Community-acquired LRTIs in Middle East: an update from microbiology to pharmacology and toxicology

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Disclosures

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- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for past personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - European Medicines Agency (as expert for the agency and for Industry)

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

Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillin

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

What shall we do ?

- Burden of the diseases (CAP / COPD)
- Epidemiological data concerning selected important pathogens
  - *Streptococcus pneumonia*
  - *Mycoplasma pneumonia*
  - *Haemophilus influenza*
- PK/PD: Efficacy and Resistance issues
- How to reach a successful (effective and safe) clinical outcome

Which burden ?

- CAP:
  - a major acute cause of death (3^{d} to 7^{th});
  - Clear association between aging and pneumonia (“a friend of the elderly.”) [1]
  - Hospitalization rates for pneumonia have also increased significantly over the last 15 years [2]
  - High levels in long-term-care facilities [3]
    → “health care associated” pneumonia ?
  - Costly treatments of elderly patients because of the increased length of hospital [4]
  - Long term survival is often poor (half of elderly patients with community-acquired pneumonia died in the next year [5]

[1] Osler W The Principles and Practice of Medicine. 3rd ed 1898 Appleton New York 109
[2] Fry *et al.* JAMA. 294:2712-2719 2005
[3] Marrie TJ. Infect Control Hosp Epidemiol. 23:159-164 2002
[4] Marston *et al.* Arch Intern Med. 157:1709-1718 1997
[5] Kaplan *et al.* Arch Intern Med. 163:317-323 2003

A quick survey of the main bacterial causative organisms of CAP

Patient characteristics	
Outpatient, no sigificant comorbidity	***Streptococcus pneumoniae*** ***Mycoplasma pneumoniae***, *Chlamydophila pneumoniae,* ***Haemophilus influenzae***, *Legionella* spp., *Mycobacterium tuberculosis*, endemic fungi)
Outpatient, comorbities or HCAP with no resistance risk factors	**Drug resistant *Streptococcus pneumoniae* (DRSP)** Enteric Gram-negative; anaerobes (with aspiration)
Inpatient, with comobidities or HCAP with no resistance risk factors	***Streptococcus pneumoniae* (including DRSP)**, ***Haemophilus influenzae***, ***Mycoplasma pneumoniae***, *C. pneumoniae*, *Legionella* spp. Enteric Gram-negatives, anaerobes, others…
Severe CAP, with no risks for *Pseudomonas aeruginosa*	***Streptococcus pneumoniae* (including DRSP)**, ***Haemophilus influenzae***, ***Mycoplasma pneumoniae,*** Legionella spp., ***Staphylococcus aureus*** Gram-negative bacilli, others
Severe CAP, with risks for *P. aeruginosa*, or HCAP with resistance risk factors	All of the above pathogens, plus ***P. aeruginosa***

Infectious Diseases (Cohen, Opal & Powderly, eds), 3d edition, Elsevier 2010,
• Niederman M.: Community-acquired pneumonia (chapter 27))
available on line at http://www.expertconsultbook.com) (accessed 12/10/2014)

Pneumococcal CAP is associated with increased severity and worsened outcome

The Burden of Pneumococcal Pneumonia – Experience of the German Competence Network CAPNETZ

M. W. Pletz[1,*], H. von Baum[3,*], M. van der Linden[4,*], G. Rohde[5,*], H. Schütte[6,*], N. Suttorp[6,*], T. Welte[2,*]

Pneumologie 2012; 66: 470–475

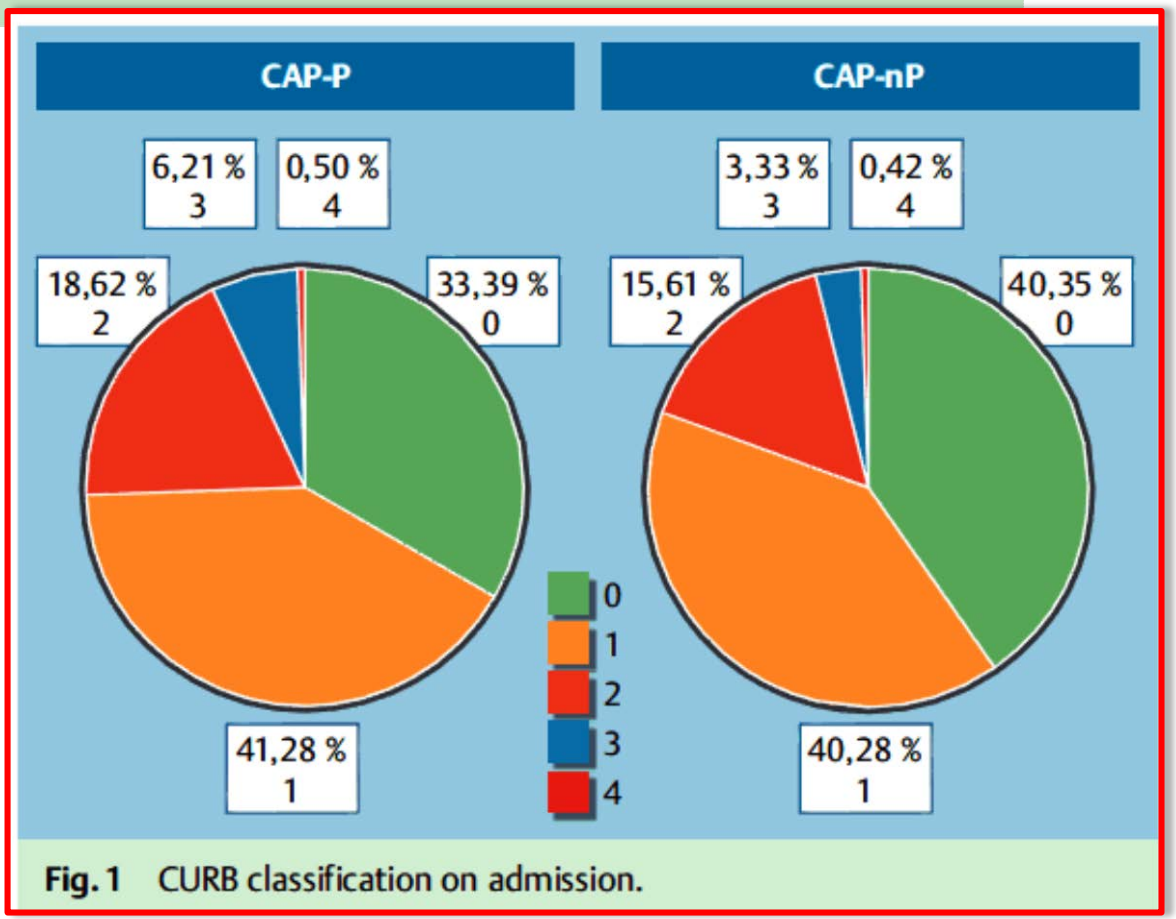

Fig. 1 CURB classification on admission.

CURB score: add 1 for each item

- **Confusion present**
- **BUN > 19 mg/dL**
- ***R*espiratory Rate ≥ 30**
- **Systolic *B*P < 90 mmHg or Diastolic BP ≤ 60 mmHg**
- **Age ≥ 65 y**

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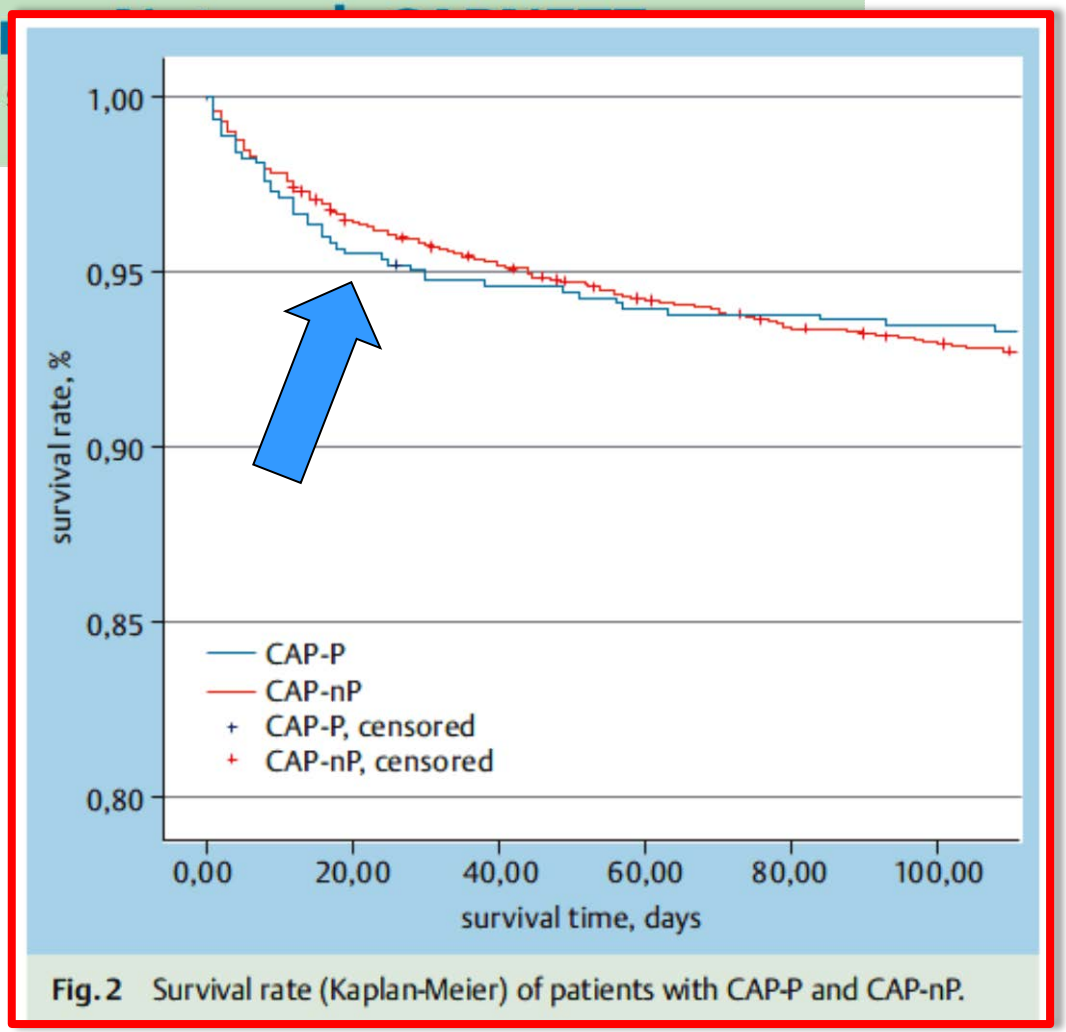


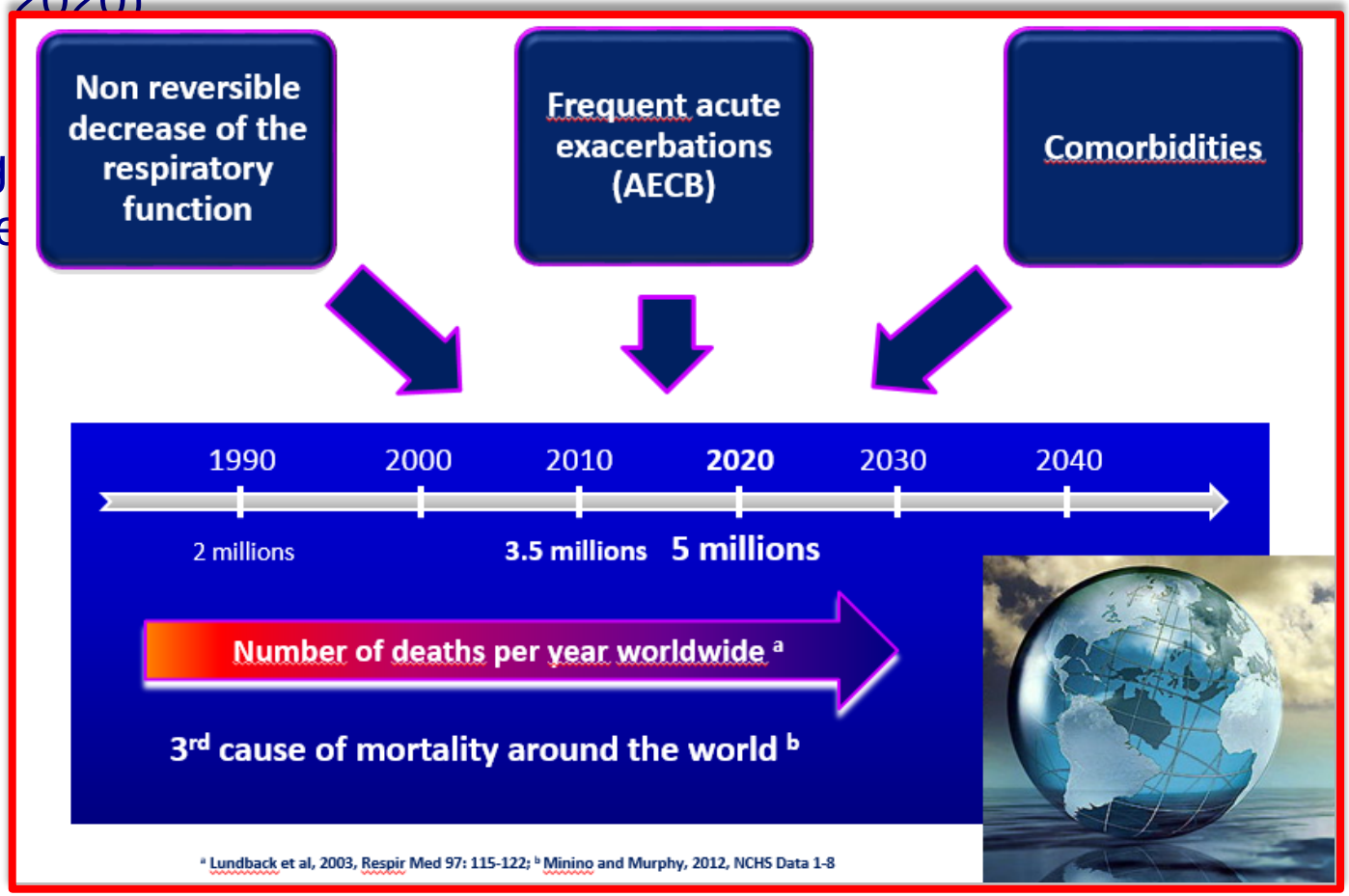
Fig. 2 Survival rate (Kaplan-Meier) of patients with CAP-P and CAP-nP.

Which burden ?

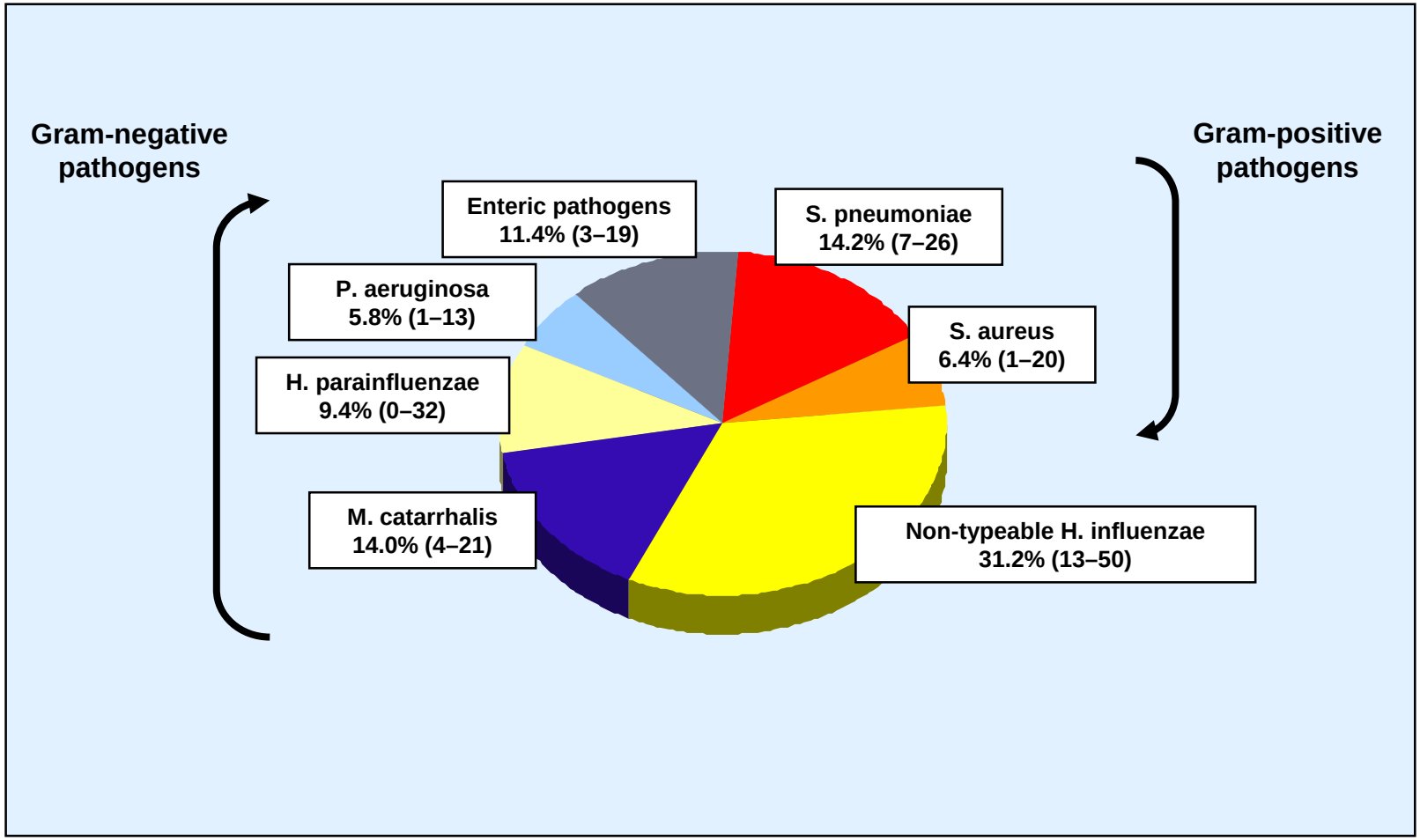
- COPD
  - also a major cause of death (4th in 2006 and projected 3d in 2020)
  - runs as often undiagnosed at early stages
  - "progresses" to decreases of respiratory function by successive infectious exacerbations

Which burden ?

- COPD
  - also a major cause of death (4th in 2006 and projected 3d in 2020)
  - runs
  - "prog
    succe



Most AECB are of bacterial origin !



Data are mean (range) percentage of total bacterial isolates
Number of patients: 687 (140–2180)
Sputum culture positive for potentially pathogenic bacteria: 53.7 (28.1–88.6)

Sethi. Clin Infect Dis 2005; 40: S489–97

What shall we do ?

- Burden of the diseases (CAP / COPD)
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  - *Streptococcus pneumonia*
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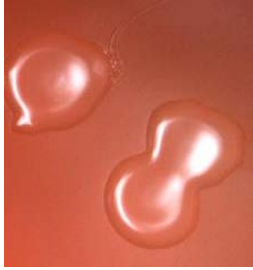
Streptococcus pneumoniae



Colonies of
S. pneumoniae
CDC Public Health
Image Library
http://phil.cdc.gov/phil

REVIEW ARTICLE

Drugs 2007; 67 (16): 2355-2382
0012-6667/07/0016-2355/$49.95/0

Multidrug-Resistant *Streptococcus pneumoniae* Infections

Current and Future Therapeutic Options

Françoise Van Bambeke,[1] *René R. Reinert,*[2] *Peter C. Appelbaum,*[3] *Paul M. Tulkens*[1] and *Willy E. Peetermans*[4]

1 Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, Brussels, Belgium
2 Institute for Medical Microbiology, National Reference Center for Streptococci, University Hospital (RWTH), Aachen, Germany
3 Department of Pathology, Hershey Medical Center, Hershey, Pennsylvania, USA
4 Department of Internal Medicine-Infectious Diseases, Katholieke Universiteit Leuven, University Hospital Gasthuisberg, Leuven, Belgium

Van Bambeke F, *et al. Drugs.* 2007;67:2355-82.

Streptococcus pneumoniae: main mechanisms of resistance

Antibiotic class	Mechanism	Genetic support	Drugs affected	Consequence
β-lactams	↘ Affinity of PNP1a, PBP2x and PBP2b	mosaic genes	all (variable extent)	↘ susceptibility
Macrolides	Methylation of 23S rRNA	*erm(B)*	all except ketolides unless multiple mutations	full resistance
	active efflux	*mef(A)*	14- and 15-membered ring	moderate (?) resistance
Fluoroquinolones	↘ affinity to DNA-gyrase/topisomer-ase complex	point mutations	all (variable extent)	full resistance if several mutations
	active efflux	(*pmrA*) *patA-patB*	gatifloxacin, gemifloxacin [1]	↘ susceptibility
Tetracyclines	ribosomal protection	*tet(A)*, *tet(O)*	all except glycylcyclines	Full resistance
Sulfonamides	↘ of inhibition of dyhydropteroate synthase	repetition of codons for aminoacids	all	Full resistance

[1] also norfloxacin and ciprofloxacin (not recommended)

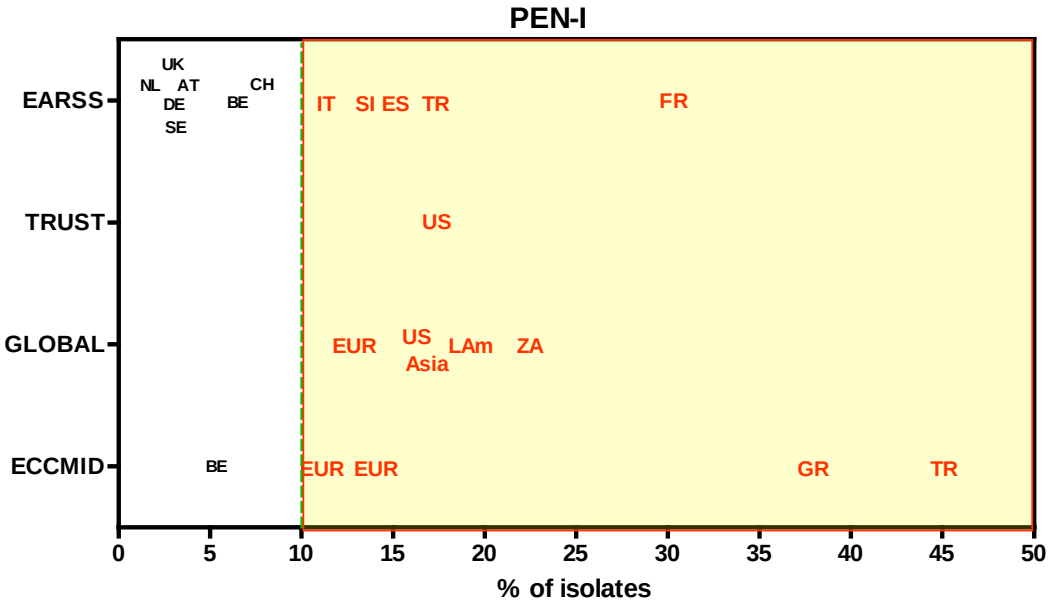
Adapted from Van Bambeke, *et al*. Drugs. 2007;67:2355-82
See also Lismond, *et a*l. JAC. 2011;66:948-51, Lismond, et al. Intern J Antimicrob Ag. 2012;39:208– 16

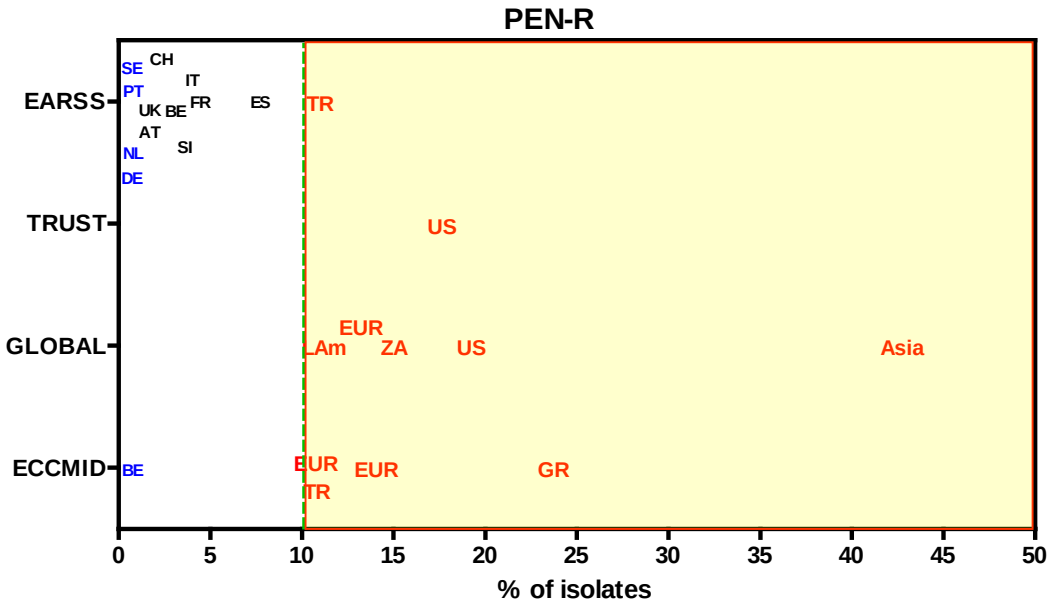
Resistance of *S. pneumoniae* to penicillins *

*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

Most studies used CLSI (non-meningitis) breakpoints





CAP: community acquired pneumonia
CLSI: Clinical and Laboratory Standards Institute (http://clsi.org)

Lismond *et al.*, in preparation

But what about the Middle East ?

ELSEVIER

International Journal of Antimicrobial Agents 23 (2004) 32–38

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Streptococcus pneumoniae in Saudi Arabia: antibiotic resistance and serotypes of recent clinical isolates

Ziad A. Memish [a,b,*], Hanan H. Balkhy [b,c,1], Atef M. Shibl [d,2], Christopher P. Barrozo [e], Gregory C. Gray [f,3]

[a] *Department of Internal Medicine,* [b] *Department of Infection Prevention and Control, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Saudi Arabia*
[c] *Department of Pediatrics, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Saudi Arabia*
[d] *Department of Microbiology, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia*
[e] *DoD Center for Deployment Health Research, Naval Health Research Center, San Diego, CA, USA*
[f] *Department of Epidemiology, College of Public Health, University of Iowa, 200 Hawkins Dr, C21K GH, Iowa City, IA, USA*

Received 7 February 2003; accepted 8 May 2003

Memish et al. Int J Antimicrob Agents. 2004;23:32-8.

154 clinical *Streptococcus pneumoniae* isolates collected from or through three major hospitals serving the Western, Central, and Eastern regions of the Kingdom of Saudi Arabia.

High variability in resistance rates in the early 2000's…

ELSEVIER

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[c] *Department of Pediatrics, King Fahad National Guard Hospital, P.O. Box*
[d] *Department of Microbiology, King Saud University, P.O. Box 2457,*
[e] *DoD Center for Deployment Health Research, Naval Health Researc*
[f] *Department of Epidemiology, College of Public Health, University of Iowa, 200 H*

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154 clinical *Streptococcus pneumoniae* isolates collected from or through three major hospitals serving the Western, Central, and Eastern regions of the Kingdom of Saudi Arabia.

Table 1
Susceptibility of *Streptococcus pneumoniae* isolates by age

Demographics	Number of isolates	Resistance to penicillin	%
Age (year)			
<10	6	5	83.3
10–19	40	30	75.0
20–29	38	18	47.4
30–39	22	11	50.0
40–49	24	13	54.2
50–59	9	5	55.6
60+	15	9	60.0

A recent review of resistance trends of resistance of *S. pneumoniae* in Saudi Arabia

Review

Antimicrobial resistance among Gram-positive pathogens in Saudi Arabia

Saber Yezli[1], Atef M. Shibl[2], David M. Livermore[3], Ziad A. Memish[4]

[1]Bioquell UK Ltd, Andover, UK, [2]King Saud University, Riyadh, Saudi Arabia, [3]University of East Anglia, Norwich, UK, [4]Saudi Ministry of Health, Riyadh, Saudi Arabia

Yezli et al. J Chemother. 2012 Jun;24(3):125-36

A recent review of resistance trends of *S. pneumoniae* to penicillin Saudi Arabia

Review

Antimicrobial resistance among Gram-positive path

Saber Y

[1]Bioquell UK, [4]Saud

Yezli et a

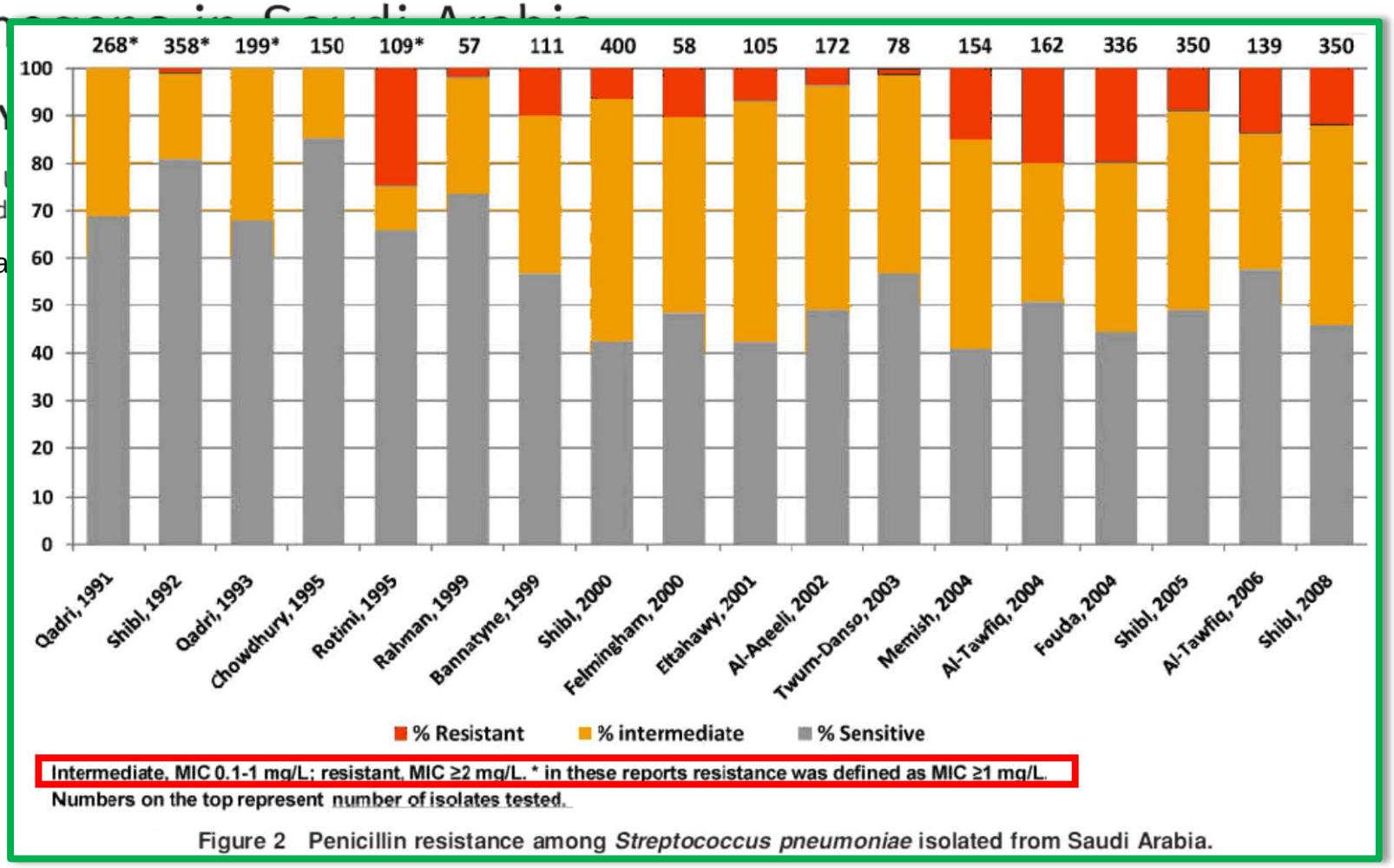


Figure 2 Penicillin resistance among *Streptococcus pneumoniae* isolated from Saudi Arabia.

A recent overview of the current situation in Saudi Arabia

Antimicrobial Original Research Paper

National surveillance of antimicrobial resistance among Gram-positive bacteria in Saudi Arabia

Atef M. Shibl[1,2], Ziad A. Memish[2,3], Abdelmageed M. Kambal[4], Yazid A. Ohaly[5], Abdulrahman Ishaq[6], Abiola C. Senok[2], David M. Livermore[7]

[1]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [2]Department of Pathology and Pharmacology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, [3]Ministry of Health, Riyadh, Saudi Arabia, [4]Microbiology Department, King Khalid University Hospital, Riyadh, Saudi Arabia, [5]Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, [6]Ministry of Health, Riyadh, Saudi Arabia, [7]Norwich Medical School, University of East Anglia, Norwich, UK

J Chemother 2014;26:13-18

- 24 Saudi Ministry of Health hospitals distributed in 6 different Administrative Regions (Riyadh, Jeddah, Makkah, Eastern Region (AsSharqiyah), Hail, and Asir, with 3 to 5 hospitals per region;
- cross-sectional design and conducted between January and December 2009;
- A total of 13750 Gram-positive isolates
  - *S. aureus* (n=8568; 62.3%)
  - non-group A beta-haemolytic *streptococci* (n=2040; 14.8%),
  - group A beta-haemolytic *streptococci* (n=975; 7.1%),
  - coagulase-negative *staphylococci* (n=913, 6.6%),
  - *S. pneumoniae* (n=828, 6.0%)
  - *enterococci* (n=426, 3.1%).

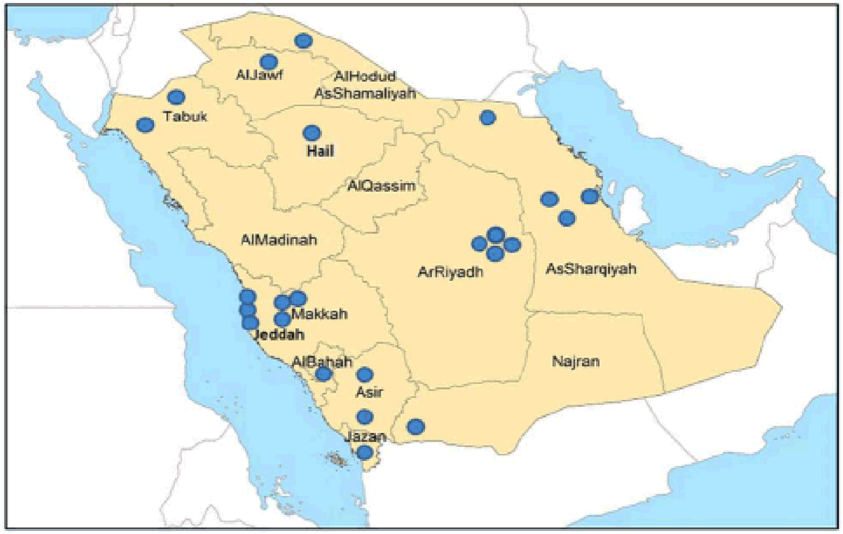


Figure 1 Map of Saudi Arabia with the 24 hospitals sharing in the study.

A recent overview of the current situation in Saudi Arabia

Antimicrobial Original Research Paper

Nati... resi... Sau...

Atef M. ... Abdul...

[1]College ... Pharmac... Arabia, [4]... Medicine, ... Riyadh, S...

J Chem...

Table 2 Antimicrobial resistance rates among different Gram-positive species during the study

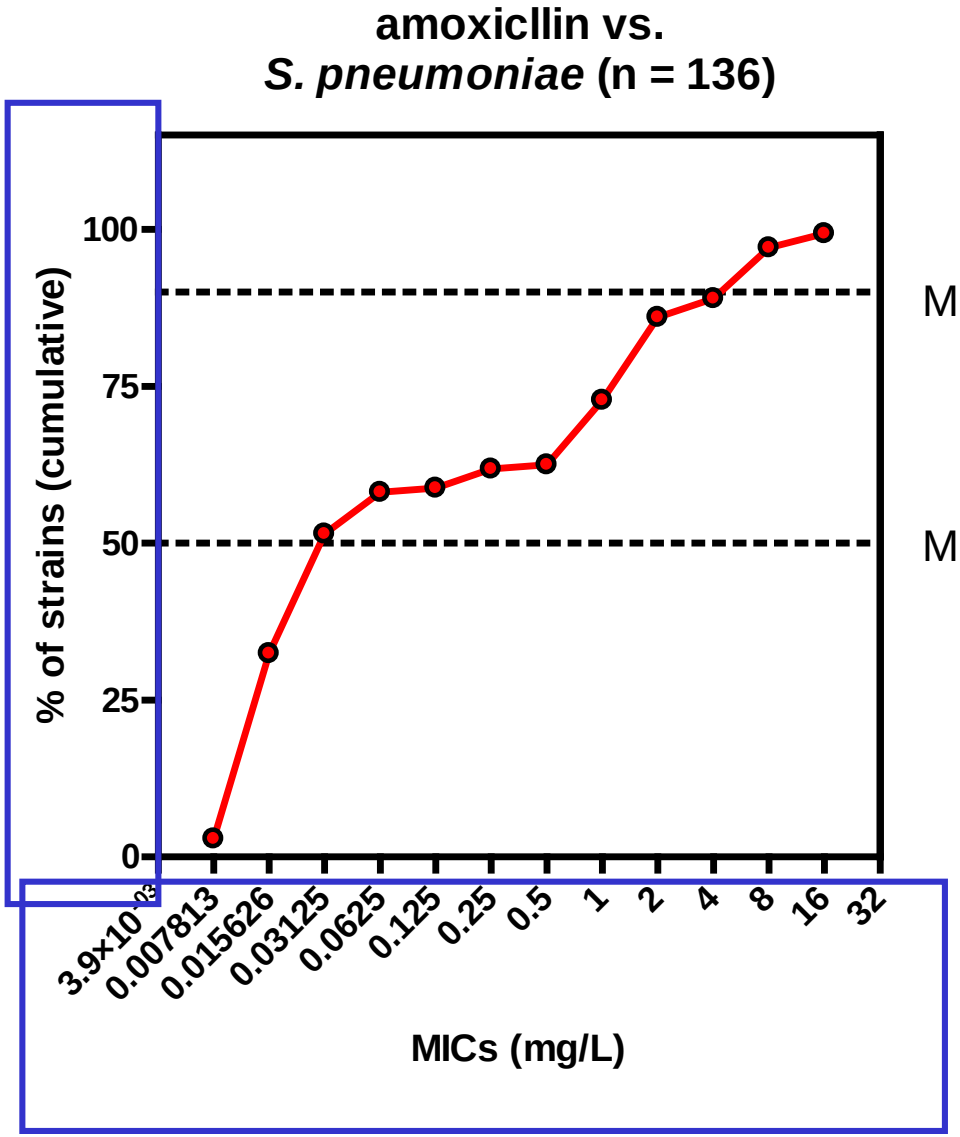
	S. aureus		Coagulase-negative staphylococci		Enterococci		*S.pneumoniae*		Beta-*haemolytic streptococci* (group A)		Beta-*haemolytic streptococci* (others)	
	T (N)	*R* (%)	*T (N)*	*R* (%)	*T (N)*	*R* (%)	T (N)	*R* (%)	*T (N)*	*R* (%)	*T (N)*	*R* (%)
Penicillins*												
Penicillin G	4741	93%	781	88%	119	55%	386	33%	866	0%	1588	0%
Oxacillin	8568	32%	913	63%								
Ampicillin					139	12%	242	4%	103	0%	881	0%
Amox/Clav					98	4%	210	4%			205	0%
Other beta-lactams												
Ceftriaxone							177	11%				
Imipenem					250	6%	76	3%				
Aminoglycosides												
Amikacin	2197	32%	211	23%								
Gentamicin	5744	32%	887	48%								
Others												
Vancomycin	4428	0%	905	0%	149	1%	474	1%	414	0%	1347	0%
Erythromycin	6737	48%	910	65%	369	89%	729	26%	864	8%	1617	5%
Clindamycin	4581	31%	693	35%			393	17%	855	8%	1567	6%
Chloramphenicol	4368	14%	878	16%	292	58%	456	6%	331	4%	627	3%
Tetracycline	4173	49%	209	25%	312	88%	417	51%	378	79%	403	88%
Ciprofloxacin	2168	32%	530	26%	32	63%						
Rifampicin	2957	6%	779	10%			87	5%			38	53%
TMP-SMX	3318	27%	893	48%			406	38%			133	91%

Note: Data were included only for relevant antibiotics tested in more than 20% of all isolates and at least 20 isolates of individual Gram-positive species were tested.
N, the number of tested isolates; *R*, resistance rate; Amox/Clav: amoxicillin/clavulanicacid; TMP-SMX, trimethoprim/sulfamethoxazole.

But which breakpoints do we need to use ?

To be honest, I always wondered ...

MIC distribution is a continuous variable…



- **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
CAP community-acquired pneumonia
COPD chronic obstructive pulmonary disease

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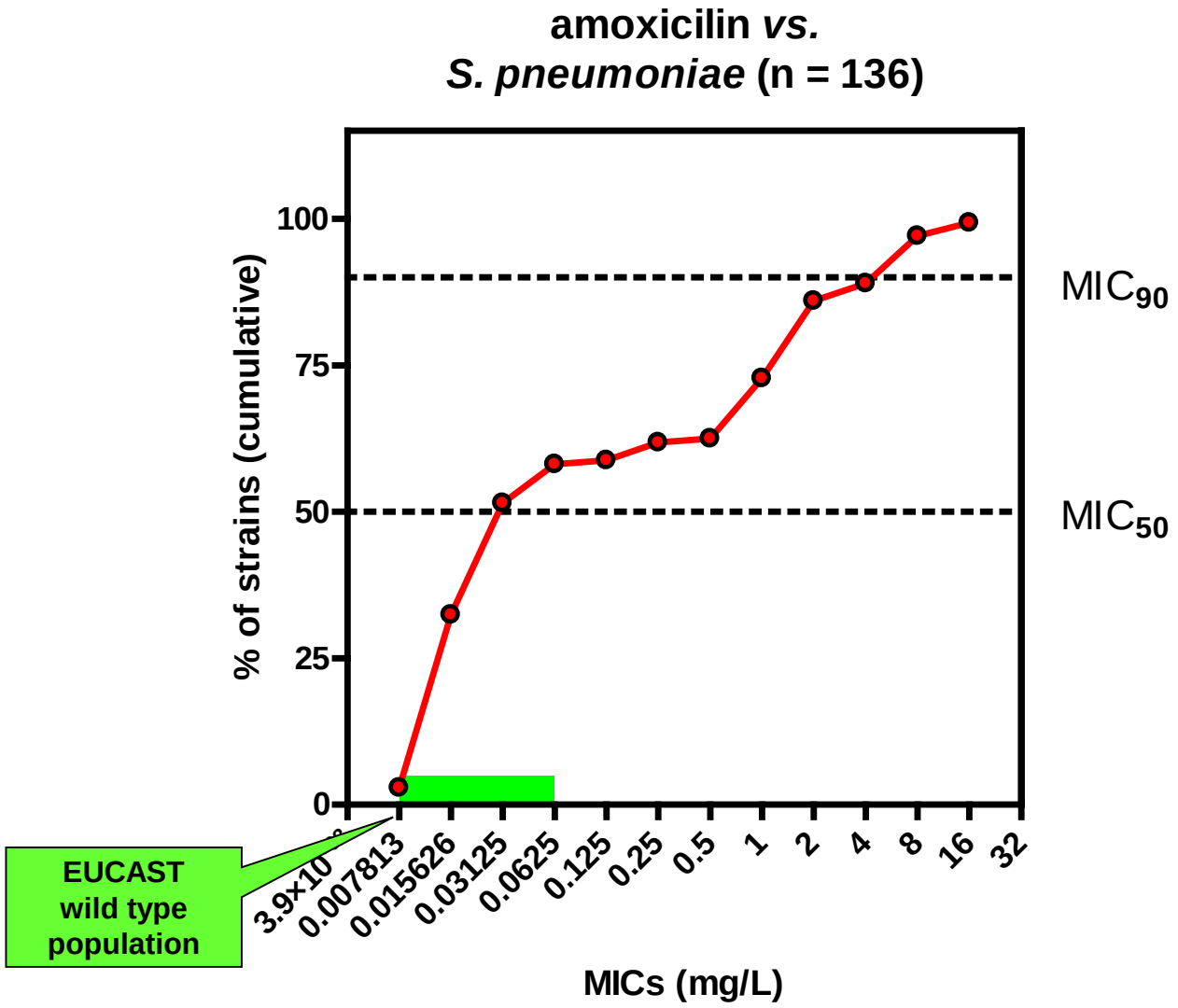

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EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease

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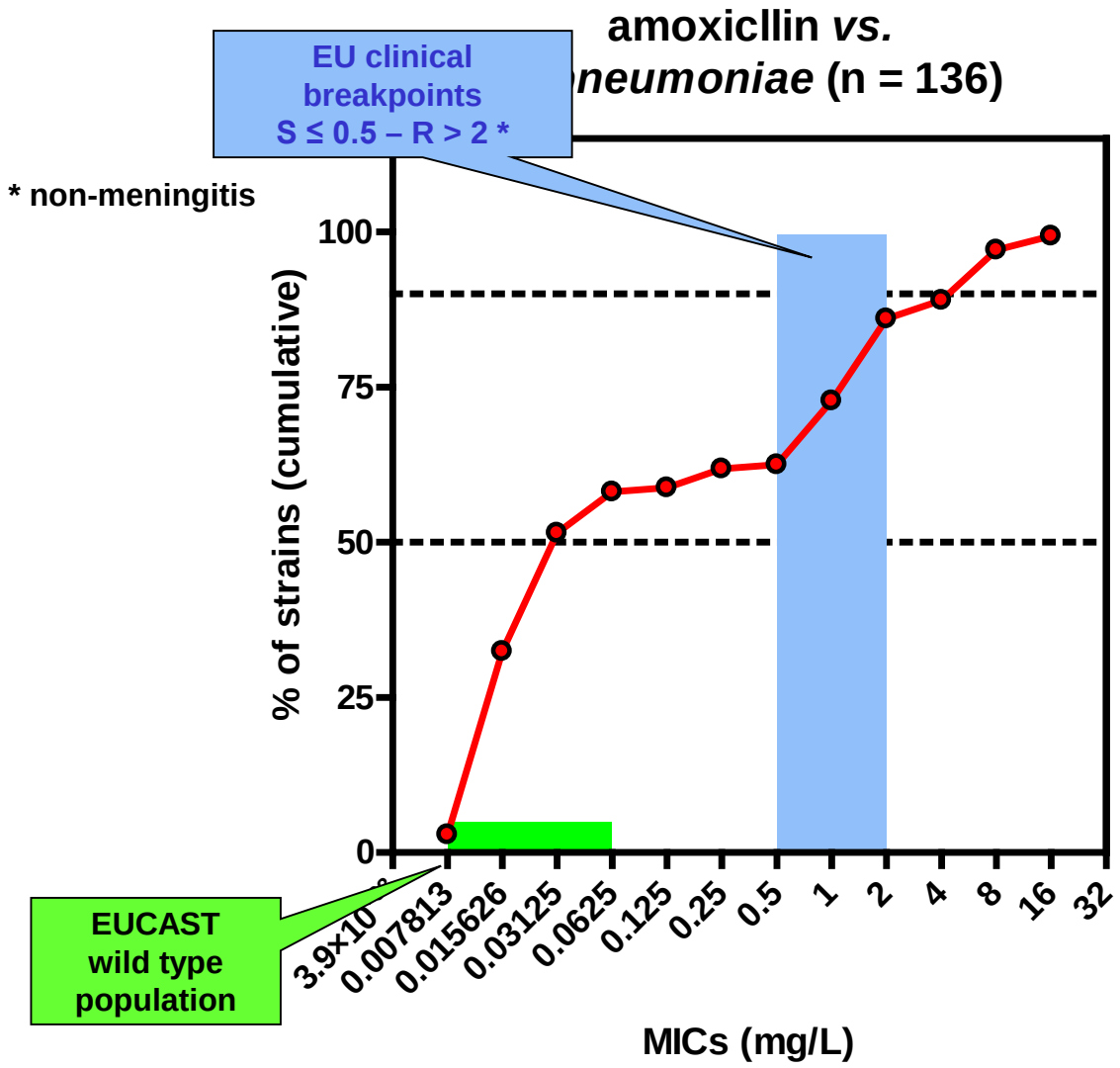

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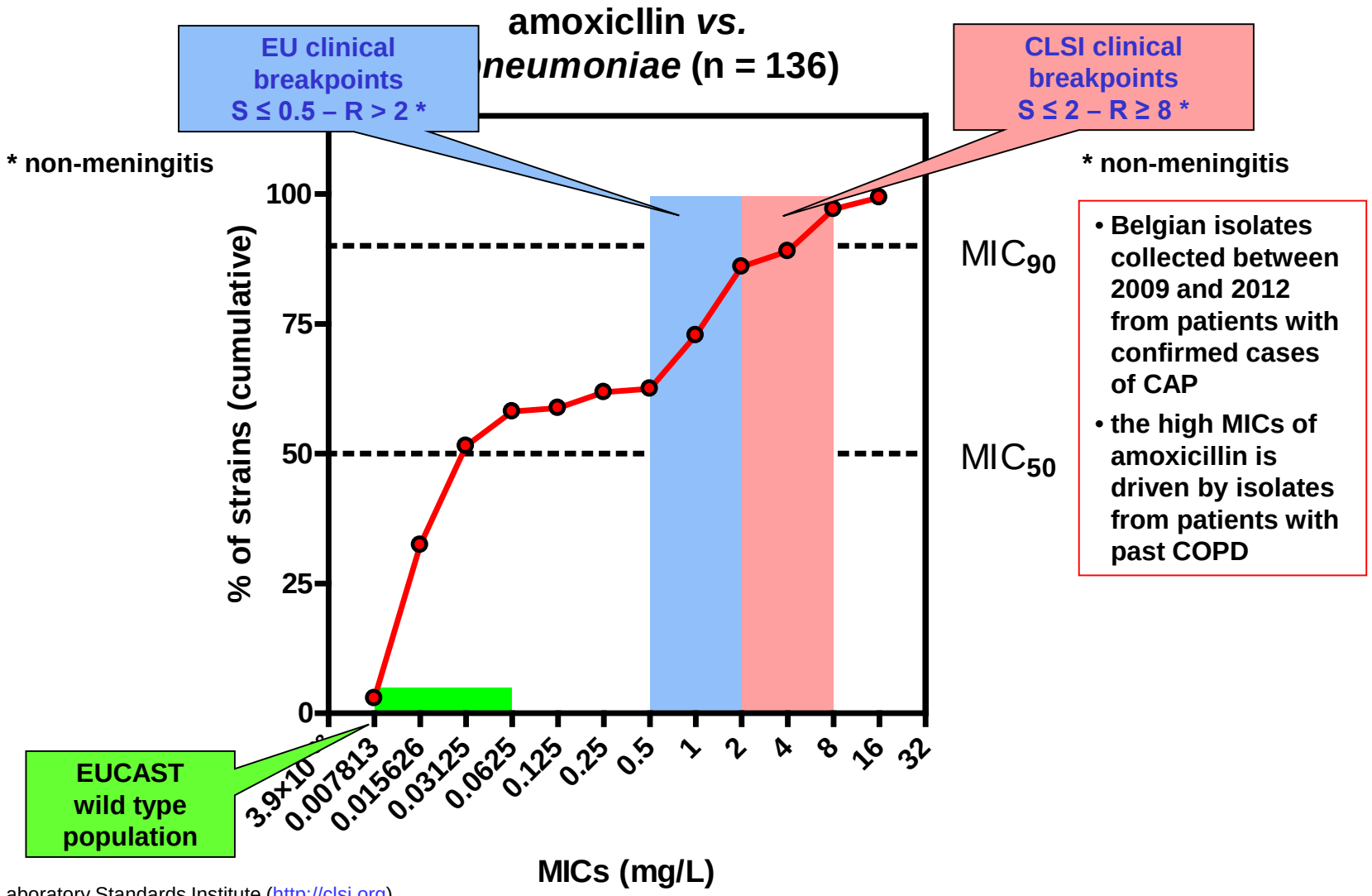

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EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
CAP: community-acquired pneumonia
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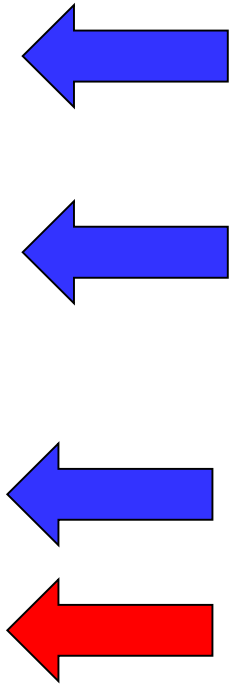
Tulkens, unpublished

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 between 0.25 and 2 mg/L (➔ 0.5 g TID, 1 g TID, … 2 g TID …)**



CLSI: Clinical and Laboratory Standards Institute
EUCAST: European Committee on Antimicrobial Susceptibility Testing
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) (accessed 20/04/2014)

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

This is what Dr Yezli *et al.* showed

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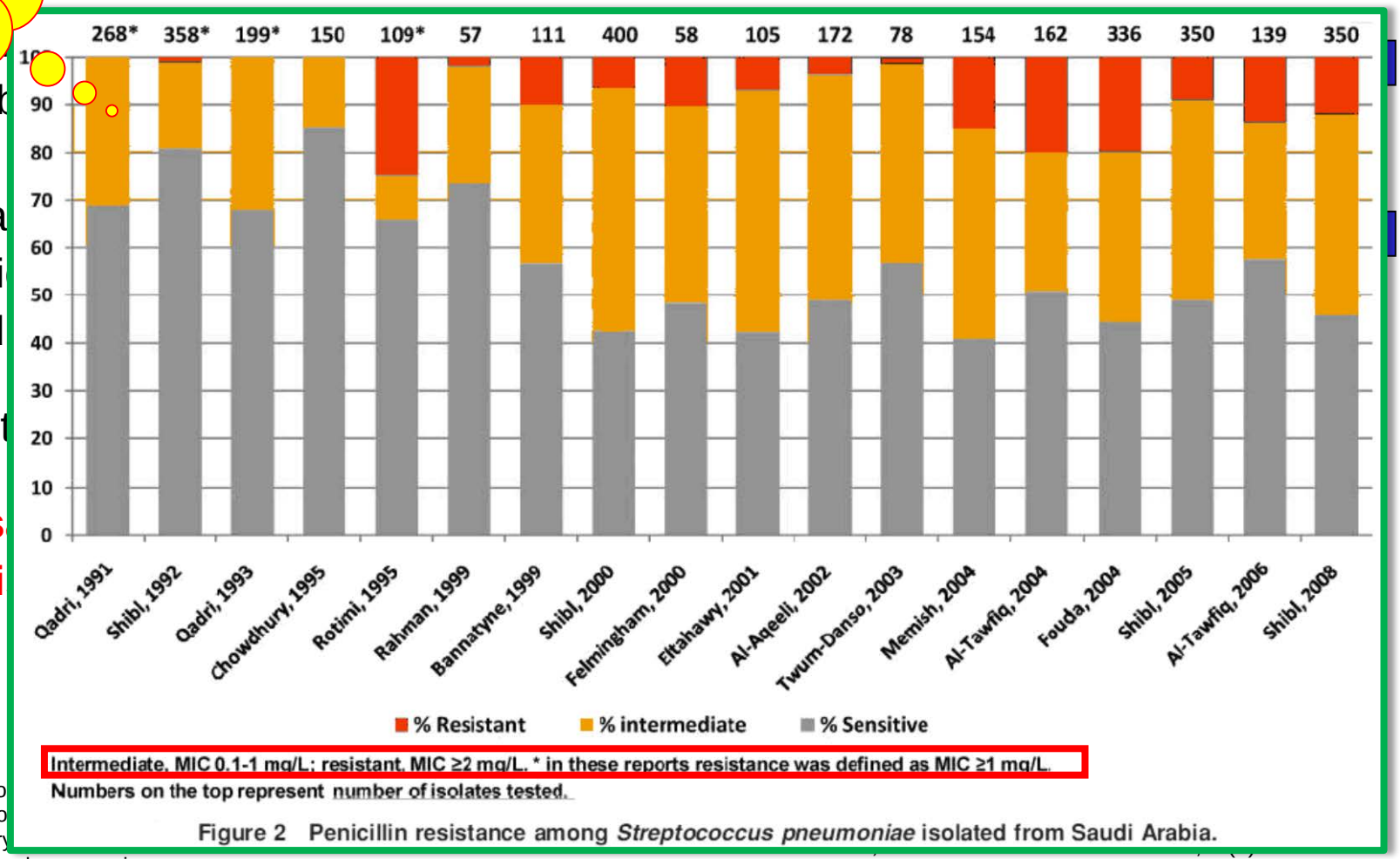


Figure 2 Penicillin resistance among *Streptococcus pneumoniae* isolated from Saudi Arabia.

CLSI: Clinical and Labo
EUCAST: European Co
MIC: minimum inhibitory
CAP: community acquired pneumonia
R: resistance
BID: twice daily; TID: 3 times daily

2. EUCAST clinical breakpoints (http://www.eucast.org) (accessed 20/04/2014)

Resistance of *S. pneumoniae* to macrolides and tetracyclines *

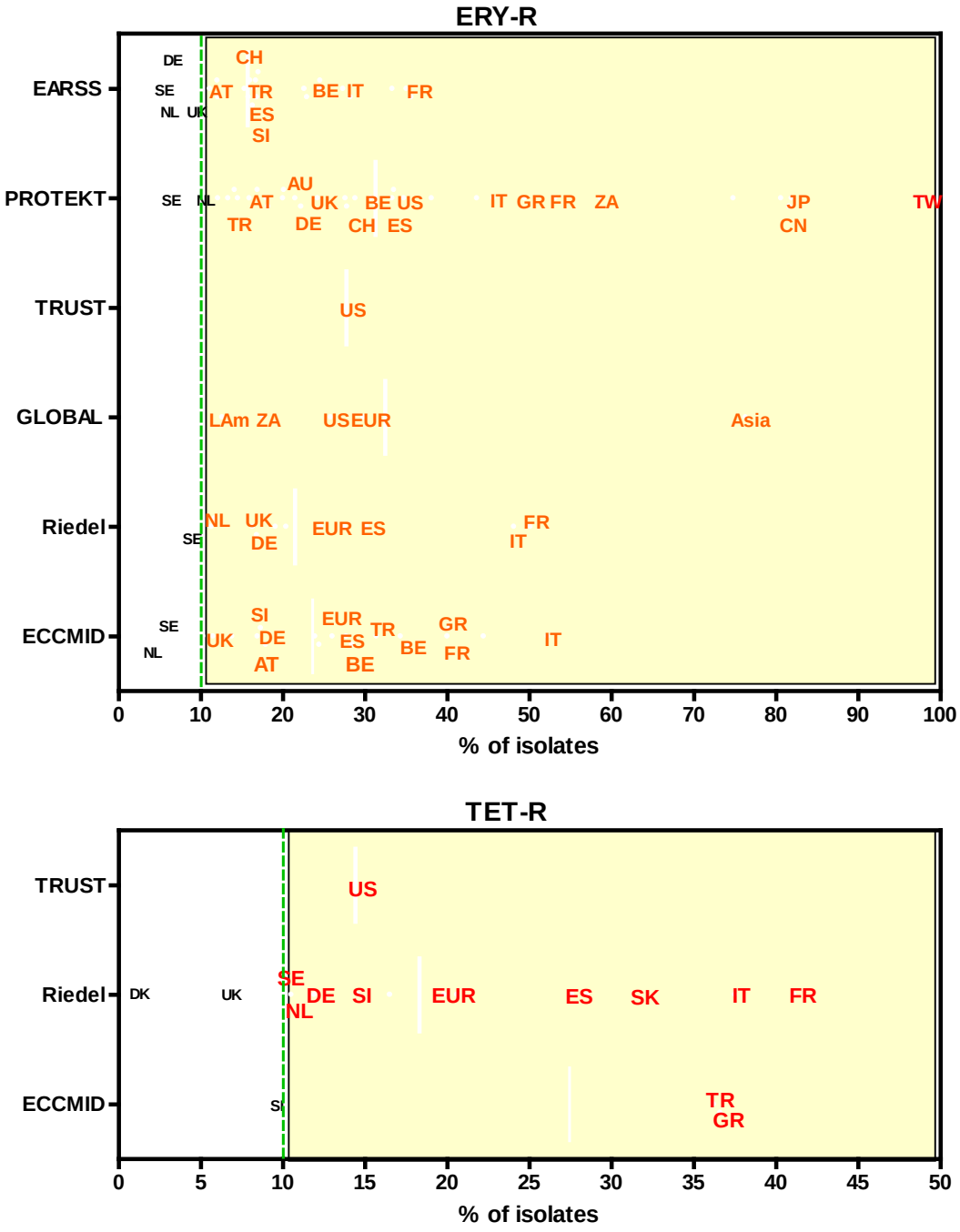
*analysis of resistance to erythromycin and doxycycline (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

- **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

Most studies used CLSI breakpoints
- erythromycin: S ≤0.25 – R ≥1
- Doxycycline: S ≤0.25 – R ≥1

Lismond *et al.*, in preparation

CAP: community-acquired pneumonia



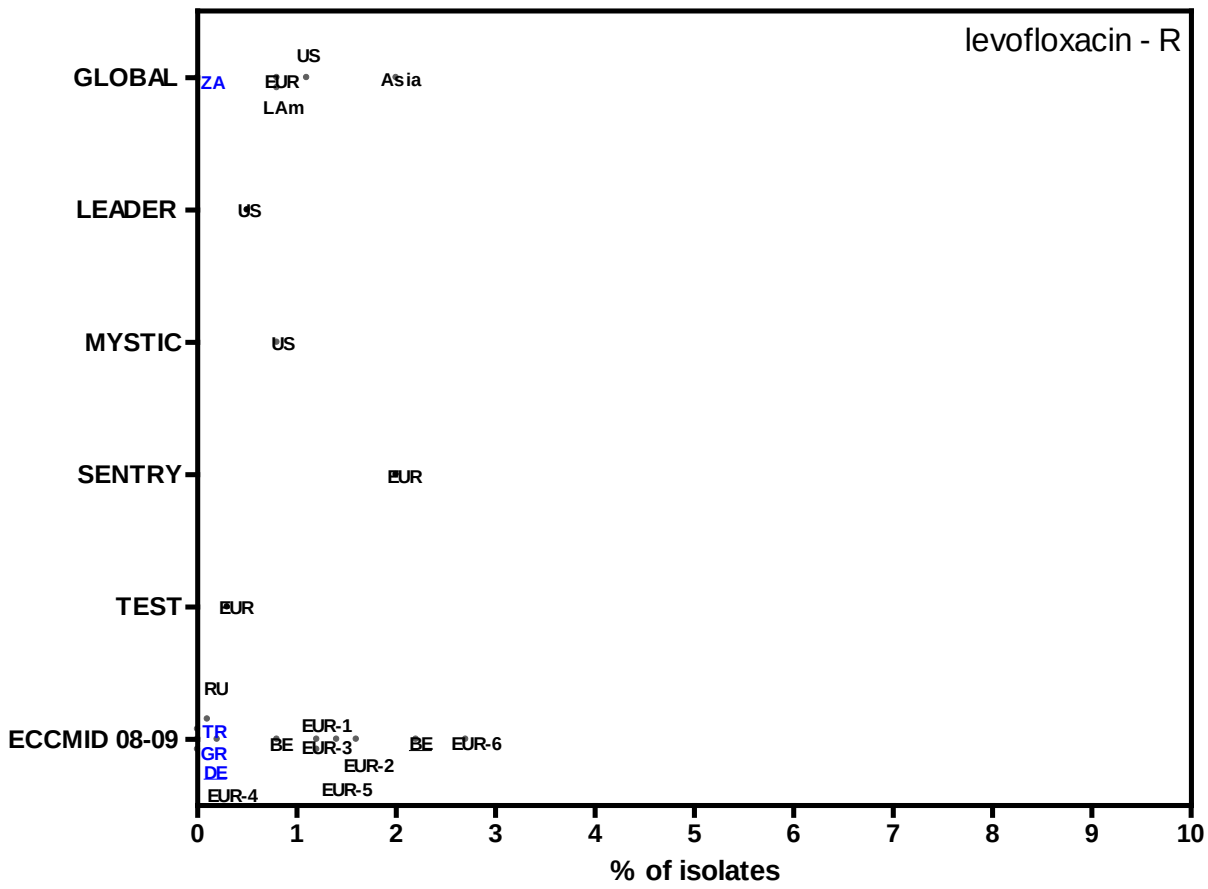
Resistance of *S. pneumoniae* to fluroquinolones

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

- **GLOBAL:** Global Landscape On the Bactericidal Activity of Levofloxacin
- **LEADER:** Linezolid Surveillance Program
- **MYSTIC:** Meropenem Yearly Susceptibility Test Information Collection
- **SENTRY:** Antimicrobial Surveillance Program (2005–2006)
- **TEST:** Tigecyline Evaluation Surveillance Trial
- **ECCMID 08-09** : abstracts of the 18th and 19th European Congresses of Clinical Microbiology and Infectious Diseases

Most studies used CLSI breakpoints

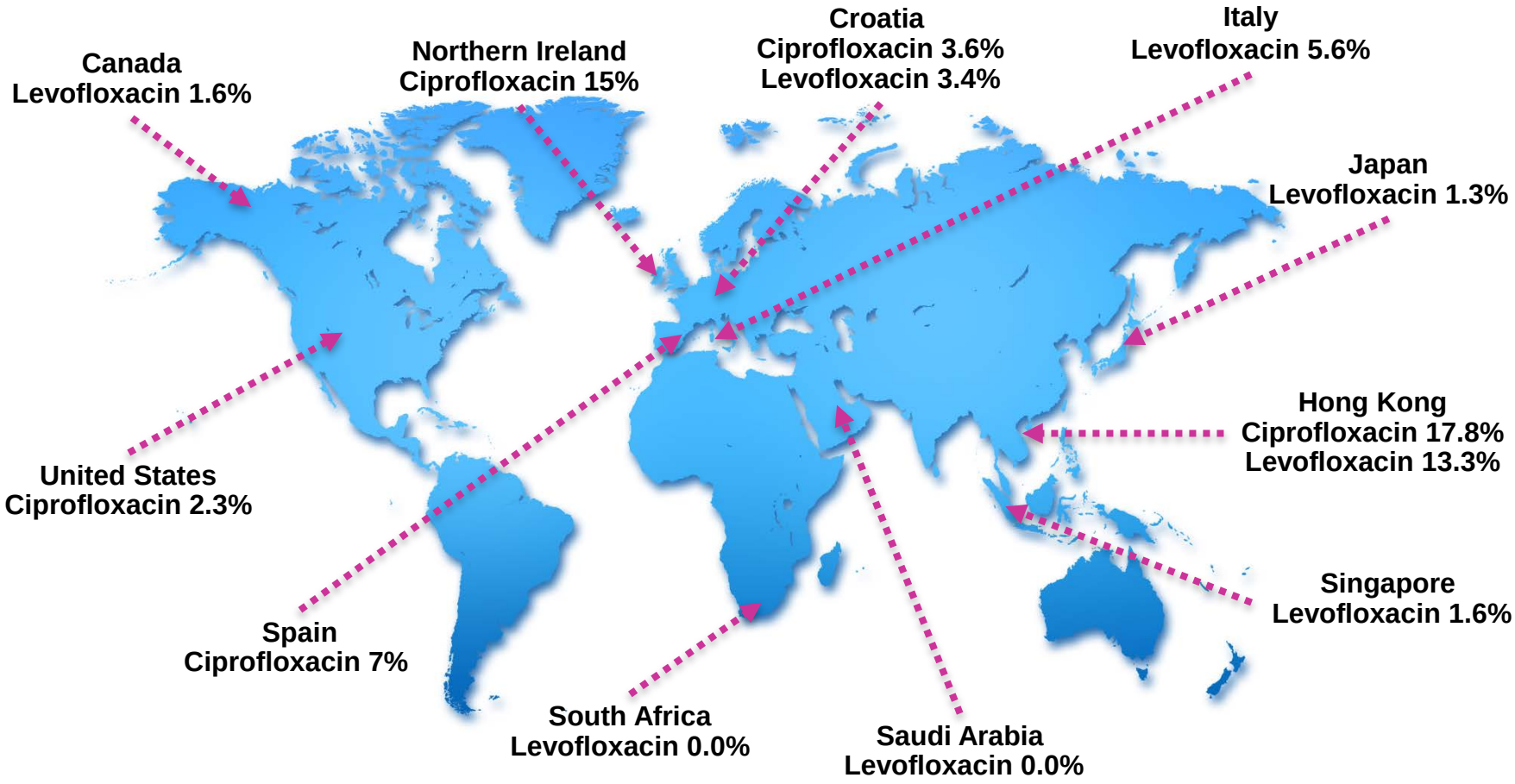
- levofloxacin: S ≤2 – R ≥8
- doxycycline: S ≤1 – R ≥4



Lismond *et al.*, in preparation

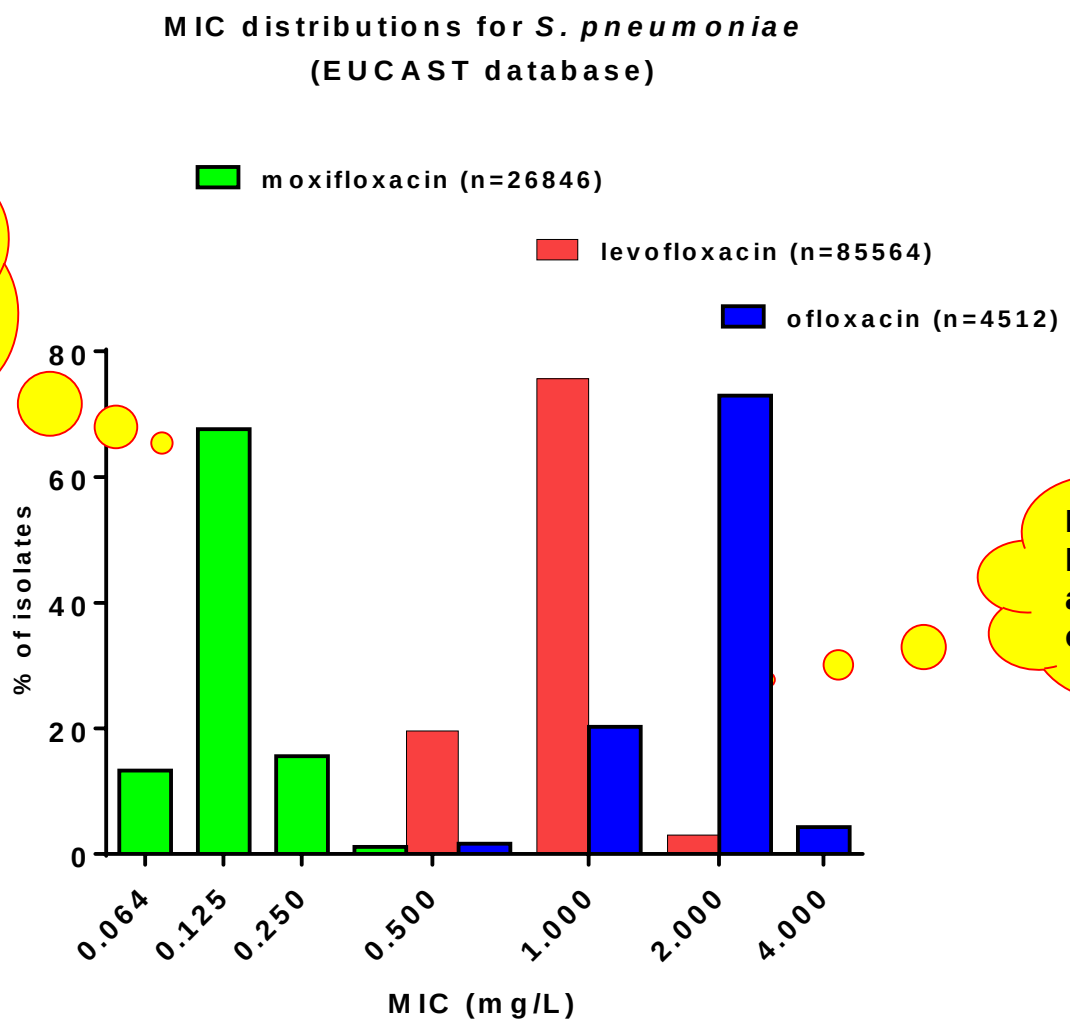
CAP: community-acquired pneumonia

Resistance of *S. pneumoniae* to fluroquinolones in the world



Deshpande et al. DMID 2000; 37: 139–142; Doern et al. Clin Infect Dis 2005; 45: 1721–29; Ho et al. J Antimicrob Chemother 2001; 48: 659–665; Thornsberry et al. Clin Infect Dis 2002; 34(Suppl 1): S4–S16; Goldsmith et al. J Antimicrob Chemother 1998; 41: 420–421; Pankuch et al. Antimicrob Agents Chemother 2002; 46: 2671–2675; Perez-Trallero et al. Antimicrob Agents Chemother 2001; 45: 3334–3340; Powis et al. Antimicrob Agents Chemother 2004; 48: 3305–3311

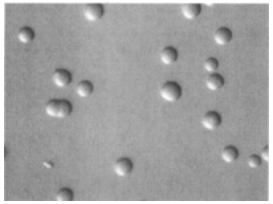
Comparing MICs of fluroquinolones (wild types)…



Moxifloxacin shows MICs 3 $\log_2$ dilutions lower (8-fold) than levofloxacin

Remember that levofloxacin is the active (*S*) isomer of ofloxacin

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- must be recognized as a real potential pathogen if performing active surveillance

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2004, p. 697–728
0893-8512/04/$08.00+0 DOI: 10.1128/CMR.17.4.697–728.2004

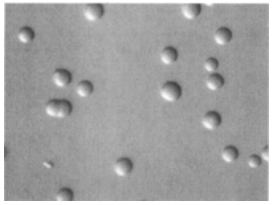
Vol. 17, No. 4

Mycoplasma pneumoniae and Its Role as a Human Pathogen

Ken B. Waites[1]* and Deborah F. Talkington[2]

Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35249,[1] and Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[2]

Mycoplasma pneumoniae



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M. PNEUMONIAE AS A HUMAN PATHOGEN 707

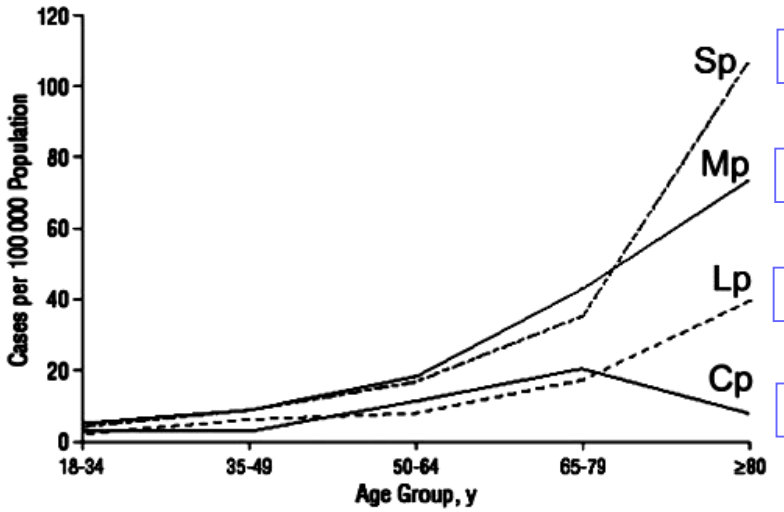


FIG. 6. Data from an active surveillance study performed in Ohio in 1991, showing age-specific rates of community-acquired pneumonia due to the major bacterial pathogens. *M. pneumoniae* infections were diagnosed by seroconversion, using CF tests. These data demonstrate that *M. pneumoniae* causes a relatively large proportion of pneumonias of sufficient severity to warrant hospitalization among persons younger than 50 years but that it is also an important cause of pneumonia in older age groups. Sp, *S. pneumoniae*; Mp, *M. pneumoniae*; Lp, *L. pneumophila*; Cp, *C. pneumoniae*. Reprinted from reference 283 with permission of the publisher.

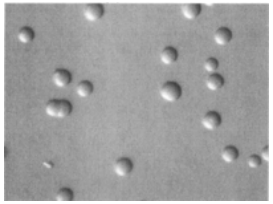
S. pneumoniae

M. pneumoniae

L. pneumophila

C. pneumonaie

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- was long considered as universally susceptible to macrolides…
- but this was no longer true in Asia since several years …

AAC Journals.ASM.org

Antimicrob Agents Chemother. 2013;57:4046-9.

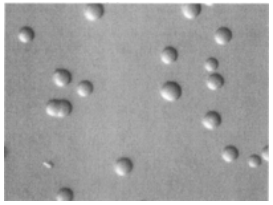
Nationwide Surveillance of Macrolide-Resistant *Mycoplasma pneumoniae* Infection in Pediatric Patients

Yasuhiro Kawai,[a] Naoyuki Miyashita,[b] Mika Kubo,[a] Hiroto Akaike,[a] Atsushi Kato,[a] Yoko Nishizawa,[a] Aki Saito,[a] Eisuke Kondo,[a] Hideto Teranishi,[a] Tokio Wakabayashi,[a] Satoko Ogita,[a] Takaaki Tanaka,[a] Kozo Kawasaki,[a] Takashi Nakano,[a] Kihei Terada,[a] Kazunobu Ouchi[a]

Department of Pediatrics[a] and Department of Internal Medicine 1,[b] Kawasaki Medical School, Okayama, Japan

We conducted nationwide surveillance to investigate regional differences in macrolide-resistant (MR) *Mycoplasma pneumoniae* strains in Japan. The prevalence of MR *M. pneumoniae* in pediatric patients gradually increased between 2008 and 2012. Although regional differences were observed, high levels of MR genes were detected in all seven surveillance areas throughout Japan and ranged in prevalence from 50% to 93%. These regional differences were closely related to the previous administration of macrolides.

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

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AAC Journals.ASM.org **Antimicrob Agents Chemot**

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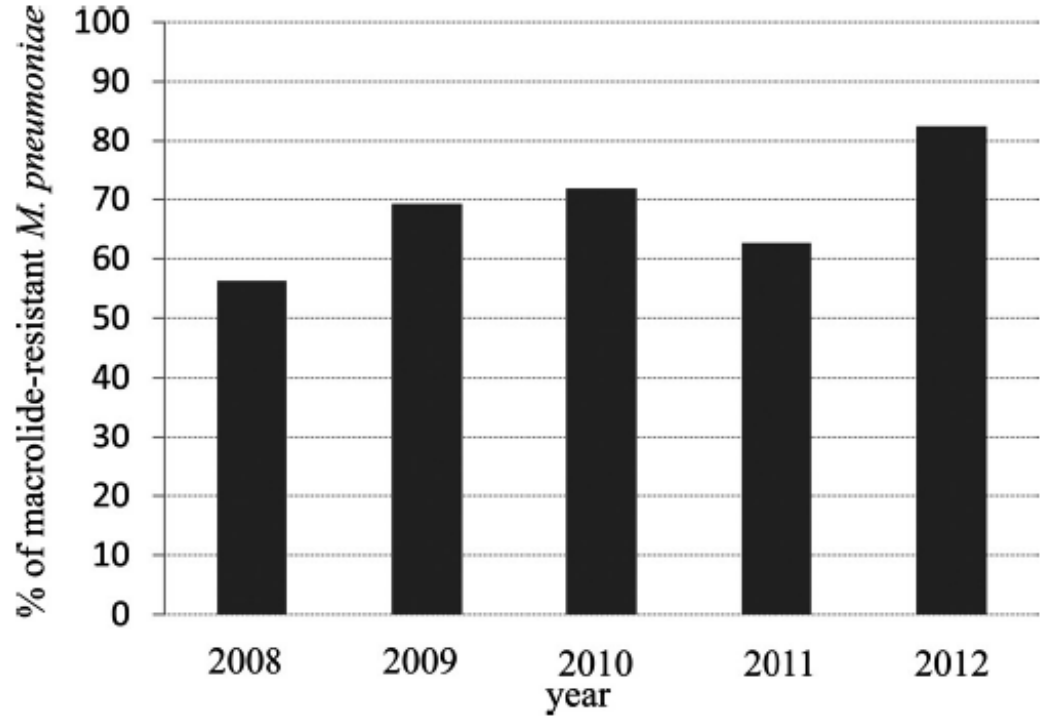
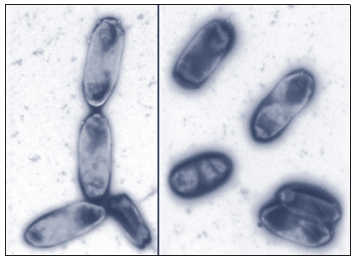


Year-by-year increases in the frequency of macrolide-resistant *Mycoplasma pneumoniae* cases from 2008 to 2012.

Haemophilus: is it important ?



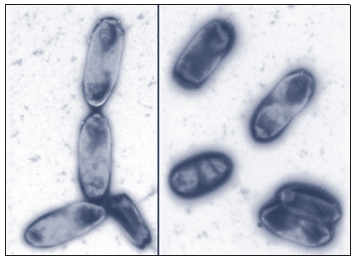
http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html

- *Haemophilus* is often considered as a colonizer of the upper respiratory tract with risks only for patients with COPD
- However, in coinfection with a preceding viral infection, *Haemophilus* may easily colonize the lung, leading to lethal secondary bacterial pneumonia.
  - We may now understand the corresponding genetic background (e.g. overexpression of an anti-oxidant protein) [1]
- β-lactamase-negative ampicillin-resistant (BLNAR) *Haemophilus* may be on the rise in some regions of the world (but not all) [2]
  - antibiotic discs may fail to fully separate between BLNAS and BLNAR populations [3]
  - the majority of invasive *H. influenzae* (including BLNAR) remain susceptible to third-generation cephalosporins and fluroquinolones in Europe [4]
- Resistance of Haemophilus to fluroquinolones may be on the rise in Asia [5]

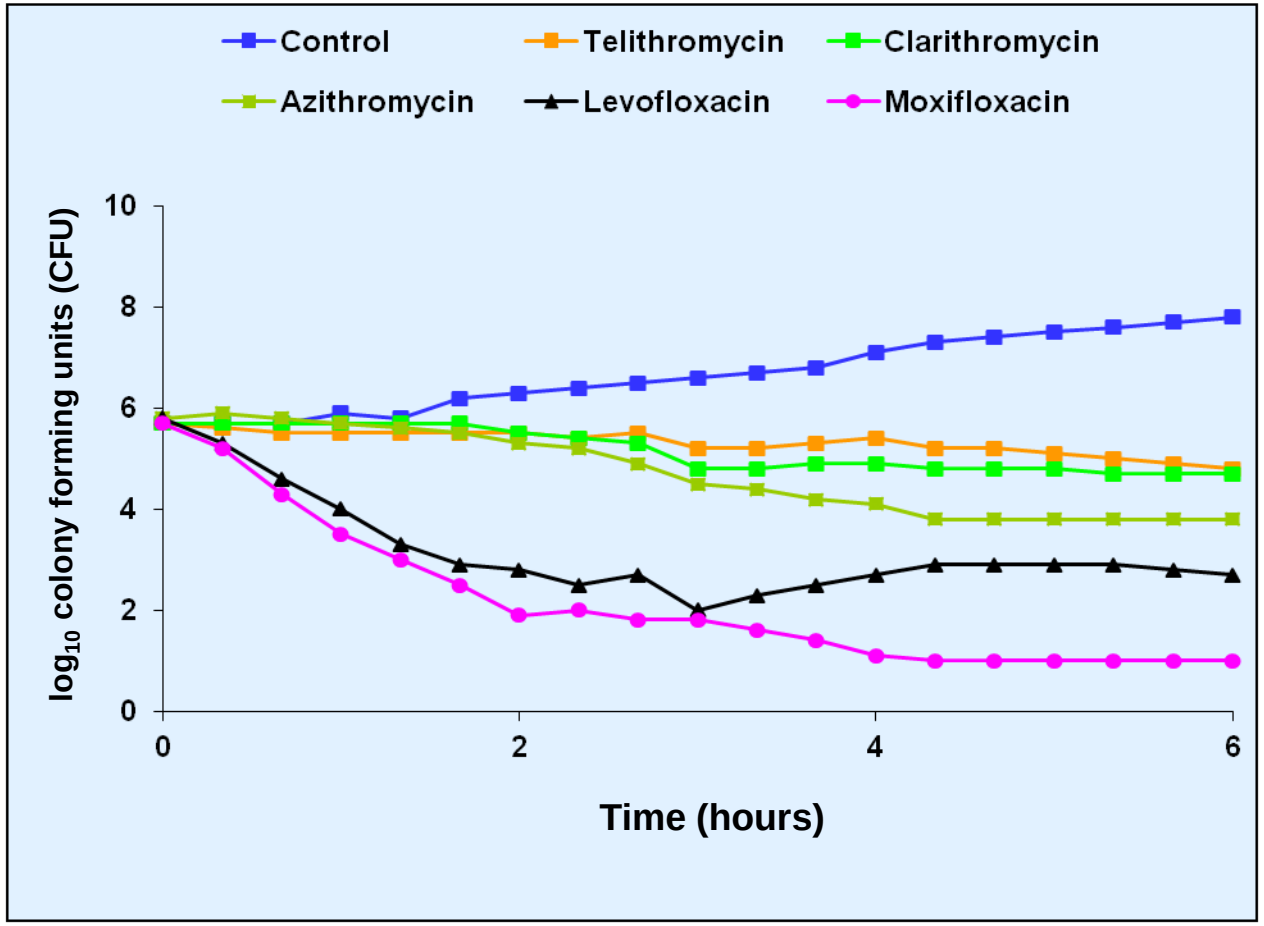
COPD chronic obstructive pulmonary disease
BLNAR β-lactamase-negative ampicillin-resistant
BLNAS β-lactamase-negative ampicillin-sensitive

1. Wong, *et al. Proc Natl Acad Sci U S A*. 2013;110:15413-8.
2. Dabernat, *et al. Eur J Clin Microbiol Infect Dis*. 2012;31:2745-53
   Geelen, *et al.* Scand J Infect Dis. 2013;45:606-11
3. Garcia-Cobos, *et al. JAC*. 2013;68: 159–63
4. Garcia-Cobos, *et al JAC*. 2014;69:111-6
   Puig, *et al.. PLoS One*. 2013;13-8:e82515
5. Shoji, *et al. J Infect Chemother*. 2014;20:250-5

Haemophilus and fluoroquinolones vs other antibiotics (in vitro data)



http://www.pathologyoutlines.com/topic/lymphnodeshinfluenzae.html



Bayer HealthCare data on file

Fluoroquinolones (and moxifloxacin in particular) are highly bactericidal against *H. influenzae*

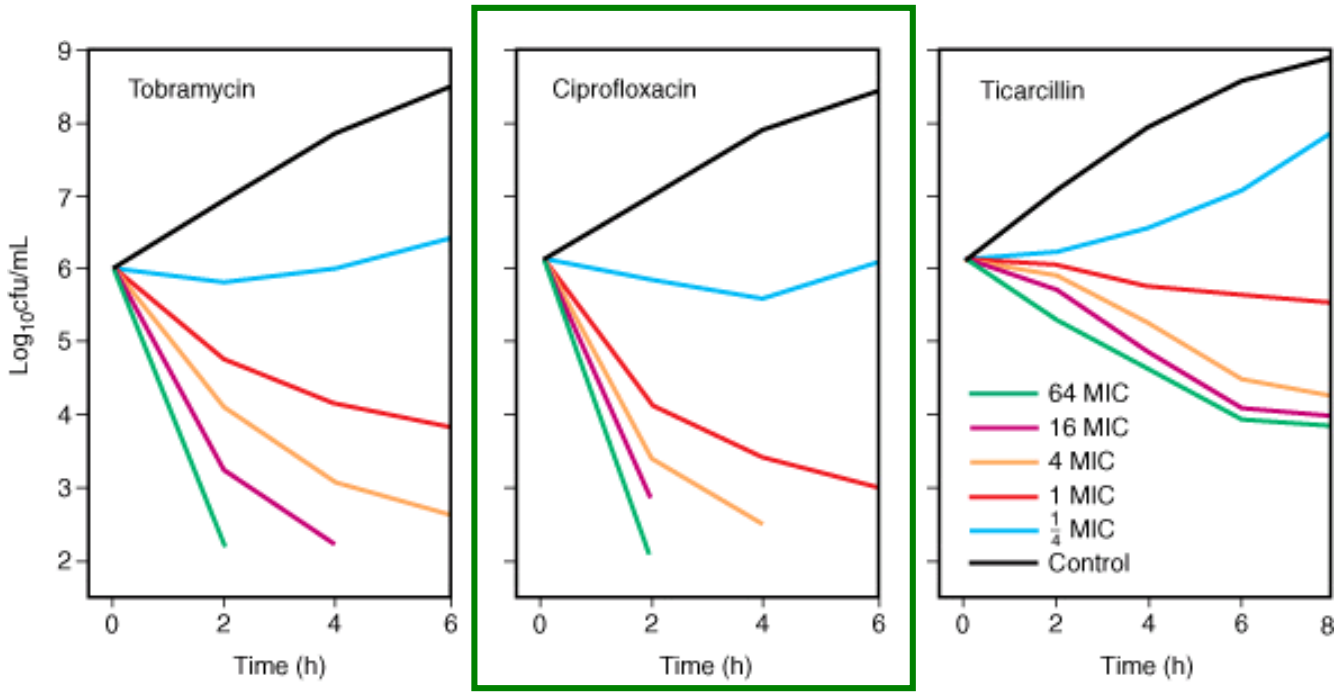
What shall we do ?

- Burden of the diseases (CAP / COPD)
- Epidemiological data concerning selected important pathogens
  - *Streptococcus pneumonia*
  - *Mycoplasma pneumonia*
  - *Haemophilus influenza*
- PK/PD: Efficacy and Resistance issues
- How to reach a successful (effective and safe) clinical outcome

Killing abilities of antibiotics: importance of the peak

in vitro kill curves: the original observations

conc. dependent



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.
(From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. Scand J Infect Dis. 1990;74:63–70.)

Killing abilities of fluoroquinolones: Are they all equal ?

in vitro kill curves: observations with *S. pneumoniae*

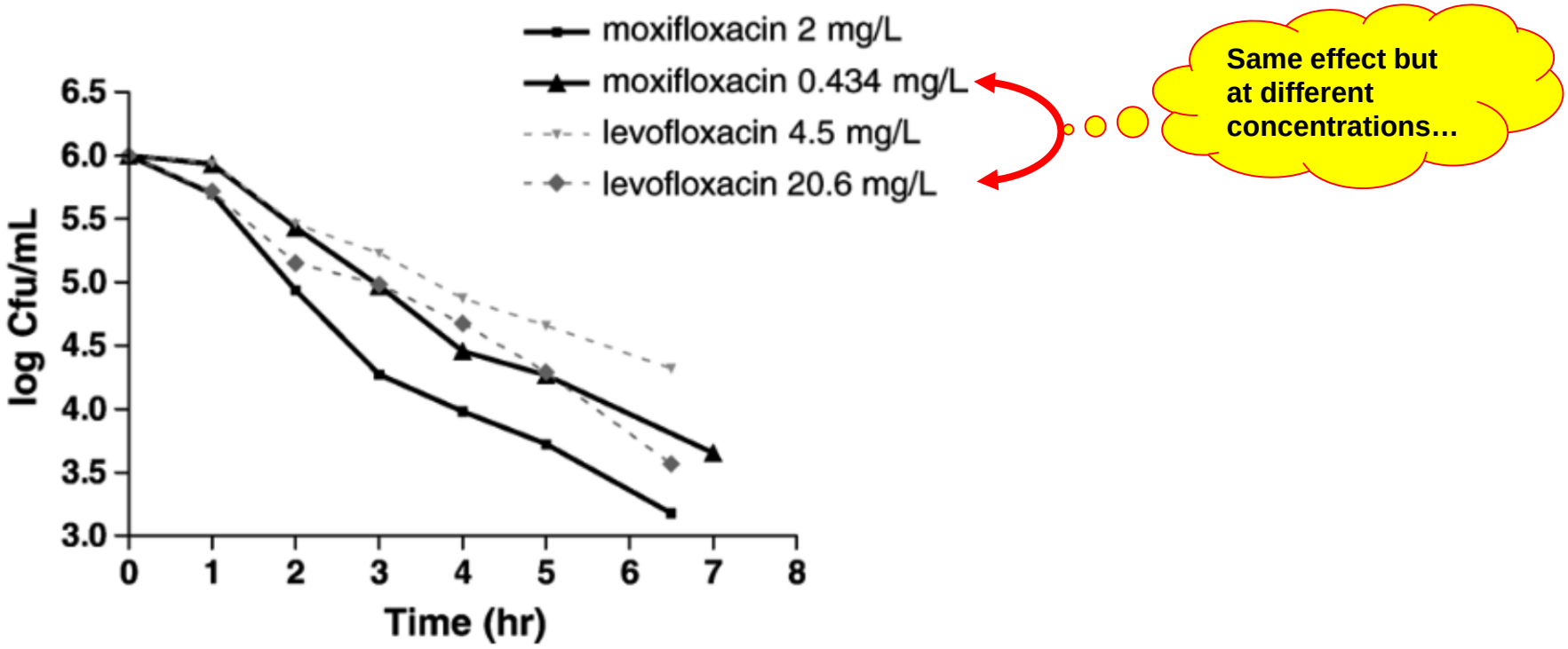


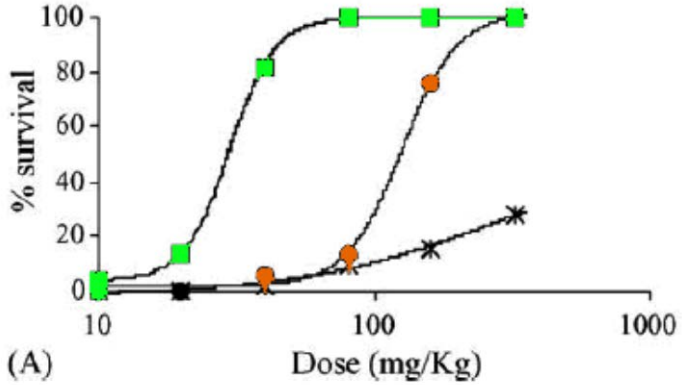
Fig. 1. Time kill curves of moxifloxacin versus levofloxacin against *S. pneumoniae* 7362 (average of 2 models).

Schafer et al. Diag Microb Infect Dis 2008; 60:155–161

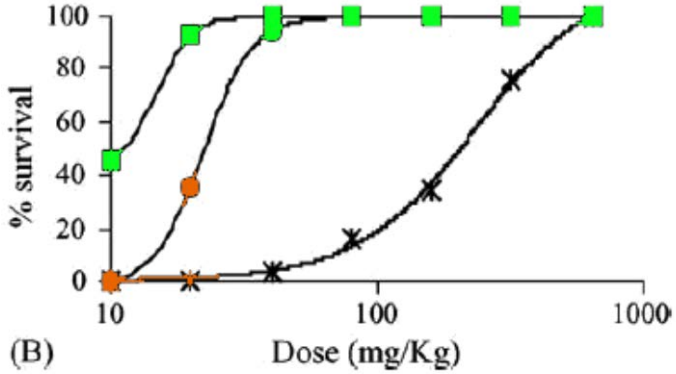
Killing abilities of fluoroquinolones: Are they all equal ?

Animal survival experiments (S. pneumonia i.p. inoculations)

Levofloxacin (LVX)



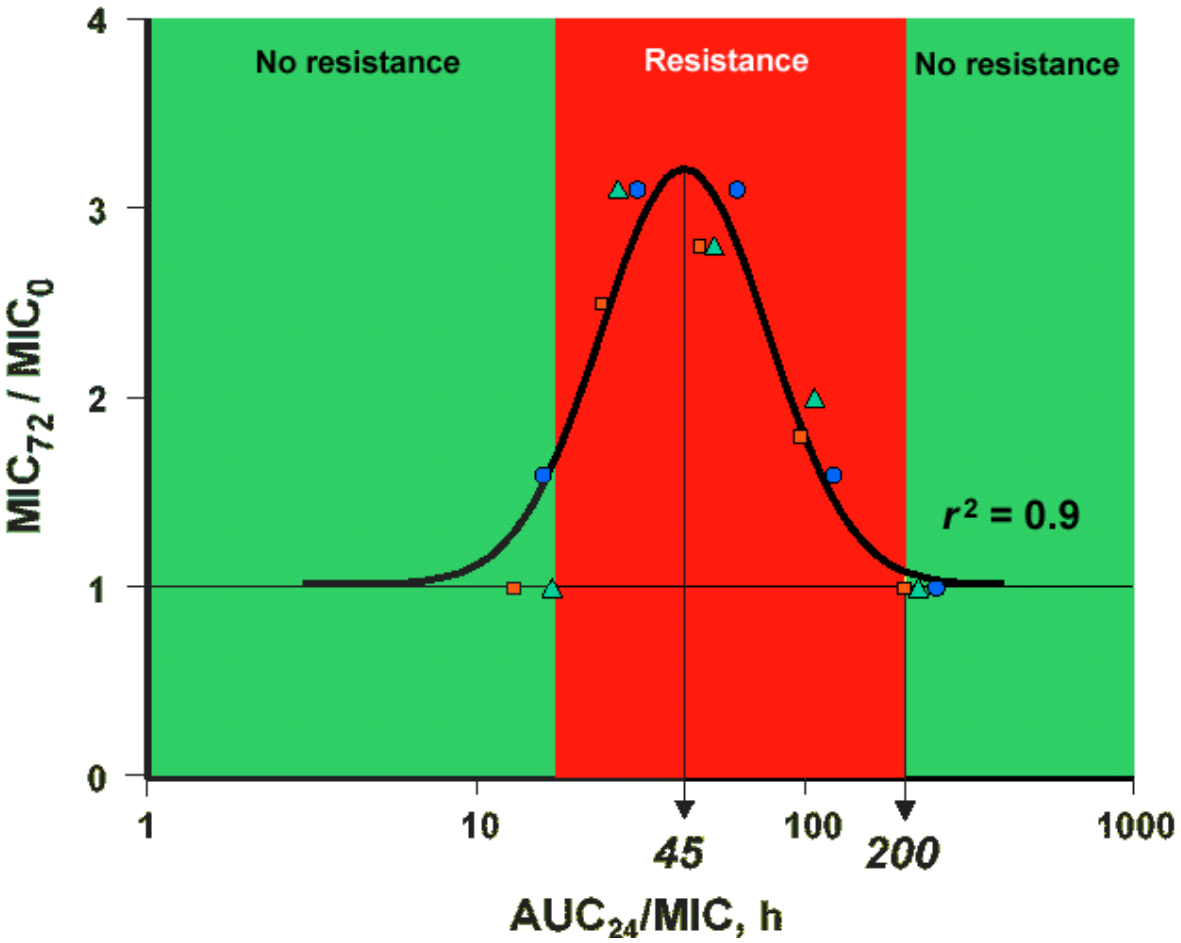
Moxifloxacin (MXF)



strain	MIC (mg/L)	
	MXF	LVX
AR33118 (■)	0.12	1
FL2812 (●)	0.25	2
FL5629 (✶)	4	32

Huelves et al. Int J Antimicrob Agents 2006; 27:294–299

Prevention of emergence of resistance: importance of AUC/MIC



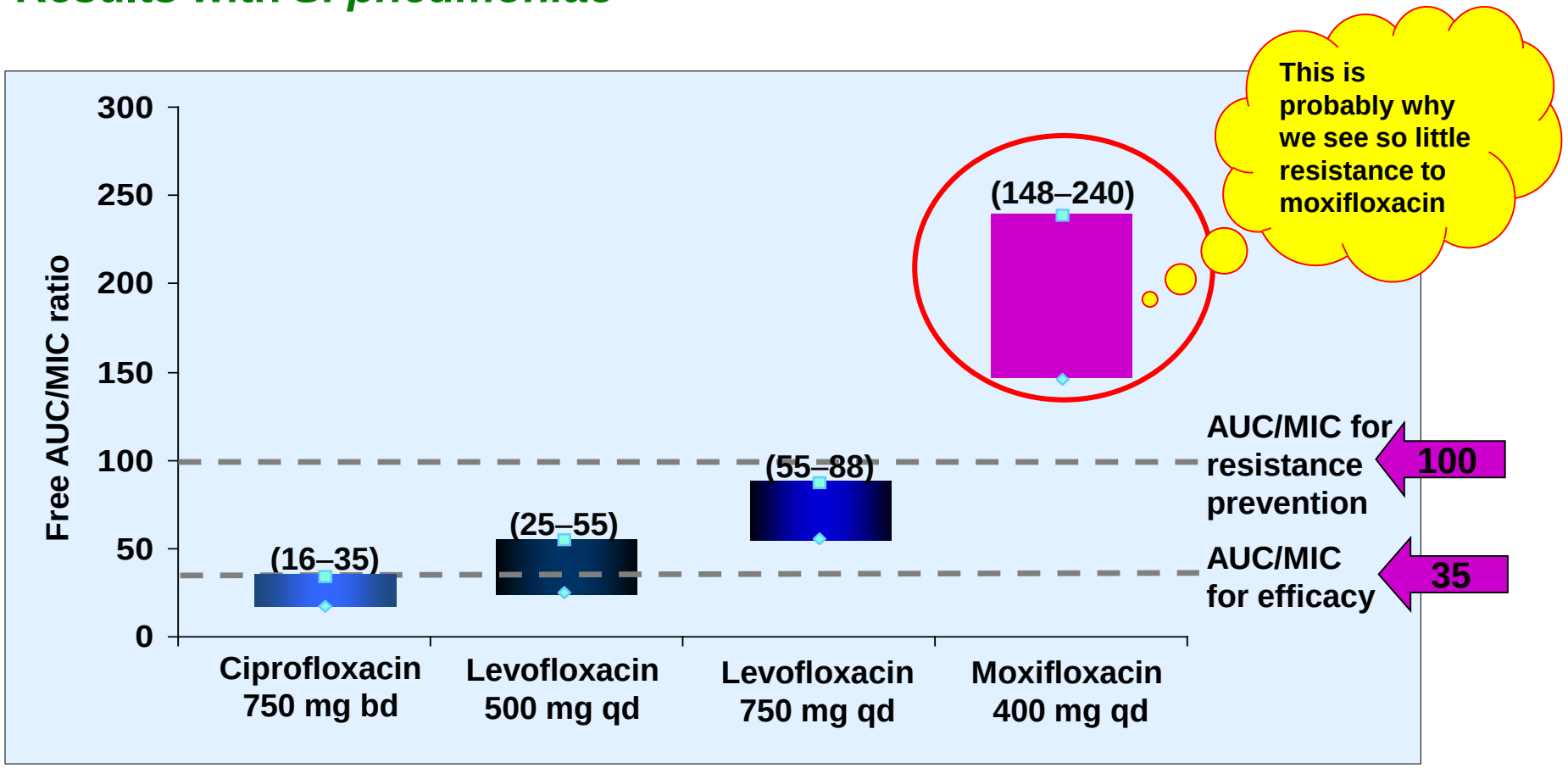
Resistance of *S. aureus* related to exposure to 3 fluoroquinolones

AUC/MIC > 100 prevents resistance selection

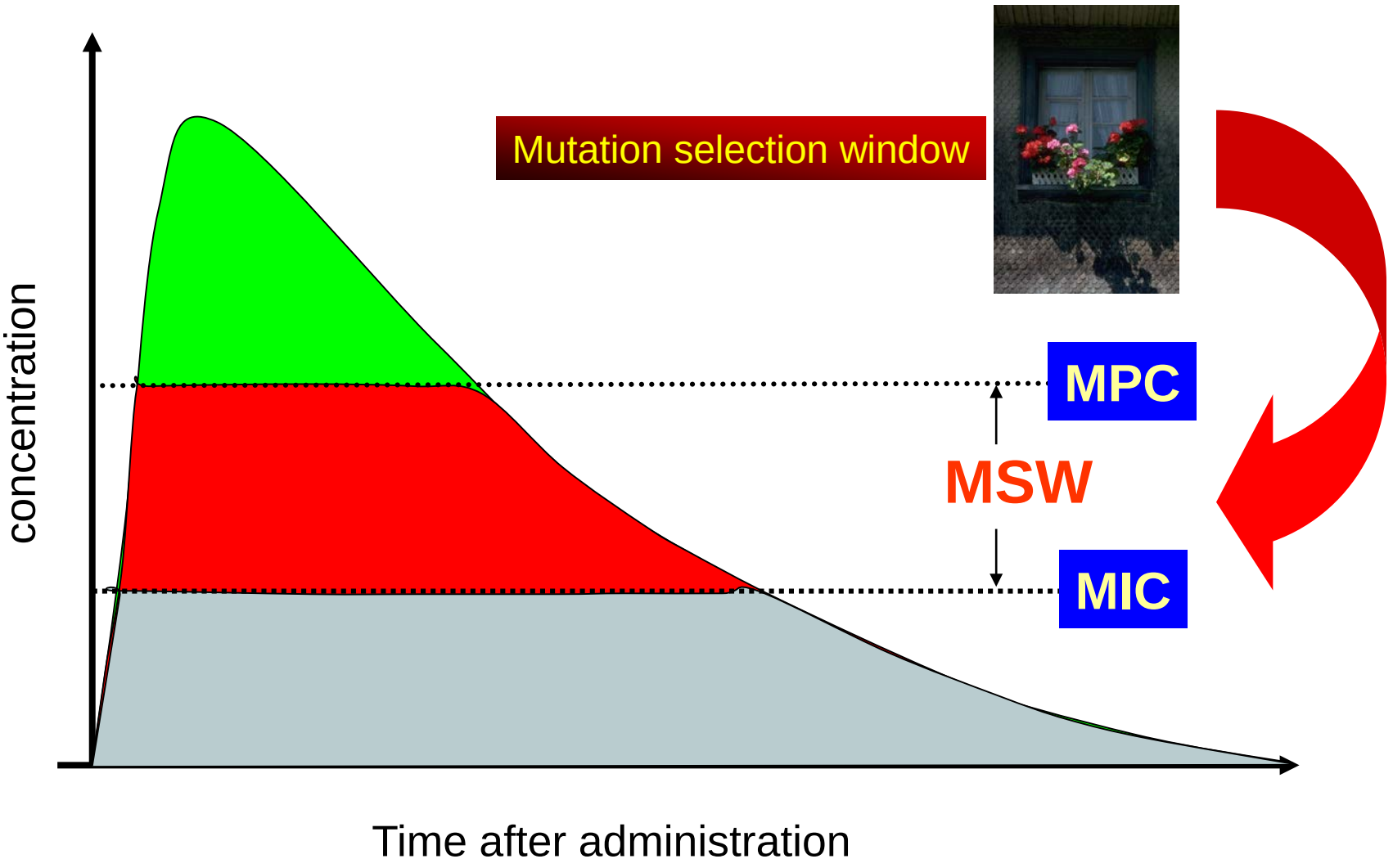
Firsov, ICAAC 2002

What differentiates fluoroquinolones for AUC/MIC ratios ?

Results with *S. pneumoniae*

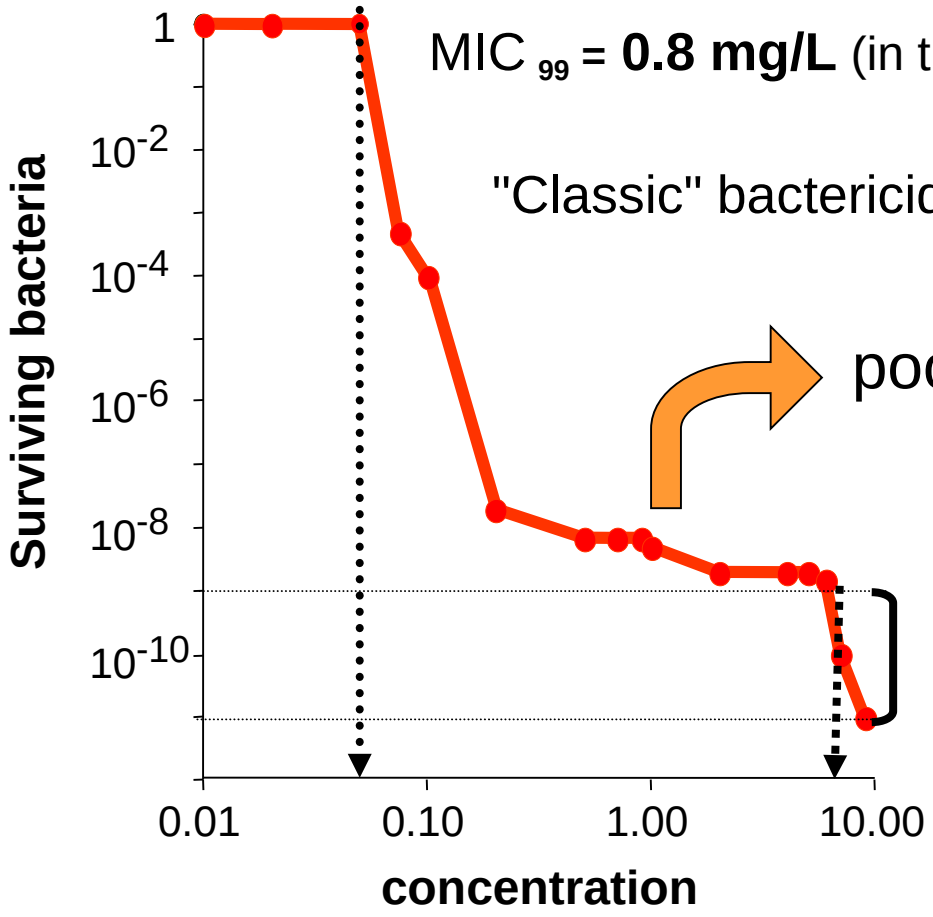


All is a matter of “Windows” …



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

C_{max} and "Mutant Prevention Concentration" (MPC) …



MIC $_{99}$ = **0.8 mg/L** (in this example)

"Classic" bactericidal effect

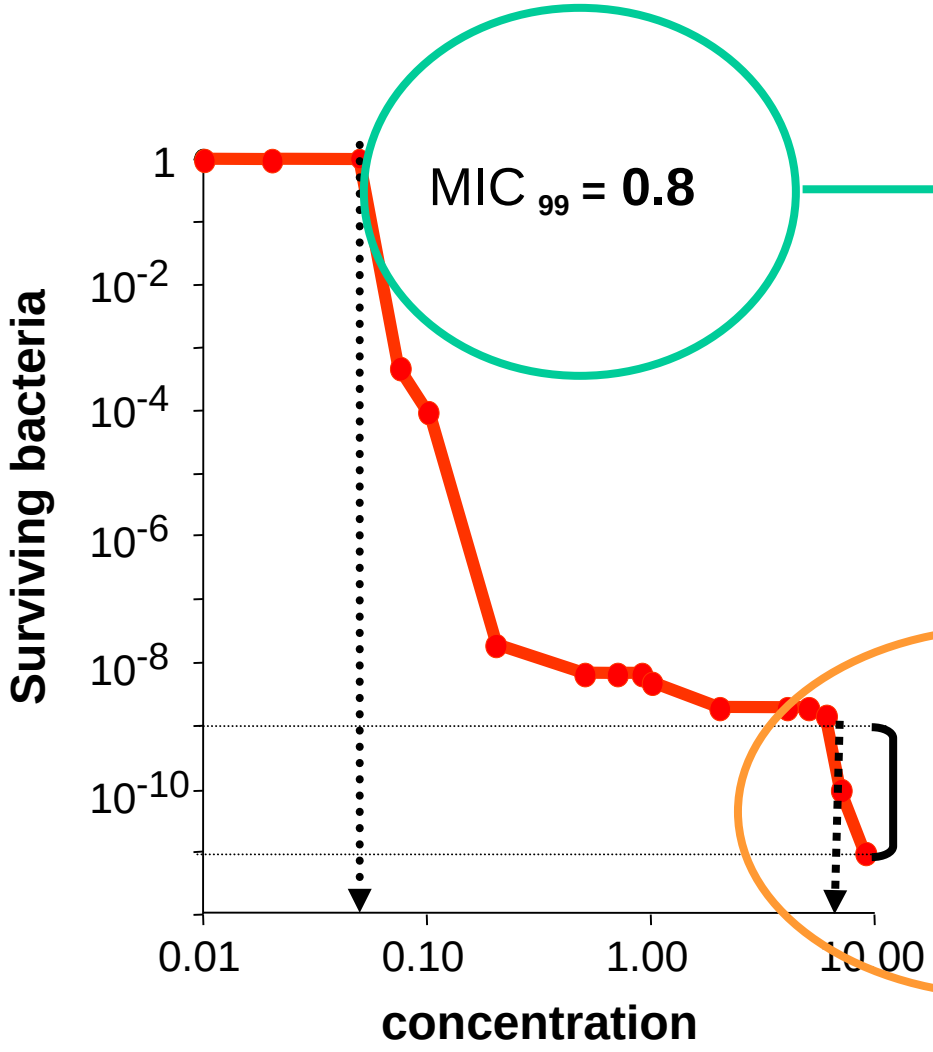
poorly sensitive organisms…

Elimination of resistant organisms

MPC_{10} = **9**

Dong et al: AAC 1999; 43:1756-1758

"Mutant Prevention Concentration …"



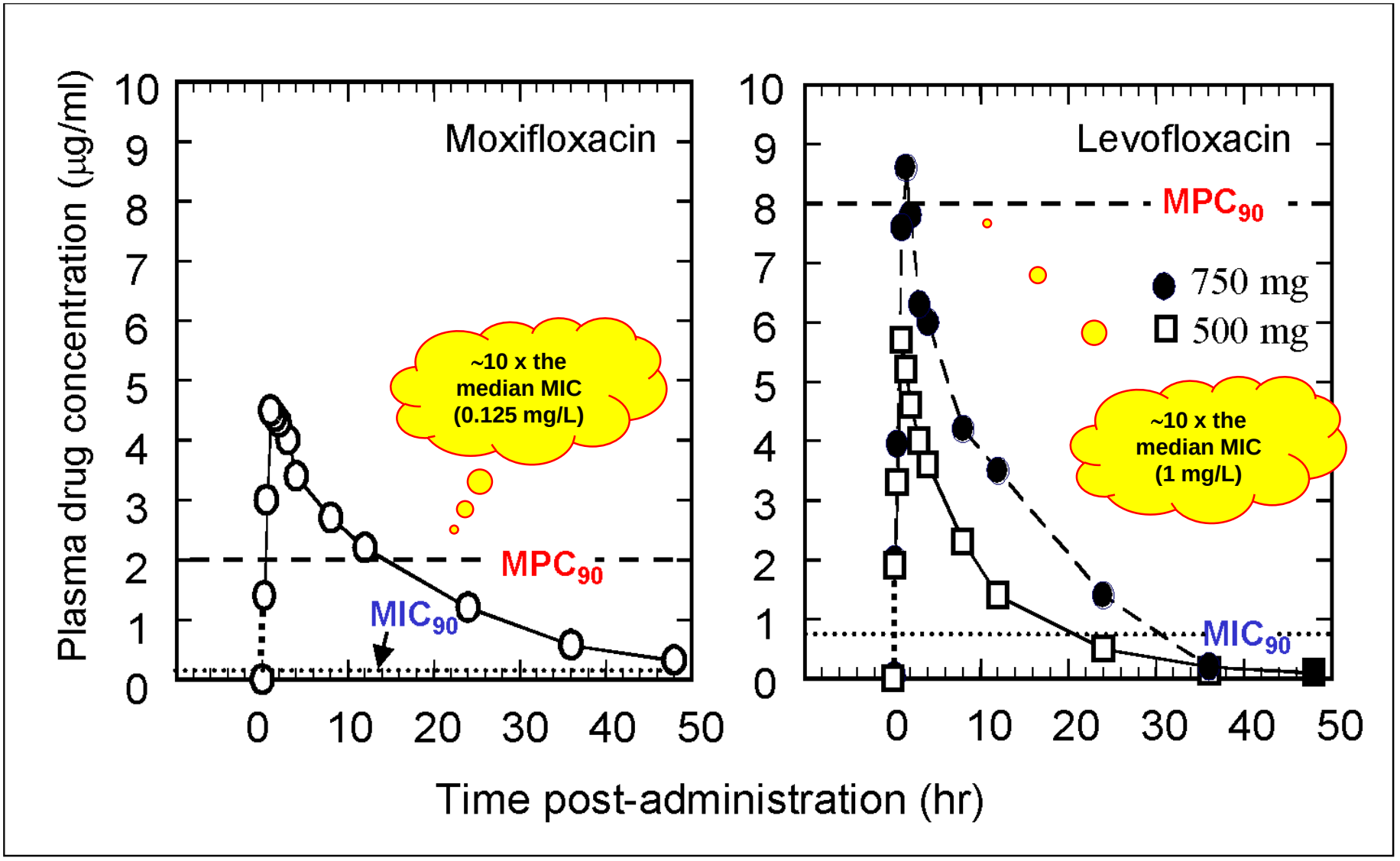
Concentration that inhibits the majority of the organisms

MPC 10 = 9

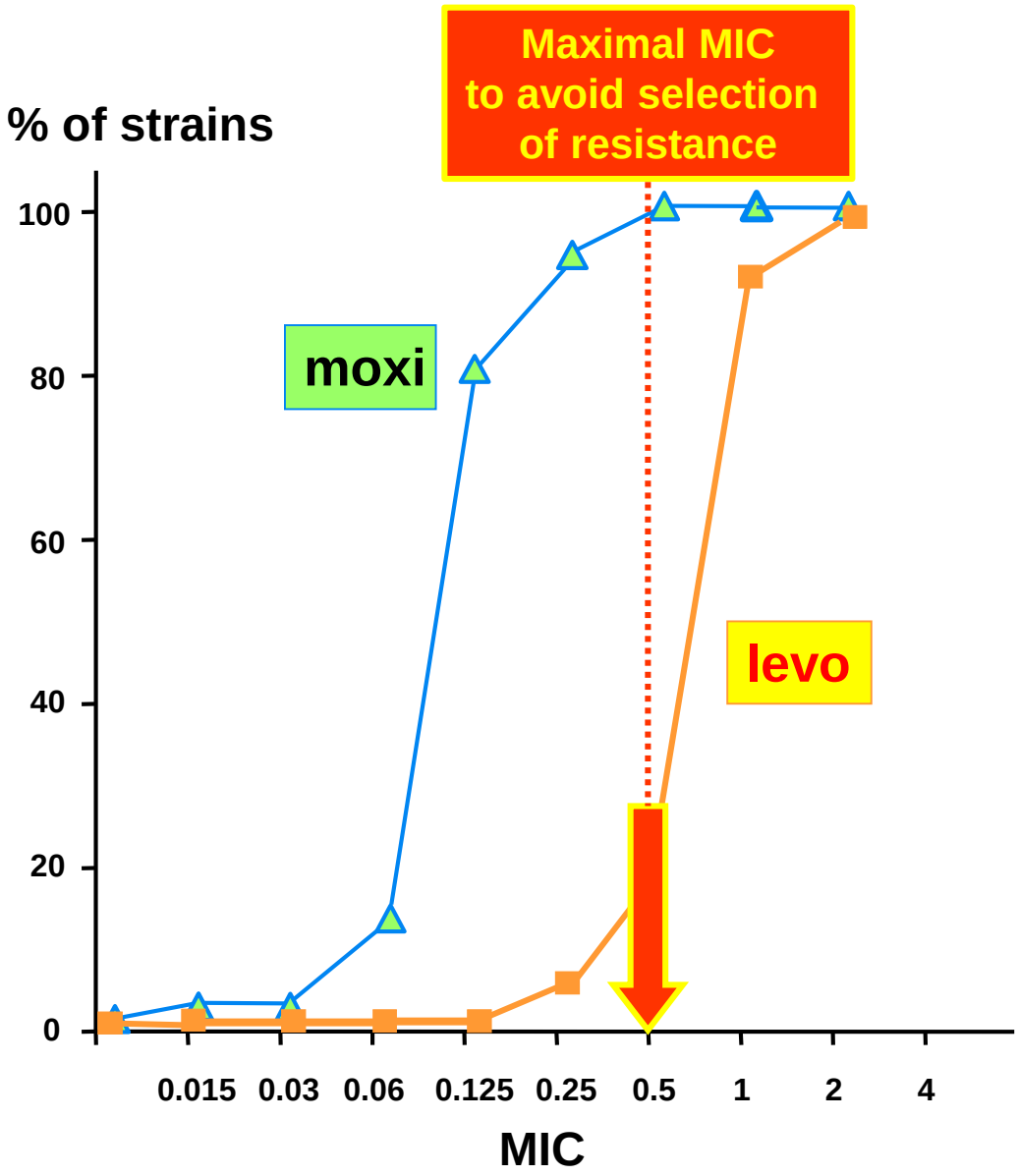
Concentration needed to prevent the **selection** of resistant organisms **(about 10 x the MIC)**

Dong et al; AAC 43:1756-1758

MPC: moxifloxacin *vs* levofloxacin



Pharmacokinetics and "resistance" breakpoint *vs.* MIC



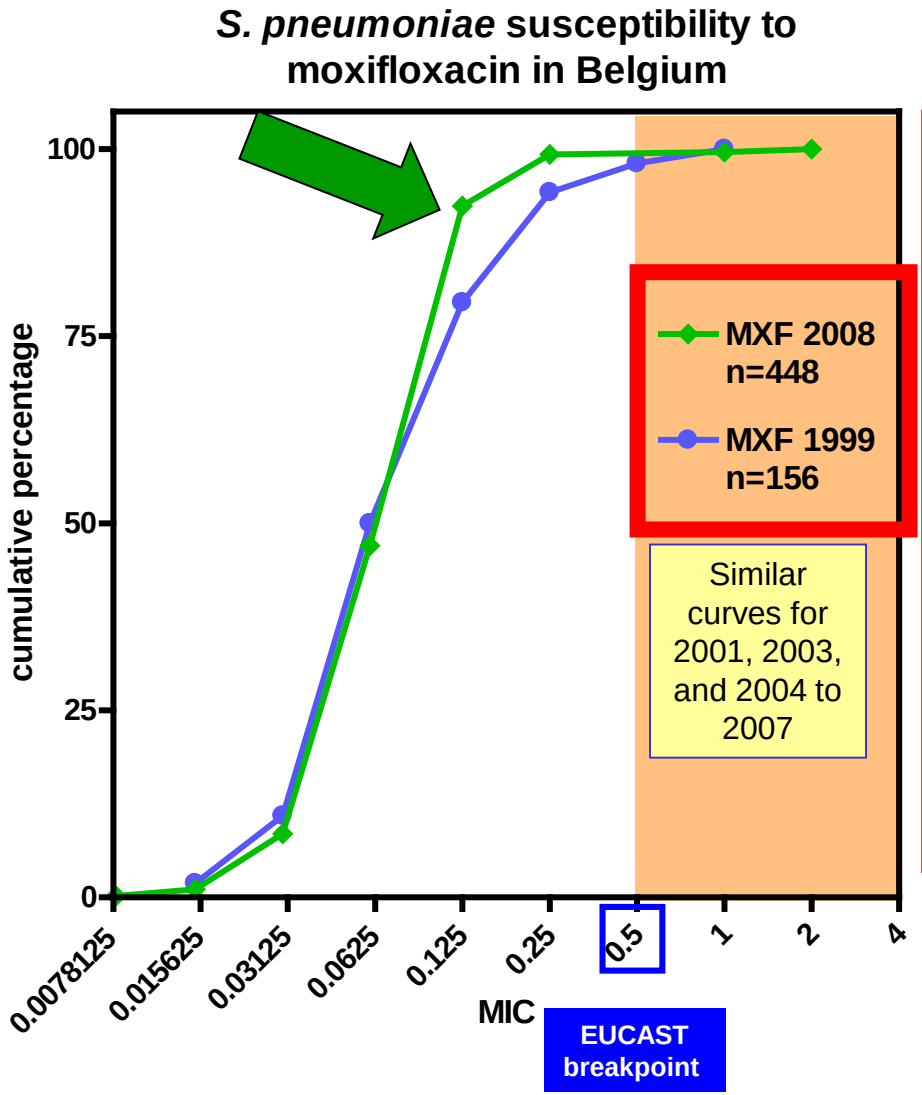
resistance breakpoint
- **AUC/MIC = 100**
- **peak/MIC = 10**

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)

Moxifloxacin MIC's against *S. pneumoniae* in Belgium from 1999 to 2008 *



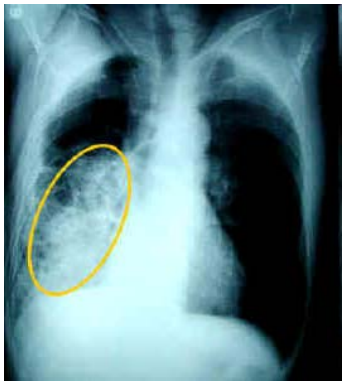
- Extract from the data of a national collection based on annual surveys made by the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates [https://www.wiv-isp.be/Programs/communicable-infectious-diseases/Pages/EN-BacterialDiseases.aspx?pflg=1033] and presented at the 19th ECCMID. May, 16-19 2009, Helsinki (Vanhoof *et al* abstract no. O467 [http://www.blackwellpublishing.com/eccmid19/abstract.asp?id=74082; last visited: 2 may 2014])
- See also
  - Vanhoof *et al* Acta Clin Belg. 2006;61:49-57
  - Vanhoof *et al* Pathol Biol (Paris) 2010;58:147-151)
- Confirmed in an independent study for the period 2004-2009 (Simoens *et al* Antimicrob Agents Chemother 2011;55:3051-3)
- Similar distribution for blood-stream isolates from patients with clinically confirmed diagnostic of CAP in 2007-2010 (Lismond *et al* Int J Antimicrob Agents. 2012;39(3):208-216)

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

What shall we do ?

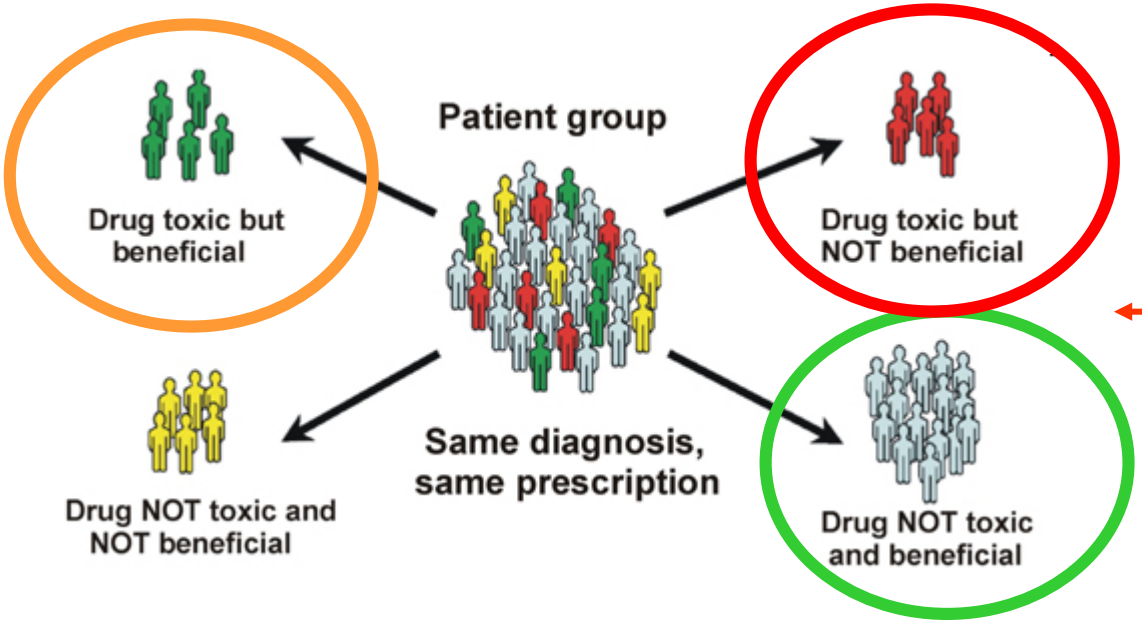
- Burden of the diseases (CAP / COPD)
- Epidemiological data concerning selected important pathogens
  - *Streptococcus pneumonia*
  - *Mycoplasma pneumonia*
  - *Haemophilus influenza*
- PK/PD: Efficacy and Resistance issues
- How to reach a successful (effective and safe) clinical outcome ?

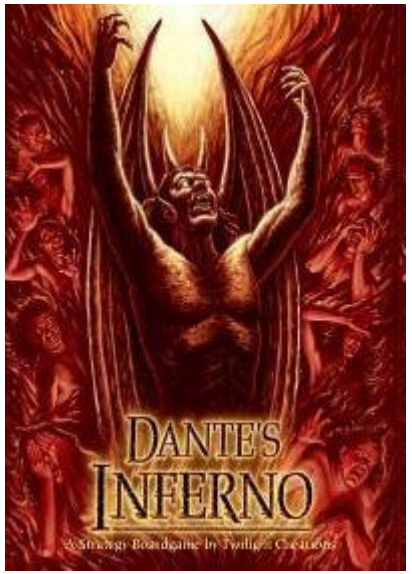
We all agree about efficacy, but what about side effects…



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

A difficult equilibrium for moxifloxacin ?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular (atypical pneumonia, tuberculosis)
- easy iv/po switch
- excellent oral bioavailability

- toxicity ?

Side effects of moxifloxacin (clinical trials database)

ORIGINAL RESEARCH ARTICLE

Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

Moxifloxacin Safety

An Analysis of 14 Years of Clinical Data

Paul M. Tulkens,[1] *Pierre Arvis*[2] and *Frank Kruesmann*[3]

1 Pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

Based on the analysis of 14,681 patients treated with moxifloxacin *vs.* 15,023 patients treated with comparators

Side effects of moxifloxacin (clinical trials database)

Distribution of patients valid for the safety analysis, stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by comparator

Study design and COMP	Treatment route [n]					
	PO [n = 21 298]		IV/PO [n = 6846]		IV only [n = 1860]	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Double-blind studies						
β-lactam	2391	2104	1077	1034	408	390
β-lactam + macrolide	274	155	0	0	0	0
Fluoroquinolone	2246	2287[a]	444	457[b]	0	0
Macrolide	3659	2929	0	0	0	0
Other	1230	1168[c]	368	365[d]	180	181[e]
Total	*8822*[f]	*8643*	*1889*	*1856*	*588*	*571*
Open-label studies						
β-lactam	1318	1301	554	547	0	0
β-lactam + macrolide	186	190	0	0	0	0
β-lactam ± macrolide	0	0	532	549	0	0
Fluoroquinolone	263	270[g]	0	0	349	352[g]
Macrolide	287	281	0	0	0	0
Other	0	0	456	463[h]	0	0
Total	*1791*[f]	*2042*	*1542*	*1559*	*349*	*352*

Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Table III. Summary of safety data for patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by study design. An asterisk (*) indicates differences observed between treatment groups in disfavor of moxifloxacin that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups and for which the number of patients experiencing an event was ≥10 in either group

Study design and event	Treatment route [n (%)]					
Double-blind studies	PO [n = 17 465]		IV/PO [n = 3745]		IV [n = 1159]	
	MXF [n = 8822]	COMP [n = 8643]	MXF [n = 1889]	COMP [n = 1856]	MXF [n = 588]	COMP [n = 571]
Any AE	3782 (42.9)	3711 (42.9)	1202 (63.6)	1138 (61.3)	305 (51.9)*	253 (44.3)
Any ADR	2211 (25.1)	2026 (23.4)	455 (24.1)	439 (23.7)	85 (14.5)	83 (14.5)
SAE	318 (3.6)	316 (3.7)	315 (16.7)	282 (15.2)	74 (12.6)*	54 (9.5)
SADR	47 (0.5)	48 (0.6)	53 (2.8)	46 (2.5)	9 (1.5)	7 (1.2)
Premature discontinuation due to AE	366 (4.1)	337 (3.9)	144 (7.6)	131 (7.1)	16 (2.7)	9 (1.6)
Premature discontinuation due to ADR	261 (3.0)	251 (2.9)	74 (3.9)	63 (3.4)	4 (0.7)	4 (0.7)
AE with fatal outcome	28 (0.3)	36 (0.4)	66 (3.5)	54 (2.9)	21 (3.6)	13 (2.3)
ADR with fatal outcome[a,b,c]	3 (<0.1)	4 (<0.1)	3 (0.2)	3 (0.2)	0 (0.0)	1 (0.2)
Open-label studies	PO [n = 3833]		IV/PO [n = 3101]		IV [n = 701]	
	MXF [n = 1791]	COMP [n = 2042]	MXF [n = 1542]	COMP [n = 1559]	MXF [n = 349]	COMP [n = 352]
Any AE	764 (42.7)*	766 (37.5)	891 (57.8)	899 (57.7)	86 (24.6)	84 (23.9)
Any ADR	330 (18.4)*	325 (15.9)	348 (22.6)	315 (20.2)	49 (14.0)	50 (14.2)
SAE	104 (5.8)	96 (4.7)	280 (18.2)	245 (15.7)	0 (0.0)	1 (0.3)
SADR	12 (0.7)*	5 (0.2)	42 (2.7)*	19 (1.2)	0 (0.0)	0 (0.0)
Premature discontinuation due to AE	70 (3.9)	67 (3.3)	137 (8.9)	109 (7.0)	21 (6.0)*	11 (3.1)
Premature discontinuation due to ADR	51 (2.8)	49 (2.4)	66 (4.3)	54 (3.5)	17 (4.9)	9 (2.6)
AE with fatal outcome	10 (0.6)	15 (0.7)	64 (4.2)	80 (5.1)	0 (0.0)	0 (0.0)
ADR with fatal outcome[d]	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	0 (0.0)	0 (0.0)

Side effects of moxifloxacin (clinical trials database)

- **AE, ADR and SADR were mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation).**
- **Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated diarrhoea were similar with moxifloxacin and comparators.**

Study design and event	Treatment route [n (%)]					
Double-blind studies	PO [n = 17 465]		IV/PO [n = 3745]		IV [n = 1159]	
	MXF [n = 8822]	COMP [n = 8643]	MXF [n = 1889]	COMP [n = 1856]	MXF [n = 588]	COMP [n = 571]
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Open-label studies	PO [n = 3833]		IV/PO [n = 3101]		IV [n = 701]	
	MXF [n = 1791]	COMP [n = 2042]	MXF [n = 1542]	COMP [n = 1559]	MXF [n = 349]	COMP [n = 352]
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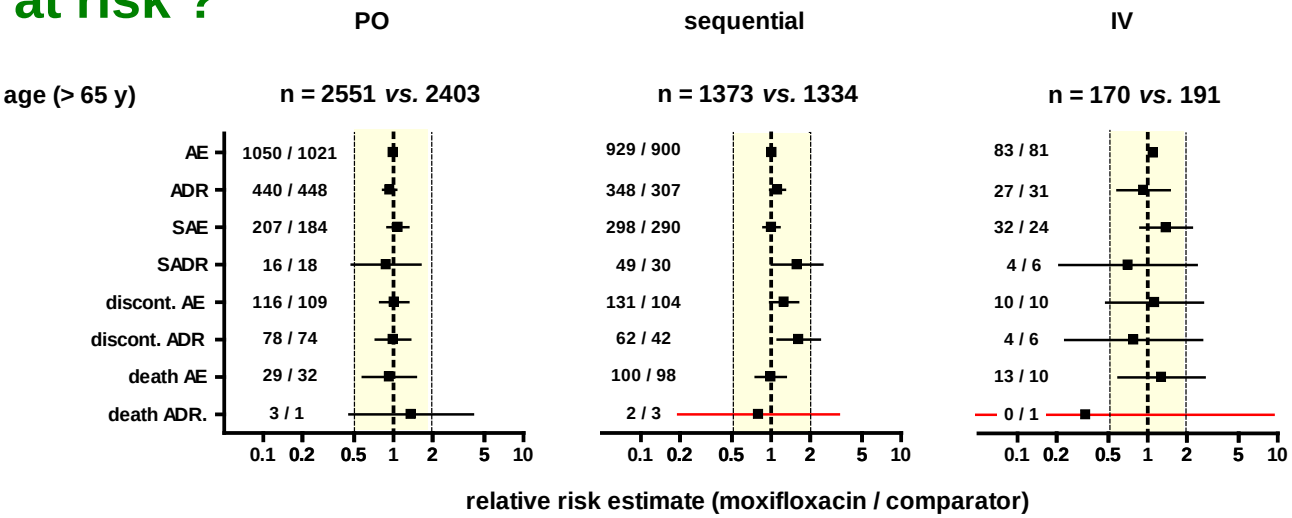
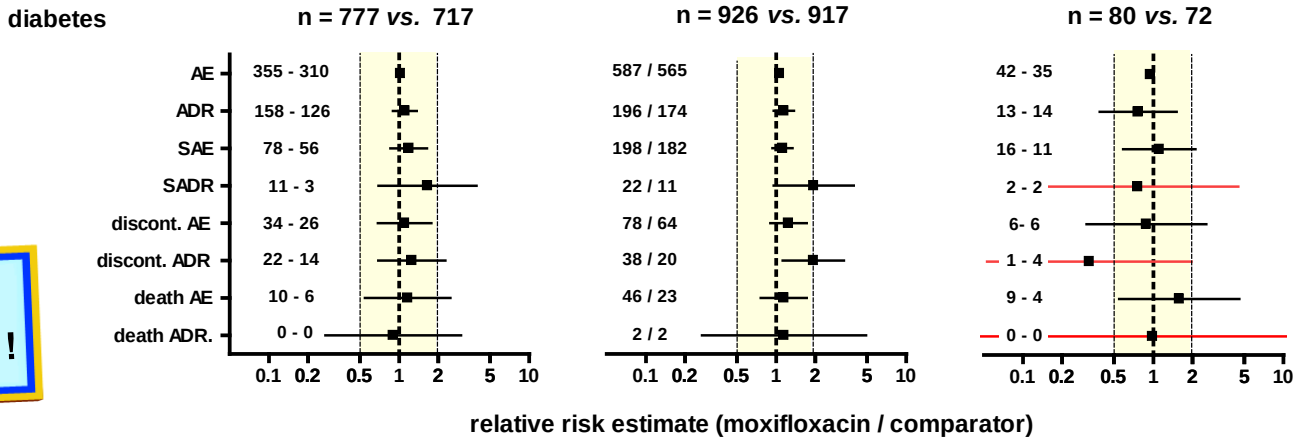
AE with fatal outcome	10 (0.6)	15 (0.7)	64 (4.2)	80 (5.1)	0 (0.0)	0 (0.0)
ADR with fatal outcome[d]	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	0 (0.0)	0 (0.0)

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?

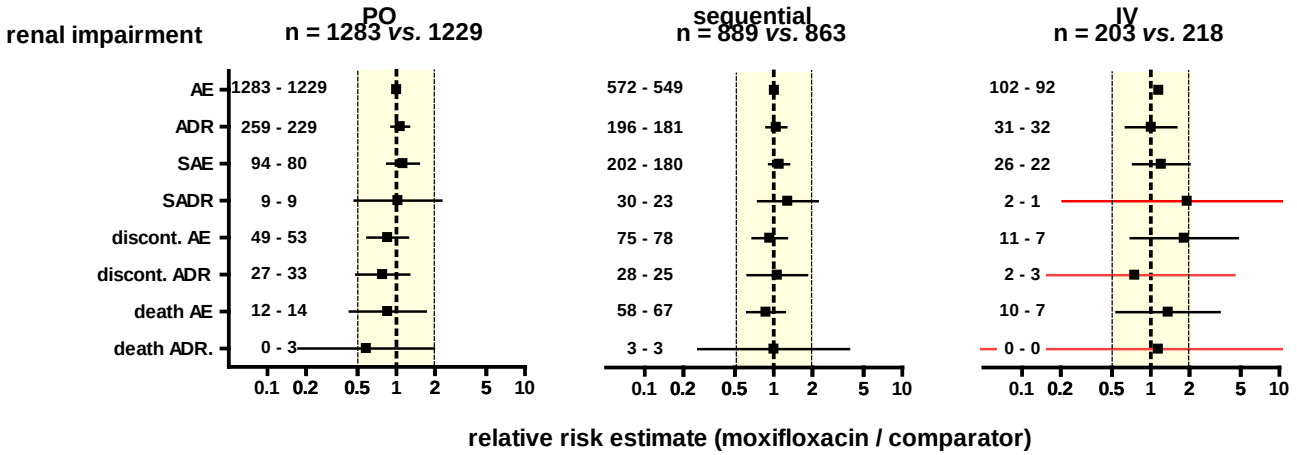


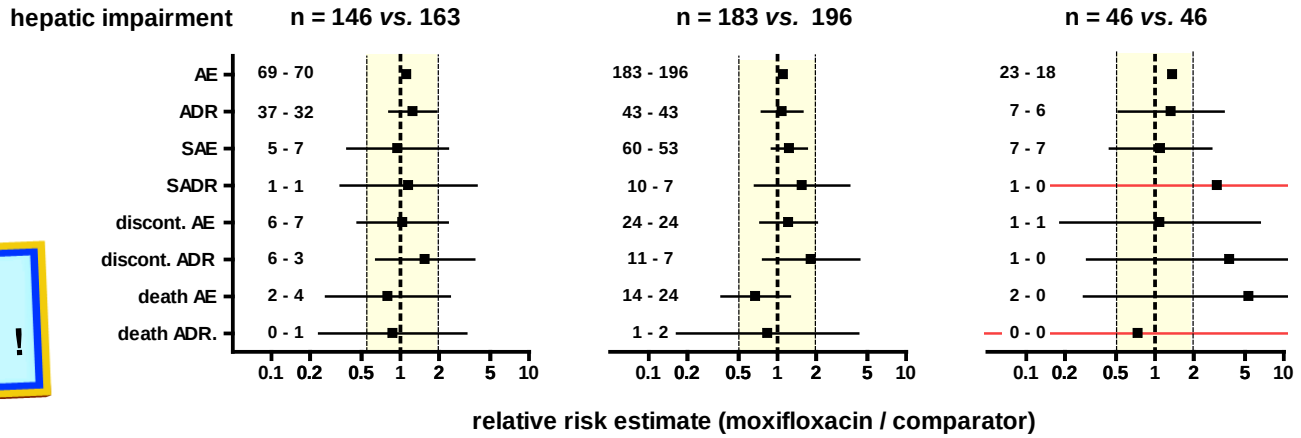


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?

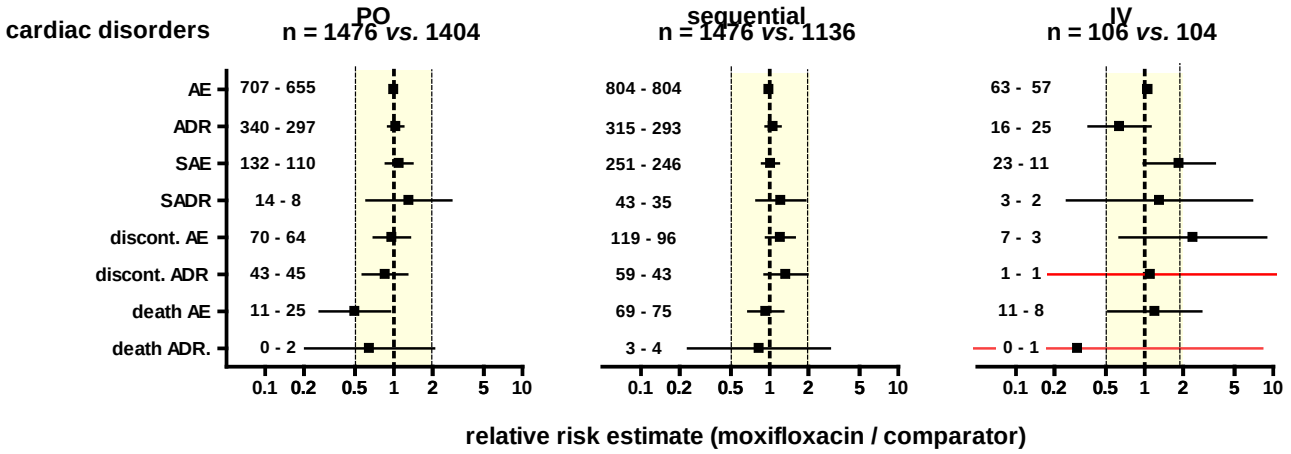


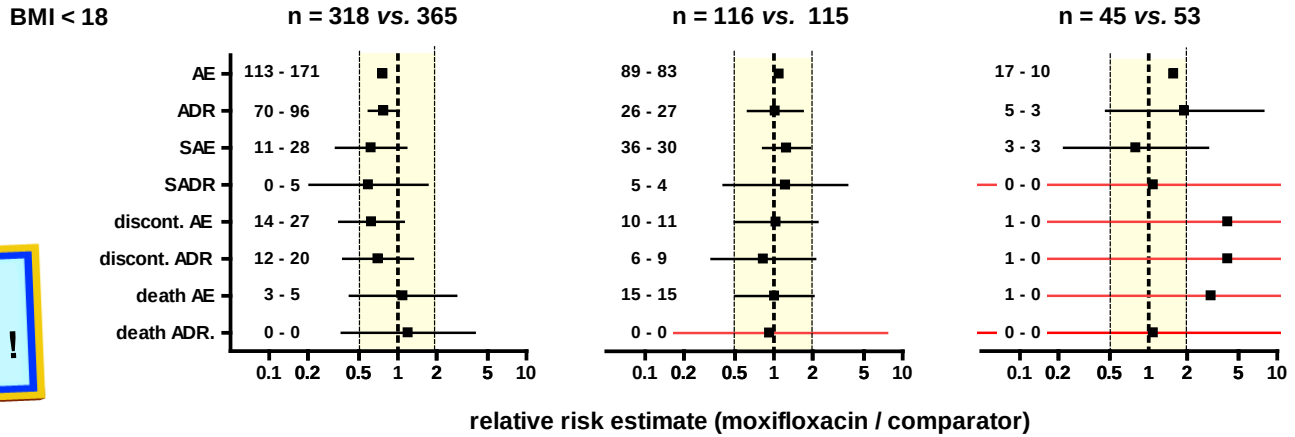


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?





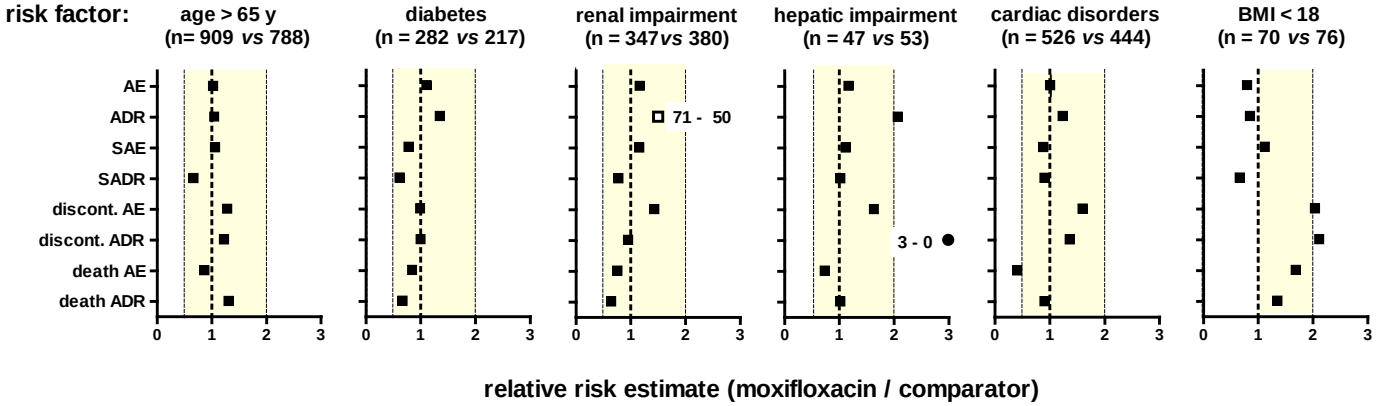
Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

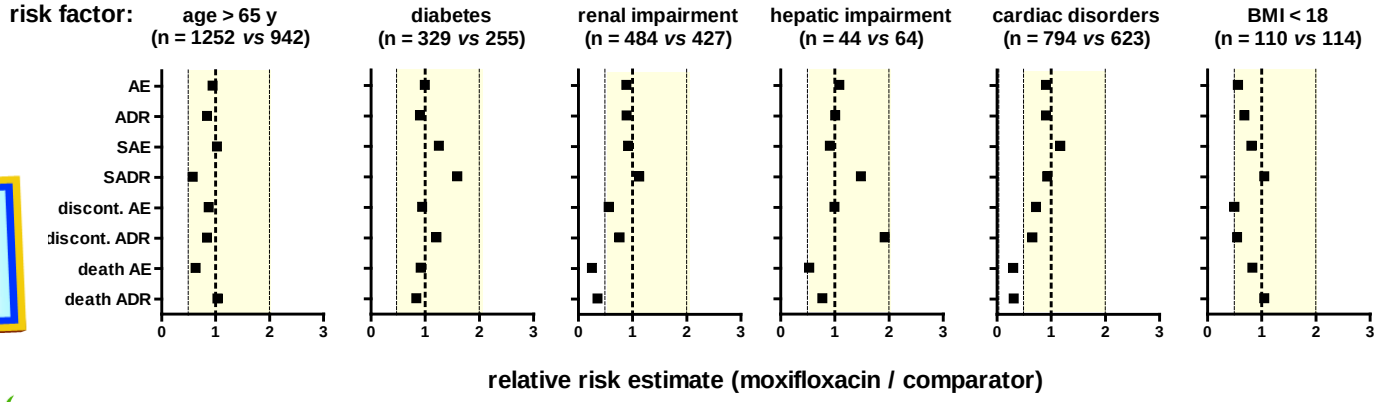
Comparison with other drugs ?

A. oral therapy

1. moxifloxacin *vs* β-lactams



2. moxifloxacin *vs* macrolides



Tulkens et al., Drugs R D (2012) 12: 71-100

Hepatotoxicity

Crude incidence rates of acute liver injury caused by antibiotics

Antibiotic	population	Incidence rate (CI)		endpoint	Ref.
		per 100,000 users	per 100,000 prescriptions		
fluoroquinolones (w/o moxifloxacin)	Outpatient clinic, Sweden (1995-2005)	0.7 (0.5-1.1)		International consensus	[1]
moxifloxacin	Outpatient clinic, Sweden (1995-2005)	0.08 (0.0-0.5)		International consensus	[1]
cotrimoxazole	Saskatchewan Health Plan, Canada (1982-1986)	1.0 (0.2-5.7)	4.9 (0.9-27.6)	International consensus, hospitalisation	[2]
erythromycin	Saskatchewan Health Plan, Canada (1982-1986)	2.0 (0.7-5.9)	14.0 (4.8-41.2)	International consensus, hospitalisation	[2]
amoxicillin-clavulanic acid	General practice research database, United Kingdom (1991-1992)	22.5 (14.7-34.4)	17.4 (11.4-26.5)	International consensus	[3]

1. De Valle et al. Aliment Pharmacol Ther 2006 Oct 15; 24(8): 1187-95
2. Perez et al. Epidemiology 1993 Nov; 4(6): 496-501
3. Garcia-Rodriguez et al. Arch Intern Med 1996 Jun 24; 156(12): 1327-32

Van Bambeke & Tulkens, Drug Safety (2009) 32:359-78

Hepatotoxicity

Hepatotoxicity risk of antibiotics

(percentage of prescriptions for antibiotics with main indications for use in the community setting)

Ciprofloxacin, levofloxacin and moxifloxacin	Tetracycline	Erythromycin, clarithromycin and penicillins	Co-trimoxazole and amoxicillin/ clavulanate	Telithromycin and trovafloxacin
				Acute liver failure, high mortality
Isolated cases and ≤0.00007	≤0.0002	≤0.004	≤0.02	?
				Withdrawal or severe restriction does not allow calculating true incidences

Andrade & Tulkens, JAC (2011) 66: 1431–46

SMQ-search for "severe events“ of moxifloxacin: Hepatic overview by event type/diagnosis (from the German database)

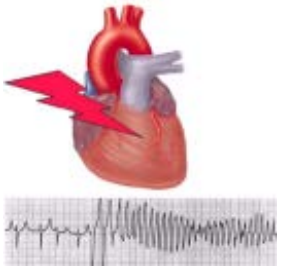
	Moxifloxacin AE [ADR]	Comparator AE [ADR]
Total	**19 [16]**	**17 [7]**
Hepatitis		
CTC grade ≥3 (severe)	3 [2]	1 [0]
CTC grade <3 (non-severe)	4 [4]	5 [3]
Hepatic failure		
CTC grade ≥3 (severe)	1 [0]	0
CTC grade <3 (non-severe)	2 [2]	1 [1]
Liver disorder		
CTC grade ≥3 (severe)	0	3 [1]
CTC grade <3 (non-severe)	9 [8]	5 [2]
Liver neoplasm	0	2 [0]
Outcomes		
Resolved/improved	17	10
Unchanged	1	2
Worsened/death	0	1
Unknown	1	4

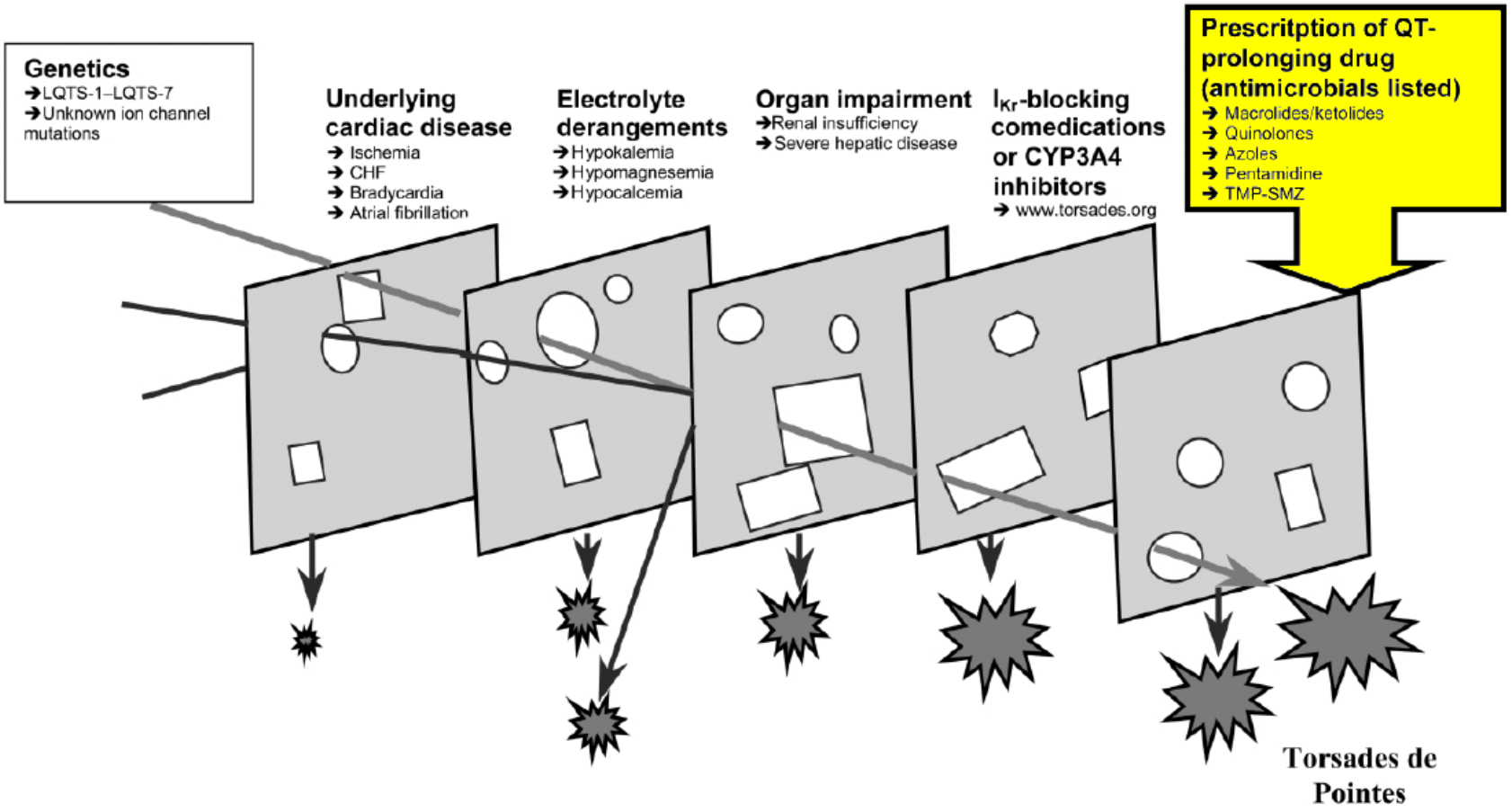
AE: adverse event; ADR: adverse drug reaction

Common Terminology Criteria for Adverse Events v3.0:

- AP, GGT, AST, ALT: Grade 1 (mild), >ULN – 2.5x ULN; Grade 2 (moderate), >2.5 – 5.0x ULN; Grade 3 (severe), >5.0 – 20.0x ULN; Grade 4 (life-threatening), >20.0x ULN
- Total bilirubin: Grade 1 (mild), >ULN – 1.5x ULN; Grade 2 (moderate), >1.5 – 3.0x ULN; Grade 3 (severe), >3.0 – 10.0x ULN; Grade 5 (life-threatening), >10.0x ULN

QTc prolongation





Owens & Ambrose CID (2005) 41:S144-157

EMA position

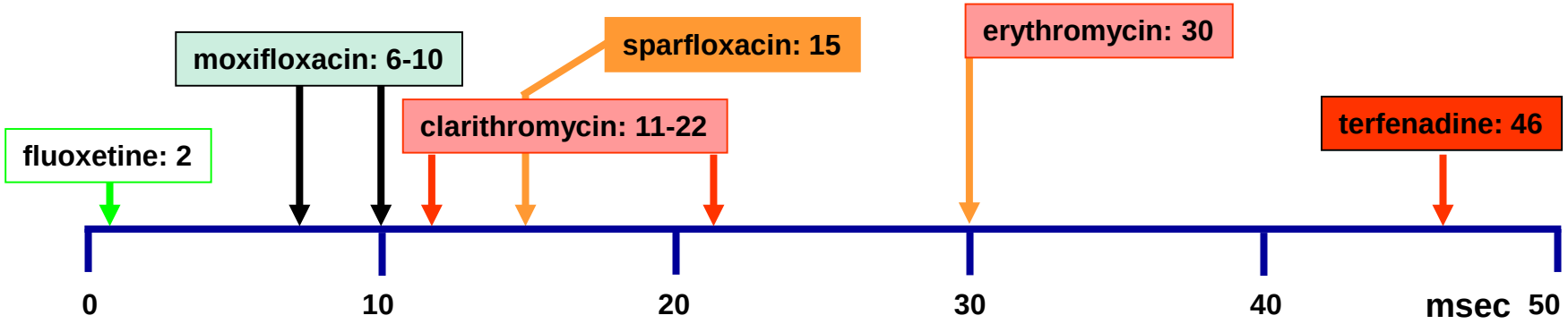
European Medicines Agency

November 2005
CHMP/ICH/2/04

NOTE FOR GUIDANCE ON THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS
(CHMP/ICH/2/04)

… the risk of arrhythmias appears to increase with the extent of QT/QTc prolongation.

- Drugs [with] QT/QTc interval by around 5 ms or less do not appear to cause TdP.
- …data on drugs [with] QT/QTc interval by… 5 to < 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.*



… decisions about [drug] development and approval will depend upon the **morbidity and mortality associated with the untreated disease** or disorder and the **demonstrated clinical benefits of the drug**, especially as they compare with available therapeutic modalities.

* this includes erythromycin and clarithromycin (Balardinelli *et al,* TIPS (2003) 24:619-625)

Is clarithromycin a cardiac-risky “antibiotic” ?

thebmj *BMJ* 2014;349:g4930 doi: 10.1136/bmj.g4930 (Published 19 August 2014)

Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study

Henrik Svanström *statistician*, Björn Pasternak *postdoctoral fellow*, Anders Hviid *senior investigator*
Department of Epidemiology Research, Statens Serum Institut, 2300 Copenhagen S, Denmark

- **Population: Danish adults, 40-74 years of age, who received seven day treatment courses with clarithromycin (n=160 297), roxithromycin (n=588 988), and penicillin V (n=4 355 309).**
- **Main outcome: risk of cardiac death associated with clarithromycin and roxithromycin, compared with penicillin**
- **Observation: A total of 285 cardiac deaths were observed.**
- **Compared with use of penicillin V (incidence rate 2.5 per 1000 person years), use of clarithromycin was associated with a significantly increased risk of cardiac death (5.3 per 1000 person years; adjusted rate ratio 1.76, 95% confidence interval 1.08 to 2.85)**

Moxifloxacin safety: a conclusion…

LEADING ARTICLE

Drug Safety 2009; 32 (5): 359-378
0114-5916/09/0005-0359/$49.95/0

Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin

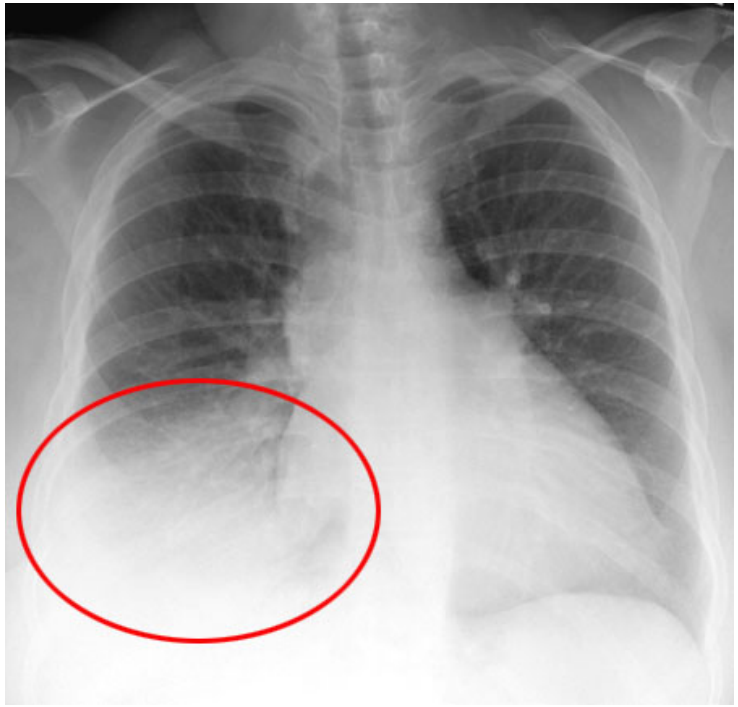
Comparison with Other Fluoroquinolones and Other Antibacterial Classes

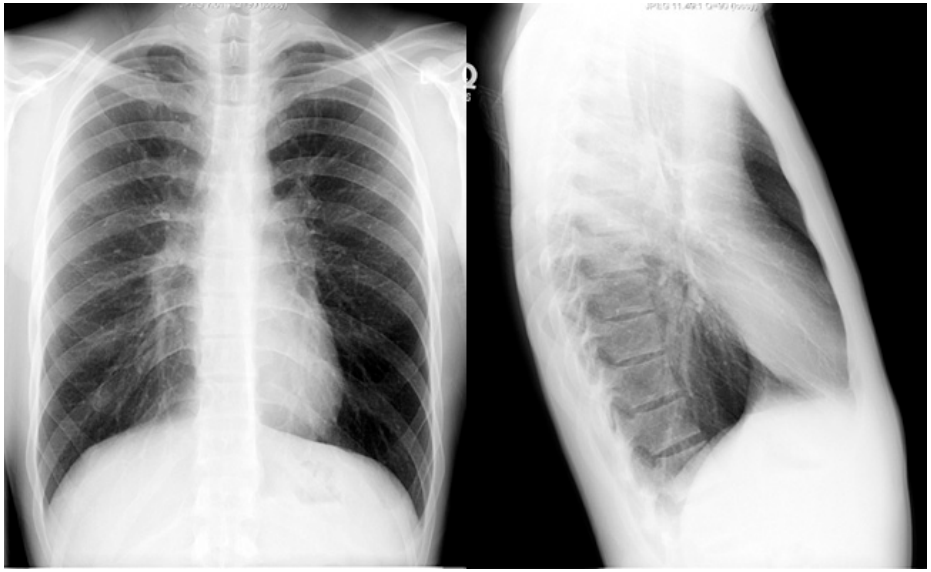
Françoise Van Bambeke and *Paul M. Tulkens*

Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

The data show that using moxifloxacin, in its accepted indications and following the corresponding guidelines, should not be associated with an excessive incidence of drug-related adverse reactions, provided the clinician takes care in identifying patients with known risk factors and pays due attention to the contraindications and warnings mentioned in the labelling.

But do not forget about the need of being efficacious…





Randomized Controlled Phase III trials with moxifloxacin in CAP

	Once daily moxifloxacin 400mg iv or iv/po	Outcome
TARGET (628pts.) [1]	Co-amoxiclav iv (1000/200mg every 6-8 h) /po (500mg/125mg tds) ± clarithromycin iv/po (500 mg) bid	Moxifloxacin had superior efficacy with comparable SAE rate in both groups
Moxirapid (397 pts.) [2]	Ceftriaxone 2g iv od ± erythromycin iv (1g every 6-8 h)	In hospitalized adult pts. with CAP, moxifloxacin was clinically equivalent to comparator but led to a faster clinical improvement.
CAPRIE (401 elderly pts.)[3]	Levofloxacin 500mg iv/po od	Moxifloxacin was efficacious & safe in elderly CAP pts. accross all severity and age groups with > 90% cure rate and associated with a faster clinical recovery than iv/po levofloxacin and a comparable safety profile
MOTIV (733 pts.) [4]	Ceftriaxone 2g iv od + 500 mg levofloxacin iv/po bd	Monotherapy with iv/po moxifloxacin was non-inferior in hospitalized CAP pts. with no difference in treatment emergent adverse effects and mortality

1: Finch et al; Antimicrob. Ag. Chemother. 2002, 46: 1746-54; 2: Welte et al; Clin. Infect. Dis. 2005, 41: 1697-705;
3: Anzueto et al; Clin. Infect. Dis. 2006, 42: 73-81; 4: Torres et al; Clin. Inf. Dis. 2008, 46: 1499-509

Randomized controlled Phase III trials with moxifloxacin in AECOPD

	Comparator vs. Once daily moxifloxacin 400mg po for 5 days	Conclusion
MOSAIC (733 pts.)[1]	Standard therapy for 7 days : Co-amoxiclav 500/125mg tds po or clarithromycin 500mg bid po or Cefuroxime-axetil 250mg po bid	5 days Moxifloxacin was equivalent to 7 days standard therapy for clinical success and showed superiority vs. standard therapy in clinical cure, bacteriologic eradication and long term outcomes.
MAESTRAL (1056 pts.)[2]	For 7 days: Co-amoxiclav 875/125 mg bid po	• In all pts., moxifloxacin was non-inferior regarding clinical failure at 8 weeks post therapy. • Bacterial erradication in pts. with confirmed bacterial infection was higher in the moxifloxacin arm (80.4% vs. 61.1%). • In pts. with confirmed bacterial AECOPD, moxifloxacin led to significantly lower clinical failure rates.
PULSE (1149 pts.)[3]	Placebo [6 courses of moxifloxacin therapy or placebo for 5 days over 48 weeks]	• Chronic intermittent therapy with moxifloxacin reduced the odds of patients with purulent or muco-purulent sputum having an exacerbation by 45%. • No evidence of resistance development.

1: Wilson et al; Chest 2004, 125: 1746-54; 2: Wilson et al; Eur. Resp. J. 2012, 42: 73-81; 3: Sethi et al. ; Resp. Res. 2010, 11/10

Summary and overall conclusions

- CAP and COPD represent a major burden in Infectious Diseases with a high level of short and long-term mortality (e.g., CAP in elderly) and unmanageable progression of disease (COPD)
- Antibiotic recommendations must be assessed based upon careful analysis of
  - current resistance rates
    (not ignoring the increasing rates for some of the antibiotics still currently recommended !)
  - PK/PD properties
    (considering both efficacy AND prevention of emergence of resistance)
- Safety issues should not be ignored but should also be viewed at real face value with respect to both severity, actual incidences of the adverse events, and balance with the life-saving properties of the drugs

Back-up

A more recent study with children in Palestine…

OPEN ACCESS Freely available online

PLOS ONE

Streptococcus pneumoniae from Palestinian Nasopharyngeal Carriers: Serotype Distribution and Antimicrobial Resistance

Abedelmajeed Nasereddin[1*], Issa Shtayeh[2], Asad Ramlawi[2*], Nisreen Salman[2], Ibrahim Salem[2], Ziad Abdeen[1]

1 Al-Quds Nutrition and Health Research Institute, Faculty of Medicine, Al-Quds University, Abu-Deis, The West Bank, Palestine, 2 Central Public Health Laboratory, Palestinian Ministry of Health, Ramallah, Palestine

Nasereddin et al. PLoS One. 2013 Dec 10;8(12):e82047

- carrier rates, serotype distribution and antimicrobial resistance patterns of *S. pneumoniae* in healthy Palestinian children (n=397) from November 2012 to the end of January 2013.
- carrier rate: 55.7% (221/397).
- Resistance to > 2 drugs: in 34.1% of the children (72/211) (all isolates sensitive to cefotaxime and vancomycin).

N=211			
antibiotic	**S**	**I**	**R**
penicillin	70	118	**23**
erythromycin	101	46	**64**
tetracycline	186	42	13
TMP/SMX (SMT)	98	16	**93**

And still another (2008-2010) from Turkey…

Kısa Bildiri/Short Communication | Mikrobiyol Bul 2013; 47(4): 684-692

Kronik Akciğer Hastalığı Olan, Akut Alevlenme ve Pnömoni Tanısı ile Başvuran Çocuklarda *Streptococcus pneumoniae* Serotip Dağılımı ve Antimikrobiyal Duyarlılıkları*

Serotype Distrubution and Antibiotic Susceptibilities of *Streptococcus pneumoniae* Causing Acute Exacerbations and Pneumonia in Children with Chronic Respiratory Diseases

Gülşen ALTINKANAT GELMEZ[1], Ahmet SOYSAL[2], Canan KUZDAN[2], Bülent KARADAĞ[3], Ufuk HASDEMİR[1], Mustafa BAKIR[2], Güner SÖYLETİR[1]

[1] Marmara Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, İstanbul.
[1] *Marmara University Faculty of Medicine, Department of Medical Microbiology, Istanbul, Turkey.*

[2] Marmara Üniversitesi Tıp Fakültesi, Çocuk Enfeksiyon Hastalıkları Bilim Dalı, İstanbul.
[2] *Marmara University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Istanbul, Turkey.*

[3] Marmara Üniversitesi Tıp Fakültesi, Çocuk Göğüs Hastalıkları Bilim Dalı, İstanbul.
[3] *Marmara University Faculty of Medicine, Department of Pediatrics, Division of Pediatrics Pulmonology, Istanbul, Turkey.*

And still another (2008-2010) from Turkey…

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- children with chronic respiratory diseases and a diagnosis of acute exacerbations (between 2008-2010)
- 61 isolates examined for antibiotic susceptibility and serotype

Akut Alevlenme ve
an Çocuklarda
rotip Dağılımı ve
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- 61 isc susce

Akut Alevlenme ve

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[3] Marmara
[3] *Marmara*

Tablo II. S.pneumoniae Kökenlerinin Antibiyotik Duyarlılık Sonuçları (n= 61)

Antibiyotikler	Duyarlı (%)	Orta dirençli (%)	Dirençli (%)
Penisilin, oral	23 (37.8)	33 (54)	5 (8.2)
Penisilin, parenteral*	60 (98.4)	1 (1.6)	0
Seftriakson	57 (93.4)	4 (6.6)	0
Eritromisin	27 (44.2)	2 (3.3)	32 (52.5)
Klindamisin	33 (54)	0	28 (46)
Tetrasiklin	35 (52.5)	0	26 (47.5)
Vankomisin	61 (100)	0	0
Levofloksasin	61 (100)	0	0
Trimetoprim-sülfametoksazol	19 (31.2)	1 (1.6)	41 (67.2)

*CLSI'nın menenjit dışı izolatlar için önerdiği kriterlere göre değerlendirilmiştir.

And in Lebanon (2005-2011)…

Vaccine 30S (2012) G11–G17

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Review

Epidemiologic characteristics, serotypes, and antimicrobial susceptibilities of invasive *Streptococcus pneumoniae* isolates in a nationwide surveillance study in Lebanon

Rima Hanna-Wakim[a,b,1], Hiba Chehab[a,b,1], Imane Mahfouz[a,b,1], Farah Nassar[c], Maysa Baroud[b], Marwa Shehab[b], Guillermo Pimentel[d], Momtaz Wasfy[d], Brent House[d], George Araj[b,e], Ghassan Matar[b,c,1], Ghassan Dbaibo[a,b,*,1], For the Lebanese Inter-Hospital Pneumococcal Surveillance Program[2]

[a] Department of Pediatrics and Adolescent Medicine, American University of Beirut, Beirut, Lebanon
[b] The Center for Infectious Diseases Research, American University of Beirut, Beirut, Lebanon
[c] Department of Experimental Pathology, Immunology and Microbiology, American University of Beirut, Beirut, Lebanon
[d] The United States Naval Medical Research Unit 3, Cairo, Egypt
[e] Department of Pathology and Laboratory Medicine, American University of Beirut, Lebanon

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[b] The Center for Inf
[c] Department of Ex
[d] The United States
[e] Department of Pa

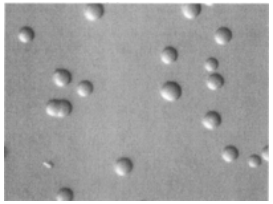
R. Hanna-Wakim et al. / Vaccine 30S (2012) G11–G17

Table 1

Antimicrobial non-susceptibility by age group: percentage (count). CLSI 2009 break-points were used.

Age group	Penicillin Non-susceptibility	Ceftriaxone Non-susceptibility	Erythromycin Resistance
<2 years	29.1% (16)	18.3% (11)	40.7% (24)
2–5 years	13.2% (5)	12.8% (5)	30.8% (12)
6–20 years	3.4% (1)	3.4% (1)	24.1% (7)
21–60 years	23.7% (9)	12.8% (5)	21.1% (8)
>60 years	13.4% (11)	13.1% (11)	26.2% (22)

Mycoplasma pneumoniae



Waites & Talkington, Clin. Microbiol. Rev. 2004;17:697-728

- But resistance may spread via Europe

OPEN ACCESS Freely available online

PLoS one

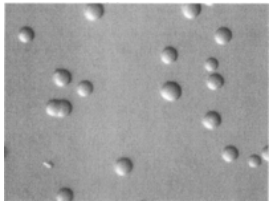
The Spread of *Mycoplasma pneumoniae* Is Polyclonal in Both an Endemic Setting in France and in an Epidemic Setting in Israel

Sabine Pereyre[1,2,3]*, Alain Charron[1,2], Carlos Hidalgo-Grass[4], Arabella Touati[1,2], Allon E. Moses[4], Ran Nir-Paz[4], Cécile Bébéar[1,2,3]

1 Université Bordeaux, USC Infections Humaines à Mycoplasmes et Chlamydiae, Bordeaux, France, 2 INRA, USC Infections Humaines à Mycoplasmes et Chlamydiae, Bordeaux, France, 3 Centre Hospitalier Universitaire de Bordeaux, Laboratoire de Bactériologie, Bordeaux, France, 4 Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Pereyre et al. PLoS One. 2012;7(6):e38585.

Mycoplasma pneumoniae



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1 Universite
Bordeaux,
Jerusalem,

Pereyr

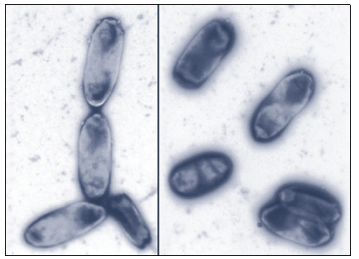
In France, between October 1st 2007 and September 30th 2010, 35 patients were positive for M. pneumoniae using a specific real-time PCR on their respiratory tract specimens.

→ Only one specimen (3.4%) harboured a macrolide-resistant A2059G genotype (*E. coli* numbering, corresponding to A2064G using *M. pneumoniae* numbering)

In Israël, a surge of M. pneumonia- associated respiratory tract infections was observed in 2010 with 55 cases in only this year !

→ A macrolide resistance-associated mutation A2058G (E. coli numbering, corresponding to A2063G using *M. pneumonia* numbering) was found in 9 patients (**22%**).

Haemophilus: is it important for the Middle East ?



://www.pathologyoutlines.c
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tml

Jpn. J. Infect. Dis., 64, 66-68, 2011

Short Communication

Biotyping, Capsular Typing, and Antibiotic Resistance Pattern of *Haemophilus influenzae* Strains in Iran

Naheed Mojgani*, Mohammad Rahbar[1], Morteza Taqizadeh,
Mehdi Perveen Ashtiani, and Mona Mohammadzadeh[1]

Biotechnology Department, Razi Vaccine and Serum Research Institute, Karadj; and
[1]Pathology Department, Microbiology Unit, Milad National Hospital, Tehran, Iran

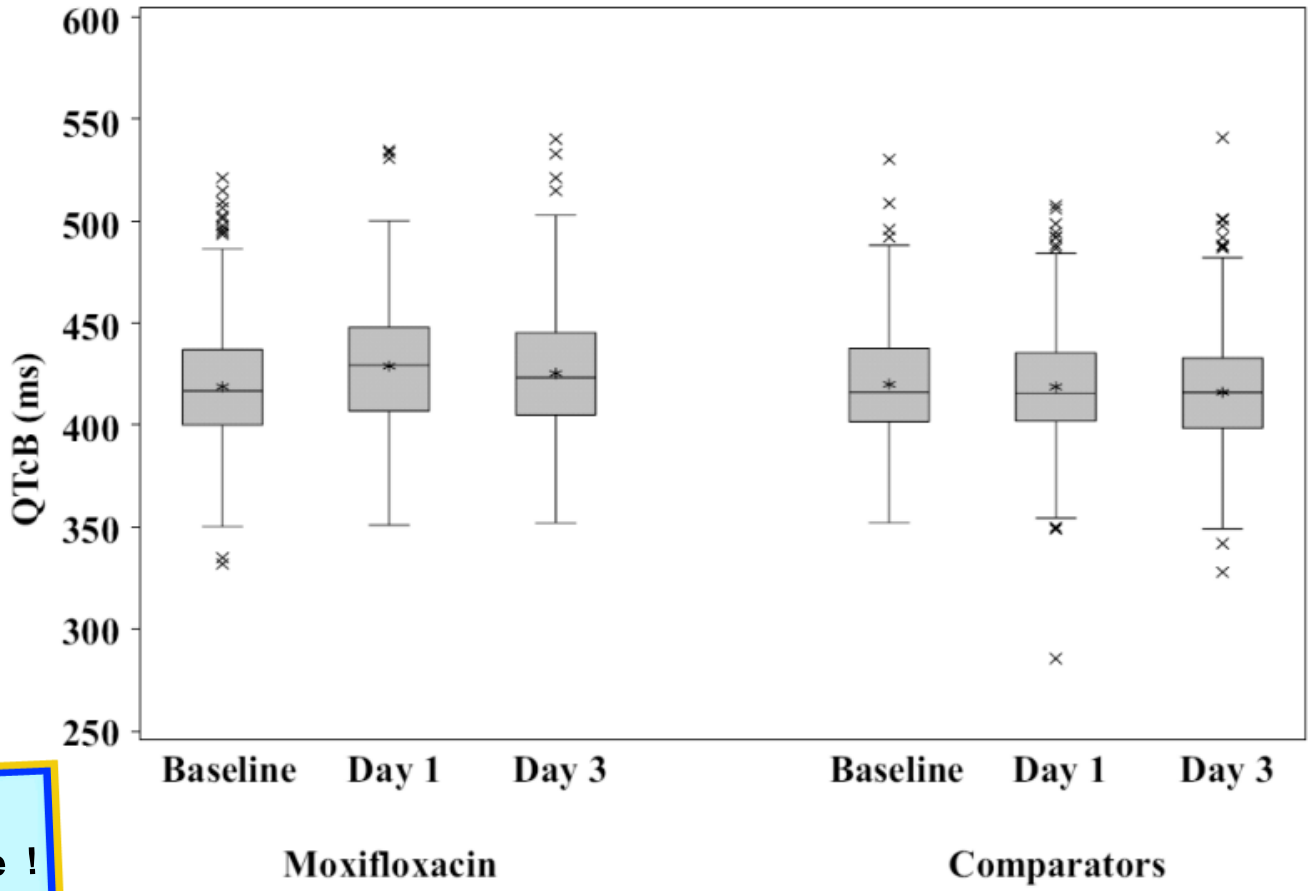
(Received August 11, 2010. Accepted November 29, 2010)

- **38 isolates from from CSF from children with meningitis, blood from patients with sepsis, eye mucus from patients with conjunctivitis,**
- **and nasopharyngeal specimens from individuals without meningitis.**

- **High rate of antibiotic resistance to cotrimoxazole (47.1 %), ampicillin (43.6 %), and tetracycline (38.28 %).**

- **Multi resistance (3 or more antibiotics) n 7 (18.4 %) of the isolates.**

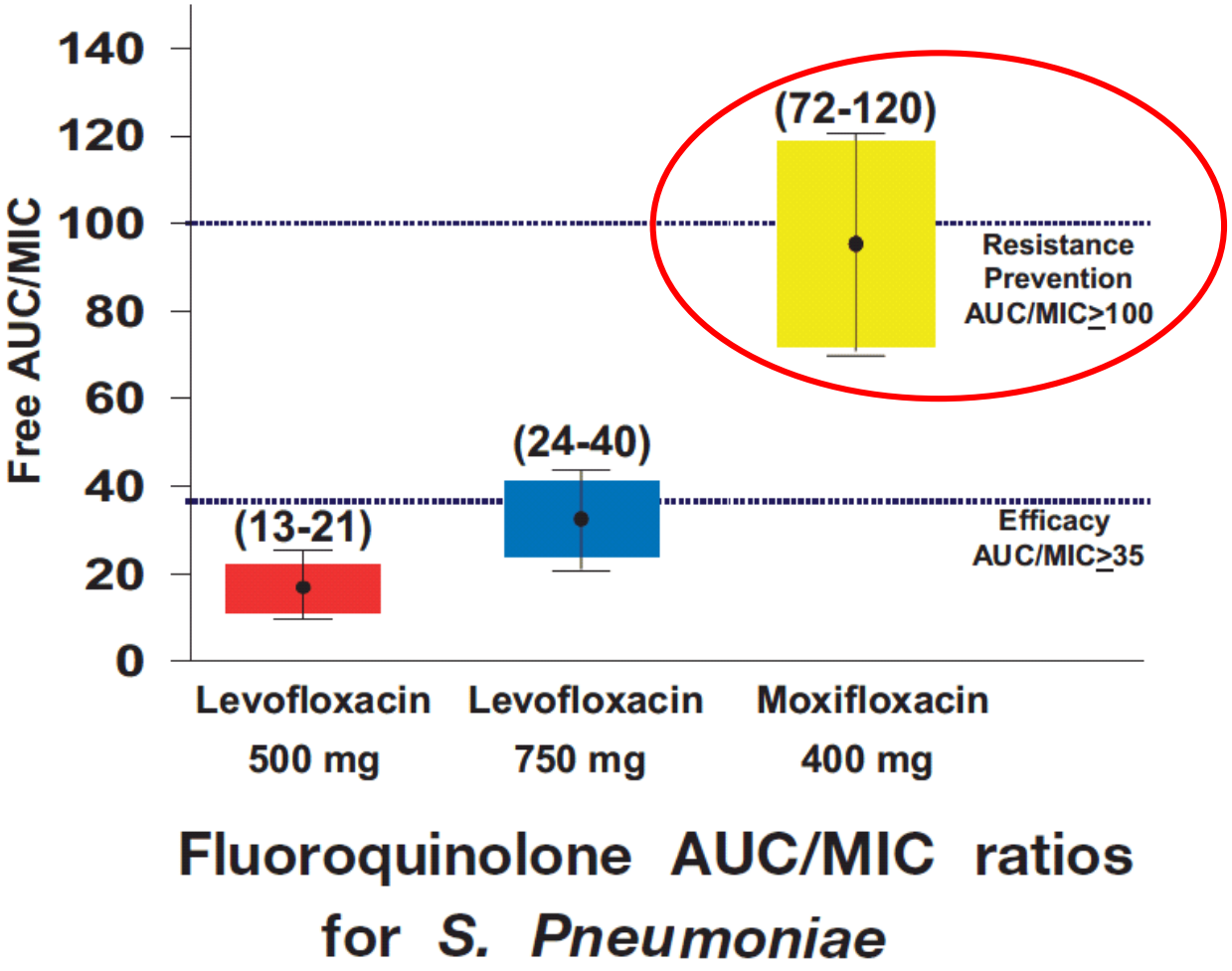
Moxifloxacin cardiac safety: data from phase II-IV trials



Haverkamp et al.,Curr Drug Saf. (2012) 7: 149–63

What differentiates fluoroquinolones ?

Results with *S. pneumoniae*



This is probably why we see so little resistance to moxifloxacin

Torsade de pointe: comparison of risk

reporting rate of *Torsades de pointe* induced by antibiotics

drug	No. of U.S. Cases Reported to the FDA	No. of Estimated Total U.S. Prescriptions (millions)	No. of Cases /10 Millions Prescriptions (95% CI)
moxifloxacin	0	1.4	0 (0-26)
ciprofloxacin	2	66	0.3 (0.0-1.1)
ofloxacin	2	9.5	2.1 (0.3-7.6)
levofloxacin	13	24	5.4 (2.9-9.3)
gatifloxacin	8	3	27 (12-53)
erythromycin	11 –17	151	0.7 -1.1
clarithromycin	16 –31	90	1.8 -3.4
azithromycin	7 –10	124	0.6–1
cefuroxime	1 -1	42	0.2 –1

used as negative control in RCT

FDA warning March 12,2013

Van Bambeke & Tulkens, Drug Safety (2009) 32:359-78