# Respiratory Fluoroquinolones: Benefit-Risk profiles


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* also

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- Former (2008-2010) member of the EUCAST (European Committee for Antibiotic Susceptibility Testing) steering committee
- Founding member and past-President (1998-2000) of the International Society of Anti-infective Pharmacology


**Belgische Vereniging voor Pneumologie – Société belge de pneumologie -- 27-11-2010**
**Slides are available on http://www.facm.ucl.ac.be → "Lectures"**

# Starting points…

- What about guidelines …
  - A quick overview of CAP guidelines

- What about Regulatory Authorities statements …
  - EMEA 2007 referral procedure

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  ➔ **Fluoroquinolones are almost always proposed as second line antibiotics**

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  - A quick overview of CAP guidelines

  ➔ **Fluoroquinolones are almost always proposed as second line antibiotics**

- What about Regulatory Authorities statements …
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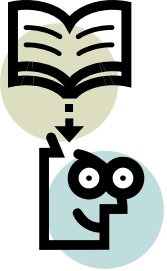
  ➔ **Use only if other antibiotics cannot be used**



# Contents of the Presentation

- All antimicrobials 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 fluroquinolones *vs* other agents
  - Overall … and specific aspects
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- And what about the efficacy ?
- Conclusions

# All antimicrobials have associated risks *

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

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

Carbonnelle *et al.*, submitted

# All antimicrobials have associated risks *

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

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

Carbonnelle *et al.*, submitted

# All antimicrobials have associated risks *

| Class | Drugs | Frequent or serious side effects |
|---|---|---|
| **fluoroquinolones** | levofloxacin | • Anaphylactic reactions and allergic skin reactions<br>• *Clostridium difficile*-associated colitis<br>• Hematologic toxicity<br>• Hepatotoxicity<br>• Central nervous system effects: headache, insomnia, dizziness, convulsions<br>• **Musculoskeletal: tendinopathies**<br>• Peripheral neuropathy<br>• Prolongation of the QTc interval and isolated cases of torsade de pointes<br>• **Digestive tract: nausea, diarrhoea** |
| | moxifloxacin | • Anaphylactic reactions and allergic skin reactions<br>• *Clostridium difficile*-associated colitis<br>• **Musculoskeletal: Tendinopathies**<br>• Peripheral neuropathy<br>• Prolongation of the QT interval<br>• Central nervous system effects: headache, insomnia, dizziness, convulsions<br>• **Digestive tract: nausea, diarrhoea** |

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

Carbonnelle *et al.*, submitted

# All antimicrobials have associated risks *

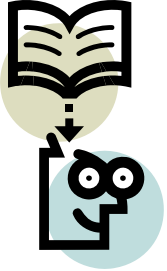
| Class | Drugs | Frequent or serious side effects |
|---|---|---|
| **tetracyclines** | doxycycline | • **Anaphylactic reactions and allergic skin reactions**<br>• *Clostridium difficile*-associated colitis<br>• Digestive tract: anorexia, glossitis, dysphagia, nausea, vomiting, diarrhoea<br>• **esophagitis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



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# Are fluoroquinolones more toxic in controlled clinical trials* ?

| | Moxifloxacin | Comparator | Moxifloxacin | Comparator | Moxifloxacin | Comparator |
|---|---|---|---|---|---|---|
| | Oral, N (%) | | Sequential, N (%) | | Intravenous, N (%) | |
| **Total** | **9394 (100)** | **9359 (100)** | **2934 (100)** | **2970 (100)** | **529 (100)** | **533 (100)** |
| **AE** | 4057 (43.2) | 3950 (42.2) | 1952 (66.5) | 1927 (64.9) | 149 (28.2) | 133 (25.0) |
| **ADR *** | 2257 (24.0) | 2059 (22.0) | 759 (25.9) | 718 (24.2) | 57 (10.8) | 59 (11.1) |
| **SAE** | 369 (3.9) | 361 (3.9) | 552 (18.8) | 492 (16.6) | 14 (2.6) | 7 (1.3) |
| **SADR *** | 56 (0.6) | 50 (0.5) | 89 (3.0) | 61 (2.1) | 0 (0) | 1 (0.2) |
| **Fatal AE** | 33 (0.4) | 44 (0.5) | 121 (4.1) | 119 (4.0) | 0 (0) | 1 (0.2) |
| **Fatal ADR** | 3 (<0.1) | 4 (<0.1) | 4 (0.1) | 5 (0.2) | 0 (0) | 0 (0) |

AE: adverse event; ADR: adverse drug reaction;
SAE: serious AE; SADR: serious ADR

* data for moxifoxacin (all clinical trials)
(Tulkens *et al.*, in preparation)

# Hepatic toxicity of antibiotics

Andrade & Tulkens, submitted

| | | | | |
|---|---|---|---|---|
| **Ciprofloxacin**<br>**Levofloxacin**<br>**Moxifloxacin** | **Tetracycline** | **Erythromycin**<br>**Clarithromycin**<br>**Penicillins** | **Co-trimoxazole**<br>**Amoxicillin/ clavulanate** | **Telithromycin**<br>**Trovafloxacin** |
| Isolated cases and ≤ 0.00007 | ≤0.0002 | ≤0.004 | ≤0.02 | **Acute liver failure high mortality**<br>? *<br>Withdrawal or severe restriction does not allow calculating true incidences |


- **Simmons C.** Beware: antibiotic-induced hepatotoxicity is rare but deadly. Hosp Pharm 2002; 37:326-330
- **Fontana RJ, Shakil AO, Greenson JK, Boyd I, Lee WM.** Acute liver failure due to amoxicillin and amoxicillin/clavulanate. Dig Dis Sci 2005; 50(10):1785-1790.[PMID: PM:16187174] .
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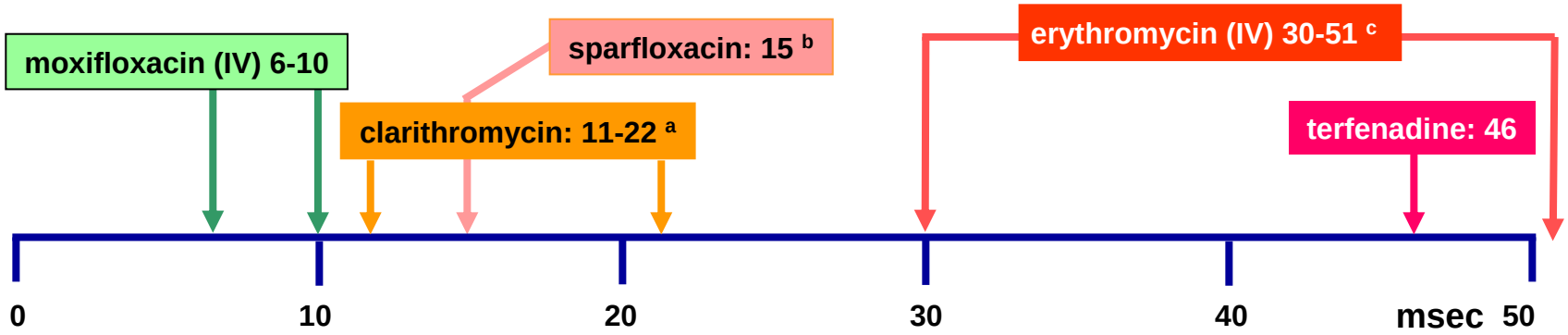
- **Hussaini SH, O'Brien CS, Despott EJ, Dalton HR.** Antibiotic therapy: a major cause of drug-induced jaundice in southwest England. Eur J Gastroenterol Hepatol 2007; 19(1):15-20.[PMID: PM:17206072]
- **Derby LE, Jick H, Henry DA, Dean AD.** Erythromycin-associated cholestatic hepatitis. Med J Aust 1993; 158(9):600-602.[PMID: PM:8479375]
- **Brinker A.** Telithromycin-Associated Hepatotoxicity. Food and Drug Administration. 2006; Accessed at http://www.fda.gov/ohrms/dockets/AC/06/slides/2006-4266s1-01-07-FDA-Brinker.ppt on 2010 Sept. 5.
- **Health Canada.** Canadian Advere Reaction Newsletter. 17, 1. 2007.
- **Carbon C.** Effets indésirables de la lévofloxacine: données des études cliniques et de la pharmacovigilance [In French (Levofloxacin adverse effects, data from clinical trials and pharmacovigilance); abstract in English]. Therapie 2001; 56(1):35-40.[PMID: PM:11322015]
- **Brinker AD, Wassel RT, Lyndly J, Serrano J, Avigan M, Lee WM et al.** Telithromycin-associated hepatotoxicity: Clinical spectrum and causality assessment of 42 cases. Hepatology 2009; 49(1):250-257.[PMID: PM:19085949]

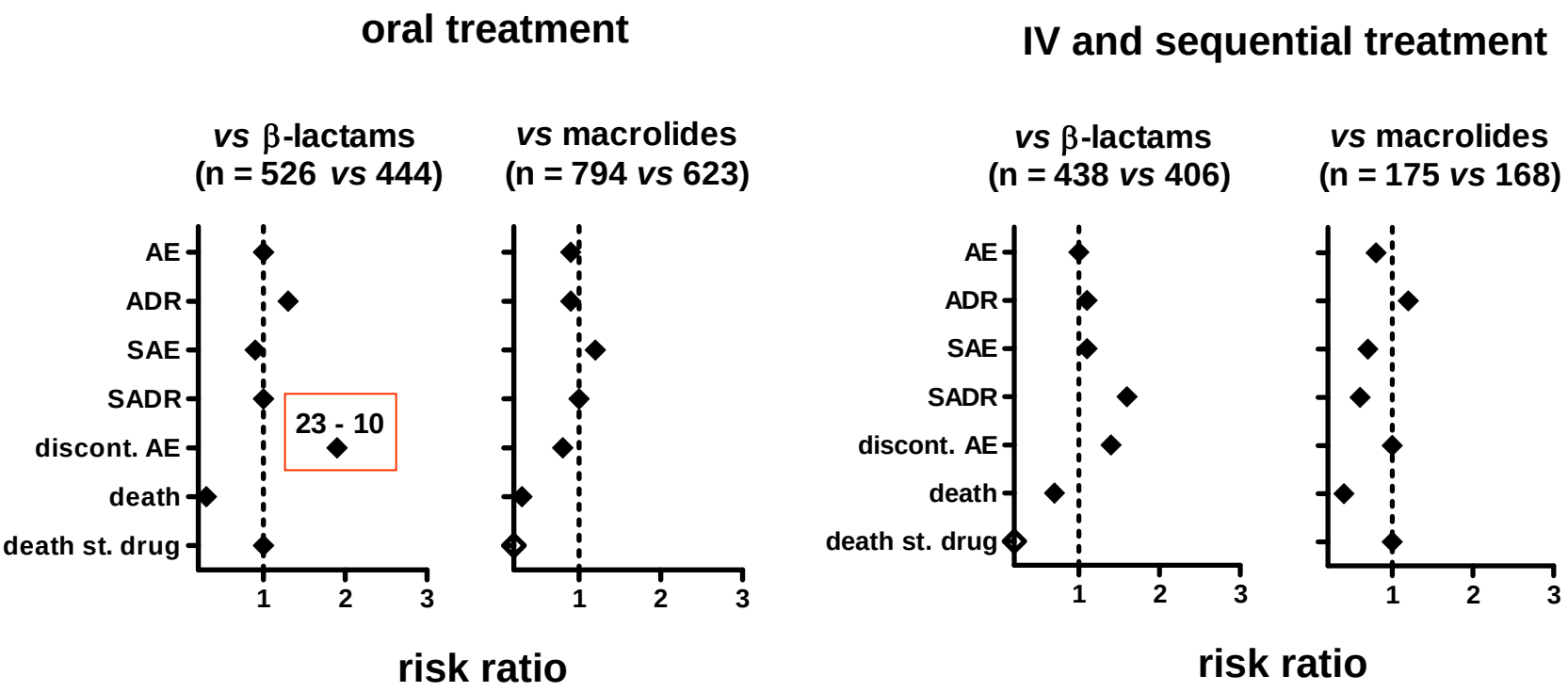
# Moxifloxacin QTc compared to other drugs




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

**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.**

# And patients with pre-existing cardiac risk factors * ?

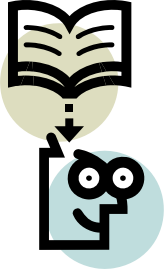



- **AE**: adverse event;
- **ADR**: adverse drug related event;
- **SAE**: serious adverse event;
- **SADR**: serious adverse drug-related event;
- **discont. AE**: discontinuation of therapy due to an adverse event;
- **death**: death of the patient for any cause;
- **death st. drug**: death related to the study drug

* based on MedDRA 13.1 (potential cardiac disease [primary or secondary linkage])

excluding patients with congenital QT interval prolongation, uncorrected hypokaliemia, clinically significant bradycardia, left cardiac insufficiency or previous rhythm disturbances, and class Ia and III antiarhythmics

Tulkens *et al.*, in preparation



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# Populations at risk *

| Class | Drugs | Populations at higher risk of side effects |
|---|---|---|
| **β-lactams** | amoxicillin | • **Allergic patients** |
| | amoxicillin/ clavulanic acid | • **Allergic patients**<br>• Erythematous skin rash: patients with mononucleosis<br>• **Hepatic toxicity: patients with hepatic dysfunction**<br>• Nephrotoxicity: elderly patients |
| **macrolides** | clarithromycin | • **Cardiac effects: patients taking other drugs with effects on QTc or class 1A or III antiarrythmics**<br>• Pregnancy<br>• Patients with severe renal impairment with or without coexisting hepatic impairment<br>• 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**<br>• **hepatotoxicity**<br>• Myopathies : co-administration of statins<br>• Patients with severe renal impairment<br>• Pregnancy<br>• Children (no studies so far) |

* as defined by the corresponding labelling

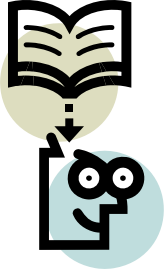
Carbonnelle *et al.*, submitted

# 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<br>• Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia<br>• CNS effects: patients at risk of epilepsy<br>• Dysglycemia: diabetic patients<br>• **Pregnancy, lactation, infants** |
| | moxifloxacin | • **Tendon disorders:** elderly, patients taking corticoids, or with kidney, heart or lung transplants<br>• Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia<br>• CNS effects: patients at risk of epilepsy<br>• **Pregnancy, lactation, infants** |
| **tetracyclines** | doxycycline | • **Pregnancy, lactation, infants** |

* as defined by the corresponding labelling

Carbonnelle *et al.*, submitted



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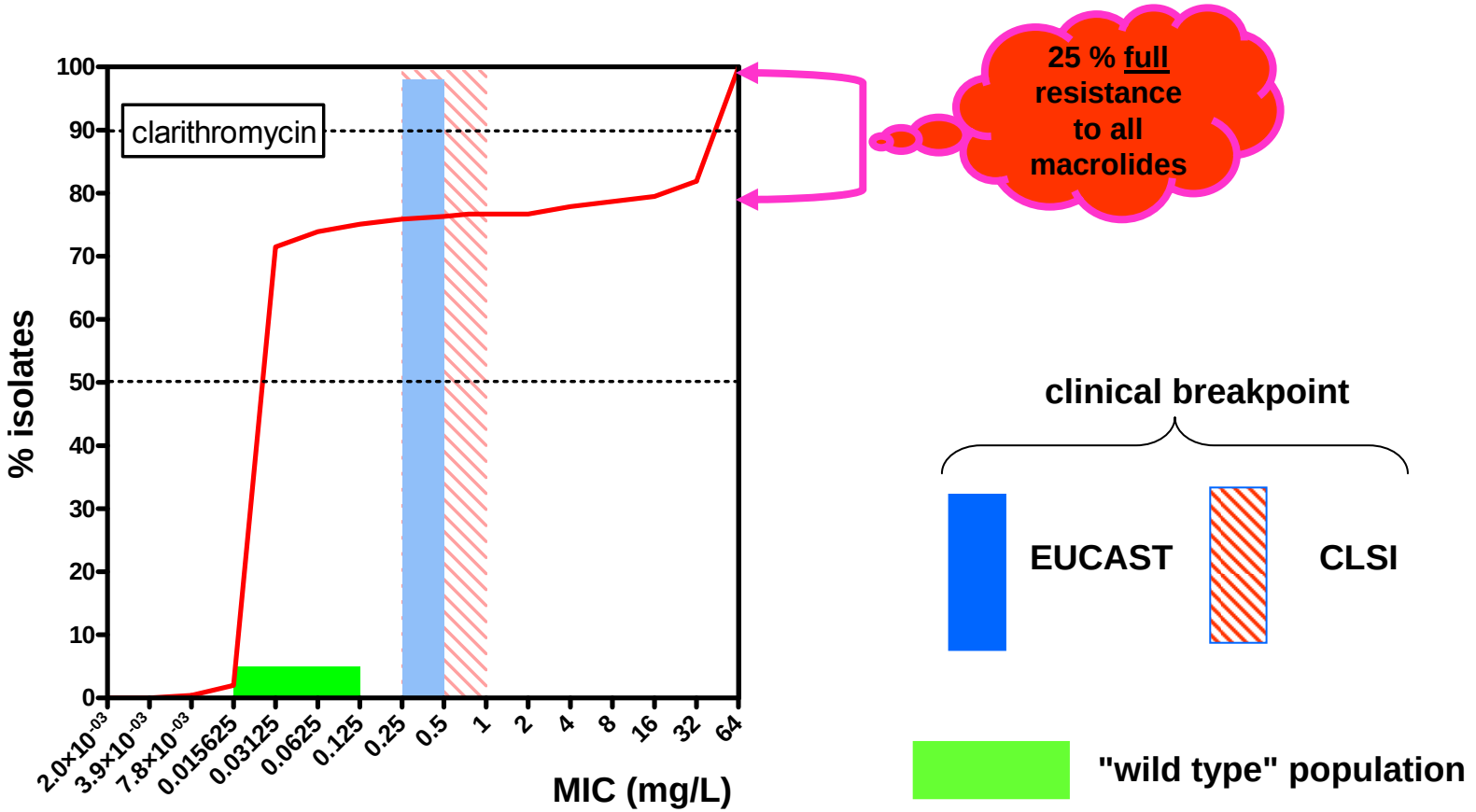
# Macrolides (alone) are no longer an option in Belgium …

***S. pneumoniae*** **prevalence (%) of macrolide-resistant and intermediate strains in 2008 in Belgium (CAP patients; n=249)**

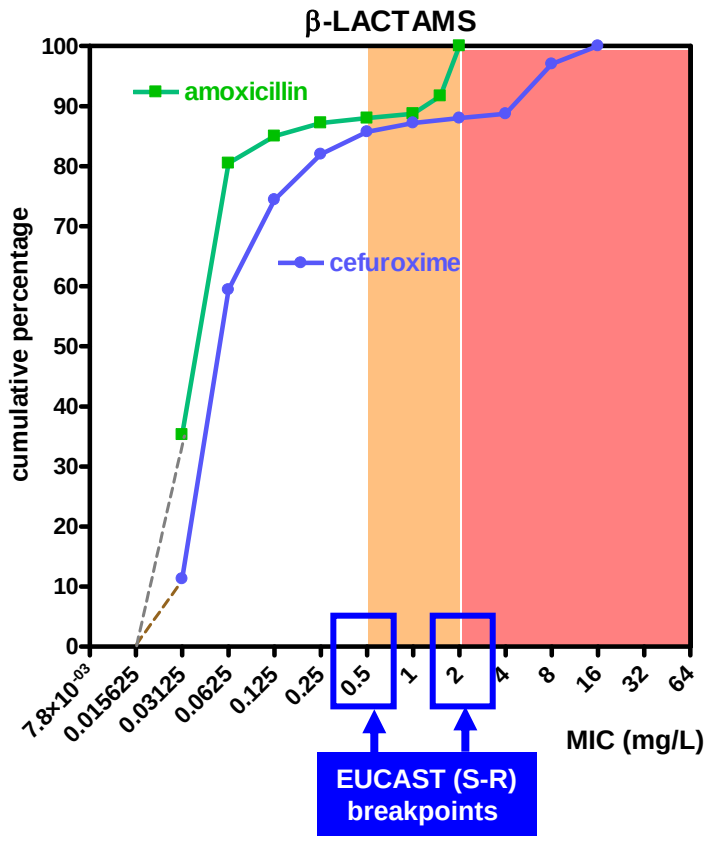



Lismond *et al.* ECCMID 2009 – poster 1099

http://www.eucast.org

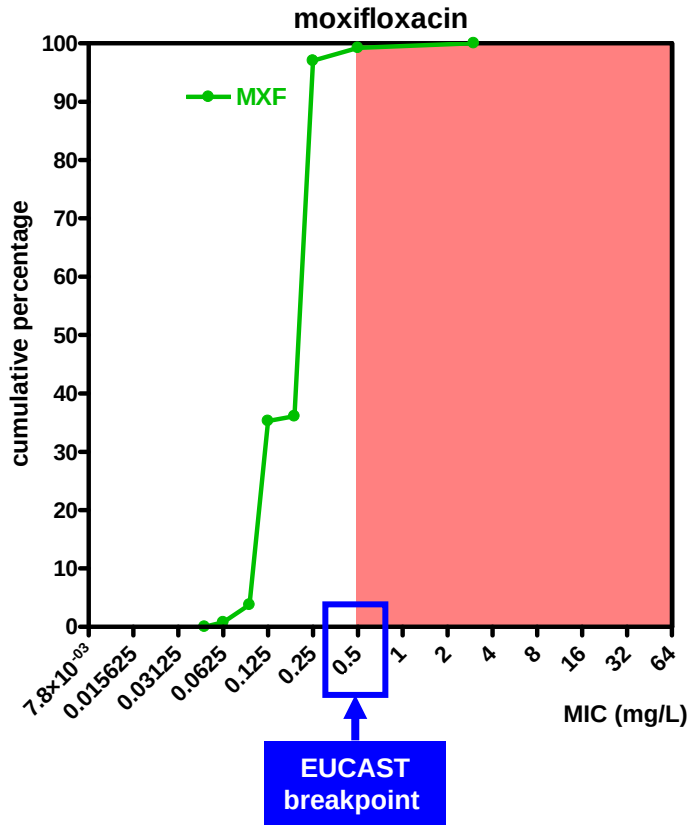
# β-lactams are reaching their limits in Belgium for CAP

## (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) ...**

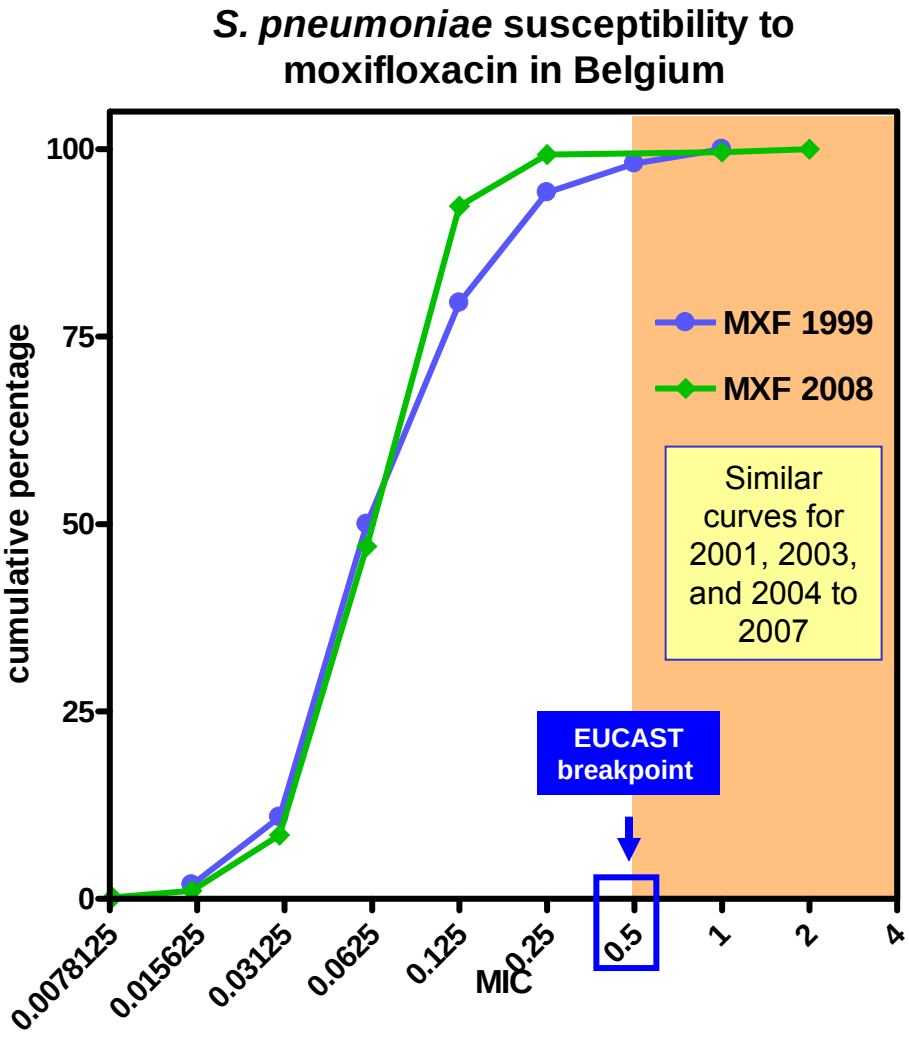
Lismond *et al.*, ECCMID 2008




**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.)

# Conclusions (1 of 2)

- The overall safety profile of fluoroquinolones (and moxifloxacin in particular) is similar or better than comparators
  - Hepatic events reactions are within range of other antibacterials, and 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
  - Class events (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 are a useful alternatives when "*1st line antibiotics*" (for CAP or COPD) have problems;
- The safety profiles of higher doses of β-lactams or of levofloxacin is not well established
- Moxifloxacin is not causing excessive toxicity if 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.