Epidemiological survey of susceptibility to β-lactams, macrolides, and fluoroquinolones in a Belgian collection of *Streptococcus pneumoniae* isolated from patients with CAP

A. Lismond,[1] S. Carbonnelle,[1] F. Jacobs,[2] M. Struelens,[2] J. Gigi,[3] A. Simon,[3] Y. Van Laethem,[4] A. Dediste,[4] D. Pierard,[5] A. De Bel,[5] F. Van Bambeke,[1] P.M. Tulkens[1]

[1] Unité de Pharmacologie cellulaire et moléculaire, Université catholique de Louvain ;
[2] Hôpital Erasme, Université Libre de Bruxelles ;
[3] Cliniques Universitaires Saint-Luc, Université catholique de Louvain ;
[4] Hôpital Saint-Pierre, Université Libre de Bruxelles ;
[5] Universitaire Ziekenhuis, Vrije Universiteit Brussel ; Bruxelles.

Objectives

Epidemiology of AB resistance in *S. pneumoniae*

Belgian Centers for *S. pneumoniae*

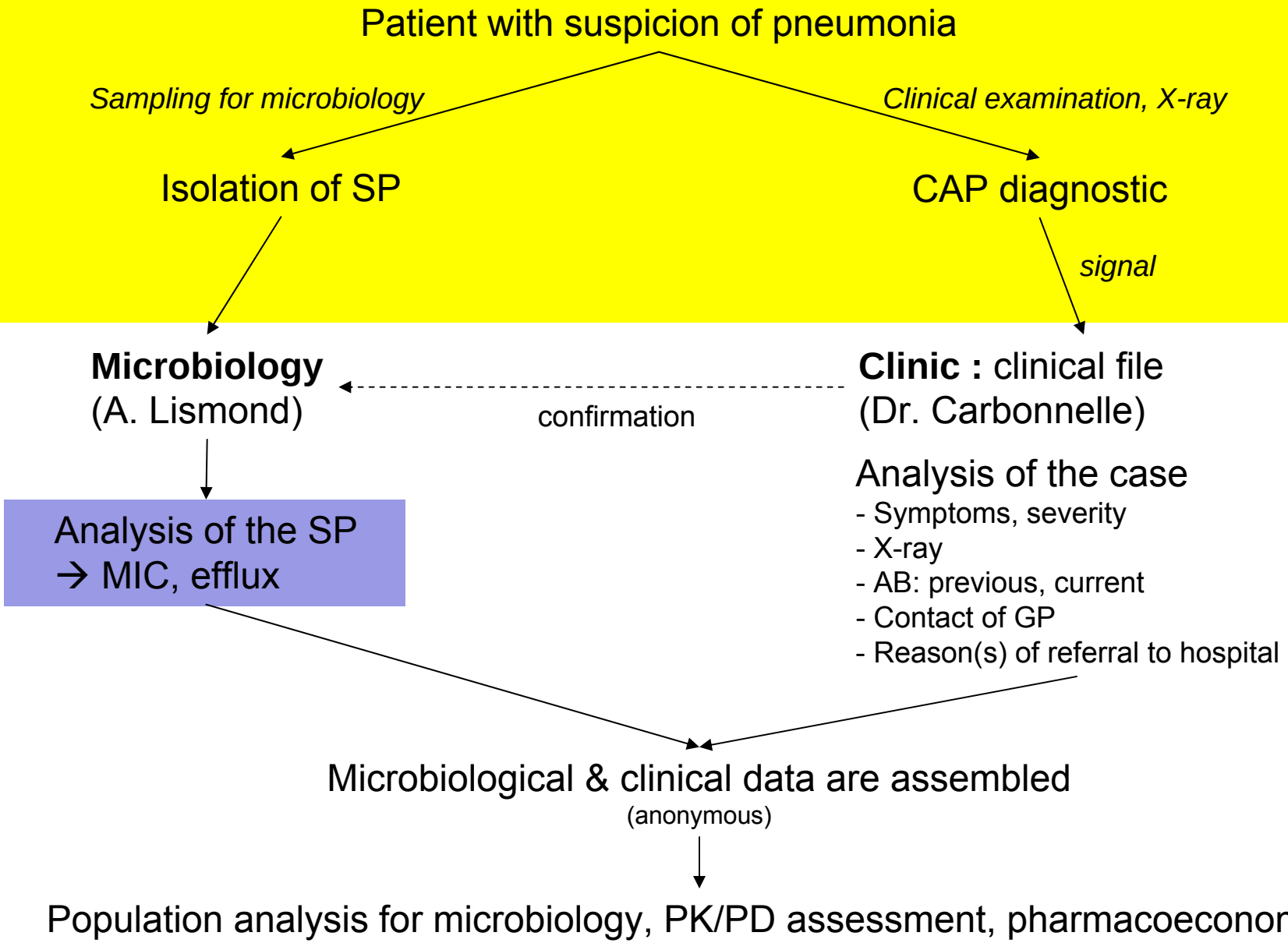
→ Pasteur Institute (R. Vanhoof)
→AB resistance evaluation (MIC) & mechanisms

→ Reference Lab. (J. Verhaegen)
→AB resistance evaluation (antibiograms) & serotyping

CAP only (from selected centers)

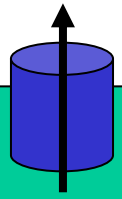
→ AB used in Belgium
resistance evaluation (MIC) & efflux mechanism
→ **link with the clinic!**

General protocol



Efflux pumps: role in antibiotic resistance *

→ AB resistance mechanism



Intrabacterial targets:
- ribosomes (macrolides)
- enzymes (fluoroquinolones)

→ AB activity depends on its capacity to reach its target

→ Efflux pumps
↘ intrabacterial concentration
↘ AB activity

→ Low level

→ usually NOT detected in the clin. microbiol. lab.

→ May affect more than one antibiotic

→ Favors emergence of high level resistance
(Avrain *et al*., JAC 2007; 60:965-972)

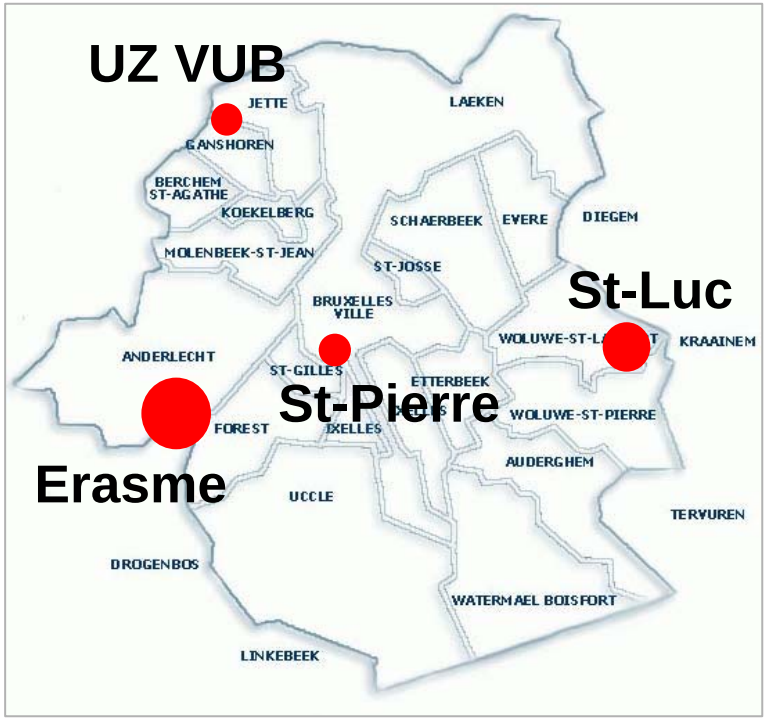
→**Therapeutic consequences???**

→Equivalent to sub-optimal treatment

* Van Bambeke et al., JAC 2003; 51:1055-1065

Methods

- Collection:



20 – 30
30 – 40
40 – 50

N = 133

Erasme: 44
St-Luc: 39
St-Pierre: 26
UZ VUB: 24

Methods

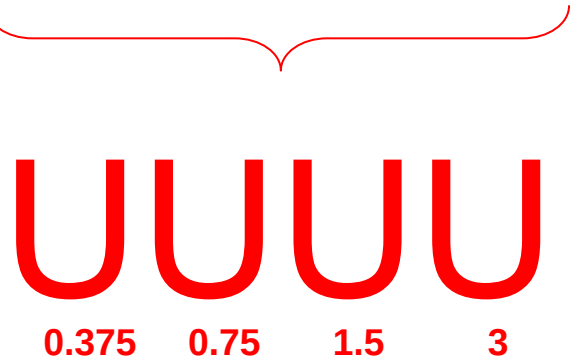
- MIC testing according to CLSI:

MIC
→ Geometric microdilutions

Methods

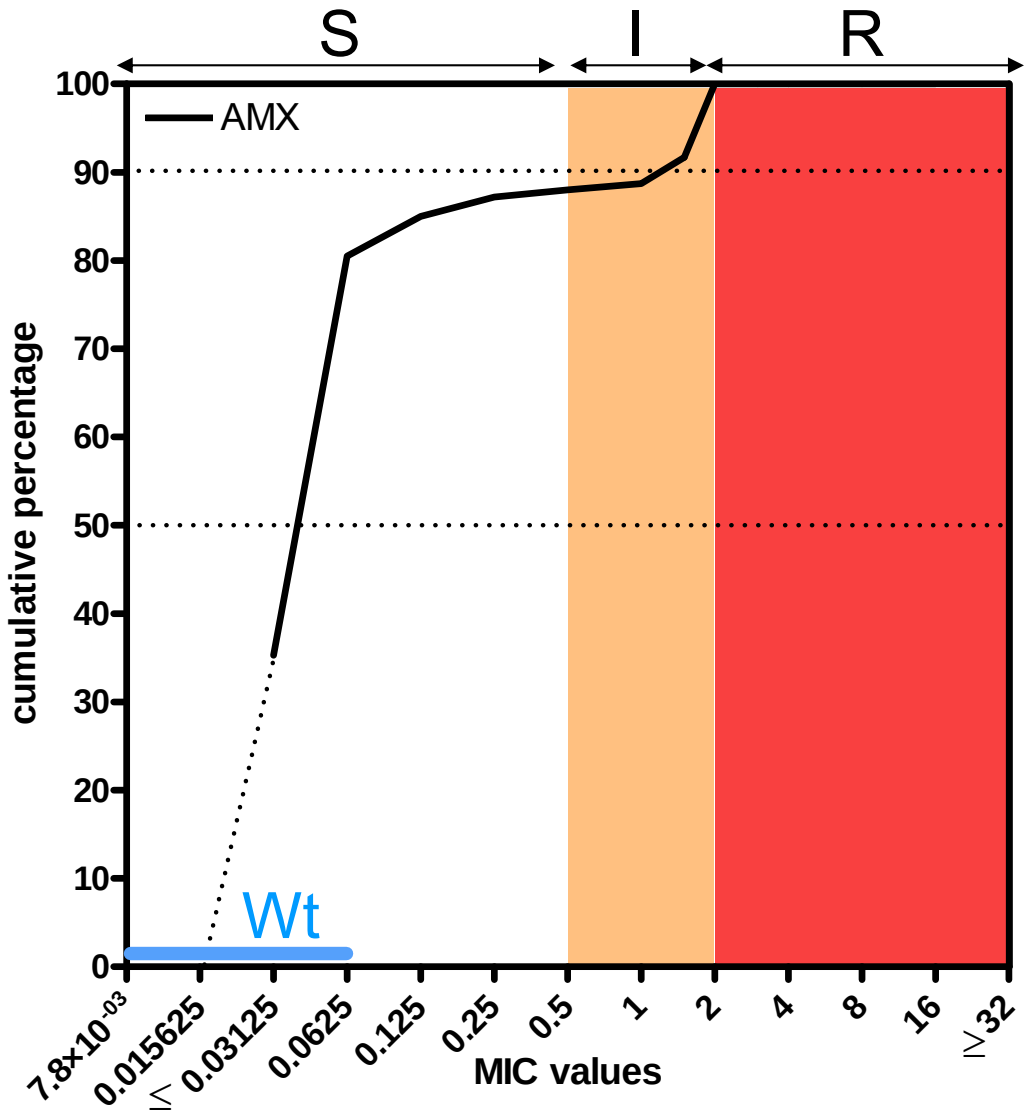
- MIC testing according to CLSI:

MIC
→ Geometric microdilutions



Semi-geometric microdilutions around breakpoint value (1 mg/L in this example):
→ **efflux detection**

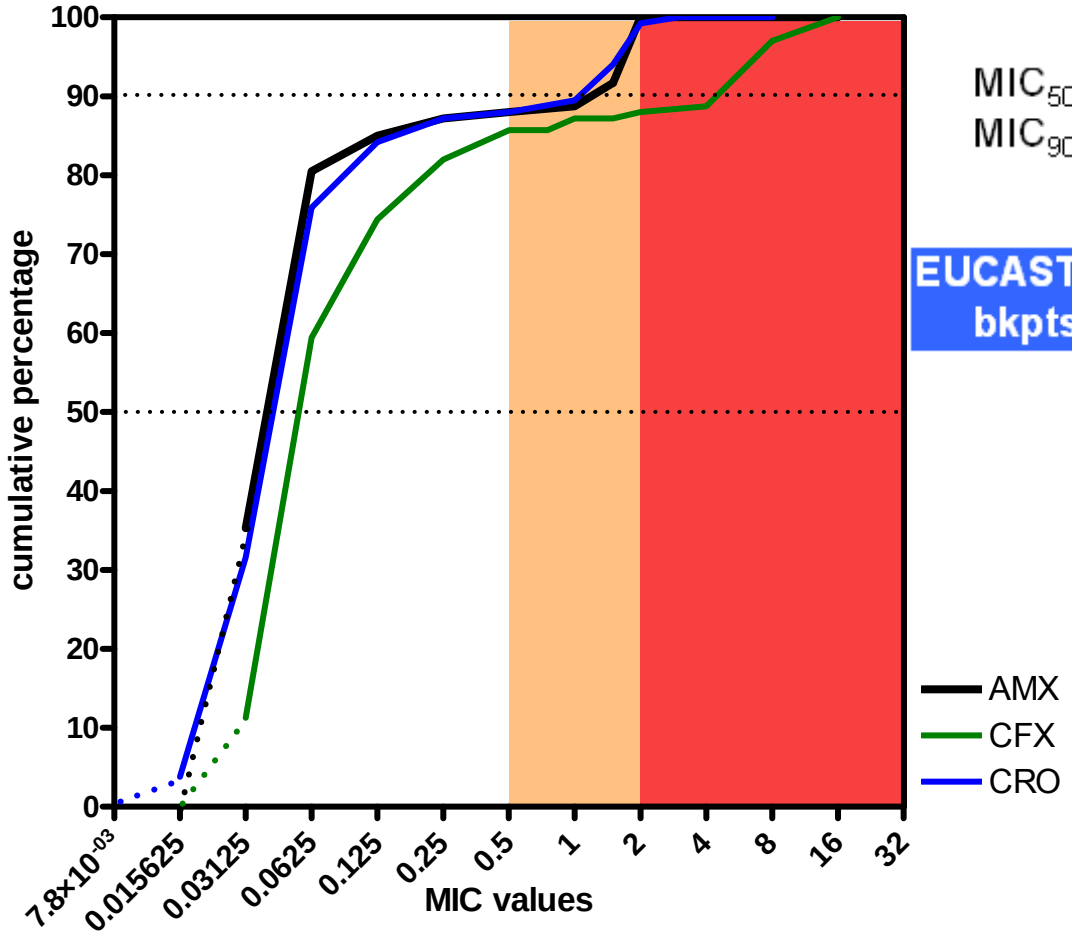
Results: Amoxicillin



- Susceptibility according to EUCAST breakpoints:
  - S ≤ 0.5: 88%
  - I: 12%
  - R > 2: 0%

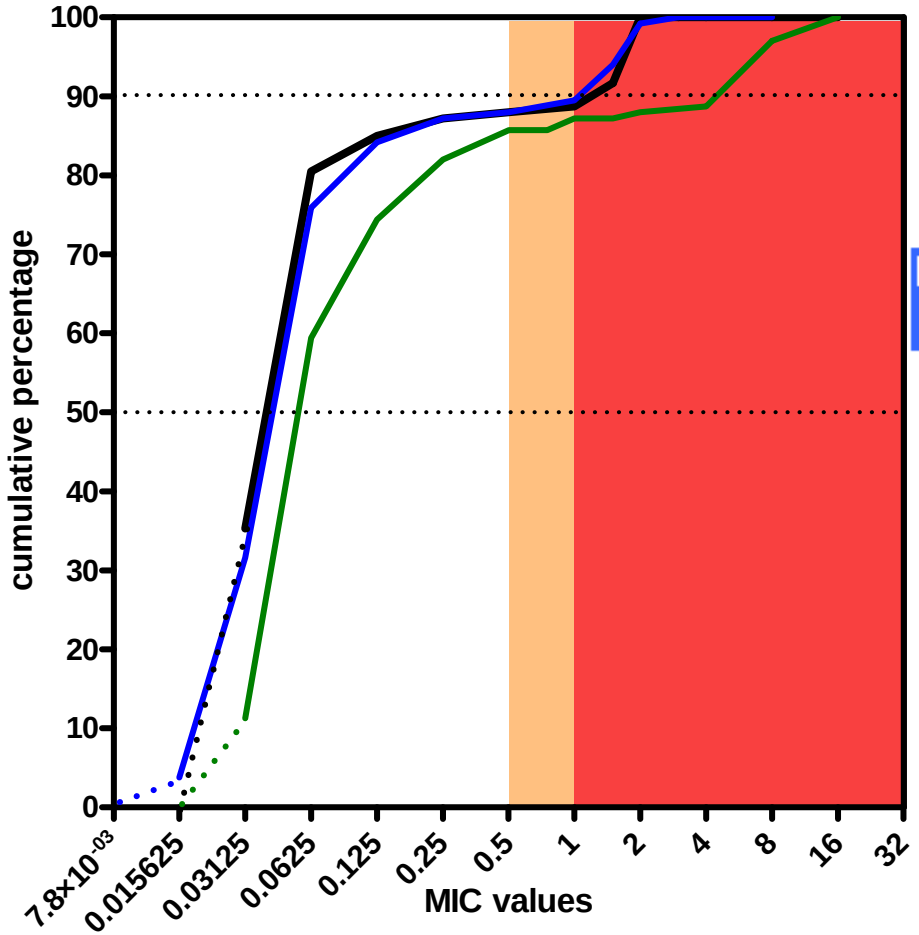
- MIC_{50} = 0.063 mg/L
- MIC_{90} = 1.5 mg/L

β-Lactams



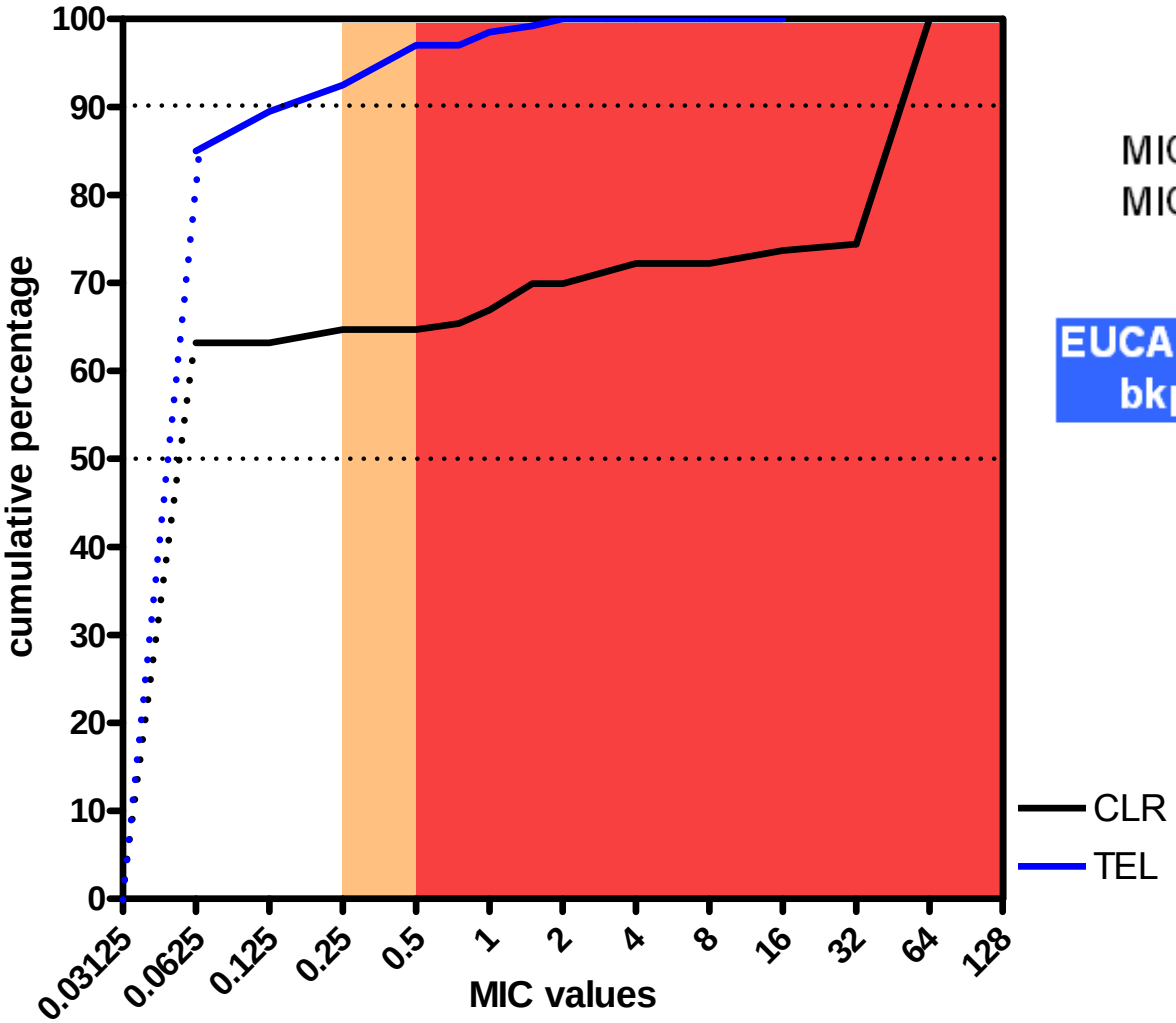
	AMX	CRO	CFX
MIC_{50} (mg/L)	0,06	0,06	0,06
MIC_{90} (mg/L)	1,5	1,5	8
EUCAST bkpts S ≤	0,5	0,5	0,5
EUCAST bkpts R >	2	2	1
S:	88,0 %	88,0 %	85,7 %
I:	12,0 %	11,2 %	1,5 %
R:	0,0 %	0,8 %	12,8 %

β-Lactams



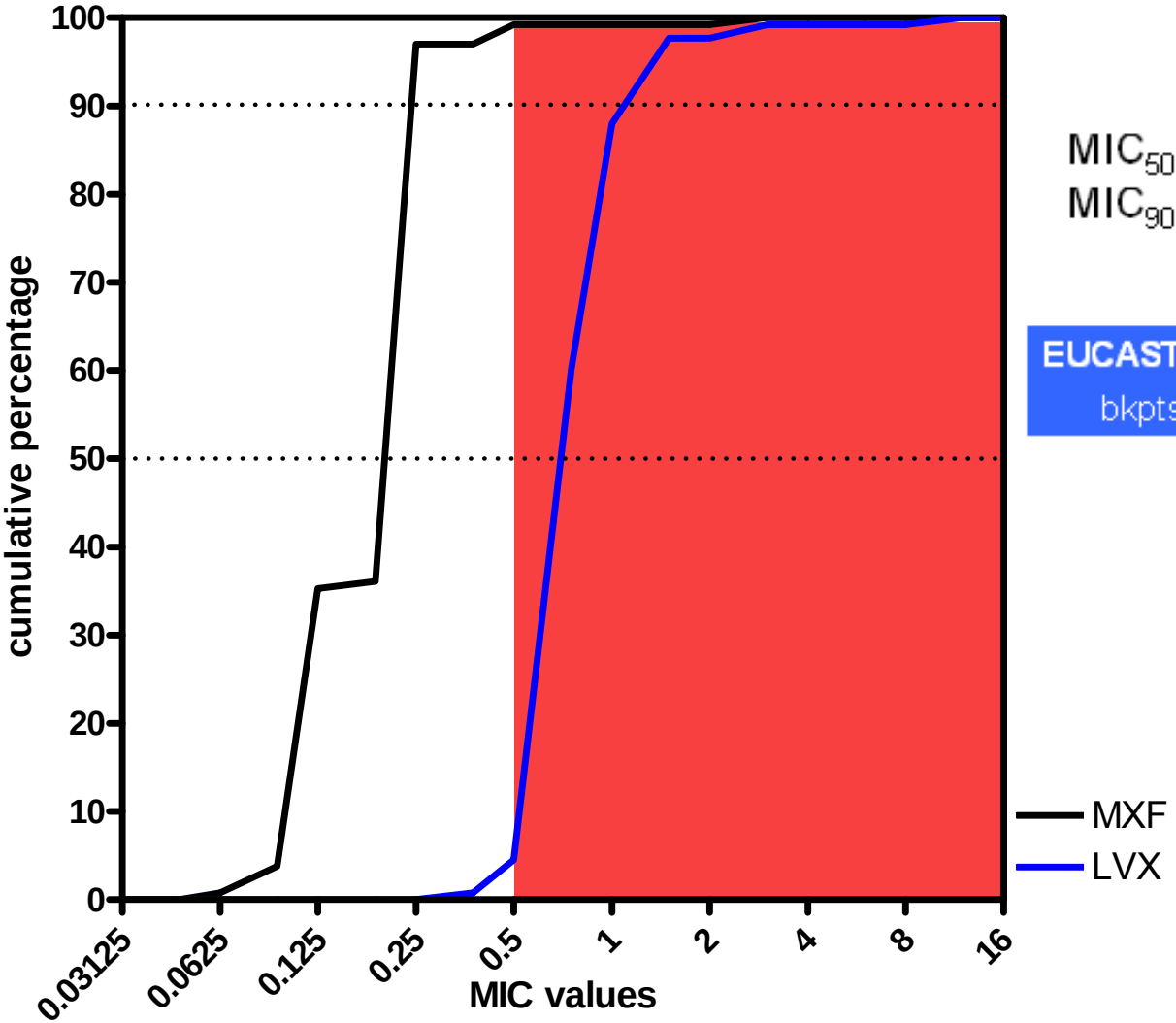
		AMX	CRO	CFX
MIC_{50} (mg/L)		0,06	0,06	0,06
MIC_{90} (mg/L)		1,5	1,5	8
EUCAST bkpts	S ≤	0,5	0,5	0,5
	R >	2	2	1
S:		88,0 %	88,0 %	85,7 %
I:		12,0 %	11,2 %	1,5 %
R:		0,0 %	0,8 %	12,8 %

Macrolides & Ketolides



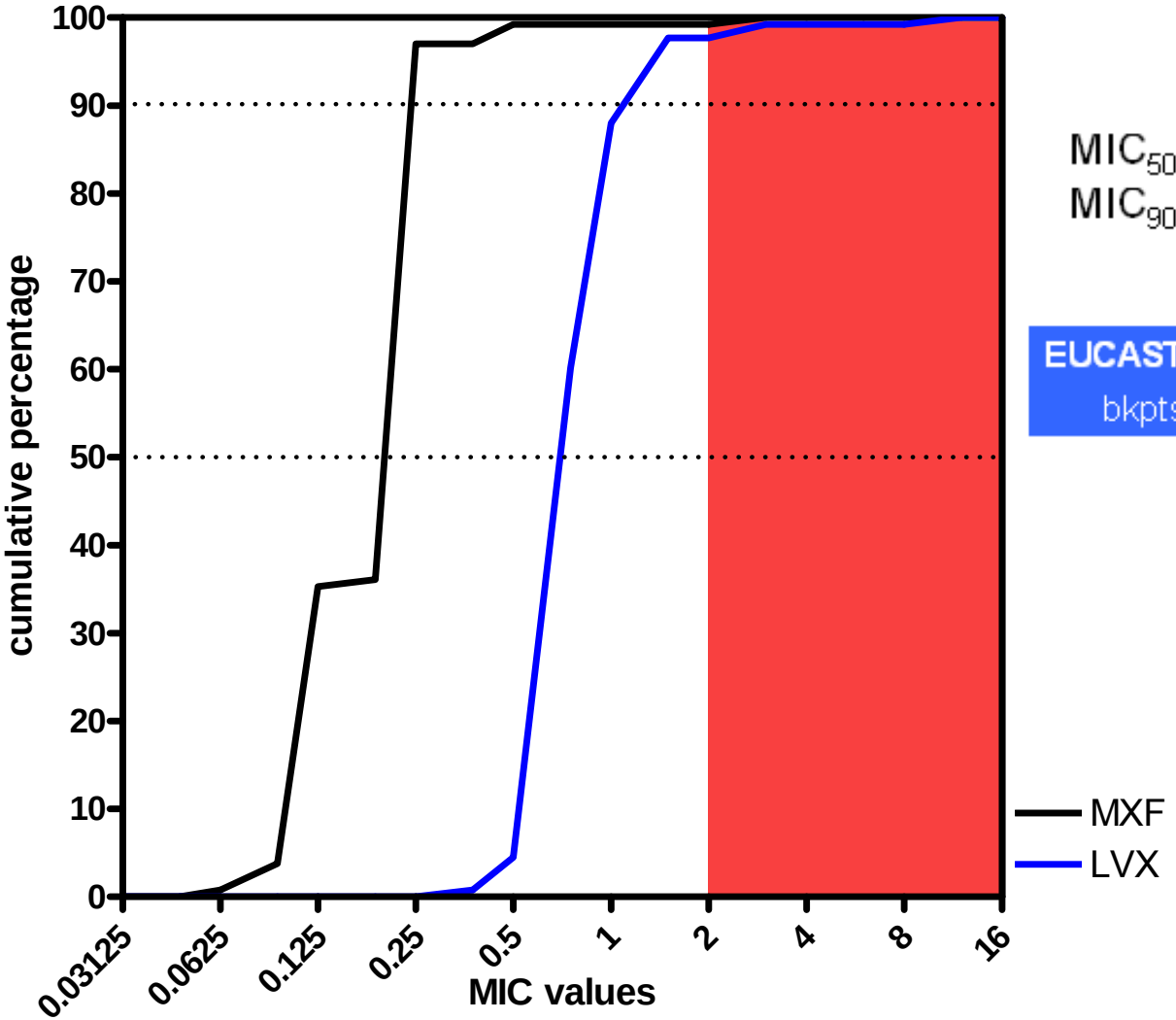
		CLR	TEL
MIC_{50} (mg/L)		≤0,06	≤0,06
MIC_{90} (mg/L)		>32	0,25
EUCAST bkpts	S ≤	0,25	0,25
	R >	0,5	0,5
S:		64,7 %	92,5 %
I:		0,0 %	4,5 %
R:		35,3 %	3,0 %

Fluoroquinolones



		MXF	LVX
MIC_{50} (mg/L)		0,25	0,75
MIC_{90} (mg/L)		0,25	1,5
EUCAST bkpts	S ≤	0,5	2
	R >	0,5	2
S:		99,2 %	97,7 %
R:		0,8 %	2,3 %

Fluoroquinolones



		MXF	LVX
MIC_{50} (mg/L)		0,25	0,75
MIC_{90} (mg/L)		0,25	1,5
EUCAST bkpts	S ≤	0,5	2
	R >	0,5	2
	S:	99,2 %	97,7 %
	R:	0,8 %	2,3 %

Results: efflux observation

- Efflux percentage?
  - Macrolides: MIC to ERY (36%R) >< CLI (28%R)

→ 8% of strains get M phenotype

→ ~20% of R strains by efflux only!

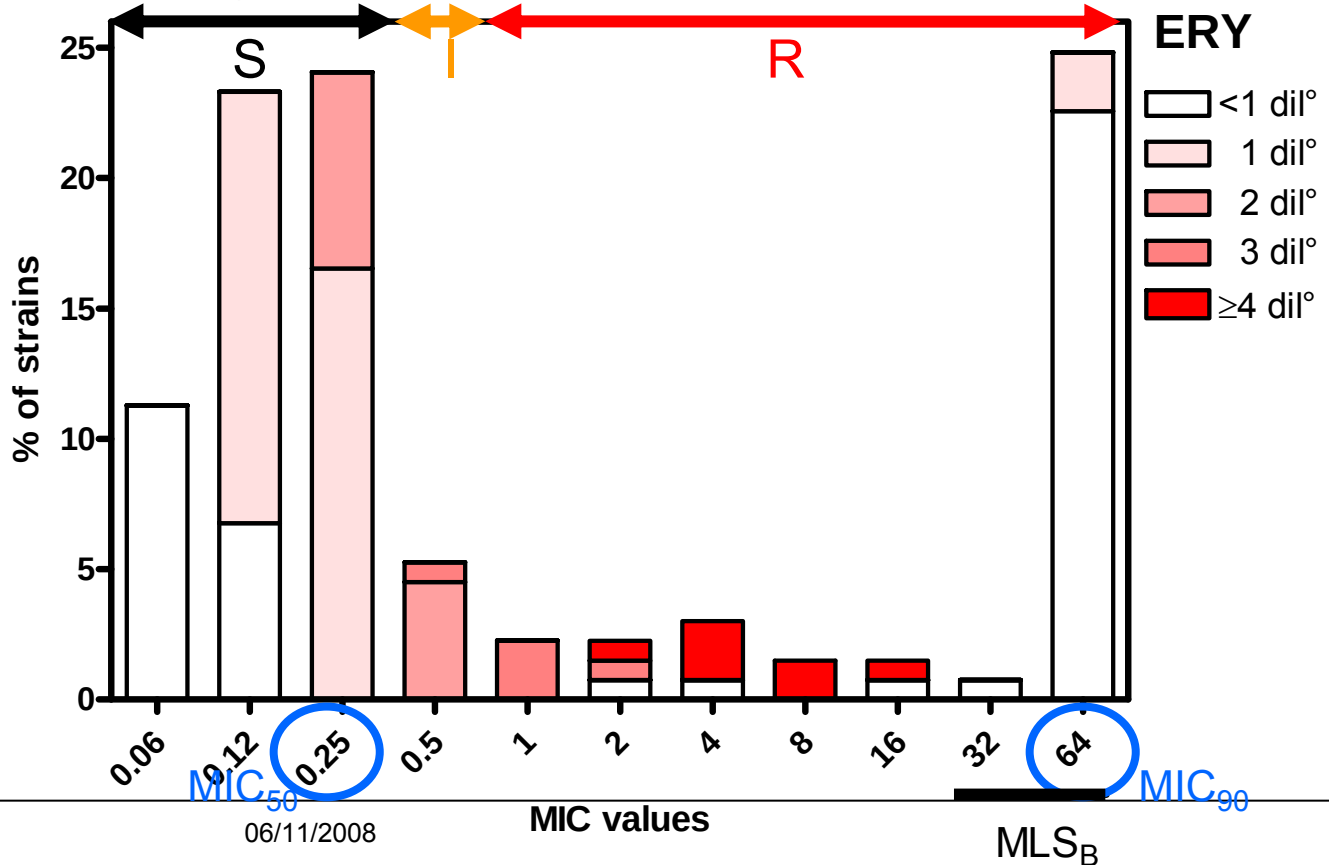
Results: efflux observation

- Efflux percentage?
  - Macrolides: MIC to ERY (36%R) >< CLI (28%R)

→ 8% of strains get M phenotype

→ ~20% of R strains by efflux only!

- Which strains get efflux?

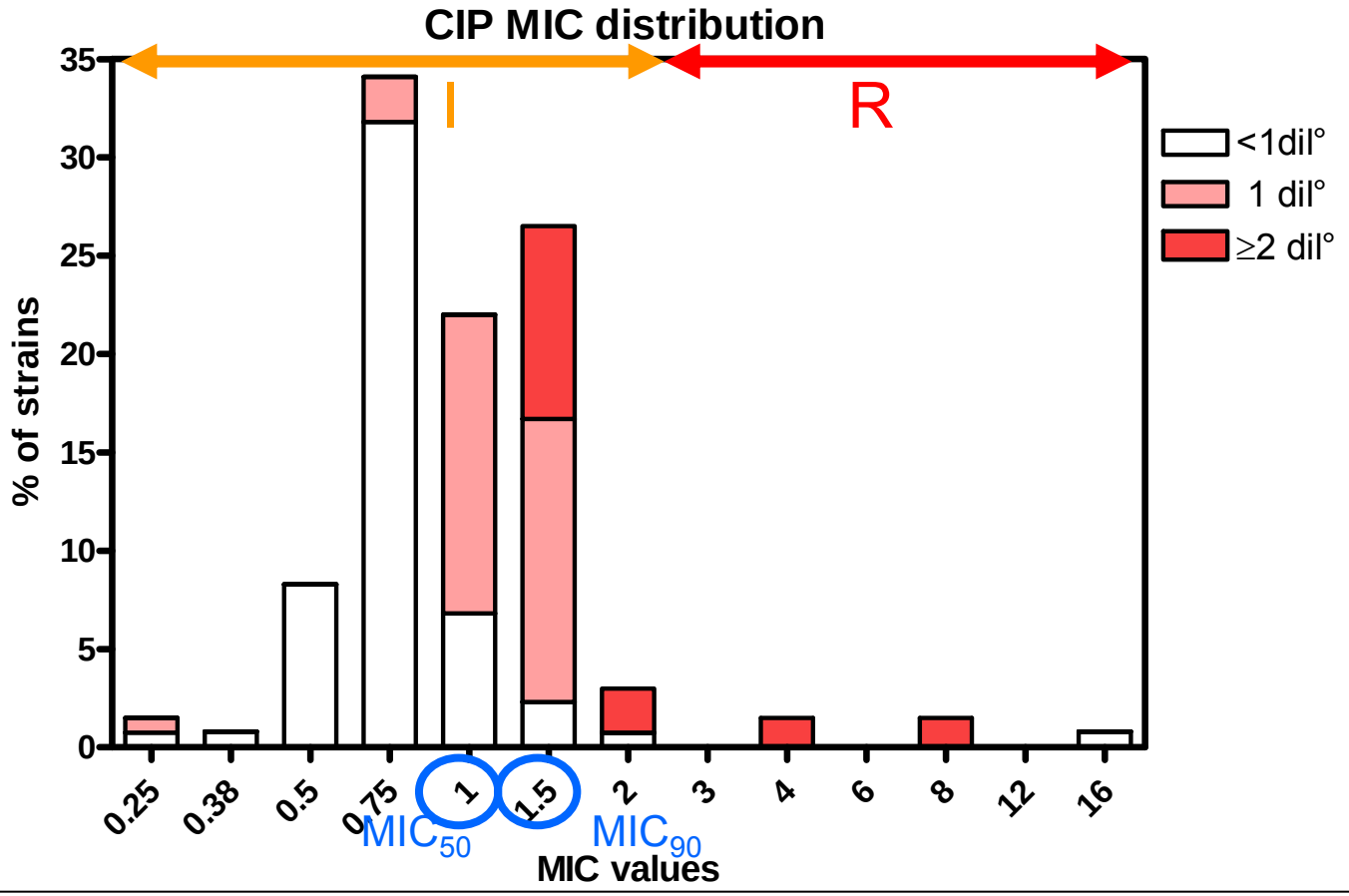


Results: efflux observation

- Efflux percentage?
  - Fluoroquinolones: MIC to CIP, MXF & LVX ± reserpine
- Which strains get efflux?

CIP

47.4%

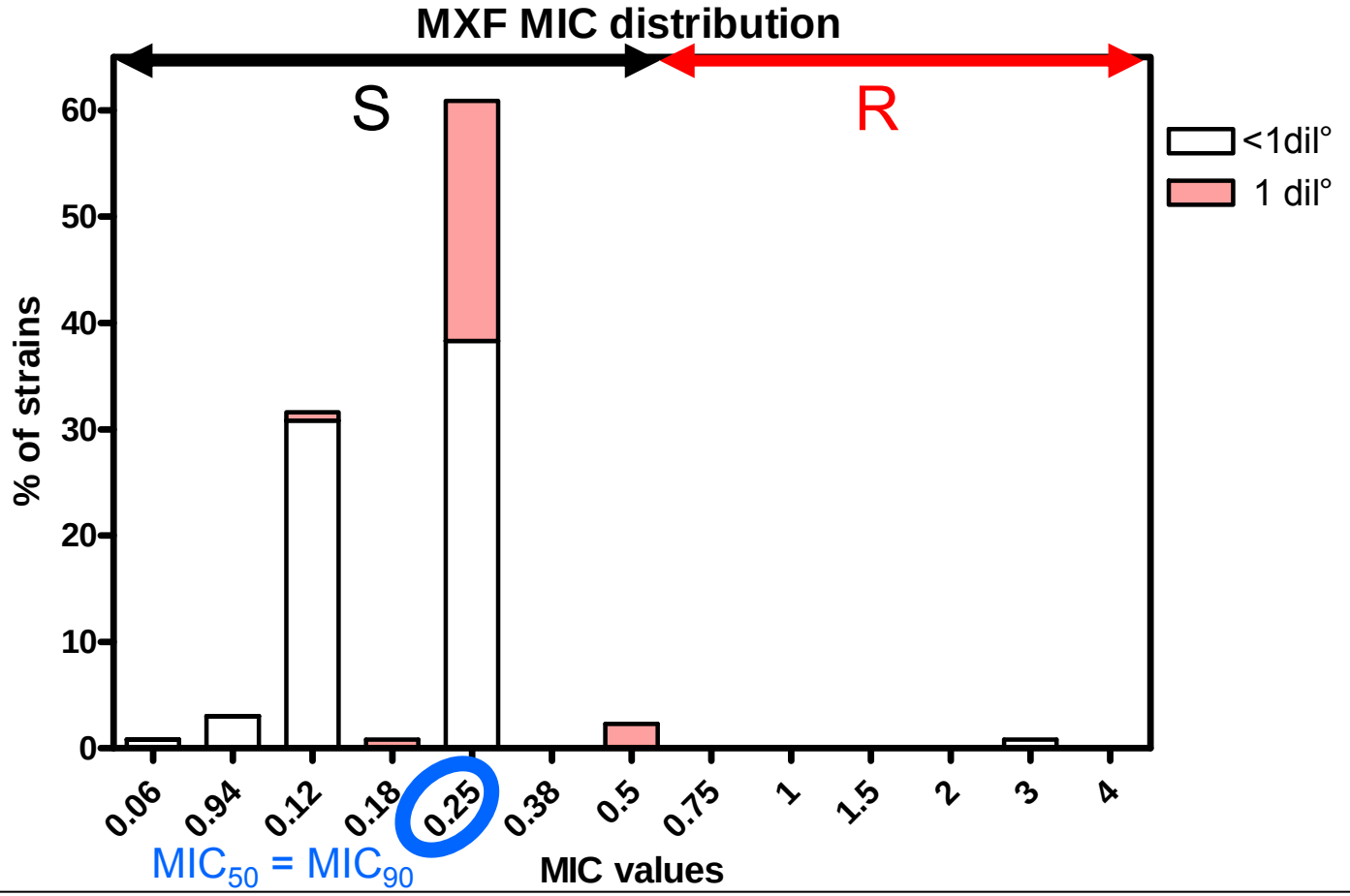


Results: efflux observation

- Efflux percentage?
  - Fluoroquinolones: MIC to CIP, MXF & LVX ± reserpine
- Which strains get efflux?

MXF

26.3%

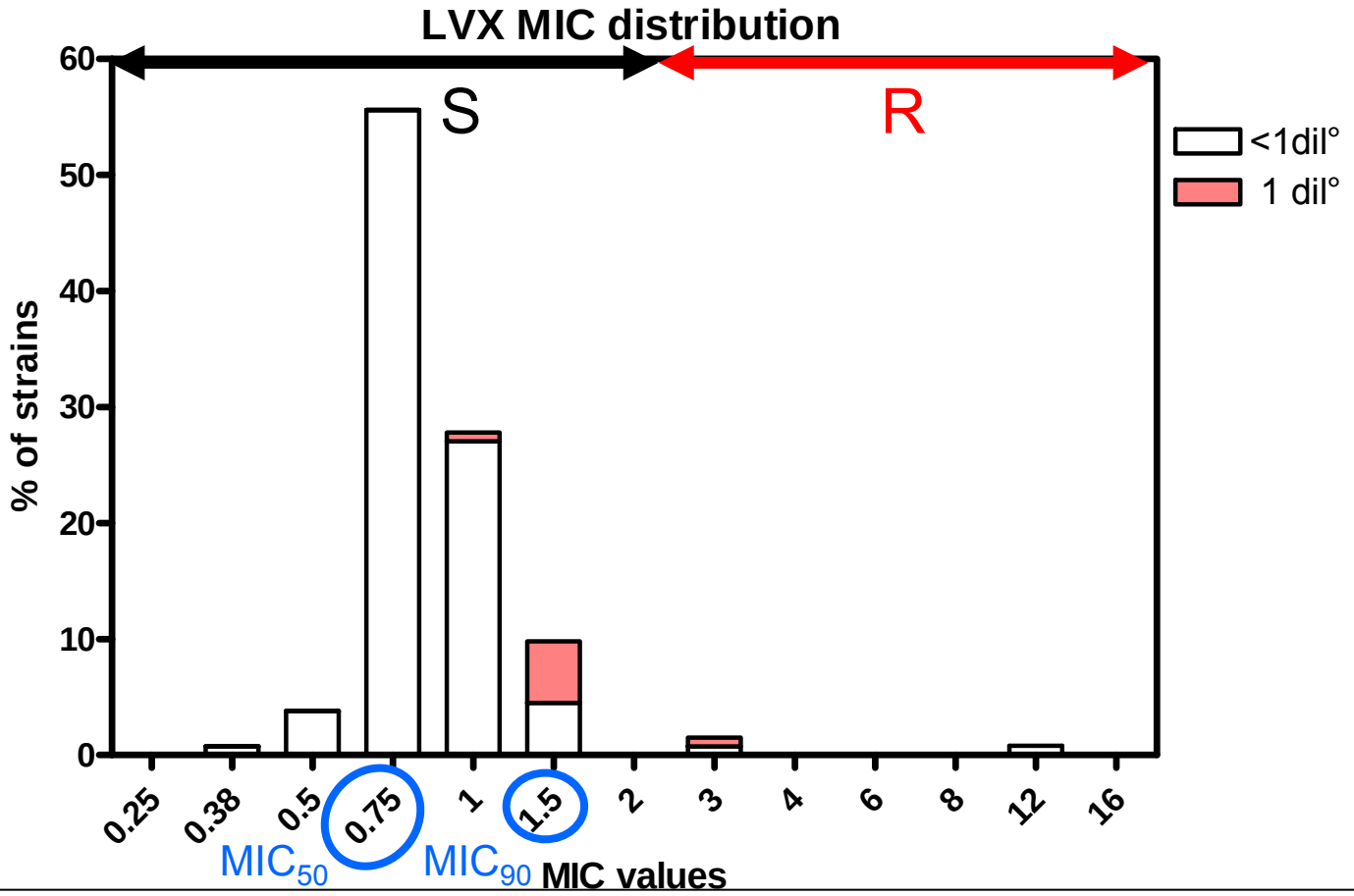


Results: efflux observation

- Efflux percentage?
  - Fluoroquinolones: MIC to CIP, MXF & LVX ± reserpine
- Which strains get efflux?

LVX

6.8%



Conclusions

From this evaluation of SP from CAP:

- β-lactams
  - Significant proportion (~12 %) of "intermediates" for AMX
    ➔ high doses are needed !!
  - Significant proportion (~13%) of "resistants" for CFX
    ➔ Can we still use it safely ?
- Macrolides/ketolides
  - Conventional ML are no longer usable with efflux being responsible for 20 % of resistance
  - Resistance to TEL becomes detectable
    ➔ follow-up is needed …
- Fluoroquinolones
  - MXF and LVX MIC's are still below breakpoints (high dose for LVX)
  - Efflux is important for CIP and marginal for LVX and MXF

	S (%)	I (%)	R (%)
β-Lactams:			
AMX	88,0	12,0	0,0
CFX	85,7	1,5	12,8
CRO	88,0	11,3	0,8
Macrolides / Ketolides:			
CLR	64,7	\	35,3
TEL	92,5	4,5	3,0
Fluoroquinolones:			
MXF	99,2	\	0,8
LVX	97,7	\	2,3