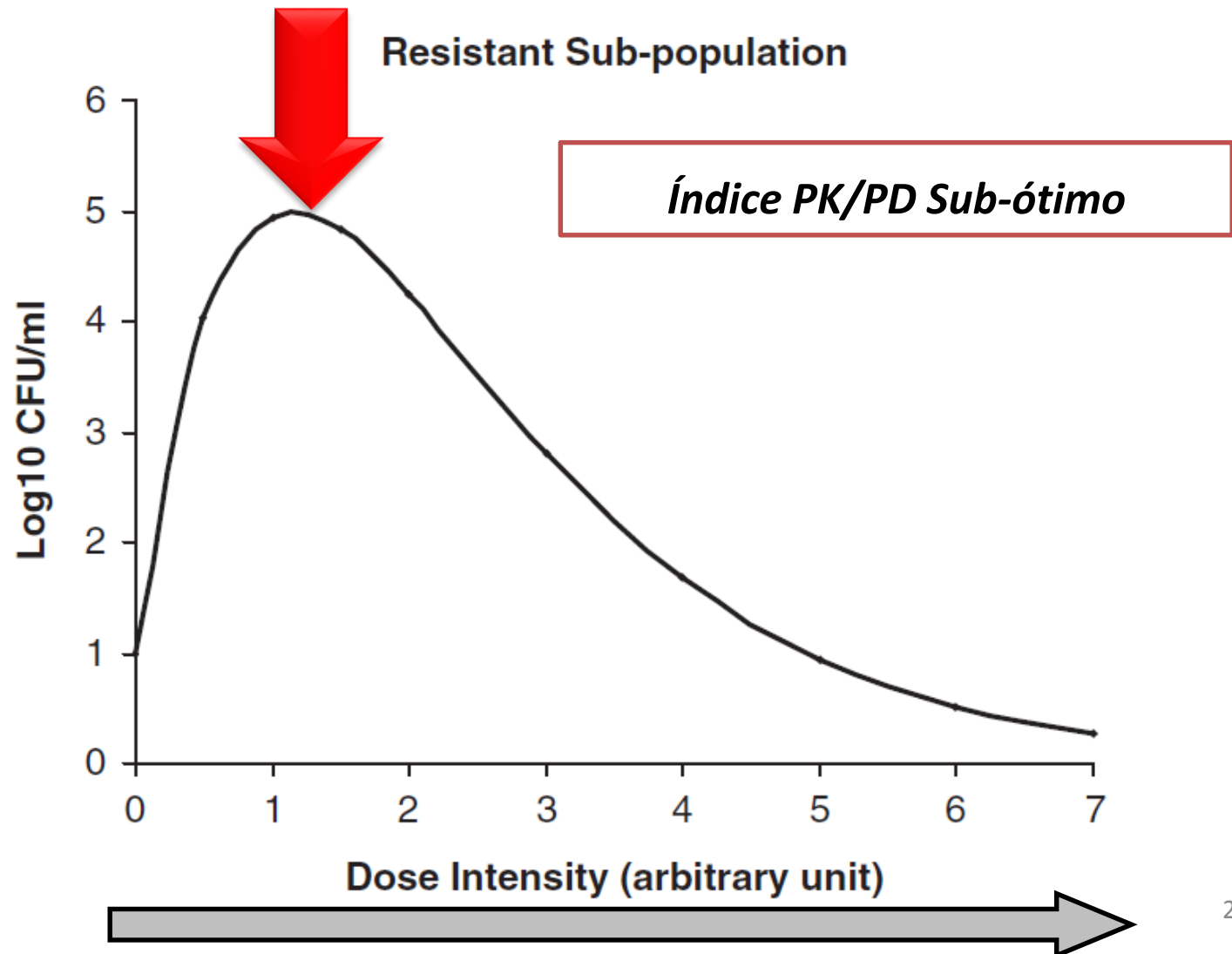
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2007, p. 744–747



The Relationship between Quinolone Exposures and Resistance Amplification Is Characterized by an Inverted U: a New Paradigm for Optimizing Pharmacodynamics To Counterselect Resistance[▽]

Vincent H. Tam,* Arnold Louie, Mark R. Deziel,† Weiguo Liu, and George L. Drusano

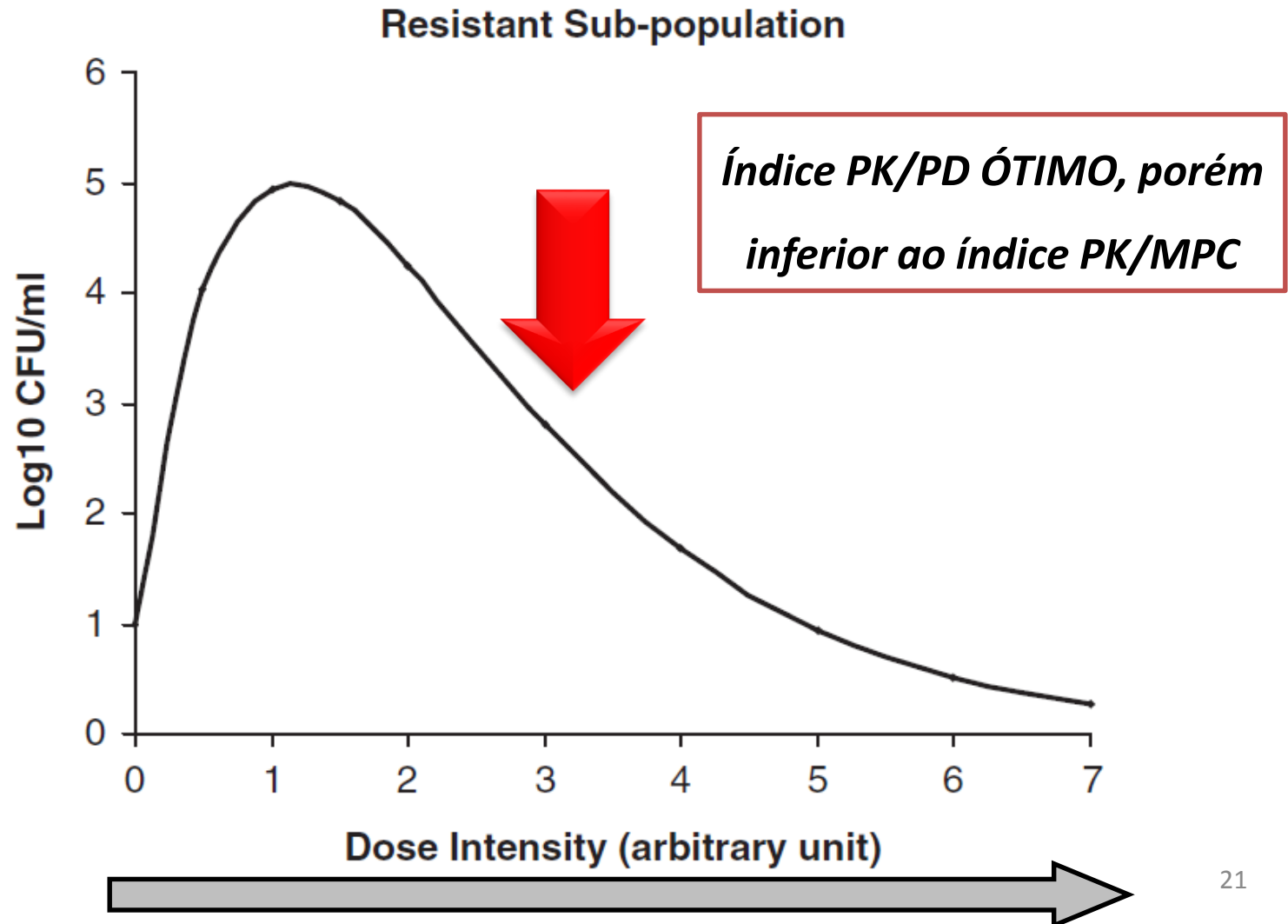
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2007, p. 744–747



The Relationship between Quinolone Exposures and Resistance Amplification Is Characterized by an Inverted U: a New Paradigm for Optimizing Pharmacodynamics To Counterselect Resistance[∇]

Vincent H. Tam,* Arnold Louie, Mark R. Deziel,† Weiguo Liu, and George L. Drusano

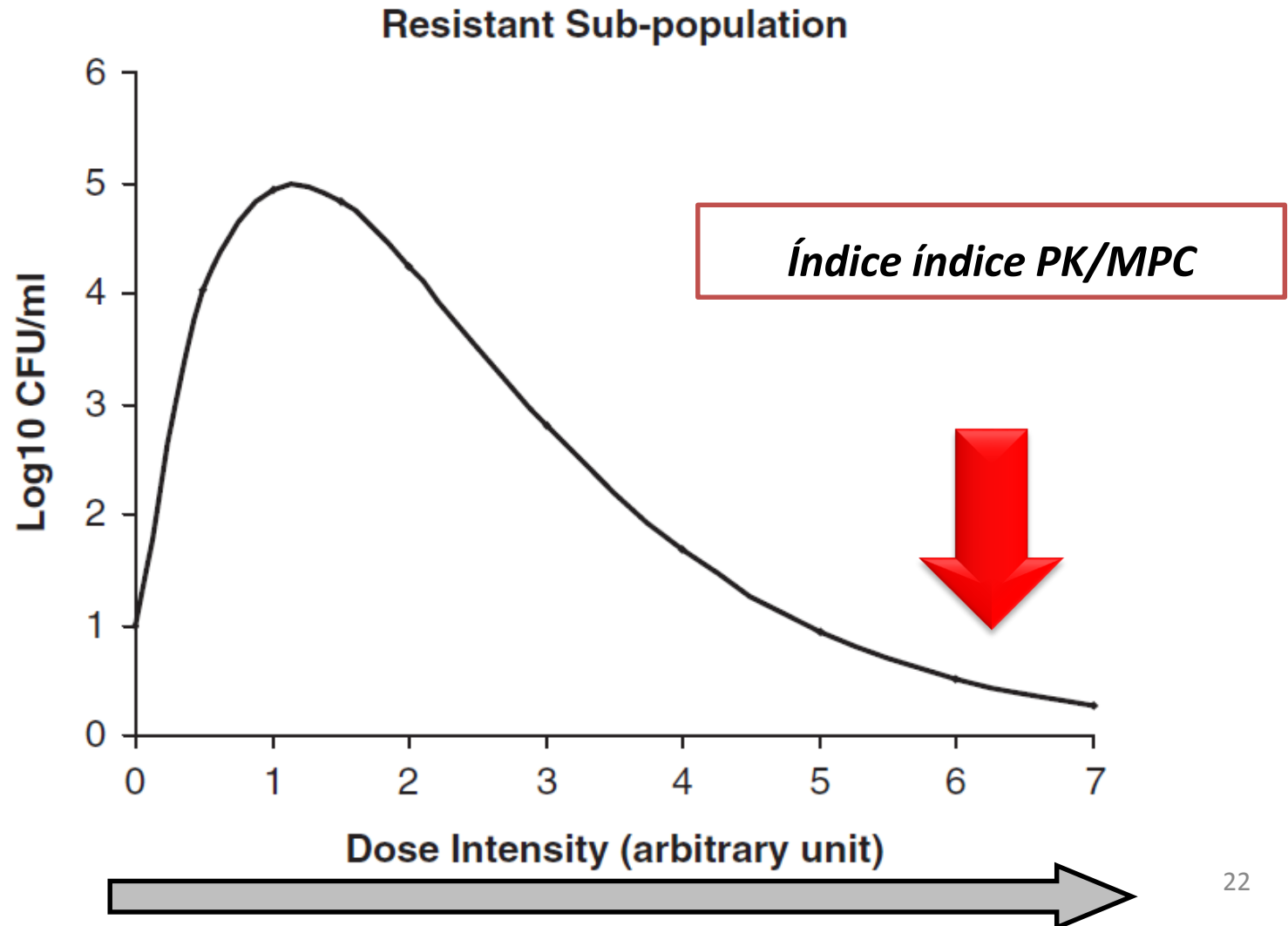
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2007, p. 744–747



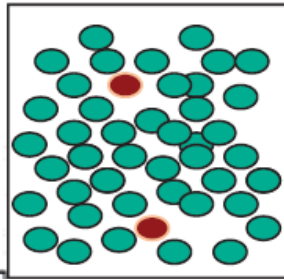
The Relationship between Quinolone Exposures and Resistance Amplification Is Characterized by an Inverted U: a New Paradigm for Optimizing Pharmacodynamics To Counterselect Resistance[∇]

Vincent H. Tam,* Arnold Louie, Mark R. Deziel,† Weiguo Liu, and George L. Drusano

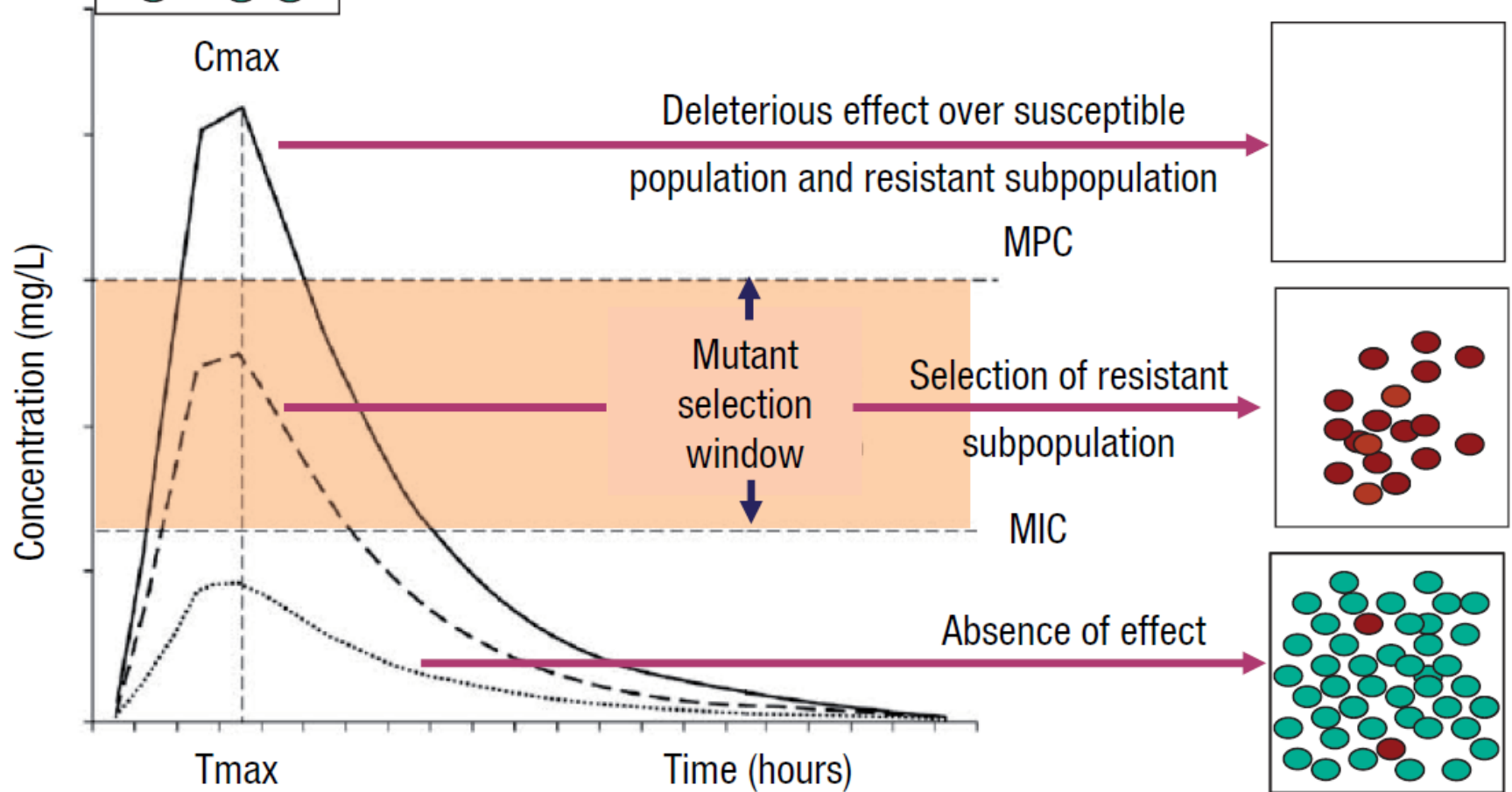
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2007, p. 744–747



Wild-type
population



- = susceptible bacteria
- = resistant mutant



Otimizando a terapia para minimizar resistência

Flaws

- **É possível, ao mesmo tempo, otimizar dosagem de forma a melhorar atividade, reduzir o potencial de seleção e minimizar toxicidade?**

Resistência *de novo* clinicamente significativas

Antibiótico	Bactéria	Gene	Ex.
Fluorquinolonas	CG+ BGN Micobactéria	<i>gyrA</i> <i>parC</i>	<i>S. pneumoniae/ S. aureus</i> <i>Enterobacteriaceae</i> <i>P. aeruginosa</i>
β-lactâmico ceftazidima carbapenêmicos	BGN	<i>ampD, ampR, ampG</i> <i>oprD, nalB, nalC</i>	<i>CESP</i> <i>P. aeruginosa</i>

Resistência *de novo* clinicamente significativas

Antibiótico	Bactéria	Gene	Ex.
Fluorquinolonas	CG+ BGN Micobactéria	<i>gyrA</i> <i>parC</i>	<i>S. pneumoniae</i> / <i>S. aureus</i> <i>Enterobacteriaceae</i> <i>P. aeruginosa</i>
β -lactâmico ceftazidima carbapenêmicos	BGN	<i>ampD, ampR, ampG</i> <i>oprD, nalB, nalC</i>	<i>CESP</i> <i>P. aeruginosa</i>
Tigeciclina	BGN	<i>adeB</i> <i>acrA</i>	<i>A. baumannii</i> <i>K. pneumoniae</i>
Polimixinas	BGN	<i>pmrB, phoQ, phoP,</i> <i>parS, parR. ...</i>	<i>P. aeruginosa</i> <i>A. baumannii</i> <i>K. pneumoniae</i>

Mutant Prevention Concentrations of Four Carbapenems against Gram-Negative Rods^{▽†}

Kim Credito, Klaudia Kosowska-Shick, and Peter C. Appelbaum*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2010, p. 2692–2695

TABLE 1. MIC ranges, MIC₅₀S, MIC₉₀S, MPC₅₀S, MPC₉₀S, (MPC/MIC)₅₀S, and (MPC/MIC)₉₀S for all 100 strains tested

Organism (no. of strains)	Drug	MIC (μg/ml)			MPC (μg/ml)		(MPC/MIC) ₅₀	(MPC/MIC) ₉₀
		Range	50%	90%	50%	90%		
<i>Acinetobacter baumannii</i> (25)	Doripenem	0.25–8.0	2.0	4.0	4.0	64.0	2	16
	Imipenem	0.25–8.0	1.0	4.0	4.0	64.0	4	16
	Meropenem	0.5–8.0	2.0	8.0	8.0	128.0	4	16
<i>Pseudomonas aeruginosa</i> (25)	Doripenem	0.125–8.0	0.5	2.0	4.0	16.0	8	8
	Imipenem	0.5–32.0	2.0	8.0	32.0	64.0	16	8
	Meropenem	0.25–8.0	0.5	2.0	8.0	32.0	16	16
<i>Escherichia coli</i> (25)	Doripenem	0.03–2.0	0.03	0.06	0.125	0.25	4	4
	Ertapenem	0.008–8.0	0.03	0.25	0.125	2.0	4	8
	Imipenem	0.125–4.0	0.25	0.5	0.5	2.0	2	4
	Meropenem	0.016–1.0	0.03	0.06	0.06	0.25	2	4
<i>Klebsiella pneumoniae</i> (25)	Doripenem	0.06–4.0	0.125	2.0	0.25	>64.0	2	>32
	Ertapenem	0.008–16.0	0.5	8.0	1.0	64.0	2	8
	Imipenem	0.125–8.0	2.0	8.0	4.0	32.0	2	4
	Meropenem	0.03–16.0	0.06	4.0	0.5	64.0	8	16
Total strains (100)	Doripenem	0.03–8.0	0.5	4.0	4.0	64.0	8	16
	Ertapenem ^a	0.008–16.0	0.06	8.0	0.5	64.0	8	8
	Imipenem	0.125–32.0	1.0	8.0	4.0	64.0	4	8
	Meropenem	0.016–16.0	0.5	4.0	8.0	32.0	16	8

Journal of Antimicrobial Chemotherapy (2007) **60**, 1302–1309

doi:10.1093/jac/dkm370

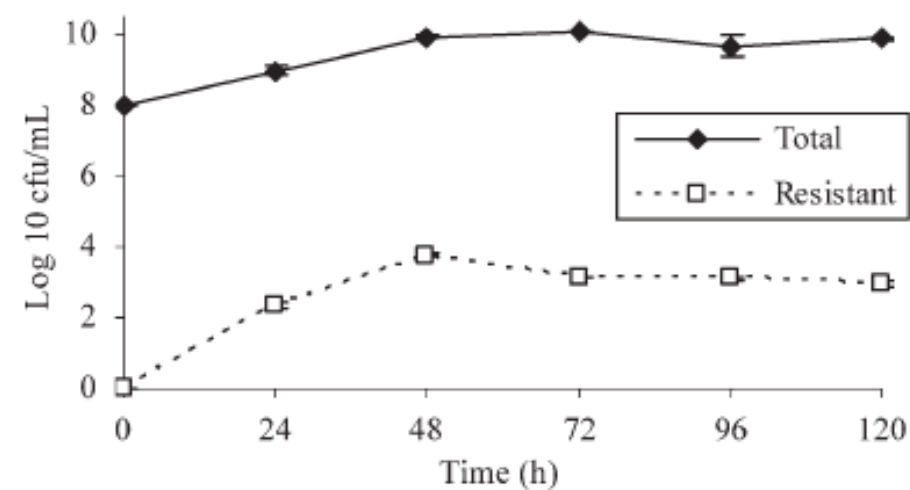
Advance Access publication 3 October 2007

JAC

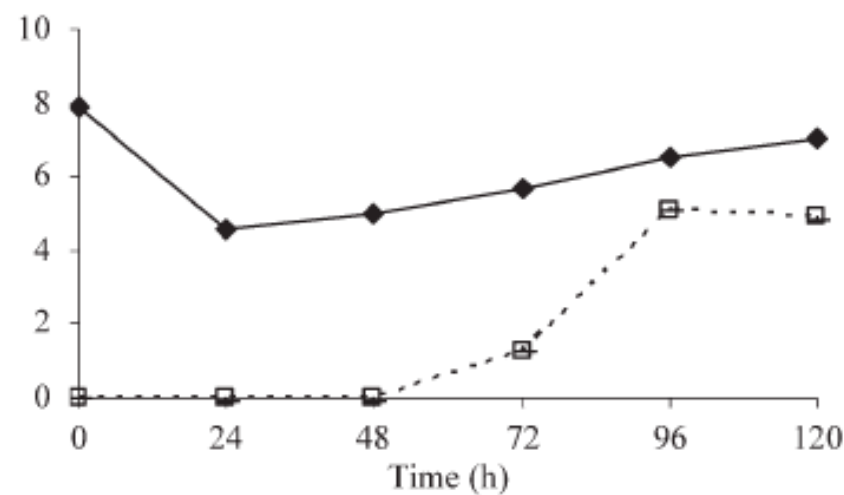
Mathematical modelling response of *Pseudomonas aeruginosa* to meropenem

Vincent H. Tam^{1*}, Amy N. Schilling¹, Keith Poole² and Michael Nikolaou³

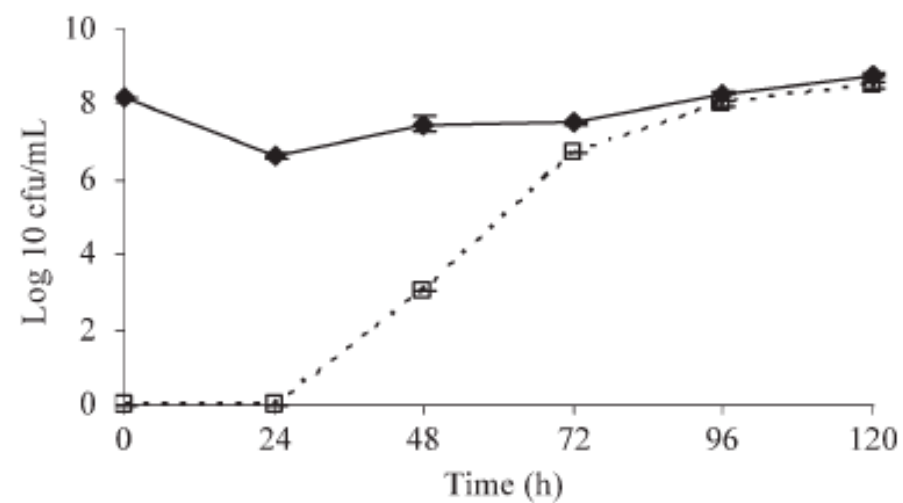
Placebo



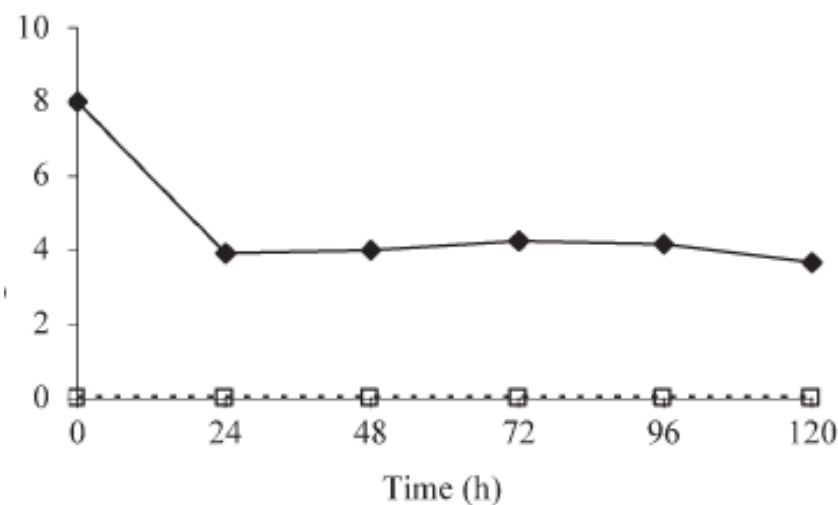
$T > \text{MIC } 100\%$, $C_{\min} / \text{MIC} = 1.7$



$T > \text{MIC } 84\%$, $C_{\min} / \text{MIC} = 0.5$



$T > \text{MIC } 100\%$, $C_{\min} / \text{MIC} = 6.0$



Strain	Exposure (C_{min} /MIC)	MIC (mg/L)							Mechanism(s) of resistance
		MEM ^a	PIP	CAZ	IPM	LVX	TOB	CAR ^a	
PA 27853	—	1	3	1	3	0.75	0.5	64	—
MR1	placebo	4	3	1	>32	0.75	0.5	ND	OprD—
MR2	0.5	64	8	2	>32	4	0.5	512	OprD— and Mex+
MR3	1.7	32	32	4	32	6	0.5	512	OprD— and Mex+

Mutant prevention concentrations of colistin for *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* clinical isolates

Myung-Jin Choi and Kwan Soo Ko*

J Antimicrob Chemother 2014

Amino acid alterations

Species/isolate	Colistin MIC (mg/L)	Colistin MPC (mg/L)	Amino acid alterations				
			PmrB	PhoP	PhoQ	ParR	ParS
<i>A. baumannii</i>							
C072	0.5	>128	P233S	NA	NA	NA	NA
<i>P. aeruginosa</i>							
P1	2	64				N24S	
P10	2	>128					Q232E
P29	1	64					G361R
P70	2	>128	V281I		K123E		
P83	1	>128				L18I, S24N	
P88	2	64		N188H			G361R
P112	2	64				Syn	
P147	2	128			Syn		
P155	1	>128			R214H		
P179	2	128			V184G		
P185	2	128	V281I		Q133E		
P199	2	128			A207R		
P206	2	128	Syn		N104I		
P213	2	128	F237L				
<i>K. pneumoniae</i>							
513 BTB	0.5	>128	Δ3 nt position 14			NA	NA
507 BTB	0.5	>128	T157P			NA	NA
08-u-899		>128	S208N, Δ3 nt position 209			NA	NA
K08-Bact-08-039	4	>128			S174N	NA	NA
YDJ	0.5	>128	T157P			NA	NA

Mutant prevention concentration of tigecycline for *Acinetobacter baumannii* and *Klebsiella pneumoniae* clinical isolates

Myung-Jin Choi^{1†}, Kyong Ran Peck^{2†} and Kwan Soo Ko^{1*}

J Antimicrob Chemother 2014

Species	Isolate	MIC (mg/L)		MPC (mg/L)	MPC/MIC	Presence of AdeAB/AdeRS efflux systems ^a	Fold change in <i>adeB</i> or <i>acrA</i> ^b (mean \pm SD)	Mutation of <i>adeRS</i> or <i>acrR</i> in single-step mutant ^c
		parent	mutant					
<i>A. baumannii</i>	E07-612	0.5	1	1	2	B, C	1.0 \pm 0.1	ND
	07AC-029	0.5	1	1	2	none	ND	ND
	06AC-23	1	16	16	16	A, B, R, S	7.1 \pm 2.8	none
	06AC-66	2	64	32	16	A, B, R, S	2.4 \pm 0.2	none
	06AC-108	0.5	4	4	8	A, B	71.6 \pm 11.5	ND
	E10-93	1	16	8	8	A, B, C, R, S	19.7 \pm 3.4	none
	H09-504	1	16	16	16	A, B, C, R, S	23.4 \pm 1.2	disruption of <i>adeS</i> by IS <i>aba1</i> ^d
<i>K. pneumoniae</i>	K01-08-10058	0.5	1	0.5	2	—	1.7 \pm 0.18	none
	LJA	1	4	4	4	—	1.7 \pm 0.14	none
	08-u-899	1	8	16	16	—	10.6 \pm 0.4	none
	08-u-819	1	8	8	8	—	12.8 \pm 0.2	none
	08-u-934	1	16	16	16	—	17.2 \pm 2.5	none
	K06-Bact-08-007	0.5	8	8	16	—	6 \pm 0.4	none
	K08-Bact-08-039	0.5	8	8	16	—	3.3 \pm 1.2	none

Considerações práticas importantes

- Maiores problemas com resistência bacteriana atualmente → RESISTÊNCIA ADQUIRIDA
- > inóculo bacteriano → > frequência de mutantes
- Quando inóculo é maior?
 - Início da infecção
 - Extensão da infecção (órgão acometido)

Foco de ações
PK/PD
PK/MPC



Otimizando a terapia para minimizar resistência

Alexandre P. Zavascki

Serviço de Infectologia - HCPA
Faculdade de Medicina – UFRGS
azavascki@hcpa.ufrgs.br