

*Séminaire de pathologie infectieuse*  
*1er avril 2008*

**And now, what about Belgium ?**

Françoise  
Van Bambeke

Pharmacologie cellulaire et moléculaire, UCL

Séminaire de pathologie infectieuse – 1er avril 2008

POISSON D'AVRIL !!



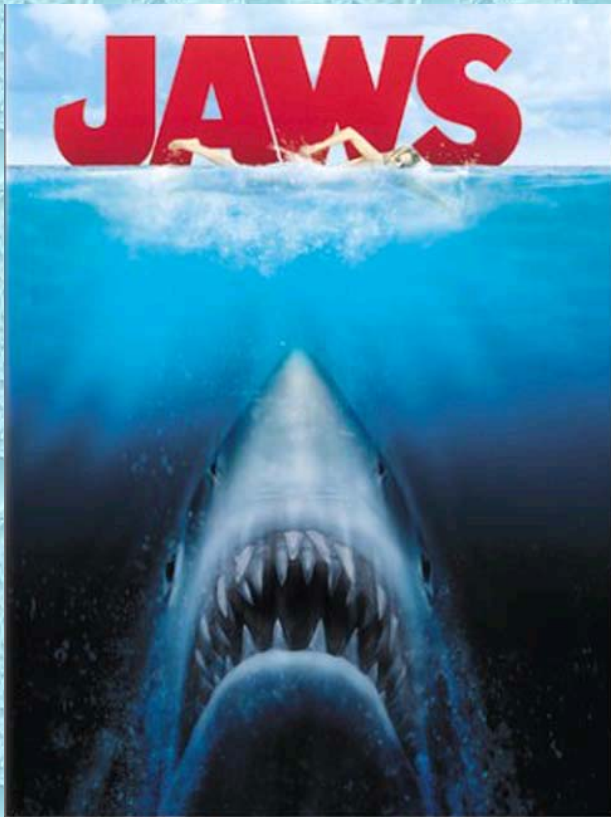
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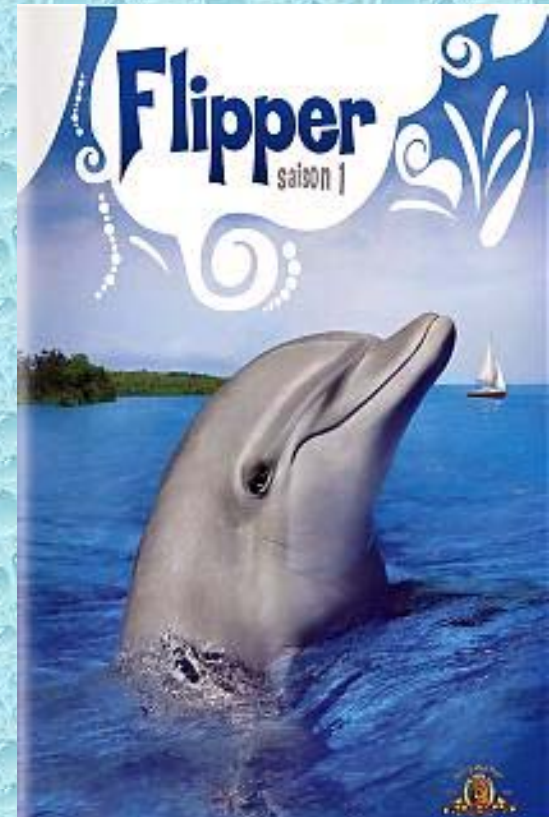
Pharmacologie cellulaire et moléculaire, UCL

# Epidemiological data

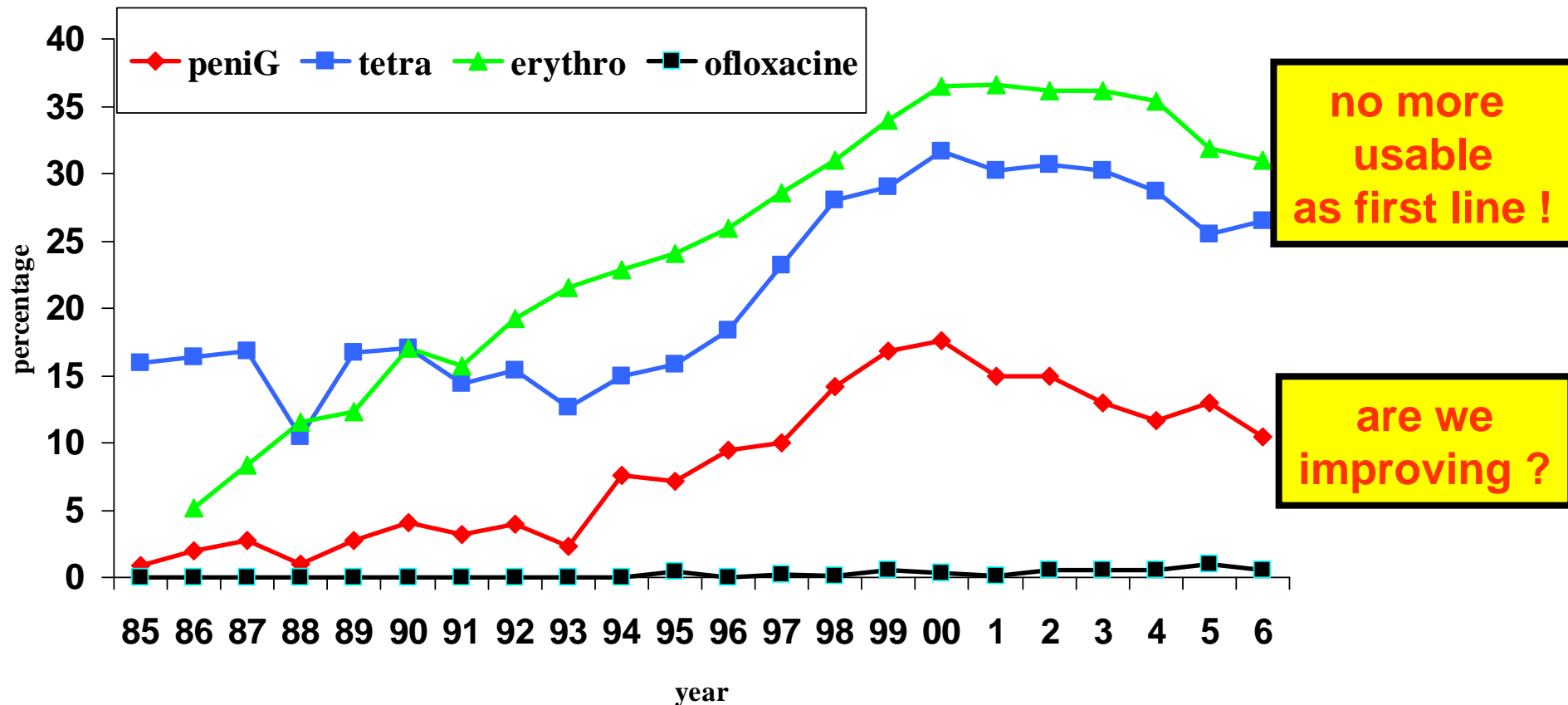
Are we bad ?



Or good ?

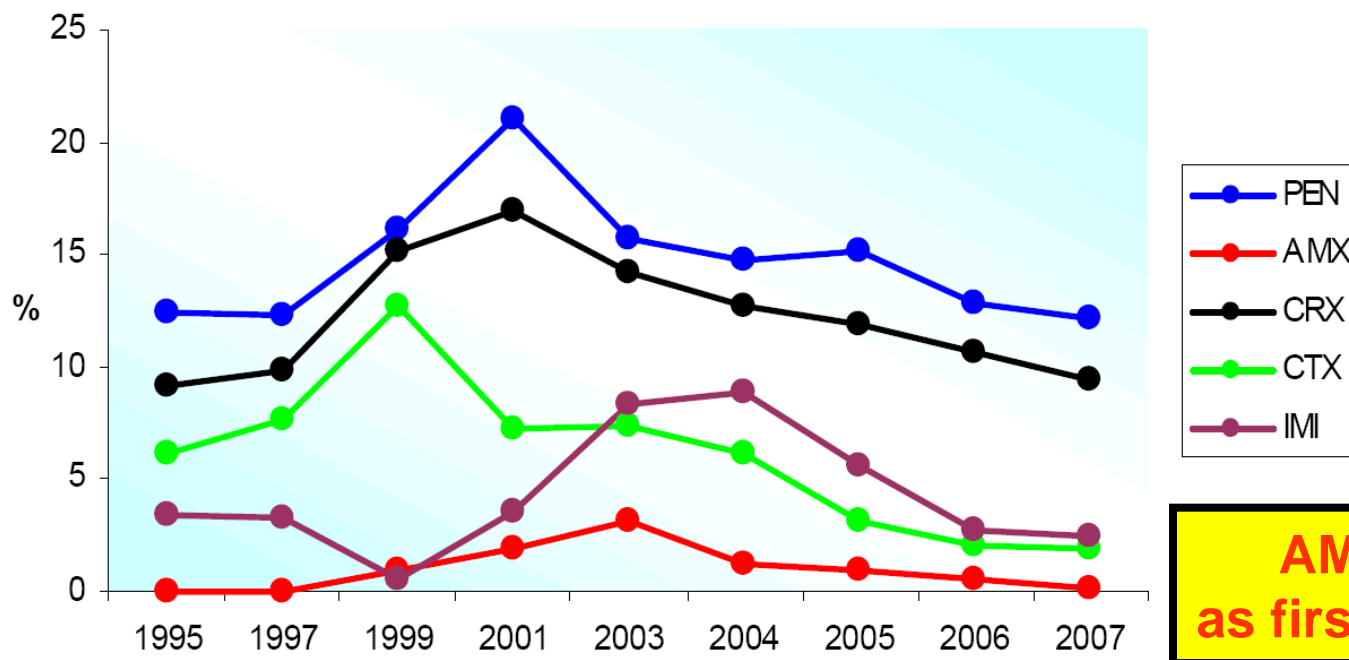


# *S. pneumoniae* resistance: Evolution over time – invasive strains



# *S. pneumoniae* resistance: Evolution over time – non-invasive strains

## Beta-Lactams



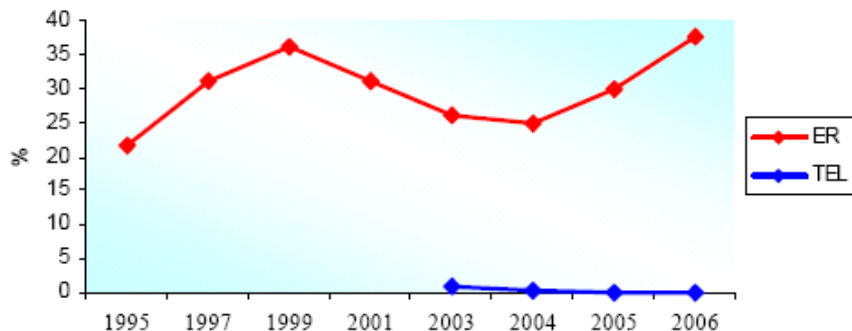
**AMX  
as first line!**

*CLSI breakpoints (I+R):*

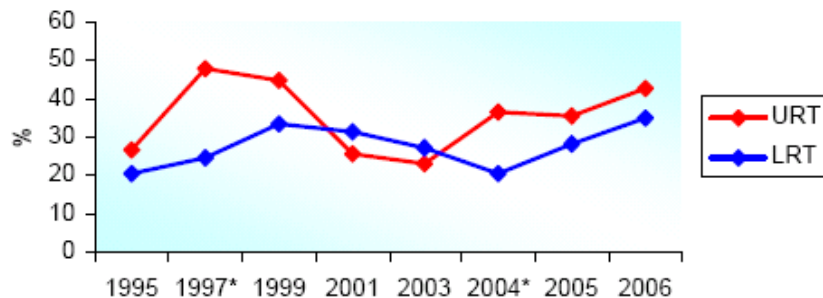
*penicillin 4, imipenem, 0.25, cefotaxime 2, cefuroxime 2, amoxicillin 4*

# *S. pneumoniae* resistance: Evolution over time – non-invasive strains

### ERY and TEL Resistance Rates

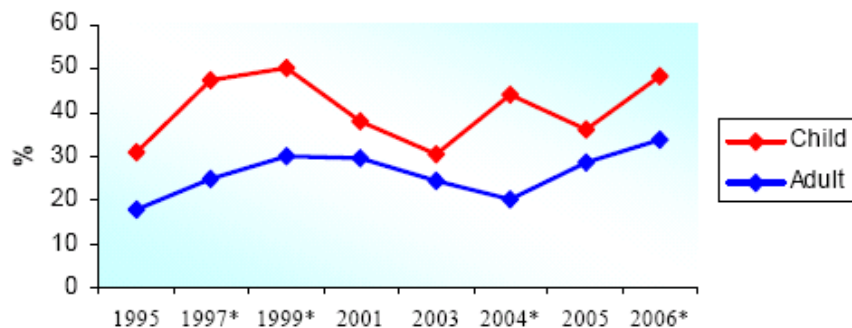


### ERY-R: Upper vs Lower Respiratory Tract



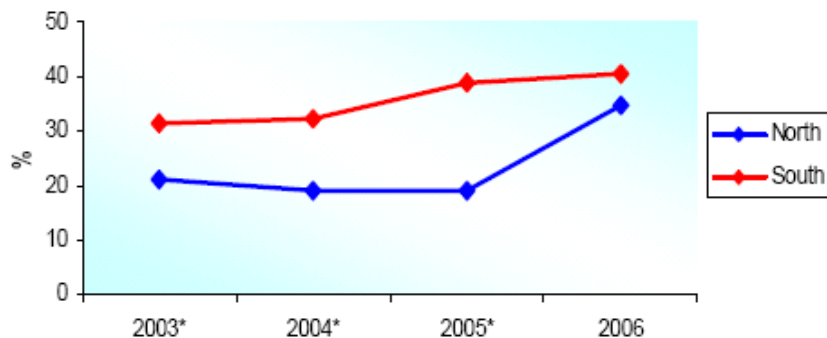
\*Significant difference

### ERY-R: Children vs Adults



\*Significant difference

### ERY-R: North vs South



\*Significant difference

# *S. pneumoniae* resistance: MDR phenotypes

## PROTEKT (1999-2001)

MDR	% isolates (n= 137)
2	7.3
3	23.4
4	4.4
5	3.6
6	2.2
7	0.0
<b>TOTAL</b>	<b>40.9</b>

### drugs under study:

penicillin G, cefuroxime,  
erythromycin, clindamycin,  
telithromycin, levofloxacin,  
quinupristin–dalfopristin,  
tetracycline, cotrimoxazole

**Pen-Ery:  
8.7 %**

**Cip-Ery:  
1.7 %**

Pen-Cip-Ery-Tet Phenotype	Number (%)
Susceptible	251 (60.8)
Ery-Tet	49 (11.9)
Ery	40 (9.7)
Pen-Ery-Tet	30 (7.3)
Pen	13 (3.1)
Cip	8 (1.9)
Tet	8 (1.9)
Pen-Ery	5 (1.2)
Cip-Ery-Tet	4 (1.0)
Cip-Ery	2 (0.5)
Cip-Tet	1 (0.2)
Pen-Tet	1 (0.2)
Pen-Cip-Ery-Tet	1 (0.2)

# *S. pneumoniae* resistance: CAP isolates

## • Bacteria:

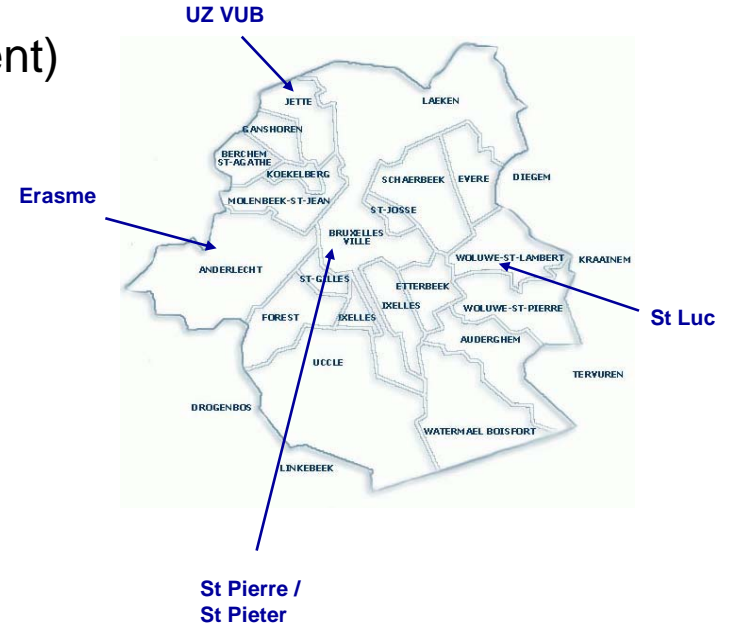
133 *S. pneumoniae* isolated between 2004-2007 in 4 hospitals in Brussels (outpatients admitted via the emergency department)

## • Patients:

CAP confirmed by examination of the medical dossier (RX, crepitant rale, cough, dyspnea, thoracic pain; severity classification following CRB 65 criteria [confusion, respiratory rate, blood pressure]).

## • Susceptibility testing:

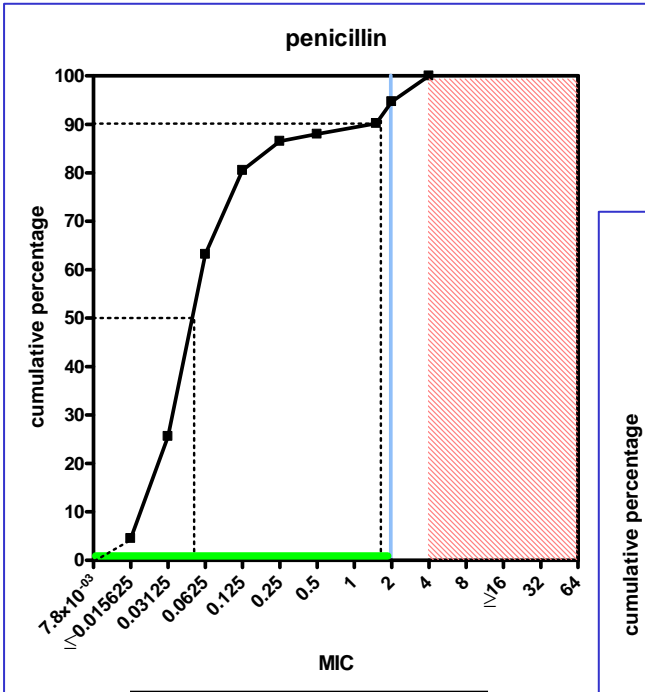
- MICs (microdilution)
- Resistance due to active efflux
  - ML: dissociated resistance to ERY and CLI
  - Q: decreased MIC with reserpine



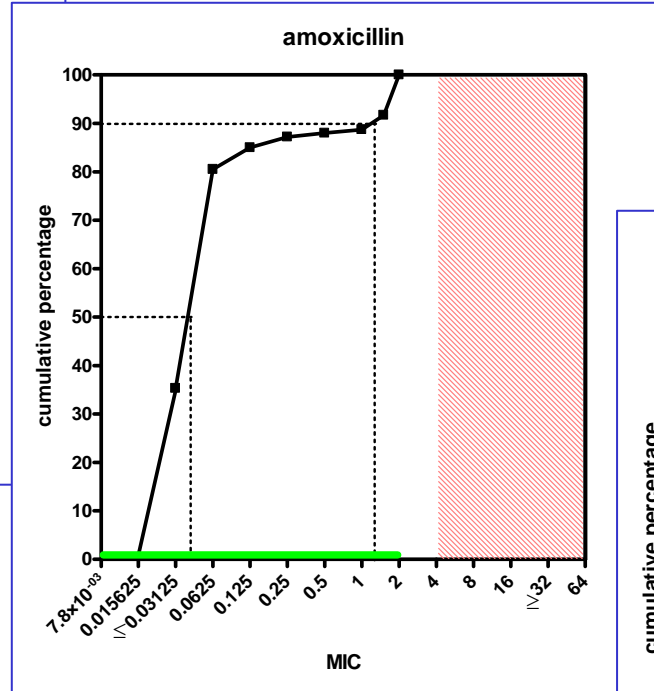
*Epidemiological survey of antibiotic resistance in a Belgian collection of CAP isolates of Streptococcus pneumoniae (SP)* A. Lismond, F. Van Bambeke, S. Carbonnelle, F. Jacobs, M. Struelens, J. Gigi, A. Simon, Y. Van Laethem, A. Dediste, D. Pierard, A. De Bel, & P.M. Tulkens, RICAI, Paris, 2007 / ECCMID, Barcelona, 2008



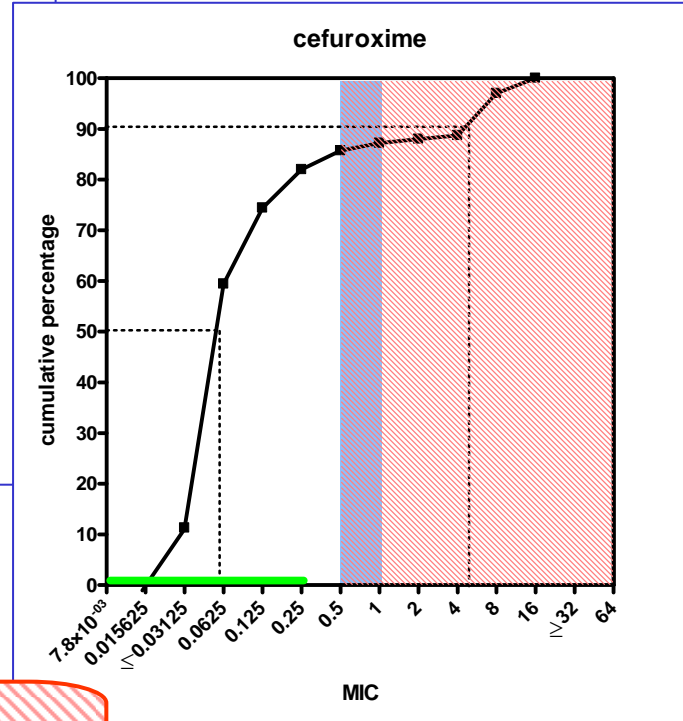
# $\beta$ -lactam resistance in CAP isolates



**MIC<sub>90</sub>: 2 mg/L**



**MIC<sub>90</sub>: 2 mg/L**

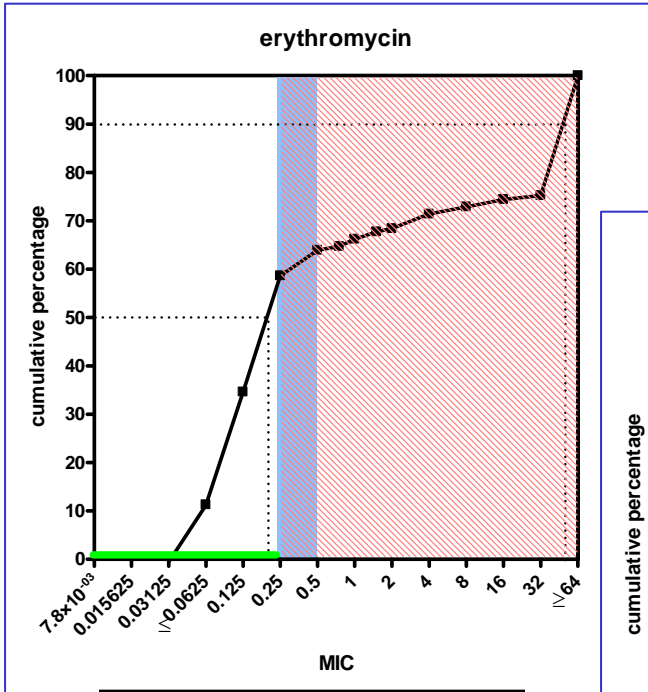


**MIC<sub>90</sub>: 4 mg/L**

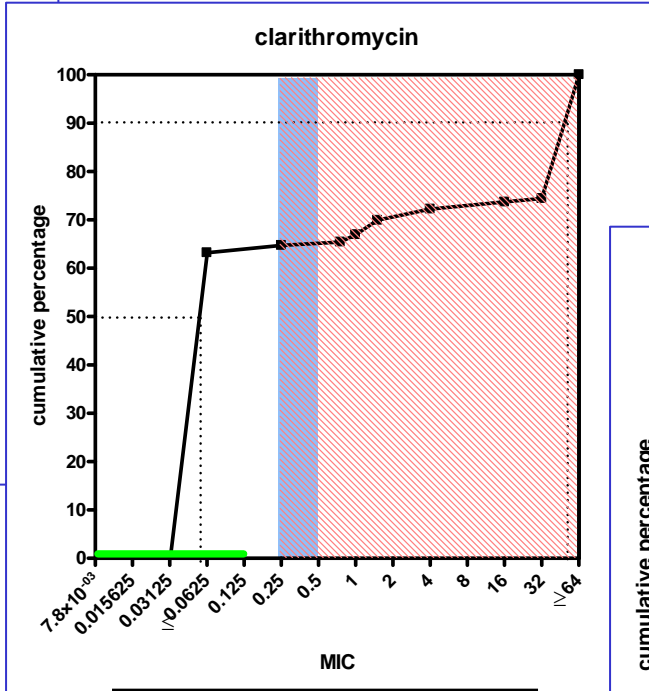
- susceptible
- intermediate (EUCAST)
- Intermediate + resistant (CLSI)

increasing Bkpt reduces resistance ...

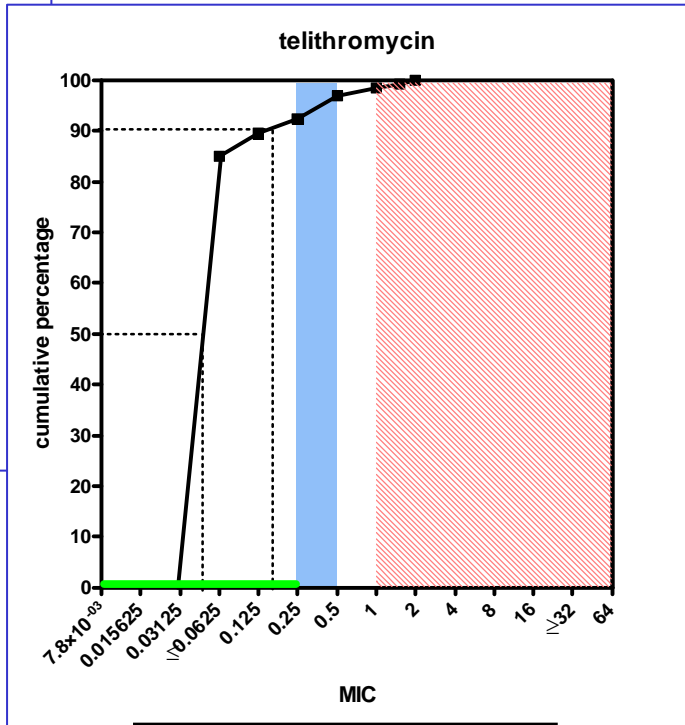
# Macrolide resistance in CAP isolates



**MIC<sub>90</sub>: > 32 mg/L**



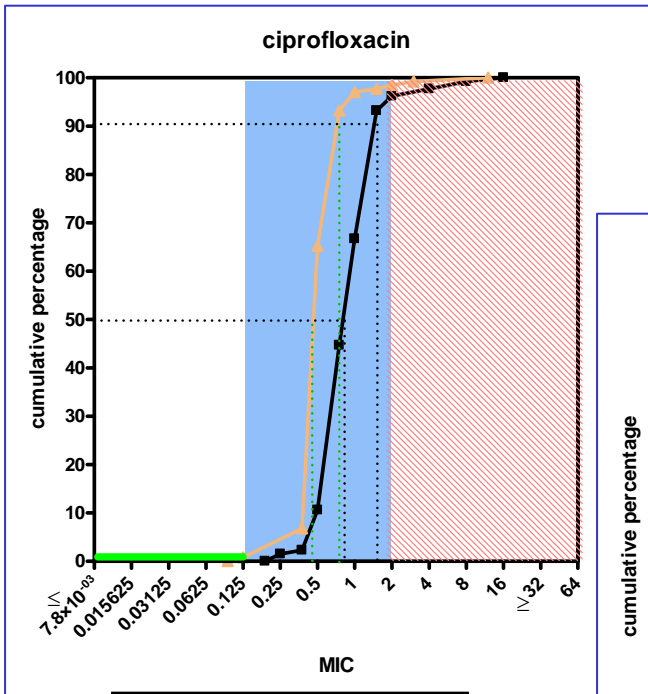
**MIC<sub>90</sub>: > 32 mg/L**



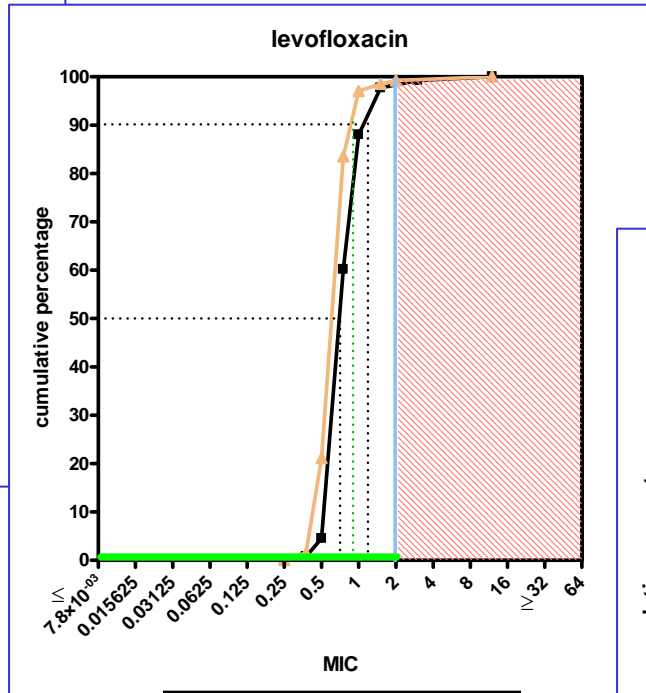
**MIC<sub>90</sub>: 0.25 mg/L**

- susceptible
- intermediate (EUCAST)
- resistant (CLSI)

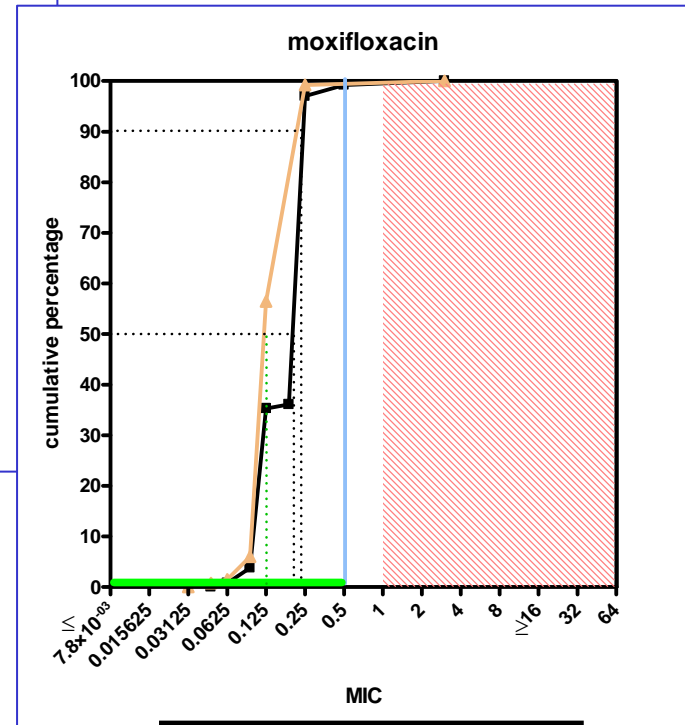
# Fluoroquinolone resistance in CAP isolates



**MIC<sub>90</sub>: 2 mg/L**



**MIC<sub>90</sub>: 2 mg/L**



**MIC<sub>90</sub>: 0.25 mg/L**

- susceptible
- intermediate (EUCAST)
- resistant (CLSI)
- + efflux pump inhibitor (reserpine)

# Therapeutic options

What are our



best choices ?

# Current recommendations for treatment

Patient	Drug	Dosage	Duration
no comorbidities	amoxicillin	3 X 1 g	8 days
+ comorbidities	amoxi-clav	3 X 875/125 mg	8 days
Allergy non IgE	cefuroxime axetil	3 x 500 mg	8 days
Allergy IgE	moxifloxacin	1 x 400 mg	8 days
No improvement in 48 h	+ azithromycin	1 X 500 mg	3 days
	+ clarithromycin	2 X 500 mg	8 days
	+ roxithromycin	2 X 150 mg	8 days

# Current recommendations for treatment

Drug	Dosage	PK/PD Indices	PK/PD breakpoint	MIC <sub>90</sub>
amoxicillin	3 X 1 g	T fconc > MIC 50 % T fconc > MIC 100 %	2 0.2	2
cefuroxime axetil	3 x 500 mg	T fconc > MIC 50 % T fconc > MIC 100 %	0.5 0.1	4
moxifloxacin	1 x 400 mg	fAUC/MIC > 25 fAUC/MIC > 125	0.5 0.2	0.25

Van Bambeke... Appelbaum et al. *Drugs* (2007) 67:2355-2382

# What about other drugs ?

Drug	Dosage	PK/PD Indices	PK/PD breakpoint	MIC <sub>90</sub>
ceftriaxone	2 X 1 g	T fconc > MIC 50 % T fconc > MIC 100 %	5 2	2
telithromycin	1 x 800 mg	fAUC/MIC > 25	0.1	0.25
levofloxacin	2 x 500 mg	fAUC/MIC > 25 fAUC/MIC > 125	3 0.5	2

*Van Bambeke... Appelbaum et al. Drugs (2007) 67:2355-2382*

And for tomorrow ? Something really new ?





# Is there a future ?

Drug	Dosage	PK/PD Indices	PK/PD bkpt	adequation ~ MIC distrib.
ceftobiprole	2 X 500 mg	T fconc > MIC 50 % T fconc > MIC 100 %	5 1	> MIC <sub>90</sub> PenR = MIC <sub>90</sub> PenR
ceftaroline	2 x 600 mg	T fconc > MIC 50 % T fconc > MIC 100 %	1 0.1	> MIC <sub>90</sub> PenR > MIC <sub>90</sub> PenI
faropenem	2 x 300 mg	T fconc > MIC 20 % T fconc > MIC 100 %	0.2 0.03	> MIC <sub>90</sub> PenI > MIC <sub>90</sub> PenI
telavancin	1 X 10 mg/kg	fAUC / MIC > 10-20	2	> MIC <sub>90</sub>
cethromycin	1 X 150 mg	fAUC / MIC > 25	0.003	= MIC <sub>90</sub> ML-S = MIC <sub>50</sub> ML-R
linezolid	2 x 600 mg	fAUC / MIC > 50	4	> MIC <sub>90</sub>
tigecycline	2 x 50 mg	AUC / MIC > 12	0.5	> MIC <sub>50</sub> Tet-R
gemifloxacin	1 x 320 mg	fAUC/MIC > 25 fAUC/MIC > 125	0.1 0.02	> MIC <sub>90</sub> Q-S = MIC <sub>90</sub> Q-S
garenoxacin	1 x 400 mg	fAUC/MIC > 25 fAUC/MIC > 125	0.5 0.12	> MIC <sub>50</sub> Q-R > MIC <sub>90</sub> Q-S

oral route

Van Bambeke... Appelbaum et al. *Drugs* (2007) 67:2355-2382

Let's try to master the situation ...



.. Before it escapes our control !

