Management of community-acquired respiratory tract infections and treatment optimisation using PK/PD principles

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الجمعية العلمية السعودية للطب الباطني
Saudi Society of Internal Medicine

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Disclosures and slides availability

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  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics…
- Other relationships in relation to this talk:
  - Belgian Antibiotic Policy Coordination Committee
  - Belgian Transparency and Reimbursement Committees
  - Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones

Slides are available at http://www.facm.ucl.ac.be → Lectures

Do we have a problem?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillins

Ann. Rev. Biochem. 1979. 48:73–101

USE OF MODEL ENZYMES IN THE DETERMINATION OF THE MODE OF ACTION OF PENICILLINS AND Δ^3-CEPHALOSPORINS[1]

Jean-Marie Ghuysen, Jean-Marie Frère, Mélina Leyh-Bouille, Jacques Coyette, Jean Dusart, and Martine Nguyen-Distèche

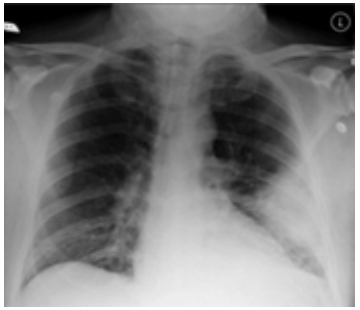
Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

and died from invasive pneumococcal infection …

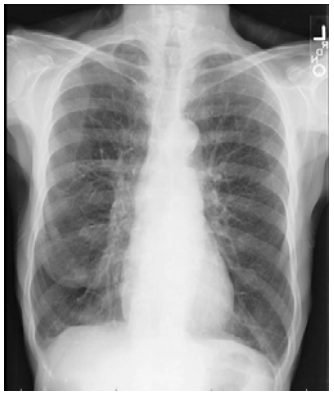
http://www.cip.ulg.ac.be/newsite/pdf/jmghuysen.pdf

Do we have a problem?

- CAP:
  - Remains a major acute cause of death (3^{d} to 7th);
  - *Streptococcus pneumoniae* is the most commonly identified pathogen, but other bacteria may be critical in specific environments (the causative organisms remains, however, unidentified in 30% to 50% of cases).
- COPD:
  - Also a major cause of death (4th in 2006 and projected 3d in 2020)
  - Runs as often undiagnosed at early stages
  - “Progresses" to decreases of respiratory function by successive infectious exacerbations



http://www.cdemcurriculum.org/index.php/ssm/show_ssm/pulmonary/pneumonia (last accessed: 5/11/2013)



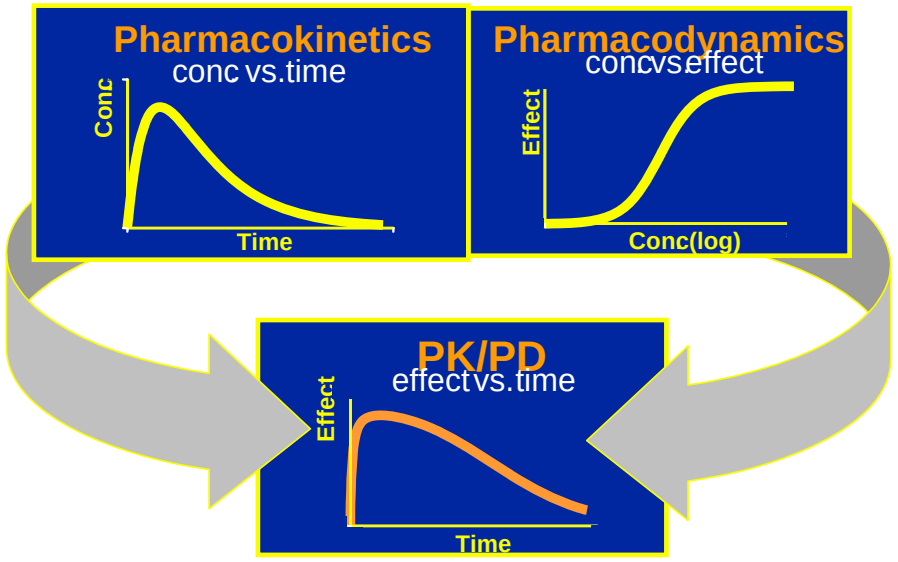
http://www.cdemcurriculum.org/index.php/ssm/show_ssm/pulmonary/copd (last accessed: 5/11/2013)

CAP: community acquired pneumonia
COPD: chronic obstructive pulmonary disease

What is my goal?

- Discuss with you two ways to try improving the treatment of CA-RTI

GUIDELINES

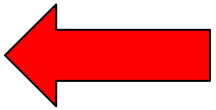


PK/PD

CA-RTI: community acquired respiratory tract infections
PK/PD: pharmacokinetics/pharmacodynamics

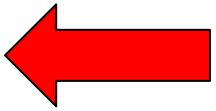
Guidelines: origin, basis and use

- Clinical guidelines aim at **guiding decisions and criteria** regarding diagnosis, management, and treatment

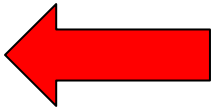


- Guidelines have been used since the beginning of medicine

- Modern medical guidelines are supposed to be based on **critical examination of current evidence**, with emphasis on **evidence-based** rather than eminence-based medicine

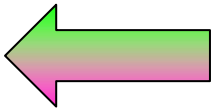


- More and more, healthcare professionals must not only know about, but **apply guidelines** or **justify why they do not follow them** for an individual patient or group of patients

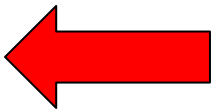


Guidelines: content and goals

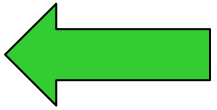
- Modern clinical guidelines should identify the **most valuable evidence** and integrate this knowledge to build **optimized decisions trees** that should be applicable to the **majority of patients**, while being sufficiently flexible to accommodate a sufficient level of **individual variation**



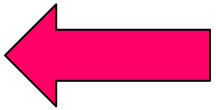
- But guidelines are also often seen as a mean to **standardise medical care** with two potential consequences/goals:



  - to **raise quality of care** while *reducing the risks* to patients

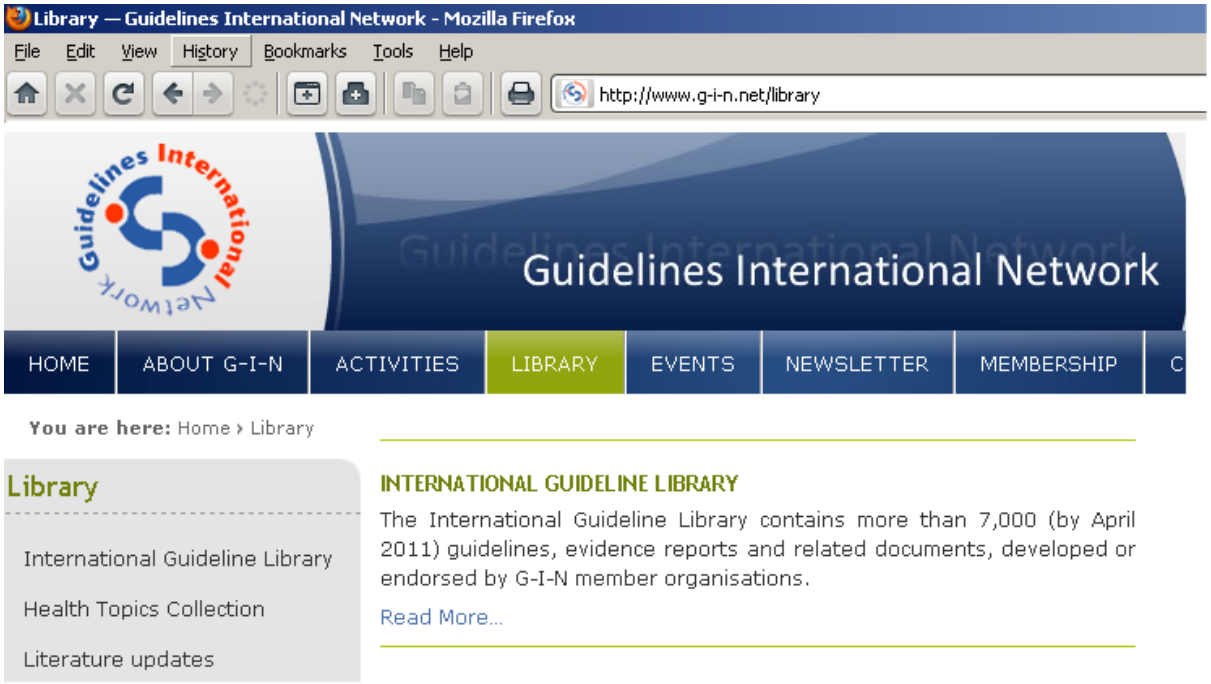


  - to achieve the **best balance between cost and medical efficacy** (broadly speaking)



Guidelines: who and where?

- Guidelines at national or international level by experts and associations that should represent not only healthcare professionals, but also patients (individual level) and society (societal level), and published in a variety of forms…
- Guidelines International Network (G-I-N) is the largest web-based database of medical guidelines worldwide



How to assess guidelines: the "AGREE" instrument

- Originally developed through a grant from the European Union
- Published in its version #1 in 2001
- Updated as version #2 in 2010

http://www.agreetrust.org/

The 6 main domains

AGREE II INSTRUMENT

I. Domain 1. Scope and Purpose

II. Domain 2. Stakeholder Involvement

III. Domain 3. Rigour of Development

IV. Domain 4. Clarity of Presentation

V. Domain 5. Applicability

VI. Domain 6. Editorial Independence

***A**ppraisal of **G**uidelines **R**esearch and **E**valuation – developed through an EU-funded research project and available on http://www.agreetrust.org/

Looking at the main critical subdomains

II. Stakeholder involvement

1. **The guideline development group includes individuals from all relevant professional groups.**
2. **The views and preferences of the target population (patients, public, etc.) have been sought.**
3. The target users of the guideline are clearly defined.

Did you really take the patient into consideration?

Looking at the main critical subdomains

III. Rigour of development

1. Systematic methods were used to search for evidence.
2. The criteria for selecting the evidence are clearly described.
3. The strengths and limitations of the body of evidence are clearly described.
4. The methods for formulating the recommendations are clearly described.
5. The health benefits, side effects, and risks have been considered in formulating the recommendations.
6. There is an explicit link between the recommendations and the supporting evidence.
7. The guideline has been externally reviewed by experts prior to its publication.
8. **A procedure for updating the guideline is provided.**

Perhaps a most critical point…

Looking at the main critical subdomains

III. Rigour of development

This is an old Flemish map…

1. Systematic methods were
2. The criteria for selecting t
3. The strengths and limitati
   describ
   …nat
   …s, side
   …ormulating
6. There is an explicit link b
   supporting evidence.
7. The guideline has been externally reviewed by experts prior to its publication.
8. **A procedure for updating the guideline is provided.**

Using this map may not be the best way to find your way today in Arabia !

Perhaps a most critical point…

Looking at the main critical subdomains

V. Applicability

1. **The guideline describes facilitators and barriers to its application.**
2. The guideline provides advice and/or tools on how the recommendations can be put into practice.
3. **The potential resource implications of applying the recommendations have been considered.**
4. **The guideline presents monitoring and/or auditing criteria.**

How real is this in your guidelines ?

Looking at the main critical subdomains

V. Applicability

1. **The guideline (… its application.**
2. The guideline p… recommendatio…
3. **The potential r… recommendati…**
4. **The guideline … criteria.**

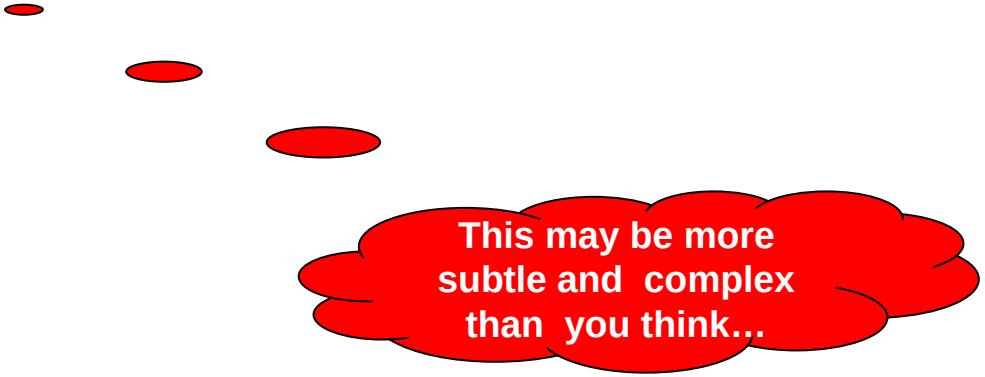
Can you find easily which connection is faulty?

How real is this in your guidelines?

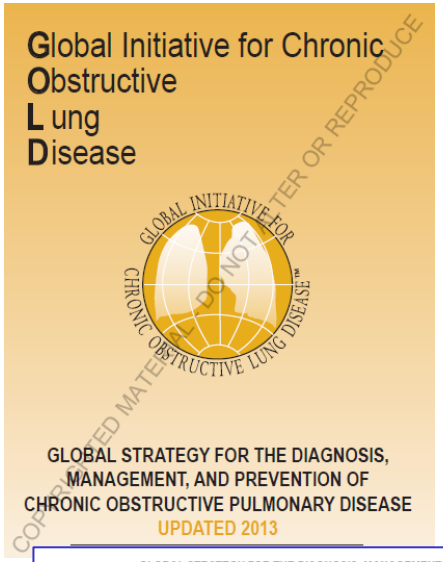
Looking at the main critical subdomains

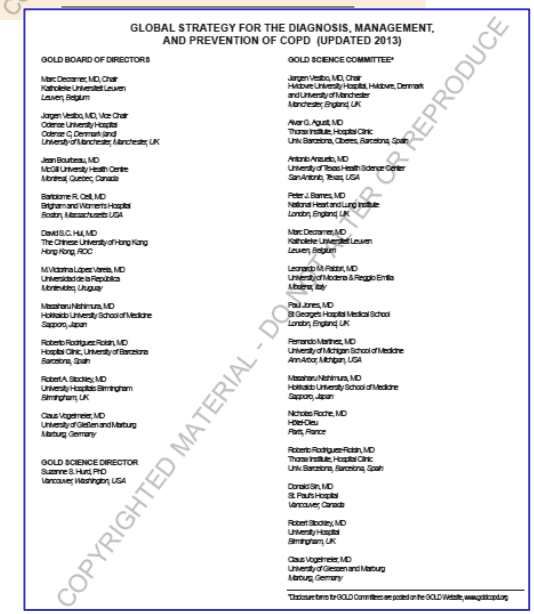
VI. Editorial Independence

1. **The views of the funding body have not influenced the content of the guideline.**
2. **Competing interests of guideline development group members have been recorded and addressed.**



Editorial independence is more than declaring...




GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (UPDATED 2013)

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GOLD SCIENCE DIRECTOR

*Disclosure forms for GOLD Committee are posted on the GOLD Website, www.goldcopd.org

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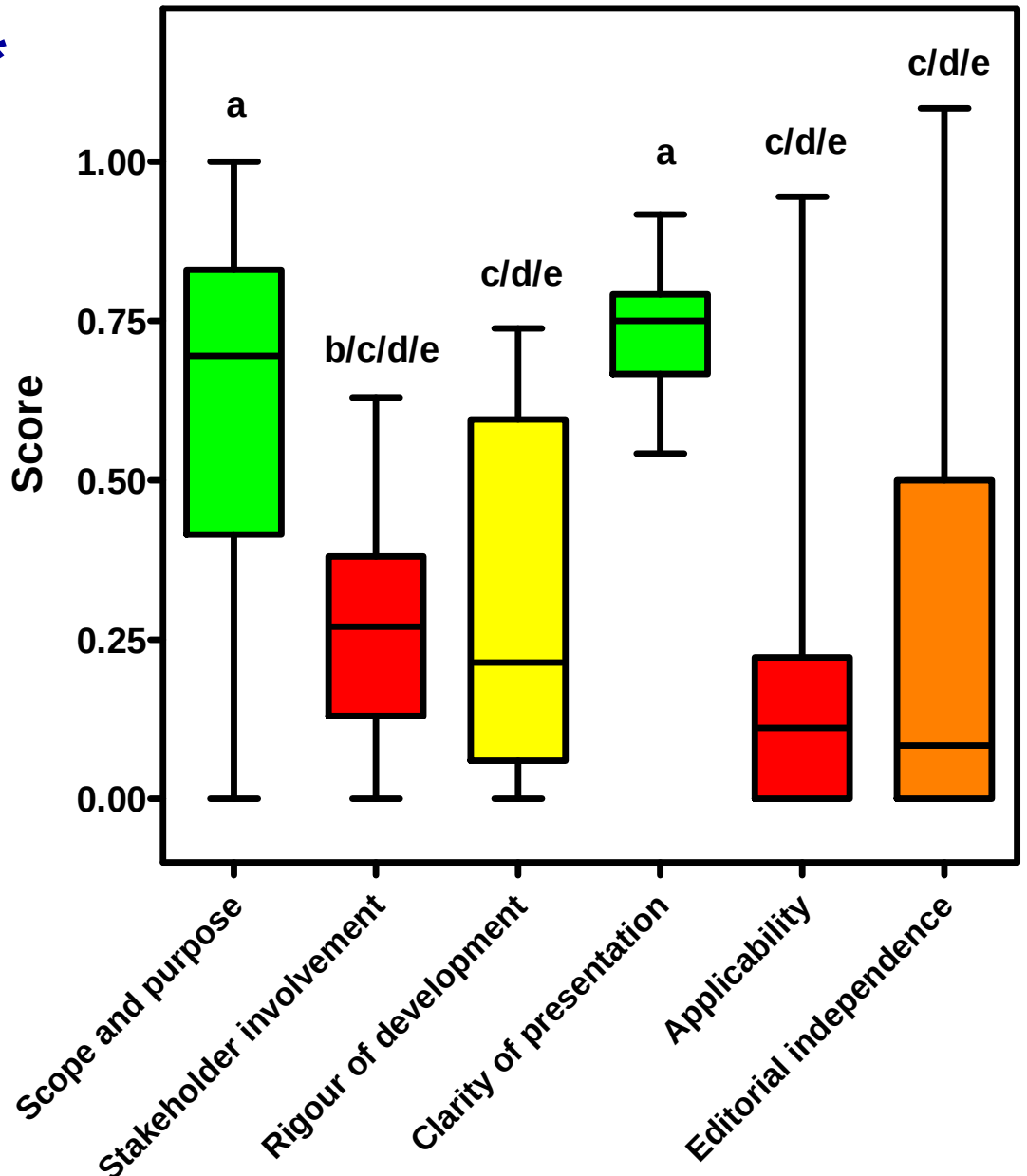
Inhibiteurs de la pompe à protons et statines

Utilisation et prescription

Analysis of 30 CAP* guidelines with the AGREE Instrument

* CAP: community acquired pneumonia



- Mean scores presented as 'boxes and whiskers' (lowest to highest with 25 -75% and median.
- Scores of domains with different letters are significantly different from each other (Kruskal-Wallis test with Dunn's Multiple Comparison Test)

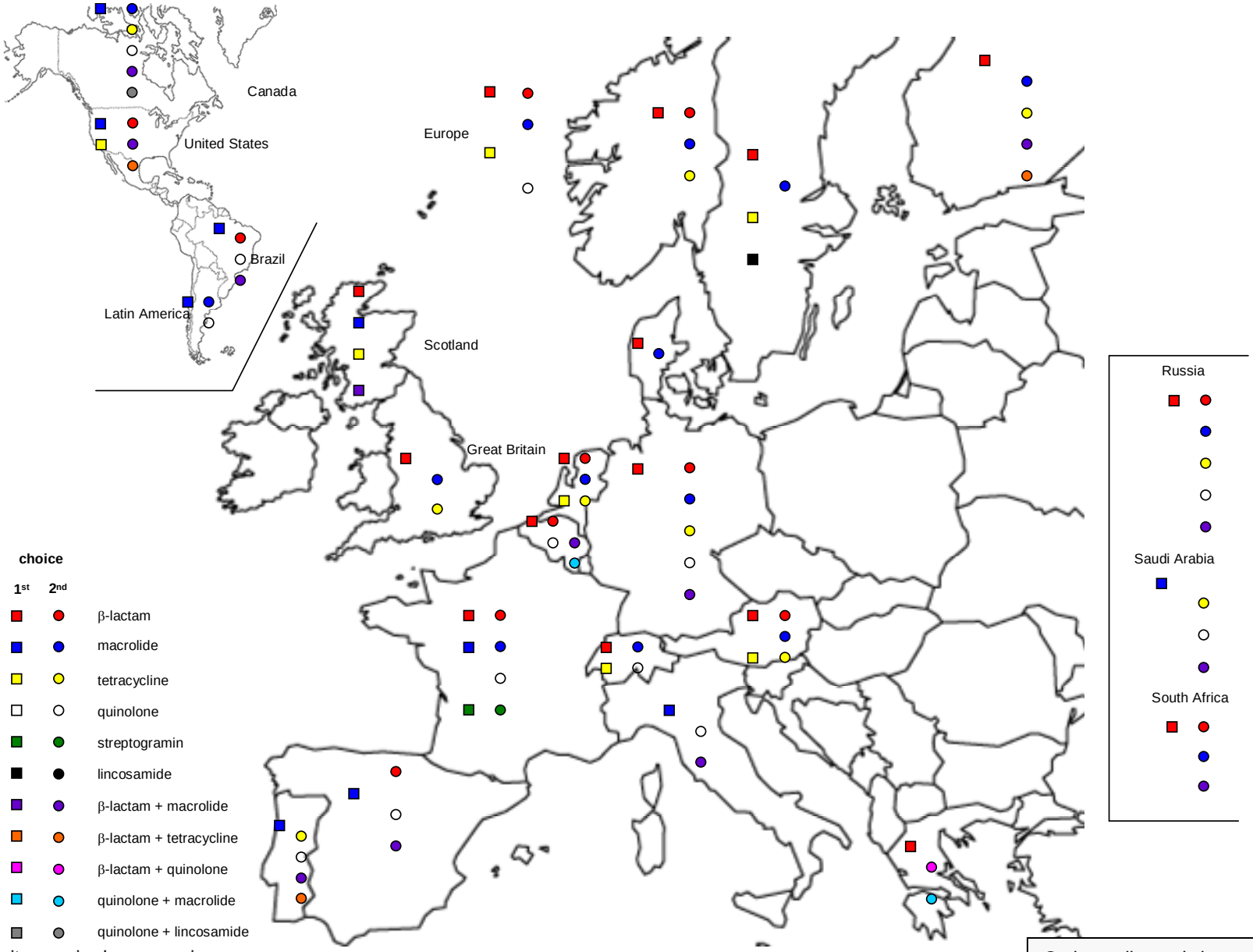
Carbonnelle *et al.*, in preparation

Guidelines: are they homogenous?

- They need not be, if:
  - the diseases are different between geographical areas or groups of patients
  - for infectious diseases, if the epidemiology is different between areas
  - if drug availability is not uniform…
  - if medical and pharmaceutical resources are different

- However, variations are often much larger than may be anticipated from the above considerations…

CAP guidelines: many variations



CAP: community-acquired pneumonia

Carbonnelle *et al.*, in preparation

A comparison of three CAP guidelines separated by (some) water



Table 4. Recommended community-acquired pneumonia therapy and management from published international guidelines *

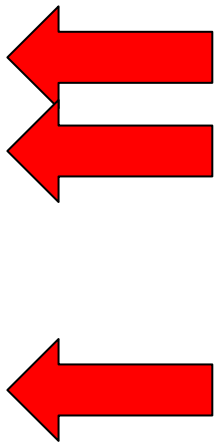
	BTS guidelines [24]	ATS/IDSA guidelines [25]	ERS/ESCMID guidelines [26]
Low severity patients*	Use CURB65 score with clinical judgement Treat with oral amoxicillin or (doxycycline or clarithromycin if hypersensitive).	Use CURB65 or PSI score to guide Outpatient treatment Stratify by risk for drug resistant *S. pneumoniae* Low risk: Treat with macrolide or doxycycline High risk: Treat with respiratory fluoroquinolone or b-lactam+macrolide	Use CRB65 to guide Outpatient treatment Treat with one of: aminopenicillin ± macrolide Aminopenicillin/b-lactamase inhibitor ± macrolide Non-antipseudomonal cephalosporin Cefotaxime or ceftriaxone ± macrolide Levofloxacin Moxifloxacin Penicillin g ± macrolide
Moderate/high severity patients*	CURB65 score 3 or more consider ICU Treat with β-lactam plus macrolide iv	Consider ICU for sepsis or >2 minor severity criteria Increased Comorbidities or prior antimicrobials (within 3 months) treat with respiratory fluoroquinolone or beta lactam plus macrolide iv	Consider ICU for respiratory failure or sepsis or >2 minor severity criteria Stratify by risk for *Pseudomonas aeruginosa* Non-antipseudomonal treat with cephalosporin III + macrolide Or Moxifloxacin or levofloxacin ± non-antipseudomonal cephalosporin III

*These are not necessarily the terms used in the guidelines but give a broad translation of what the guidelines state.

Asrar Khan & Woodhead F1000Prime Rep. 2013 Oct 1;5:43
Free access: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3790563/pdf/medrep-05-43.pdf

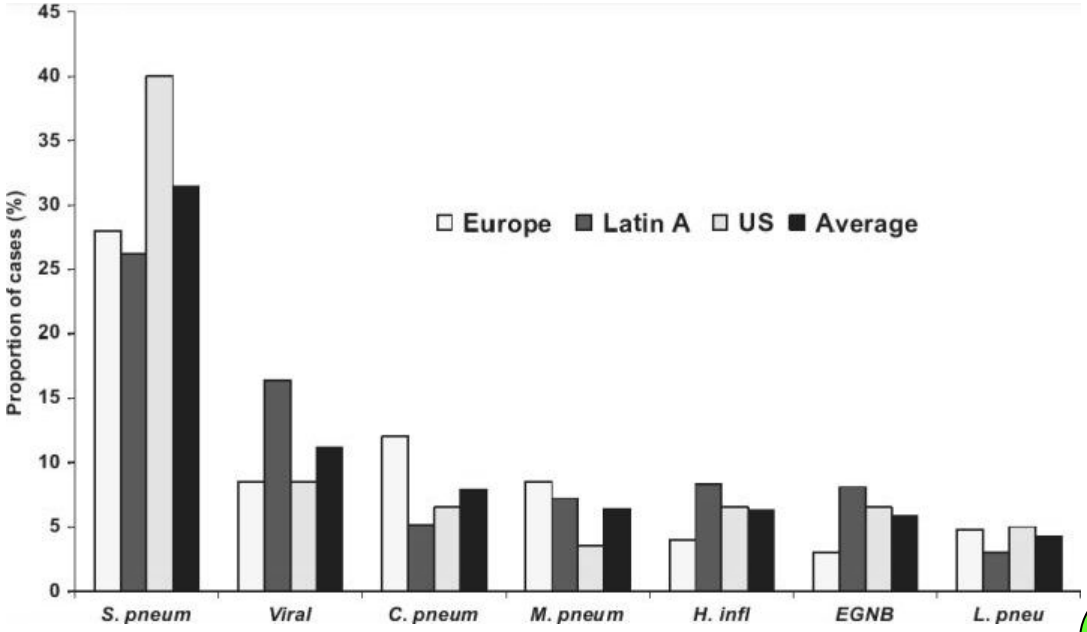
Key questions to ask when setting guidelines in infectious diseases (with application to CAP/COPD)

- How sure are you of the diagnosis?
- **Which are the main pathogens?**
- **What are their current resistance patterns?**
- How should the therapy be initiated (empiric *vs.* directed) ?
- **Which level of adverse effects is acceptable?**
- Which patients do you mainly treat?
- Does cost matter?
- What are your real choices?



CAP: community acquired pneumonia
COPD: chronic obstructive pulmonary disease

Do CAP pathogens vary between countries/regions ?



Etiology of community-acquired pneumonia in Europe, Latin America, and the United States, and overall, according to published epidemiological studies aimed at reporting such etiology performed in more than 10,000 patients from Europe, Latin America, the United States, and on average in all those sites.

Niederman *et al.* Semin Respir Crit Care Med 2012; 33(03): 298-310

Prof. Niedeman says NO, but

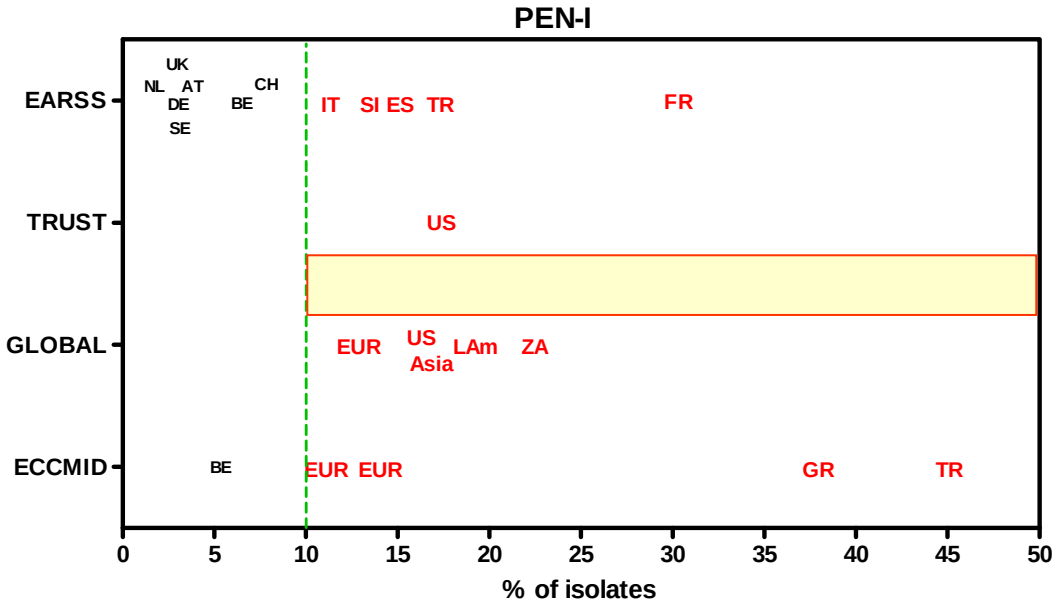
- **HIV/AIDS could impact...**
- **Tuberculosis needs to be considered**
- **Unusual pathogens (e.g. melioidosis in Southeast Asia)**

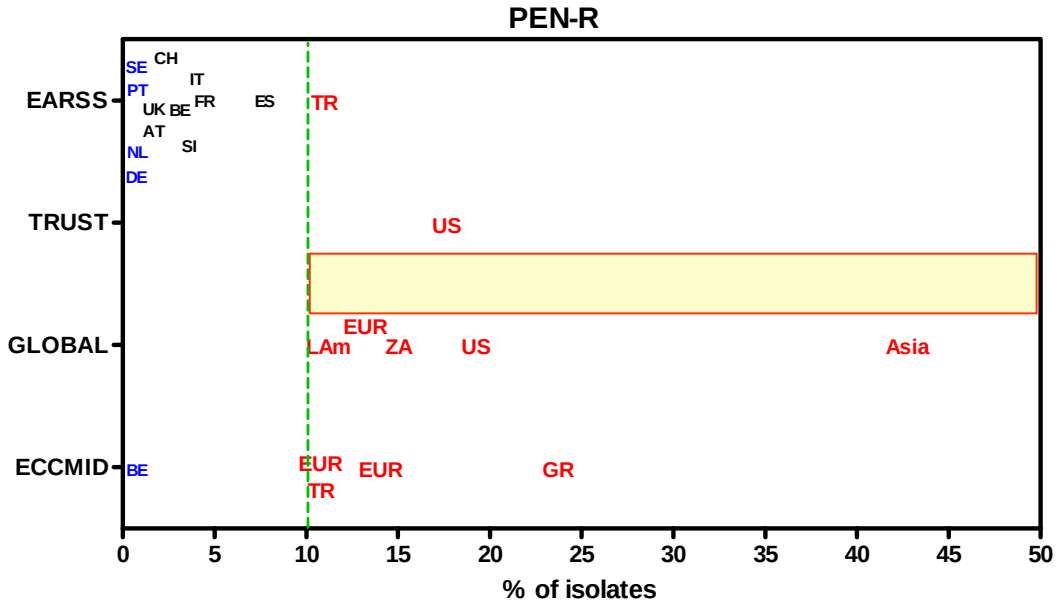
CAP: community-acquired pneumonia

Resistance of *S. pneumoniae* *

*Analysis of resistance to penicillins (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

- **EARSS**: European Antimicrobial Surveillance system
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **ECCMID**: abstracts of the 18-20th European Congress of Clinical Microbiology and Infectious Diseases





CAP: community-acquired pneumonia

Lismond *et al.*, in preparation

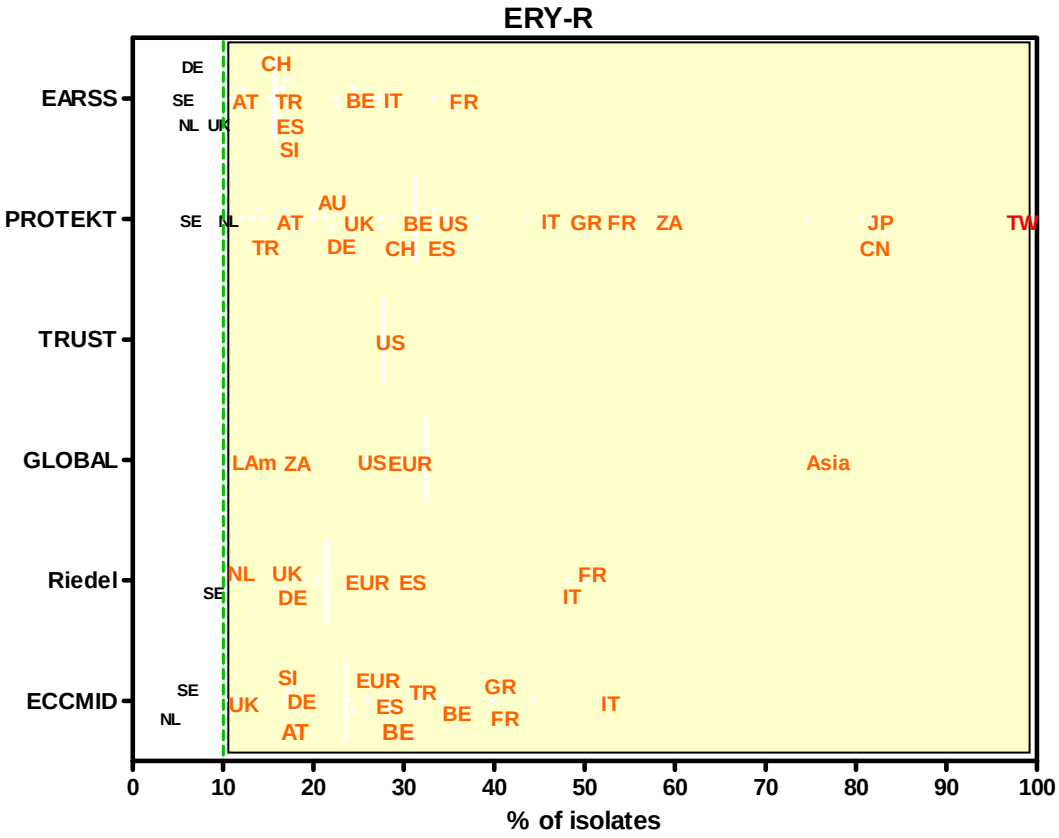
CAP: community acquired pneumonia

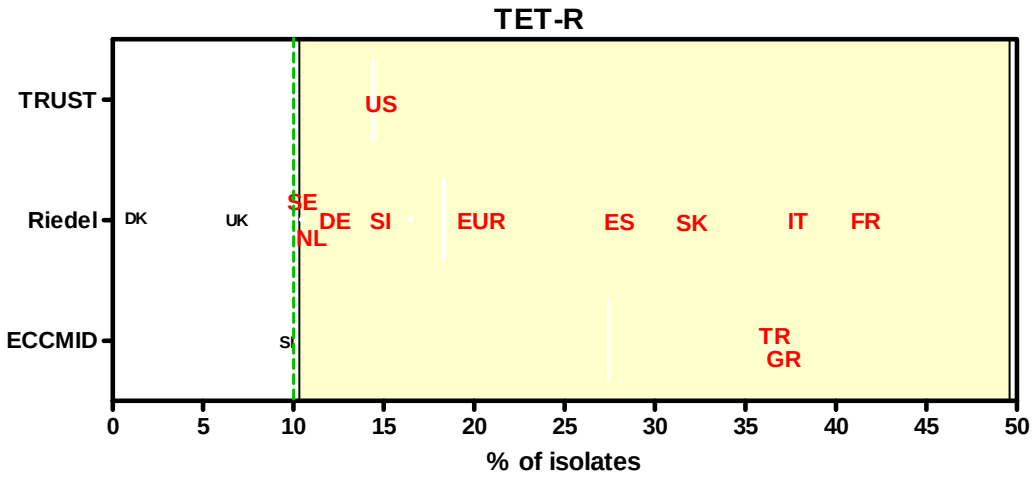
Resistance of *S. pneumoniae* *

*analysis of resistance of erythromycin and doxycycline (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

- **EARSS**: European Antimicrobial Surveillance system
- **PROTEKT**: Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **Riedel:** Eur J Clin Microbiol Infect Dis. 2007 Jul;26(7):485-90.
- **ECCMID**: abstracts of the 18th European Congress of Clinical Microbiology and Infectious Diseases

Lismond *et al.*, in preparation





Susceptibility in United Arab Emirates

Original Article

Antimicrobial resistance among *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates in the United Arab Emirates: 2004-2006

Abiola Senok,[1] Mansour Al-Zarouni,[2] Jalila Al-Najjar,[2] Abeer Nublusi,[2] Debadatta Panigrahi.[1]

[1]Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; [2]Al Qassimi Hospital Laboratory Sharjah, Ministry of Health, United Arab Emirates.

J Infect Developing Countries 2007; 1(3):296-302.

- Patients with community acquired respiratory tract infections attending healthcare facilities across the UAE from October 2004 to March 2006
- Blood, sputum, bronchoalveolar lavage, nasal, throat and ear swabs

Susceptibility in United Arab Emirates

Original Article

Antimicrobial resistance am
***Haemophilus influenzae* isol**

Abiola Senok,[1] Mansour Al-Zarouni

[1]*Department of Clinical Sciences, College of M*
Hospital Laboratory Sharjah, Ministry of Health,

J Infect Developing Countries 2007; 1(3):296-3

- Patients with community acquired respiratory tract infections attending healthcare facilities across the UAE from October 2004 to March 2006
- Blood, sputum, bronchoalveolar lavage, nasal, throat and ear swabs

Table 3. Susceptibility of *S. pneumoniae* to antimicrobial agents based on CLSI and PK/PD breakpoints.

			CLSI breakpoints			PK/PD breakpoints	
Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	S (%)	R (%)
Penicillin	0.032	1	57	38	5	-	-
Amoxicillin-clavulanate	0.016	1	98		2	98	2
Cefaclor	0.5	64	57	11	32	43	57
Cefproxil	0.125	2	92	3	5	82	18
Cefuroxime	0.064	2	87	9	4	87	13
Azithromycin	0.125	>256	67.4	1.1	31.5	48.3	51.7
Clarithromycin	0.064	>256	68.5	-	31.5	68.5	31.5
Erythromycin*	-	-	69	1	30	-	-
Clindamycin*	-	-	77	1	22	-	-
Ciprofloxacin	-	2	-	-	-	63	37
Ofloxacin	2	4	64	33	3	64	36
Co-trimoxazole*	-	-	3	20	77	-	-
Tetracycline*	-	-	81.4	1.7	16.9	-	-
Chloramphenicol	-	-	97	-	3	-	-

*Data based on disk susceptibility testing
S: Sensitive; I: Intermediate resistant; R: Resistant.

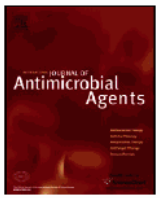
Susceptibility in Arabian Peninsula and Egypt

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

(2009) 410.e1–410.e9

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



Review

Epidemiology of invasive pneumococcal disease in the Arabian Peninsula and Egypt

Atef Shibl[a,*], Ziad Memish[b], Stephen Pelton[c]

[a] King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[b] King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Saudi Arabia
[c] Boston University School of Medicine, Boston, MA 02118, USA

Shibl et al. Int J Antimicrob Agents. 2009; 33:410.e1-9.

In the Arabian Peninsula and Egypt, resistance to

- penicillin (≥2 mg/L) : from 0% in KSA (<13 years) and Kuwait (<12 years) to 78% in KSA (<20 years);
- erythromycin (≥1 mg/L) : from 8% (<14 years) to 26% (<5 years) in KSA;
- cephalosporins (≥4 mg/L) : from 0% in KSA and Egypt (<14 years) to 12% in Qatar (<12 years)

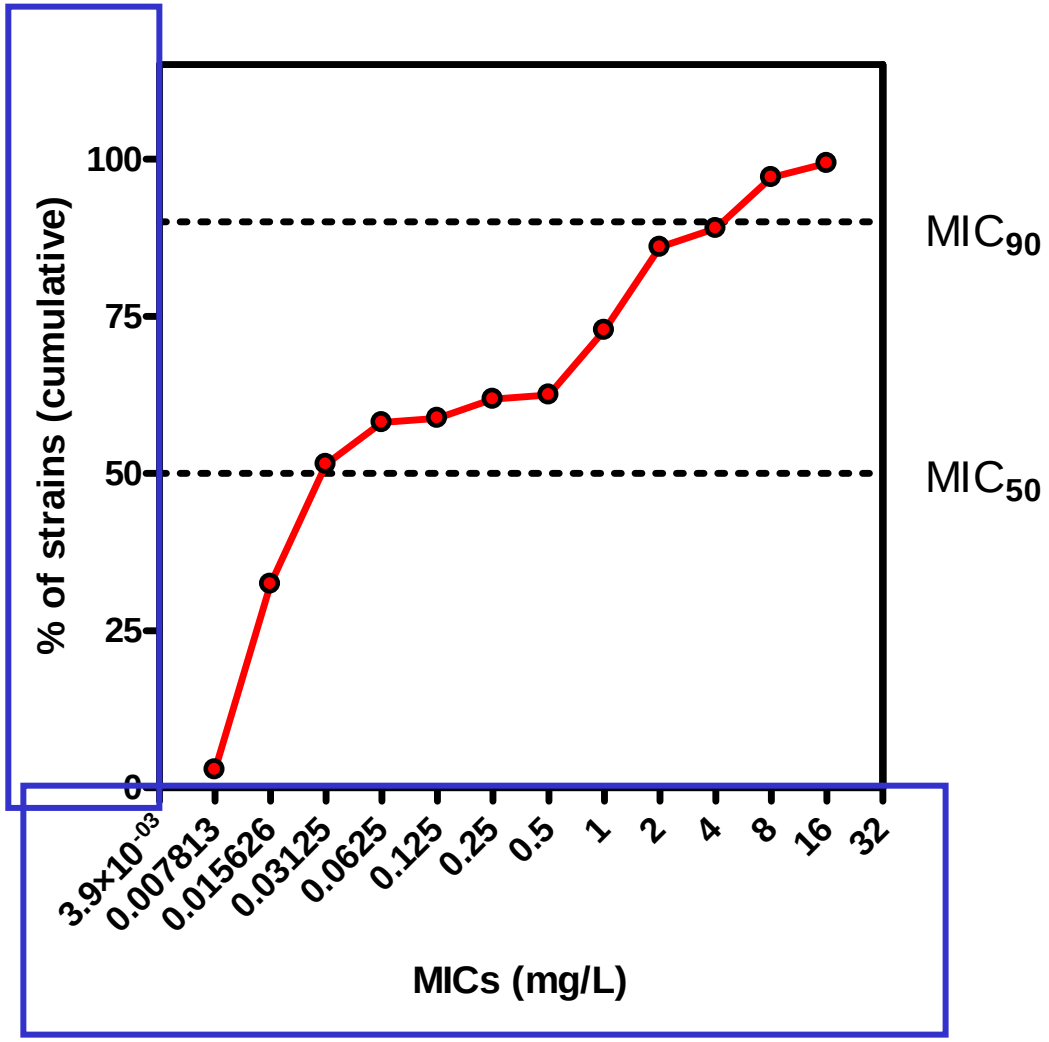
KSA: Kingdom of Saudi Arabia

But which breakpoints do we need to use?

To be honest, I always wondered ...

MIC distribution is a continuous variable…

S. pneumoniae **(n = 136)**



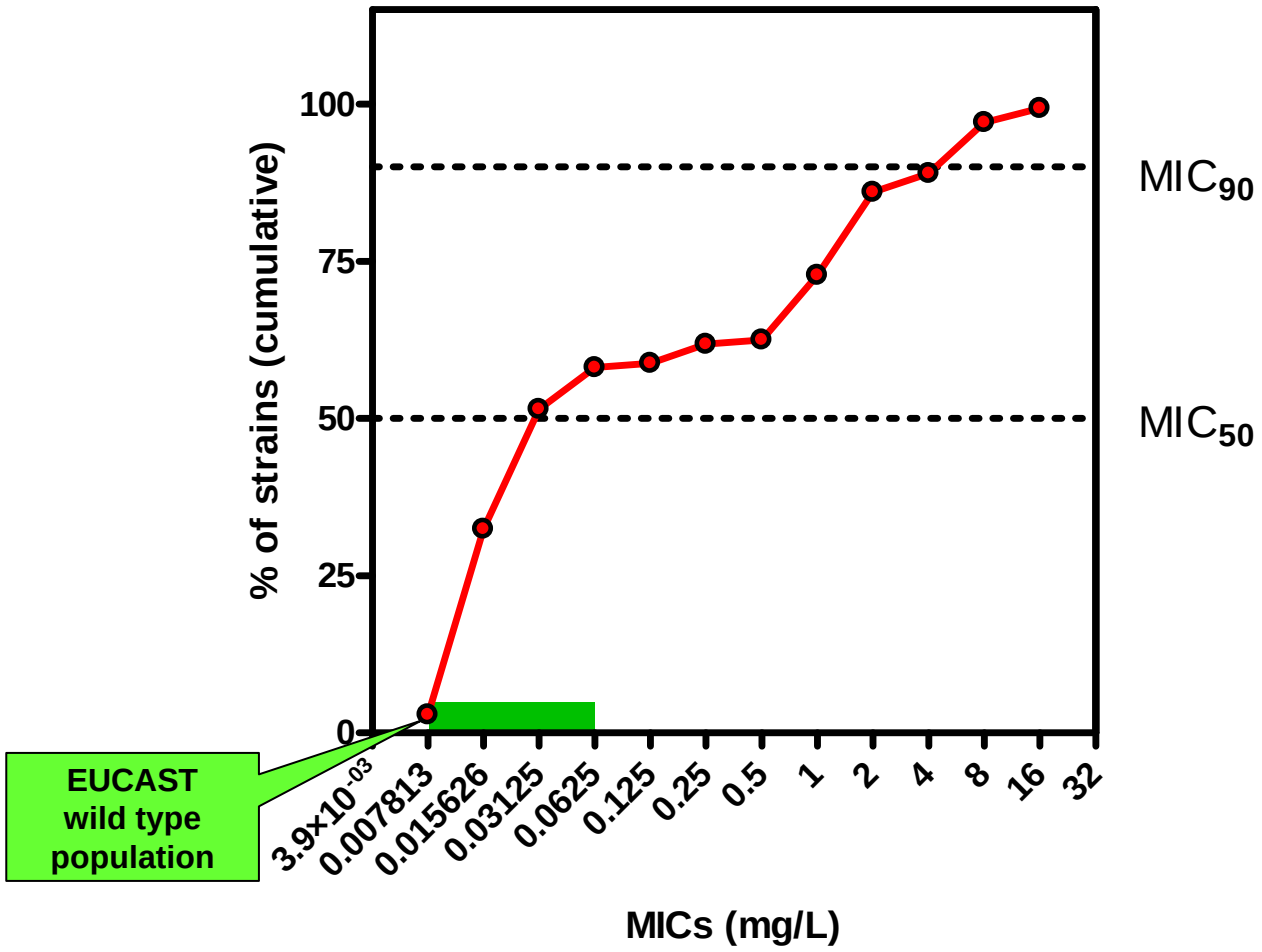
- Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP
- the high MICs of amoxicillin is driven by isolates from patients with past COPD

Tulkens, unpublished

MIC: minimum inhibitory concentration

... across which you can set limits...: "wild type"

S. pneumoniae **(n = 136)**

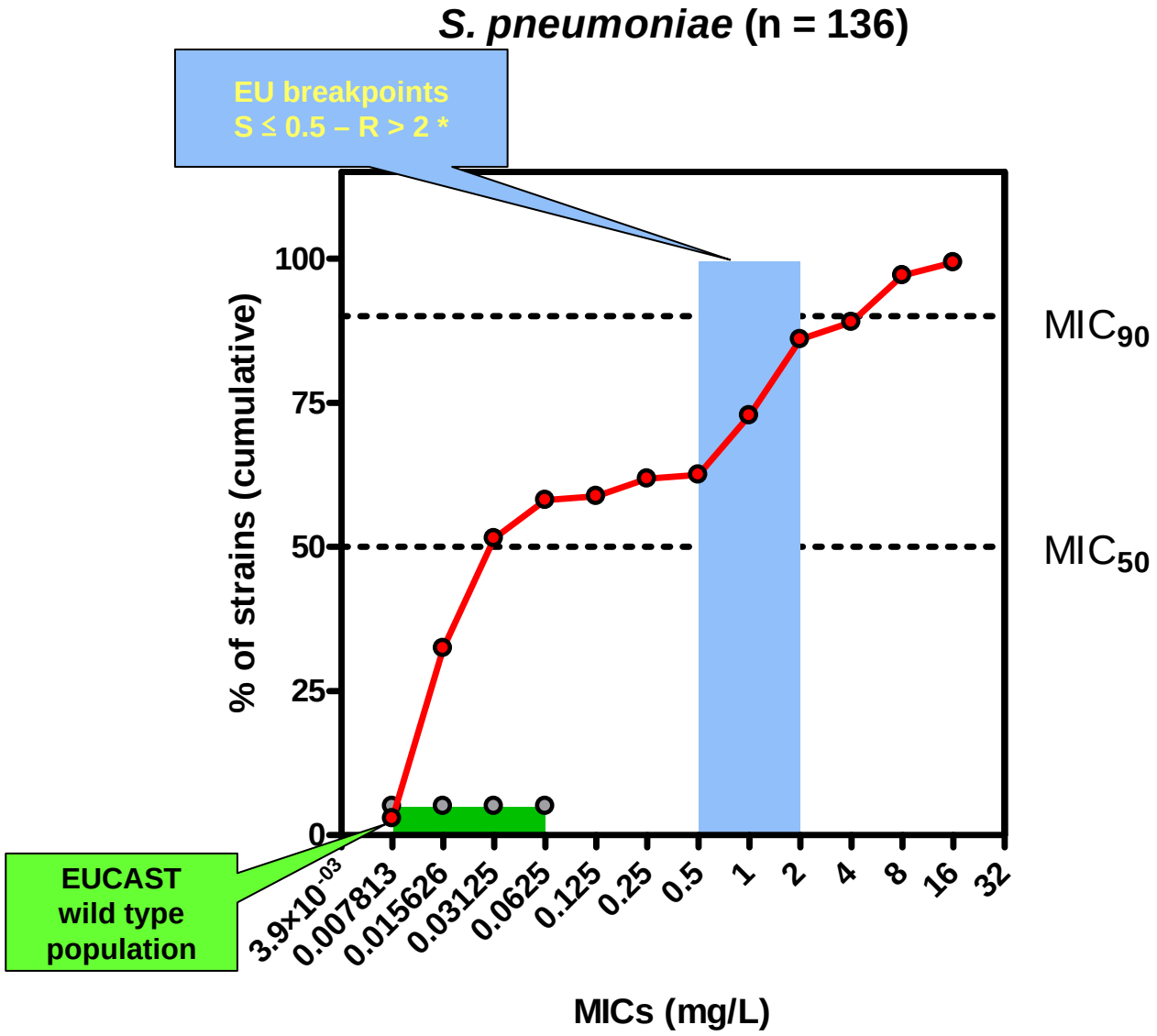


- Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP
- the high MICs of amoxicillin is driven by isolates from patients with past COPD

Tulkens, unpublished

MIC: minimum inhibitory concentration

... across which you can set limits...: "breakpoints"

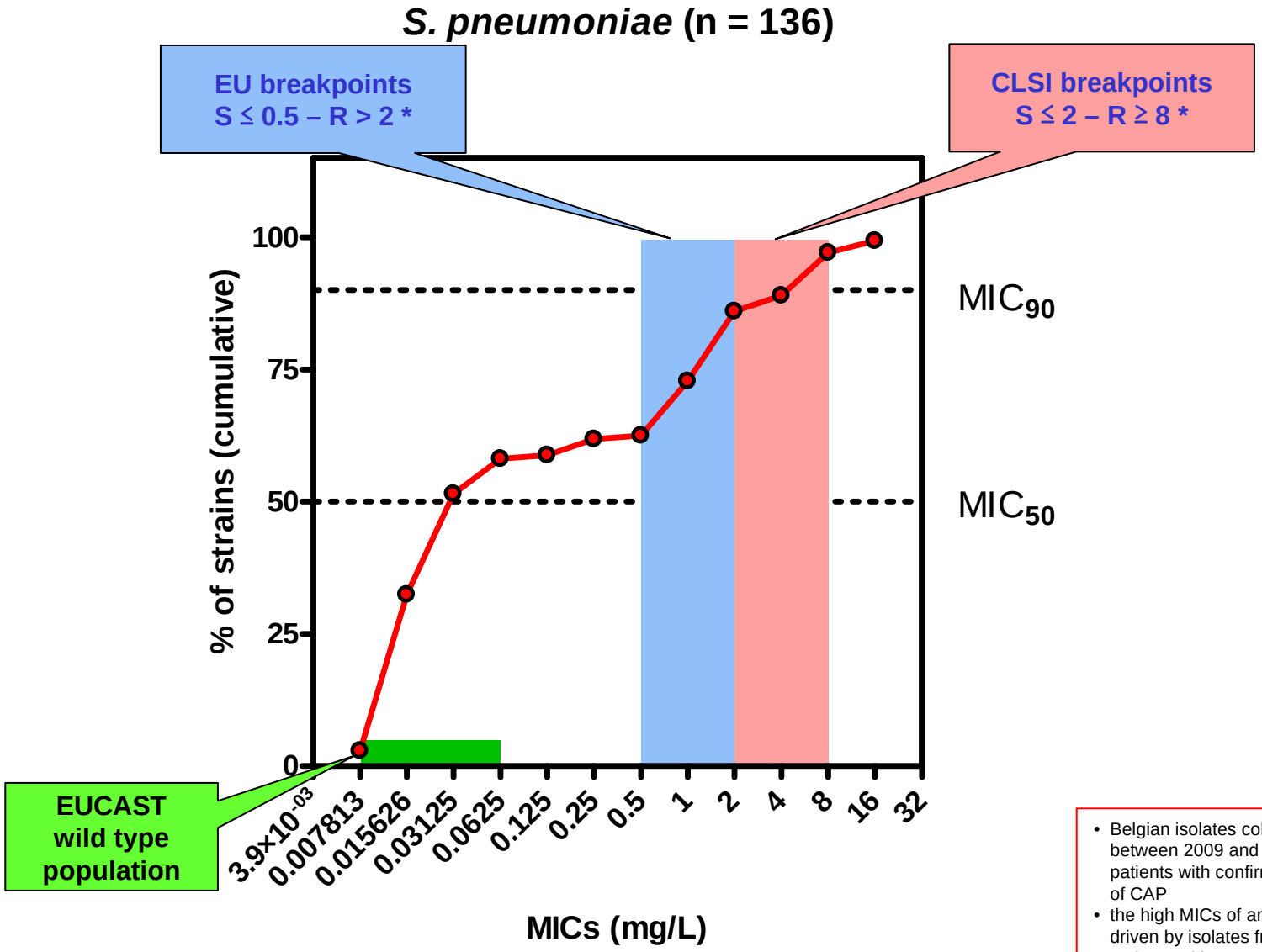


- Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP
- The high MICs of amoxicillin is driven by isolates from patients with past COPD

Tulkens, unpublished

MIC: minimum inhibitory concentration

... across which you can set limits...: "breakpoints"



- Belgian isolates collected between 2009 and 2012 from patients with confirmed cases of CAP
- the high MICs of amoxicillin is driven by isolates from patients with past COPD

Tulkens, unpublished

MIC: minimum inhibitory concentration

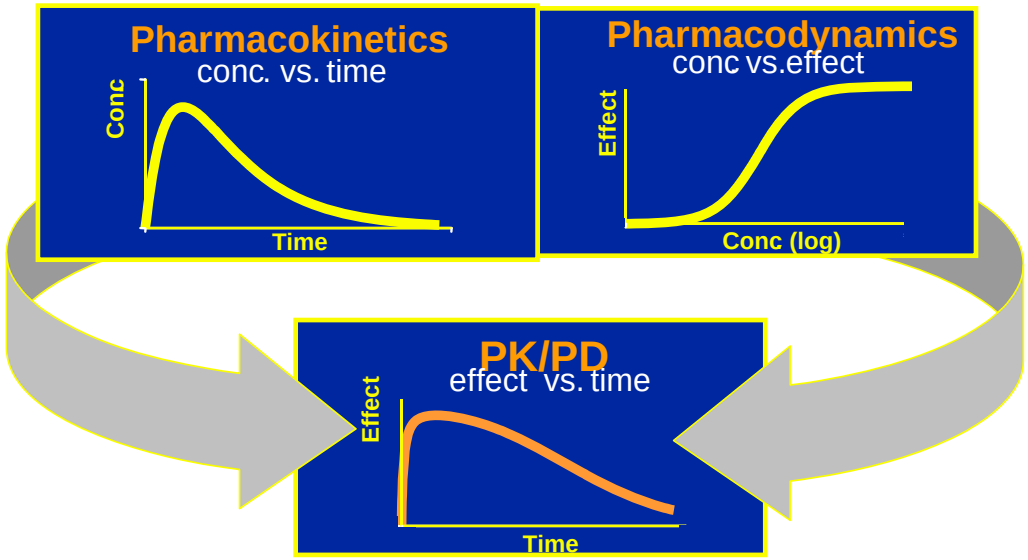
Warning about breakpoints (EUCAST *vs.* CLSI) for *S. pneumoniae* (non meningitis)

- With the [new] CLSI breakpoint (MIC ≥ 8 mg/L), very few isolates will be defined as resistant….
- In fact, most experts believe that CAP caused by organisms with a penicillin MIC of 4 mg/L or higher (still an uncommon finding), can lead to an increased risk of death.[1]
- For that reason, Europe has set its "R" breakpoint at > 2 mg/L.[2]
- **Dosage adaptation over the original 250 mg BID is necessary for isolates with MIC > 0.125 mg/L**
  (➔ 0.5 g TID, 1 g TID, …)

MIC: minimum inhibitory concentration
CAP: community acquired pneumonia
R: resistance
BID: twice daily; TID: 3 times daily

1. Feikin DR, *et al.* Am J Public Health 2000;90(2):223-9.
2. EUCAST clinical breakpoints (http://www.eucast.org)

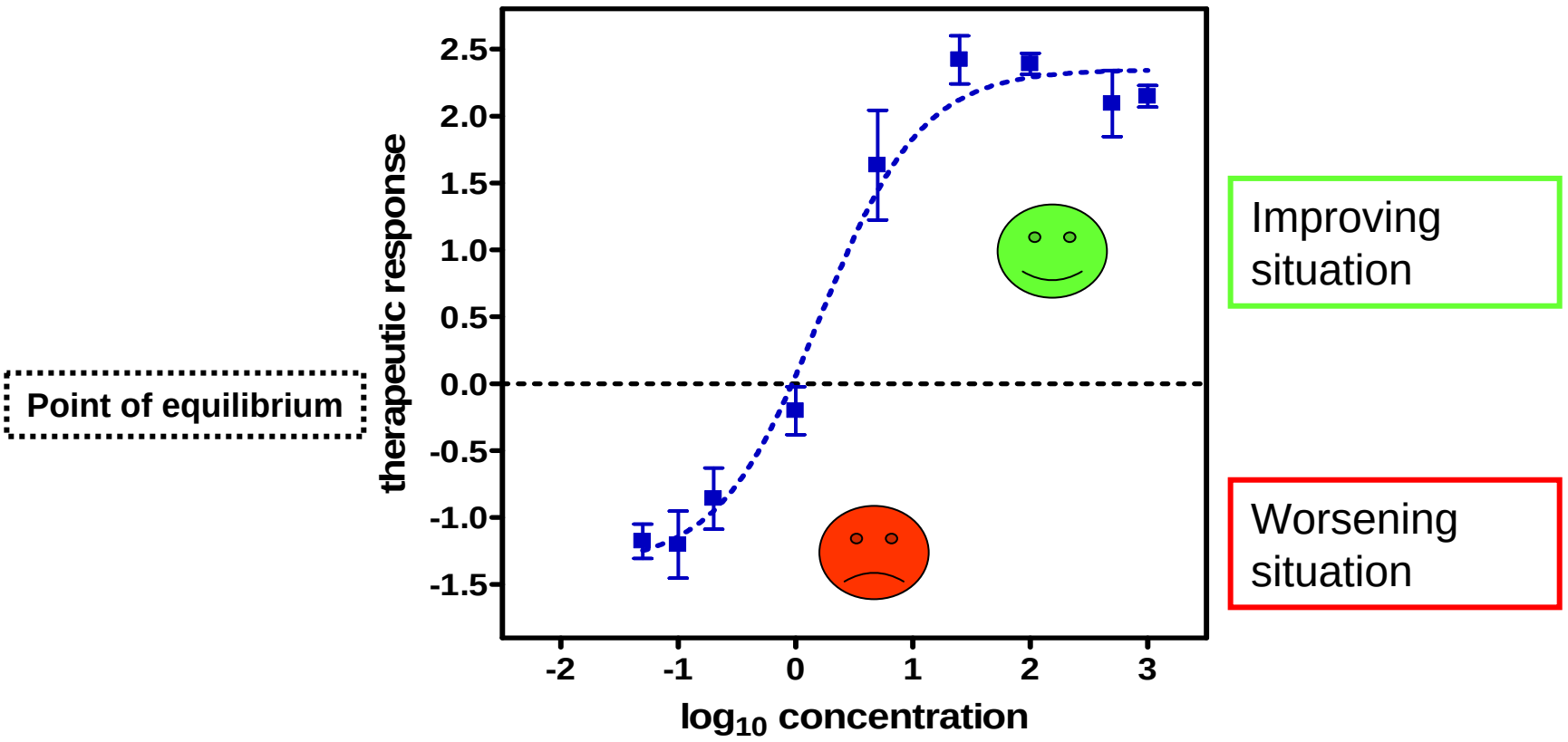
And this brings me to PK-PD…



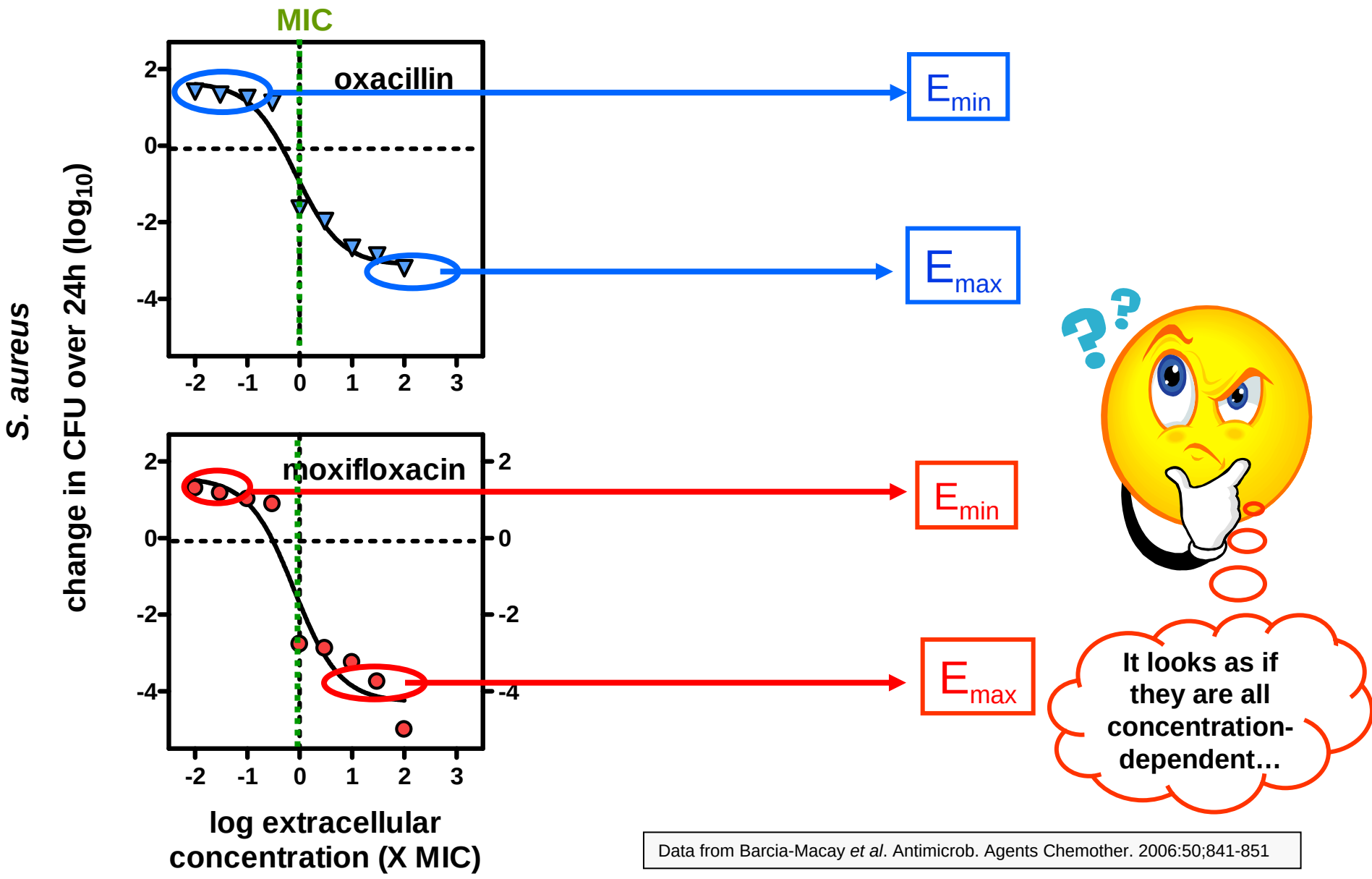
PK/PD

A simple pharmacological concept…

The dose must be adapted to the goal…

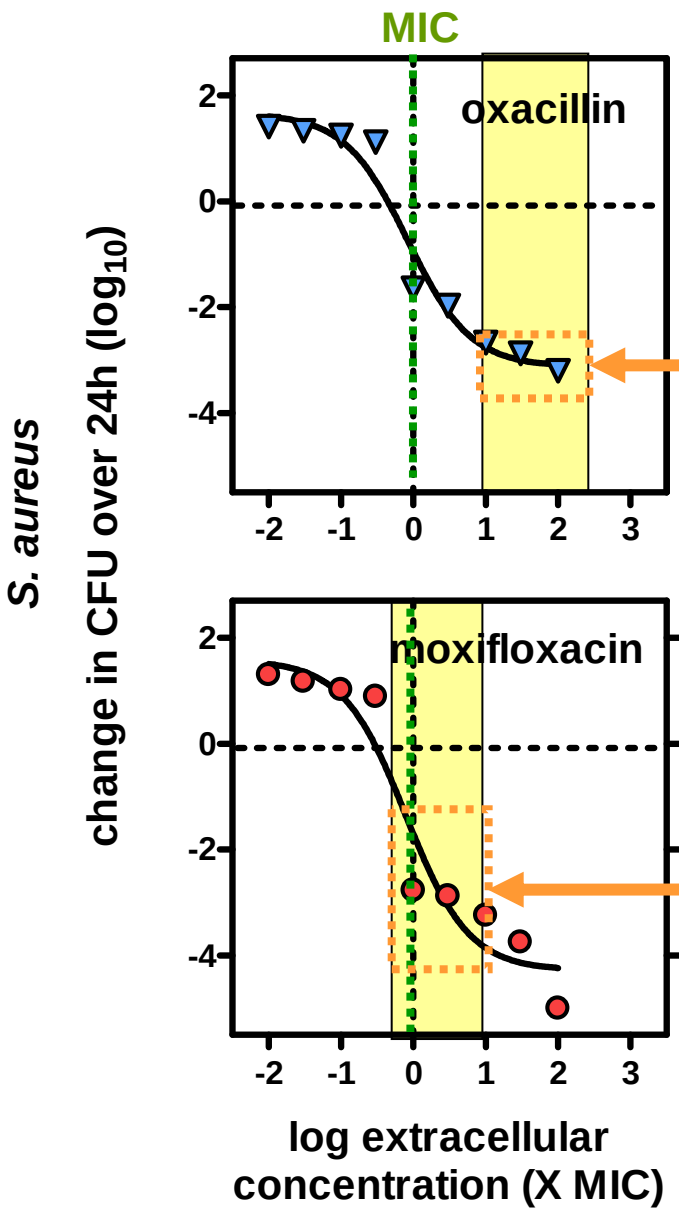


What is the relationship between MIC and effect?



Data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. 2006:50;841-851

But here comes pharmacokinetics …



Weak concentration-dependence (max. effect) over the C_{min}–C_{max} range

➔ **TIME will emerge as the main parameter in vivo**

C_{min}–C_{max}

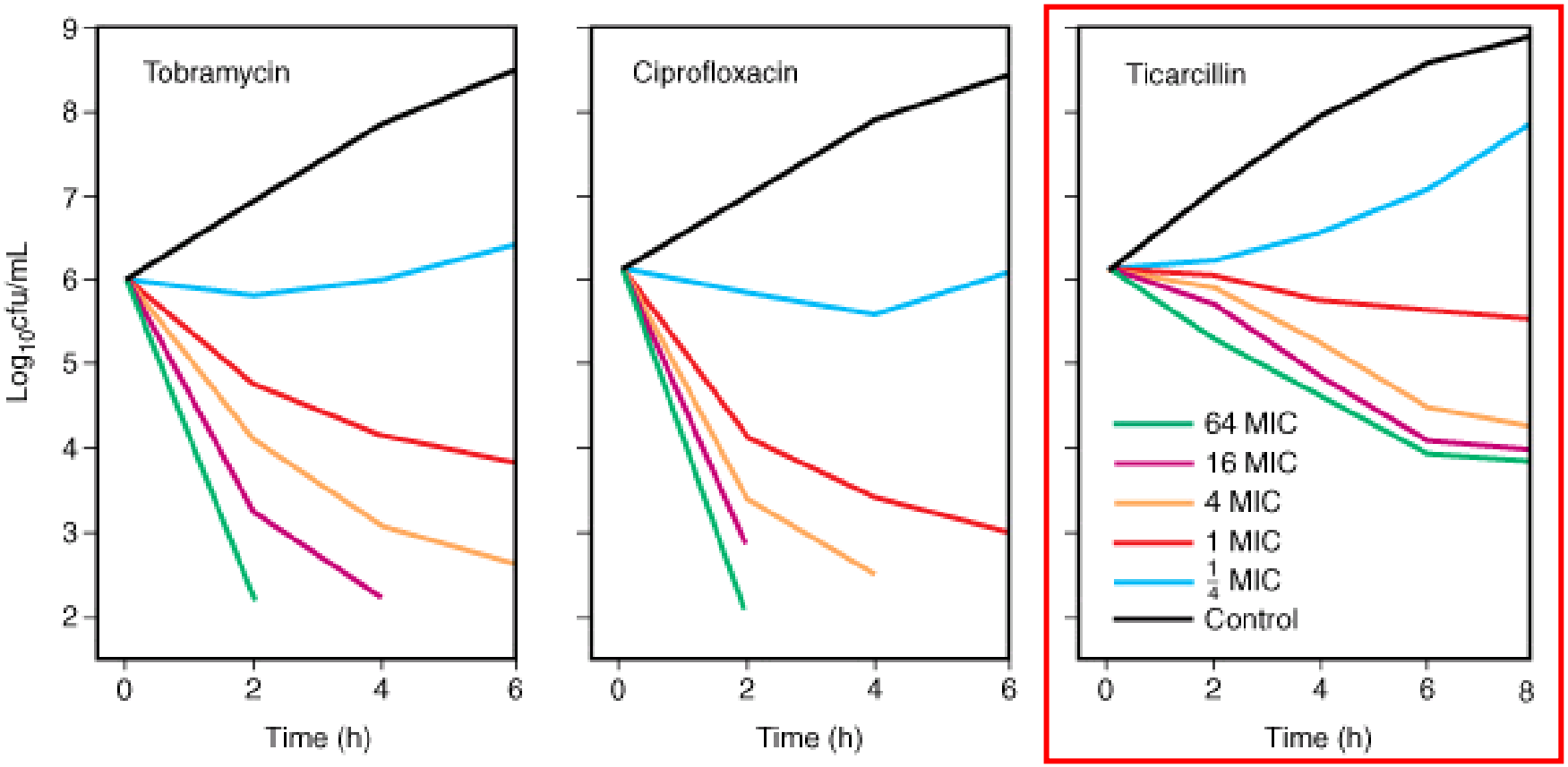
high concentration-dependence over the C_{min}-C_{max} range

➔ **CONCENTRATION will emerge as an important parameter in vivo**

- data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851
- C_{min}-Cmax: Principles and Practice of Infectious Diseases, 7th Ed. Mandell *et al*. eds., Elsevier

A further comparison: in vitro kill curves

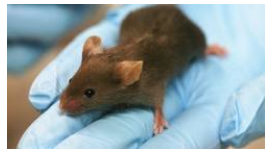
Time-dependence



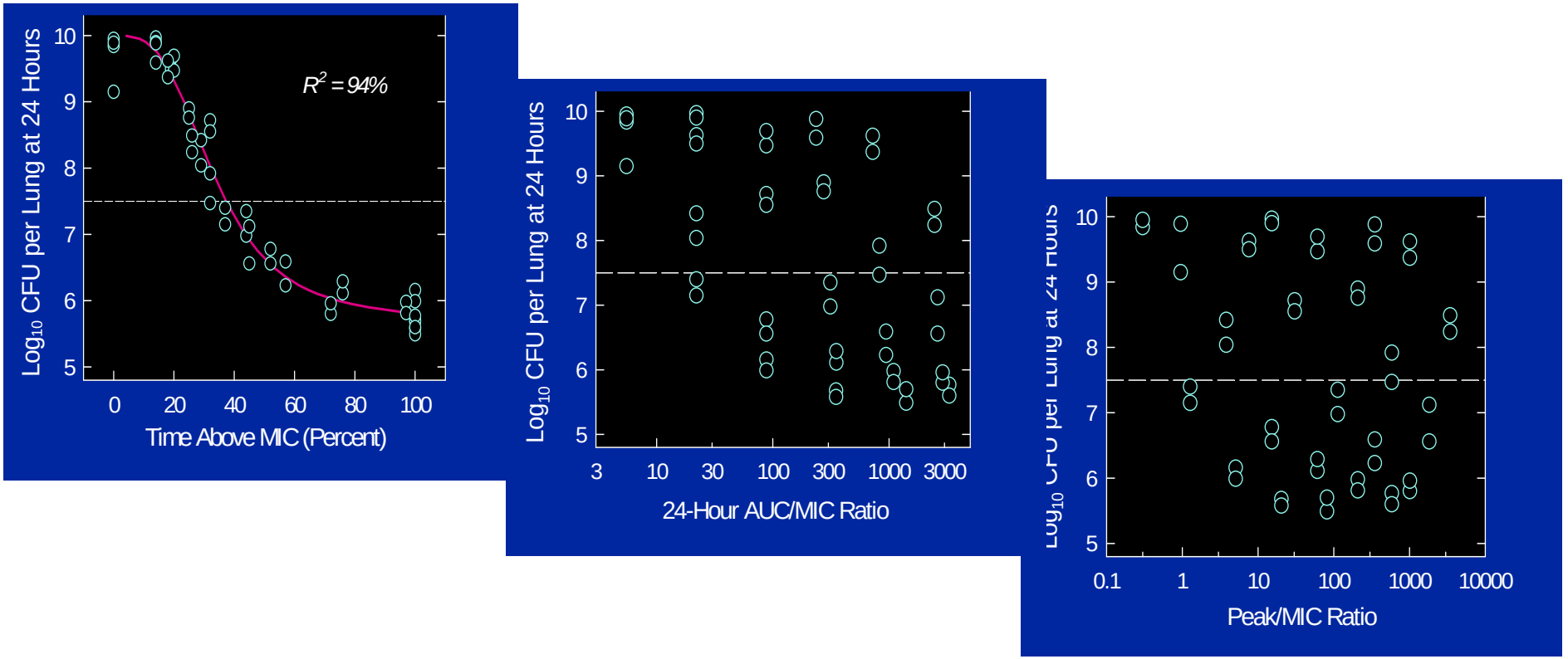
Time kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration.

Craig WA, Ebert SC. Scand J Infect Dis. 1990;74:63–70.

PK/PD in animals: β-lactams

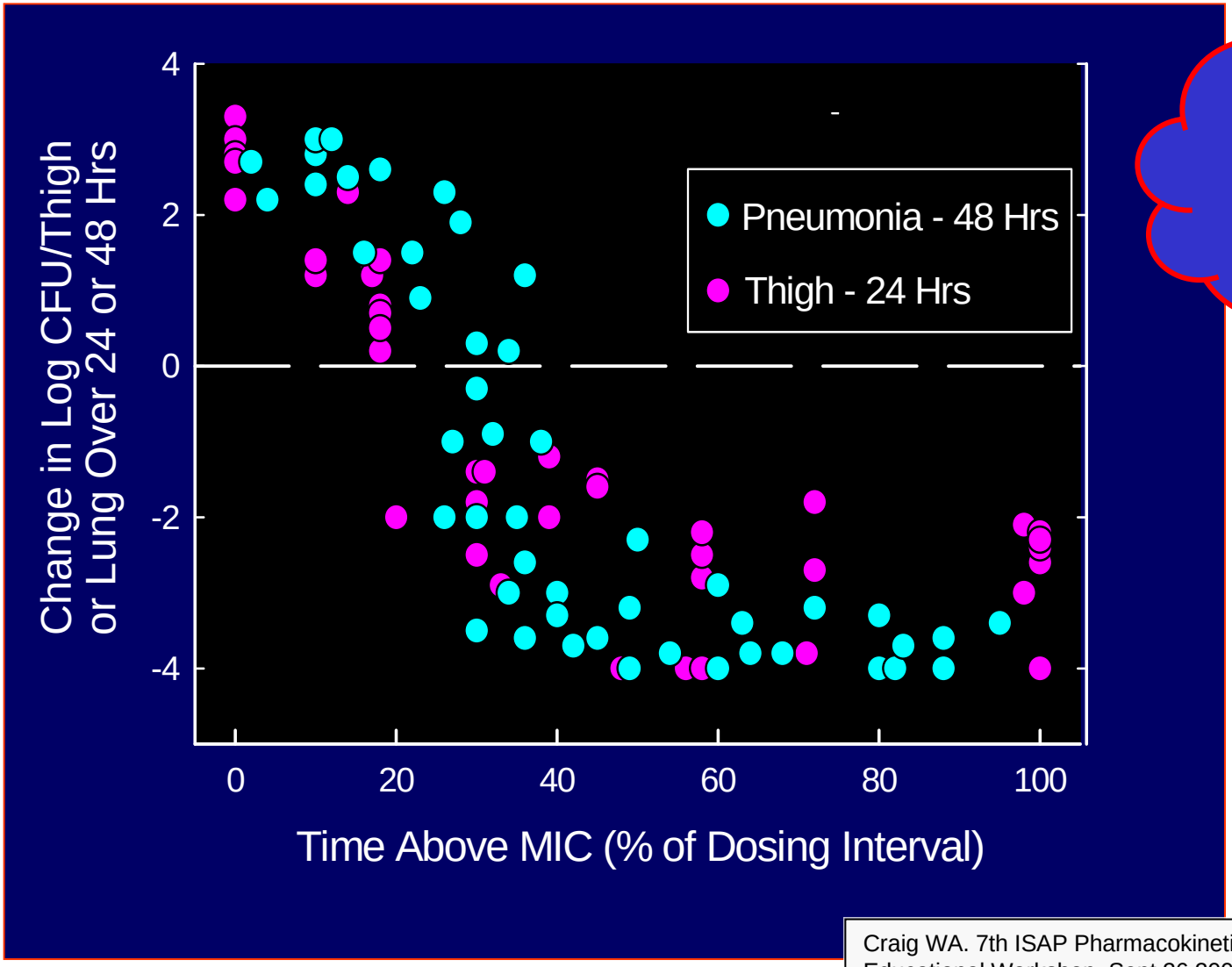


1. For β-lactams, time > MIC is the only key index for efficacy



Correlation of PK/PD Indices with Efficacy of Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (W.A. Craig – ISAP workshop – Stockholm, Sweden, 2000)

Relationship between T>MIC and efficacy of amoxicillin against *S. pneumoniae* in rat pneumonia and murine thigh infection models



Craig WA. 7th ISAP Pharmacokinetics/Pharmacodynamics (PK/PD) Educational Workshop. Sept 26 2001, San Diego, CA.

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

EUCAST

Amoxicillin EUCAST rationale document

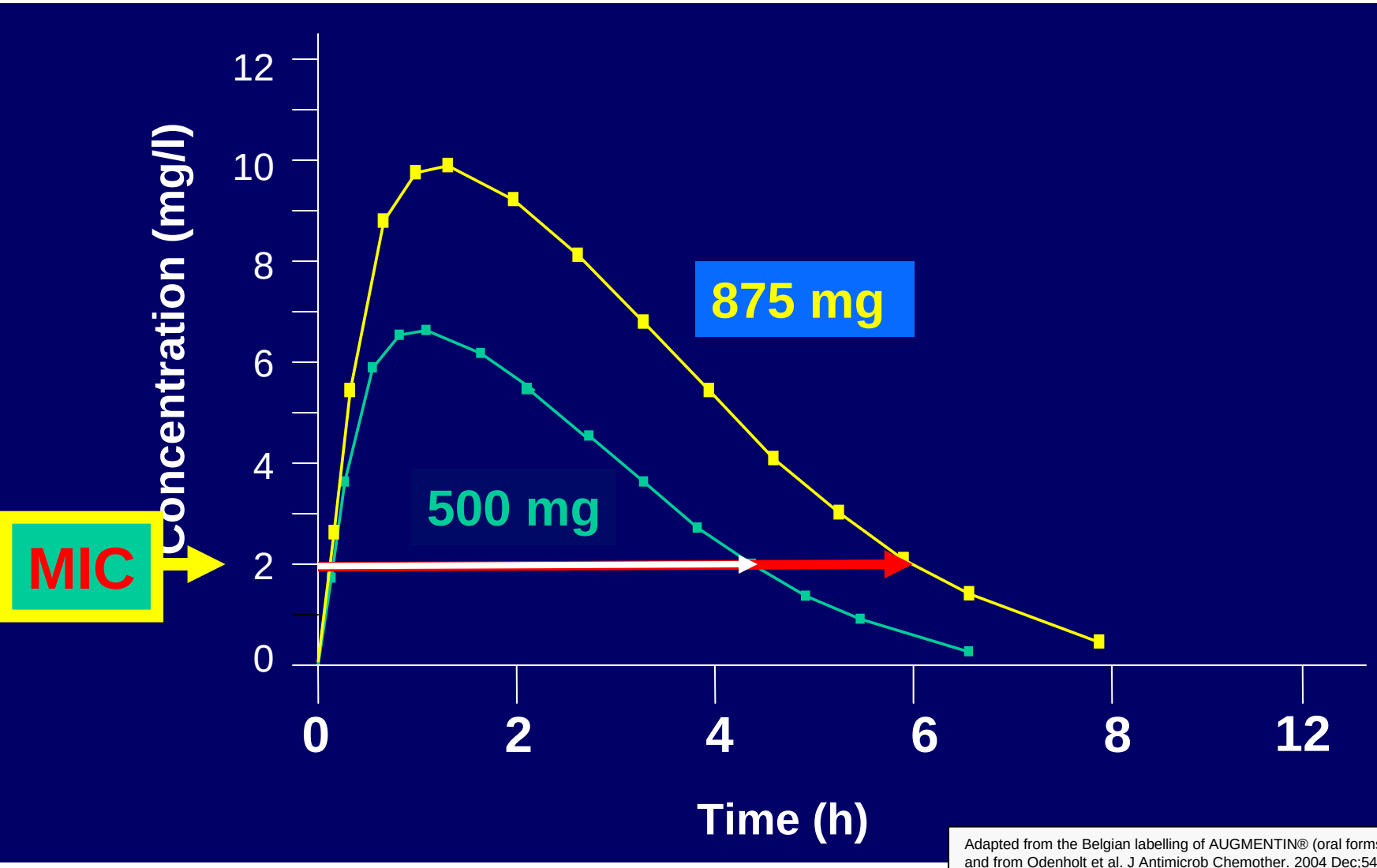
5. Pharmacodynamics

	Enterobacteriaceae	*Streptococcus pneumoniae*	*Haemophilus influenzae*
%*f*T>MIC for stasis : exp	30 – 35	25 – 35	25 – 35
%*f*T>MIC for 2 log drop : exp		35 – 45	35 - 45
%*f*T>MIC from clinical data		40	40
References	• Gerber AU et al. *J Infect Disease* 1986; 153: 90-97 • Craig WA et al. 33rd ICAAC 1993; Abstract 86 • Craig WA. In Antimicrobial Pharmacodynamics Theory and Clinical Practice 2002. Ambrose. Marcel Dekker Inc, Basel: 1-22 • MacGowan AP. *Clin Microbiol Infect* 2004: 52: 6-11		

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf

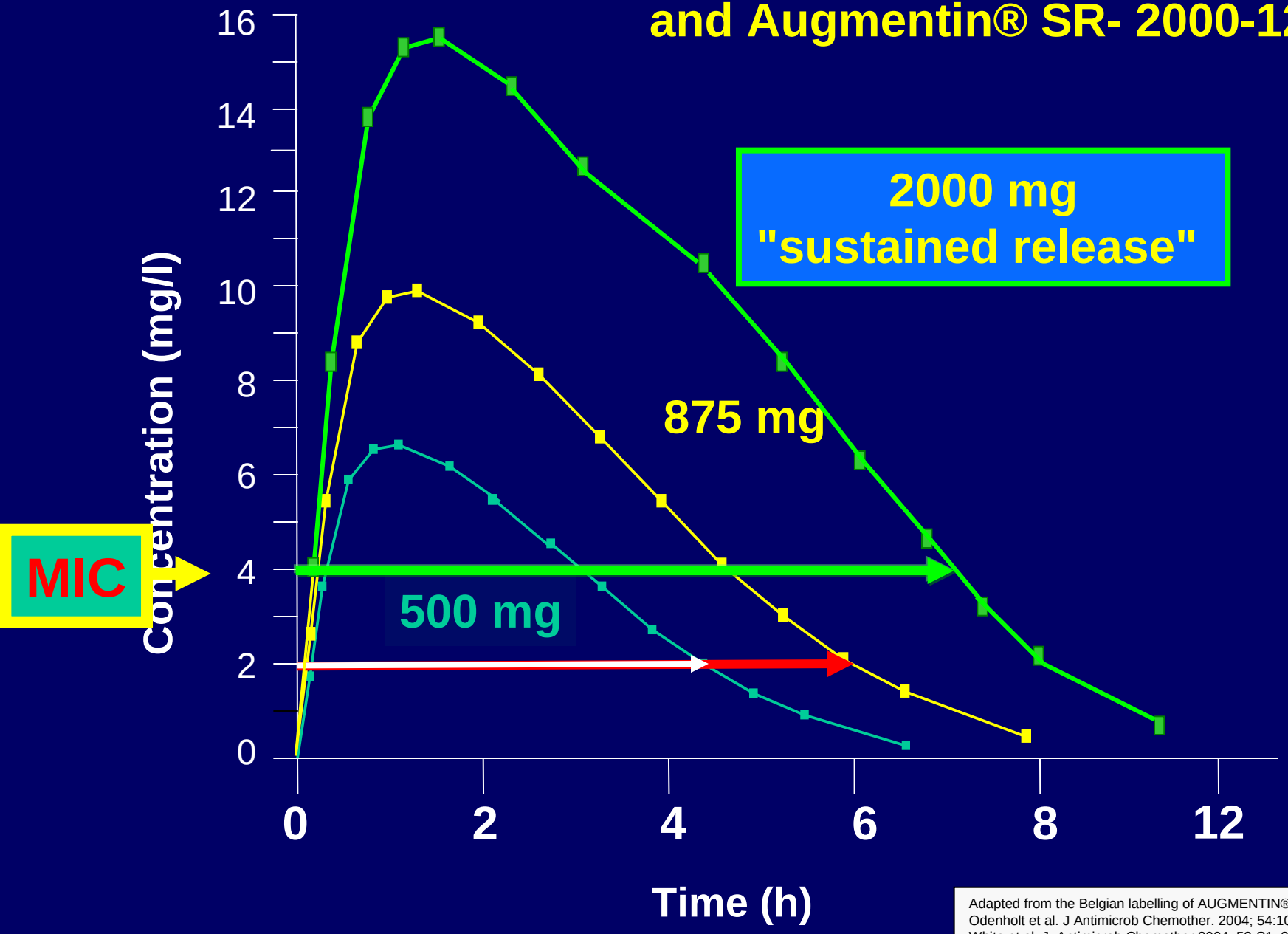
Oral penicillins: How to increase "Time > MIC" ?

Augmentin® 500/125 and 875/125...



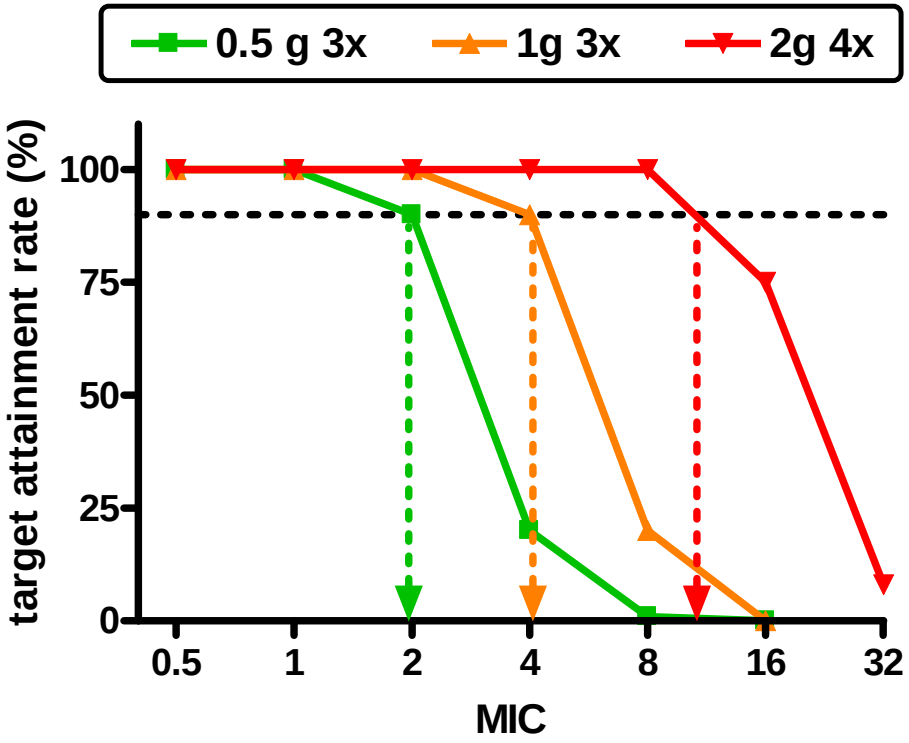
Adapted from the Belgian labelling of AUGMENTIN® (oral forms) and from Odenholt et al. J Antimicrob Chemother. 2004 Dec;54(6):1062-6.

and Augmentin® SR- 2000-125 ...



Adapted from the Belgian labelling of AUGMENTIN® (oral forms), Odenholt et al. J Antimicrob Chemother. 2004; 54:1062-6, and White et al. J Antimicrob Chemother 2004; 53-S1: 3–i20.

EUCAST calculations of target attainment rate

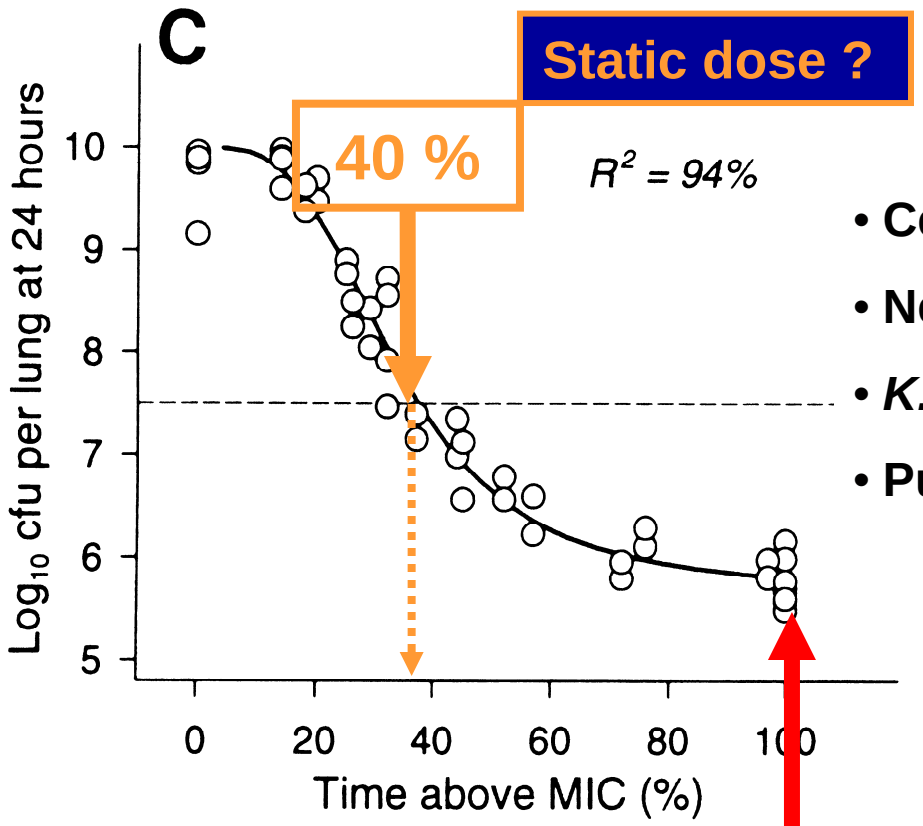


*** for *f* T >MIC = 40%**

By increasing the dose and multiplying the number of daily administration, you may cover bacteria with MIC up to 8 mg/L…

Graph prepared from data in http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf

But is 40% T >MIC sufficient?



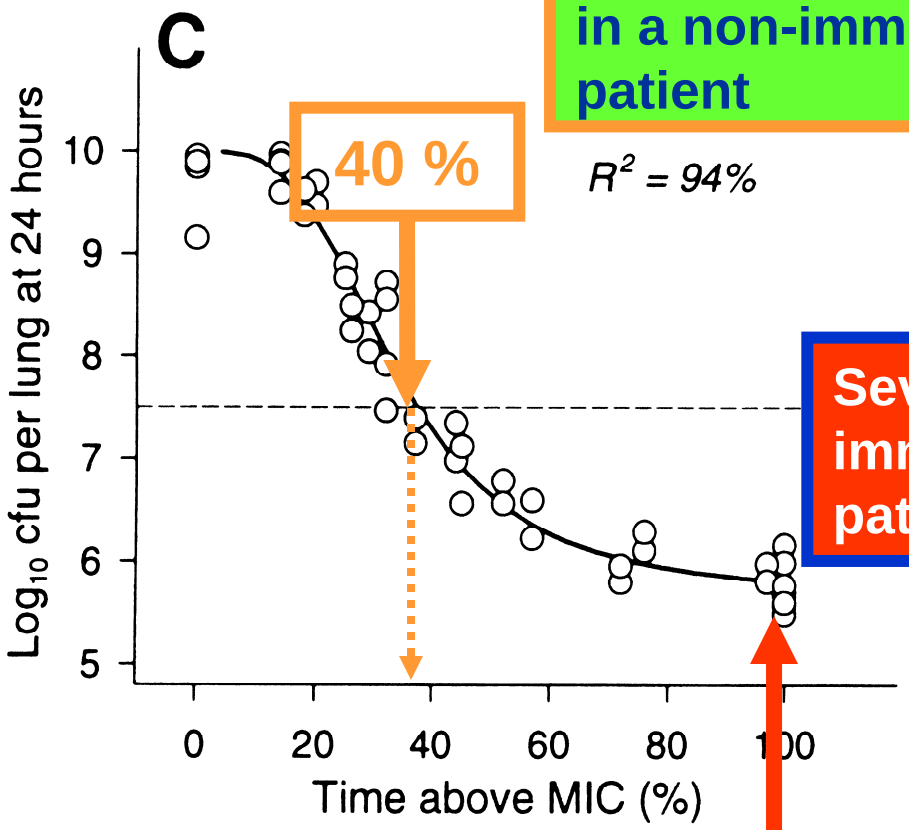
- **Cefotaxime**
- **Neutropenic mice**
- ***K. pneumoniae***
- **Pulmonary infection**

100% – Maximal effect?

- Data: W.A. Craig, 2d ISAP Educational Workshop, Stockholm, Sweden, 2000 (see also Intern. J. Antimicrob. Agents 19 (2002) 261-268)
- Interpretation: P.M. Tulkens, ICAAC - ISAP PK/PD Workshop - Clinical Implications of PK/PD Modelling, Chicago, IL, 2005

Here is a proposal ...

Moderately severe infection in a non-immunosuppressed patient



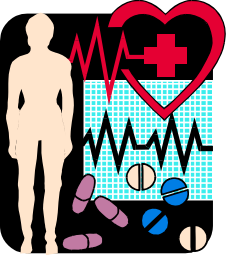
Severe infection in immunosuppressed patient

100%?

- Data: W.A. Craig, 2d ISAP Educational Workshop, Stockholm, Sweden, 2000 (see also Intern. J. Antimicrob. Agents 19 (2002) 261-268)
- Interpretation: P.M. Tulkens, ICAAC - ISAP PK/PD Workshop - Clinical Implications of PK/PD Modelling, Chicago, IL, 2005

How do you adjust the dose for a given 'Time >MIC'?

- 'Out of the package insert' PK data
- Monte-Carlo simulations and target attainment approaches



Pharmacokinetics of a typical IV β-lactam *

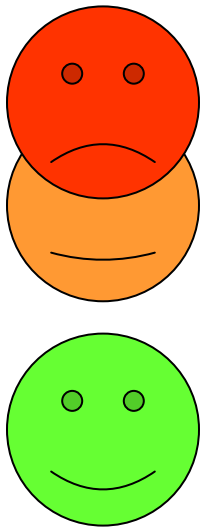
Time (hours)	Serum concentration (mg/L)		
	0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

*Modelled according to typical PK data of ceftazidime single administration - half-life, 2h; V_d = 0.2 l/kg

Pharmacokinetics of a typical IV β-lactam*

Where would you like to be ?

Time (hours)	Serum concentration (mg/L)		
	0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

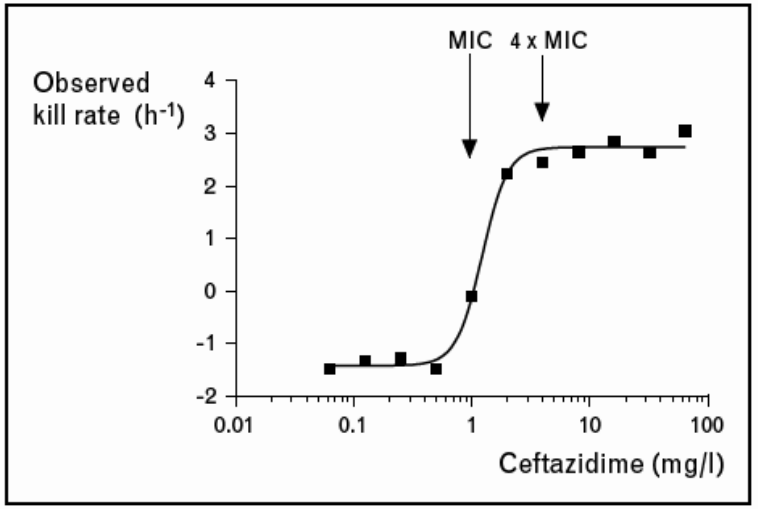


*Modelled according to typical PK data of ceftazidime single administration - half-life, 2h; V_d = 0.2 l/kg

The next frontier: continuous infusion with monitoring

- Maximum effect time-kill at 4 x MIC [1]
- Maximum effect *in vitro* 4 x MIC [2]
- Effect in endocarditis model 4 x MIC [3]
- Effect in pneumonia model dependent on severity of infection

Figure 2 Relationship between concentration of ceftazidime and kill rate

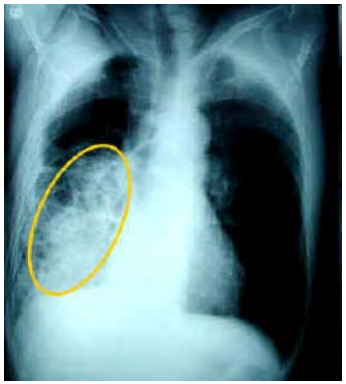


The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

1.Mouton JW, Vinks AA. Curr Opin Crit Care 2007;13:598-606.
2.Craig WA & Ebert SC, Antimicrob Agents Chemother. 1992; 36:2577-83.
3.Xiong YQ, Potel G, Caillon J, et al. 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 4-7 1994, Orlando, FL. A88.

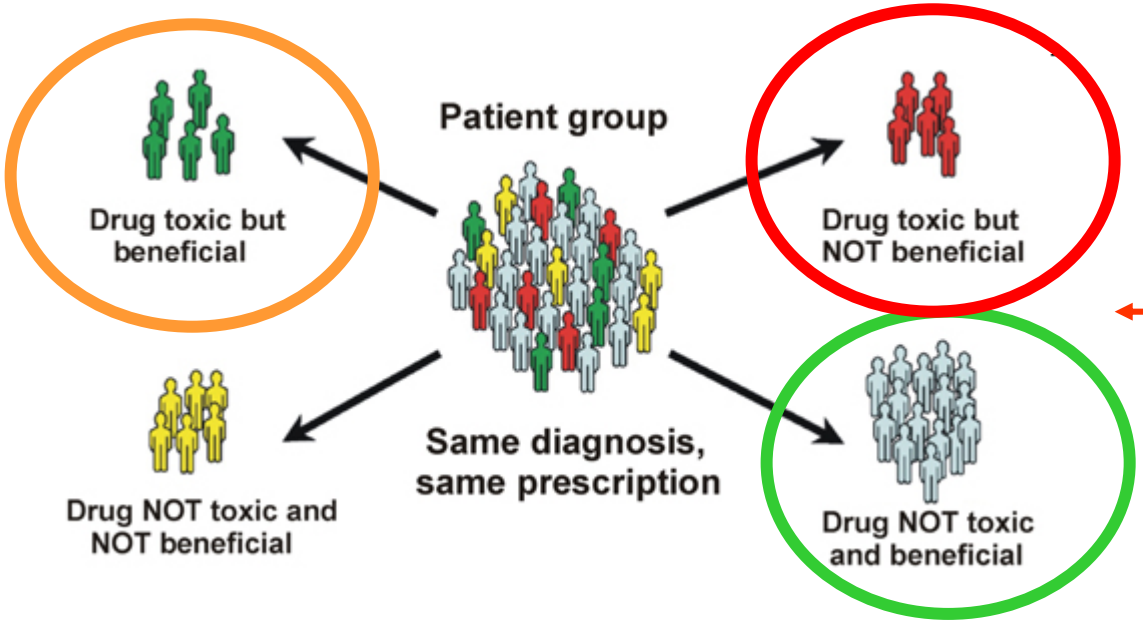
Returning to guidelines …

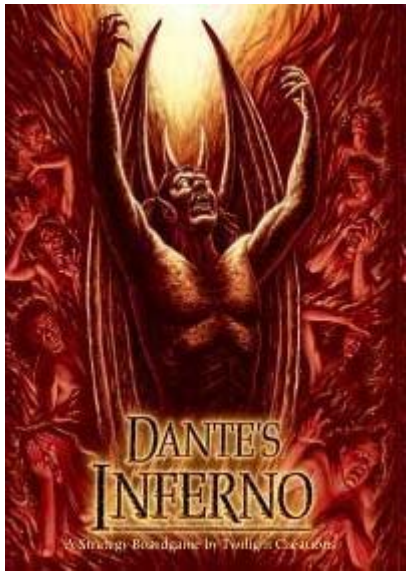
What about side effects…



therapy ?

side effects ?





All antimicrobials have associated risks*

Class	Drugs	Frequent or serious side effects
β-lactams	**amoxicillin**	• **Anaphylactic reactions** ← • *Clostridium difficile*-associated colitis • Digestive tract: diarrhoea, nausea • CNS: agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness.
	amoxicillin – clavulanic acid	• **Anaphylactic reactions** ← • *Clostridium difficile*-associated colitis • **Hepatic toxicity, including hepatitis and cholestatic jaundice** ← • Digestive tract: diarrhoea, nausea • CNS : agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness
	cefuroxime	• **Anaphylactic reactions and cutaneous eruptions** ← • Nephrotoxicity (aggrav. with loop diuretics) • Hepatic toxicity • *Clostridium difficile*-associated colitis
	ceftriaxone	• **Anaphylactic reactions and cutaneous eruptions** ← • Digestive tract:diarrhoea, nausea • *Clostridium difficile*-associated colitis • Hematologic disturbances (éosinophilia, leucopenia, granulopenia, thrombopenia) • Hepatic and biliary toxicities (precipitation of Ca^{++} salt) • CNS: cephalalgia, vertigo

* based on an analysis of the respective labelling (European SmPC or equivalent)

Carbonelle *et al.*, in preparation

All antimicrobials have associated risks*

Class	Drugs	Frequent or serious side effects
Macrolides	**clarithromycin**	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • **Drug interactions (CYP450)** • **Hepatic toxicity, including hepatitis and cholestatic jaundice** • **Palpitations, arrhythmias including prolonged QTc** • Digestive tract: diarrhoea, nausea, vomiting, abnormal taste • CNS: headache, confusion, …
	azithromycin	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • Drug interactions (CYP450), less frequent than with other macrolides • **Hepatic toxicity, including hepatitis and cholestatic jaundice** • Digestive tract: diarrhoea, nausea, abdominal pain • CNS: dizziness, fatigue, vertigo, … • Genitourinary: nephritis, vaginitis
	telithromycin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity** • Visual disturbance • Loss of consciousness • Respiratory failure in patients with myastenia gravis • **QTc prolongation** • **Drug interactions (CYP450)** • Digestive tract: diarrhoea, nausea, vomiting, dysgueusia • CNS: headache, dizziness

* based on an analysis of the respective labelling (European SmPC or equivalent)

Carbonelle *et al*., in preparation

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
fluoroquinolones	levofloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • Hematologic toxicity • **Hepatotoxicity (ALT-AST elevation [common])** • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Musculoskeletal: tendinopathies** • Peripheral neuropathy • Prolongation of the QTc interval (cardiac disorders [rare]) • **Hypoglycaemia (rare)** • **Digestive tract: nausea, diarrhoea**
	moxifloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity (ALT-AST elevation [common])** • **Musculoskeletal: Tendinopathies** • Peripheral neuropathy • Prolongation of the QT interval (cardiac disorders [rare]) • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Digestive tract: nausea, diarrhoea**

* based on an analysis of the current respective labelling (European SmPC)
- common: 1/10 to 1/100
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:

- *For [community-acquired pneumonia], TAVANICc should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*
- *Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*

Carbonelle *et al.* , in preparation

All antimicrobials have associated risks

Conclusions so far:

- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the **specific environment** and for the **specific patient**

Never say that …

and check for specific risks

RTI: respiratory tract infection

The 3 major "points for attention" in guidelines

Are they not too dogmatic ?

Are they geared to the REAL patient

Are they regularly updated and modernised ?

Conclusions (and food for thought)

- Guidelines are **interesting** and most probably **useful**
- Their writing is a **difficult exercise** and their implementation is a long journey (unsurprisingly)… that **never ends** (no surprise either) …
- They MUST remain open to accommodate for local and special situations, with primary emphasis on **epidemiology** and **optimized use of drugs** and geared at **real patients**…
- At the end of the day, it will be the doctor's choice, but that choice MUST be rational and based on **best evidence applied to the patient**
- Societal responsibility (in this case, the **emergence of resistance**) should not be ignored*
- Economic responsibility is also important, although the acquisition costs of ~~antibiotic~~s are MUCH lower than those of many other drugs*

***Not addressed in this lecture but do ask questions…**