Antibiotic resistance and global overview of the use of fluoroquinolones against *S. pneumoniae*

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with data obtained in collaboration with A. Lismond, N. Vandevelde, F. Van Bambeke and M. Van der Linden* & R. Vanhoof…**

* National Reference Center for Streptococci & University Hospital Aachen, Germany

** Scientific Institute of Public Health, Brussels, Belgium

The role of fluoroquinolones in managing *S. pneumoniae*
Singapore,16th December 2016

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/8979/086081

Disclosures

Financial support from

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

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

Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillin

Ann. Rev. Biochem. 1979. 48:73–101

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

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

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

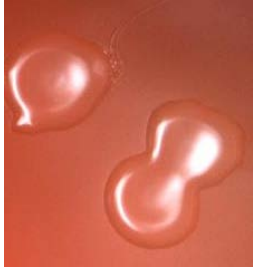
and died from invasive pneumococcal infection …

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

What shall we do ?

- Present and discuss the main mechanisms of resistance of *S. pneumoniae* to "*guidelines*" antibiotics
- Showing what MIC distributions are and mean in terms of interpretation of susceptibility
- A quick discussion about breakpoints (EUCAST *vs* CLSI) and its impact on epidemiological surveys
- Changes (or no change) of fluoroquinolone susceptibility and the reasons thereof
- Activity of fluoroquinolones on *S. pneumoniae* biofilm formation and disruption, and clinical implications

Is resistance of *S. pneumonia* a problem ?



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

REVIEW ARTICLE

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

Multidrug-Resistant *Streptococcus pneumoniae* Infections

Current and Future Therapeutic Options

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

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

Van Bambeke F, *et al. Drugs.* 2007;67:2355-82 – PMID: 17983256

Streptococcus pneumoniae: main mechanisms of resistance

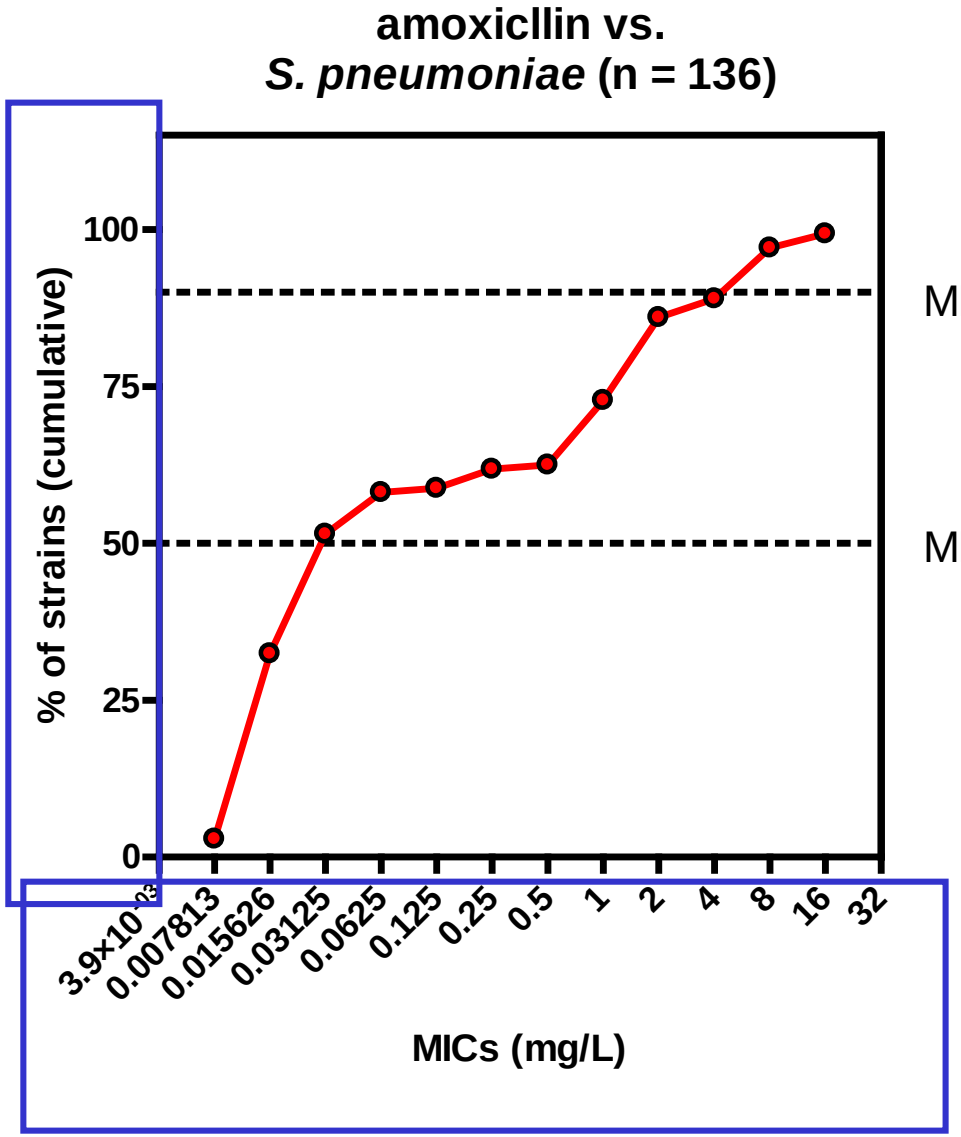
Antibiotic class	Mechanism	Genetic support	Drugs affected	Consequence
β-lactams	↘ Affinity of PNP1a, PBP2x and PBP2b	mosaic genes	all (variable extent)	↘ susceptibility
Macrolides	Methylation of 23S rRNA	*erm(B)*	all except ketolides unless multiple mutations	full resistance
	active efflux	*mef(A)*	14-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

[1] also norfloxacin and ciprofloxacin (not recommended)

Adapted from Van Bambeke F, *et al. Drugs.* 2007;67:2355-82 – PMID: 17983256

See also Lismond, *et a*l. J Antimicrob Chemother. 2011;;66:948-51 – PMID: 21393137. , Lismond, *et al.* Intern J Antimicrob Ag. 2012;39:208–16 – PMID:: 22245497

MIC distribution is a continuous variable…



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

MIC data from a presentation at ECCMID 2015
(Tulkens et al. e-poster EV0153)

MIC minimum inhibitory concentration
CAP community-acquired pneumonia
COPD chronic obstructive pulmonary disease

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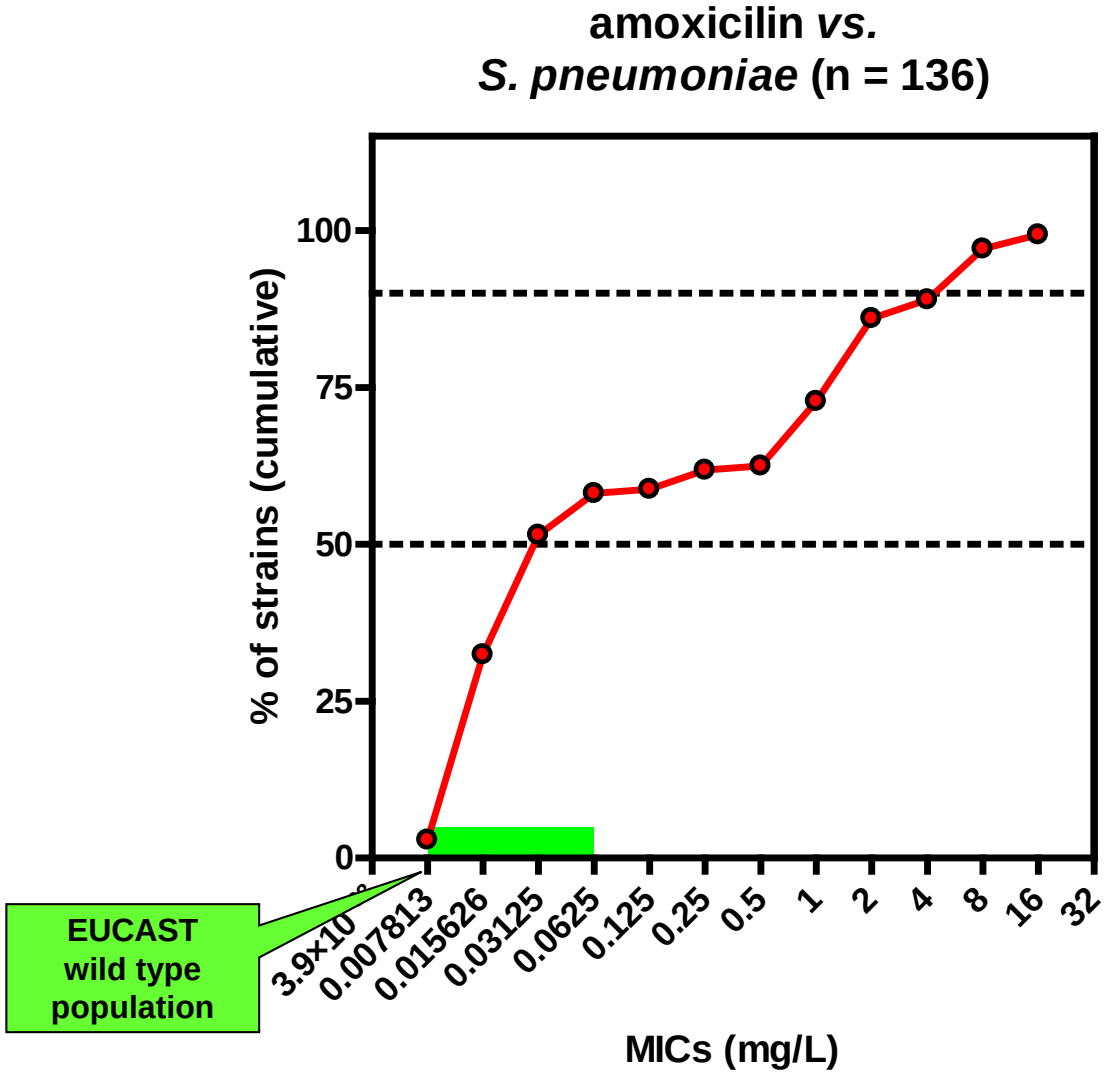

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EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease

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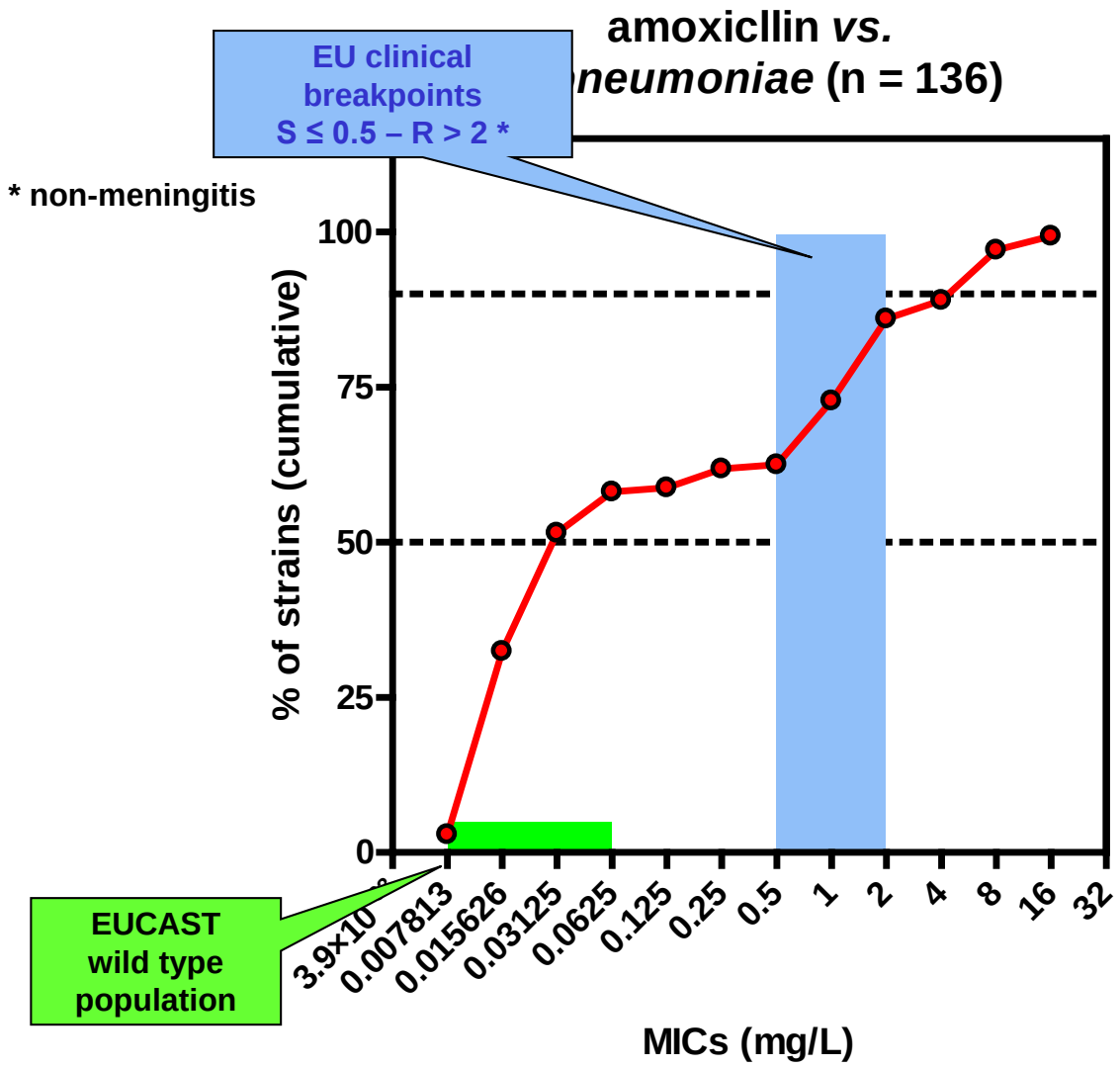

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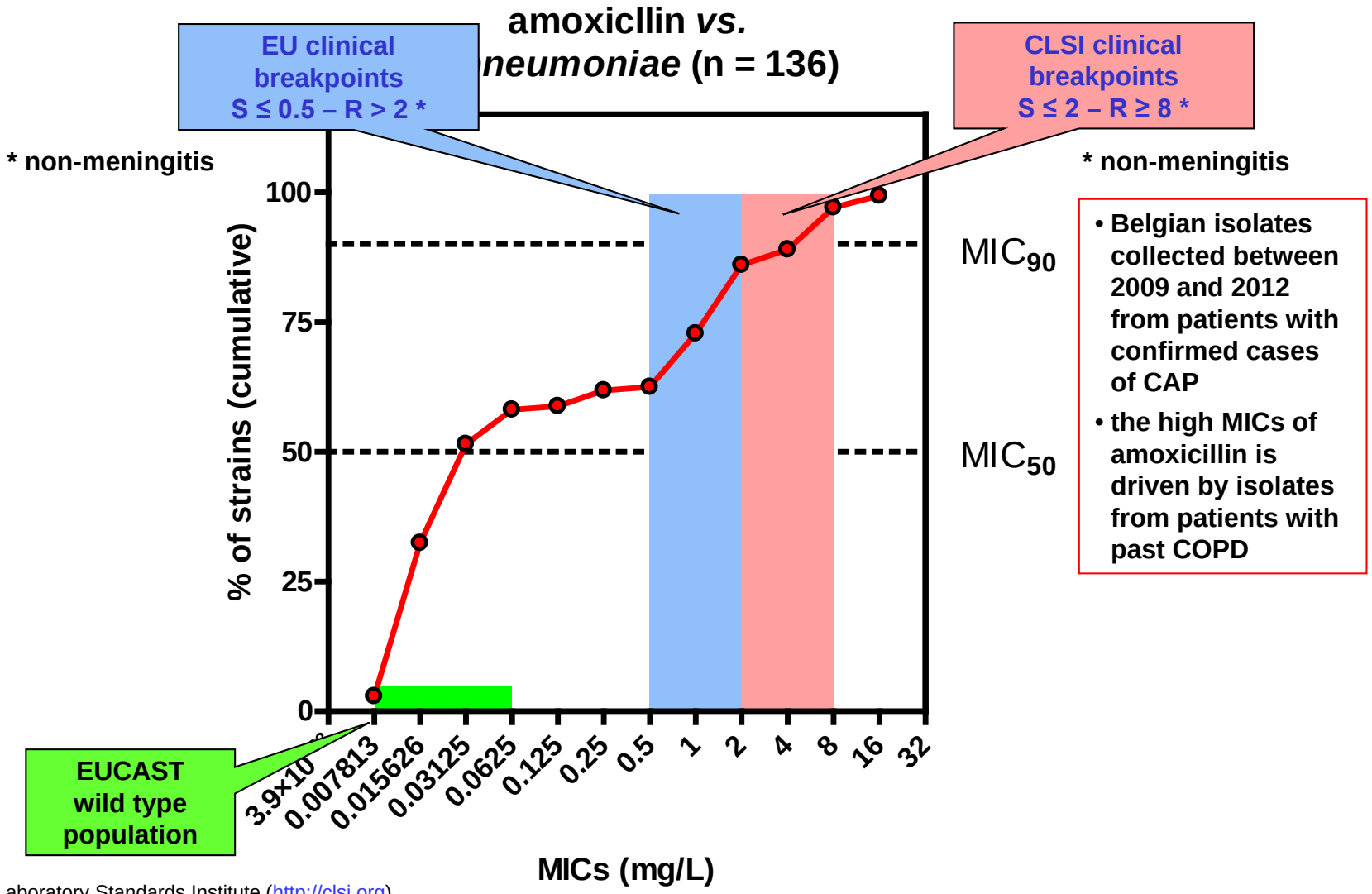

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CLSI: Clinical and Laboratory Standards Institute (http://clsi.org)
EUCAST: European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org)
MIC: minimum inhibitory concentration
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MIC data from a presentation at ECCMID 2015
(Tulkens et al. e-poster EV0153)

Breakpoints ?

Vérité en-deçà des Pyrénées, erreur au-delà.

The frontispiece of Geert Hofstede's influential book, *Culture's consequences: Comparing values, behaviors, institutions, and organizations across nations* (Hofstede, 2001) includes the following quote: "Vérité en-deça des pyrénées, erreur au-delà". Written about 350 years ago by the French mathematician and physicist Blaise Pascal and included in his *Pensées*, Hofstede's translation is "There are truths on this side of the Pyrenees that are falsehoods on the other."

A few words about breakpoint setting…

- **The USA story…**
  - **Historically**, most breakpoints were set by the US National Committee for Clinical Laboratory Standards (**NCCLS**) but were often much too high (due to Industry pressure)
  - **Since 2006**, the **US FDA** has reasserted its right to set breakpoints, and this is for all new antibiotics (starting with tigecyclin…). Those are included in the "Product Information" (PI; "label") and are official US breakpoints
  - As a consequence, the NCCLS was no longer considered "national" and changed its name (into Clinical Laboratory Standard Institute [**CLSI**]) and has **no right to define official US breakpoints**[1]

[1] Access to CLSI breakpoints is not free and must be subscribed to (http://www.clsi.org). The "21st Century Cures Act", which passed the US House on July 7, 2015 and is now in the US Senate proposes to establish a public web site with all official US breakpoints

A few words about breakpoint setting…

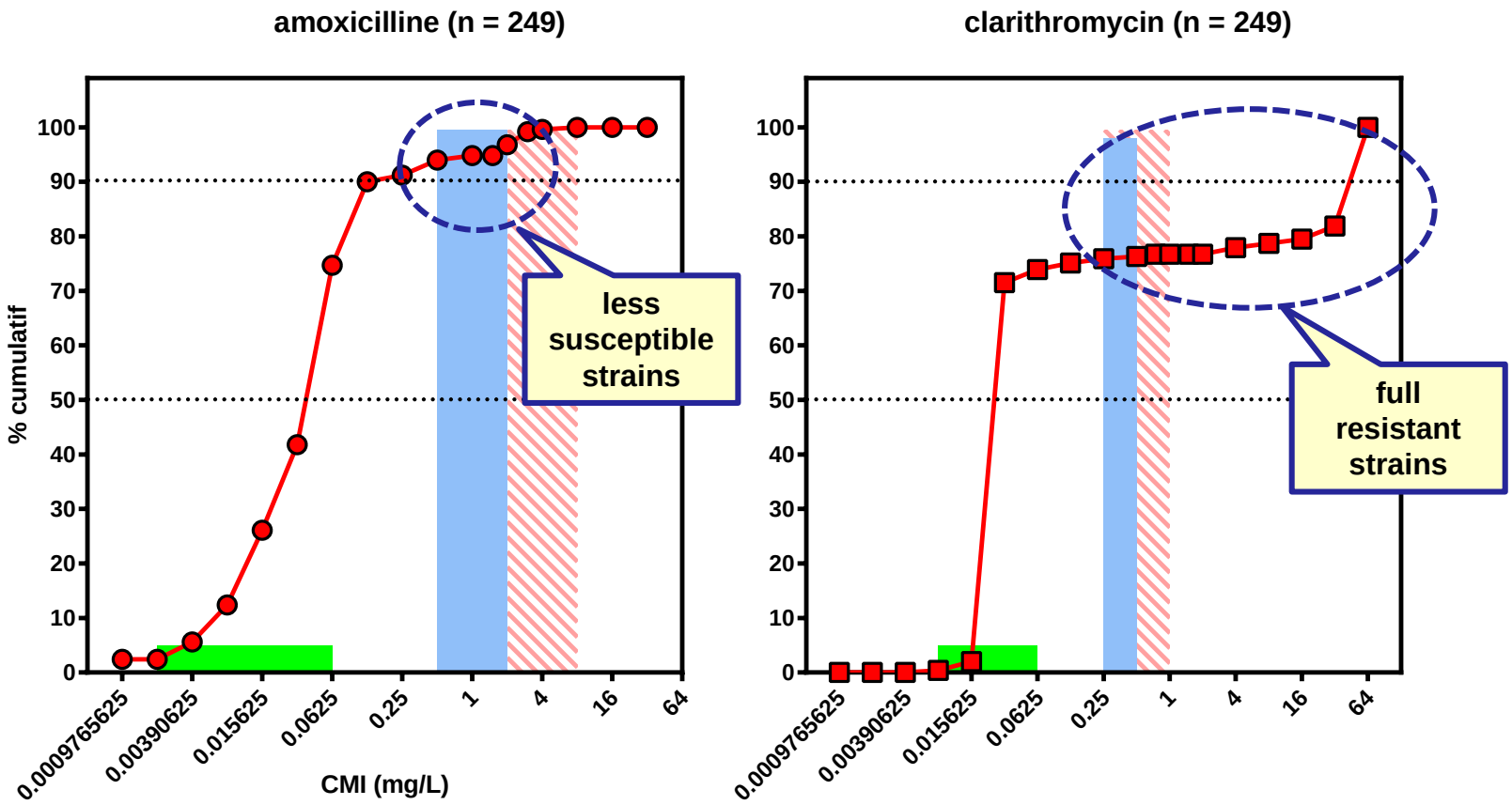
- **In Europe**
  - the European Committee for Antimicrobial Susceptibility Testing (**EUCAST**; created in 1997) sets breakpoints in cooperation with the European Medicines Agency (**EMA**). Those become official breakpoints (included in the Summary of Product Characteristics (SmPC; "label") [2] in the 28 EU member states plus the 3 EEA countries (Norway, Iceland and Liechtenstein)
  - **most EUCAST breakpoints for antibiotics approved before 2005 are (considerably) lower than those historically proposed by the NCCLS**, and, for antibiotics approved after 2005, often close (but lower) than those decided by the US FDA
  - Beyond EU + EEA, EUCAST breakpoints are increasingly used in other parts of the world (see map)

[2] Access to EUCAST breakpoints and the corresponding rational documents is free (http://www.eucast.org)

Implementation of EUCAST breakpoints, April 2016

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Statistics/EUCAST_status_Europe_April_2016.pdf

A first analysis of susceptibility of Belgian *S. pneumoniae:* CAP (2008-2010)



Consequences:

1. **use higher doses (or more frequent administration) of amoxicillin (1g q8h)**
2. **do NOT use macrolides in monotherapy !**

Lismond *et al*. Int J Antimicrob Agents. 2012;39:208-16 - PMID: 22245497

Breakpoints differences between EUCAST and CLSI for *S. pneumoniae* and fluoroquinolones *

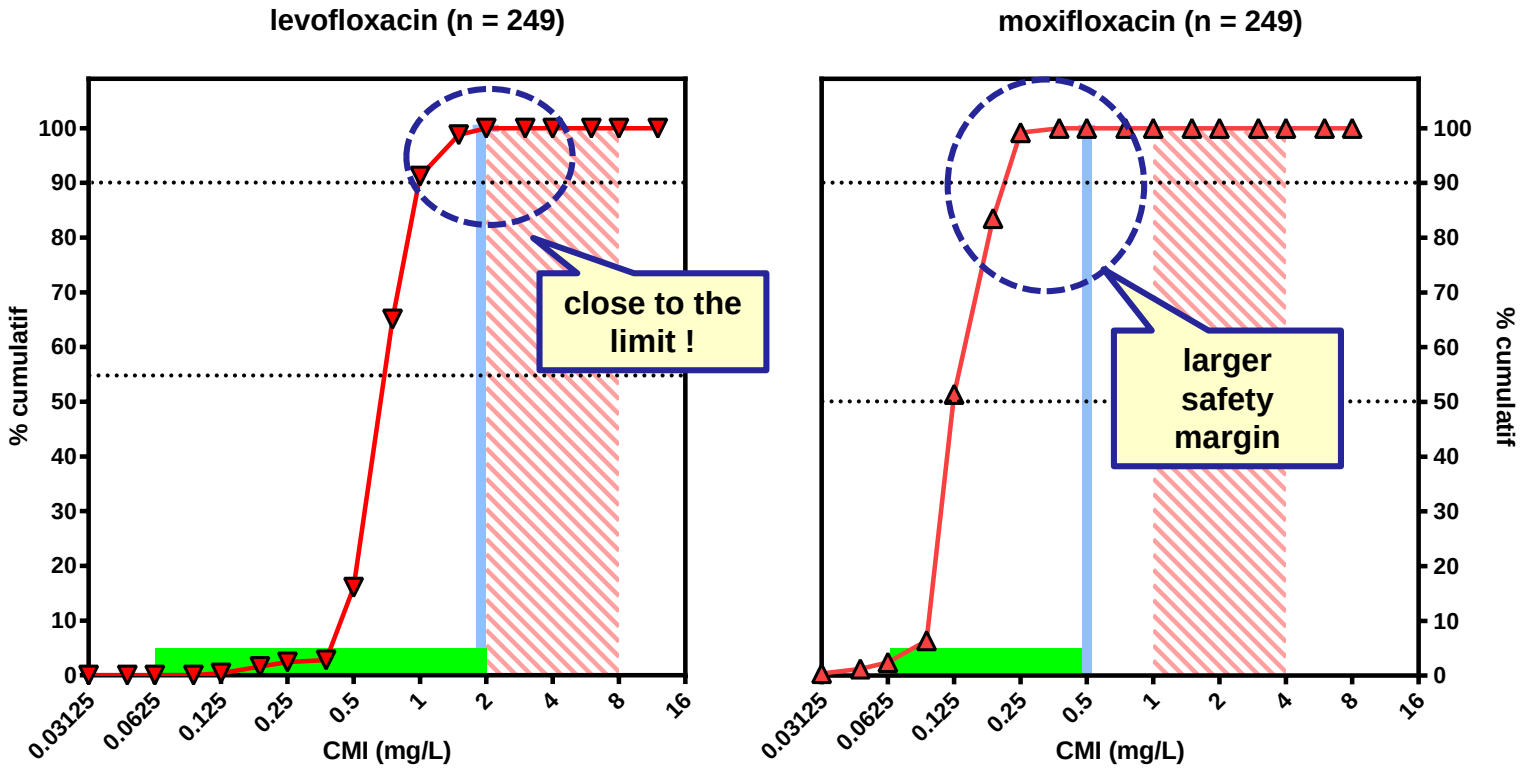
antibiotic	EUCAST		CLSI	
	S	R	S	R
ciprofloxacin	≤ 0.125	> 2 [a]	-- [b]	
ofloxacin	≤ 0.125	> 2 [a]	≤ 2	≥ 8
levofloxacin	≤ 2	> 2	≤ 2	≥ 8
moxifloxacin	≤ 0.5	> 0.5	≤ 1	≥ 4

[a] For EUCAST, wild type S. pneumoniae are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorised as intermediate.
[b] no longer included in the 2015 CLSI edition; was ≤ 1 and ≥ 4 in the 2004 NCCLS recommendations
[c] For EUCAST, breakpoints of levofloxacin are based on high dose therapy (500 mg x 2)
[d] For CLSI, S. pneumoniae susceptible to moxifloxacin cannot be assumed to be susceptible to levofloxacin.

*** Sources:**

- The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, 2016. http://www.eucast.org
- M100-S25Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement, Wayne, PA 19087 USA, 2015. http://www.clsi.org

A first analysis of susceptibility of Belgian *S. pneumoniae:* CAP (2008-2010)

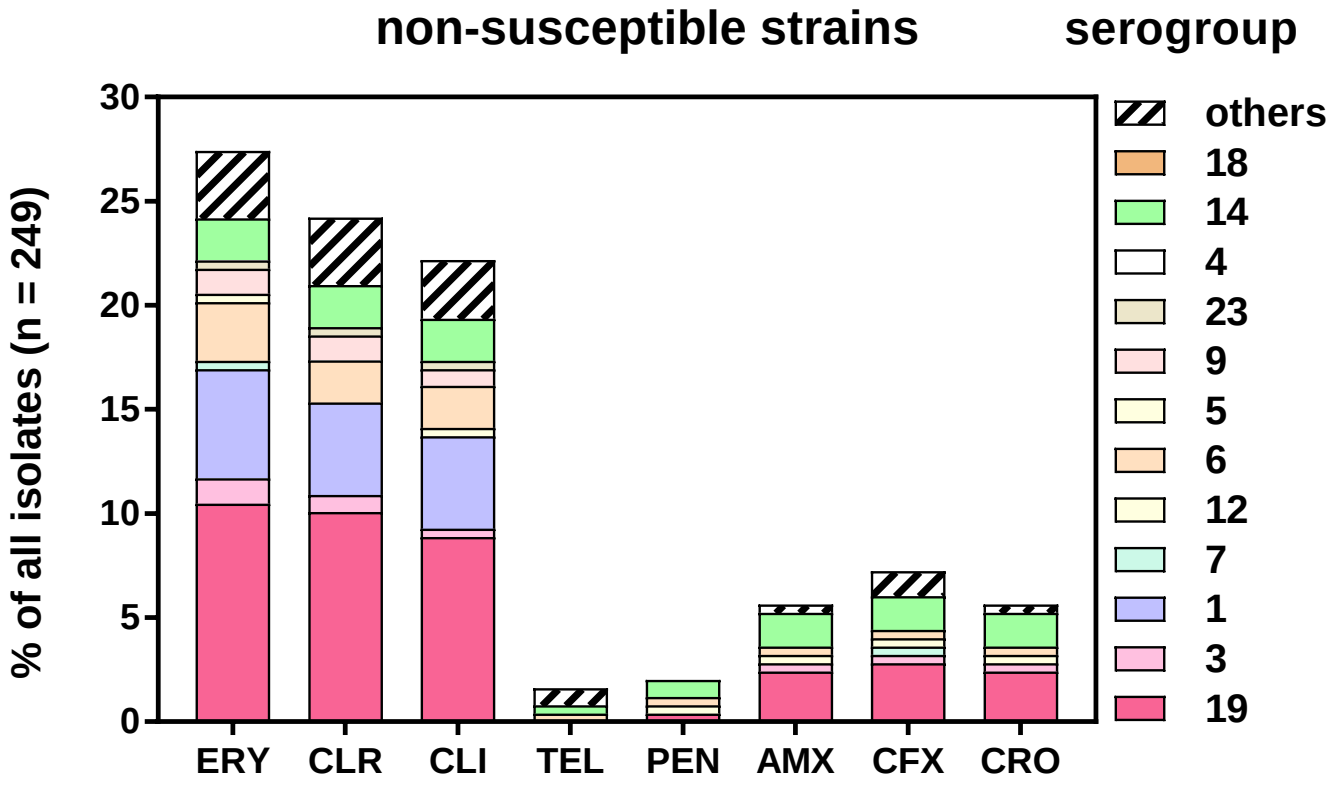


Consequences:

1. **levofloxacin should better be used at 750 mg QD or 500 mg BID**
2. **but, actually, we do not use much any more for respiratory tract infections**

Lismond *et al*. Int J Antimicrob Agents. 2012;39:208-16 - PMID: 22245497

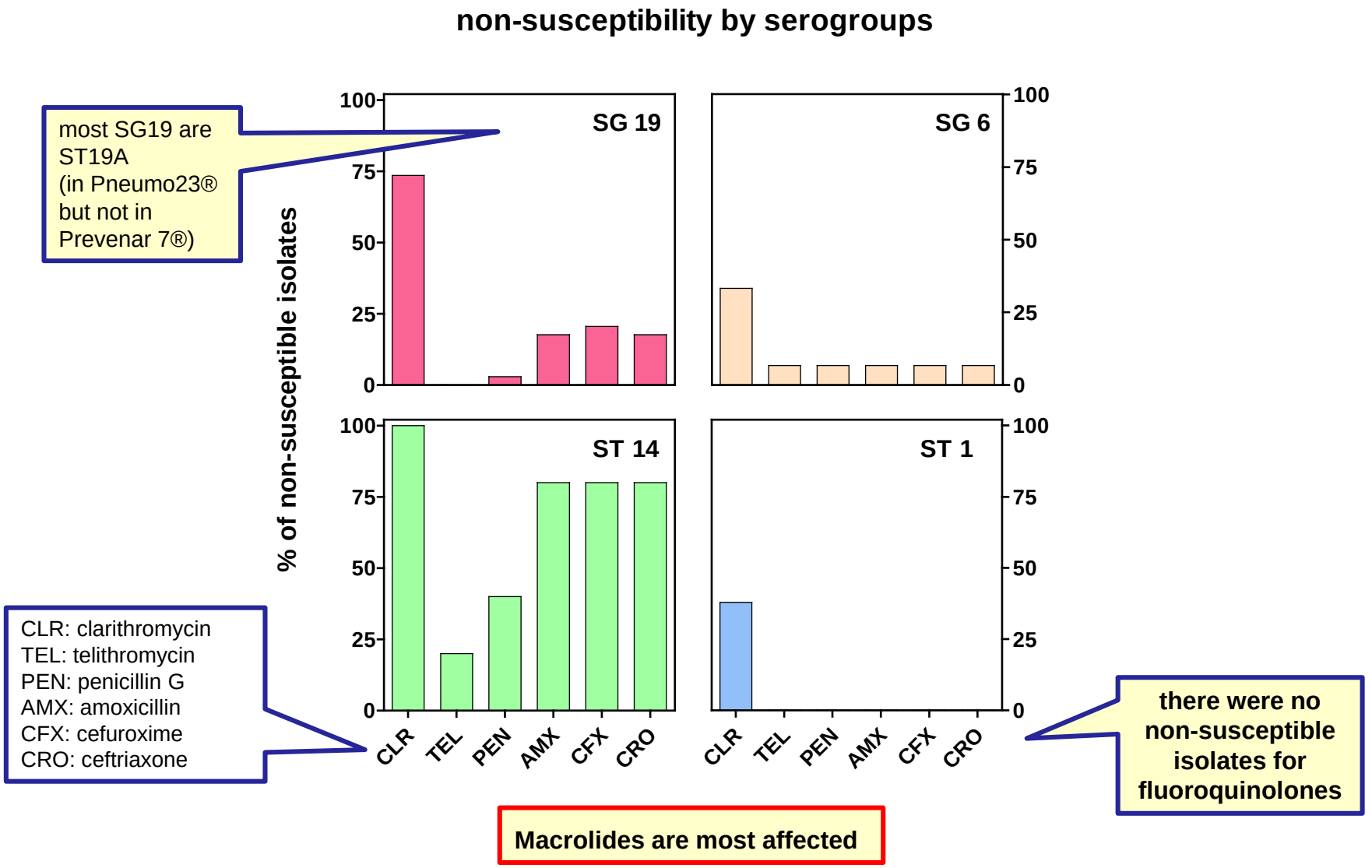
Susceptibility and serotypes/serogroups (CAP)



Serogroup 19 (96% ST 19A) shows the largest proportion of resistant strains

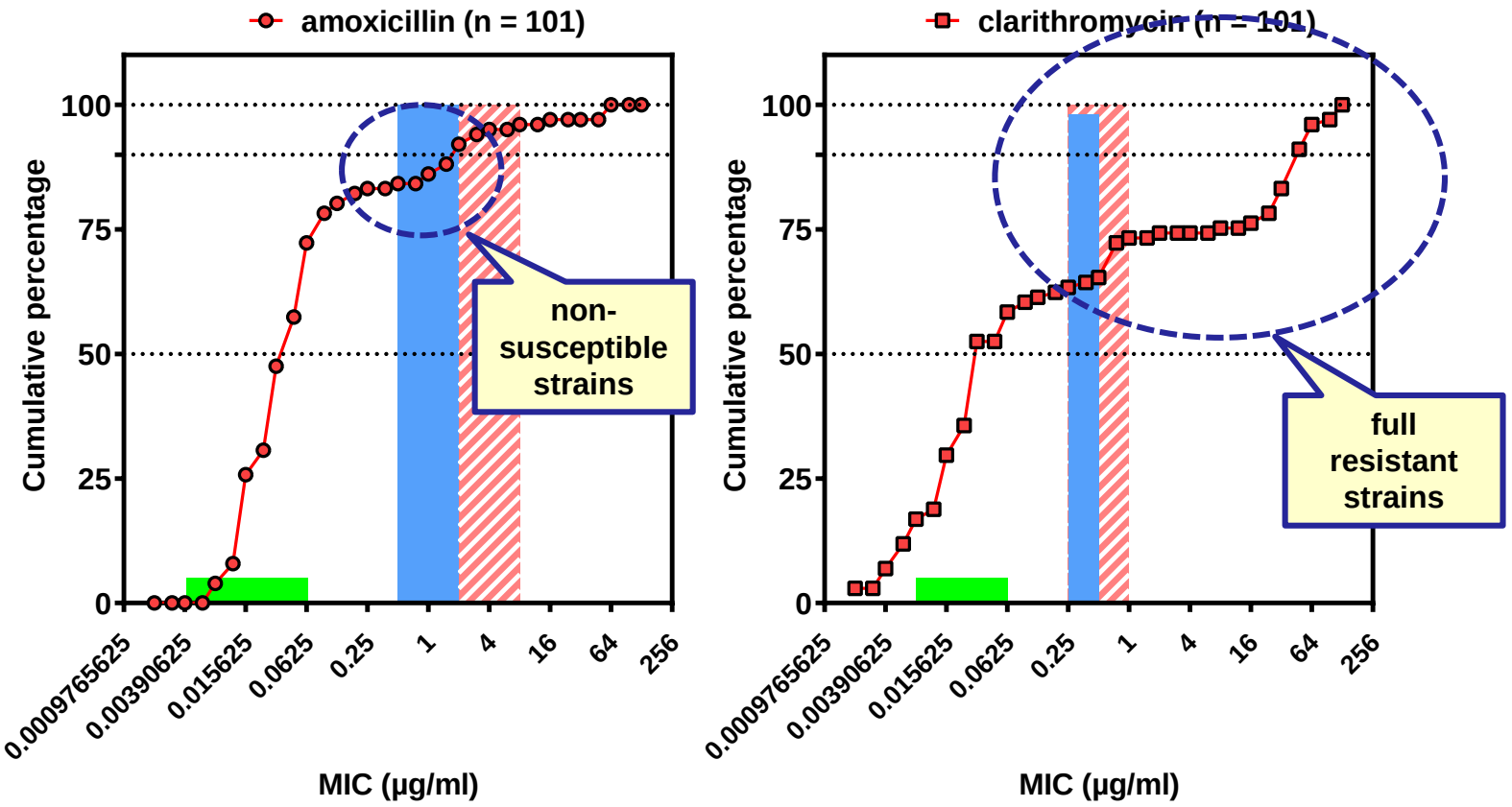
Lismond *et al.* Int J Antimicrob Agents. 2012;39:208-16 - PMID: 22245497

Susceptibility and serotypes/serogroups (CAP)



Lismond *et al.* Int J Antimicrob Agents. 2012;39:208-16 - PMID: 22245497

A second analysis of susceptibility of Belgian *S. pneumoniae:* COPD (2006-2013)

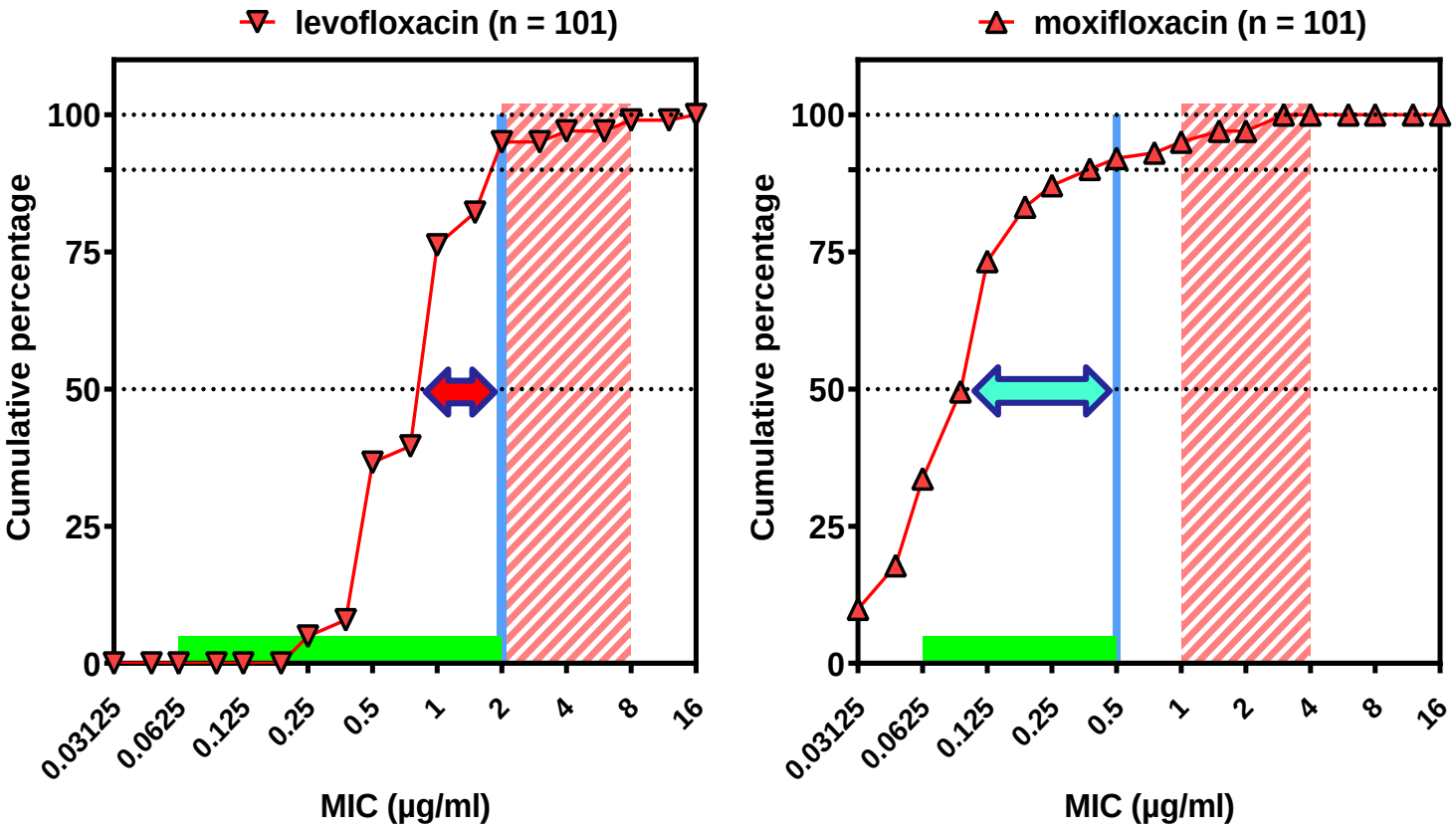


Consequences:

1. **use <u>certainly</u> higher doses (or more frequent administration) of amoxicillin (> 1g q8h)**
2. **STOP using macrolides in monotherapy !**

Vandevelde *et al.* Int J Antimicrob Agents 2014;44:209-17 - PMID: 25123808.

A second analysis of susceptibility of Belgian *S. pneumoniae:* COPD (2006-2013)



Consequences:

1. **levofloxacin starts lagging beyind and gets very close even to CLSI breakpoint**
2. **moxifloxacin is not immune but still shows a much wider safety margin**

Vandevelde *et al.* Int J Antimicrob Agents 2014;44:209-17 - PMID: 25123808.

You can get resistance to moxifloxacin …

Journal of Antimicrobial Chemotherapy (2007) **60**, 965–972
doi:10.1093/jac/dkm292
Advance Access publication 10 August 2007

JAC

Selection of quinolone resistance in *Streptococcus pneumoniae* exposed *in vitro* to subinhibitory drug concentrations

Laetitia Avrain[1], Mark Garvey[2], Narcisa Mesaros[1], Youri Glupczynski[3], Marie-Paule Mingeot-Leclercq[1], Laura J. V. Piddock[2], Paul M. Tulkens[1], Raymond Vanhoof[4] and Françoise Van Bambeke[1]*

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and Françoise Va

You simply expose them to sub-Mic concentrations

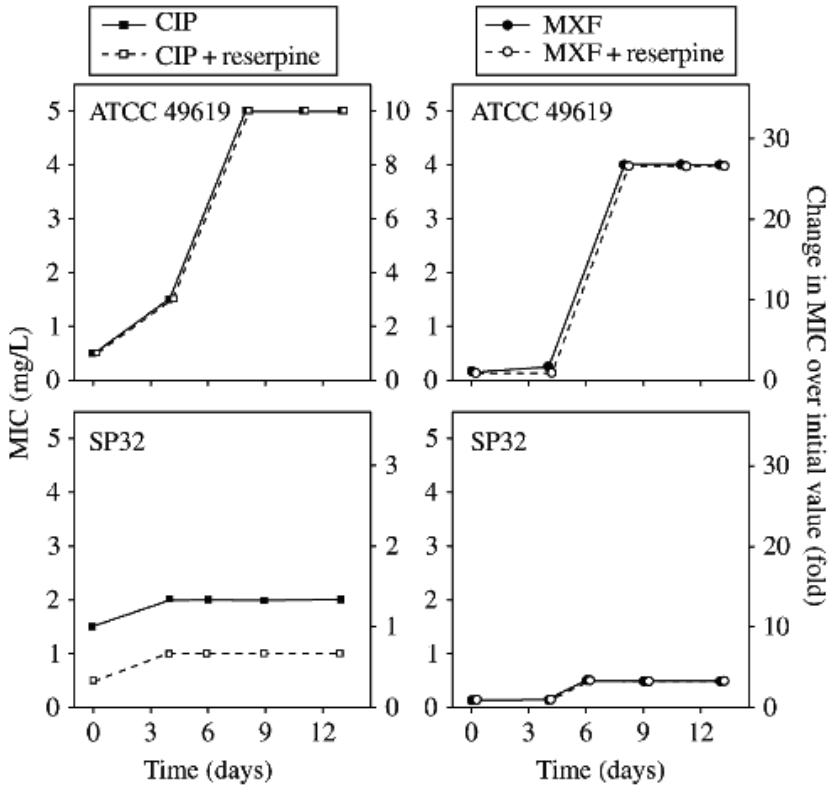

Figure 2. Evolution of the MIC of ciprofloxacin (CIP; left-hand panels) and of moxifloxacin (MXF; right-hand panels) for *S. pneumoniae* ATCC 49619 (top panels) and SP32 (bottom panels) after exposure to half-MIC concentrations of moxifloxacin for the indicated times. MICs were determined in the absence (filled symbols and continuous lines) or in the presence (open symbols and broken lines) of 10 mg/L reserpine and the concentration of the inducer antibiotic was re-adjusted each day to remain equivalent to half the MIC. MICs are plotted as actual values as measured by arithmetic dilutions (left-hand axis) or as multiples of the initial values as determined in the absence of reserpine (right-hand axis).

More on acquisition of resistance to fluoroquinolones …

J Antimicrob Chemother 2015; **70**: 2499–2506
doi:10.1093/jac/dkv134 Advance Access publication 1 June 2015

Journal of Antimicrobial Chemotherapy

Insights into the evolutionary trajectories of fluoroquinolone resistance in *Streptococcus pneumoniae*

Gang Zhang[1], Chao Wang[1], Zhihai Sui[1] and Jie Feng[1,2]*

[1]*State Key Laboratory of Microbial Resources, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China;*
[2]*Beijing Key Laboratory of Microbial Drug Resistance and Resistome, Beijing 100101, China*

More on acquisition of resi

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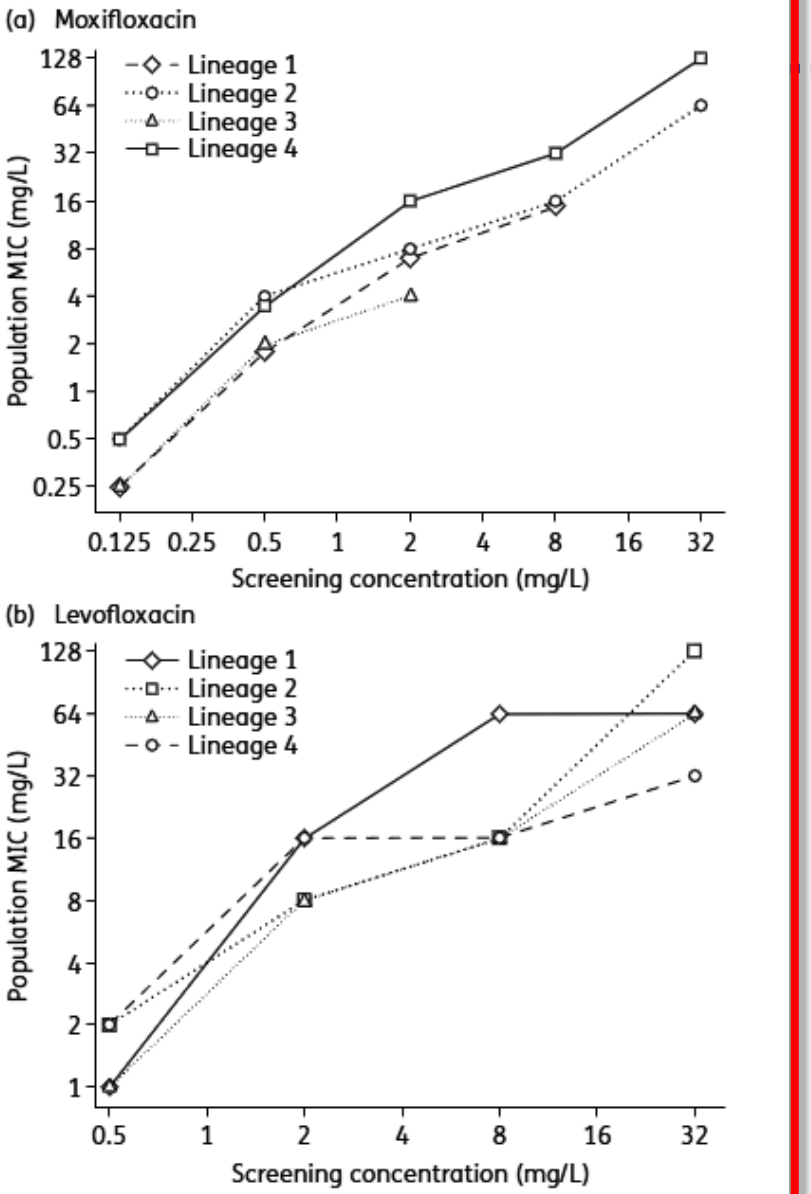

Figure 1. Resistance levels in evolved populations of eight lineages under stepwise increased screening concentrations of fluoroquinolones.

Resistance acquisition by lineage

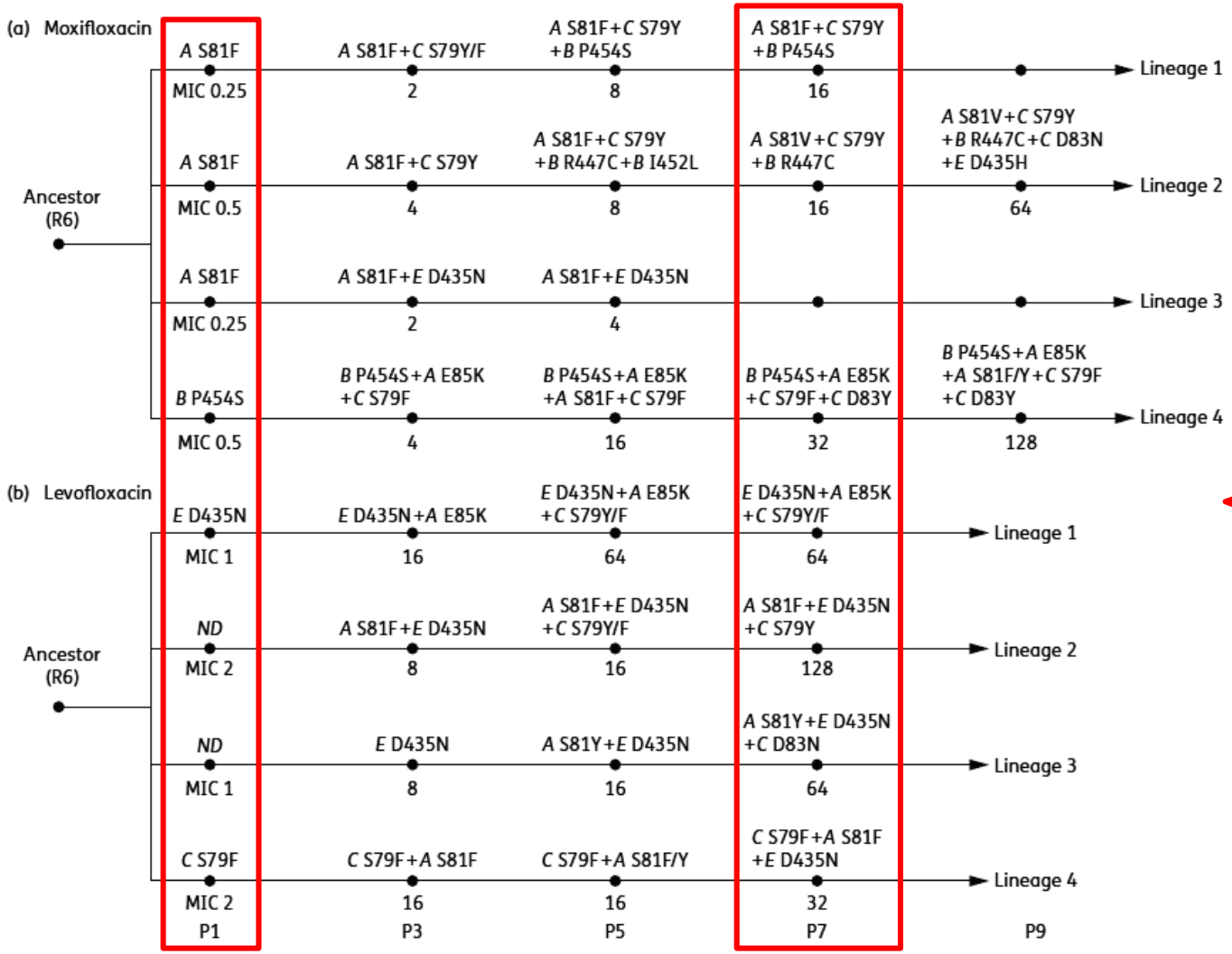

Figure 2. Evolutionary trajectories of fluoroquinolone resistance in the eight lineages founded from the *S. pneumoniae* R6 strain. Evolutionary paths to (a) moxifloxacin resistance and (b) levofloxacin resistance. *A*, *B*, *C* and *E* indicate the coding region of *gyrA*, *gyrB*, *parC* and *parE*, respectively. S79F, S79Y, S81F and S81Y represent *parC* S79F, *parC* S79Y, *gyrA* S81F and *gyrA* S81Y, respectively. MIC units=mg/L. These resistant populations were sampled at different passages. For moxifloxacin, P1, P3, P5, P7 and P9 denote 0.125, 0.5, 2, 8 and 32 mg/L screening concentrations, respectively. For levofloxacin, P1, P3, P5 and P7 denote 0.5, 2, 8 and 32 mg/L screening concentrations, respectively. ND, not detected. The amino acid positions of the substitutions are given in accordance with the *S. pneumoniae* R6 coordinates.[24]

increases are <u>stepwise</u> over wild type MIC level

But resistance did not emerge in the community in Belgium …

PLOS ONE

RESEARCH ARTICLE

Molecular Analysis of Rising Fluoroquinolone Resistance in Belgian Non-Invasive *Streptococcus pneumoniae* Isolates (1995-2014)

Pieter-Jan Ceyssens[1], Françoise Van Bambeke[2], Wesley Mattheus[1], Sophie Bertrand[1], Frédéric Fux[1], Eddie Van Bossuyt[1], Sabrina Damée[1], Henry-Jean Nyssen[3], Stéphane De Craeye[3], Jan Verhaegen[4], The Belgian *Streptococcus pneumoniae* Study Group[¶], Paul M. Tulkens[2], Raymond Vanhoof[1]*

1 Unit of Bacterial Diseases, Scientific Institute of Public Health (WIV-ISP), 1050 Brussels, Belgium, 2 Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université Catholique de Louvain, 1200 Brussels, Belgium, 3 Unit of Foodborne Pathogens, Scientific Institute of Public Health (WIV-ISP), 1050 Brussels, Belgium, 4 Laboratory of Clinical Bacteriology and Mycology, KULeuven, 3000 Leuven, Belgium

Ceyssens *et al.* PLosOne 2016;11:e0154816 - PMID: 27227336

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RESEARCH ARTICLE

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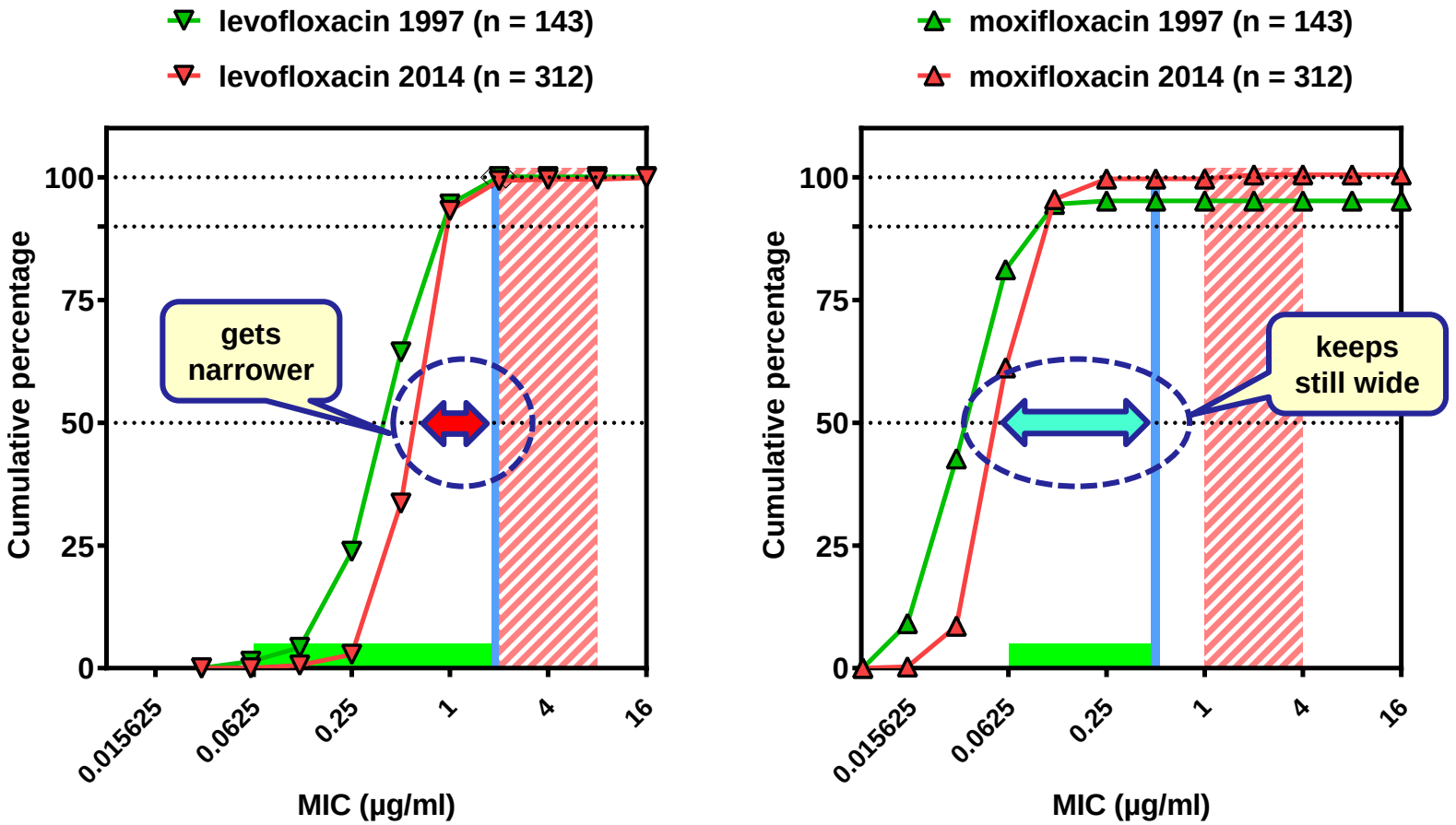
1 Unit of Bacterial Diseases, Scientific Institute o 2 Pharmacologie cellulaire et moléculaire, Louva Louvain, 1200 Brussels, Belgium, 3 Unit of Food ISP), 1050 Brussels, Belgium, 4 Laboratory of Cl Belgium

Ceyssens *et al.* PLosOne 2016;11:e

Longitudinal surveillance study (1995–2014) on fluoroquinolone resistance (FQ-R) among Belgian non-invasive *Streptococcus pneumoniae* isolates between 1995 through 2014 (n = 5,602).

- For many years, the switch to respiratory fluoroquinolones for the treatment of (a)typical pneumonia had no impact on FQ-R levels.
- However, since 2011 we observed a significant decrease in susceptibility towards ciprofloxacin, ofloxacin and levofloxacin with peaks of 9.0%, 6.6% and 3.1% resistant isolates, respectively.
- **Resistance to moxifloxacin aroused sporadically, and remained <1% throughout the entire study period**.

Here are the distributions *…

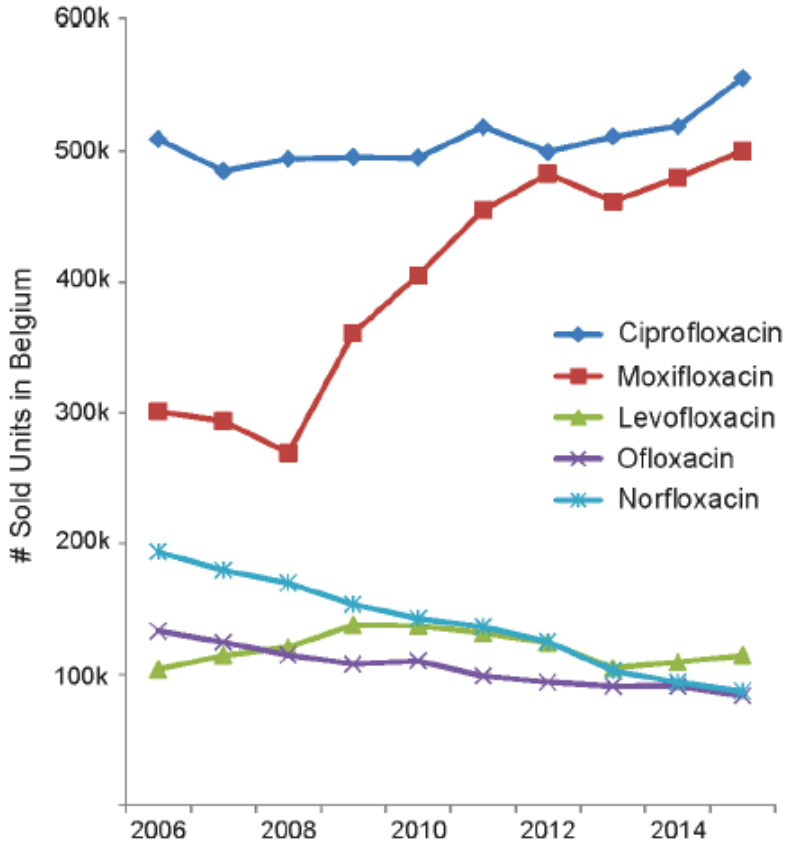


*** non invasive isolates collected over whole Belgium**

Graphed from numeric data in Ceyssens *et al.* PLosOne 2016;11:e0154816 - PMID: 27227336

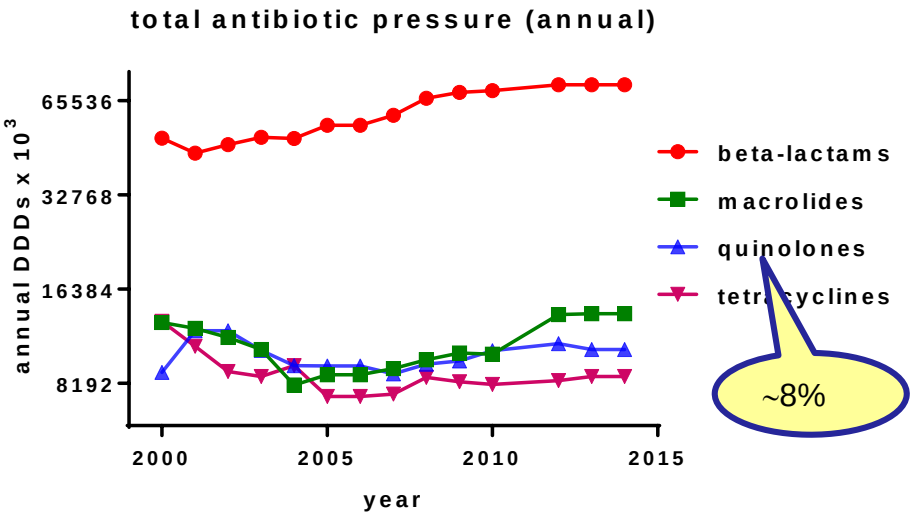
But do you use moxifloxacin in Belgium?

Fluoroquinolones sales data



source: IMS dataview, data December 2015
(download from http://ims-dataview.software.informer.com/)

Reimbursement comparative data for all antibiotics (in the community)



Source: National Institute for Health and Disability Insurance
Tiny URL: http://tinyurl.com/hwu74sf (in French)

More from Asia…

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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

Antimicrobial susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated from community-acquired respiratory tract infections in China: Results from the CARTIPS Antimicrobial Surveillance Program

Yawei Zhang [a], Feifei Zhang [a], Hui Wang [a,*], Chunjiang Zhao [a], Zhanwei Wang [a], Bin Cao [b], Yan Du [c], Xianju Feng [d], Yunjian Hu [e], Bijie Hu [f], Ping Ji [g], Zhiyong Liu [h], Yong Liu [i], Wanzhen Liao [j], Juan Lu [k], Hongli Sun [l], Zhongxin Wang [m], Xiuli Xu [n], Xuesong Xu [o], Qing Yang [p], Yunsong Yu [q], Rong Zhang [r], Chao Zhuo [s]

we have heard about this…

"*In conclusion, the results of this study confirmed the excellent activities of fluoroquinolones, including levofloxacin and moxifloxacin, against S. pneumoniae, H. influenzae and M. catarrhalis.*"

Zhang et al. J Glob Antimicrob Resist. 2016;5:36-41- PMID: 27436464

Risks of using "low activity" fluoroquinolones

The continuous exposure of *S. pneumoniae* to sub-MIC levels of ciprofloxacin and levofloxacin has been shown to select for efflux overexpression

J Antimicrob Chemother 2013; **68**: 1130–1138
doi:10.1093/jac/dks537 Advance Access publication 29 January 2013

Journal of Antimicrobial Chemotherapy

Comparative antibacterial effects of moxifloxacin and levofloxacin on *Streptococcus pneumoniae* strains with defined mechanisms of resistance: impact of bacterial inoculum

K. E. Bowker*, M. I. Garvey, A. R. Noel, S. G. Tomaselli and A. P. MacGowan

Bristol Centre for Antimicrobial Research and Evaluation, North Bristol NHS Trust and University of Bristol, Department of Microbiology, Lime Walk Building, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

Bowker *et al.* J Antimicrob Chemother. 2013;68:1130-8 - PMID: 23361641

Risks of resistance emergence with levofloxacin

PK Bioflo® 1000 *in vitro* model **simulating** free drug serum concentrations associated with the **oral administration** of

- **400 mg of moxifloxacin** once daily,
- **750 mg of levofloxacin** once daily or
- **500 mg of levofloxacin twice daily.**

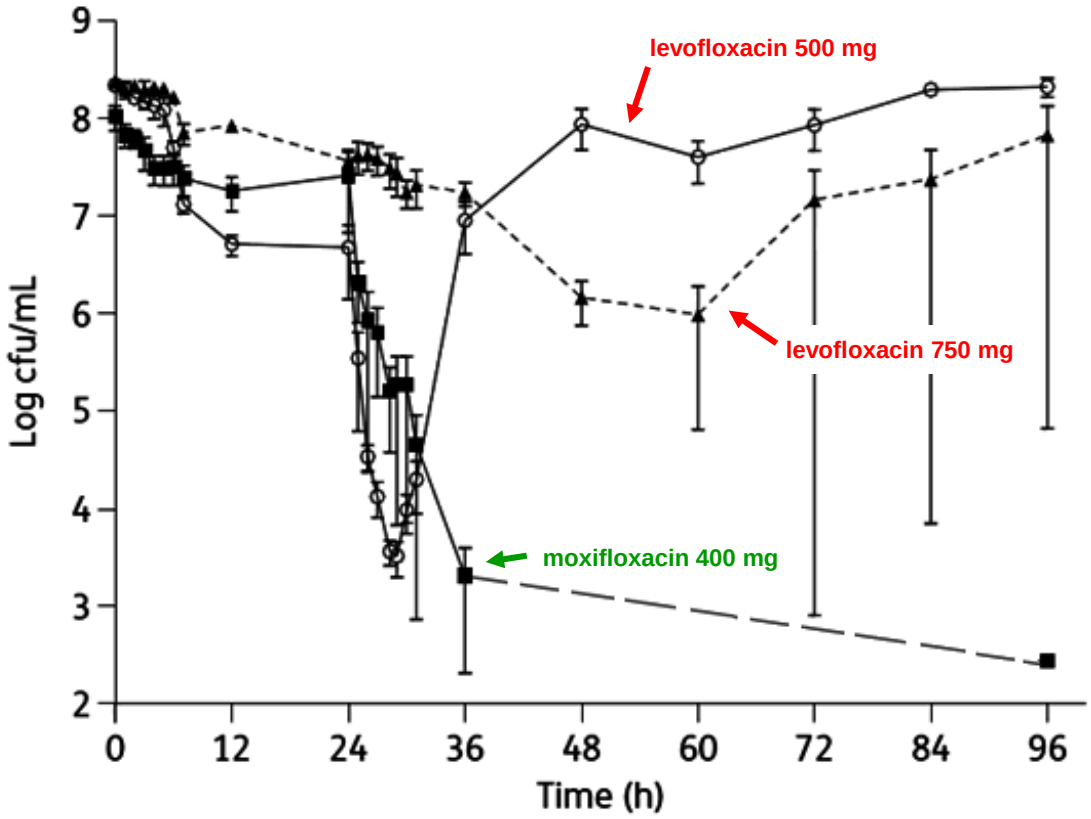


Figure 1. Comparative activity of moxifloxacin and levofloxacin against *S. pneumoniae* 21843 (wild-type). Inoculum of 10^8 cfu/mL. Squares, 400 mg of moxifloxacin once daily; triangles, 500 mg of levofloxacin twice daily; circles, 750 mg of levofloxacin once daily.

Adapted from Bowker *et al.* J Antimicrob Chemother. 2013;68:1130-8 - PMID: 23361641

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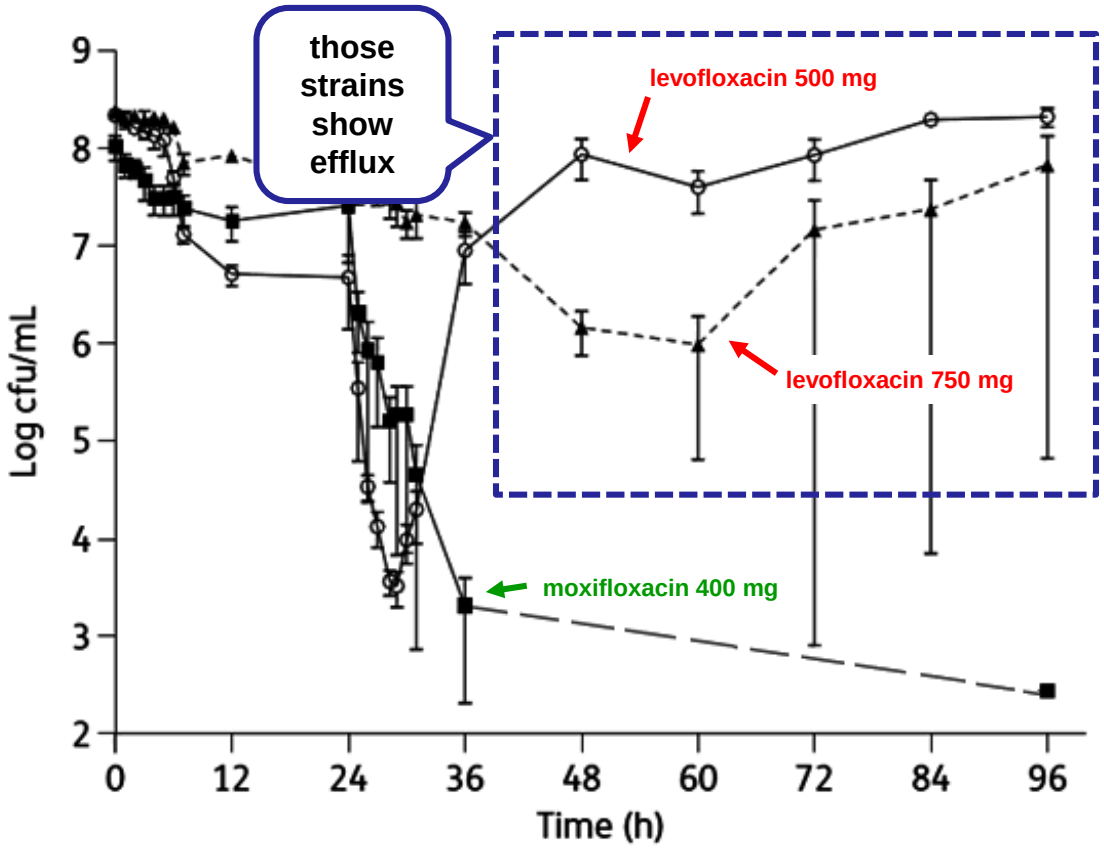

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Risks of resistance emergence with levofloxacin

J Antimicrob Chemother 2013; **68**: 1130–1138
doi:10.1093/jac/dks537 Advance Access publication 29 January 2013

Journal of Antimicrobial Chemotherapy

Comparative antibacterial effects of moxifloxacin and levofloxacin on *Streptococcus pneumoniae* strains with defined mechanisms of resistance: impact of bacterial inoculum

K. E. Bowker*, M. I. Garvey, A. R. Noel, S. G. Tomaselli and A. P. MacGowan

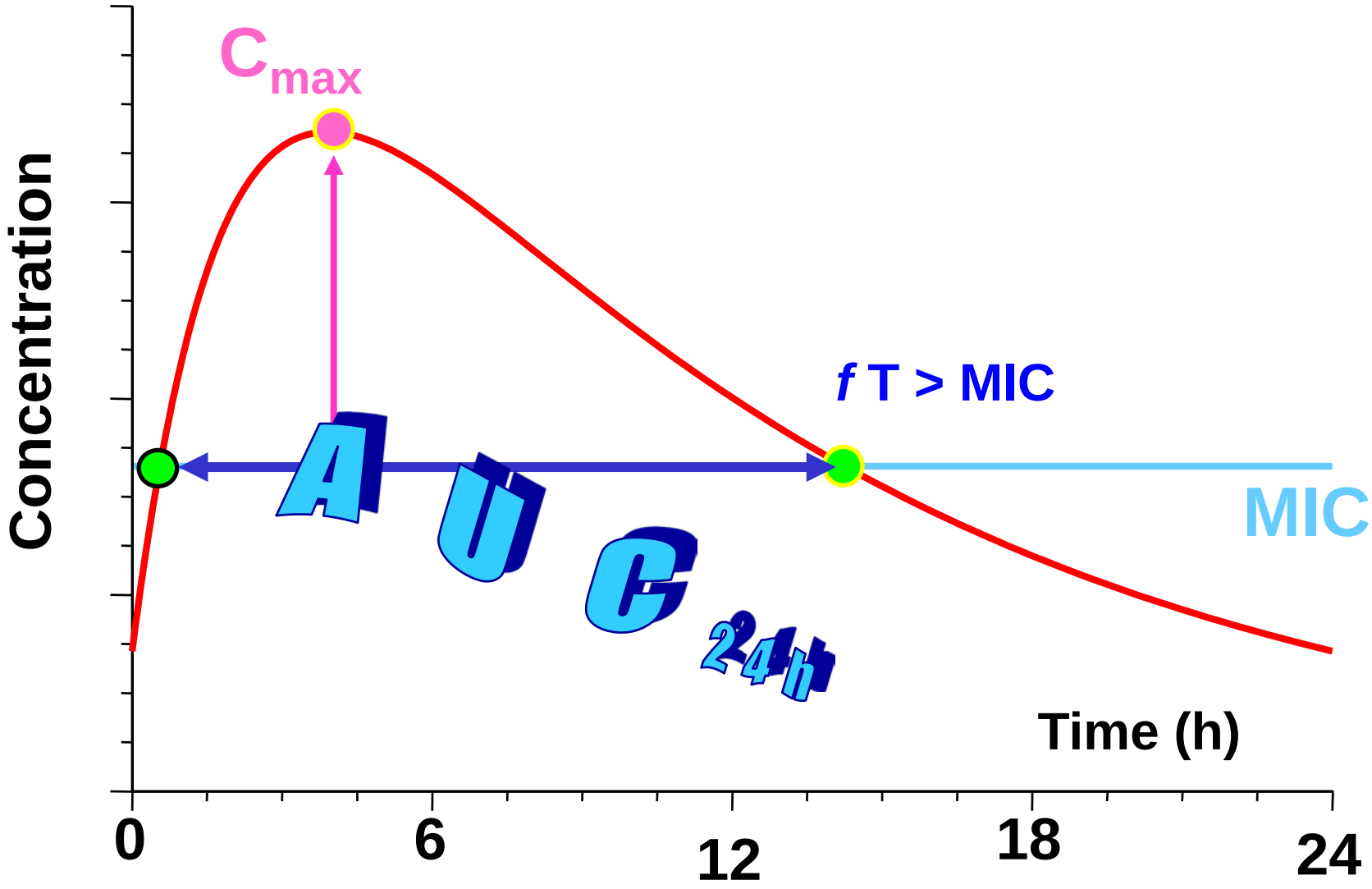
Bristol Centre for Antimicrobial Research and Evaluation, North Bristol NHS Trust and University of Bristol, Department of Microbiology, Lime Walk Building, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

Bowker *et al.* J Antimicrob Chemother. 2013;68:1130-8 - PMID: 23361641

Conclusions:

- *"Levofloxacin dosing regimens with low AUC/MIC ratios select for efflux pump overexpression, leading to fluoroquinolone resistance.*
- *Levofloxacin dosing may select for gyrA mutations, inducing moxifloxacin resistance.*
- *These data confirm that a fluoroquinolone **AUC/MIC ratio of > 100** is required for prevention of emergence of resistance.*"

What do you mean by an AUC/MIC ratio > 100 and why does it impact on emergence of resistance ?



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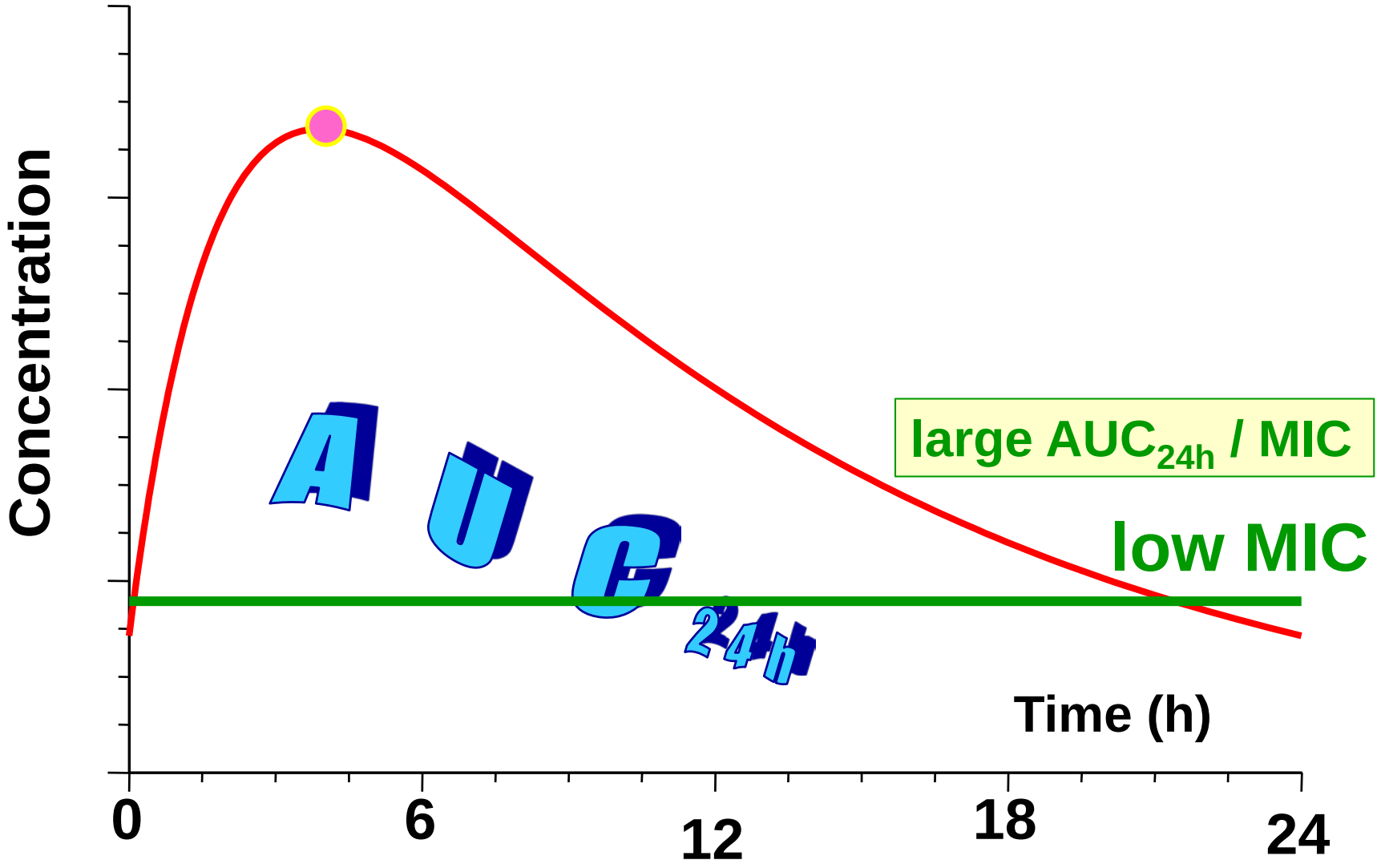

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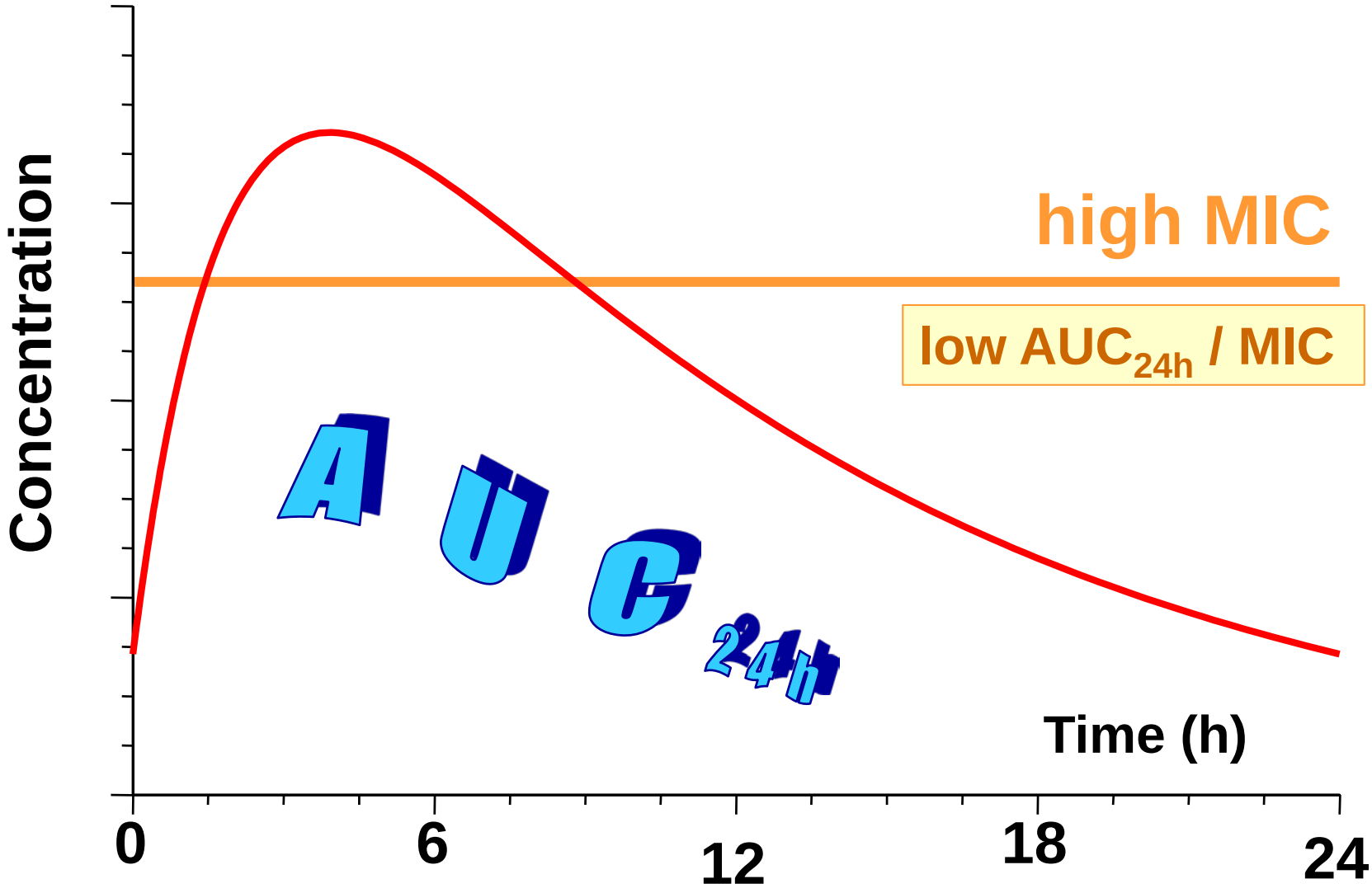


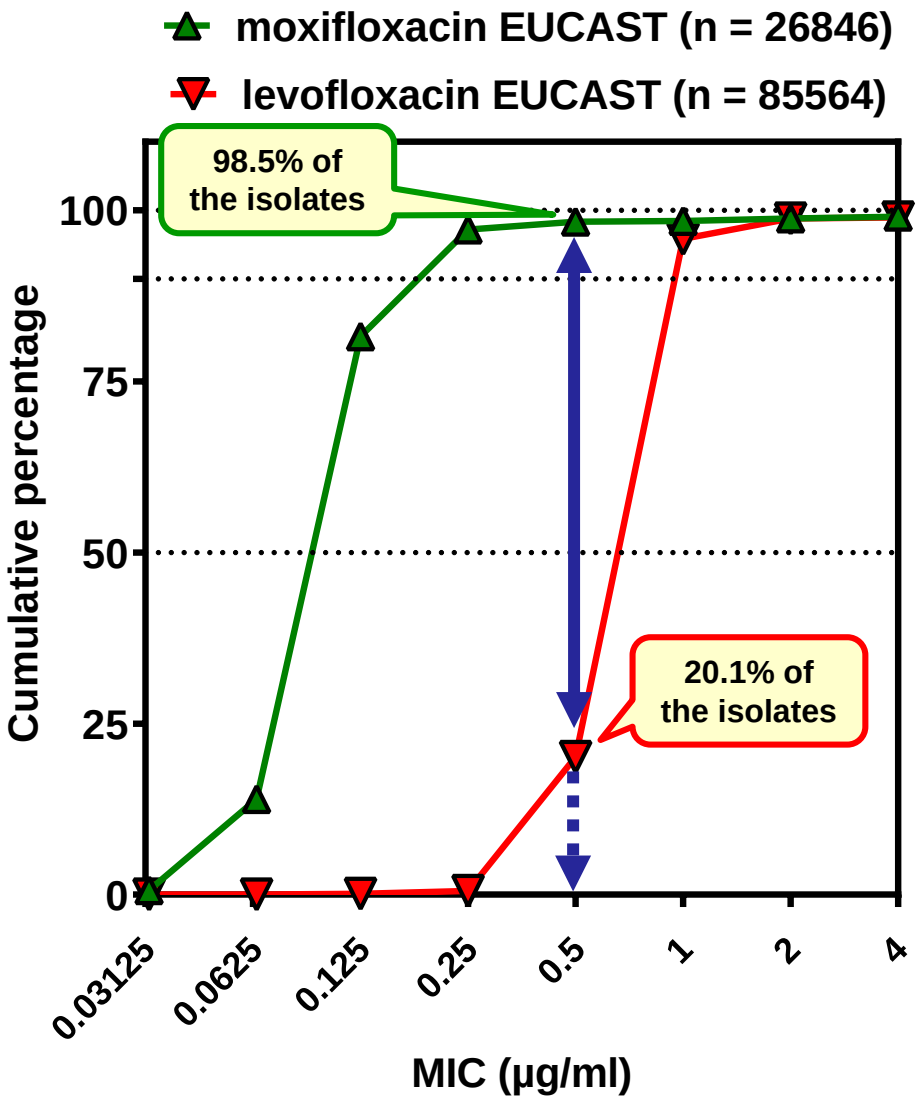
What do you mean by an AUC/MIC ratio > 100 and why does it impact on emergence of resistance ?

Levofloxacin 500 mg 1x/d

- **AUC [(mg/l)xh] = 47**
  - ➢ **MIC max: 0.5**

Moxifloxacin 400 mg 1x/d

- **AUC [(mg/l)xh] = 48**
  - ➢ **MIC max: 0.5**



Pharmacokinetic data:

- from the corresponding Summary of Product characteristics
- see also Van Bambeke et al. Clin Microbiol Infect. 2005;11:256-80 - PMID: 15760423

MIC data from EUCAST MIC data base (2016) (http://mic.eucast.org/Eucast2/)

Resistance of *S. pneumoniae* to levofloxacin in the Eurasia *

- **4%** for penicillin-resistant S. pneumoniae in China [1]
- **8.6 %** (6/70) in adults in China [2]
- **4.7 %** in Korea, Hong-Kong and Taiwan, in association with previous treatment with fluoroquinolones, cerebrovascular disease, and healthcare-associated infection [3]
- **16.2 %** in Russia (n=148; EUCAST breakpoints; no resistance to moxifloxacin) [4]
- **30 %** in Malaysia (n=19) [5]
- **2.6 %** (n=608; serotype 11A) [6] and **2%** (n=208)[7] in single hospitals in South Korea
- increase of non-susceptible isolates (from **1.6** to **4.6%**) and decrease (to **1.5**%) in a Taiwan Hospital [8]

* CLSI breakpoints (MIC > 8 mg/L) unless indicated otherwise

1 Jones *et al.* Diagn Microbiol Infect Dis. 2013;77:258-66
2 Guo *et al.* Eur J Clin Microbiol Infect Dis 2014;33:465–70
3 Kang *et al*. Eur J Clin Microbiol Infect Dis. 2014;33:55-9
4 Biedenbach *et al.* Infect Dis Ther 2016;5:139–153
5 Akter *et al.* Malaysian J Pathol 2014;36:97-103
6 Park *et al.* Emerg Infect Dis. 2016;22:1978-1980
7 Kim *et al*. Diagn Microbiol Infect Dis. 2016;86:181-3
8 Chen *et al*. J Microbiol Immunol Infect. 2016;pii: S1684-1182(16)30044-5 [Epub ahead of print]

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Table 2 Independent risk factors associated with pneumonia caused by levofloxacin-nonsusceptible *S. pneumoniae*

Variables	Adjusted OR (95 % CI)	*P*
Previous treatment with fluoroquinolone	3.22 (1.05–9.85)	0.041
Cerebrovascular disease	2.88 (1.36–6.06)	0.005
Healthcare-associated infection	2.28 (1.14–4.55)	0.019

Kang *et al.* Eur J Clin Microbiol Infect Dis. 2014;33:55-9

66
2 Guo Q, et al. Eur J Clin Microbiol Infect Dis 2014;33:405–70
3 Kang CI, et al. Eur J Clin Microbiol Infect Dis. 2014;33:55-9
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Fluoroquinolone-nonsusceptible pneumococci

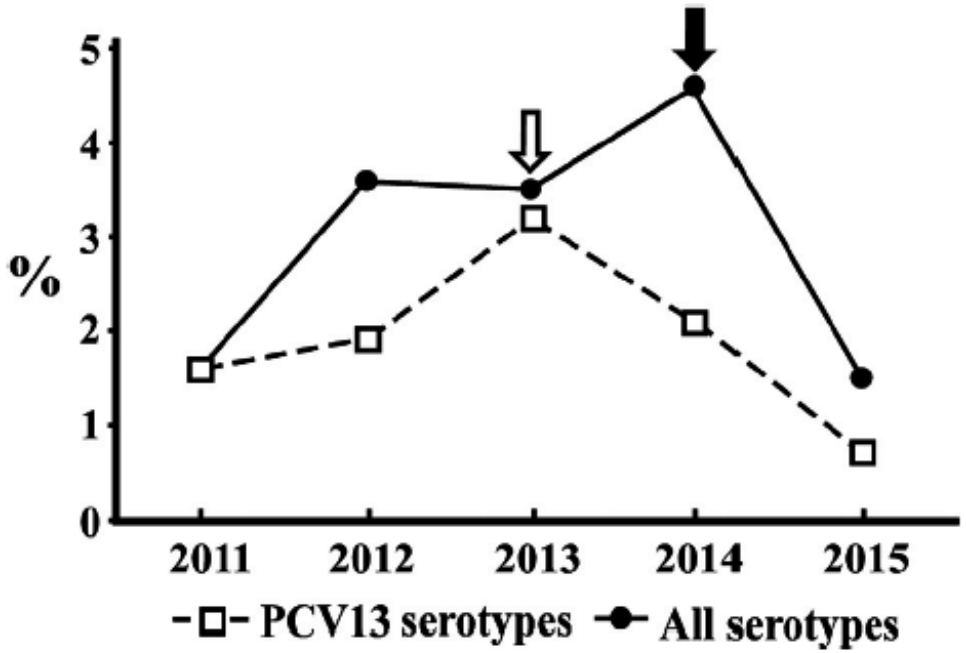

Figure 1. Incidence of fluoroquinolone-nonsusceptible *Streptococcus pneumoniae* isolates among different serotypes from January 2011 to July 2015 in Chang Gung Memorial Hospital. The nationwide catch-up program was launched in 2013 (white arrow) and national immunization program with a three-dose schedule in 2015 (black arrow). The decrease in 2015 reached statistical significance, comparing to either 2014 ($p = 0.012$) or 2011–2014 ($p = 0.043$).

Chen *et al.* J Microbiol Immunol Infect. 2016;pii: S1684-1182(16)30044-5 [Epub ahead of print]

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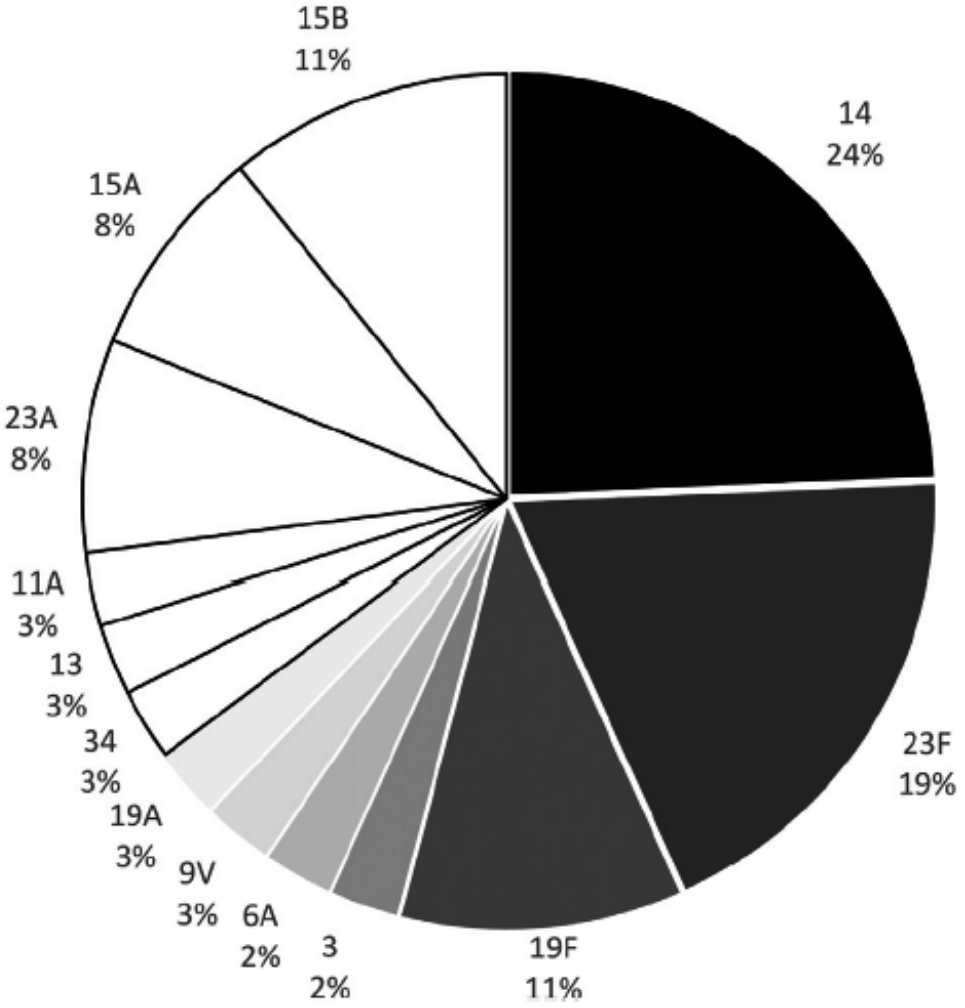

Figure 2. Distribution of serotypes among the 42 fluoroquinolone-nonsusceptible *Streptococcus pneumoniae* isolates.

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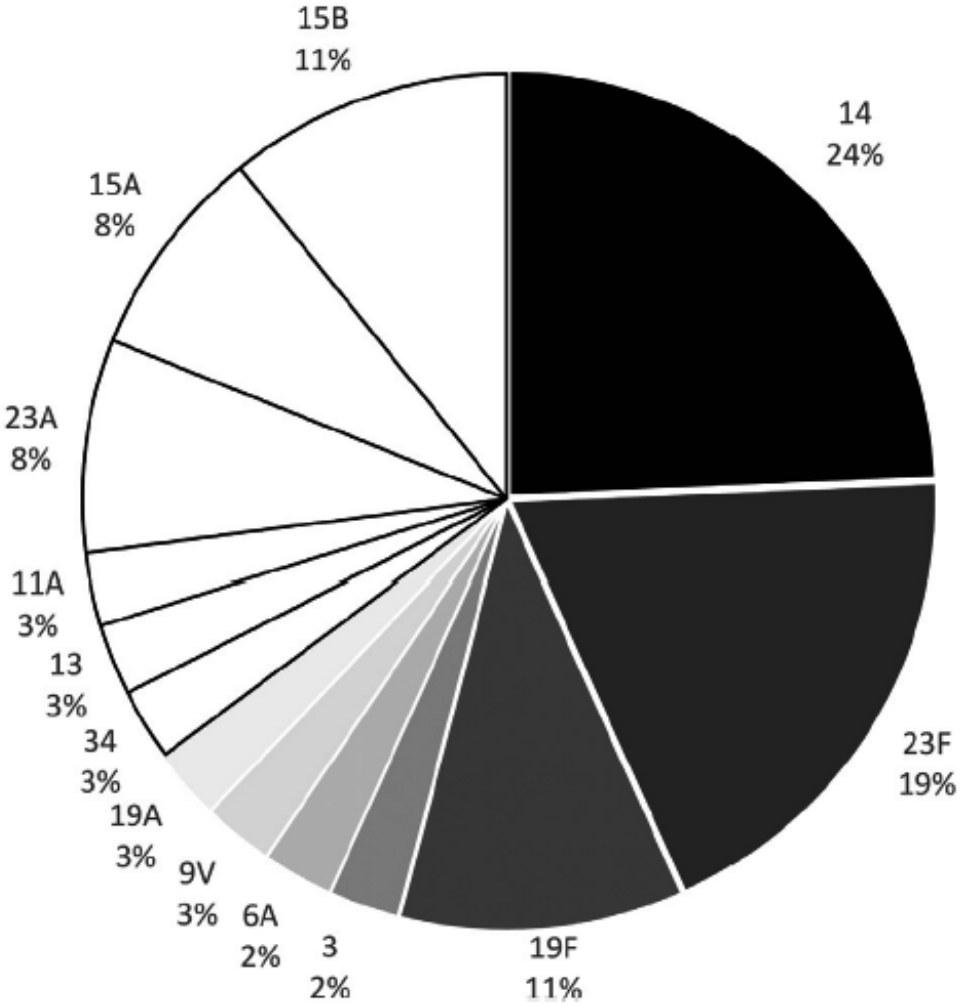

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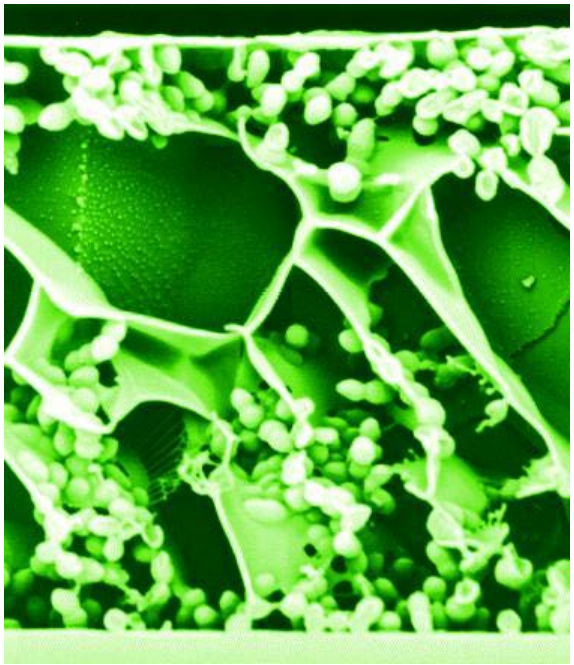
And briefly about biofilms…

Growth within biofilms :

- 3D-communities of cells embedded in a structured matrix
- adhering to inert/living surfaces
- protected from the immune system and antibiotics



Low Temperature Scanning Electron Microscopy (LTSEM) of a *S. pneumoniae* R6 biofilm formed on a glass surface (Moscoso *et al.*, 2006).

And briefly about biofilms…

Mechanisms of Persistent Bacterial Infection in COPD

- Pathogen
  - Intracellular persistence
  - Biofilm formation
  - Phase variation of surface molecules
  - Molecular mimicry
  - Mucin binding
  - Mucoid phenotype
- Host
  - Ineffective innate immunity
  - Ineffective adaptive immunity

http://www.slideshare.net/drsarkar/bacterial-infection-in-copd-10311586

Can moxifloxacin help ? …

J Antimicrob Chemother 2015; **70**: 1713–1726
doi:10.1093/jac/dkv032 Advance Access publication 23 February 2015

Journal of Antimicrobial Chemotherapy

Modulation of the activity of moxifloxacin and solithromycin in an *in vitro* pharmacodynamic model of *Streptococcus pneumoniae* naive and induced biofilms

Nathalie M. Vandevelde[1], Paul M. Tulkens[1], Giulio G. Muccioli[2] and Françoise Van Bambeke[1]*

[1]*Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium;*
[2]*Bioanalysis and Pharmacology of Bioactive Lipids, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*

Vandevelde *et al.* J Antimicrob Chemother.2015;70:1713-26 - PMID: 25712316..

Can moxifloxacin help ? ...

J Antimicrob Chemother 2015; **70**: 1713–172
doi:10.1093/jac/dkv032 Advance Access publi

Modulation of the activit
***in vitro* pharmacodynar**
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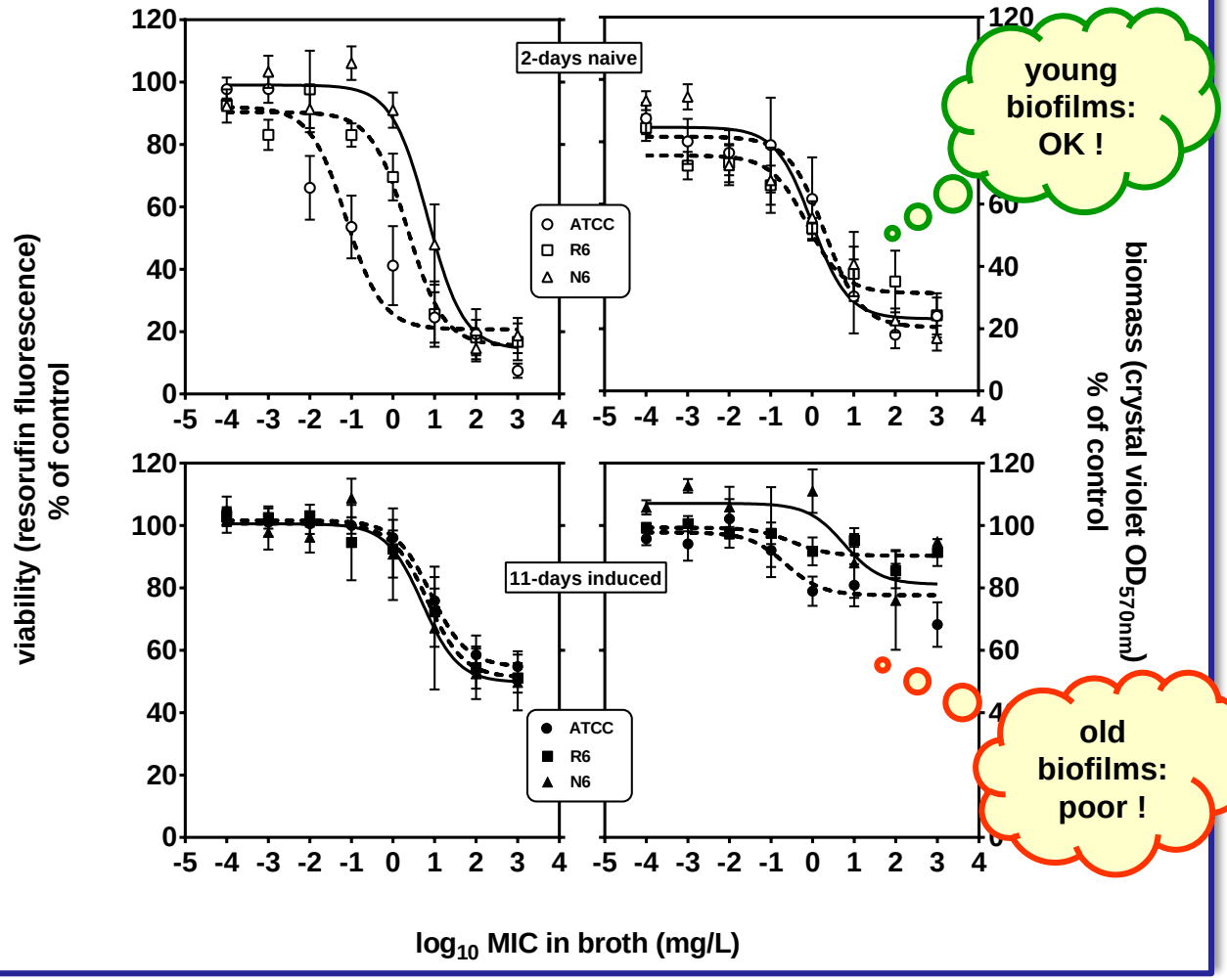
Nathalie M. Vandevelde[1], Paul M

[1]*Pharmacologie cellulaire et moléculaire, Louva*
[2]*Bioanalysis and Pharmacology of Bioactive Lipids, L*

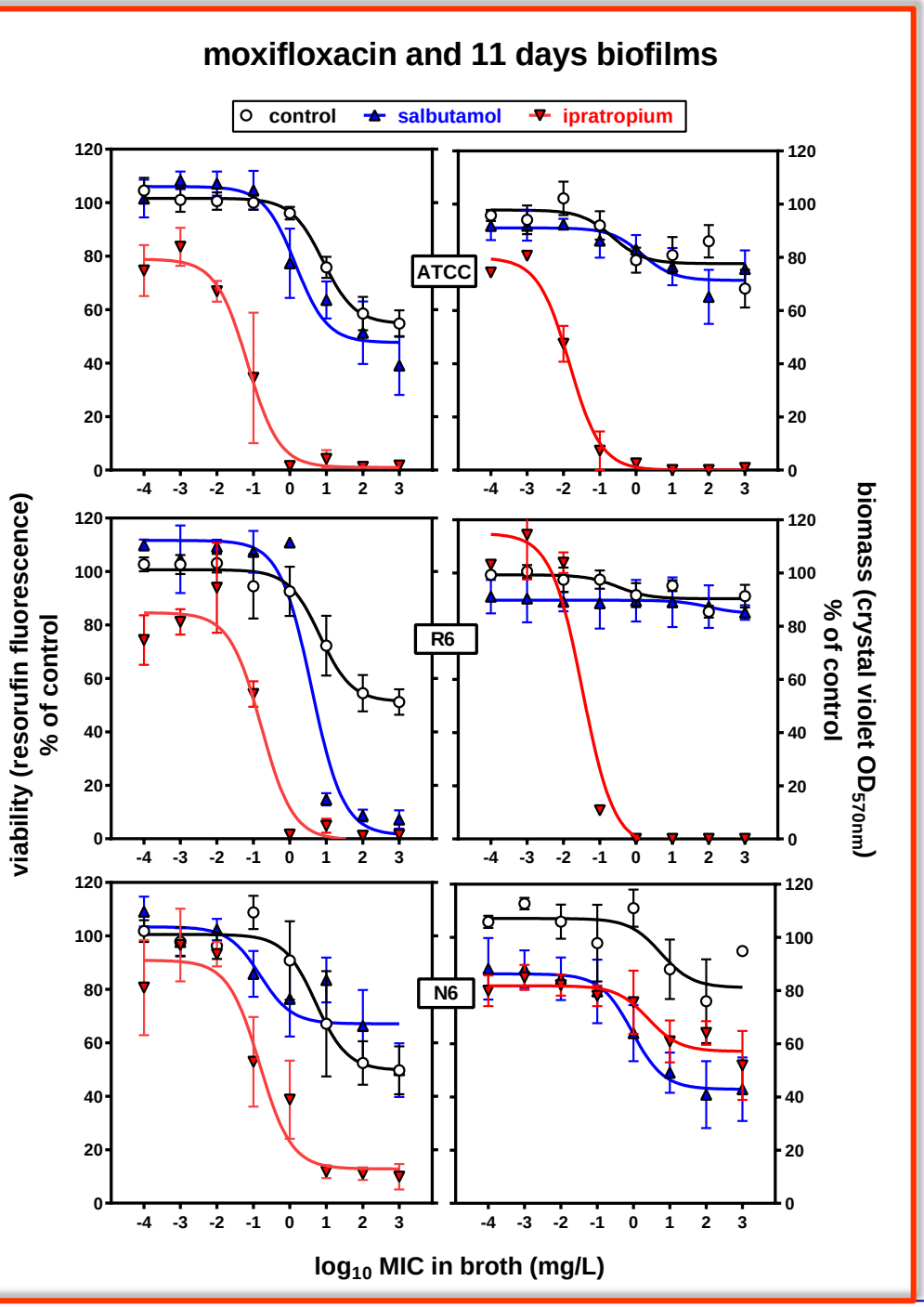
The model:
Concentration–response effects of moxifloxacin on viability (left) and biomass (right) of 2-day-old naive (open symbols) and 11-day-old induced (filled symbols) biofilms produced from strains ATCC, R5 and N6



Vandevelde *et al.* J Antimicrob Chemother.2015;70:1713-26 - PMID: 25712316..

An unanticipated cooperation …

Addition of ipratropium (and to some extent salbutamol) allow moxifloxacin to act on old (mature) biofilms



Vandevelde *et al.* J Antimicrob Chemother 2015;70:1713-26 - PMID: 25712316

At this point …

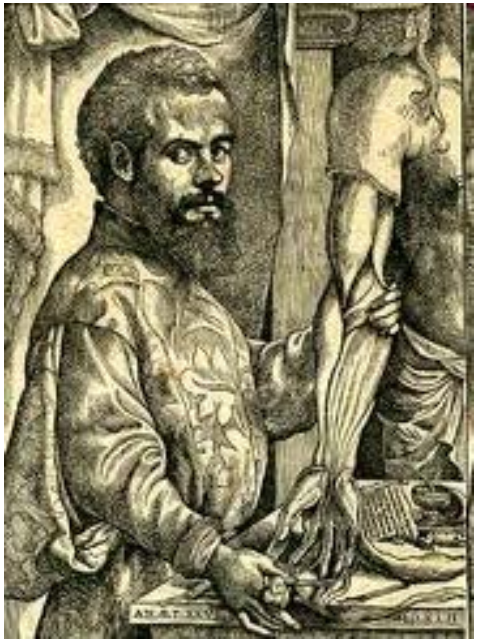
- Moxifloxacin shows excellent activity against *S. pneumoniae*, including isolates resistant to β-lactams and macrolides …
- There are compelling microbiological and pharmacological reasons to support the use of moxifloxacin over that of levofloxacin to more successfully fight *S. pneumoniae* infections...
- Resistance of *S. pneumoniae* to moxifloxacin is possible, but has not materialized to significant extent in the clinics
  (probably due to its favourable AUC_{24h}/MIC ratio *, which is not the case for levofloxacin)…
- Ipratropium and salbutamol ** may cooperate with moxifloxacin to eliminate *S. pneumoniae* biofilms.

---

* also because of C_{max} > Mutant Prevention Concentration (MPC; not shown here but ask…)

** commonly used in COPD patients for bronchodilatation

Please, ask questions …



be critical,
ask for facts !

Vesalius – Anatomy *

All slide are available on http://www.facm.ucl.ac.be → Lectures

* ***ANDREAE VESALII Bruxellensis Scholae "De humani corporis fabrica libri septem"*** is a set of books on human anatomy written by Andreas Vesalius and published in 1543. It represented a major advance in the history of anatomy by moving from reiteration of past statements to actual observations