Fluoroquinolones: are they all the same (or not) ?

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With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/7383/078554

Disclosures and slides availability

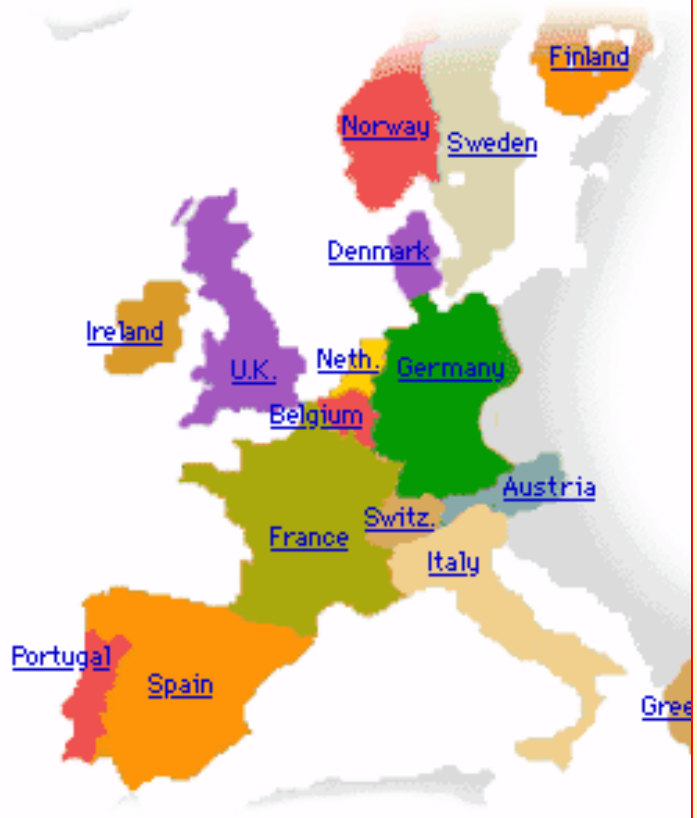
- Research grants
  - Theravance, Astellas, Cempra, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Debiopharm, Eumedica
  - Fund for Sientific Research (*F.R.S.-FNRS*), Federal Public Service "Public Health", Walloon and Brussels Regions, European Union (FP7 and JPIAMR)

- Speaker's honoraria
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, Vifor
  - Flemish Education Program on Antibiotics *(Opleidingsprogramma Antibioticabeleid Vlaanderen)*

- Advisory Committees and Decision-making Bodies
  - US National Institutes of Health (*grant reviewing*)
  - General Assembly and former member of the Steering committee of EUCAST
  - External expert for the European Medicines Agency (EMA)
  - Former member Belgian Drug Reimbursement Committee (*CRM* / *CTG*)
  - Member of the Belgian Antibiotic Policy Coordination Committee (BAPCOC)
  - Governance of the EU program "DRIVE AB" (new economical framework for antibiotics)

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

Belgium



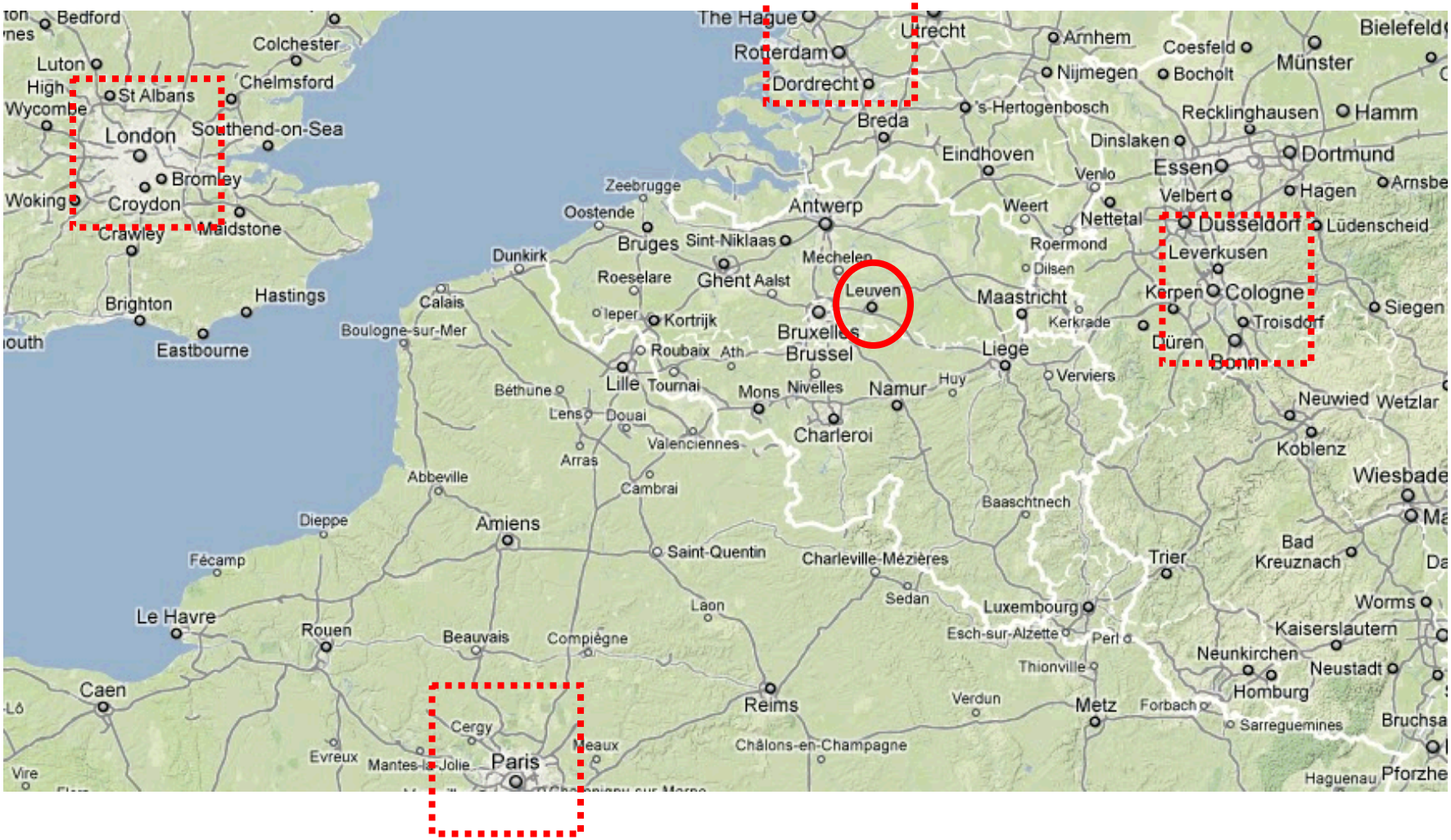
10 millions inhabitants …

10 Nobel prizes (10/850)

- **Peace**
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)
- **Literature**
  - Maurice Maeterlinck, Ghent (1911)
- **Medicine**
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)
- **Chemistry**
  - Ilya Prigogyne, Brussels (1977)
- **Physics**
  - François Englert, Brussels (2013)

The *Catholic University of Louvain* in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)

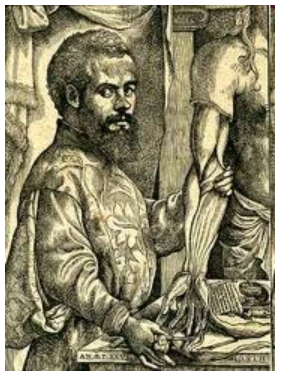


The *Catholic University of Louvain* in brief (2 of 4)

- It was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's

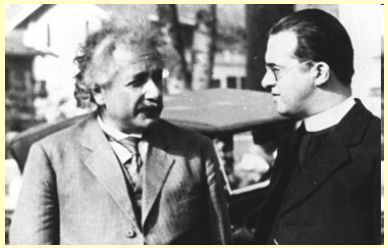
Erasmus



Vesalius

The *Catholic University of Louvain* in brief (3 of 4)

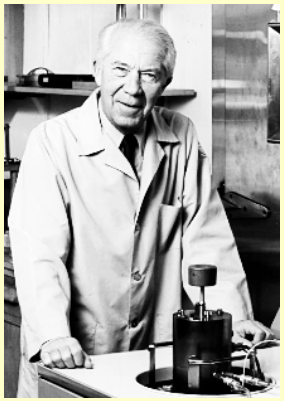
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("*big bang*")
(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)

(here in front of a centrifuge)



- in 1968, the University was divided into
  - a French-speaking ***Université catholique de Louvain***
  - a Flemish-speaking ***Katholieke Universiteit Leuven…***

The *Catholic University of Louvain* in brief (4 of 4)

- The Flemish-speaking ***Katholieke Universiteit Leuven*** has remained in Louvain (Leuven) and is named in English "**Catholic Universiteit Leuven**".
- The French-speaking ***Université catholique de Louvain*** has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwé)

Université catholique de Louvain
http://www.uclouvain.be

Katholieke Universiteit Leuven
http://www.kuleuven.be

- Together, the two Universities have about **55,000 students**

What do we do ?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- one-line monitoring of β-lactams
- novel antibiotics (and last studied)
  - lipoglycopeptides (oritavancin…)
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacin…)
  - ketolides (solithromycin…)
  - oxazolidinones (tedizolid …)

www.facm.ucl.ac.be

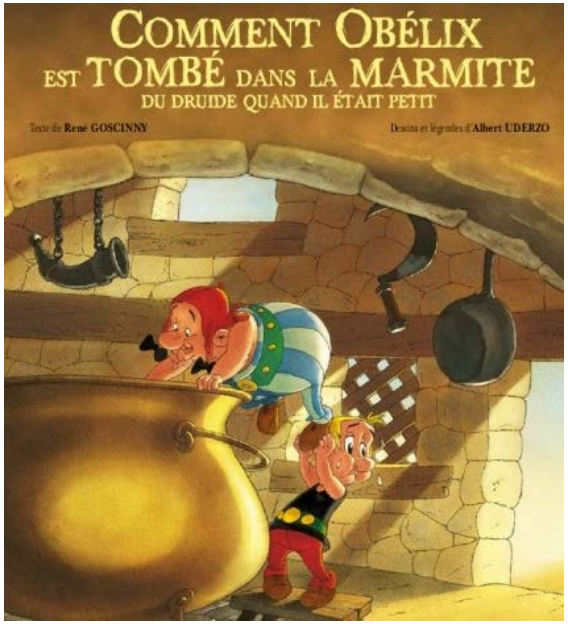
A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

www.isap.org

Why do I have an interest in fluoroquinolones ?

Because, like Obélix, I fell into when I was young …



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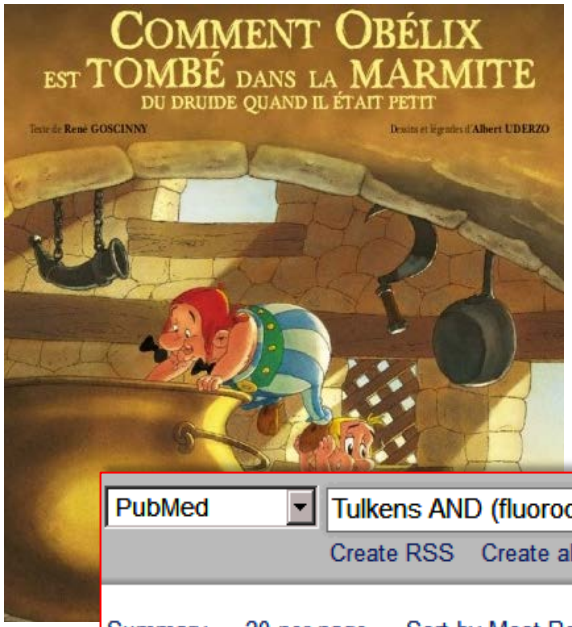

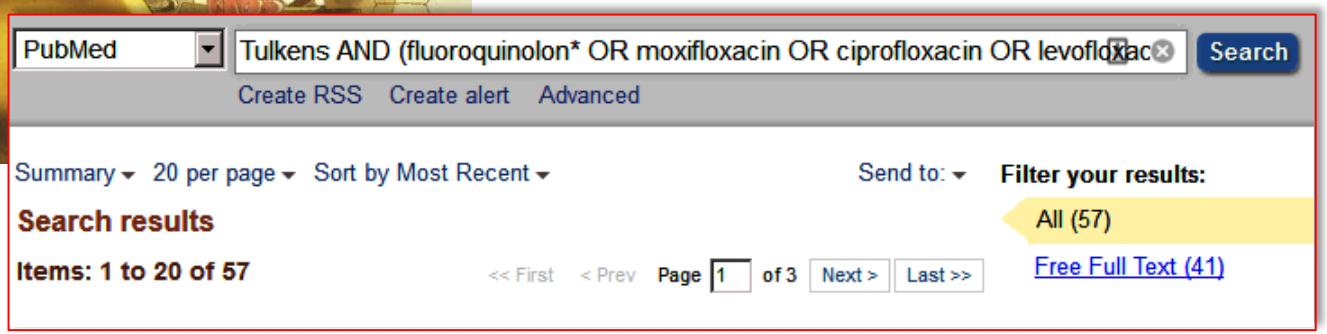

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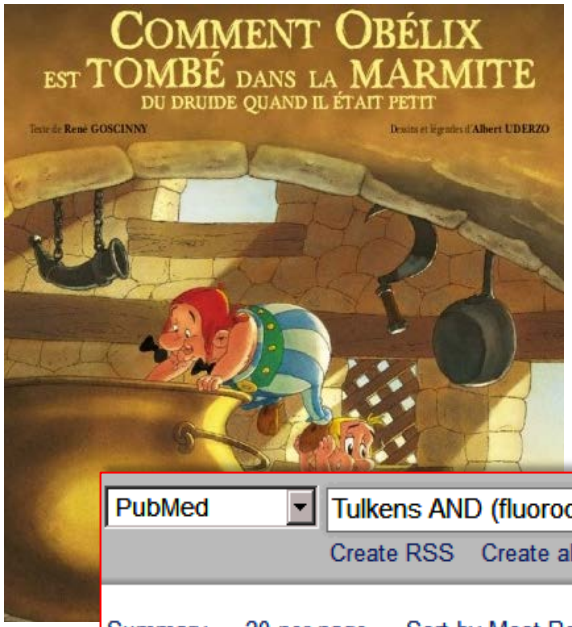


1990

Journal of Antimicrobial Chemotherapy (1990) **26**, *Suppl. B*, 27–39

Cellular uptake, localization and activity of fluoroquinolones in uninfected and infected macrophages

Marie-Béatrice Carlier[a], Bernard Scorneaux[a], Andrée Zenebergh[a,*], Jean-François Desnottes[b] and Paul M. Tulkens[a]

[a]*Laboratoire de Chimie Physiologique, and International Institute of Cellular and Molecular Pathology, Université Catholique de Louvain, Avenue Hippocrate 75, Bte 75.49, B-1200 Bruxelles, Belgium;* [b]*Rhône-Poulenc Santé, Centre de Recherches de Vitry/Alfortville, 13, Quai Jules Guesde, B.P. 14, F–94403 Vitry s/Seine, France*

2005

REVIEW ARTICLE

10.1111/j.1469-0691.2005.01131.x

Quinolones in 2005: an update

F. Van Bambeke[1], J.-M. Michot[1], J. Van Eldere[2] and P. M. Tulkens[1]

[1]Unit of Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels and [2]Department of Microbiology and Immunology, Rega Institute and Centre for Molecular Diagnostics, University Hospital, Catholic University of Leuven, Louvain, Belgium

Clin Microbiol Infect 2005; 11: 256–280

2012

ORIGINAL RESEARCH ARTICLE

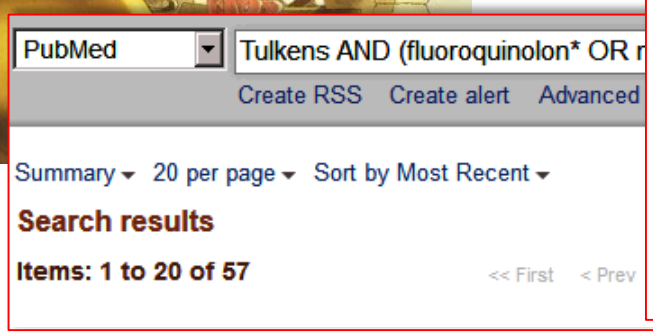
Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

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



What shall we discuss ?

- **The basics: how were quinolones invented ?**
  (are they different by design ?)

- **The real life in the lab: microbiological properties and risk of resistance…**
  (or how to really differentiate them …)

- **The real life in the doctor's office: efficacy and tolerance…**
  (is there a difference) ?

- **Should we use the "best in class" ?**

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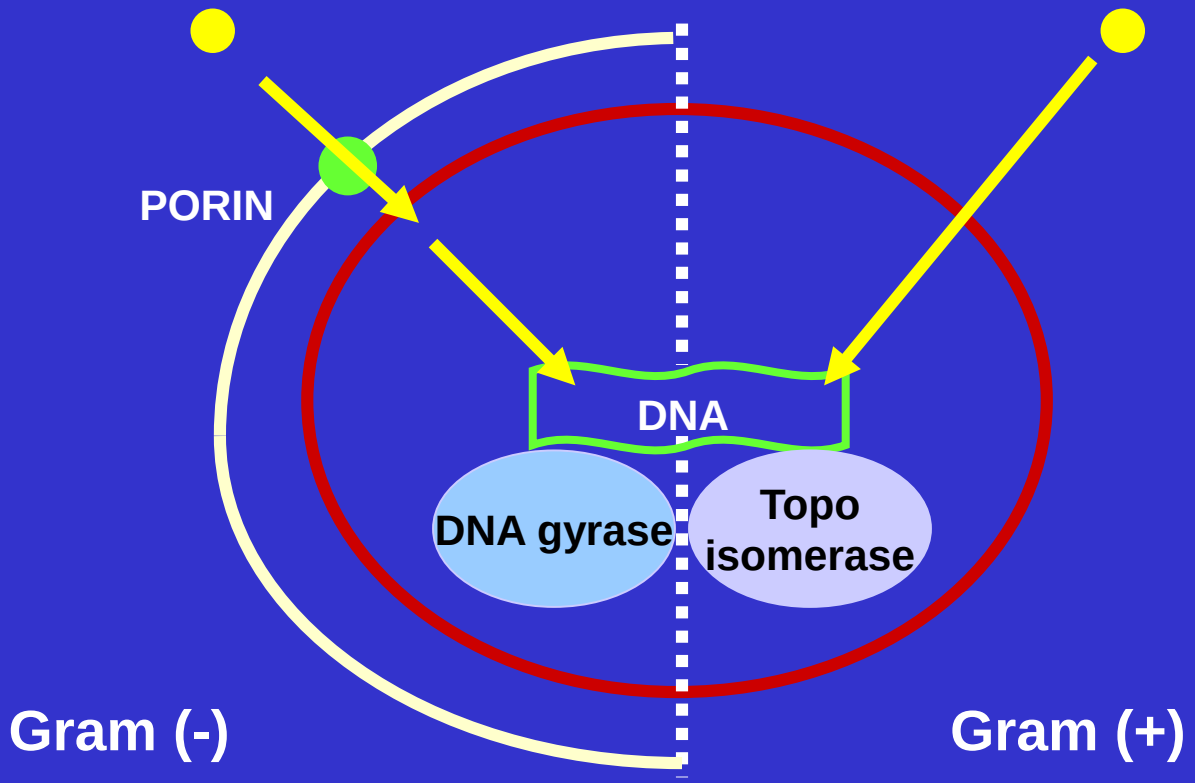
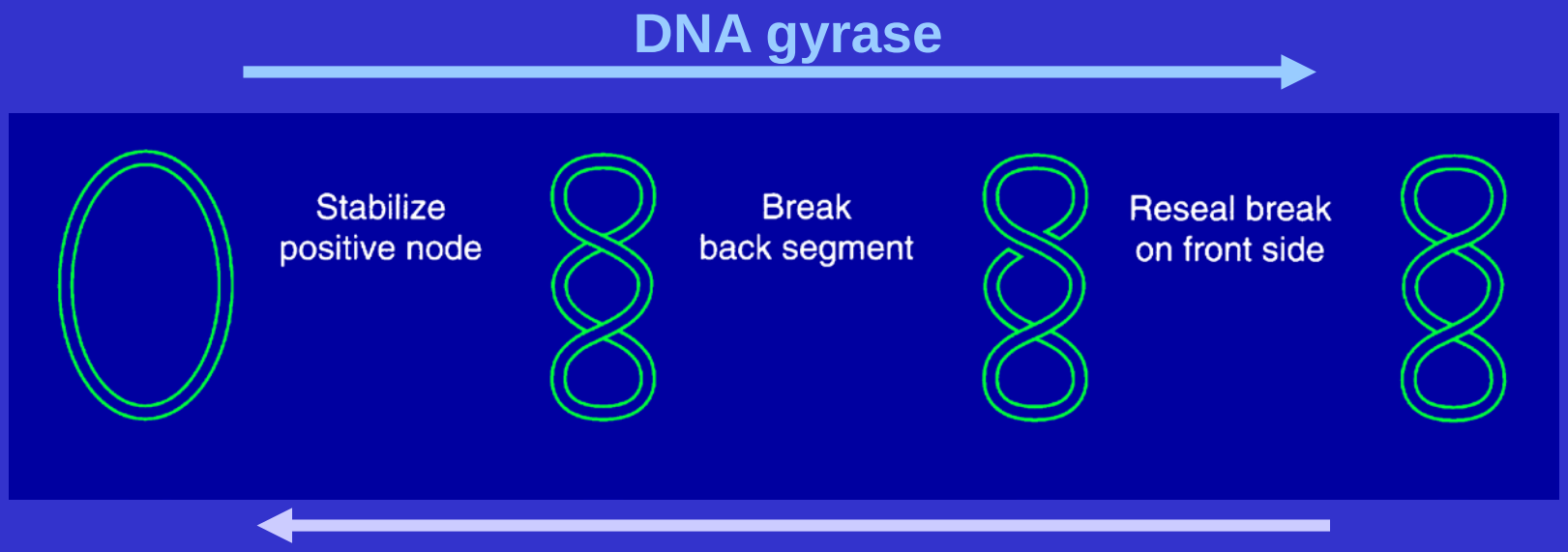
Mechanism of action of fluoroquinolones: the basics...

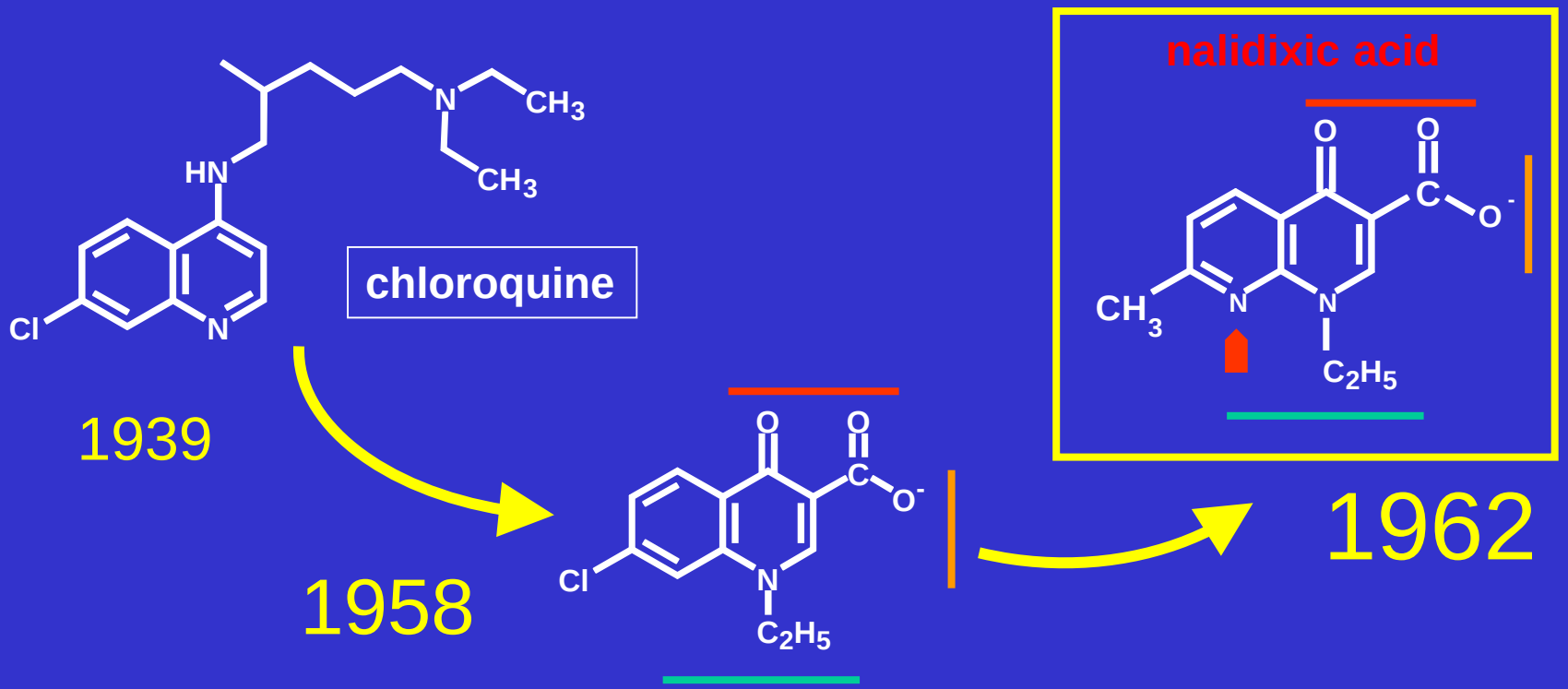


2 key enzymes in DNA replication:



bacterial DNA is supercoiled

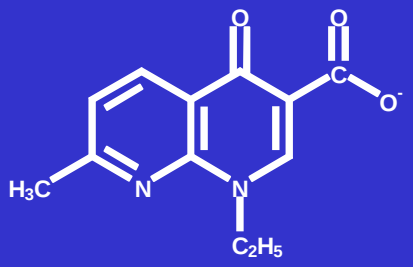
A bit of history: from chloroquine to nalidixic acid...



7-chloroquinoline
(synthesis intermediate found to display antibacterial activity)

From nalidixic acid to the 1st fluoroquinolone

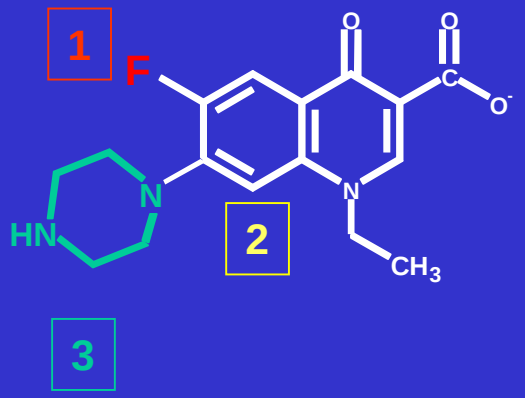
nalidixic acid



3 key modifications *...

1978

norfloxacin *



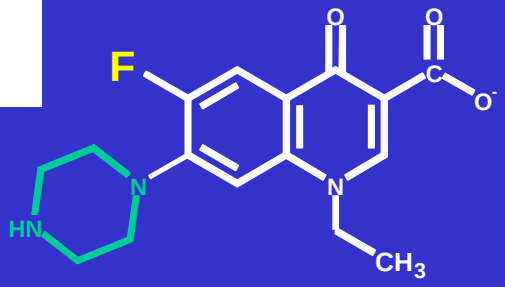
1. broader Gram(-) activity
2. less protein binding (50%)
3. longer half-life (3-4h)

* Belgian patent 863,429, 1978 to Kyorin

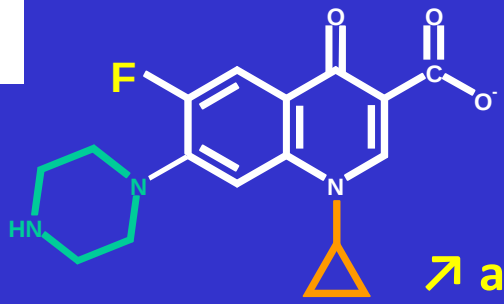
* 6-fluoro-7-pyrimidino-quinoleine

From norfloxacin to ciprofloxacin and ofloxacin

norfloxacin

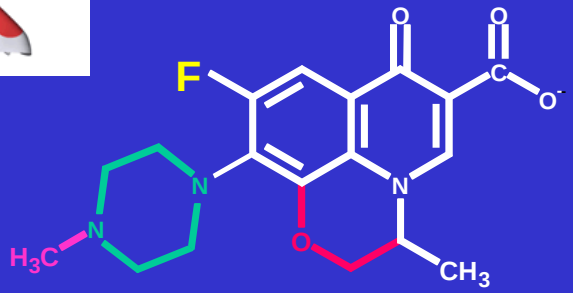


Ciprofloxacin *



↗ activity
(cyclopropyl)

Ofloxacin **



↗ half-life
(methyl)

check this…
(morpholine)

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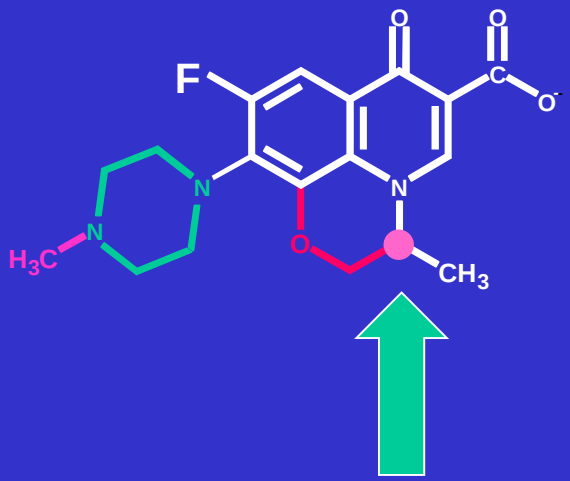
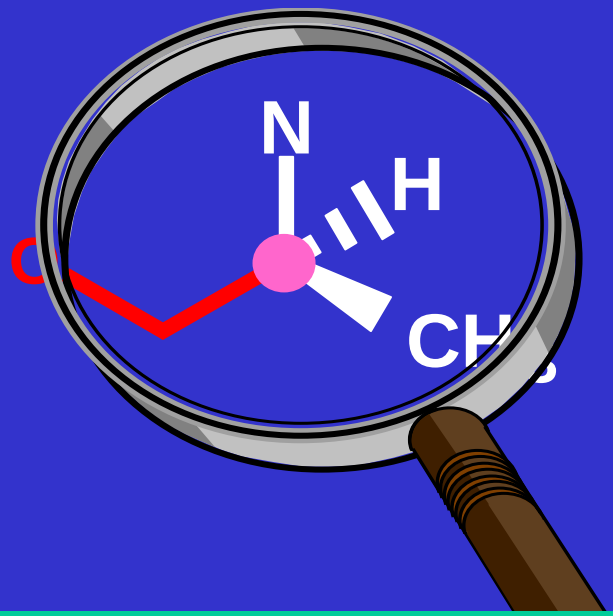
* Ger. pat. 3,142,854 to Bayer AG, 1983

** Eur. pat. Appl. 47,005 to Daiichi, 1982

Levofloxacin is the active isomer of ofloxacin

Ofloxacin is a racemic mixture 50/50





Levofloxacin is the pure (-) S isomer of ofloxacin *

The active form of ofloxacin is the (-) S isomer
The (+) R isomer is inactive but toxic

* Eur. pat. 206,283 to Daiichi, 1987

The present "first generation" of fluoroquinolones ...

- Nalidixic acid
- Oxolinic acid
- Flumequine
- Pipemidic acid

		$t_{1/2}$	activity
• Norfloxacin	Mainly anti Gram (-) activity	3-4 h	++
• Ofloxacin		6 h	++
• Ciprofloxacin		3-4 h	+++
• Levofloxacin		6 h	++/++

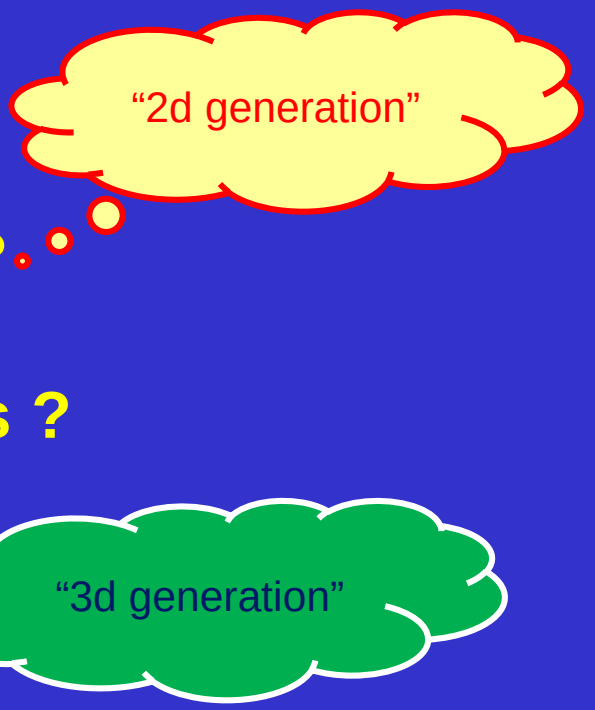
2 x more active than ofloxacin **per g**

How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity ?

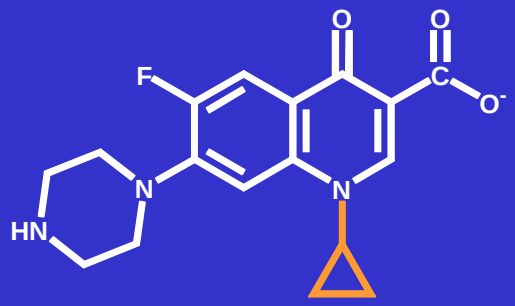
2. Further Improve Gram(+) activity ?

3. Acquire activity against anaerobes ?

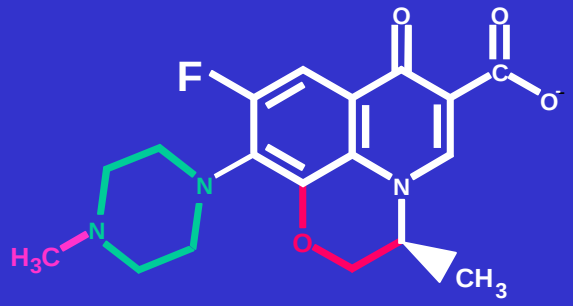


Activity against *S. pneumoniae*

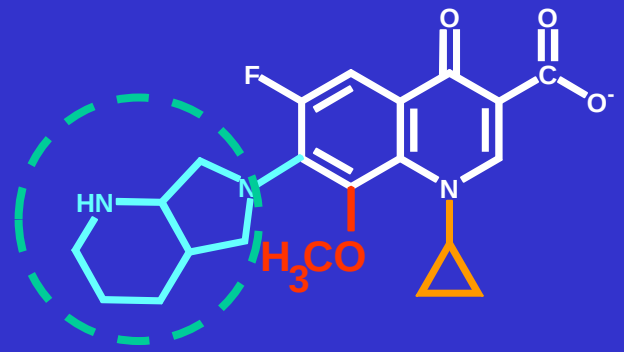
I | II | III / IV



ciprofloxacin
MIC = 0.5 - 2



levofloxacin
MIC = 0.5 -2



moxifloxacin
MIC = 0.01 - 0.5

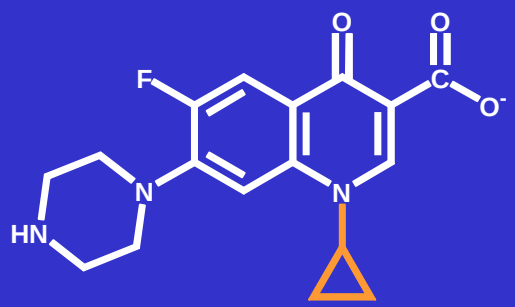
Hint:
lower MICs = a more potent antibiotic !

Activity against *B. fragilis (anaerobe)*

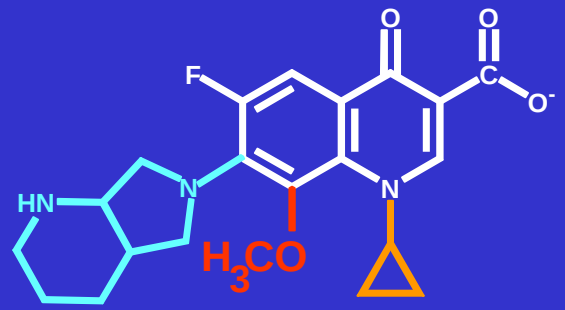
I

II

III / IV



ciprofloxacin
MIC = 2-128

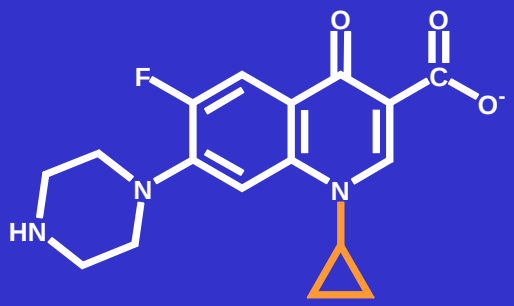


moxifloxacin
MIC= 0.125-8

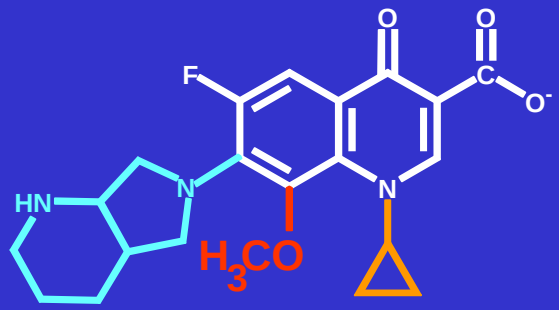
At this point …

Gram (-) **Gram (+)**

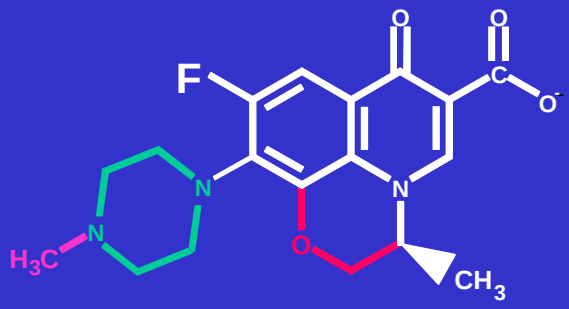
anaerobes



ciprofloxacin



moxifloxacin



levofloxacin

This is by design !

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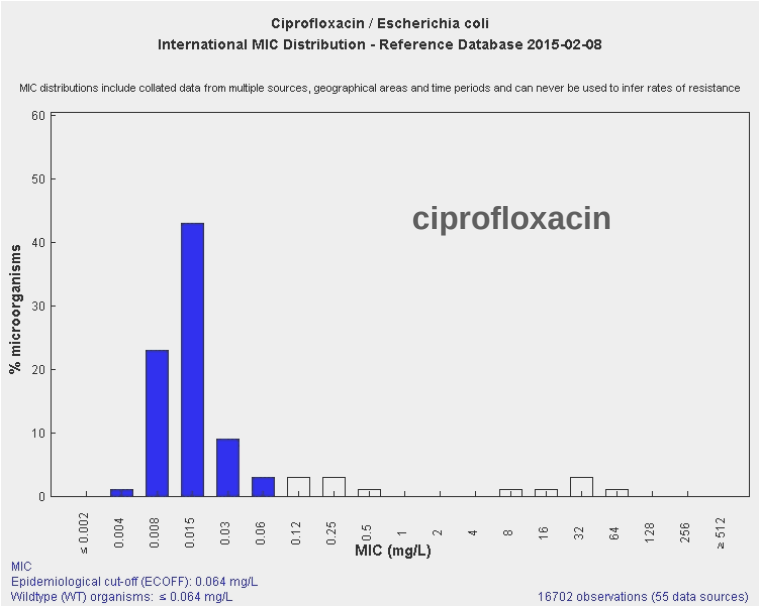
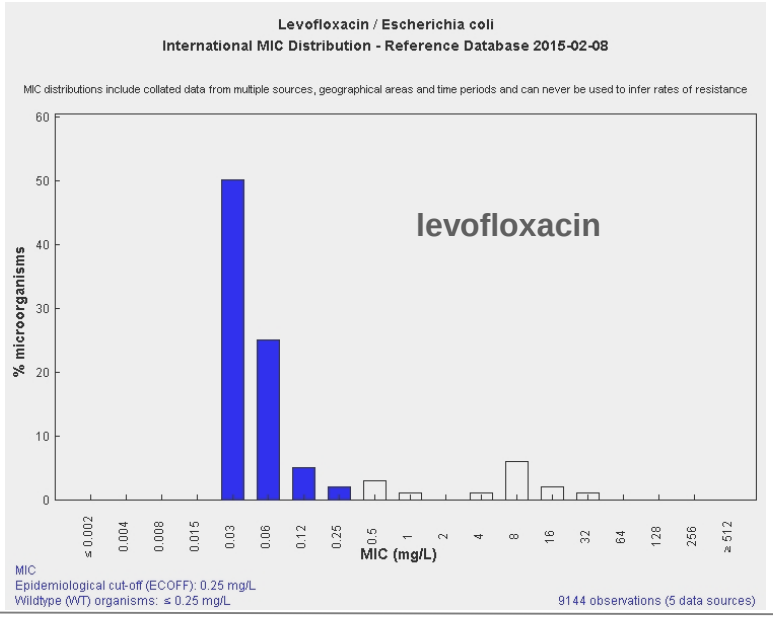
- **Should we use the "best in class" ?**

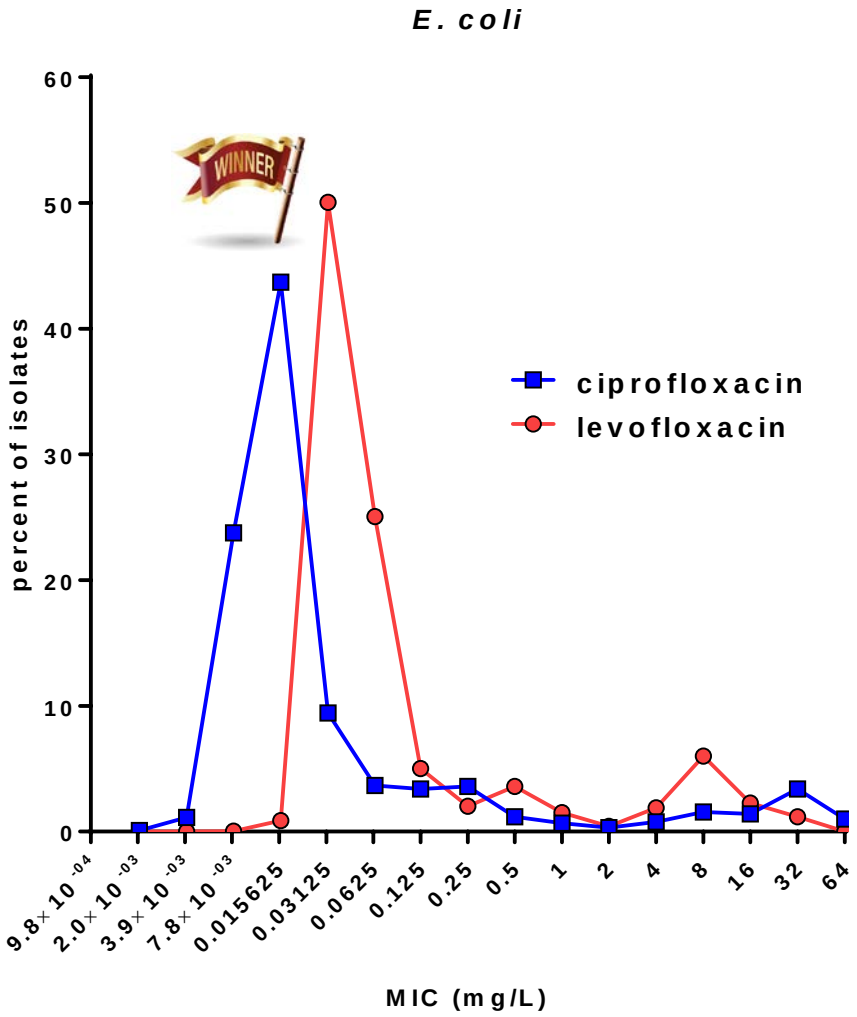
A unbiased estimation of antibiotic activity (in the absence of resistance)

MIC distributions and epidemiological cut-off

MIC for Gram-negative bacteria : *E. coli* as an example

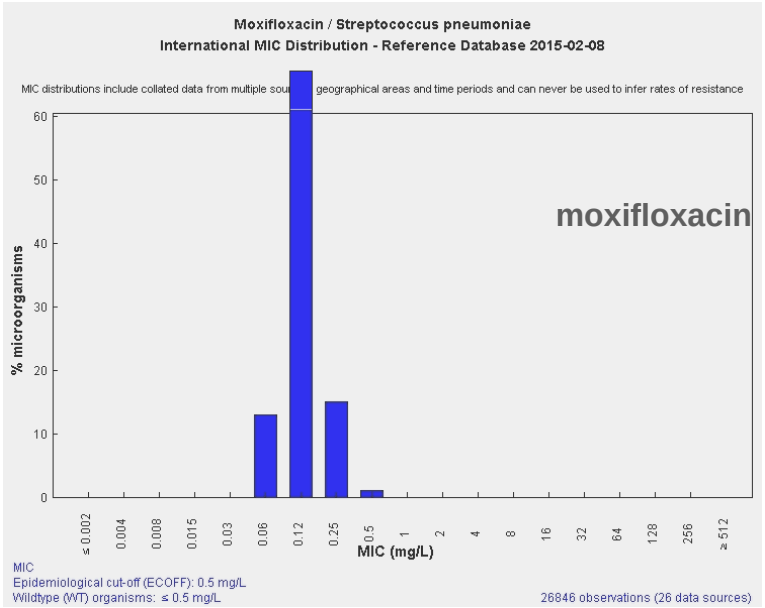


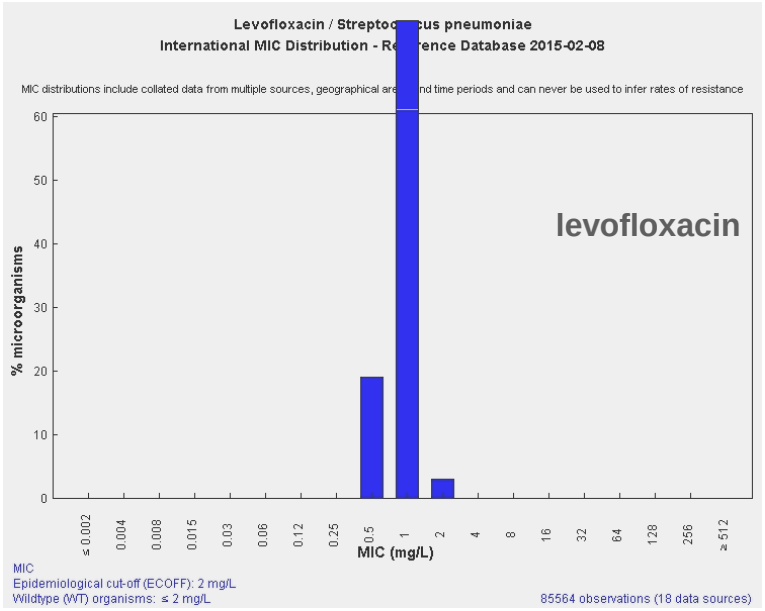


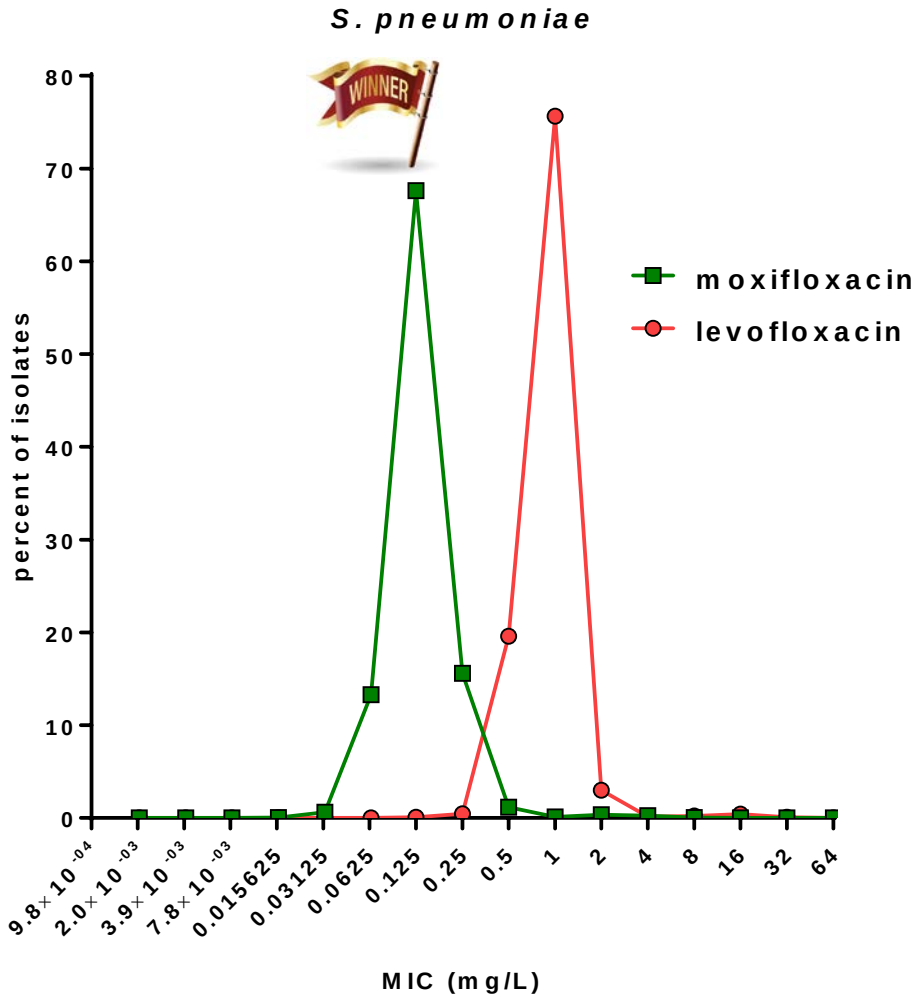


http://mic.eucast.org/Eucast2/regShow.jsp?Id=1022
http://mic.eucast.org/Eucast2/regShow.jsp?Id=1072
Last accessed: 8/2/2015

MIC for Gram-positive bacteria: *S. pneumoniae* as an example

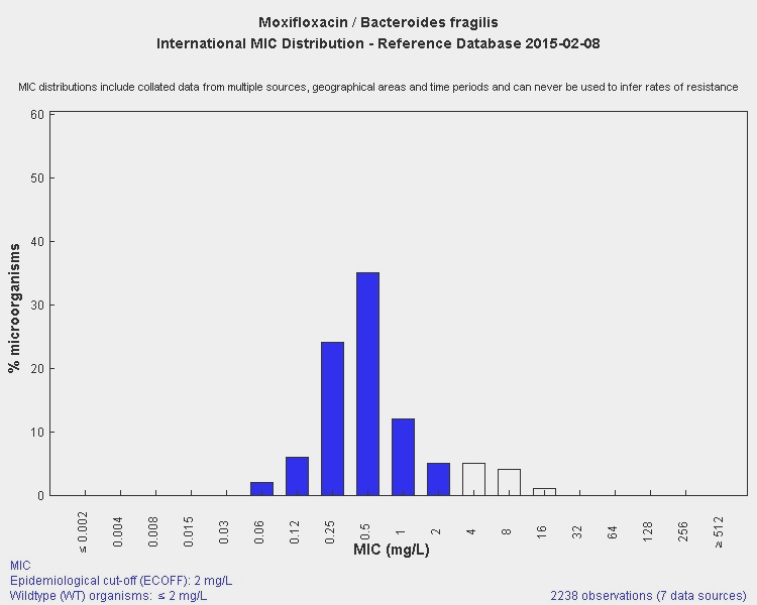


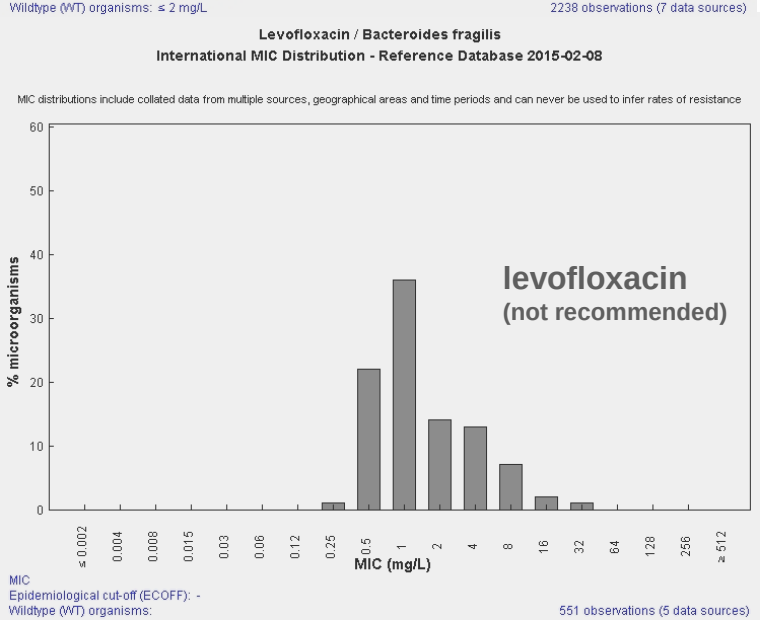


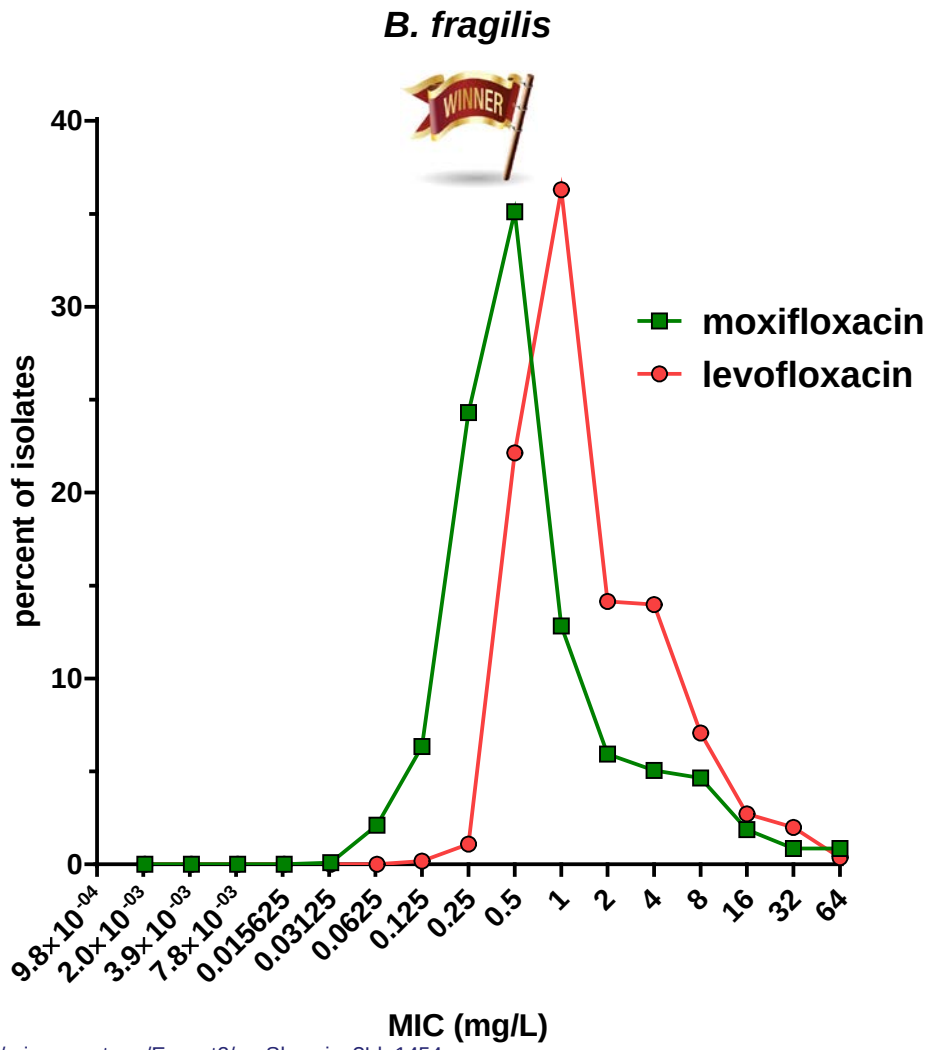


http://mic.eucast.org/Eucast2/regShow.jsp?Id=1099
http://mic.eucast.org/Eucast2/regShow.jsp?Id=1310
Last accessed: 8/2/2015

Anaerobes: *B. fragilis*







http://mic.eucast.org/Eucast2/regShow.jsp?Id=1454
http://mic.eucast.org/Eucast2/regShow.jsp?Id=1066
Last accessed: 8/2/2015

Killing abilities of fluoroquinolones: Are they all equal against susceptible strains ?

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

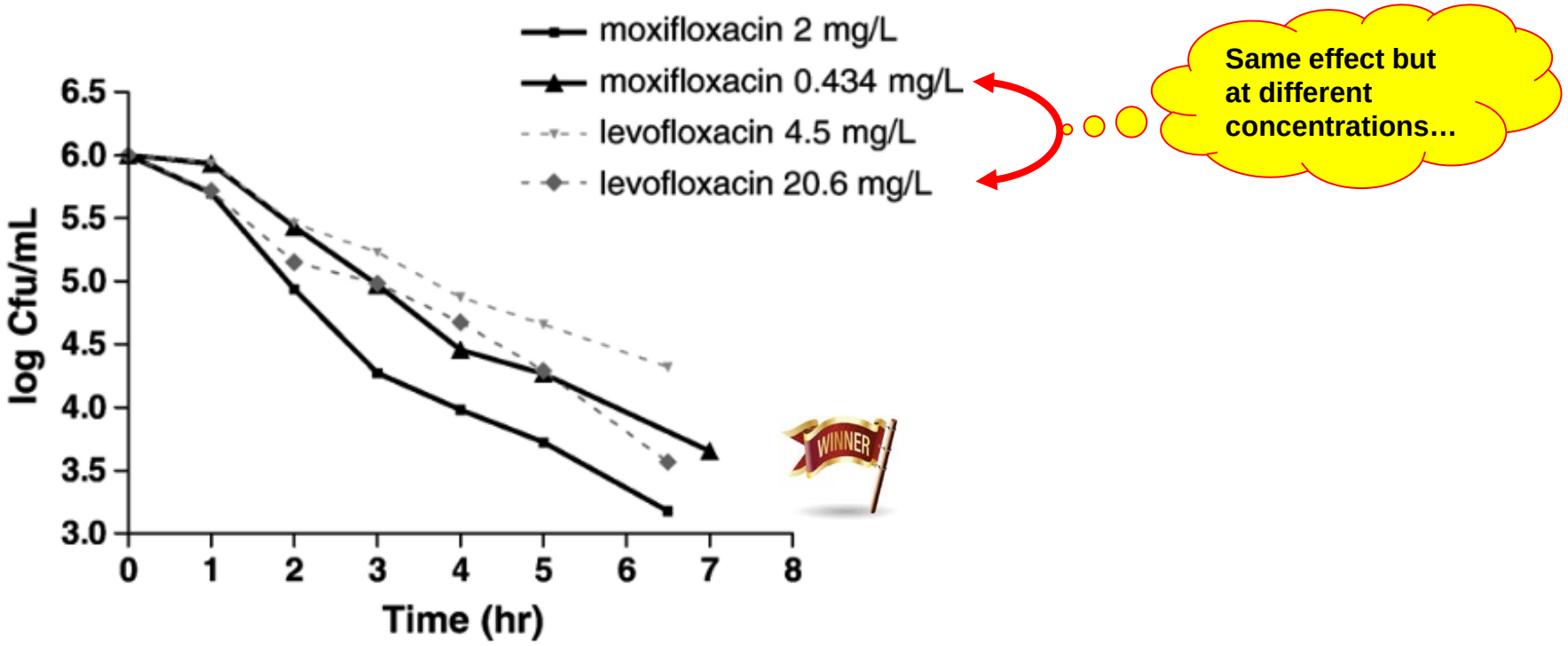


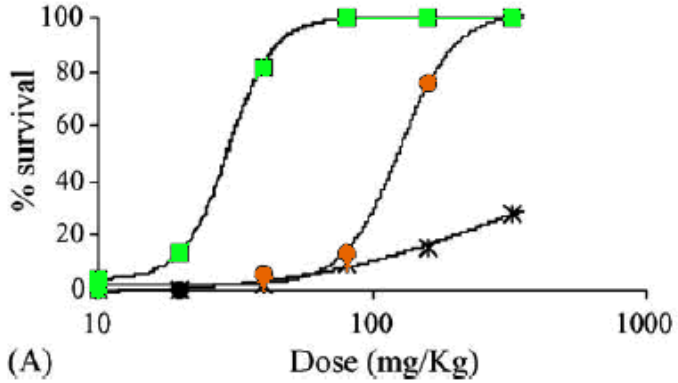
Fig. 1. Time kill curves of moxifloxacin versus levofloxacin against *S. pneumoniae* 7362 (average of 2 models).

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

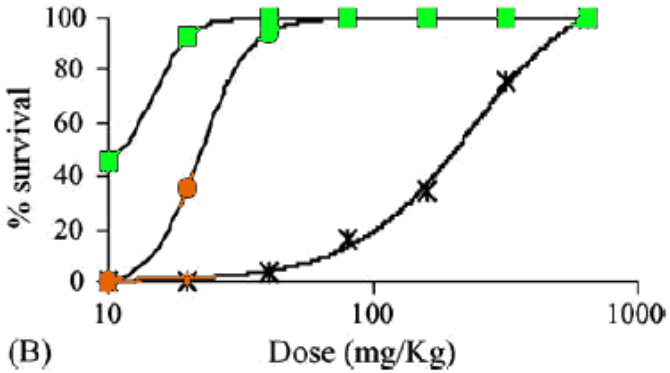
Killing abilities of fluoroquinolones: Are they all equal against less susceptible strains ?

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

Levofloxacin (LVX)



Moxifloxacin (MXF)

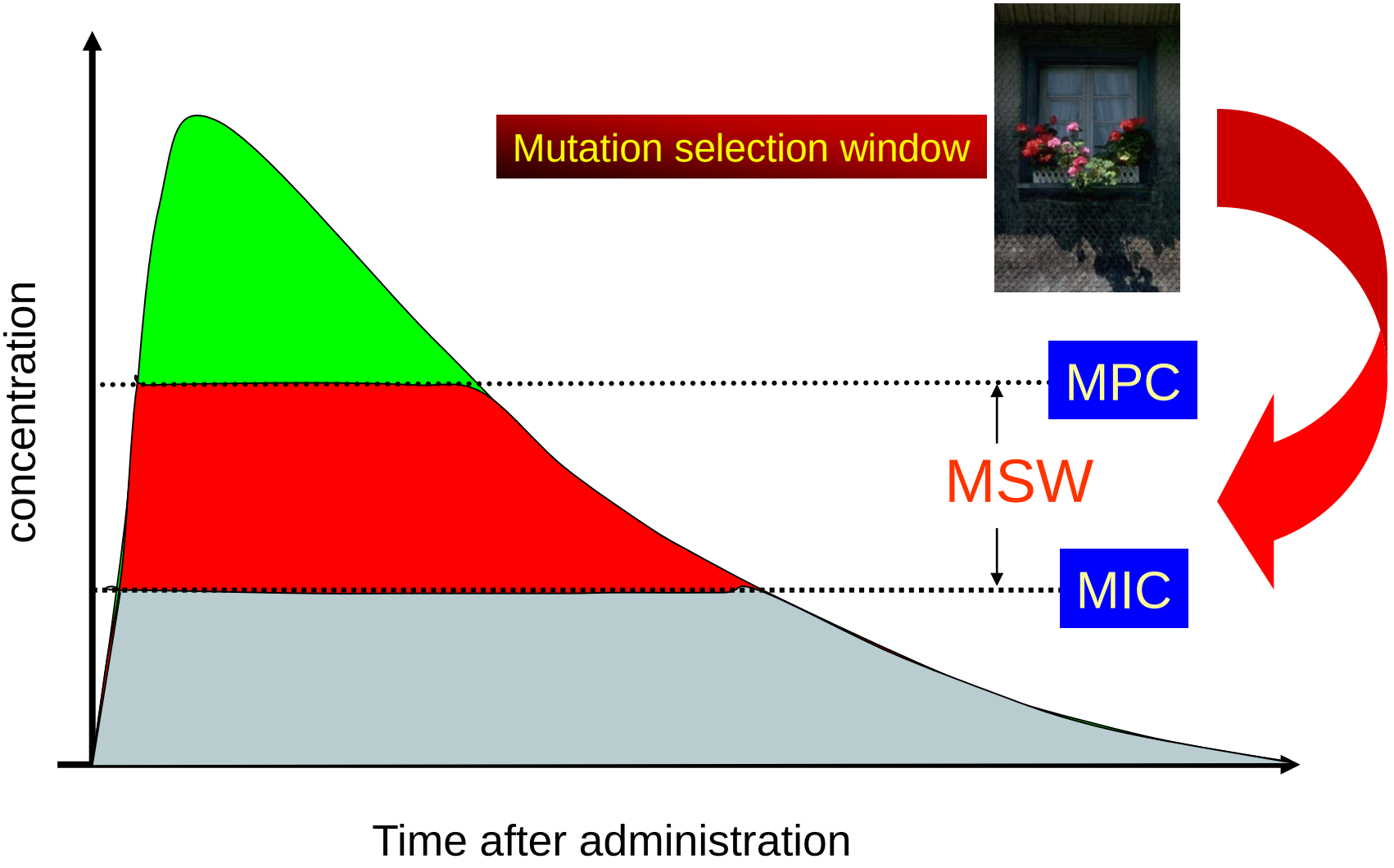


strain	MIC (mg/L)	
	MXF	LVX
AR33118 (■)	0.12	1
FL2812 (●)	0.25	2
FL5629 (✶)	4	32

Hint: lower dose (more to the left) → more potent antibiotic !

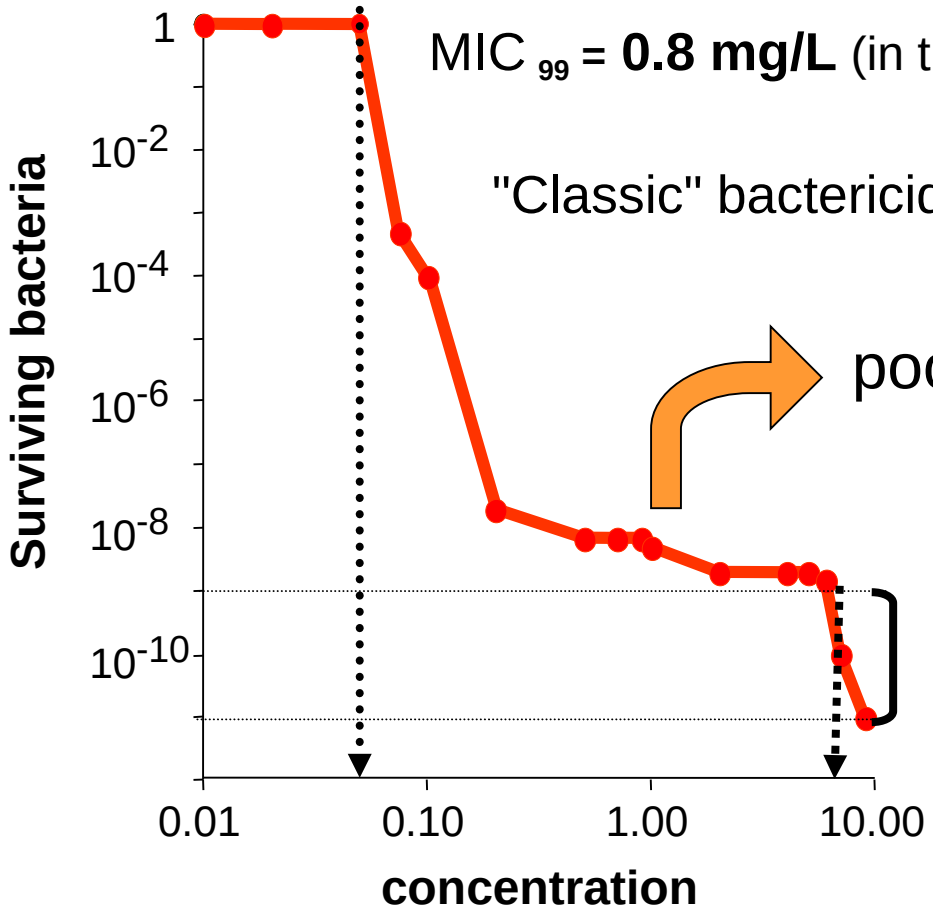
Huelves et al. Int J Antimicrob Agents 2006; 27:294–299

The risk for resistance to fluoroquinolones is to be "within the mutation selection window" …



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

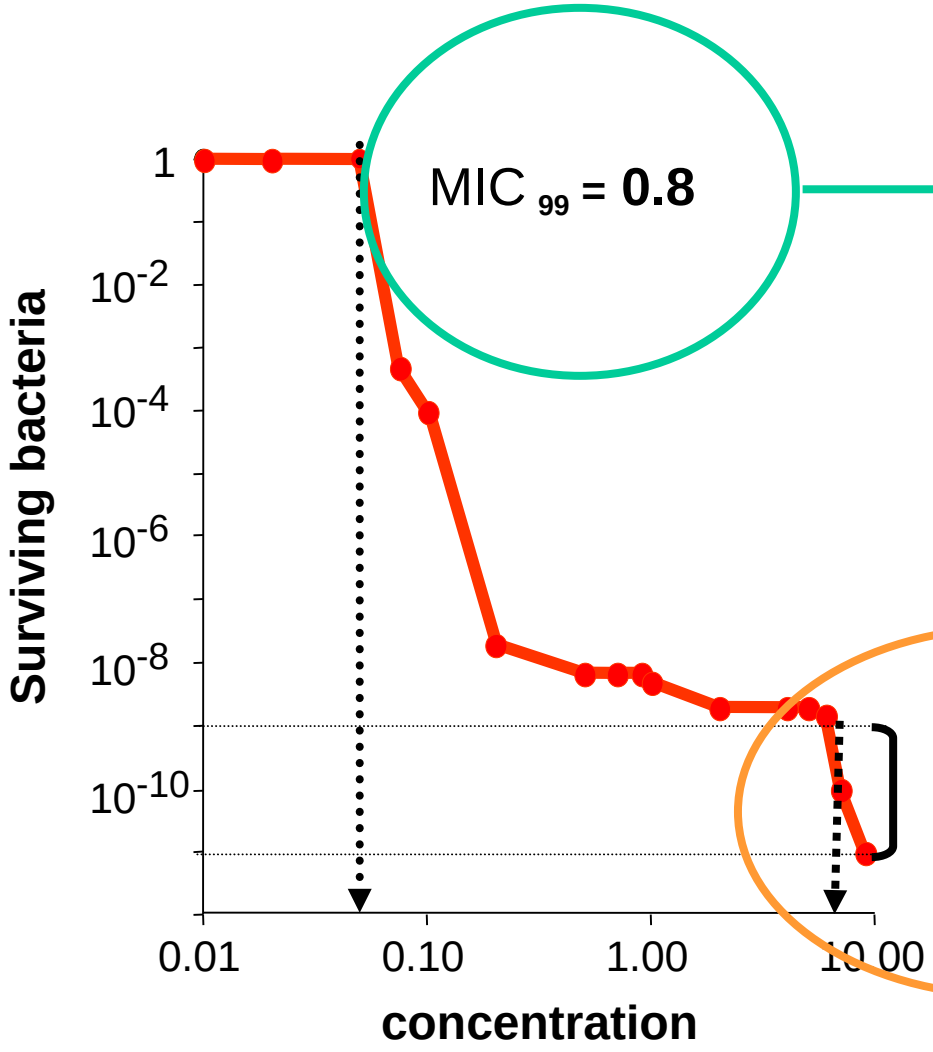
poorly sensitive organisms…

Elimination of resistant organisms

MPC_{10} = **9**

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

"Mutant Prevention Concentration …"



MIC $_{99}$ = **0.8**

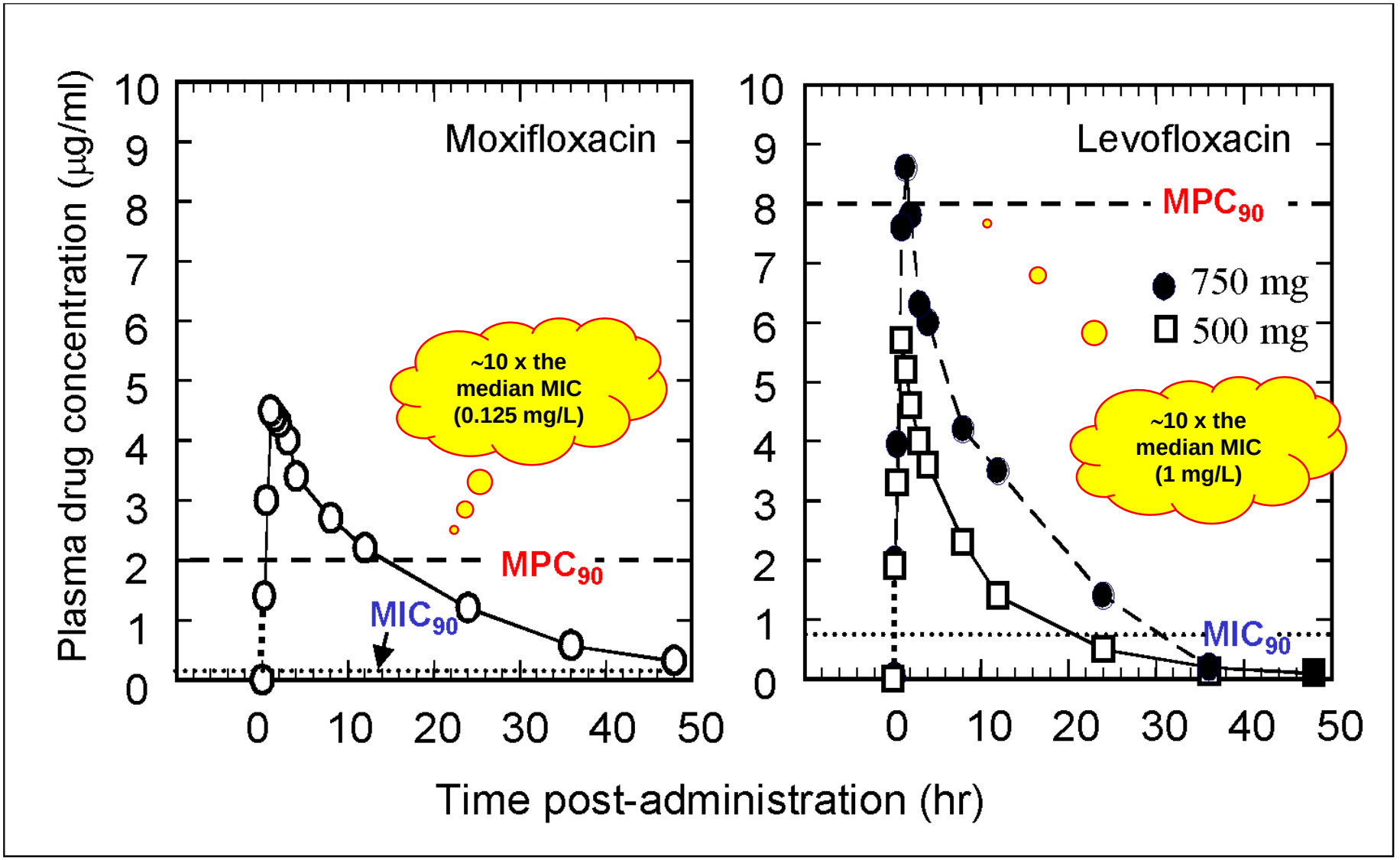
Concentration that inhibits the majority of the organisms

MPC $_{10}$ = **9**

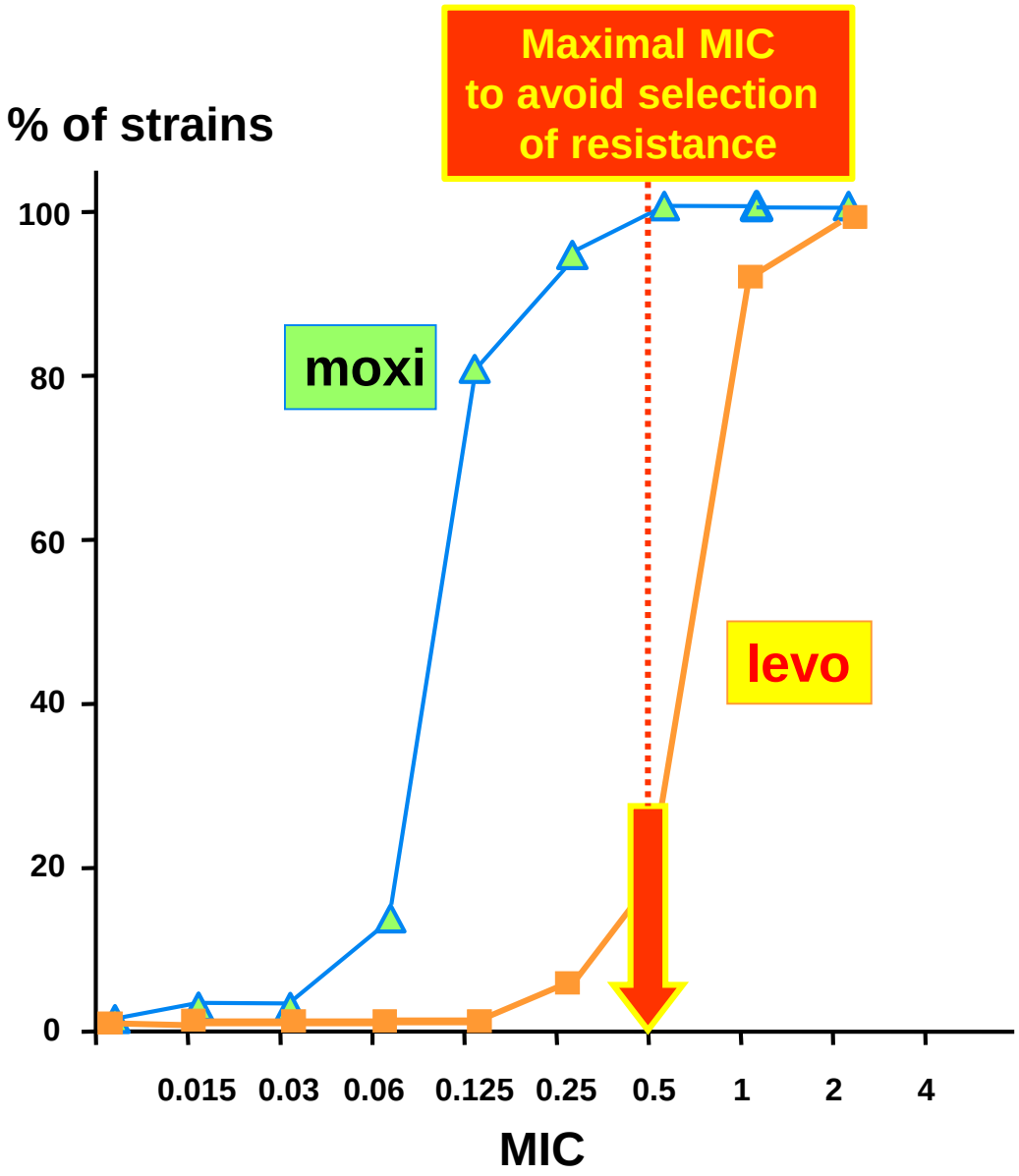
A concentration of about **10 x the MIC** is needed to prevent selecting resistant subpopulations !

Dong et al; AAC 43:1756-1758

MPC: moxifloxacin *vs* levofloxacin



Pharmacokinetics and "resistance" breakpoint *vs.* MIC



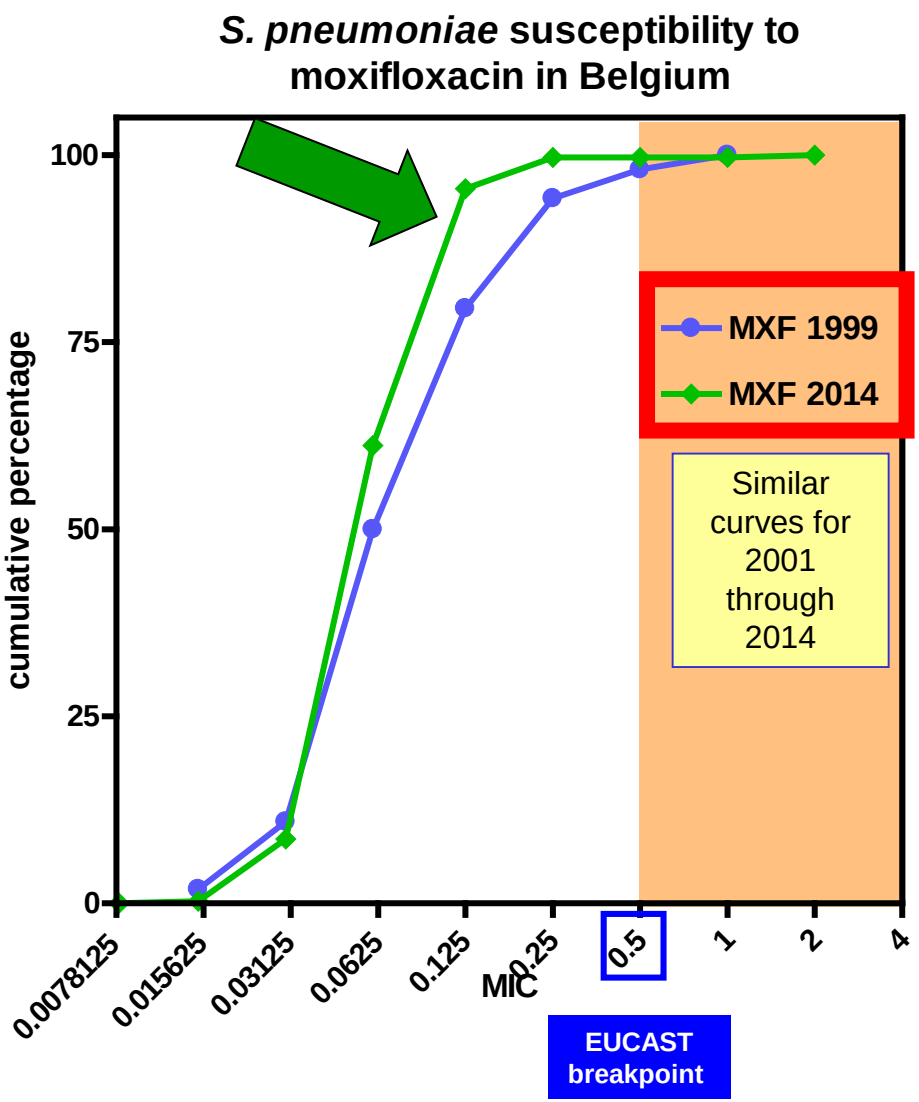
resistance breakpoint
- **AUC/MIC = 100**
- **peak/MIC = 10**

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)

Hs resistance to moxifloxacin materialized: evidence for *S. pneumoniae* in Belgium from 1999 to 2014 *



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

From data of a <u>national</u> collection

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S.pneumoniae* from clinically-confirmed CAP (n=132)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)
- Data available yearly for 1999 through 2014 at http://www.iph.fgov.be

Vanhoof *et al*. 19th ECCMID, Helsinki, 2009
Ceyssens *et al*. 35th RICAI, Paris, 2015
Ceyssens *et al.* submitted

What shall we discuss ?

- **The basics: how were quinolones invented ?**
  (are they different by design ?)

- **The real life in the lab: microbiological properties and risk of resistance…**
  (or how to really differentiate them …)

- **The real life in the doctor's office: efficacy and tolerance…**
  (is there a difference) ?

- **Should we use the "best in class" ?**

Head to head comparison…

Clinical Infectious Diseases 2006;42:73-81.

MAJOR ARTICLE

Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus that of Levofloxacin Therapy

Antonio Anzueto,[1,2] Michael S. Niederman,[3] James Pearle,[4] Marcos I. Restrepo,[1,2] Albrecht Heyder,[5] and Shurjeel H. Choudhri,[6] for the Community-Acquired Pneumonia Recovery in the Elderly Study Group[a]

[1]Department of Medicine, University of Texas Health Science Center, and [2]Veterans Evidence Based Research Dissemination and Implementation Center, Department of Medicine, South Texas Veterans Healthcare System, San Antonio, Texas; [3]Department of Medicine, Winthrop-University Hospital, Mineola, New York; [4]California Research Medical Group, Fullerton, California; [5]Carolina Research Specialists, Elizabeth City, North Carolina; and [6]Bayer Pharmaceuticals, West Haven, Connecticut

Head to head comparison…

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MAJOR ARTICLE

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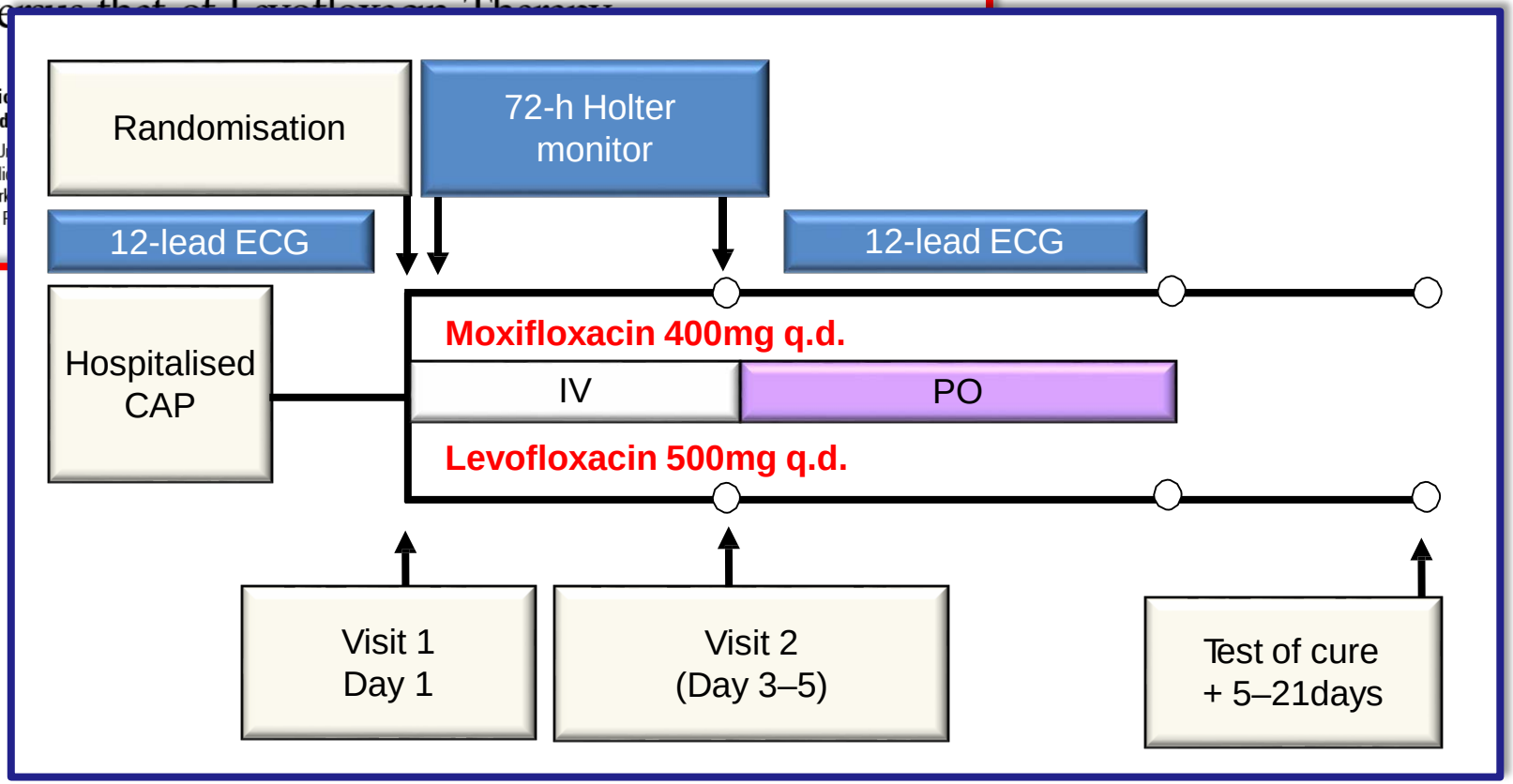
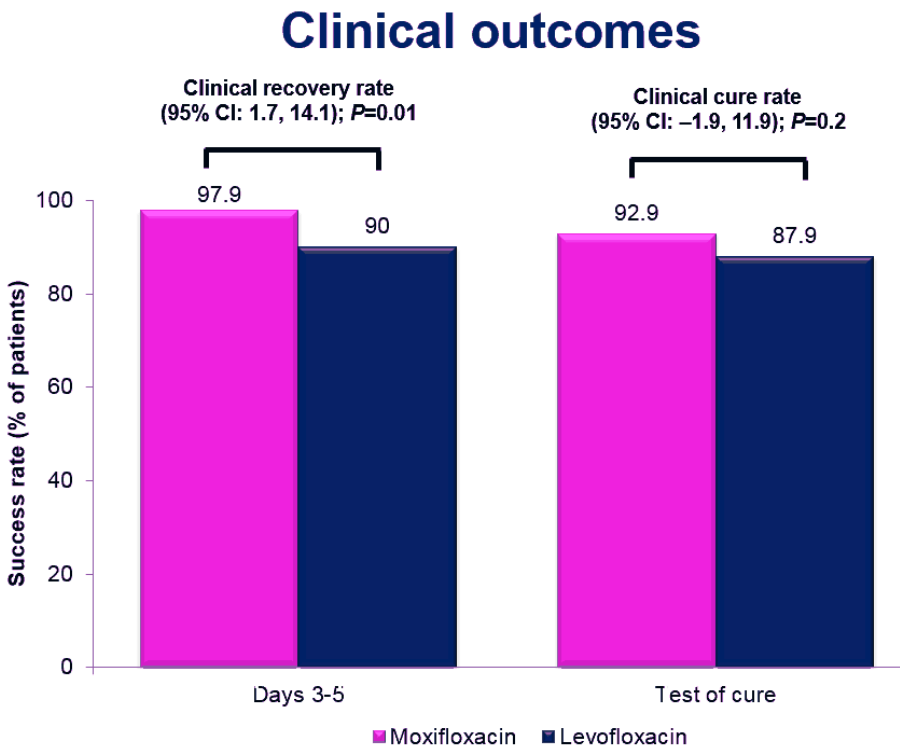
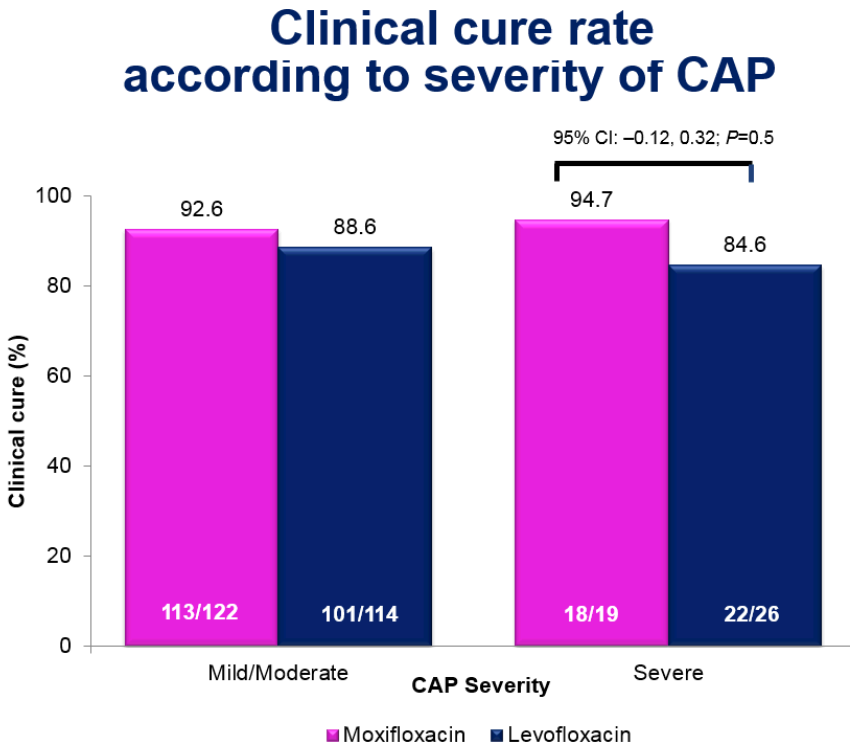


and results in a snapshot…





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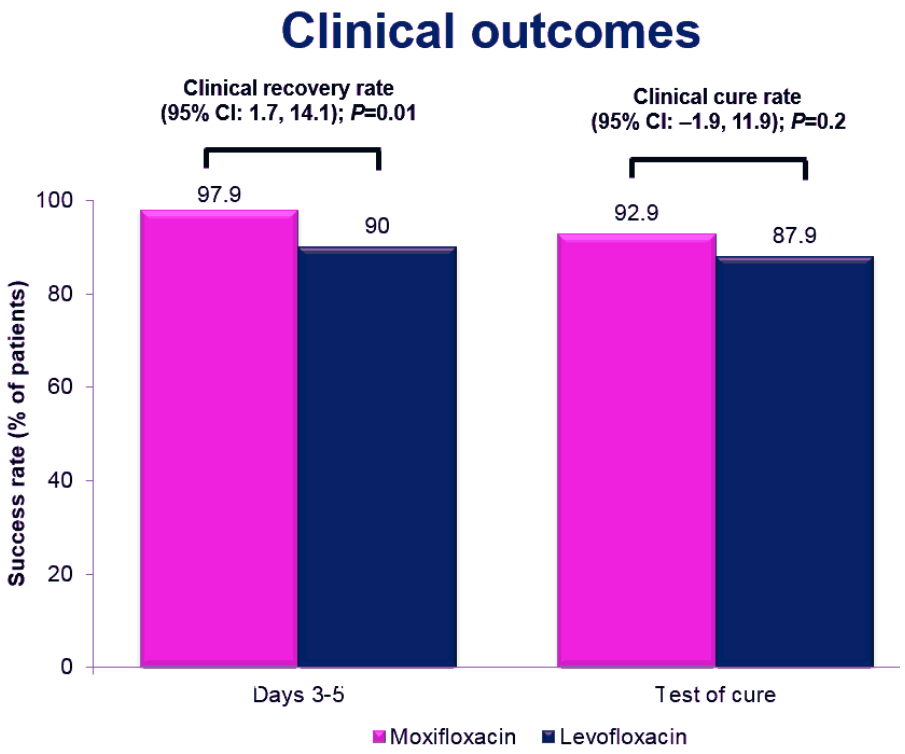

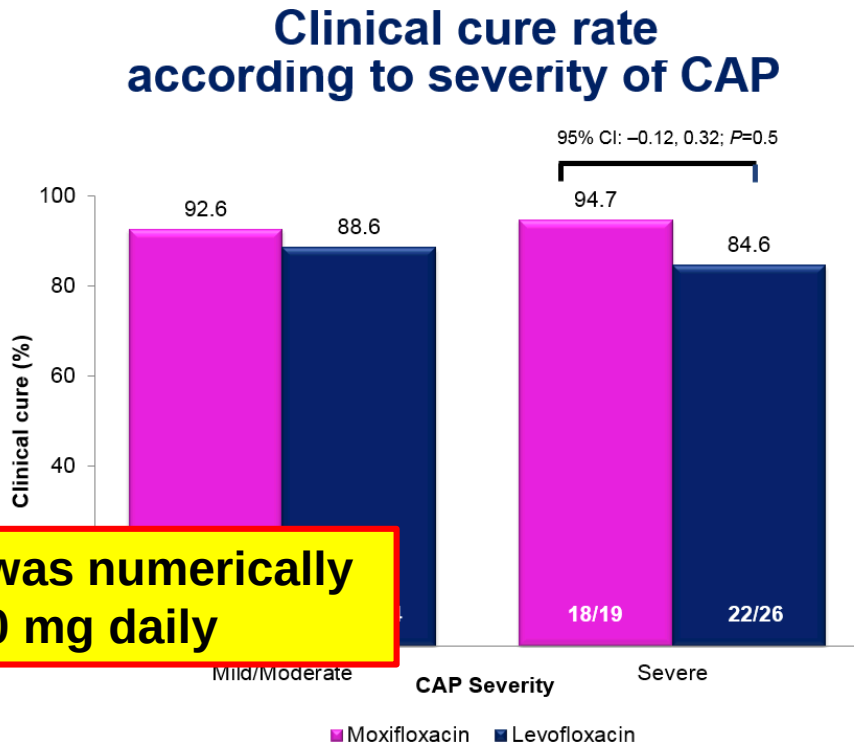

moxifloxacin 400 mg daily was numerically superior to levofloxacin 500 mg daily

Efficacy over combination: moxifloxacin alone against levofloxacin PLUS ceftriaxone in CAP !

Clinical Infectious Diseases 2008; 46:1499-509.

MAJOR ARTICLE

Moxifloxacin Monotherapy Is Effective in Hospitalized Patients with Community-Acquired Pneumonia: The MOTIV Study—A Randomized Clinical Trial

Antoni Torres,[1] Javier Garau,[2] Pierre Arvis,[3] Jean Carlet,[4] Shurjeel Choudhri,[5] Amar Kureishi,[6] Marie-Aude Le Berre,[3] Hartmut Lode,[7] John Winter,[8] and Robert C. Read,[9] for the MOTIV (MOxifloxacin Treatment IV) Study Group[a]

[1]Servei de Pneumologia i Allèrgia Respiratòria, Institut Clinic del Torax, Hospital Clínic de Barcelona, IDIBAPS, Facultat de Medicina, Consorcio CIBER del área de Enfermedades Respiratorias (CB06/06/0028), and [2]Hospital Mútua de Terrassa, University of Barcelona, Barcelona, Spain; [3]Bayer HealthCare, Puteaux, and [4]Intensive Care Unit and Infectious Diseases Department, Fondation-Hôpital Saint-Joseph, Paris, France; [5]Bayer HealthCare Pharmaceuticals, Toronto, Canada; [6]Bayer HealthCare Company, Beijing, People's Republic of China; [7]Institute for Clinical Pharmacology, Charité-Universitätsmedizin, Berlin, Germany; and [8]Department of Medicine, Ninewells Hospital and Medical School, Dundee, and [9]Section of Infection, Immunity and Inflammation, Sheffield University Medical School, Sheffield, United Kingdom

Efficacy: moxifloxacin alone against levofloxacin PLUS ceftriaxone in CAP !

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MAJOR ARTICLE

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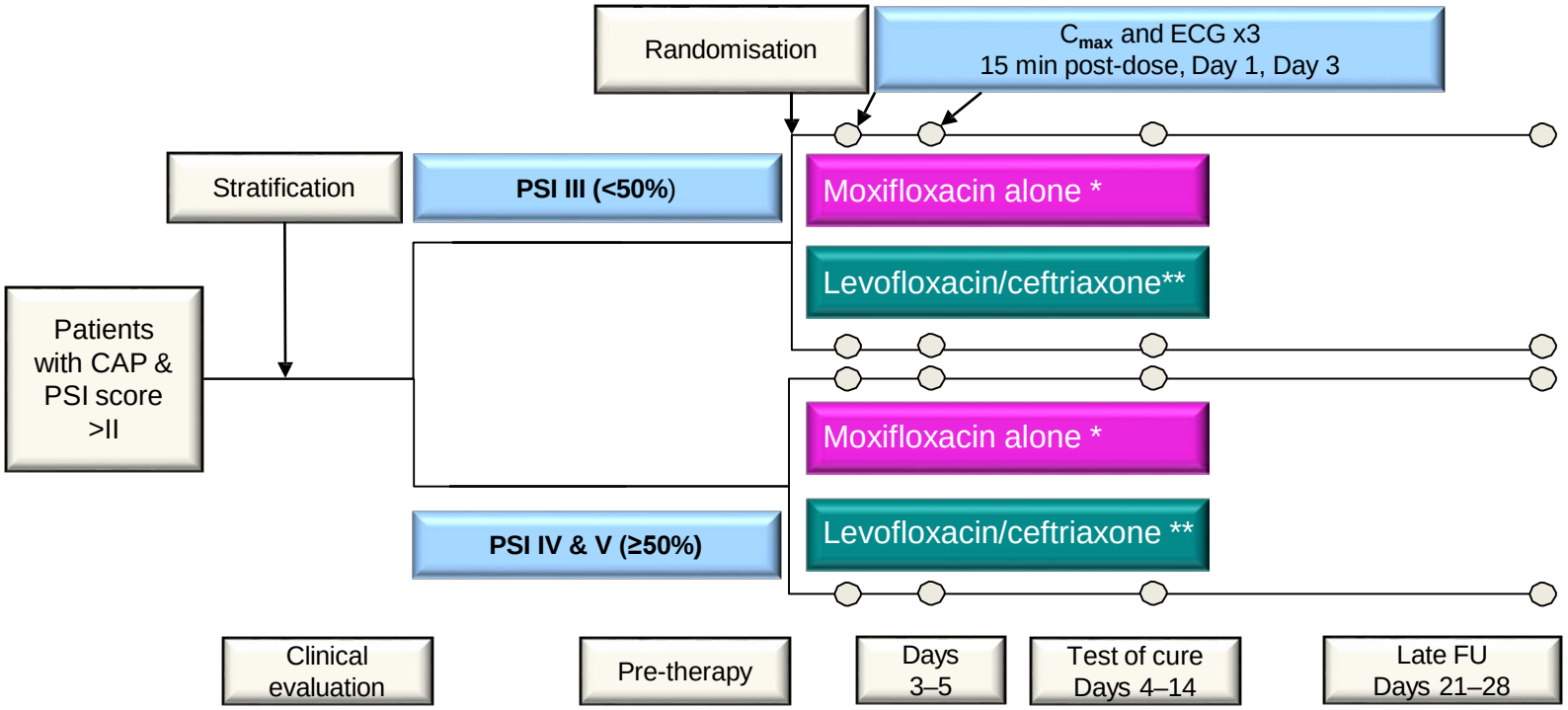
Antoni Torres,[1] Javier
Hartmut Lode,[7] John
[1]Servei de Pneumologia i A
CIBER del área de Enferme
[3]Bayer HealthCare, Puteaux
[5]Bayer HealthCare Pharmac
Pharmacology, Charité-Univ
and [9]Section of Infection, I

Background to the study

- Designed to further demonstrate the **efficacy** and **safety** of moxifloxacin in CAP
- According to European (EMA; CPMP) guidelines
  - **Potent comparator** (ceftriaxone/levofloxacin b.i.d.)
  - Review of the data by **independent committees** (clinical response, chest X-ray, cardiac events)
  - Non-inferiority trial: can do as well as this combination ?

What was done in MOTIV ?



*** moxifloxacin: 400 mg/day**
**** levofloxacin: 500 mg twice a day /ceftriaxone: 2g/day**

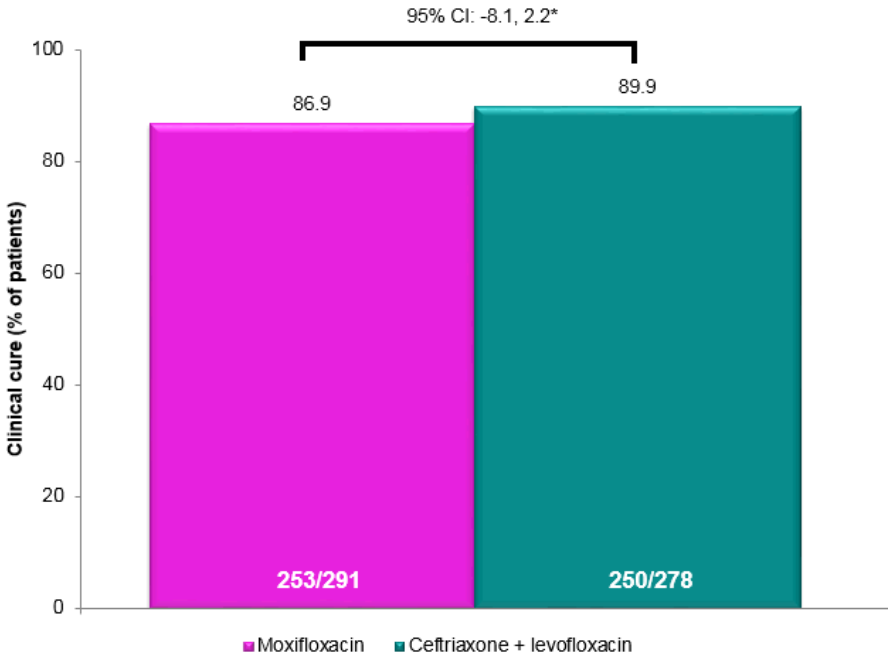
Which patients ?

Characteristic		Moxifloxacin (N=291)	Ceftriaxone + levofloxacin (N=278)
Age (years; mean ± SD)		66.0 ± 16.2	64.8 ± 16.7
Male sex, n (%)		191 (65.6)	164 (59.0)
Cardiac comorbidity, n (%)		89 (30.6)	90 (32.4)
Duration of CAP symptoms prior to enrolment, mean days ± SD		5.0 ± 3.5	4.6 ± 2.8
Failure on previous systemic antimicrobials, n (%)		39 (13.4)	40 (14.4)
Intensive care admission, n (%)		25 (8.6)	30 (10.8)
PSI distribution	Class III, n (%)	122 (41.9)	111 (39.9)
	Class IV, n (%)	138 (47.4)	134 (48.2)
	Class V, n (%)	31 (10.7)	33 (11.9)

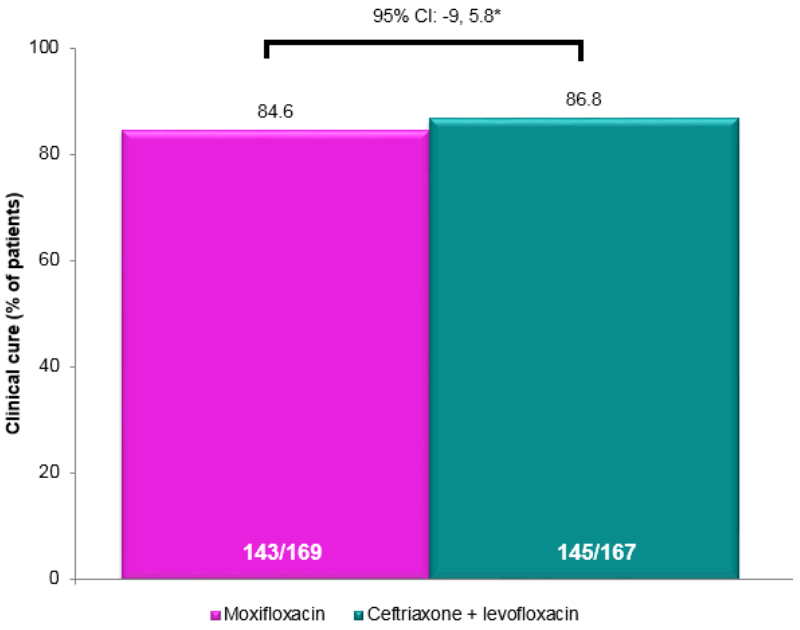
All differences were non-significant

And what did you get ?

Clinical cure at test of cure – overall

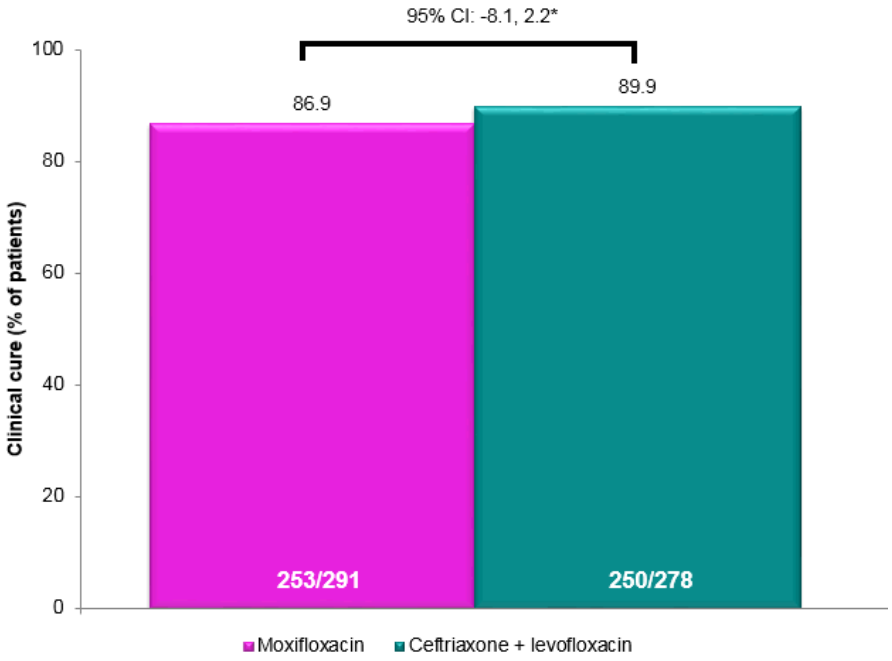


Clinical cure at test of cure PSI class IV–V

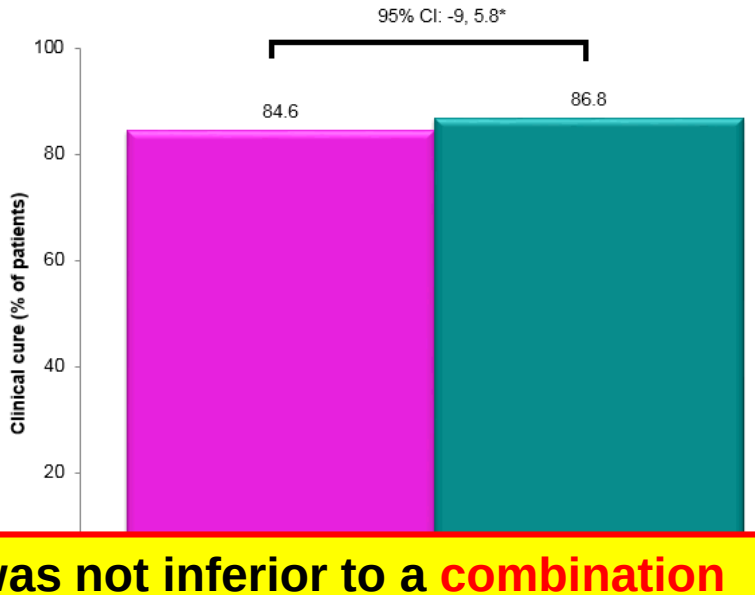


And what did you get ?

Clinical cure at test of cure – overall

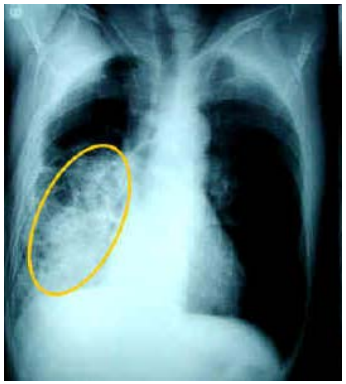


Clinical cure at test of cure PSI class IV–V



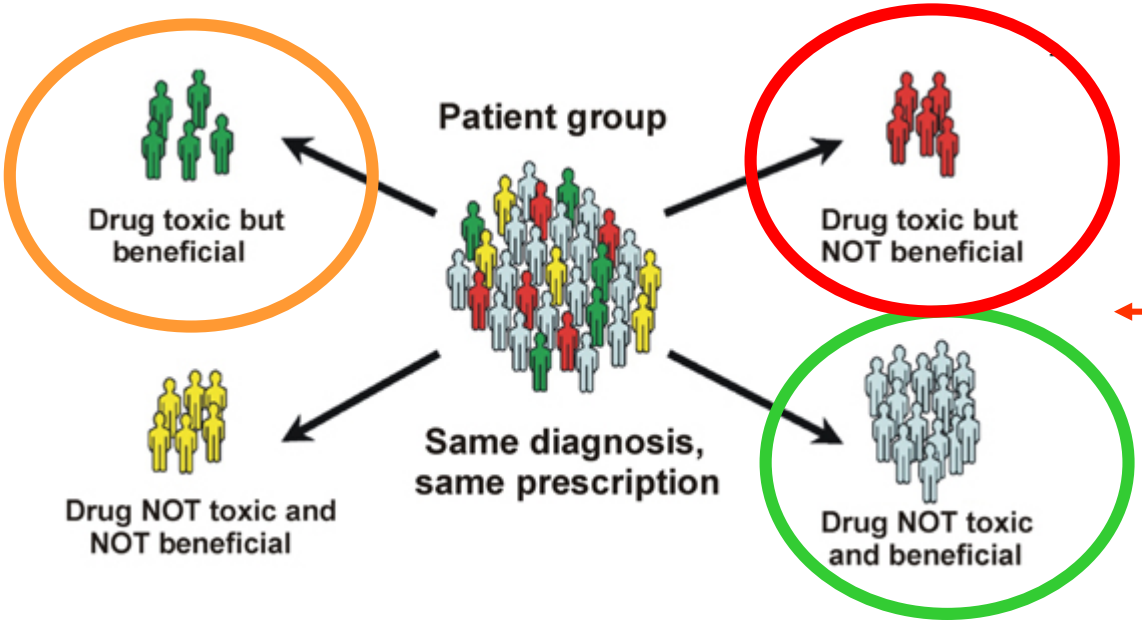
moxifloxacin 400 mg daily was not inferior to a combination of levofloxacin 2 x 500 mg daily plus ceftriaxone 2 g daily

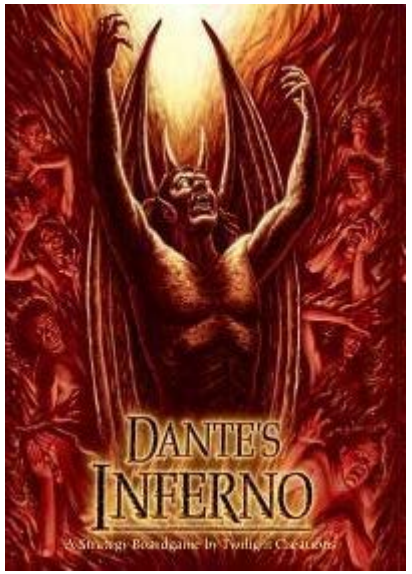
We all agree about efficacy, but what about side effects…



therapy ?

side effects ?





All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
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 reasonable 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 = 10613]	COMP [n = 10685]	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*

PO= oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator (see left column)

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)

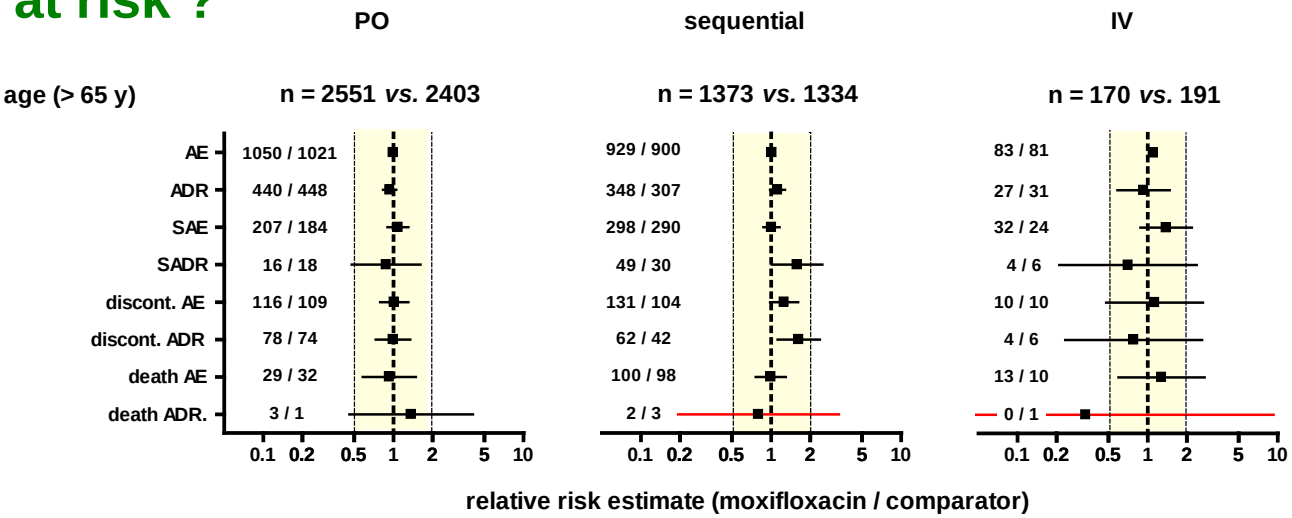
Side effects of moxifloxacin (clinical trials database)

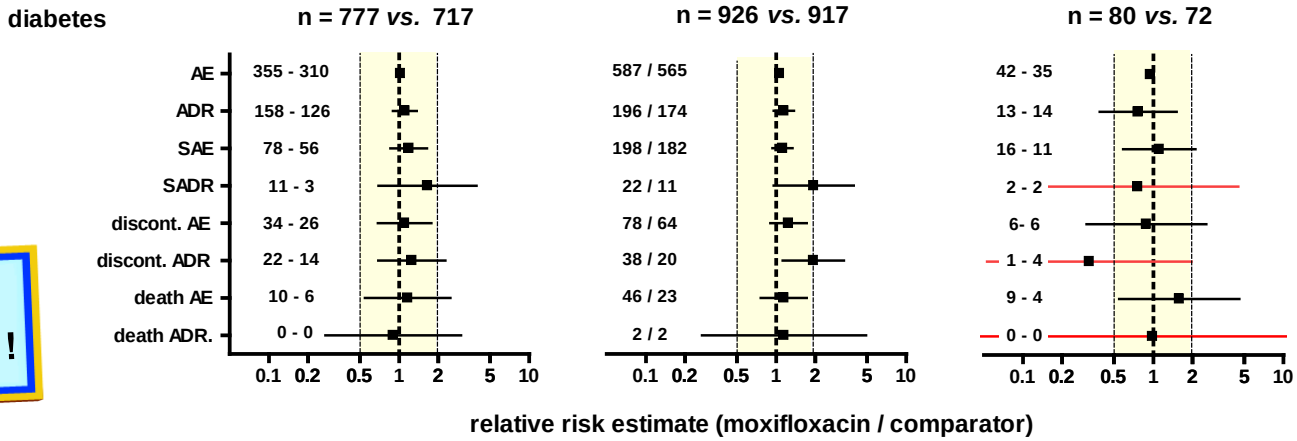
- **AE, ADR and SADR were mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation.**
- **Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated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

Patients at risk ?

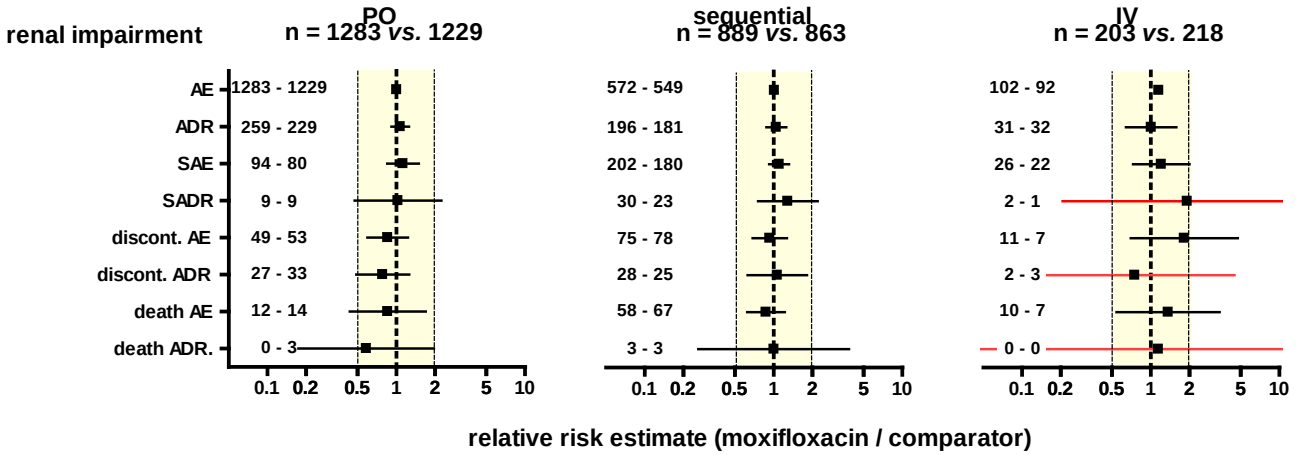


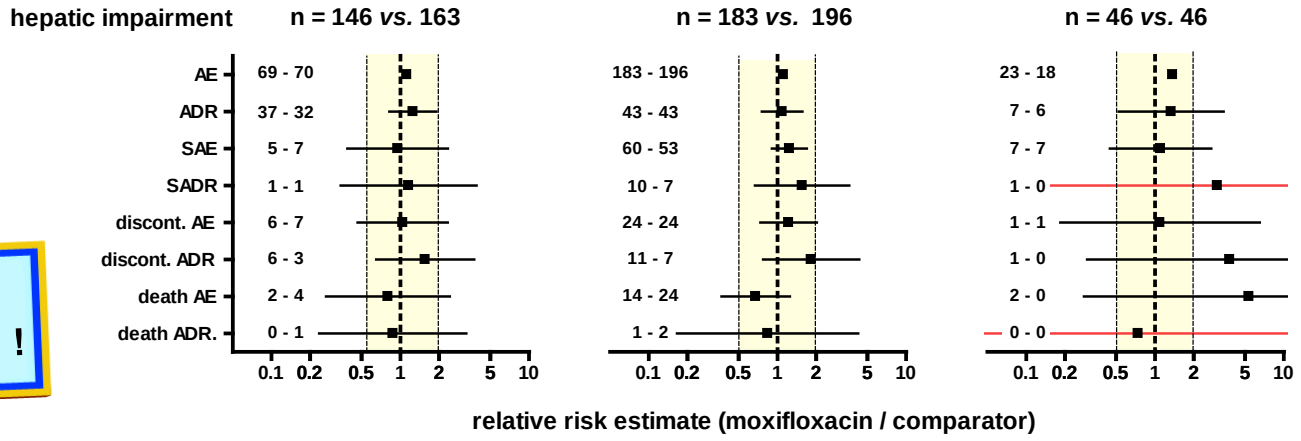


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?

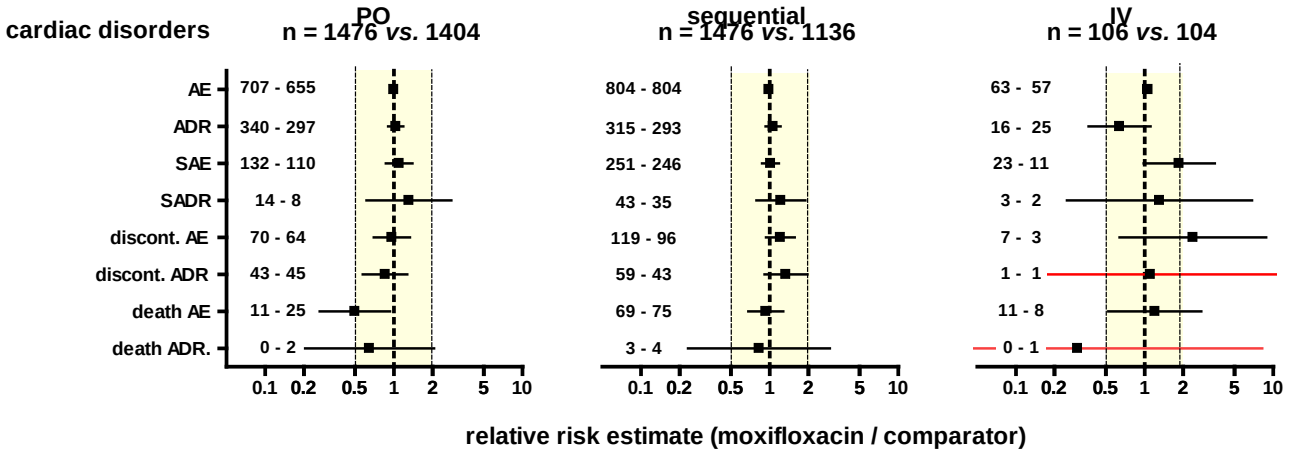


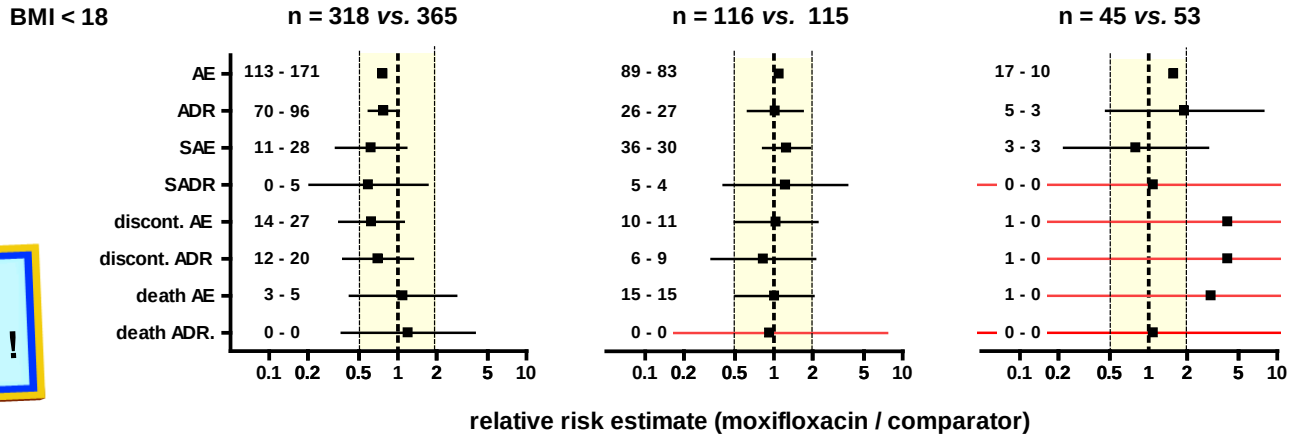


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?





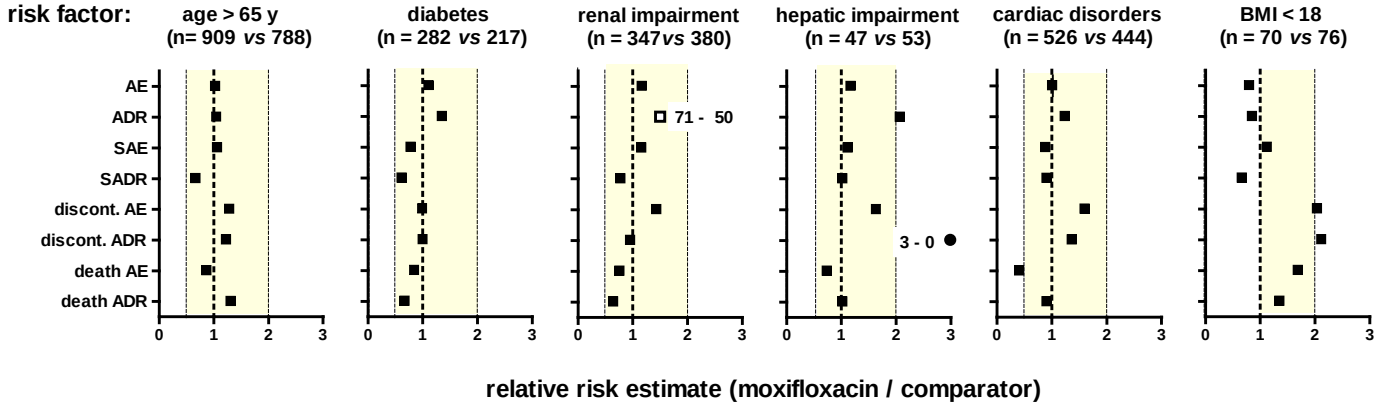
Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

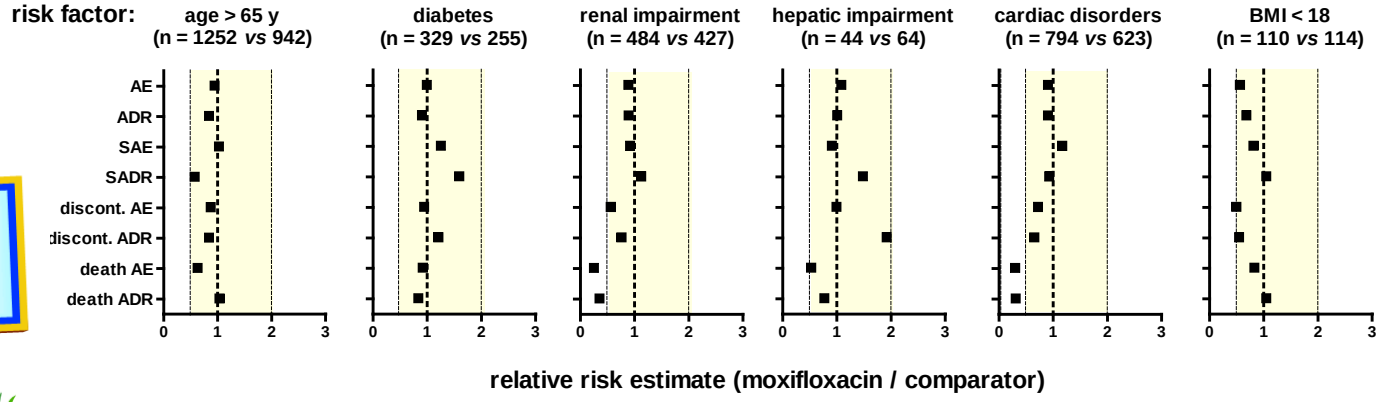
Comparison with other drugs ?

A. oral therapy

1. moxifloxacin *vs* β-lactams



2. moxifloxacin *vs* macrolides



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

Hepatotoxicity in large populations

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 from literature surveys

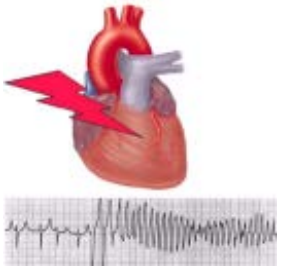
Hepatotoxicity risk of antibiotics

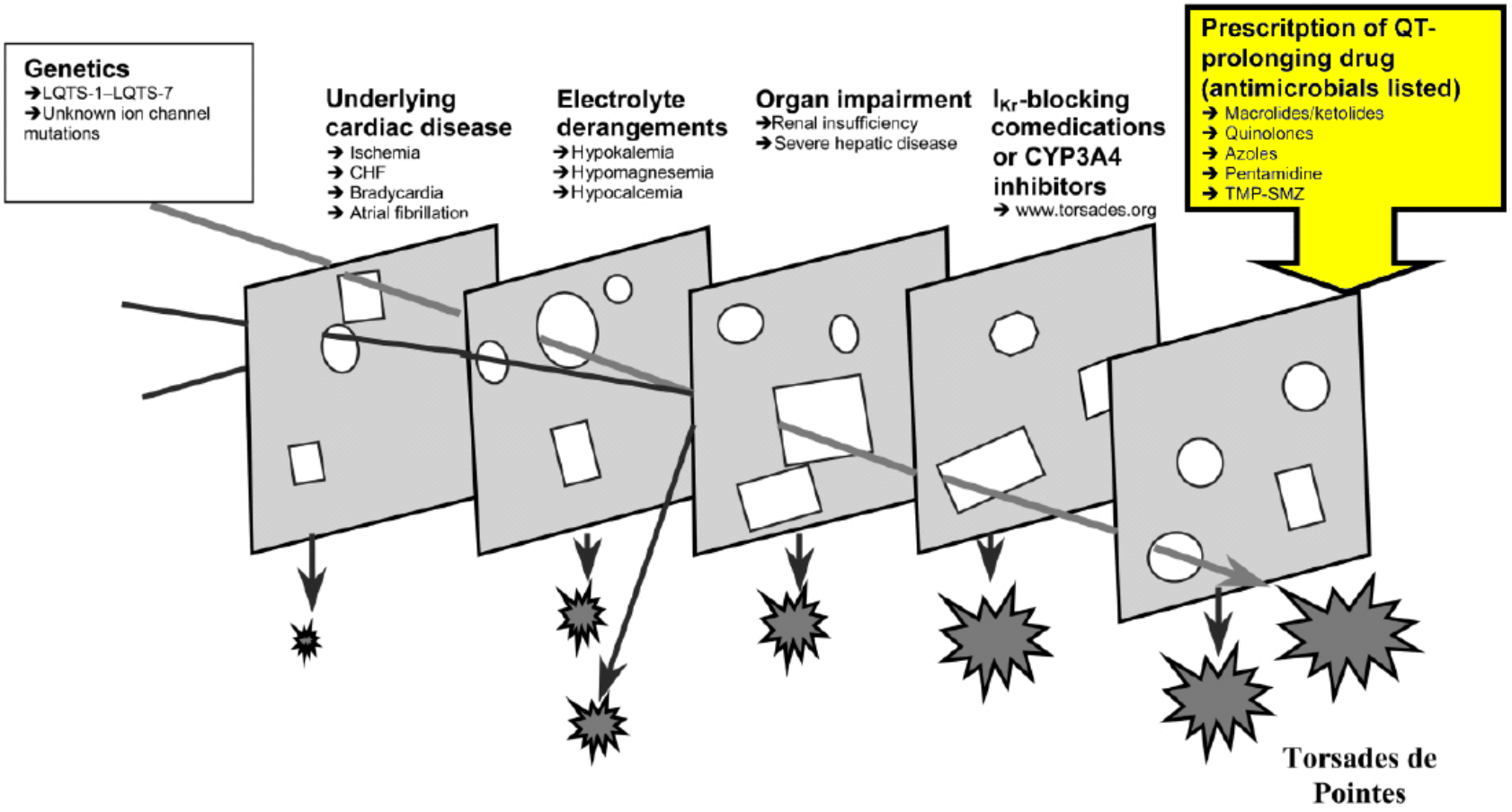
(percentage of prescriptions for antibiotics with main indications for use in the community setting)

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

QTc prolongation





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

EMA position

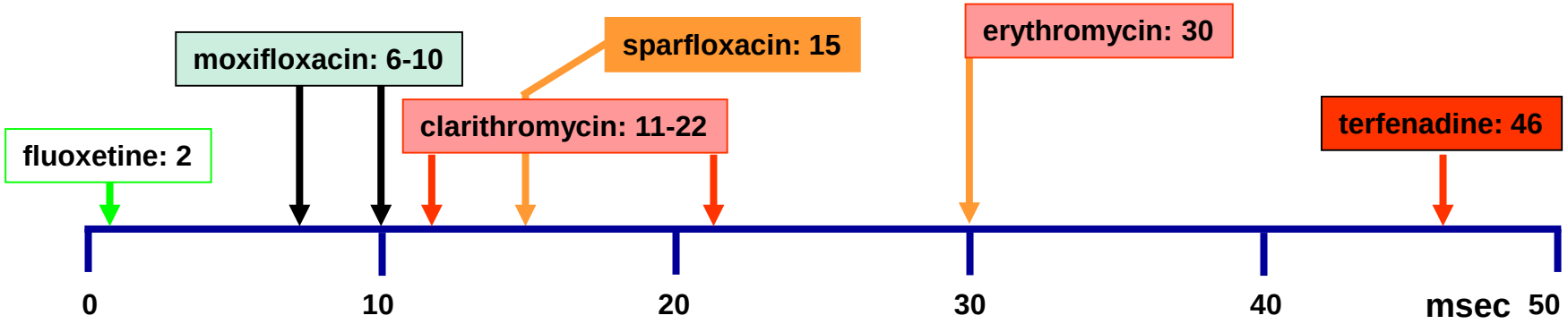
European Medicines Agency

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)

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

Tendinopathies: main features and incidence…

TABLE 1. Characteristic features of fluoroquinolone-induced tendinopathy/tendon rupture

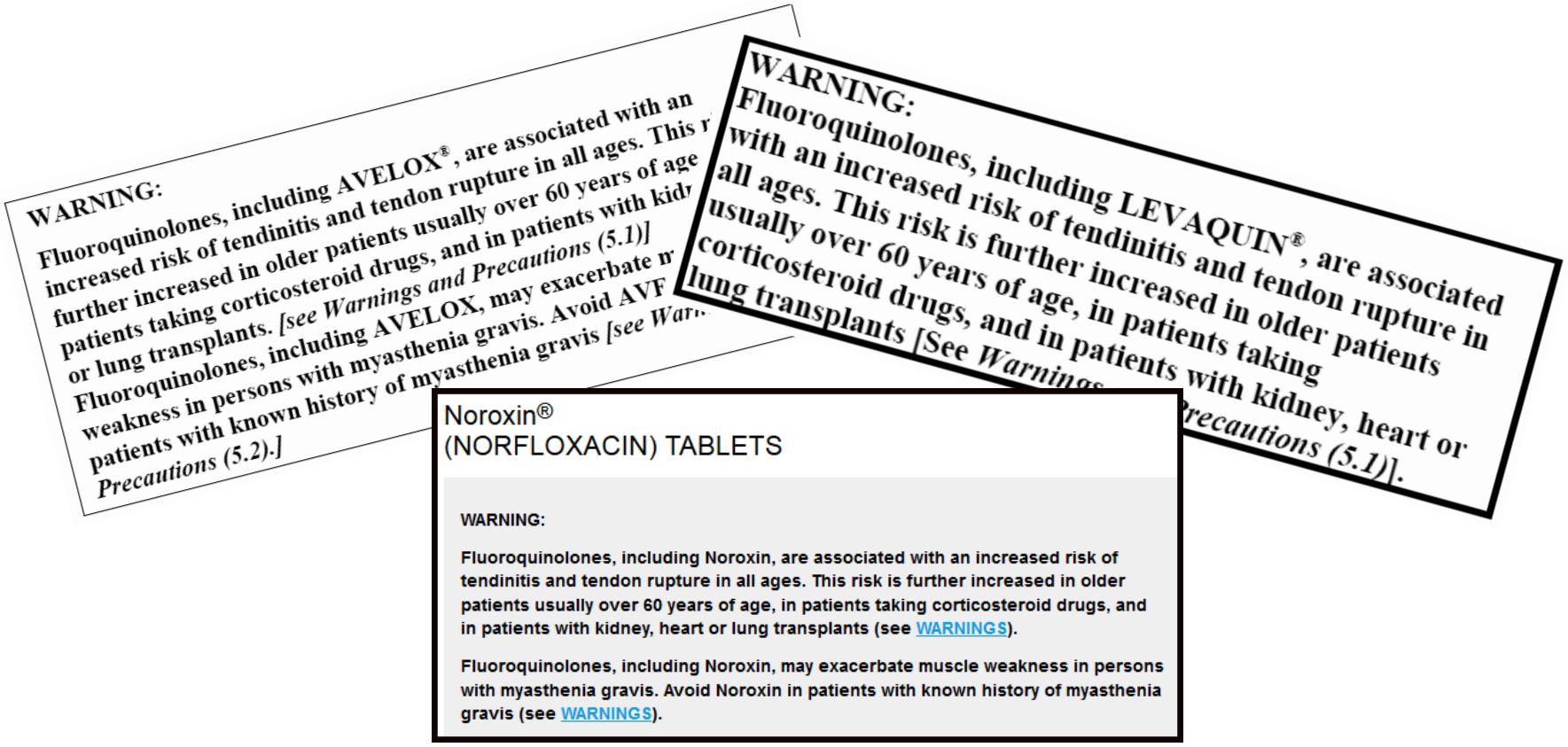
in 2010

FEATURE	OBSERVATIONS/FINDINGS
Causative quinolones reported[6,9,10]	Ciprofloxacin (most commonly reported), norfloxacin, pefloxacin, ofloxacin, levofloxacin
Associated risk factors[11,31,33–37]	Age >60 years, corticosteroid therapy, renal failure, diabetes mellitus, history of tendon rupture
Relative risk of tendon disorders[3,16,31]	1.7-fold increase for all tendinopathies 1.3-fold increase for tendon rupture 4.1-fold increase of Achilles tendon rupture 46-fold increase of tendon rupture with concurrent corticosteroid exposure 1.5-fold increase in tendon disorders if age >60 years 2.7-fold increase in tendon rupture if age >60 years
Affected tendons[11,33,44]	Achilles tendon most commonly affected (89.8% of cases) Multiple other tendons reported Up to 50% of cases with bilateral involvement Symptoms of tendinitis often precede tendon rupture by up to 2 weeks
Latency period of tendinopathy[3,4,6,15]	Median onset of 6 days (85% of cases within first month) Up to 50% of cases after fluoroquinolone discontinued

Kim & Del Rosso, J Clin Aesthet Dermatol. 2010; 3:49–54.

Tendinopathies…

- In 2005, all fluoroquinolones marketed in the US have received a black box label about tendinopathies



Tendinopathies…

- But this is what we found for moxifloxacin in our survey of the whole clinical trial datbase

Table VII. Incidence of selected treatment-emergent adverse events presented by Standard MedDRA Queries/ Bayer MedDRA Queries and preferred terms in 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).

SMQ/BMQ and preferred term	Treatment route [n (%)]					
	PO		IV/PO		IV	
	MXF [n=10 613]	COMP [n=10 685]	MXF [n=3431]	COMP [n=3415]	MXF [n=937]	COMP [n=923]
Tendinopathies	11 (0.1)	10 (<0.1)	3 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)

very rare and no difference

no case

PO= oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator

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

Tendinopathies: incidences (revisited)…

QuarterWatch: 2010 Quarter 2

Monitoring MedWatch Reports

January 27, 2011

Signals for Varenicline, Levofloxacin and Fentanyl

http://www.ismp.org/quarterwatch/2010Q2.pdf
Last accessed: 20/02/2015

in 2011

Levofloxacin (LEVAQUIN) Cases Lead Antibiotics

While antibiotics rank among the safest drugs we monitor, levofloxacin (LEVAQUIN) was suspect in more reports of serious injury than any other antibiotic. Most cases involved tendon rupture and other muscle, tendon and ligament injuries. Case reports of this problem substantially outnumbered those for two chemically similar drugs—ciprofloxacin (CIPRO), with greater volume of prescriptions, and moxifloxacin (AVELOX), with somewhat less frequent medical use.

Tendinopathies: incidences (revisited)…

Institute for Safe Medication Practices
A Nonprofit Organization Educating the Healthcare Community and Consumers About Safe Medication Practices
A federally certified Patient Safety Organization

in 2011

QuarterWatch: 2010 Quarter 2

Table 2. Tendon disorders for fluoroquinolone antibiotics 2010q2.

	Levofloxacin	Ciprofloxacin	Moxifloxacin
Total Rx (millions)*	2.1	5.3	1.5
Case Reports	246	105	93
% Direct to FDA	52%	71%	42%
% Health Professionals	53%	59%	76%
Tendon Disorders (HLT)	93	29	10
All Musculoskeletal	156	62	20

*IMS Health National Prescription Audit ™ 2010

(AVELOX), with somewhat less frequent medical use.

http://www.ismp.org/quarterwatch/2010Q2.pdf
Last accessed: 20/02/2015

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.

What shall we discuss ?

- **The basics: how were quinolones invented ?**
  (are they different by design ?)
- **The real life in the lab: microbiological properties and risk of resistance…**
  (or how to really differentiate them …)
- **The real life in the doctor's office: efficacy and tolerance…**
  (is there a difference) ?
- **Should we use the "best in class" ?**

What shall we discuss ?

- **The basics: how were quinolones invented ?**
  (are they different by design
- **The real life in the lab: mic**
  resistance…
  (or how to really differentiate
- **The real life in the doctor's**
  (is there a difference) ?

Why not leaving this to the discussion ?

but remembering:

- **400 mg once daily**

or

- **2 x 500 mg daily**

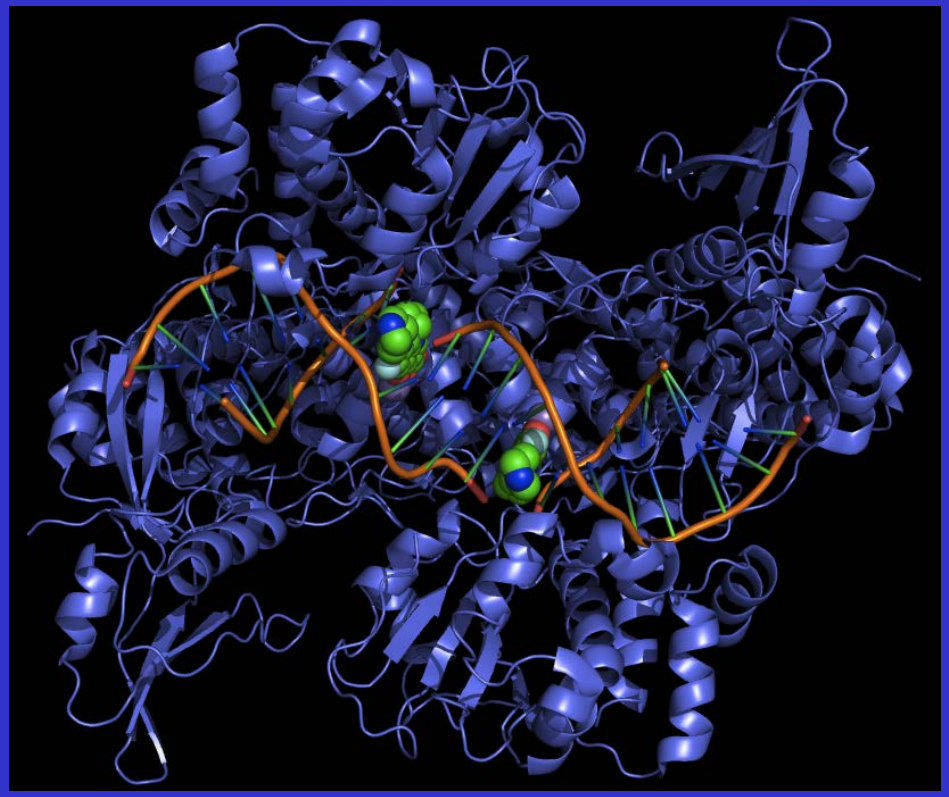
or … (have your pick !)

- **Should we use the "best in class" ?**

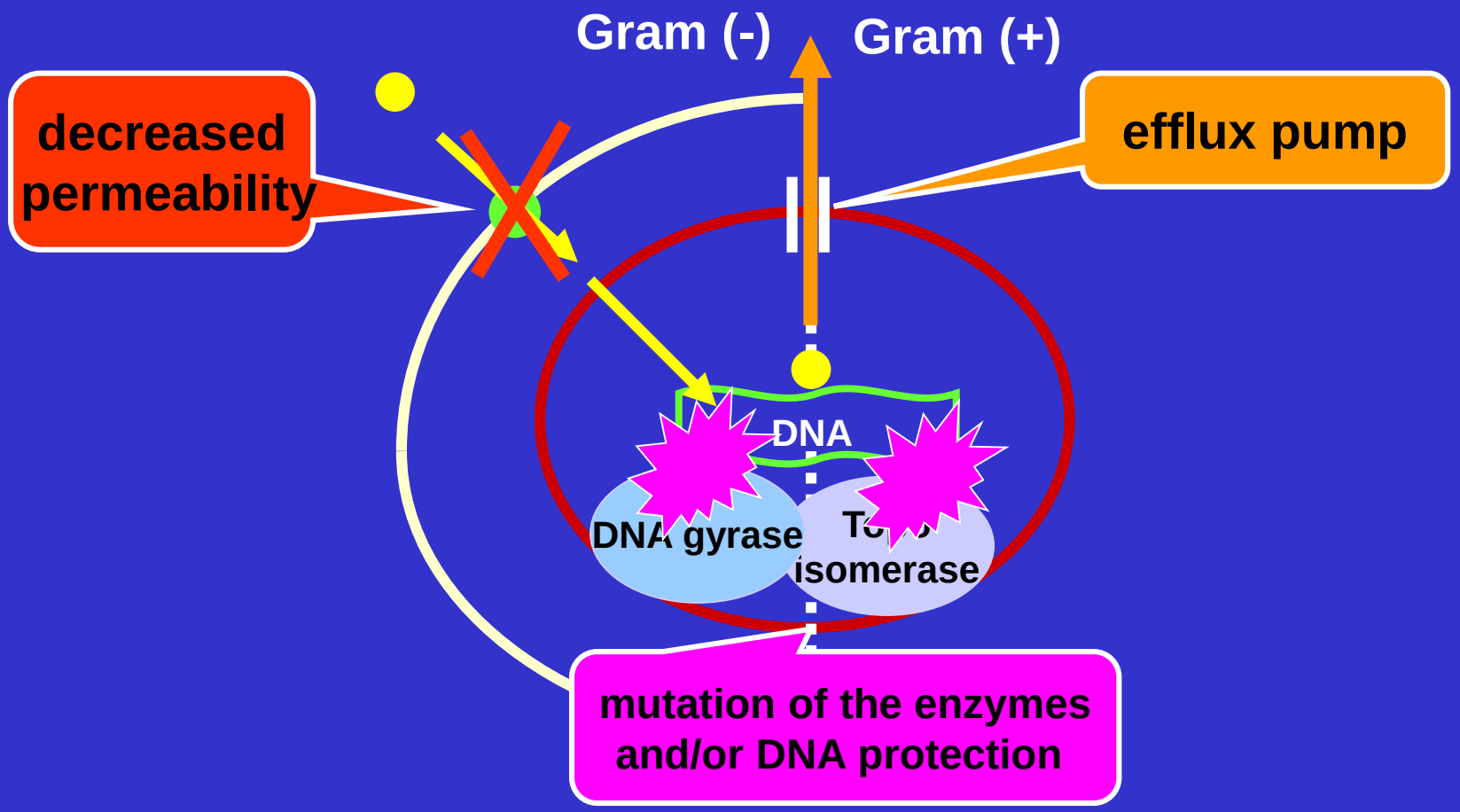
Thank you for your attention!

And ask questions

Ternary complex
DNA - enzyme - fluoroquinolone



Resistance to fluoroquinolones: the basics

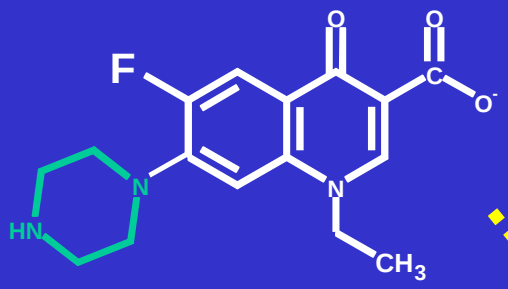


Chemistry and Activity

This is where
it all began..

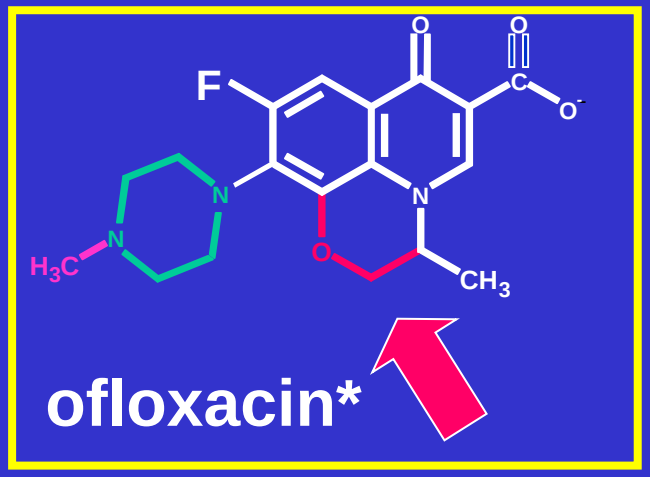
From norfloxacin to ciprofloxacin and ofloxacin

norfloxacin



tricyclic compound
(as in flumequine but morpholine ring)

pefloxacin

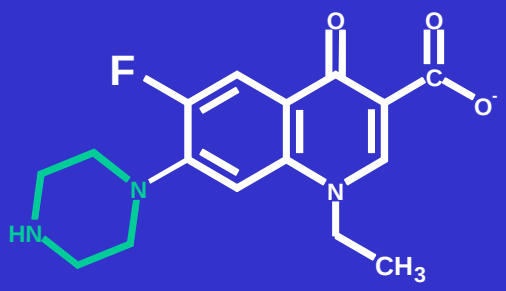


ofloxacin*

* Eur. pat. Appl. 47,005 to Daiichi, 1982

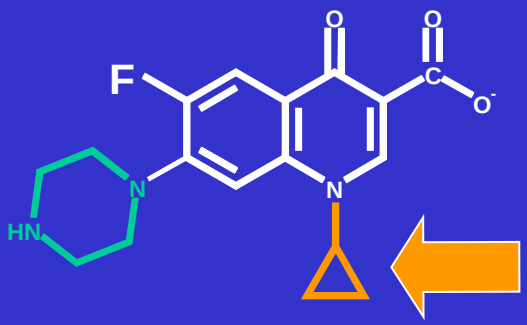
From norfloxacin to ciprofloxacin

norfloxacin



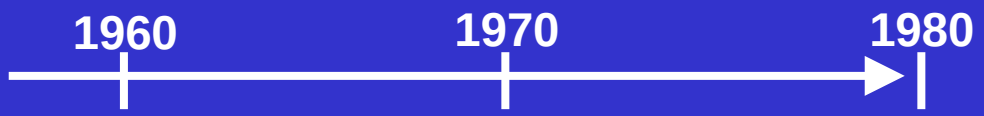
cyclopropyl to increase potency

ciprofloxacin *



* Ger. pat. 3,142,854 to Bayer AG, 1983

The "first generation" of fluoroquinolones



- Nalidixic acid
- Oxolinic acid
- Cinoxacin
- Pipemidic acid

- Norfloxacin
- Pefloxacin
- Ofloxacin
- Ciprofloxacin
- Fleroxacin
- Rufloxacin

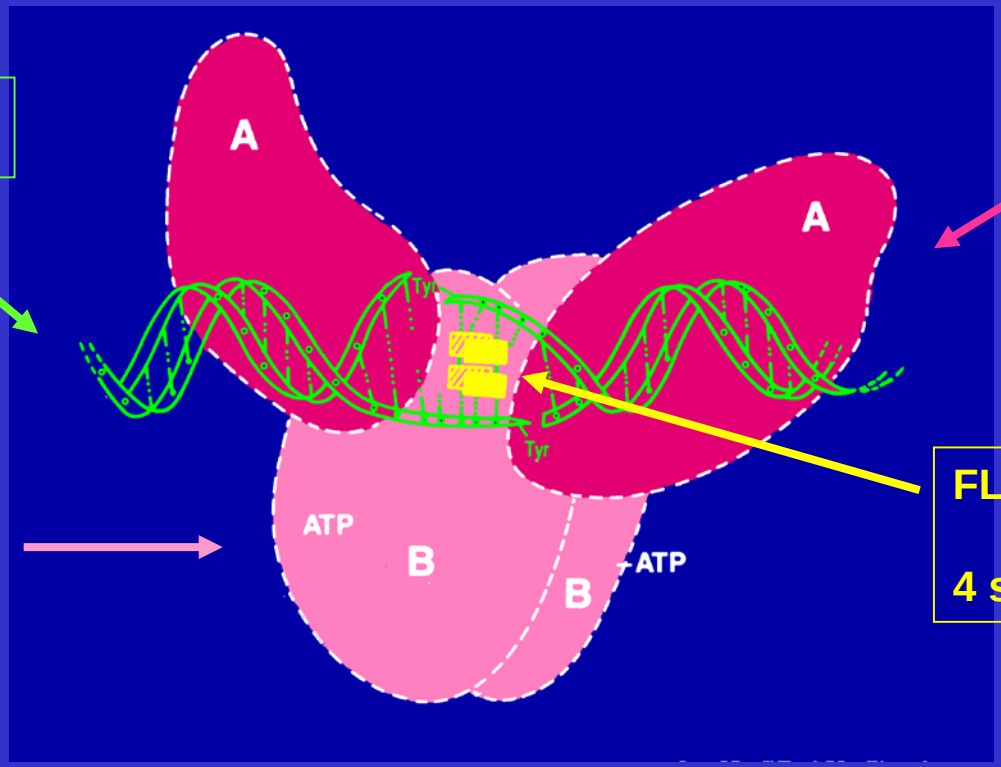
improved anti Gram (-) activity

$t_{1/2}$	activity
3-4 h	++
11 h	+
6 h	++
3-4 h	+++

Ternary complex
DNA - enzyme - fluoroquinolone

COVALENTLY CLOSED
CIRCULAR DNA

DNA GYRASE
catalytic subunits



DNA GYRASE
ATP binding subunits

FLUOROQUINOLONES:

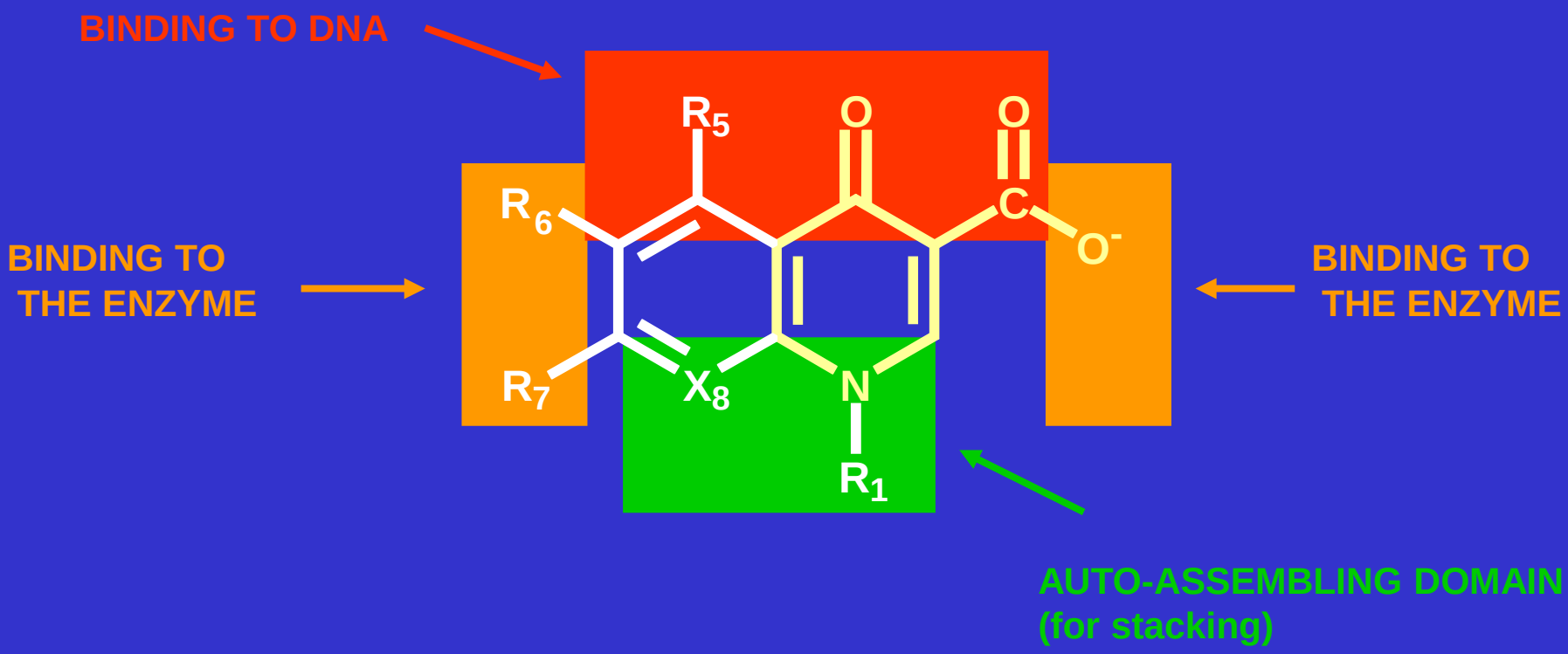
4 stacked molecules

(Shen, *in* Quinolone Antimicrobial Agents, 1993)

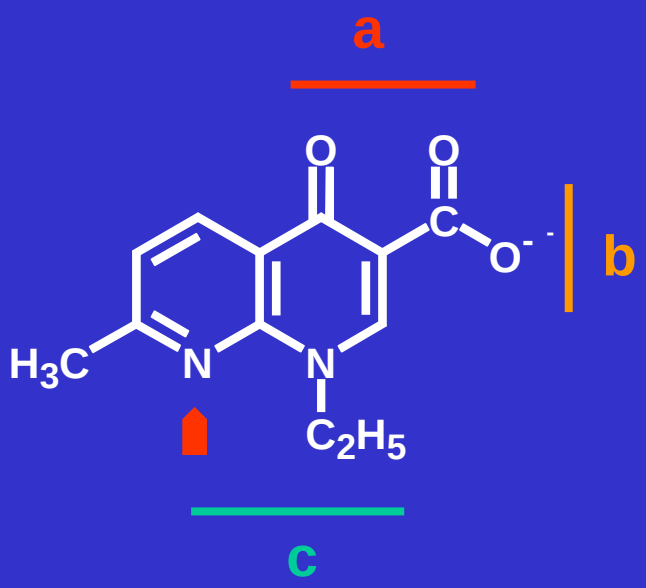
Fluoroquinolones are the first entirely man-made antibiotics: do we understand our molecule ?

Don’t panic, we will travel together….

The pharmacophore common to all fluoroquinolones



Nalidixic acid *



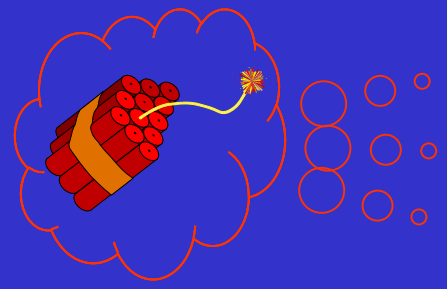
- typical chemical features of fluoroquinolones (a, b, c)
  BUT a naphthyridone
  (N at position 8:)

- limited usefulness as drug
  - narrow antibacterial spectrum (*Enterobacteriaceae* only)
  - short half-life (1.5h)
  - high protein binding (90%)

* Belg. pat. 612,258 to Sterling Drugs, 1962

The “second generation” fluoroquinolones

1960 — 1970 — 1980 — 1990 — 2000



- Temafloxacin [a]
- Sparfloxacin [b]
- Grepafloxacin [c]
- Gatifloxacin [d]

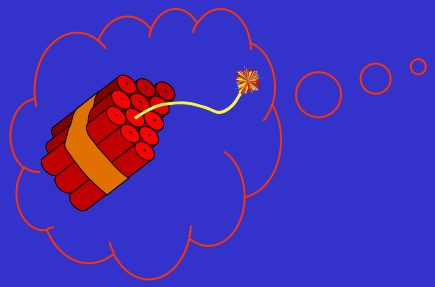
→ anti-anaerobe

- Gram (-);
- improved Gram (+)

a: Toyama, 1988 (?) ; b: Dainippon, 1985-1987; c: Otskuda, 1989; d: Kyorin, 1988

The “third / fourth generation” fluoroquinolones

1960 — 1970 — 1980 — 1990 — 2000



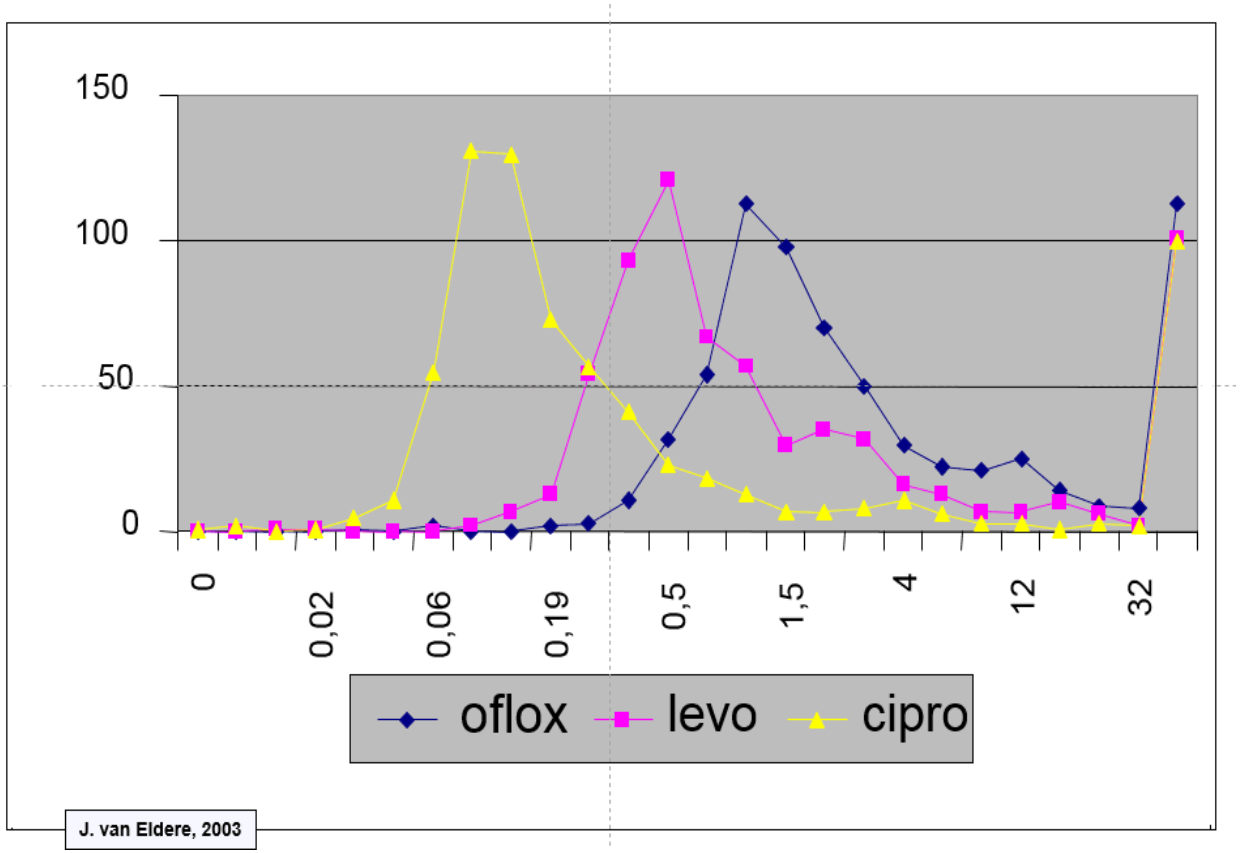
- Clinafloxacin [a]
- Trovafloxacin [b]
- Moxifloxacin [c]
- Gemifloxacin [d]

anti-Gram (-)
anti-Gram (+)
anti-anaerobe

a:Kyorin, 1987; b: Pfizer, 1993; c: Bayer, 1994; d: LG Chemical Ltd., S. Korea, 1994-98

Resistance must first be assessed by MIC distributions

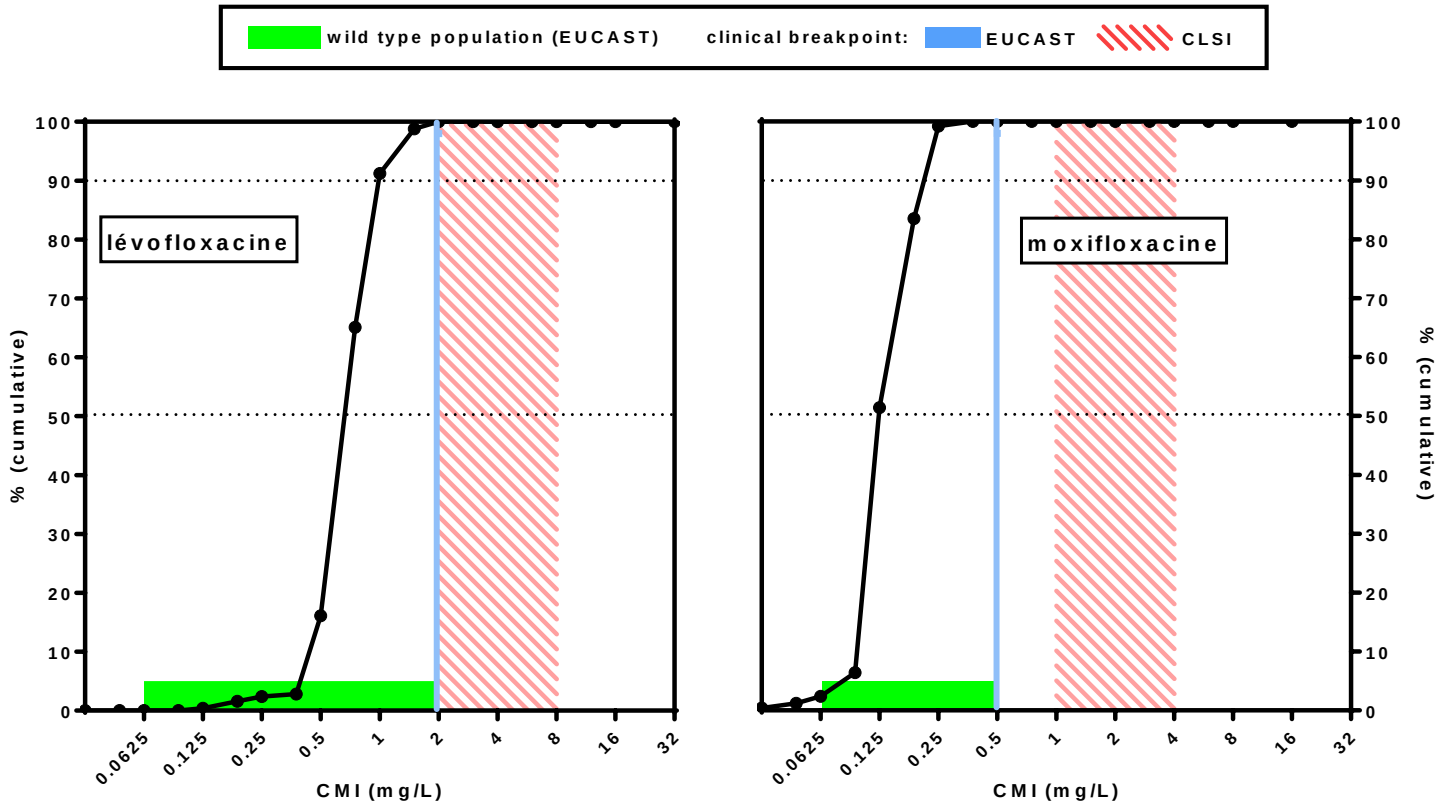
- Resistance of Gram-negative (ciprofloxacin/levofloxacin) is widespread and must be assessed locally (often ward by ward)



MIC distributions of fluoroquinolones against P. aeruginosa **in the Academic Hospital of the University of Leuven, Belgium**

Resistance must first be assessed by MIC distributions

- Conversely, resistance of Gram-positive is variable
  - High for MRSA (co-resistance frequent)
  - Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)



MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

Lismond *et al*. Int J Antimicrob Agents. 2012 Mar;39(3):208-16.

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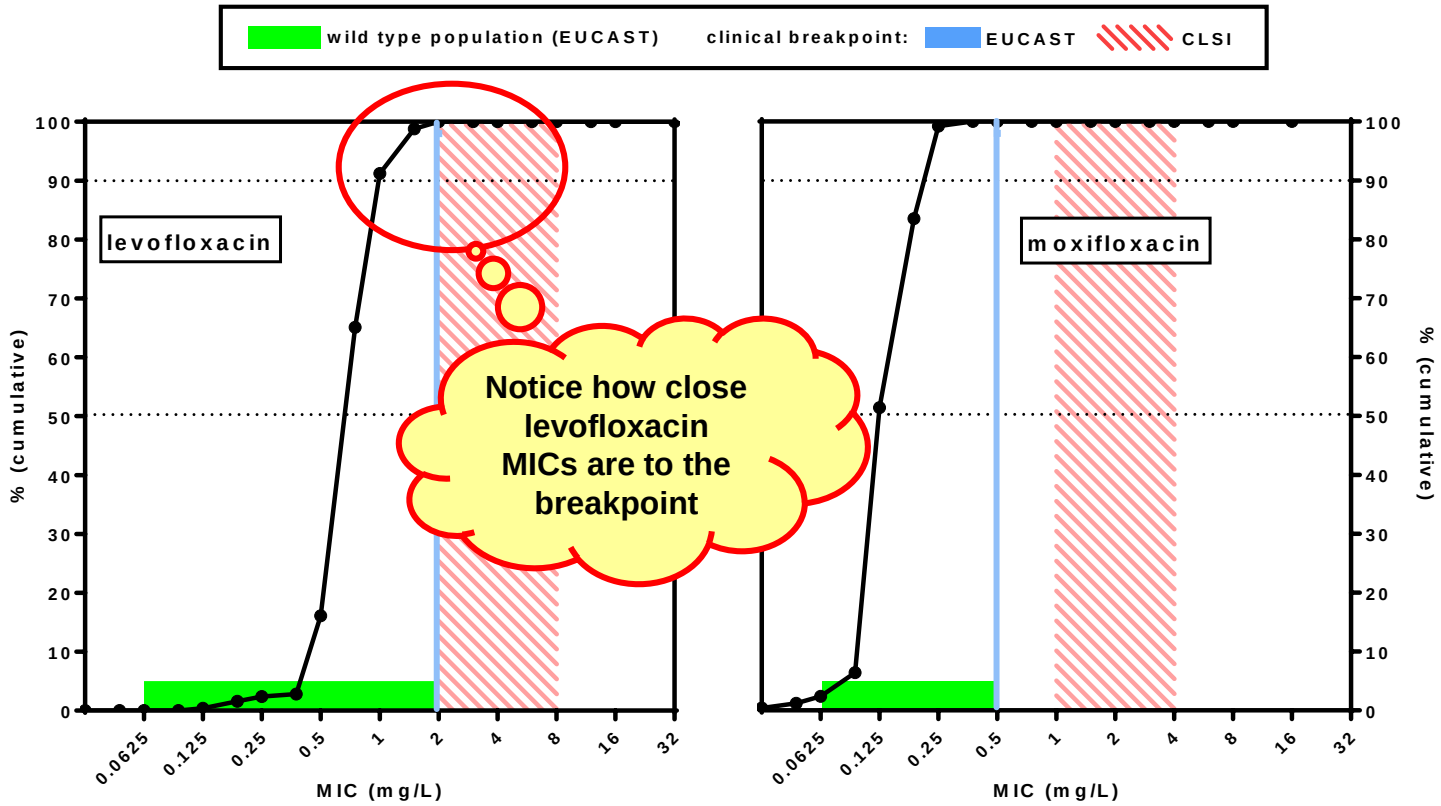

MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

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A recent paper…

International Journal of Antimicrobial Agents 45 (2015) 79–83

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Short Communication

Impact of poor compliance with levofloxacin and moxifloxacin on respiratory tract infection antimicrobial efficacy: A pharmacokinetic/pharmacodynamic simulation study

N. Carral[a], J.C. Lukas[a,b], I. Oteo[a], E. Suarez[a,*]

A very recent paper…

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Table 1
Interindividual variability of $fAUC_{0-24h}$ for levofloxacin (LFX) and moxifloxacin (MOX), estimated for various drug dosing regimens in simulated patients.

Parameter	Mean (S.D.)	Range
AUC_{0-24h} (mg h/L)		
LFX 500 mg q24 h	45.78 (3.72)	37.21–57.13
LFX 750 mg q24 h	68.68 (5.58)	55.82–85.69
LFX 500 mg q12 h	91.57 (7.34)	77.66–115.48
MOX 400 mg q24 h	43.63 (8.60)	26.43–72.20

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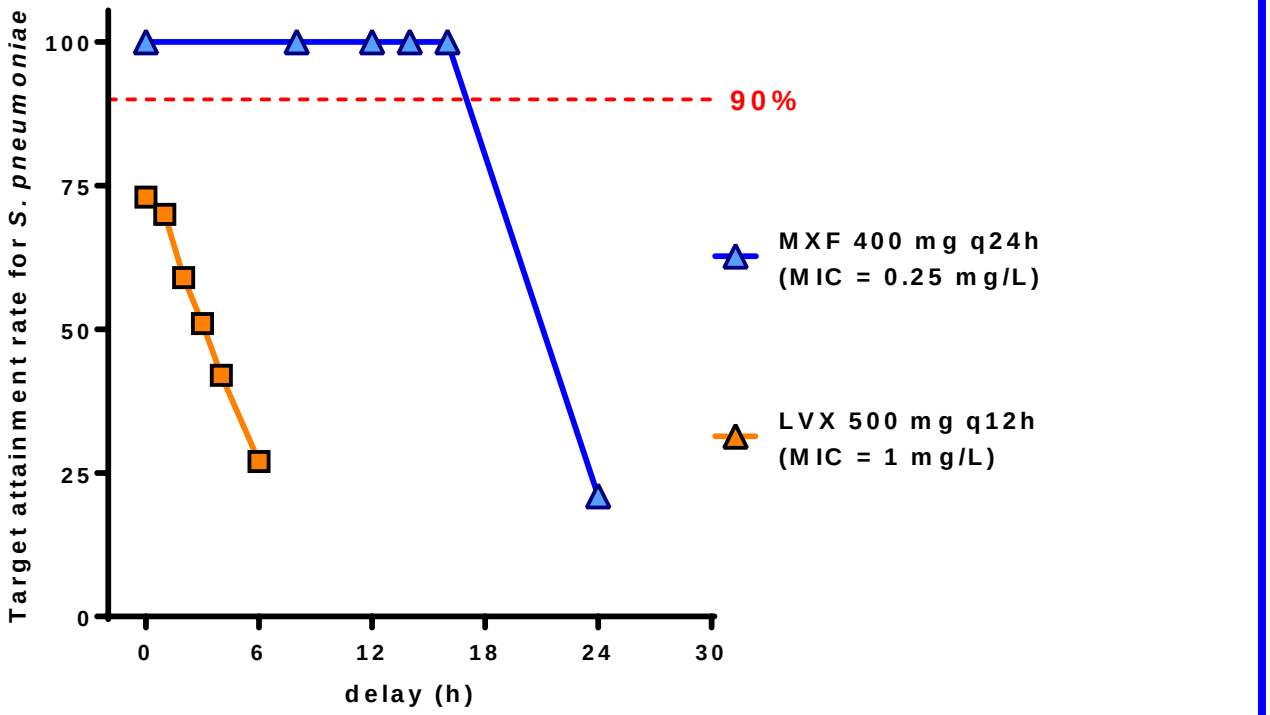

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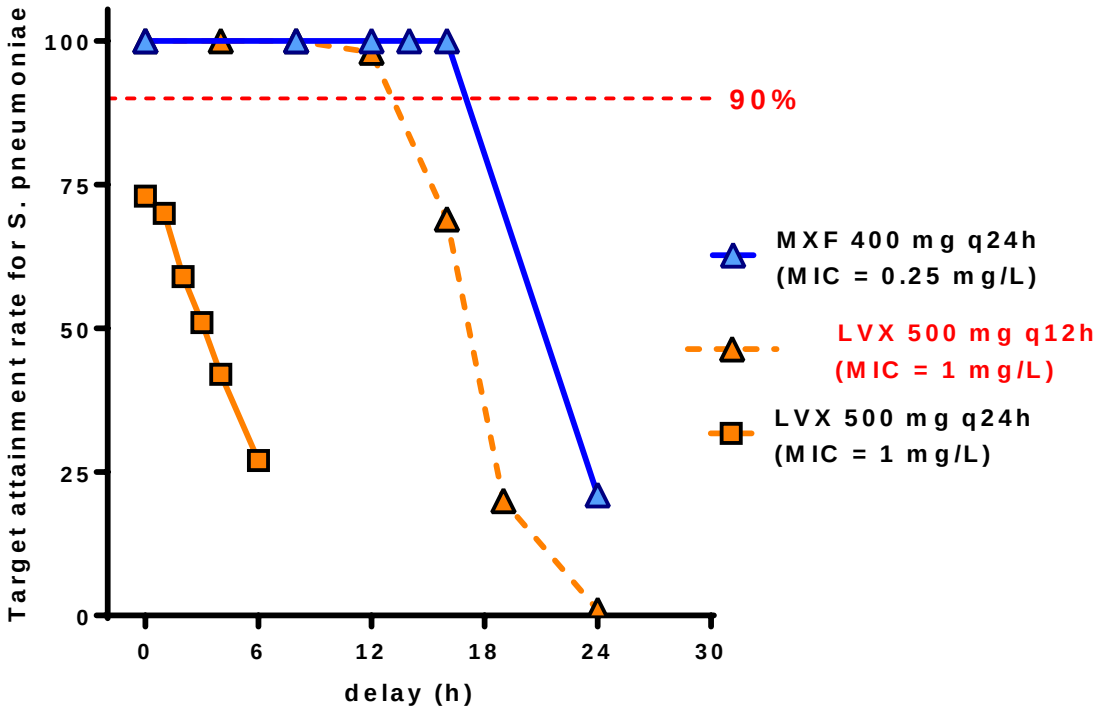
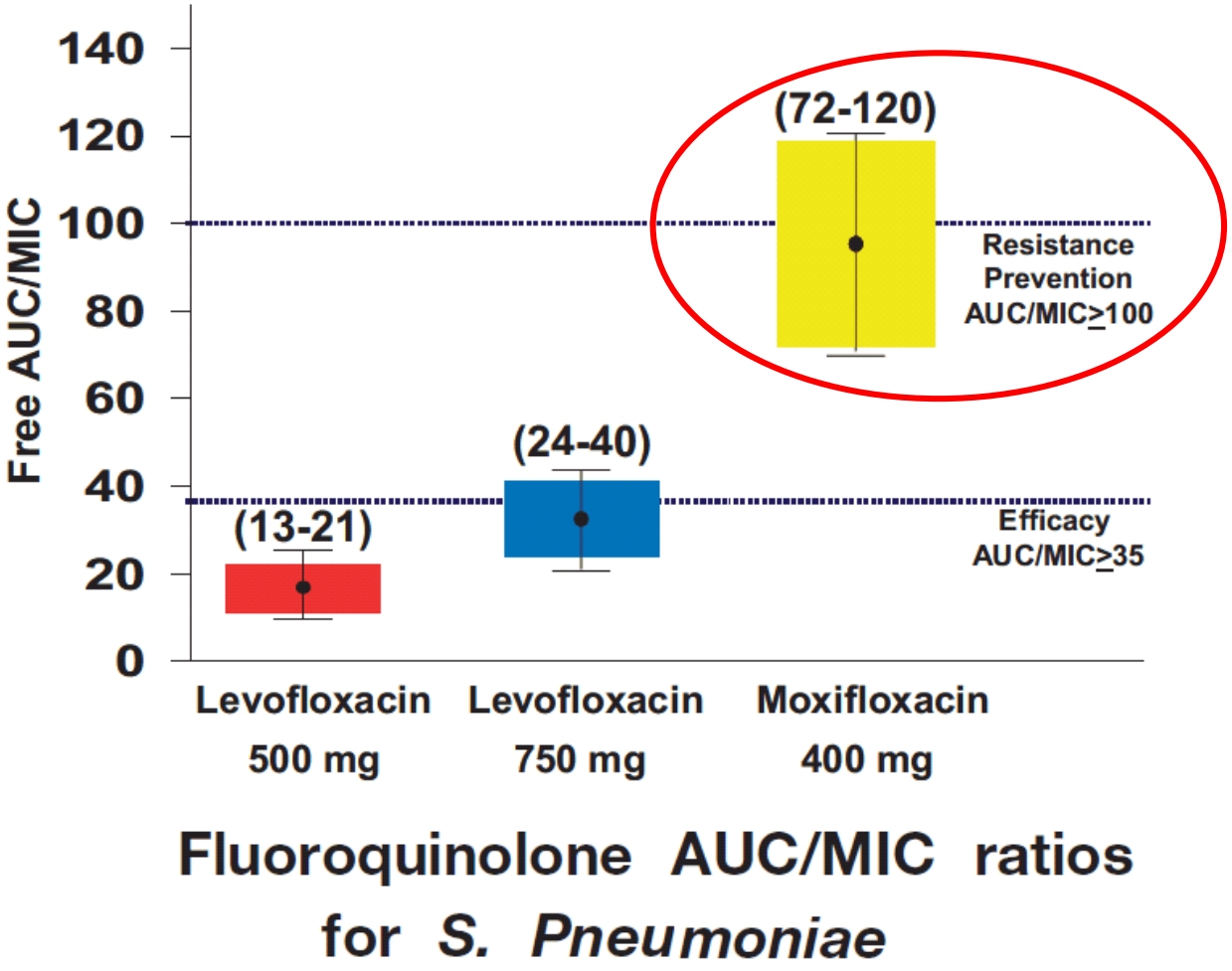


to be as protective, you need a **twice daily** dosing with levofloxacin

What differentiates fluoroquinolones ?

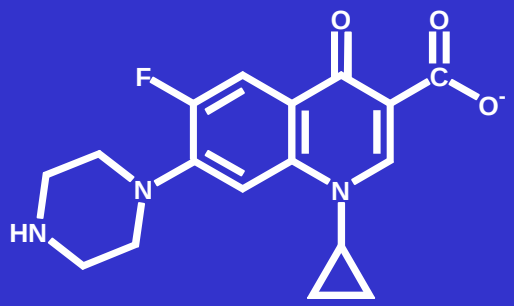
Results with *S. pneumoniae*



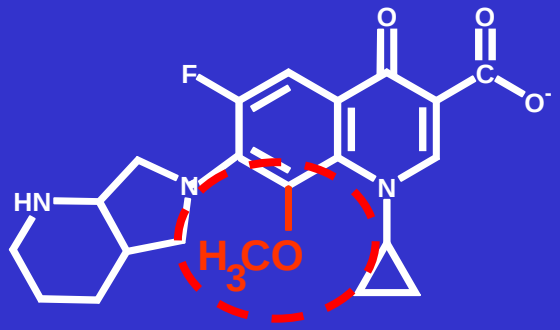
This why me may have less emergence of resistance …

Is there a molecular basis for a lesser emergence of resistance with moxifloxacin ?

A C8-methoxy group lowers the MPC for an N-1-cyclopropyl-f luoroquinolone"



ciprofloxacin



moxifloxacin

FULL PRESCRIBING INFORMATION

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf
Last accessed: 8/2/2015