How to translate an antibiogram into a treatment: Gram+ organisms

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Streptococci

S. pyogenes

S. agalactiae **(Strepto B)**

always sensitive to penicillins!

$\rightarrow$ **don't believe in any resistance**

$\Rightarrow$ **Contact your microbiologist**

and/or

publish about it!

Enterococci

Always - R to cephalosporins/oxacillin

- R to clindamycin (except some *E. faecium*)

- low-level R to aminoglycosides (MIC genta < 250 µg/ml)

Enterococci

Penicillin-R

Pen-S strains have already relatively high MICs

(intrinsic "low-level" resistance to beta-lactams of all enterococci)

and MBCs > 100 are frequent, especially in *E. faecium*

→ *In vivo* resistance

⇒ treat with glycopeptide

(VRE with pen-R are frequent in the US

rare in Belgium)

Enterococci

High-level aminoglycoside-R (MIC genta ≥ 500 µg/ml)

No *in vivo* synergy with penicillins/glycopeptides

!!! *In vitro* R expressed only with gentamicin

⇒ don't believe in amika or netil results!

Enterococci

Glycopeptide-R

Rare in Belgium:

- **<7% before 1997**
- **lower since avoparcin banned from animal feeding**
- **very rare in real infections**

⇒ contact your microbiologist!

! *E. gallinarum*

! *E. casselliflavus* | **are naturally R to vancomycin**

Treatment: linezolid

Undetected vancomycin resistance

Van B VRE: detection problems with some automated methods (Vitek, …)

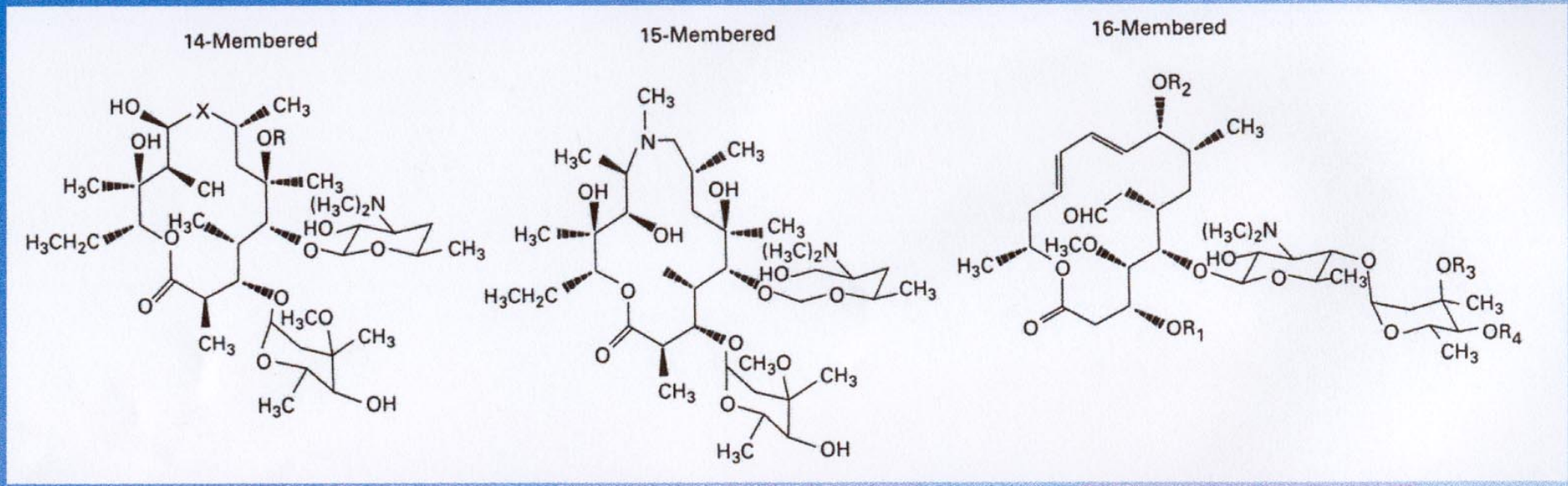
Enterococci

FQ-R

Marginal activity

If S → use only for lower UTI or UTI without sepsis

The family ...



erythromycin
roxithromycin
clarithromycin
dirithromycin

azithromycin

josamycin
spiramycin
miocamycin

From: European Conference on Antibiotic Use in Europe (ESAC), Brussels, Belgium (Nov 15-17, 2001), Workshop # 6 :Towards an European Consensus Indications for Major Antibiotic Classes: an Exercise with the Macrolides (http://www.facm.ucl.ac.be/esac/Workshop6.htm)

S. pyogenes

Mechanisms of R to macrolides

1. **MLS_B: - encoded by *erm* gene (A and C in Belgium)**

   - modification of 23S subunit of ribosomal RNA → high-level resistance (MIC ≥ 32 µg/ml)

   - **constitutive (56% in Belgium – 2003)**
     → resistant to all macrolides/azalide/lincosamines *in vitro* and *in vivo*
   - **inducible (6% in Belgium – 2003)**
     → resistant *in vitro* to all macrolides/azalide
     → susceptible *in vitro* to licosamines (D-test)
     ⇒ *in vivo* R to all macrolides/azalide/lincosamines for all severe/deep infections

S. pyogenes

Mechanisms of R to macrolides

2. M phenotype: efflux-mediated, encoded by *mef* gene (38% in Belgium – 2003)

→ low-level R to 14- and 15-membered macrolides/azalide

→ susceptible to - 16-membered macrolides (miokamycin)

- lincosamines

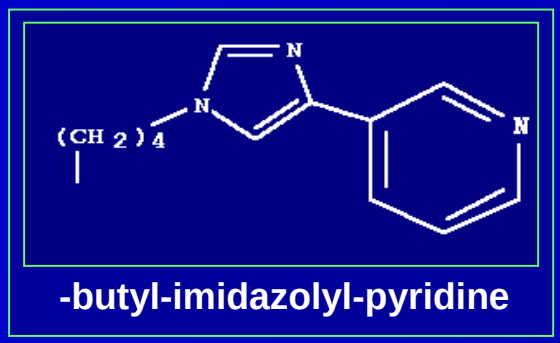
⇒ *in vivo* - activity of lincosamines and 16-membered macrolides (?)

- some activity of 14-/15-membered macrolides, but to be considered as R, especially in severe/deep infections

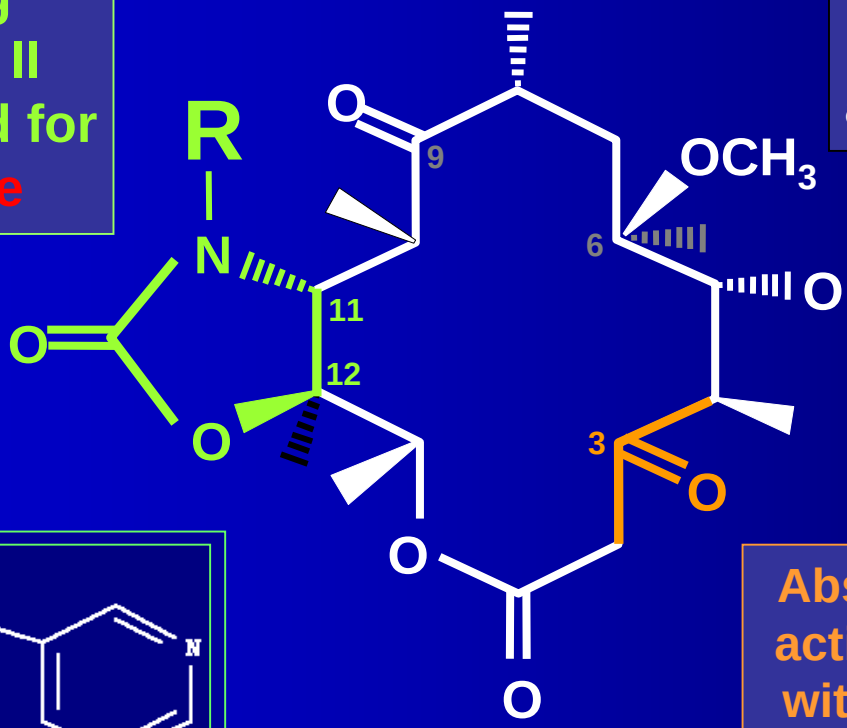
(↑ expression of efflux pump *in vitro*?)

Telithromycin (RU66647/HMR 3647): key differences with erythromycin A

Side chain for anchoring to domain II (activity) and for PK profile



-butyl-imidazolyl-pyridine



6-methoxy: for acid stability as in clarithromycin

D - desosamine

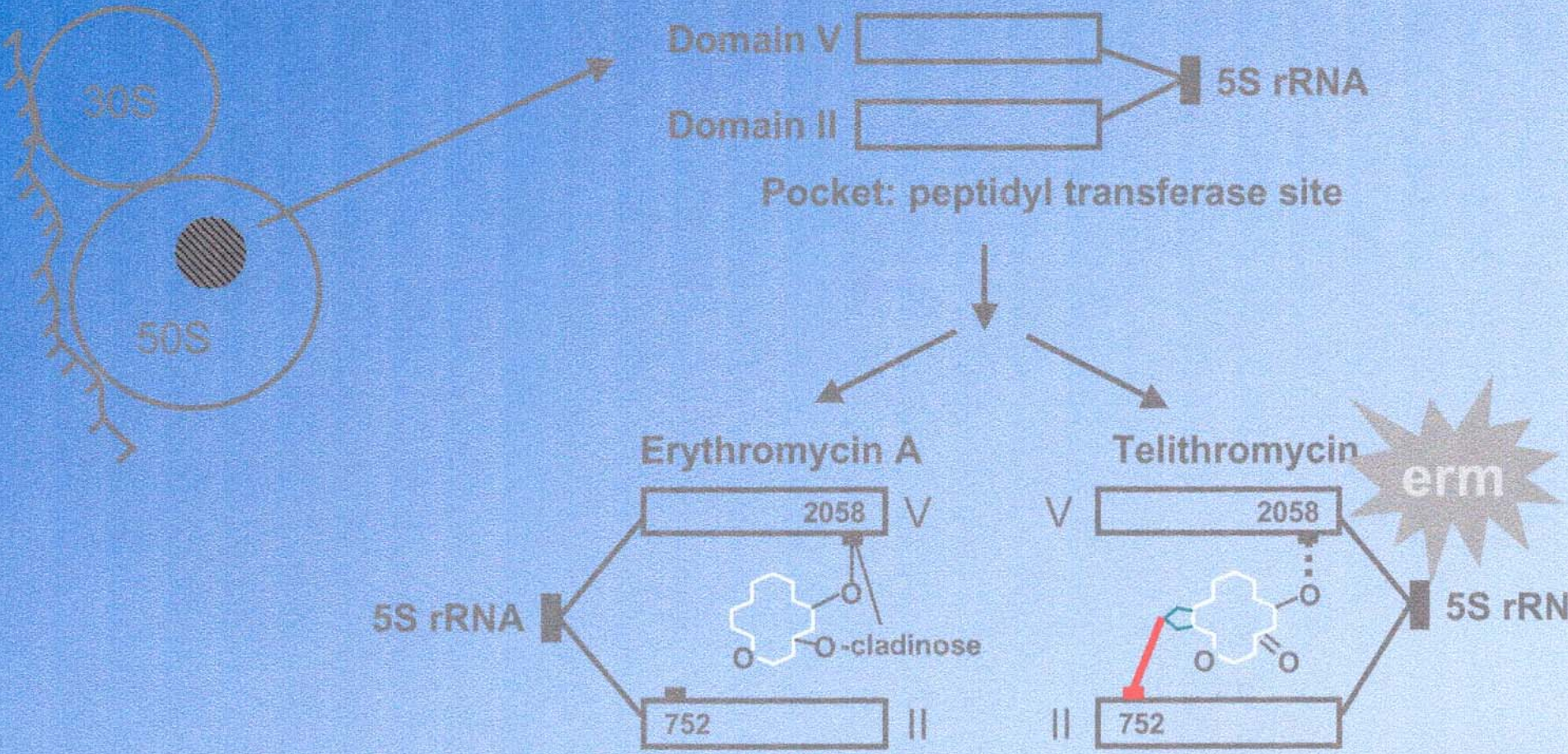
The molecule is also unsensitive to the *mef* efflux mechanism

Absence of cladinose for activity against organims with the *erm* mechanism of resistance

http://www.md.ucl.ac.be/seminfect/resume.htm

Inhibition of Protein Synthesis (2)

- Inhibition of peptidyl transferase activity



From Bryskier,
FDA presentation of KETEK®

TELITHROMYCIN

- **Second binding site → strength :**
  10 times erythro if erythro Ⓢ
  25 times erythro if erythro ®
- **Less able than macrolides to select ® strains in sub-MIC concentrations**

Davies et al AAC 2000

S. pyogenes

Telithromycin

Not tested by most laboratories

Registration studies: active against "all" *S. pyogenes* except some *erm*B constitutive strains

In Belgium: ≥95% of high-level R strains express *erm*B…

→ "High" MICs (0.5-… µg/ml?)

⇒ Be cautious with severe infections!

MIC_{50} [µg/ml] of wild type and mutant strains

		Erythromycin	Telithromycin
S. pyogenes	(WT)	0.03	0,08
	(*ermTR* ind.)	4	0,06
	(*ermTR* const.)	>64	0,25
	(*ermB* ind.)	>64	0,5 - 1
	(*ermB* const.)	>64	8
	(*mef*)	8	0,5
S. pneumoniae	(WT)	0,03	0,008
	(*ermB* const.)	>64	0,06
	(*mef*)	2	0,125

S. pneumoniae

Penicillin-R

R due to altered PPB

→ ↓ substrate affinity

(does not involve beta-lactamases!)

→ can be overcomed by increased beta-lactam doses

⇒ *in vitro* resistance (reduced susceptibility) does not translate in ↑ clinical failure rate… at least until MIC ≥ 4 µg/ml

Clinical significance of 'in vitro' reduced susceptibility of *S. pneumoniae* to β-lactams

- "MIC breakpoint above which Peni (and other β-lactams) likely ineffective in respiratory tract infections is probably > or = 4"
  - » Strachan and Friedland, J Med Microbiol, '95, 43, 237
- Up to now, no *S. pneumoniae* strains with MIC values ≥ 4 to commonly used respiratory β-lactams have been isolated in Belgium
  - » Reference lab for Pneumococci, UZLeuven

Treatment of pneumococcal pneumonia

Oral therapy: pharmacokinetic/pharmacodynamic parameters

Mean % of dosing interval for which serum concentration exceeds MIC

Antibiotic	*Dose & frequency*	*MIC*				
	Oral administration/adults	*0.5*	*1*	*2*	*4*	*8*
Amoxicillin	500 mg tid →	80	63	44	21	1
	500 mg qid →	100	84	59	28	1
	1 g bid →	74	61	48	33	16
	1 g tid →	100	92	72	50	24
Amoxi/ clavulanate	875 mg bid →	62	50	41	27	11
	875 mg tid →	93	75	62	41	17
Cefuroxim axetil	500 mg bid →	>>40	≥40	<40	<<40	<<<40
	500 mg tid →	>>>40	>>40	≥40	<40	<<40

S. pneumoniae

Penicillin-R

Several clinical studies have shown that in vitro R is not closely linked to morbidity/mortality

- in the 90s, same mortality:

Klugman, *AJDC* 1992

Pallares, *NEJM* 1995

Plouffe, *JAMA* 1996 (longer LOS for pen-R)

Clinical significance of Peni-Resistance in Pneumococcal CAP

Metlay et al. Clin Inf Dis 2000;30:520

- **Invasive pneumococcal CAP 3 – 4**
- **n = 192; 19% Peni-I; 4% Peni-R**
- **Mortality 14% :**
  - **related to older age and co-morbidity**
  - **no ss increased mortality in Peni-I and -R**
  - **MIC $\geq$ 2 mcg/ml : suppurative complications : x4 !!**

Clinical significance of Peni-Resistance in Pneumococcal CAP

Feikin et al. Am J Publ Health 2000;90:223

- **Invasive pneumococcal CAP 3 – 4**

- **n = 5837; 9% Peni-I; 8.6% Peni-R**

- **Mortality 12 % :**
  - **related to older age and co-morbidity**
  - **MIC 0.12 - 2 mcg/ml : no increased mortality**
  - **MIC $\geq$ 4 mcg/ml : mortality after >4d hospit. : x7 !!**

S. pneumoniae

Penicillin-R

International prospective study of pneumococcal bacteremia
(Yu et al., *CID* 2003)

844 + blood cultures

pen-I (MIC ≤0.06 µg/ml): 15%

pen-R (MIC ≥2 µg/ml): 9.6%

⇒ similar mortality/time to defervescence and frequency of suppurative complications

in pen-I/R or pen-S infected patients

IF treated with penicillins/cefotaxime/ceftriaxone

N.B.: not valid for cefuroxime though questionable because of elevated mean MIC (3 µg/ml) and low dosage (750 mg tid)

Clinical re-definition of Peni-Resistance of *S. pneumoniae* in RTI

- **NCCLS (1) :**

  ***S*ensitive :** **MIC ≤ 0.06 mcg/ml**

  ***I*ntermediate :** **MIC 0.1 – 1.0 mcg/ml**

  ***R*esistant :** **MIC ≥ 2.0 mcg/ml**

- **Suggested clinical re-definition (2) :**

  ***S*ensitive :** **MIC ≤ 1.0 mcg/ml**

  ***I*ntermediate :** **MIC 2.0 mcg/ml**

  ***R*esistant :** **MIC ≥ 4.0 mcg/ml**

(1) NCCLS, 1998

(2) Arch Intern Med 2000;160:1399

S. pneumoniae

Macrolide-R

Similar to S pyogenes

- **High-level R: R to all macrolides/azalide/lincosamines**

  ***erm* gene (A and C in Belgium)**

  > 80-90% in Europe

  < 50% in the US

- **Low-level R: efflux-mediated, *mef* gene**

  MIC 1-16 µg/ml

  < 10% in Belgium

  > 50% in the US

Due to the high rate of high-level macrolide-R, if erythro-R:

R to all macrolides/azalide/lincosamines

S. pneumoniae

Macrolide-R

Several clinical failures reported

- in Europe (high-level and low-level R)

Garau: *CID* 2002

- in US (mostly low-level R)

Kelley: *CID* 2000

Fogarty: *CID* 2000

S. pneumoniae

Telithromycin

Not tested in most laboratories

Retains *in vitro* activity against macrolide-R strains

BUT MICs shifting to the right

⇒ **May be used in macrolide-R *S. pneumoniae* infections**

but - few data in more severe cases/bacteremia

- close follow-up of patients and surveillance mandatory

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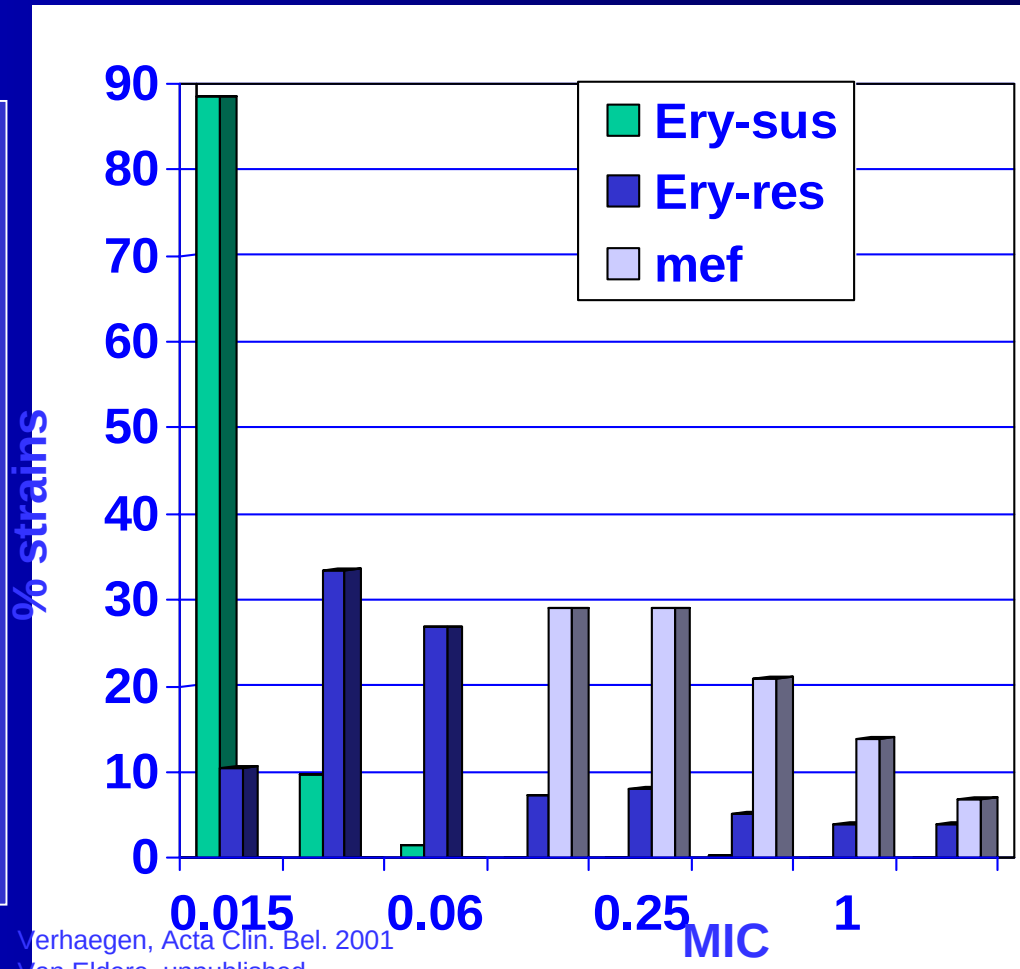
Telithromycin and Belgian *S. pneumoniae*

- 392 Erythro-sus *S.pneumoniae*
  - $MIC_{50\ Telithro}$: 0.015
  - $MIC_{90Telithro}$: 0.03
- 245 Erythro-res *S.pneumoniae*
  - $MIC_{50Telithro}$: 0.06
  - $MIC_{90Telithro}$: 0.5



Verhaegen, Acta Clin. Bel. 2001
Van Eldere, unpublished

S. pneumoniae

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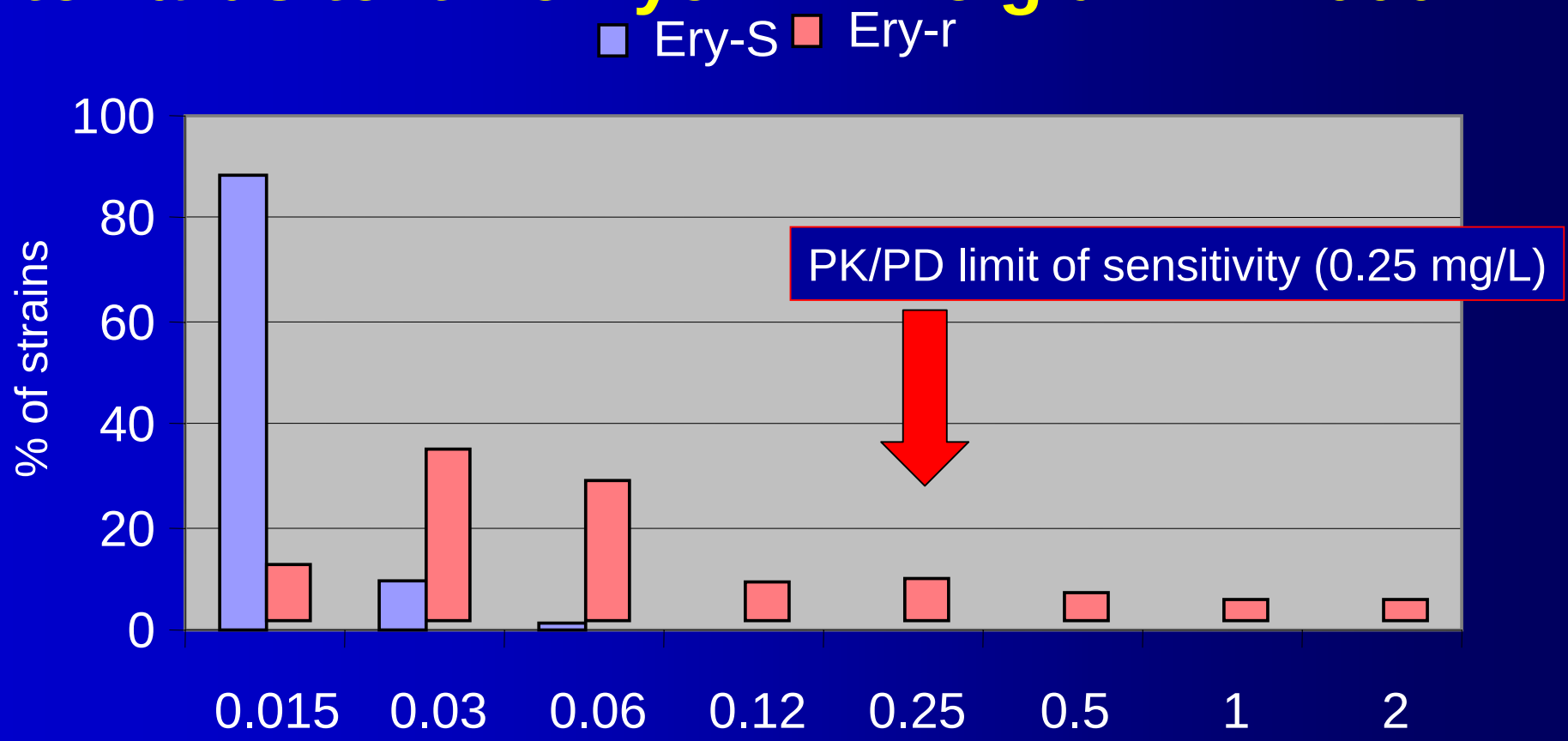
Which are the sensivities of *S. pneumoniae* towards telithromycin in Belgium in 2000 ?



Verhaegen & Verbist, Acta Clin. Belg. 2001, 56: 351

MIC_{90} for Ery-s strains: < 0.06 ...

But MIC_{90} for Ery-r strains: 0.25-0.5 ...

http://www.md.ucl.ac.be/seminfect/resume.htm

S. pneumoniae

FQs

> 99% of Belgian strains are S

BUT

- MICs close to MIC breakpoint for most FQs (except moxifloxacin)

- AUIC and peak/MIC even closer to PK/PD breakpoint

due to 1st step mutation in several strains (?)

⇒ If FQ-S: - don't use oflo or cipro

- use high-dose levofloxacin

- prefer moxifloxacin

NFQ: PK/PD *vs. S. pneumoniae*

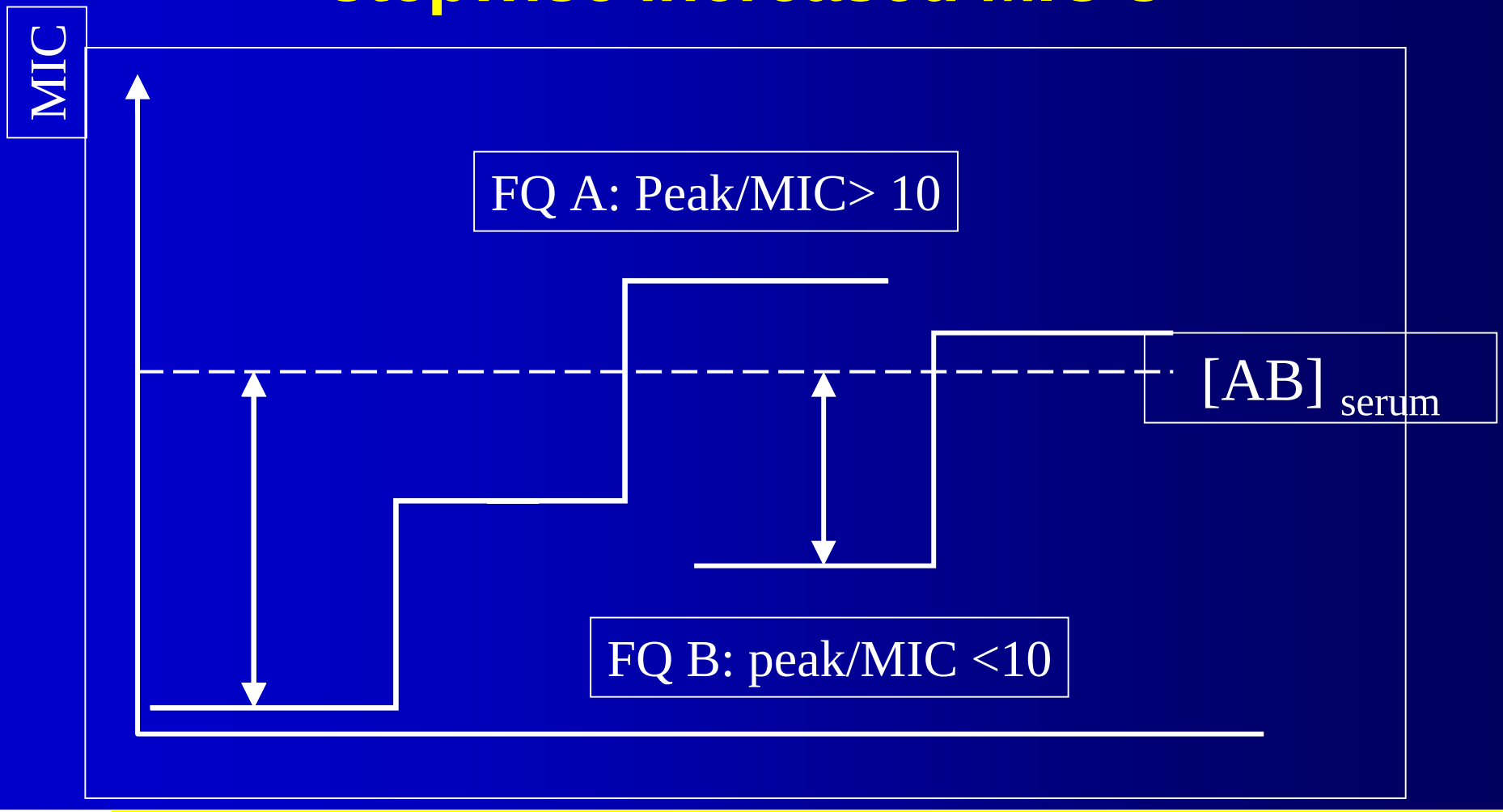
	DOSE (mg)	MIC_{90} (mcg/ml)	Peak/MIC	AUIC (mcg/ml/h)
LFX	500	1-2	3-6	24-48
MOX	400	0.125-0.25	9-18	96-192

AUIC breakpoint for successful outcome = 35 - 40

Peak/MIC > 10: important for prevention of resistance selection

JAC 2000;46:669

FQ's resistance development & selection: stepwise increased MIC's



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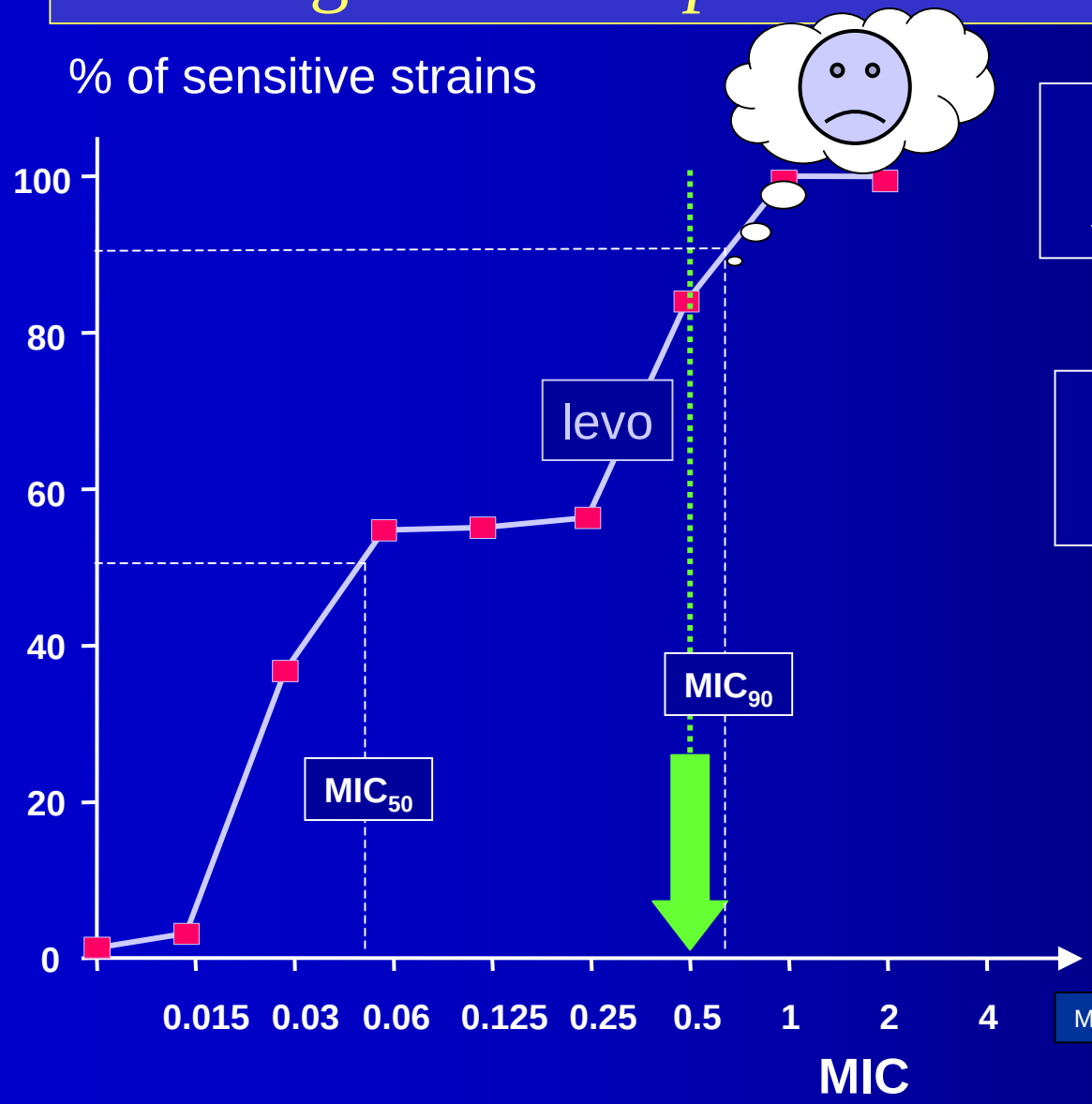
How does this translate in “real practice” in Belgium for *S. pneumoniae* and levofloxacin ?



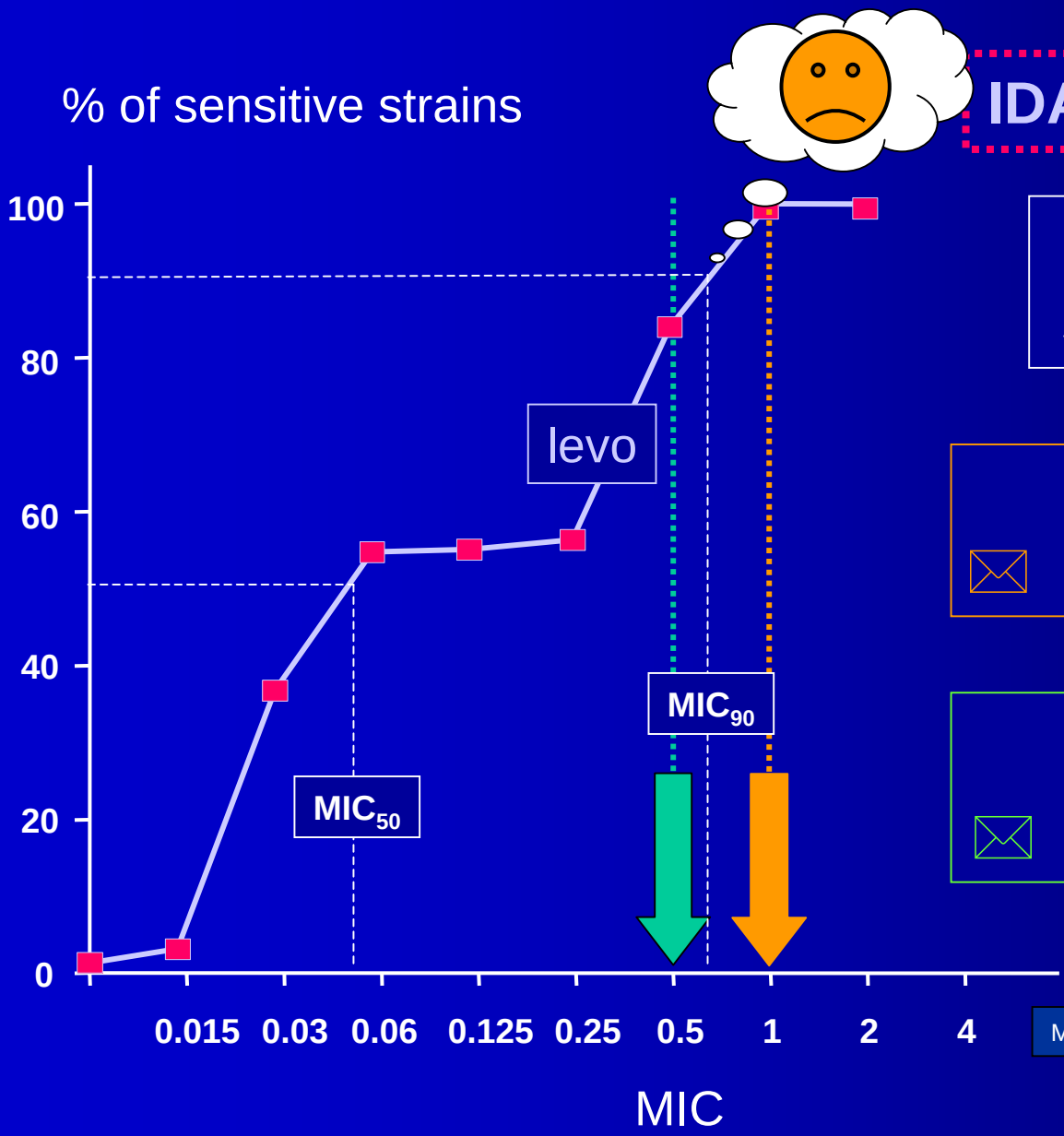
Levofloxacine
500 mg once-a-day

AUC = 47 (mg/l)xh
peak = 5 mg/l

✉ MIC_{max} = 0.5

MIC data: J. Verhaegen et al., 2001

Can we improve the situation with levofloxacin ?



IDAB recommendations:

Levofloxacine
500 mg TWICE daily

AUC = 94 (mg/l)xh

✉ MIC_{max} = 1.0 for AUC/MIC

peak = 5 mg/l

✉ MIC_{max} = 0.5 for peak/MIC

MIC data: J. Verhaegen et al., 2001

S. pneumoniae

FQs

> 99% of Belgian strains are S

BUT

- MICs close to MIC breakpoint for most FQs (except moxifloxacin)

- AUIC and peak/MIC even closer to PK/PD breakpoint

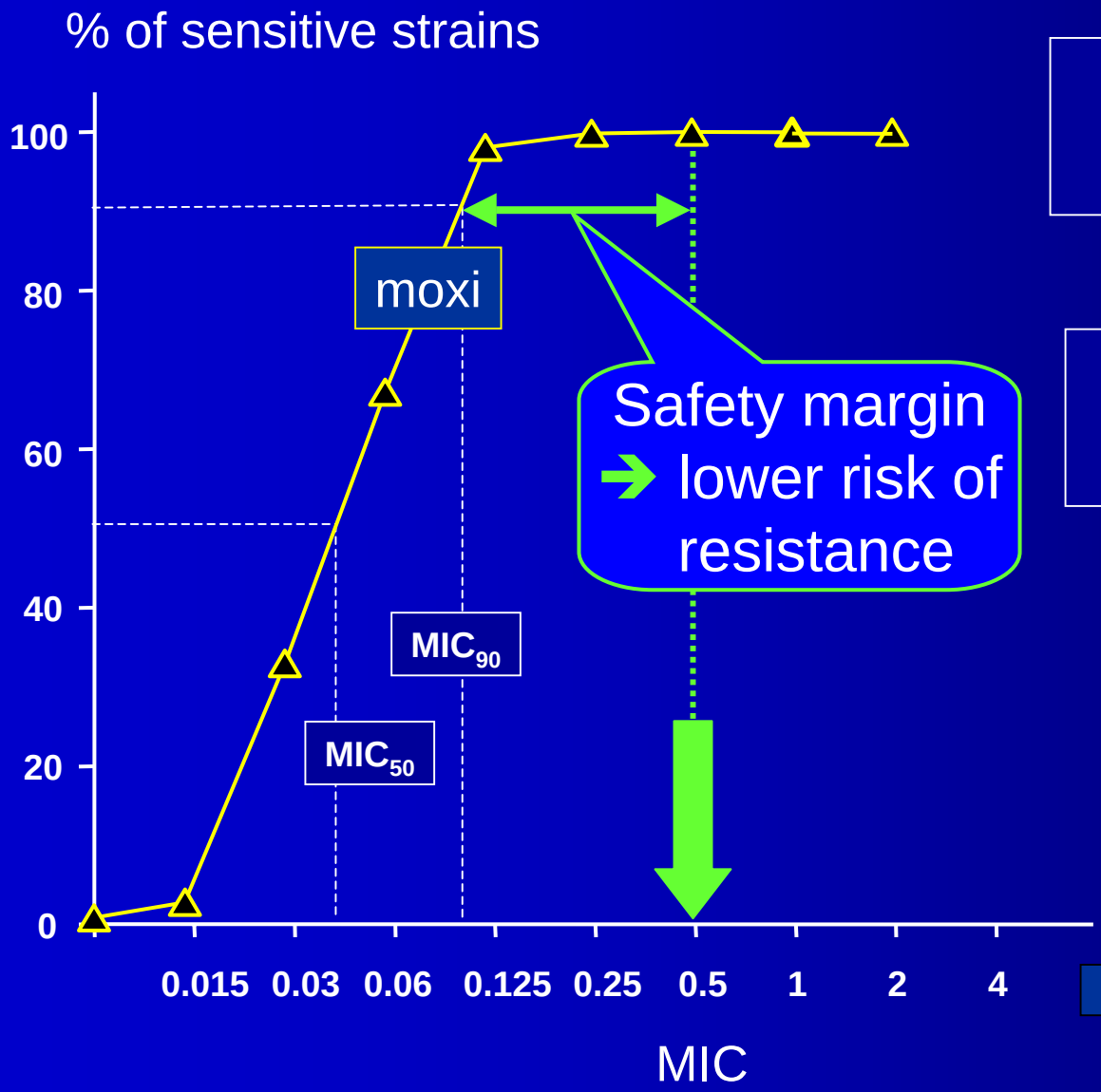
due to 1st step mutation in several strains (?)

⇒ If FQ-S: - don't use oflo or cipro

- use high-dose levofloxacin

- prefer moxifloxacin

What about moxifloxacin and *S. pneumoniae* in Belgium ?



Moxifloxacin
400 mg once-a-day

AUC = 48 (mg/l)xh
peak = 4.5 mg/l

✉ MIC_{max} = 0.5

MIC data: J. Verhaegen et al., 2001

S. aureus oxa-S

- Do not question!

- Do not use glycopeptide
  in non-IgE-mediated allergy!

  ⇒ suboptimal clinical outcome:

  prolonged | fever
  | bacteremia

(Levine *et al. Ann Int Med* 1991)

S. aureus oxa-S

FQ-S

***In vivo*: FQs active clinically**

S. aureus oxa-S/MRSA

FQ-R

***In vivo*: FQs inactive clinically**

S. aureus

Macrolide-R

Same mechanisms as for streptococci

1. **MLS_B: *erm* gene-encoded (A and C in Belgium)**

   - **constitutive**
     → R *in vitro*
     → R *in vivo*
     | to all macrolides/azalide/lincosamines

   - **inducible (D-test)**
     - macrolides/azalide: | R *in vitro*
     R *in vivo*

     - lincosamines: | S *in vitro* → R if D-test performed
     R *in vivo*, at least in deep, severe infections

2. **Efflux: *msr* gene-encoded; no "D-zone"**
   ⇒ | macrolides/azalide: R *in vitro* → R *in vivo*
   lincosamines: S *in vitro* → S *in vivo*

MRSA

Always Ⓡ to | **cephalosporins (all)**
carbapenems

MRSA

SXT-S

>99% S in Belgium since 10 years

Clinically: scarce data

- **animal models of endocarditis:**
  SXT < vanco
  (de Gorgolas, *AAC* 1995)
- **humans (IVDU) with septicemia in a RDB study:**
  (Markowitz *et al., Ann Int Med 1992*)
  SXT < vanco (p 0.02)
  for MRSA + MSSA
  failure | mostly in right-side endocarditis
  only in MSSA-infected patients

⇒ everyday use in mild to moderate infections:
valuable alternative

MRSA

Glycopeptide-S

- **Cure rate in severe infections**
  often disappointing
  50-70% (HAP, VAP, endocarditis, …)

- **Recent studies show that significant risk for vancomycin treatment failure could begin to emerge**
  not only for MICs between 4-16 µg/ml [(h)GISA]
  (Fridkin, *CID* 2003)
  but also with increasing vancomycin MICs in the (S)-range:
  successful treatment:
  MIC < 0.5 µg/ml: 55.6%
  MIC 1-2 µg/ml: 9.5%
  (Sakoulas *et al., JCM 2004*)

⇒ What about other drugs (linezolid)
in such instances?

MRSA

Glycopeptide-R/I

1. Call your microbiologist!
   ? Mistake, from Petri dish to computer…
2. First detected in 1997 for
   (h)VISA
   VISA
   and in 2002 for
   GRSA (3 strains, all in the US)
3. Very rare in Belgium

BUT
- (I) frequently reported as (S) with disk method
  (Etest should be mandatory…)
- (I) or (R) "not" detected by Vitek or Microscan
  Problem of inoculum size
  - NCCLS recomends 5.10^5 CFU
  - vanco-(I) subpopulations: 10^{-6} to 10^{-7}

MRSA

Glycopeptide-R/I

Suspect "vanco-S" strains if
glycopeptide therapy is failing

Key clinical features
- positive BC > 7 days of treatment
- MRSA still present in a usually sterile site
> 21 days of treatment
and/or in deep or prosthetic infections
(high bacterial load)

(Howden, *CID* 2004; *EJCMID* 2005)
(Charles, *CID* 2004)

Treatment: high failure rates with glycopeptides
→ linezolid
(or: combination of high dose vancomycin
+ rifampicin or fusidic acid
+ SXT)