Antibiotic selection in community-acquired pneumonia (CAP): appropriate benefit-risk profiles

Paul M. Tulkens, MD, PhD *

Françoise Van Bambeke, PharmD, PhD

Cellular and Molecular Pharmacology Unit

& Centre for Clinical Pharmacy

Université catholique de Louvain, Brussels, Belgium

co-workers: Ann Lismond, MSc (resistance studies) – S. Carbonnelle, MD, PhD (clinical studies)

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* also

- Professor of Human Biochemistry and Biochemical Pathology
  Université de Mons/Hainaut, Mons, Belgium
- member of the EUCAST (European Committee for Antibiotic Susceptibility Testing) steering committee
- founding member and past-President of the International Society of Anti-infective Pharmacology

Einige Wörter…

- Ich bedauere, diese Darstellung nicht auf deutsch geben zu können...
- Die Deutsche Sprache ist jedoch sowohl sehr schön als auch sehr logisch...
- Und ich bin ein begeisteter Zuhörer von J.S. Bach's Passionnen oder Operns von Wagner ...
- Aber ich musste bereits alle Tage Französisch, Flämisch und Englisch sprechen... und Deutsch ist für einen Französigsprachigen schwierig...
- Ich werde versuchen, die Fragen auf deutsch zu verstehen ...

Die Lokalisierung der *Université catholique de Louvain* in Brüssel

Die Gebäude der medizinischen Fakultät und das Krankenhaus

Die Gruppe der Pharmakologie/Toxikologie der Antibiotika

Contents of the Presentation

- All antimicrobials used for CAP have associated toxicity risks …
  - Major non-serious and serious side-effects associated with the main antimicrobials used in the treatment of CAP (β-lactams, macrolides, tetracyclines, fluoroquinolones).
- Adverse effects of moxifloxacin *vs* other agents
  - a comprehensive analysis
- The risk of bacterial failure
  - are guidelines "safe" ?
- Conclusions

All antimicrobials used for CAP 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 (SmPC or equivalent)

Carbonnelle *et al.*, in preparation

All antimicrobials use for CAP 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 (SmPC or equivalent)

Carbonnelle *et al.*, in preparation

All antimicrobials used for CAP 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 • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Musculoskeletal: tendinopathies** • Peripheral neuropathy • Prolongation of the QTc interval and isolated cases of torsade de pointes • **Digestive tract: nausea, diarrhoea**
	moxifloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Musculoskeletal: Tendinopathies** • Peripheral neuropathy • Prolongation of the QT interval • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Digestive tract: nausea, diarrhoea**

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

Carbonnelle *et al.*, in preparation

All antimicrobials used for CAP have associated risks *

Class	Drugs	Frequent or serious side effects
tetracyclines	doxycycline	• **Anaphylactic reactions and allergic skin reactions** • *Clostridium difficile*-associated colitis • Digestive tract: anorexia, glossitis, dysphagia, nausea, vomiting, diarrhoea • **esophagitis and esophageal ulcerations** • Blood cells: hemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia • Hepatotoxicity • **Photosensitivity**

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

Conclusions (# 1):

- 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

Carbonnelle *et al.*, in preparation

A note about *C. difficile* *

in 1993-1994 …

Frequent Induction	Infrequent Induction	Rare or No Induction
Ampicillin and amoxicillin	Tetracyclines	Parenteral aminoglycosides
Cephalosporins	Sulfonamides	Bacitracin
Clindamycin	Erythromycin	Metronidazole
	Chloramphenicol	Vancomycin
	Trimethoprim	
	Quinolones	

- Kelly CP, LaMont JT. Treatment of Clostridium difficile diarrhea and colitis. In: Wolfe MW, ed. Gastrointestinal pharmacotherapy. Philadelphia: W.B. Saunders, 1993:199-212
- Kelly CP, Pothoulakis C, LaMont JT *Clostridium difficile* Colitis. N Engl J Med 1994;330:257-262

C. difficile risk factors in hospitalized patients *

from an 2001 study in Israel (date of sample collection) **…**

Toxin-positive patients (90/585) were

- older ($P < 0.0001$),
- from nursing homes ($P < 0.05$),
- had higher leukocyte counts ($P < 0.001$), higher BUN ($P < 0.01$), lower serum albumin ($P < 0.01$)
- more often received diuretics ($P < 0.01$) and clindamycin ($P < 0.05$);

Significant risk factors were

- antibiotic-associated diarrhoea ($P < 0.001$)
- clindamycin treatment ($P < 0.005$);
- patients also received macrolides ($P < 0.05$).

* data from in-patients from whom stool was sent to detect *C. difficile* toxin during the year 2001 (n=535)

Raveh D, Rabinowitz B, Breuer GS, Rudensky B, Yinnon AM. Risk factors for Clostridium difficile toxin-positive nosocomial diarrhoea. Int J Antimicrob Agents. 2006 Sep;28(3):231-7.

Are out-patients receiving anti-anaerobe fluoroquinolones more at risk ? *

from samples collected in 2002-2005 …

TABLE 2. Fluoroquinolone use and hospitalization for *C. difficile*-associated disease

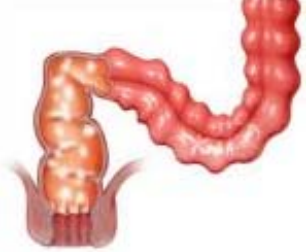
Antibiotic	No. (%) with antibiotic use within 30 days		Odds ratio (95% CI)	
	Cases (n = 96)	Controls (n = 941)	Unadjusted	Adjusted[a]
Levofloxacin	28 (29)	266 (28)	1.00 (reference)	1.00 (reference)
Ciprofloxacin	44 (46)	286 (52)	0.85 (0.52–1.41)	1.00 (0.59–1.70)
Gatifloxacin or moxifloxacin	24 (25)	189 (20)	1.23 (0.69–2.19)	1.37 (0.75–2.49)
Gatifloxacin	8 (8.3)	57 (6.1)	1.33 (0.58–3.05)	1.46 (0.62–3.44)
Moxifloxacin	16 (16.7)	132 (14.0)	1.18 (0.61–2.27)	1.32 (0.67–2.61)

[a] Multivariate adjustment includes terms for number of medications dispensed in the previous year; diabetes; end-stage renal disease; treatment with immunosuppressive medications, oral corticosteroid therapy, antineoplastic medications, proton-pump inhibitor, and H_2-receptor antagonists; residence in a nursing home; malignancy-related hospitalizations; and neighborhood socioeconomic status.

* Data based on a 3 year observation (2002-2005) of outpatients prescribed fluoroquinolones and admitted to hospital with a diagnosis of *Clostridium difficile*-associated disease (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10-CA], code A04.7) within 30 days of the prescription-dispensing date

Dhalla IA, Mamdani MM, Simor AE, et al. Are broad-spectrum fluoroquinolones more likely to cause Clostridium difficile-associated disease? Antimicrob Agents Chemother (2006) 50:3216–9

C. difficile and fluoroquinolones … *



Main conclusion:

- The majority of studies found an association with of *C. difficile* associated diarrhoea and various antibiotics, …. but most limited in their ability to establish a causal relationship
- So far, association is mainly with clindamycin, cephalosporins, penicillins …
- Yet, the participation of fluoroquinolone-resistant strains in hospital-acquired infections cannot be ignored (epidemic situation)
- Outside epidemic situations, antimicrobials and the risks for *C. difficile* associated diarrhoea remain very topical
- The role of infection control initiatives cannot be overstated.

- Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. J Antimicrob Chemother (2003) 51:1339–50
- Blondeau JM. What have we learned about antimicrobial use and the risks for Clostridium difficile-associated diarrhoea? J Antimicrob Chemother. 2009 Feb;63(2):238-42

Adverse effects of moxifloxacin *vs* other agents

- Overall
- Hepatic
- QTc and cardiac toxicity
- Tendonitis
- Phototoxicity

Side effects (non-serious) from clinical trials: moxi *vs.* comparators (oral)

event	Moxifloxacin: n (%)			comparators: n (%)		
	< 65 y (n=4939)	65-74 y (n=842)	> 74 y (n=489)	< 65 y (n=4732)	65-74 y (n=479)	> 74 y (n=435)
Tx effect	2161 (43.8)	382 (45.4)	221 (45.2)	2056 (43.4)	351 (44.2)	194 (44.6)
Drug effect	1344 (27.2)	183 (21.7)	111 (22.7)	1154 (24.4)	169 (21.3)	93 (21.4)
Nausea	381 (7.7)	40 (4.8)	19 (3.9)	260 (5.5)	35 (4.4)	11 (2.5)
Diarrhea	274 (5.5)	39 (4.6)	29 (5.5)	236 (5.0)	28 (3.5)	21 (4.8)
Vomiting	89 (1.8)	5 (0.6)	6 (1.2)	80 (1.7)	8 (1.0)	3 (0.7)
Dyspepsia	72 (1.5)	8 (1.0)	1 (0.2)	59 (1.2)	8 (1.0)	3 (0.7)
Liver test	58 (1.2)	11 (1.3)	3 (0.6)	55 (1.2)	6 (0.8)	9 (1.2)
Flatulence	37 (0.7)	2 (0.2)	1 (0.2)	25 (0.5)	4 (0.5)	6 (1.4)
GGTP ↑	8 (0.2)	0	0	11 (0.2)	1 (0.1)	5 (1.1)
Headache	91 (1.8)	12 (1.4)	4 (0.8)	101 (2.1)	12 (1.5)	4 (0.9)
Abdo. Pain	106 (2.1)	10 (1.2)	8 (1.6)	81 (1.7)	13 (1.6)	4 (0.9)
Asthenia	48 (1.0)	7 (0.8)	4 (0.8)	43 (0.9)	3 (0.4)	4 (0.9)
Dizziness	123 (2.5)	30 (3.6)	12 (2.5)	116 (2.5)	9 (1.1)	5 (1.1)
Insomnia	23 (0.5)	0	5 (1.0)	32 (0.7)	2 (0.3)	3 (0.7)
Rash	44 (0.9)	3 (0.4)	6 (1.2)	33 (0.7)	7 (0.9)	1 (0.2)
Taste perv.	45 (0.9)	7 (0.8)	5 (1.0)	67 (1.4)	18 (2.3)	9 (2.1)

Comparators: amoxi/clav, cefuroxime, cefexime, clarithro, azithro, trova, levo, sulfamethoxazole

Andriole et al. (2005) Drug Safety 28:443-53

Serious side effects from clinical trials: moxi *vs* comparators (oral)

event	moxifloxacin: n (%)			comparators: n (%)		
	< 65 y (n=4939)	65-74 y (n=842)	> 74 y (n=489)	< 65 y (n=4732)	65-74 y (n=479)	> 74 y (n=435)
Any system	24 (0.5)	5 (0.6)	5 (1.0)	26 (0.5)	5 (0.6)	4 (0.9)
Body as a whole	11 (0.2)	1 (0.1)	0	9 (0.2)	1 (0.1)	0
CV	3 (< 0.1)	1 (0.1)	1 (0.2)	3 (< 0.1)	1 (0.1)	1 (0.2)
Dig.	4 (< 0.1)	0	1 (0.2)	5 (0.1)	2 (0.3)	1 (0.2)
Endo	1 (< 0.1)	0	0	0	0	0
Haemic	2 (< 0.1)	1 (0.1)	0	1 (< 0.1)	0	0
Metabolic	0	0	0	2 (< 0.1)	1 (0.1)	0
Nervous	1 (< 0.1)	0	0	2 (< 0.1)	0	1 (0.2)
Respir.	4 (< 0.1)	2 (0.2)	3 (0.6)	5 (< 0.1)	1 (0.1)	0
Skin	3 (< 0.1)	0	0	1 (< 0.1)	1 (0.1)	0
Senses	1 (< 0.1)	0	0	0	0	0
Urogenital	1 (< 0.1)	1 (0.1)	0	3 (< 0.1)	0	1 (0.2)

Comparators: amoxi/clav, cefuroxime, cefexime, clarithro, azithro, trova, levo, sulfamethoxazole

Andriole et al. (2005) Drug Safety 28:443-53

Hepatic toxicity of antibiotics

- Usually idiosyncratic (can be associated with other allergic reactions). [1]
- Clavulanic acid: genetic deficiency in glutathione S-transferases ? [2] (longer latency period than other antibiotics…)
- Macrolides: related to reactive metabolites (nitrosoalkanes) that covalently bind to proteins, forming modified antigens (immunoallergic hepatitis) [3]
- Tetracyclines: related to inhibition of mitochondrial β-oxidation of fatty acids [4]
- Fluoroquinolones: remains anecdotal and unpredictable,[1] except for for molecules with substituent-generating reactive intermediates
  - difluoroaniline (temafloxacin and trovafloxacin) [5]
  - cyclopropylamine (trovafloxacin; for which co-exposure to lipopolysaccharide may also be critical) [6]

1. Robles M, Andrade RJ. Rev Esp Quimioter. 2008 Dec;21(4):224-33
2. Lucena et al., Hepatology. 2008 Aug;48(2):588-96.
3. Pessayre et al. J Antimicrob Chemother 1985 Jul; 16 Suppl A: 181-94
4. Freneaux et al. Hepatology 1988 Sep; 8(5): 1056-62
5. Blum et al. Clin Infect Dis 1994 Jun; 18(6): 946-50; Chen et al. N Engl J Med 2000 Feb 3; 342(5): 359-60; Lucena et al. Clin Infect Dis 2000 Feb; 30(2): 400-1
6. Sun et al. Chem Res Toxicol 2008 Mar; 21(3): 711-9
7. Shaw et al. Toxicol Sci. 2009 Jan;107(1):270-80

Crude incidence rates of acute liver injury caused by antibiotics *

Antibiotic	population	Incidence rate (CI)		endpoint	reference
		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]

* see Van Bambeke & Tulkens, Drug Safety (in press) for full Table and details

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

FDA reporting rate per 10,000,000 prescriptions (spontaneous reports)

Antibiotic class	Acute liver failure [a]
Moxifloxacin	6.6
Levofloxacin	2.1
Trovafloxacin	58
Telithromycin	23

[a] Empiric Bayes Geometric Mean (EBGM) study
www.fda.gov/ohrms/dockets/AC/06/slides/2006-4266s1-01-07-FDA-Brinker.ppt
presented December 2006 to FDA Advisory Committee

Liver failure was defined as "acute or severe liver injury with encephalopathy, liver transplant following acute illness, death in the setting of acute liver injury (hospital. with transaminase elevation, or hyperbilirubinaemia, or clinical jaundice)"

Moxifloxacin hepatotoxicity
(in an nutshell)

- There is no evidence from currently available data that reactions are more frequent than with comparators
  - Clinical trials:
    - Apparent imbalance in drug-related “severe events” detected in the EU Periodic Safety Report was based on clinically non-severe, non-serious events (the number of serious, or clinically severe ADRs is too small for meaningful conclusions)
  - Spontaneous and registry data:
    - all data show a lower incidence for fluoroquinolones *vs* macrolides and amoxicillin/clavulanic acid
    - No signal in EBGM analysis conducted by FDA in 2006

QTc interval: observations and clinical impact

Moxifloxacin is known to cause modest QTc prolongation

➔ 6 – 7 msec in healthy volunteers, Phase II/III – po and Phase II/III – iv

But clinical impact of this is minor

Agent	Serious cardiac events * (no. per 10 millions patients treated or as indicated)
Moxifloxacin	4 [a] (in 13 millions)
Ciprofloxacin	8
Ofloxacin	18
Levofloxacin	18
Gatifloxacin	27 (in 3 millions)
Sparfloxacin	> 100
Grepafloxacin	> 150

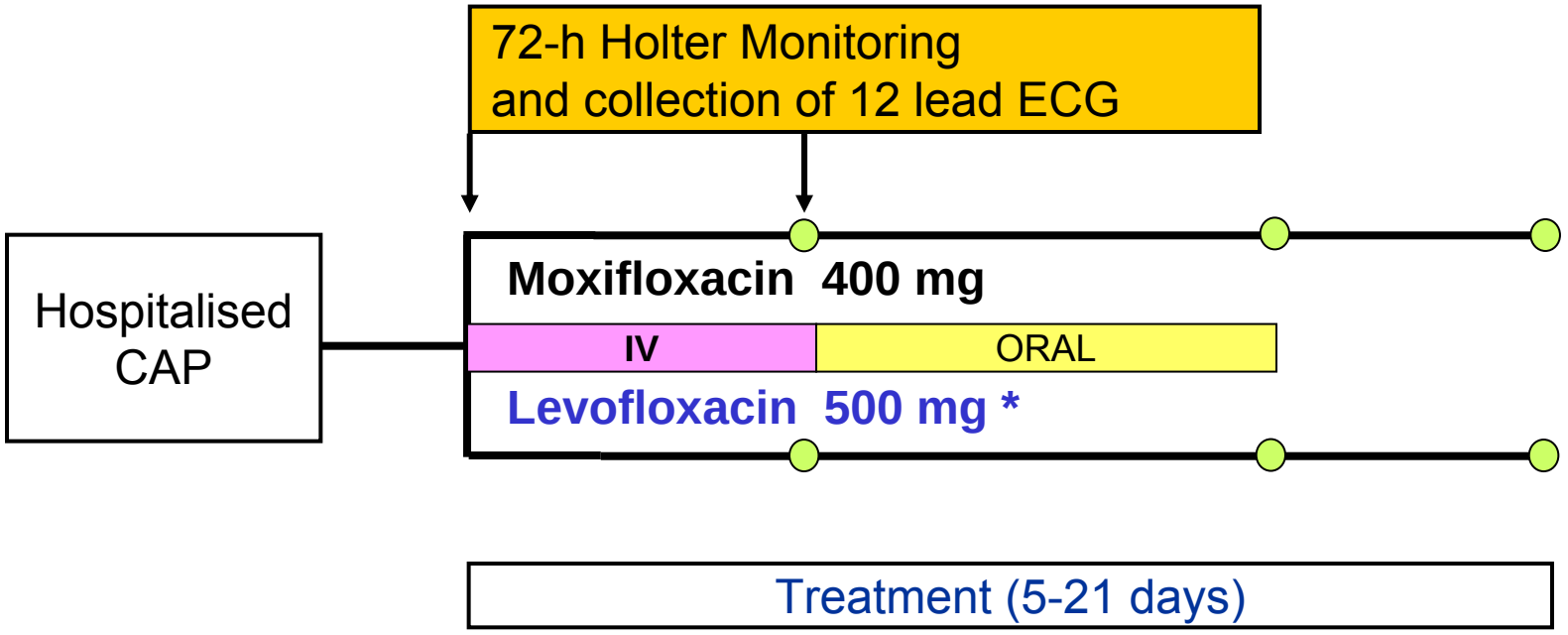
*** Torsades de Pointes, ventricular tachycardia, or bradycardia**

[a] current observed rate is 5.8 per 10 millions

Ianini (2004) Drug Benefit Trends (suppl) 34-41
PSUR Bridging Report July 18, 2008

See also: Owens & Ambrose (2005) CID 41S2: S144-57
Falagas et al (2007) Int. J. Antimicrob. Ag. 29:374-9
Veyssier et al. (2006) Med. Mal. Infect. 36:505-12

CAPRIE Study (10872 - CAP study in elderly patients)
Design to test for cardiac safety



- very elderly (mean age >75 years)
- 60% patients with PSI Risk Class III or higher
- no difference in efficacy between groups

Anzueto A et al, Clin Infect Dis 2006.

* Low dose by EUCAST standards

Caprie Study: analysis of all adverse events

- Analysis of the safety data of the CAPRIE study* failed to demonstrate significant occurrence of cardiac toxicity of moxifloxacin *vs* the comparator in elderly patients

Table 3. Overview of adverse events for hospitalized elderly patients eligible who received moxifloxacin or levofloxacin for the treatment of community-acquired pneumonia.

Variable	No. (%) of patients: Moxifloxacin arm (n = 195)	Levofloxacin arm (n = 199)	P
Treatment-emergent adverse event	164 (84.1)	146 (73.4)	.01
Discontinued treatment due to adverse event	15 (7.7)	20 (10.1)	.5
Serious adverse event	46 (23.6)	45 (22.6)	.9
Death	15 (7.7)	11 (5.5)	.5
Any drug-related adverse event	51 (26.2)	45 (22.6)	.5
Drug-related adverse event reported by >1.5% of patients in either treatment group			
Diarrhea	11 (5.6)	10 (5.0)	1.0
Oral candidiasis	7 (3.6)	7 (3.5)	1.0
Nausea	3 (1.5)	4 (2.0)	1.0
Clostridium difficile infection/colitis	1 (0.5)	6 (3.0)	.1
Cardiac event	2 (1.0)	7 (3.5)	.2
Atrial fibrillation	0	3 (1.5)	
Ventricular tachycardia	1 (0.5)	1 (0.5)	
Acute myocardial infarction	0	1 (0.5)	
Atrial flutter	0	1 (0.5)	
Congestive heart failure	0	1 (0.5)	
Cardiorespiratory arrest	0	1 (0.5)	
Supraventricular tachycardia	1 (0.5)	0	
Torsade de pointes	0	1 (0.5)	
Chest pain	0	1 (0.5)	
Increased heart rate	0	1 (0.5)	

* Anzueto et al. Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus That of Levofloxacin Therapy Clin. Infect. Dis. 2006; 42:73–81

CAPRIE Study : Primary Composite Cardiac Safety End Point (Based only on Holter Monitor Findings [ECG])

Findings observed on Holter	Moxifloxacin N = 192 (%)	Levofloxacin N = 195 (%)
Nonsustained VT ≥10 sec, ≤30 sec	14 (7.3)	9 (4.6)
Sustained VT >30 sec	1 (0.5)	0 (0)
Torsade de pointes	0	1 (0.5)
Cardiac arrest	1 (0.5)[#]	0 (0)
Total patients with findings	**16** (8.3 [4.5 to 12.2])	**10** (5.1 [2.1 to 8.2])

VT: Ventricular tachycardia

[#] Respiratory failure following DNR orders

Relative risk = 1.262 (NS)
95% Confidence Interval: 0.9149 to 1.741

- no significant difference for primary composite safety variable between moxifloxacin and levofloxacin
- most Holter findings were asymptomatic (most often not reported as AEs by investigators)
- drug-related cardiac AEs reported in 2 (1%) of moxifloxacin- and 7 (3.5%) of levofloxacin-treated patients (P = NS)

Morganroth et al, Chest 2005; 128:3398

Why a 6-10 msec QTc prolongation without clinical signs ?

Literature search shows discordance between QTc data and actual cardiac toxicity of moxifloxacin may result from

- its relatively large IC_{20} towards the hERG* channel (31-35 µM; ~12.6 mg/L **free** drug [corresponding to a serum total concentration of ~ 25 mg/L]), with significant risk of TdP demonstrated in animals at 100 µM (40 mg/L free drug)
  (Chen et al., Br J Pharmacol. 2005;146:792-9.)**

  Quoting: "*the lack of TdP report by moxifloxacin in patients without other risk factors might be attributable to its well-behaved pharmacokinetic profile and other dose-limiting effects*."

  Infusion time (if > 30 min) is not of major concern.

- the fact that TdP is also related to at least one additional parameter (beat-to-beat alternations in monophasic action potential duration (MAPD) on which moxifloxacin has little effect
  (Wisialowski et al. J Pharmacol Exp Ther. 2006;318:352-9).

- absence of cytochrome P450 interactions (main cause for terfenadine or cisapride-induced TdP)
  (Roden DM. N Engl J Med 2004;350:1013-22.)

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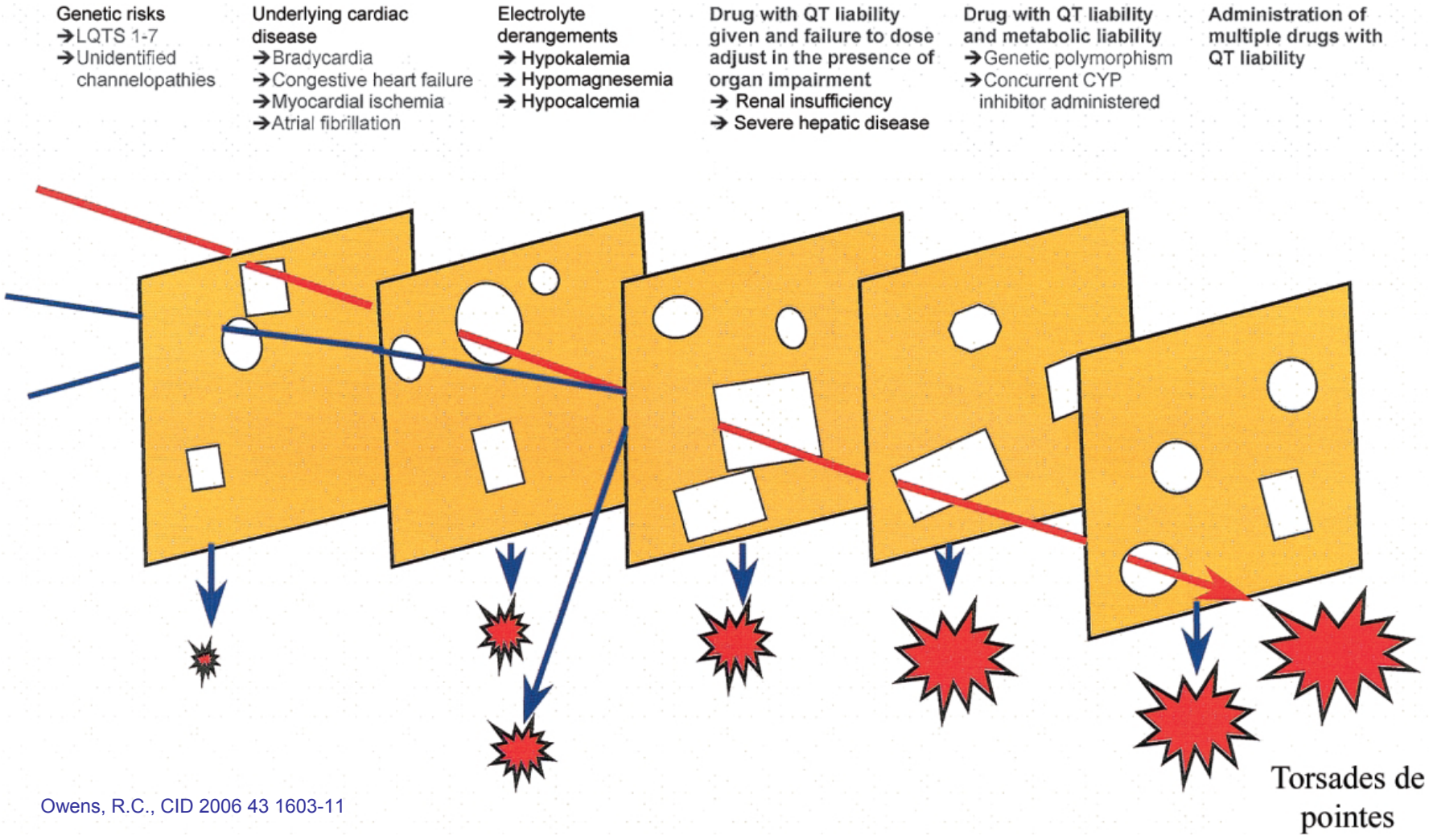
* **h**uman **E**ther-a-go-go **R**elated **G**ene (KCNH2) encoding the Kv11.1 potassium ion channel responsible for the repolarising IKr current in the cardiac action potential.

** independently, Patmore et al. (Eur. J. Pharmacol. 2000; 406:449-452) showed rank order of potency sparfloxacin > grepafloxacin = moxifloxacin > ciprofloxacin.

Multiple risk factors that increase the probability of torsades de pointes [23]



Owens, R.C., CID 2006 43 1603-11

Risk of Torsade de pointes and inhibitors of CYP450 metabolism

Table 1
QT interval prolonging drugs metabolized by CYP 3A4, which may possibly interact both pharmacokinetically and phamacodinamically with macrolides and imidazole antifungals.

Antiarrhythmics	Amiodarone (with roxithromycin [23]), quinidine (with erythromycin [116]), disopyramide (with clarithromycin [117, 118])
Antifungals	Fluconazole, ketoconazole, itraconazole, miconazole
Prokinetics	Cisapride (with clarithromycin, [119, 120], with erythromycin [121])
Antihistamines	Terfenadine (with erythromycin [122, 123], with troleandomycin [124]), astemizole (with erythromycin [125]), loratidine
Antipsychotics	Pimozide (with clarithromycin [126, 127]), chlorpromazine, haloperidol, ziprasidone, risperidone, clozapine, quetiapine
Immunsuppressive drugs	Tacrolimus
Opioid agonists	Methadone
Antimalarials	Quinine, chloroquine, halofantrine

Case reports on torsades de pointes or QT prolongation during coadministration of macrolide agents and other repolarization prolonging drugs are in brackets

Simkó et al., Infection 2008;36:194-206

The use of macrolides without paying attention to other drugs may put patients at risk …

Torsade de pointes: case reports (PubMed)

PubMed Search for "<drug name> AND Torsade de pointes" limited to "Case Reports" (search performed on 21-02-2009)

- Moxifloxacin: 4
  - Koide et al. Cases J. 2008 Dec 19;1(1):409. PMID: 19099576
  - Sherazi et al. Cardiol J. 2008;15(1):71-3. PMID: 18651388
  - Altin et al. Can J Cardiol. 2007 Sep;23(11):907-8. PMID: 17876386
  - Dale et al. Ann Pharmacother. 2007 Feb;41(2):336-40. PMID: 17284508
- levofloxacin: 3 (2001-2004)
- ciprofloxacin: 5 (2004-2007)

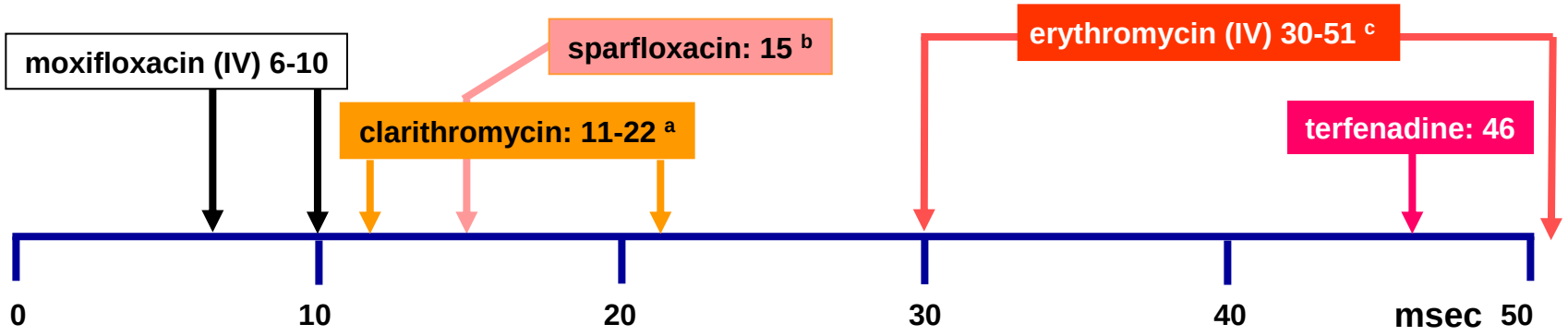
- erythromycin: 54 (1985-2008)
- clarithromycin: 12 (1997-2008)
- azithromycin: 5 (2001-2007)

In an update of his 2001 study, and using 16,868 U.S. FDA ADE reports, Frothingham noted the following numbers of unique US *Torsades de pointes*: 3 ciprofloxacin, 51 levofloxacin, 37 gatifloxacin, and 20 moxifloxacin (Emerg. Infect. Dis. 2005;11:986-987)

Moxifloxacin IV Cardiac Safety: Conclusions and Discussion

- Moxifloxacin IV produces a predictable increase in QT_C interval only marginally incremented by increasing its concentration (within clinically-meaningful limits)
- The frequency of cardiac adverse events and drug-related cardiac adverse events are similar for moxifloxacin- and comparator-treated patients
- **No increased risk** of cardiac morbidity or mortality was seen in hospitalised patients with CAP (including high risk ones) treated with IV moxifloxacin

Moxifloxacin is used as a positive control for QT_C effect(s) in Phase I studies because it offers a positive signal without risk of clinical adverse events to the volunteers.



Ref.:[a] Carr et al. Antimicrob Agents Chemother. 1998; 42:1176-80; Germanakis et al. Acta Paediatr. 2006;95:1694-6.
[b] Jaillon et al. J Antimicrob Chemother. 1996; 37 Suppl A:161-7; Jaillon et al. Br J Clin Pharmacol. 1996; 41:499–503.c
[c] Tschida et ak. Pharmacotherapy. 1996;16(4):663-74; Oberg et al. Pharmacotherapy. 1995;15:687-92

Tendonitis

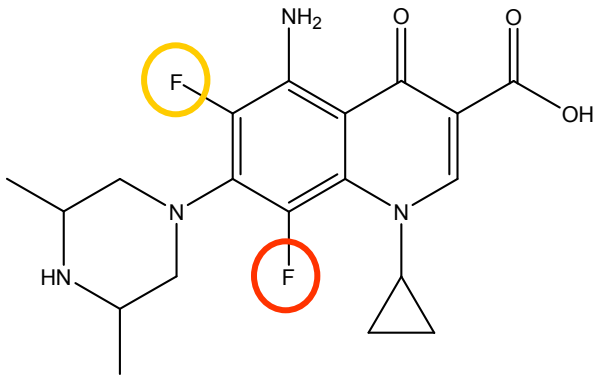
- well known effect of fluoroquinolones (included now in all US labelling)
- mechanism remains uncertain…
  - direct toxicity for collagen fibers and formation of reactive oxygen species …
  - increased expression of matrix metalloproteinases …
  - complexation of Mg^{2+} ions in joint and cartilages (class effect ?)…
- incidence: 0.14 to 0.4 % [1]
- Risk factors: age, corticoid use, renal failure, diabetes mellitus, gout, hyperparathyroidism, peripheral vascular disease, sportive activities, or rheumatic disease [2]
- more frequently mentioned in spontaneous reporting systems for levofloxacin than for ciprofloxacin or norfloxacin [3]
- isolated cases reported with moxifloxacin but no tendon rupture noted in MOSAIC study (COPD patients; 63.8 ± 9.7 y; concomitant use of corticosteroids [57 %]) [4]

1. Mehlhorn & Brown. Ann Pharmacother 2007 Nov; 41(11): 1859-66
2. van der Linden et al. Arch Intern Med 2003 Aug 11; 163(15): 1801-7; Khaliq & Zhanel. Clin Infect Dis 2003 Jun 1; 36(11): 1404-10
3. Leone et al. Drug Saf 2003; 26(2): 109-20; Khaliq & Zhanel. Clin Infect Dis 2003 Jun 1; 36(11): 1404-10
4. Wilson et al. Chest 2004 Mar; 125(3): 953-64

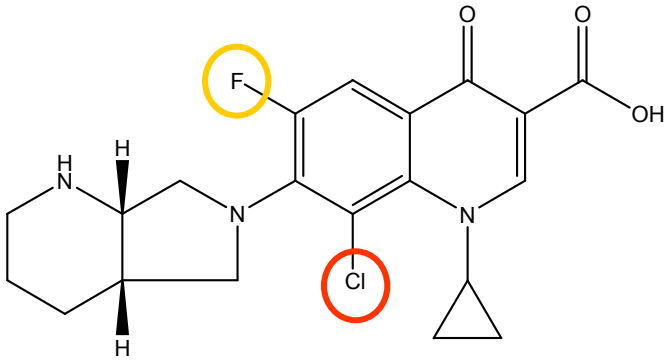
Phototoxicity

Associated to certain fluoroquinolones only

- favoured by the F substituent in position 6
- markedly enhanced for molecules with additional halogen substituent (Cl or F) in position 8 (sparfloxacin, BAY y 3118, e.g.)
- lomefloxacin > fleroxacin > enoxacin > pefloxacin > ciprofloxacin > grepafloxacin > gemifloxacin > levofloxacin > norfloxacin > ofloxacin > moxifloxacin [1]
- incidences:
  - ciprofloxacin: < 1 %) [2]
  - moxifloxacin or gemifloxacin: < 0.1 % in the absence of excessive exposure to light [3].



sparfloxacin



Bay y 3118

in moxifloxacin, the Cl is replaced by a methoxy

1. Owens & Ambrose PG. Clin Infect Dis 2005 Jul 15; 41 Suppl 2: S144-S157
2. US Cipro® Package insert (http://www.univgraph.com/bayer/inserts/ciprotab.pdf)
3. US Avelox® Package insert (http://www.univgraph.com/bayer/inserts/avelox.pdf)
   US Factive® Package insert (http://www.factive.com/pdf/prescribing_info.pdf)

Populations at risk *

Class	Drugs	Populations at higher risk of side effects
β-lactams	amoxicillin	• Allergic patients
	amoxicillin/ clavulanic acid	• Allergic patients • Erythematous skin rash: patients with mononucleosis • Hepatic toxicity: patients with hepatic dysfunction • Nephrotoxicity: elderly patients
macrolides	clarithromycin	• Cardiac effects: patients taking other drugs with effects on QTc or class 1A or III antiarrythmics • Pregnancy • Patients with severe renal impairment with or without coexisting hepatic impairment • Patients taking drugs metabolized by CYP450
	azithromycin	• Hepatotoxicity: patients with liver failure
	telithromycin	• Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia • Myopathies : co-administration of statins • Patients with severe renal impairment • Pregnancy • Children (no studies so far)

* as defined by the corresponding labelling

Carbonnelle *et al.*, in preparation

Populations at risk *

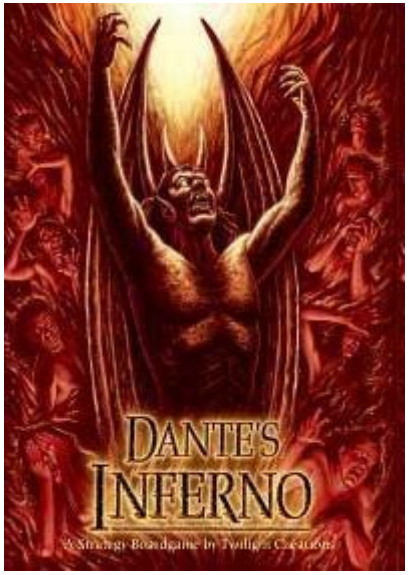
Class	Drugs	Populations at higher risk of side effects
fluoroquinolones	levofloxacin	• Tendon disorders: elderly, patients taking corticoids, or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia • CNS effects: patients at risk of epilepsy • Dysglycemia: diabetic patients • Pregnancy, lactation, infants
	moxifloxacin	• Tendon disorders: elderly, patients taking corticoids, or with kidney, heart or lung transplants • Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia • CNS effects: patients at risk of epilepsy • Pregnancy, lactation, infants
tetracyclines	doxycycline	• Pregnancy, lactation, infants

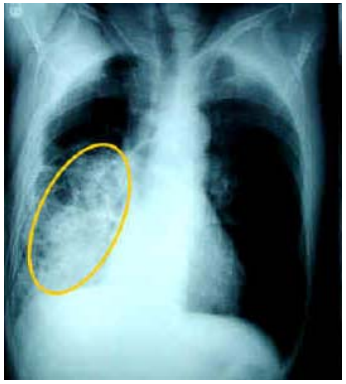
* as defined by the corresponding labelling

Carbonnelle *et al.*, in preparation

But what is "risk" ?

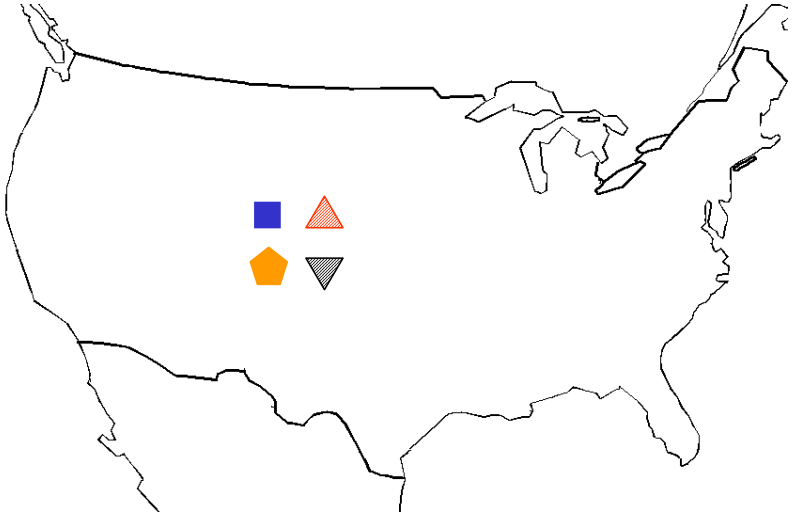
→ side effects ?

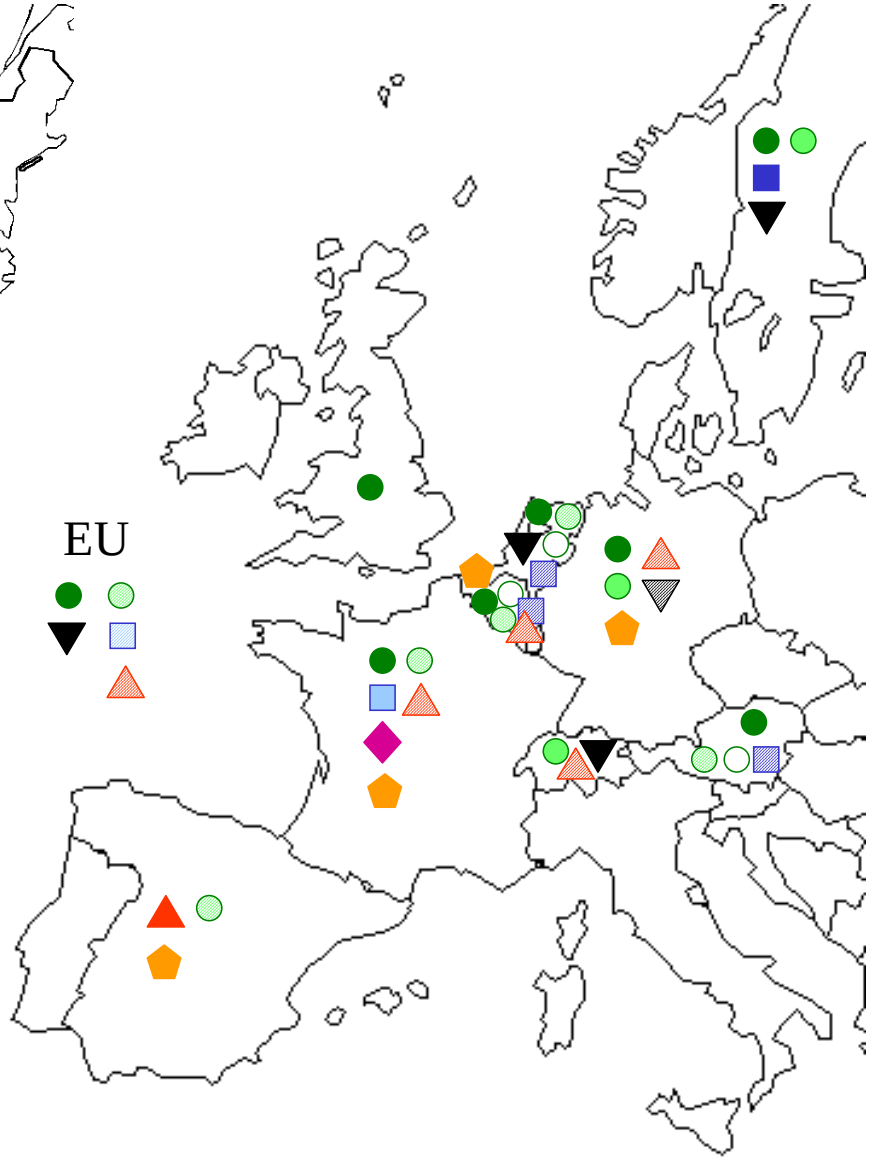




→ therapeutic failure ?

Which guidelines do you need to follow ?



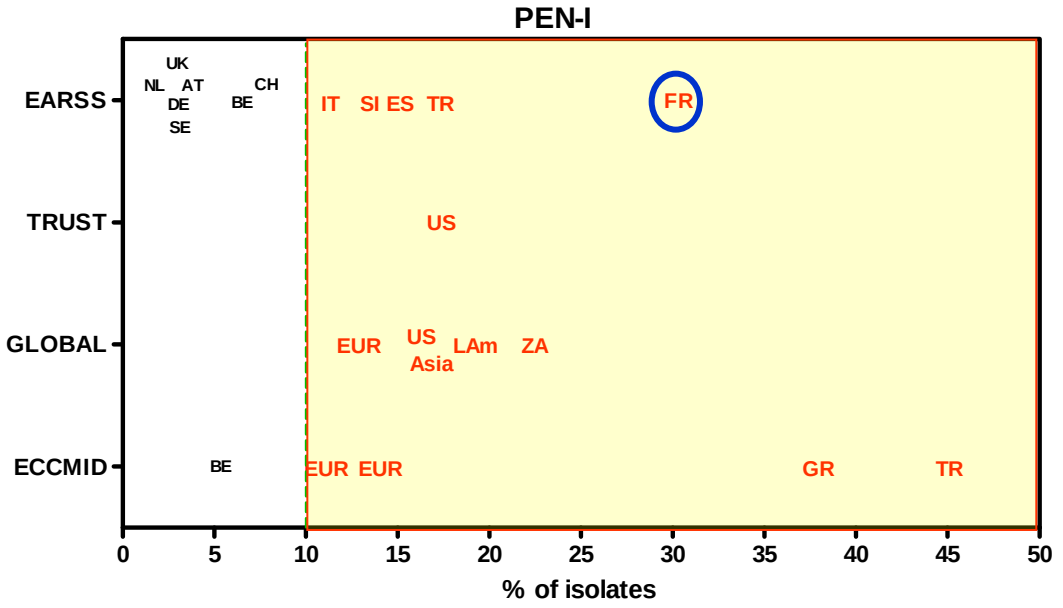


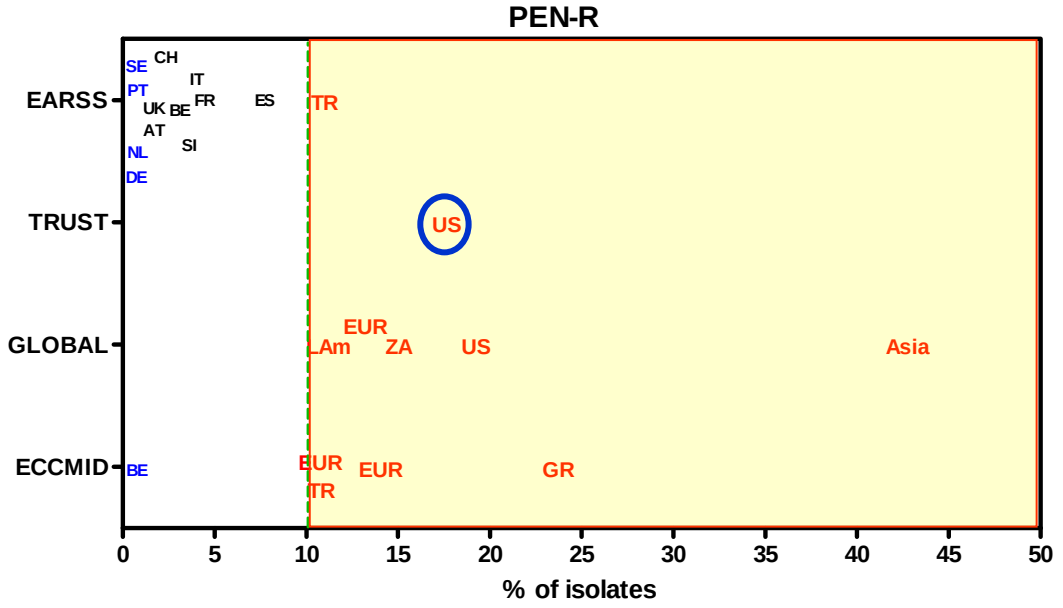
1st line	alternative	
●	●	amoxicillin
●	●	amoxi/clav
	○	other β-lactam
■	▨	macrolide
□	□	ketolide
▲	△	fluoroquinolone
▼	▽	tetracycline
◆		pristinamycin
⬟		β-lactam + macrolide

Populations at risk of bacteriological failure with penicillins*

*analysis of resistance of 1st line antibiotics (penicillins) for CAP as reported by the surveillance systems or publications (*S. pneumoniae*)

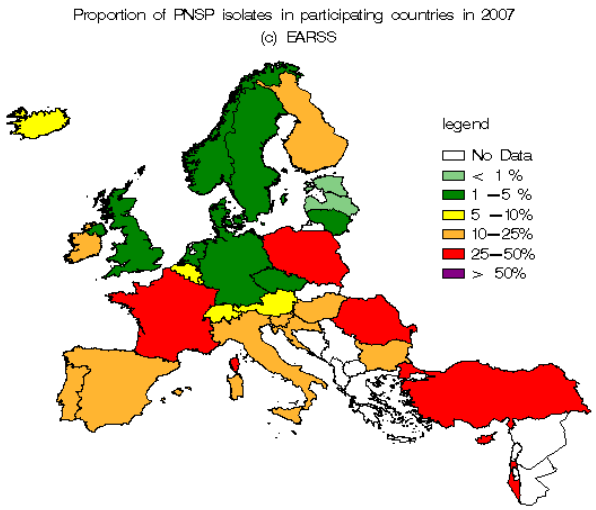
- **EARSS**: European Antimicrobial Surveillance system
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **ECCMID**: abstracts of the 18th European Congress of Clinical Microbiology and Infectious Diseases





Carbonnelle *et al.*, in preparation

Can we treat pneumococcal CAP with penicillin throughout Europe ?



About half of EARSS countries have between 10 and 50 % of "poorly susceptible" *S. pneumoniae*

Penicillins - EUCAST clinical MIC breakpoints 2008-06-27 (version 1.2)

Penicillins Click on antibiotic name to see wild type MIC distributions.		Species-related breakpoints			
		Strepto-coccus A,B,C,G[F]	*S.pneu-moniae*[G]	*Other strepto-cocci*[H]	*H.influ-enzae*[I]
Benzylpenicillin	RD	0.25/0.25	0.06/2	0.25/2	IE
Ampicillin[N]	RD	Note[F]	0.5/2	0.5/2	1/1
Amoxicillin	RD	Note[F]	Note[G]	0.5/2	1/1
Amoxicillin/clavulanate[O]	RD	Note[F]	Note[G]	Note[H]	1/1

G. *Streptococcus pneumoniae*:

In pneumonia, strains with with MIC ≤0.5 mg/L should be regarded as susceptible to benzylpenicillin at doses of at least 1.2 g x 4, with MIC ≤1 mg/L at doses of 2.4 g x 4 or 1.2 g x 6 and strains with MIC ≤2.0 mg/L susceptible at doses of 2.4 g x 6.

EUCAST, 2008

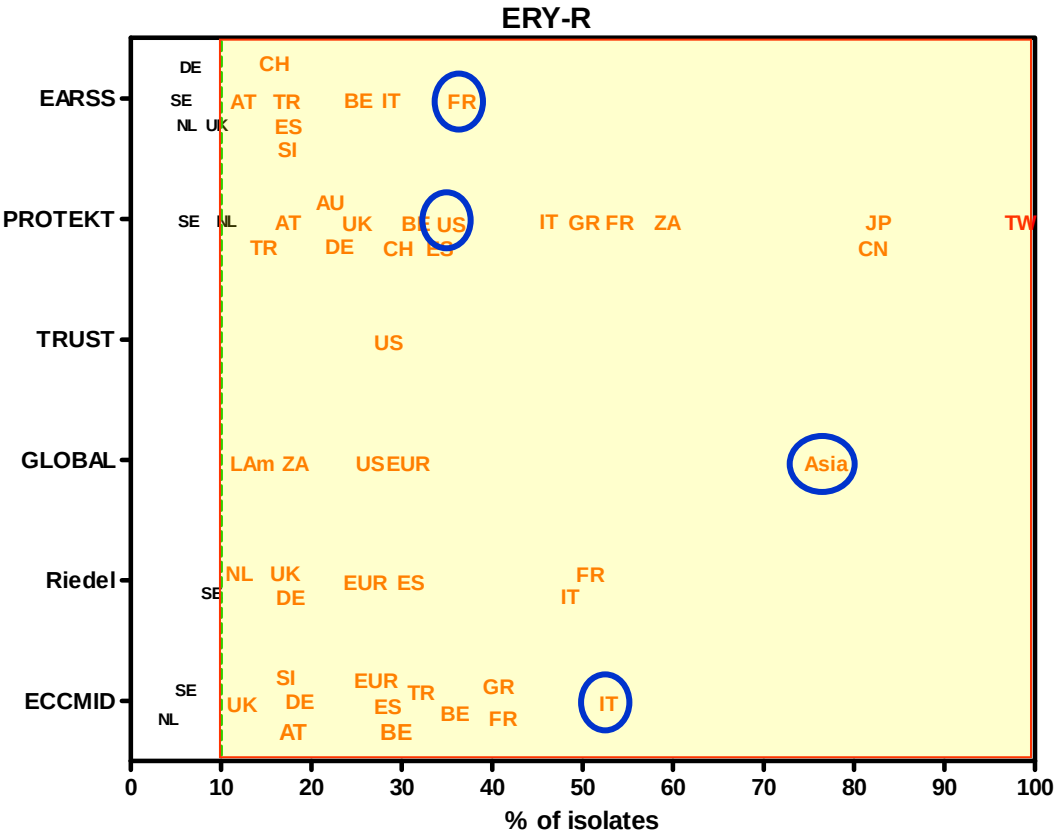
EUCAST will tell you that in order to cover *S. pneumoniae* with penicillin in the "orange" and "red" countries, its dose need to be pushed from 1.2 g every 6h (4.8 g/day) to 2.4 g every 4 h (14.4 g/day)…

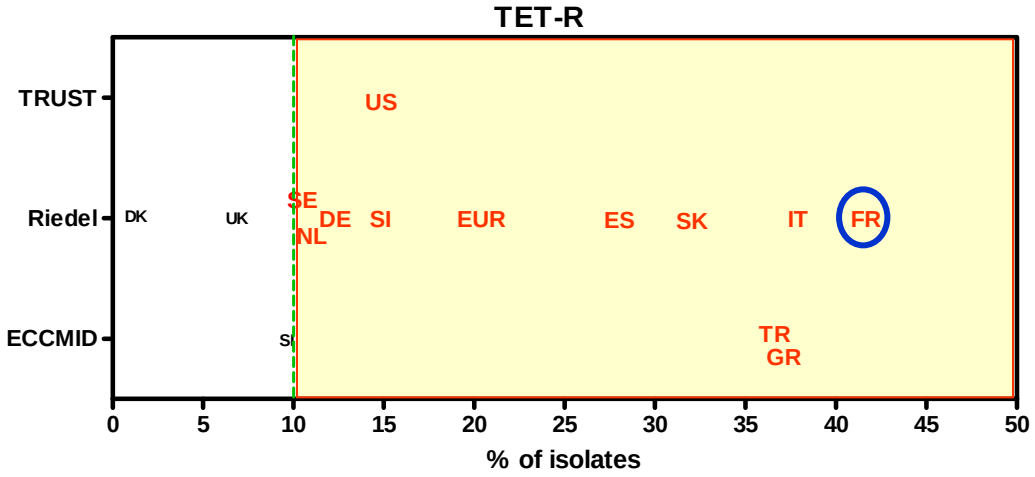
Populations at risk of bacteriological failure with macrolides and tetracyclines*

*analysis of resistance of often recommended 1st line antibiotics for CAP (macrolides, doxycycline) as reported by 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

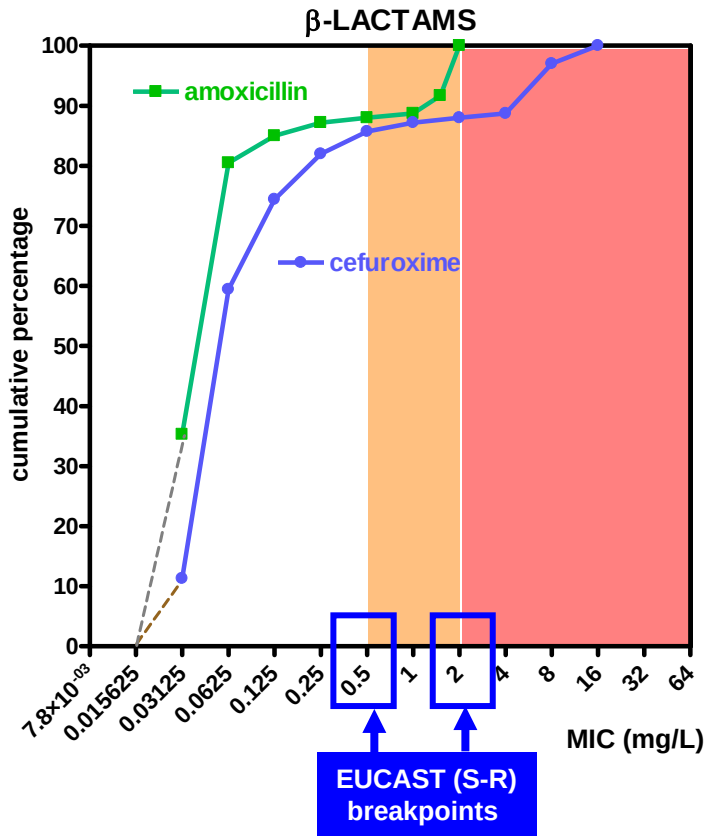
Carbonnelle *et al.*, in preparation





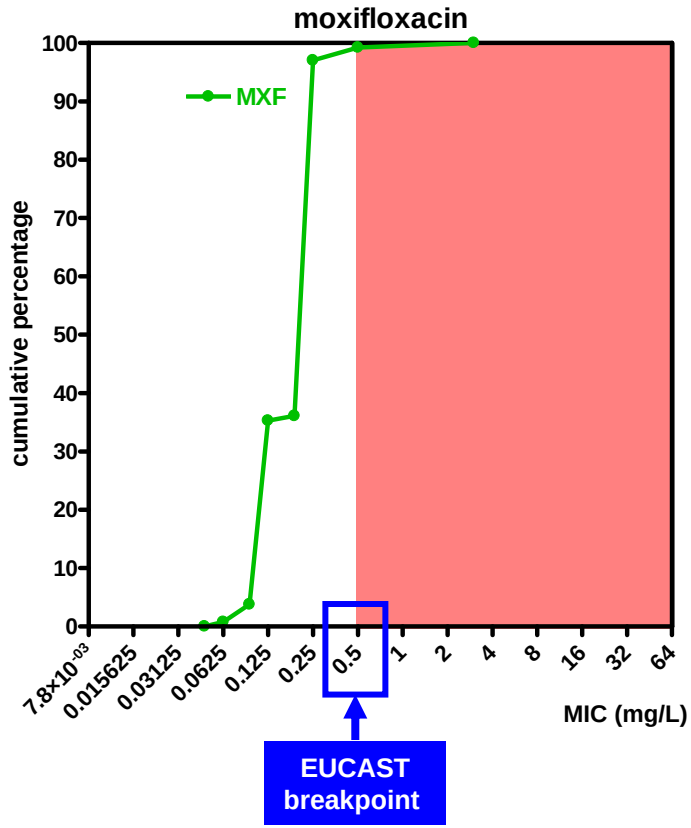
β-lactams are reaching their limits in Belgium for CAP

(which is the reason why physicians tend to use moxifloxacin more frequently)



About 15 % of isolates are "poorly susceptible" to amoxicillin and cefuroxime (requiring high dosages of these antibiotics) ...

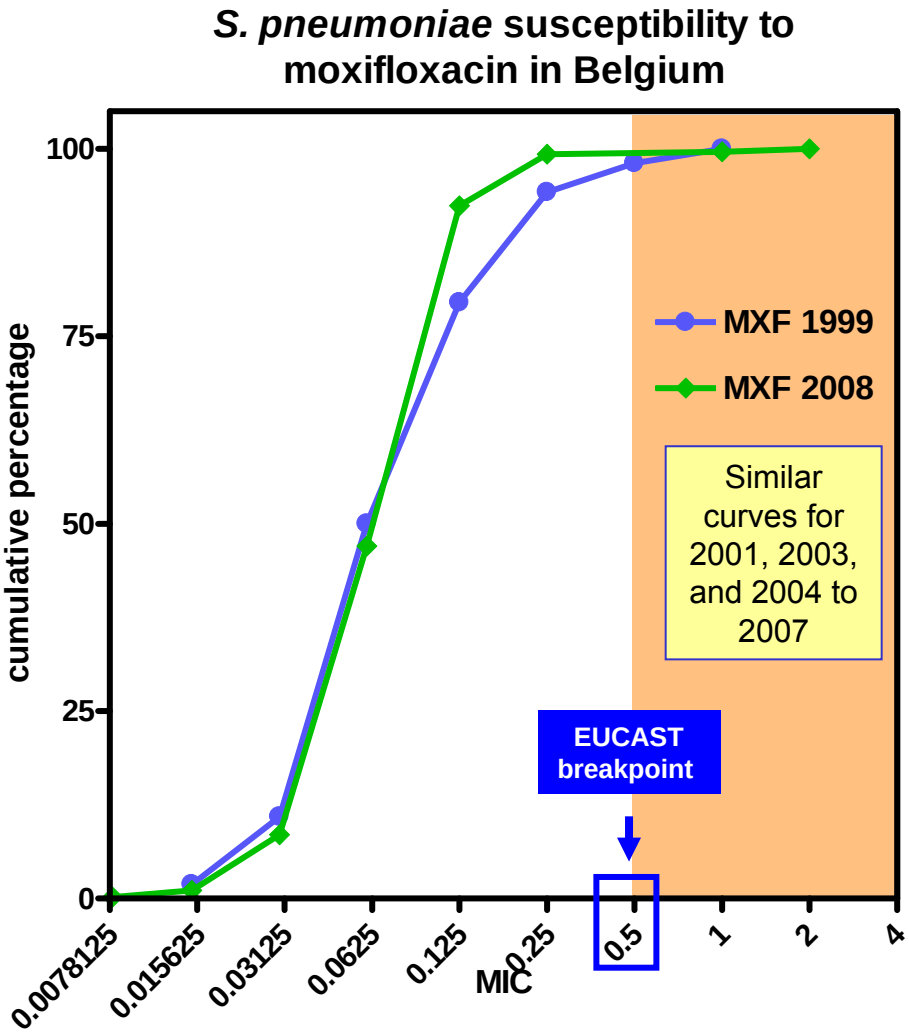
Lismond *et al.*, ECCMID 2008



99 % of isolates are below the breakpoint with the registered dosage of 400 mg 1 x day

Lismond *et al.*, ECCMID 2008; Vanhoof *et al*, ECCMID 2009

Moxifloxacin MIC's against *S. pneumoniae* have not increased in Belgium from 1999 to 2008



Facts:

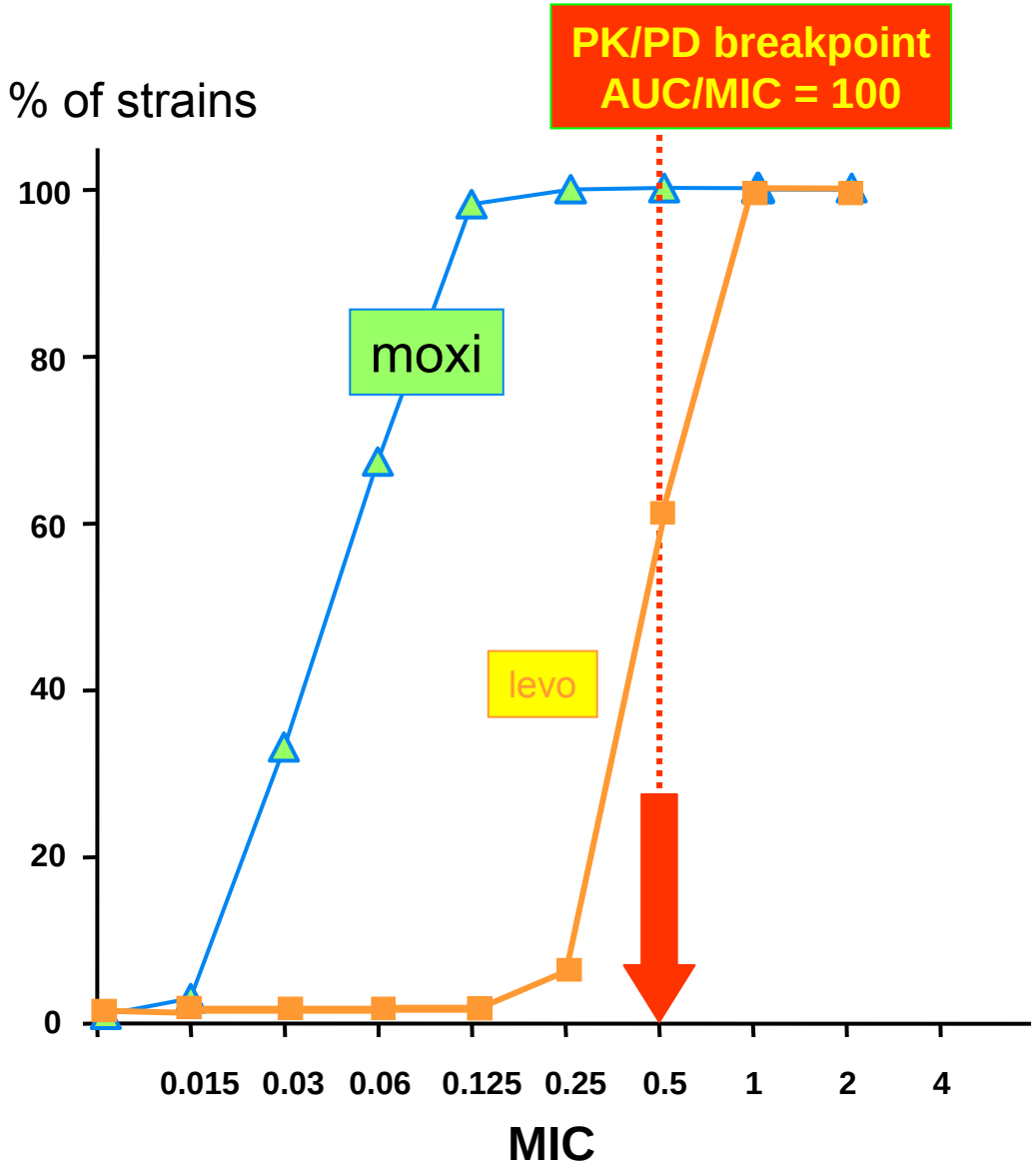
From data of a <u>national</u> collection * independent from our own collection (shown on the previous slide)

- No change (and even improvement) in *S. pneumoniae* susceptibility to moxifloxacin from 1999 (pre-commercialization) to 2008 (7 years after launching **)
- in 2008, 99.3 % isolates were still below the EUCAST breakpoint (0.5 mg/L) **and at MIC values > 10-fold lower than the $C_{max.}$**

* Non invasive respiratory tract infections
** 1st respiratory quinolone in BE

Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 448 in 2008)
http://www.iph. fgov.be
Data available yearly for 1999 through 2008.
Presented at 19th ECCMID, May 2009, Helsinki, Finland (Vanhoof et al.)

Pharmacokinetics and breakpoint



Levofloxacin 500 mg 1X / jr

- AUC [(mg/l)xh] 47
- peak [mg/l] 5

➔ MIC_{max} < 0.5

Moxifloxacin 400 mg 1X /jr

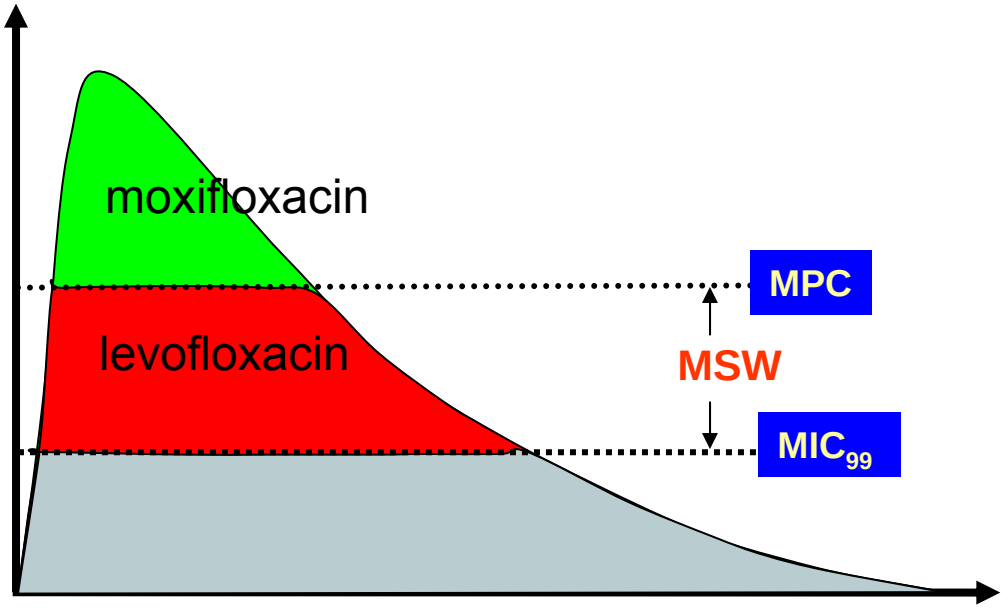
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5

➔ MIC_{max} < 0.5

MIC data: J. Verhaegen et al., 2003

Why has moxifloxacin remained active for so many years even if used as in Belgium

- Its registered dosage (400 mg) ensures a C_{max} that goes far above the MIC of all target organisms, and reaches and exceeds the so-called "*mutant prevention concentration* [MPC; about 10 x the MIC]) *,**



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

* this may include first mutants as well as efflux-overexpressing bacteria (Avrain et al., JAC 2008; …)

** this is NOT the case for levofloxacin, which may explain its MIC creep in the U.S.A. and some places in EU

Conclusions (1 of 2)

- The overall safety profile of fluoroquinolones (and moxifloxacin in particular) is similar or better than comparators from clinical trials and spontaneous report systems. More specifically, and with regard to recent questions:
  - Hepatic events reactions are well within range of other commonly used antibacterials, or lower than amoxicillin/clavulanic acid or macrolides
  - QTc prolongation is well characterized but cardiac events/TdP are not different from other fluoroquinolones and lower than those of macrolides
  - Specific toxicities (tendonitis, e.g.) are well known and can be taken care of
  - skin events are very rare and, in any case, much less frequent than with β-lactams

Conclusions (2 of 2)

- Fluoroquinolones (and moxifloxacin in particular, for PK/PD reasons) are a useful alternative in those countries (or specific situations) where resistance to so-called "*1st line antibiotics*" (for CAP or COPD) is becoming worrying, or where or when a fast-acting agent may be advantageous;

- The safety profiles of higher doses of β-lactams or of levofloxacin (needed to meet the resistance levels patterns of *S. pneumoniae*) are not well characterised, and potentially worse than established profiles from low doses studies.

- Conversely, and based on all available evidence, the use of moxifloxacin should not be vitiated by excessive toxicity if it is prescribed for the correct indications and with due attention to the contraindications and warnings mentioned in the labeling

  (Van Bambeke & Tulkens, Drug Saf. 2009;32(5):359-78)

Flämischer Maler Hieronymus Bosch (c1450-1516) zeigt großer Fantasie in seinem Triptychon Altarpiece „das letzte Urteil“ (c1510-15, Akademie, Wien)

"Was auch als
Wahrheit oder Fabel
In tausend Büchern
dir erscheint,
Das alles ist ein Turm
zu Babel,
Wenn es die Liebe
nicht vereint."

J.W. von Goethe

Disclosures

Financial support from

- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics
- the Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Pharmaceutical Industry for specific drug-related studies

Note:

- all work, irrespective the source of funding, is published in peer-reviewed journals and is available from our web site *
- P.M. Tulkens is member of the Committee organising public campaigns for appropriate use of antibiotics in Belgium since 2000 **

* http://www.facm.ucl.ac.be/publicat_facm.htm
** http://www.antibiotiques.org/

Selected publications in relation to this presentation:

- Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. Drug Saf. 2009;32(5):359-78. PubMed PMID: 19419232.
- Van Bambeke F, Reinert RR, Appelbaum PC, Tulkens PM, Peetermans WE. Multidrug-resistant Streptococcus pneumoniae infections: current and future therapeutic options. Drugs. 2007;67(16):2355-82. Review. PubMed PMID: 17983256.
- Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM. Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. Review. Erratum in: Clin Microbiol Infect. 2005 Jun;11(6):513. PubMed PMID: 15760423.