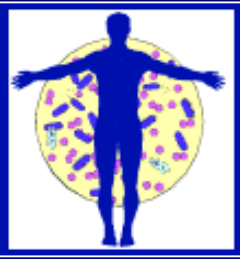


Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

# NEW ANTI-INFECTIVE AGENTS IN 2003 : SPECTRUM AND INDICATIONS

20th Symposium (spring 2003)

Thursday May 22nd 2003

# Ketolides and respiratory fluoroquinolones

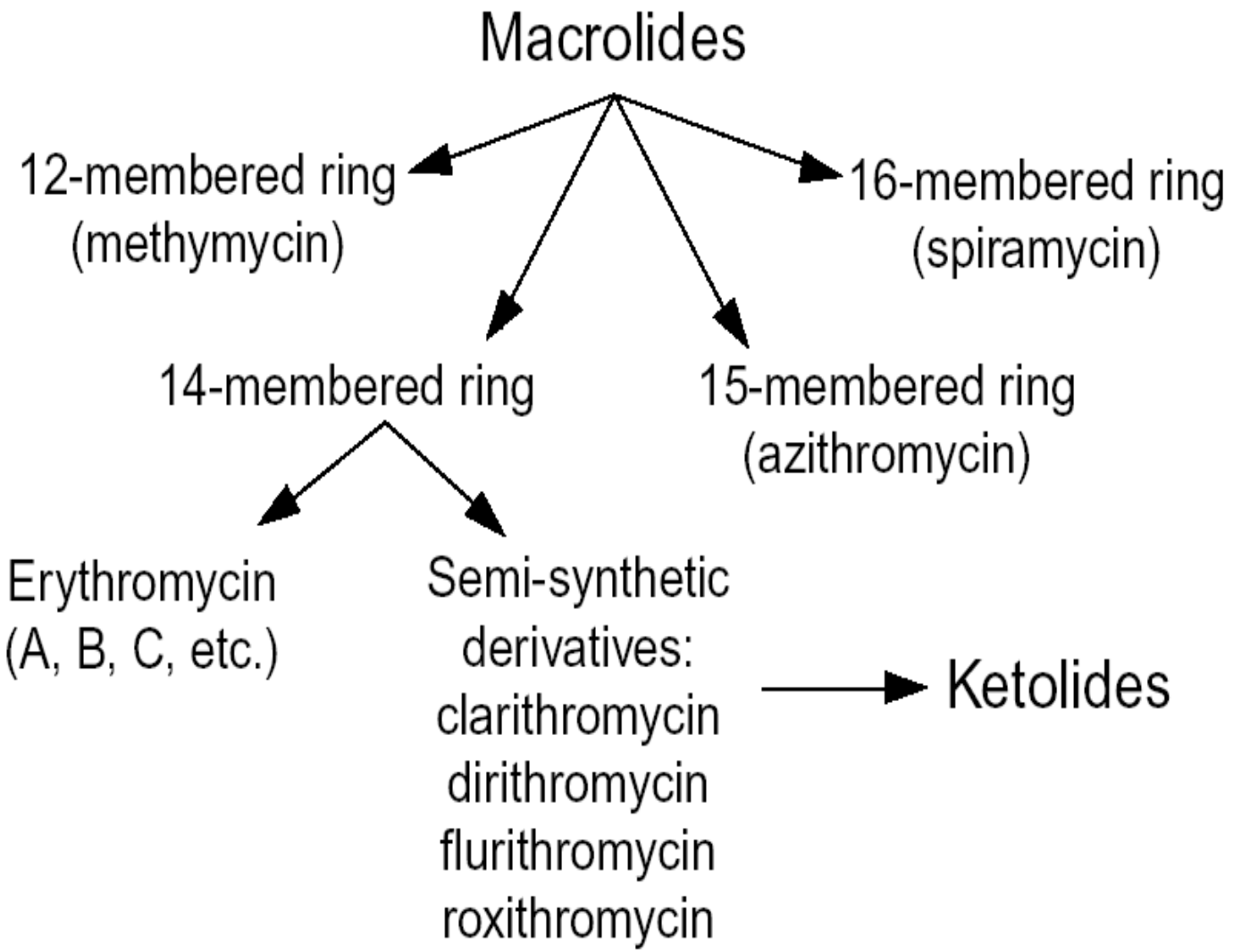
J. Van Eldere

Rega Institute and University Hospital KULeuven

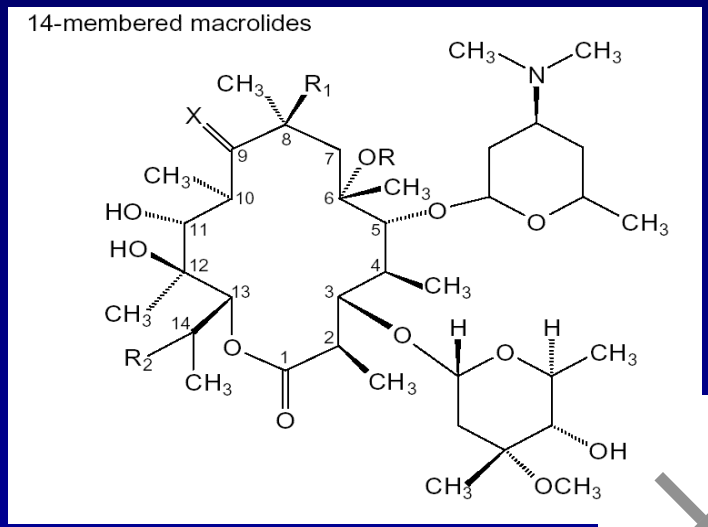
# content

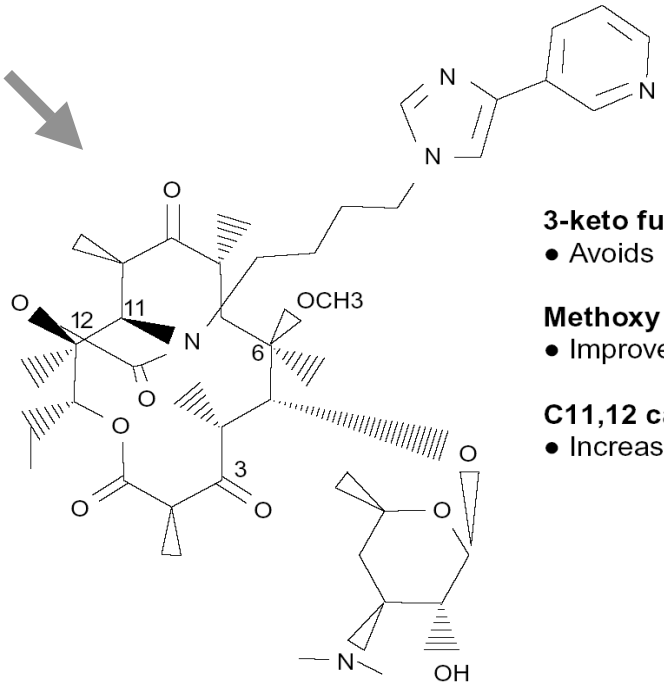
- Ketolides
  - The macrolide superfamily
  - Mechanisms of action and resistance
  - In vitro activity
  - Pharmacokinetics and pharmacodynamics
  - Clinical trial
- Respiratory fluoroquinolones
- Treatment of RTI and place of ketolides and FQ's

# The macrolide superfamily



# The macrolide superfamily : telithromycin



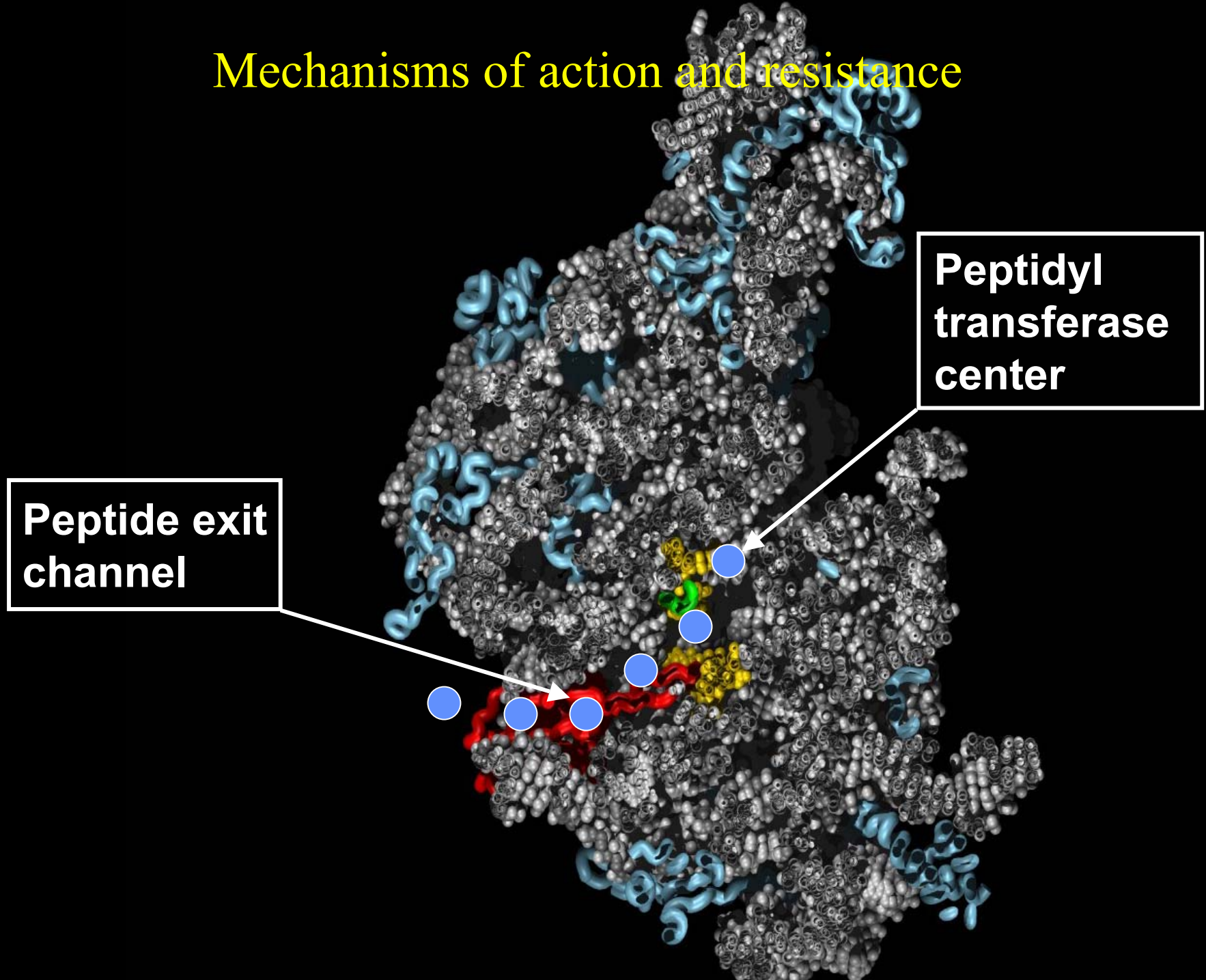




**3-keto function**
- Avoids $MLS_B$ resistance induction

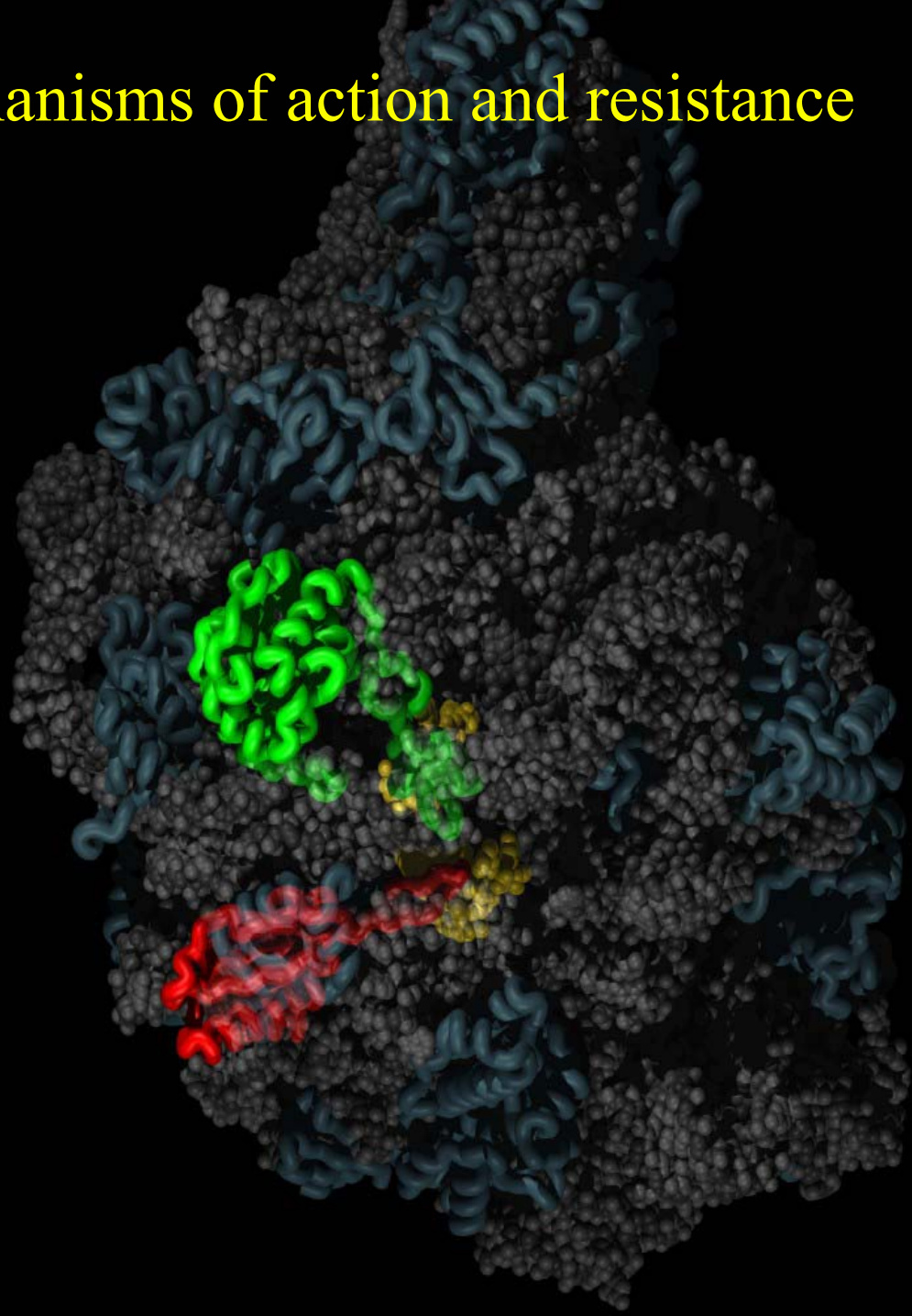
**Methoxy group at C6**
- Improves acid stability

**C11,12 carbamate side chain**
- Increases affinity for the ribosomes

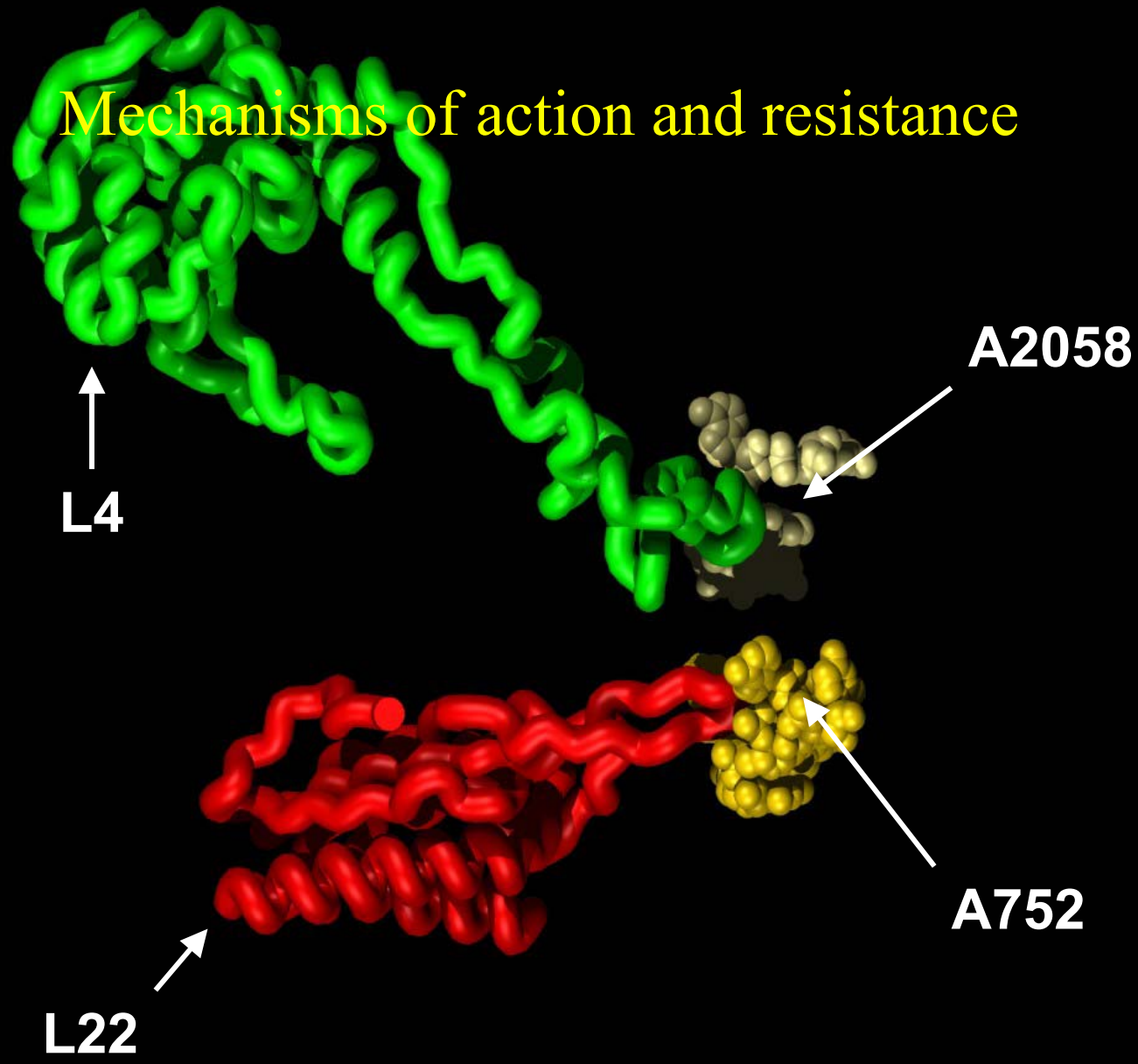
# Mechanisms of action and resistance



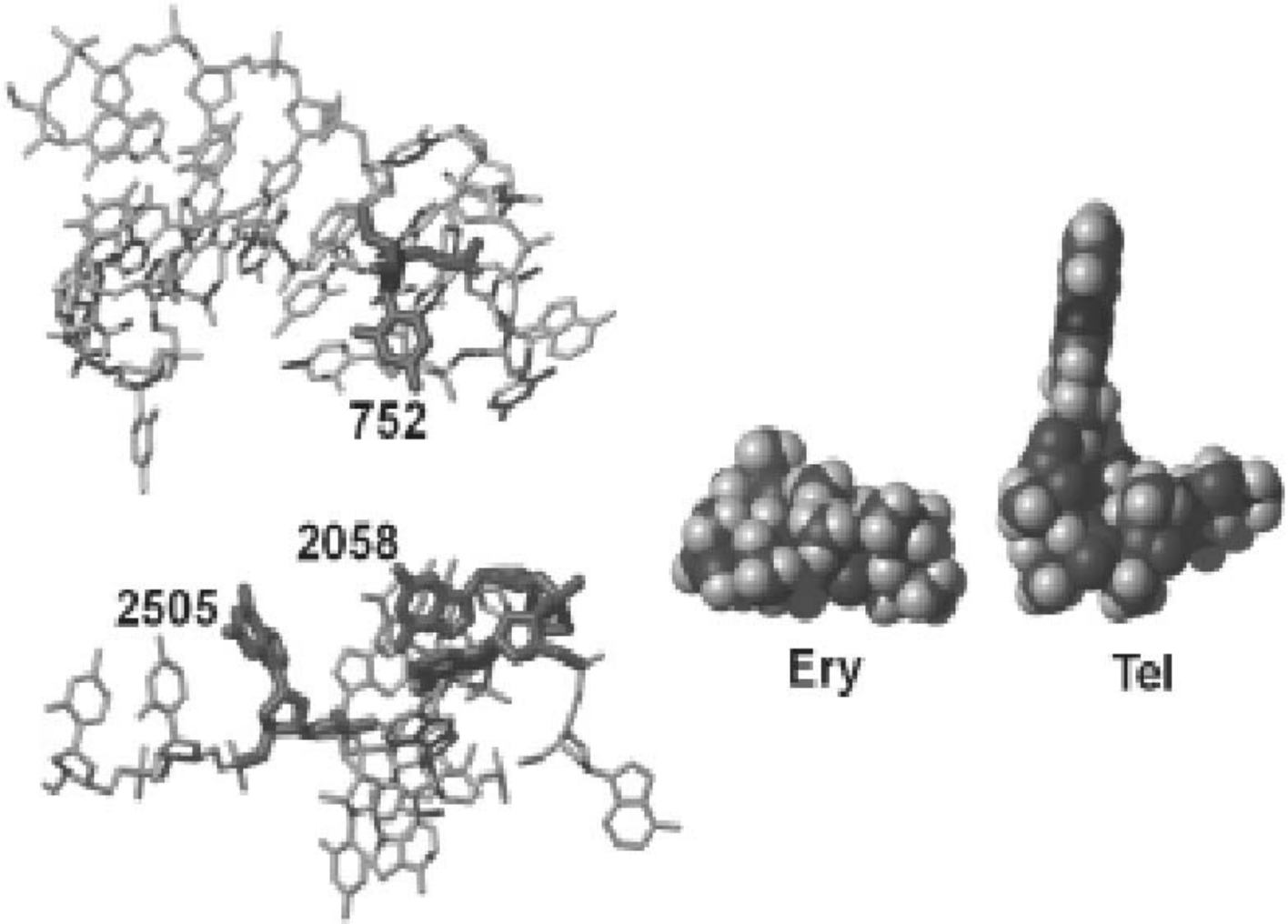
# Mechanisms of action and resistance



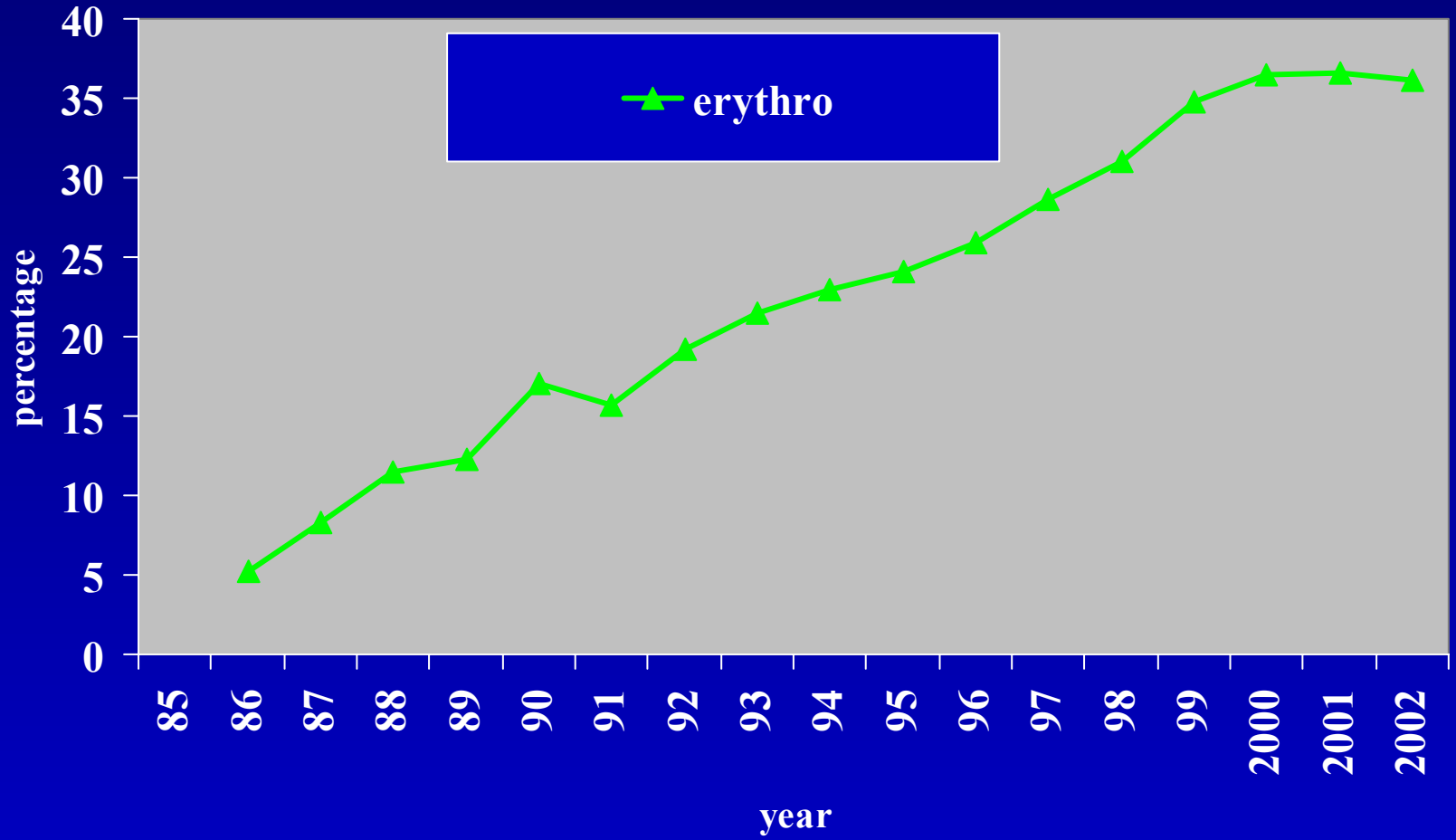
# Mechanisms of action and resistance



# Mechanisms of action and resistance



# Mechanisms of action and resistance : *S. pneumoniae* resistance in Belgium



# Mechanisms of action and resistance

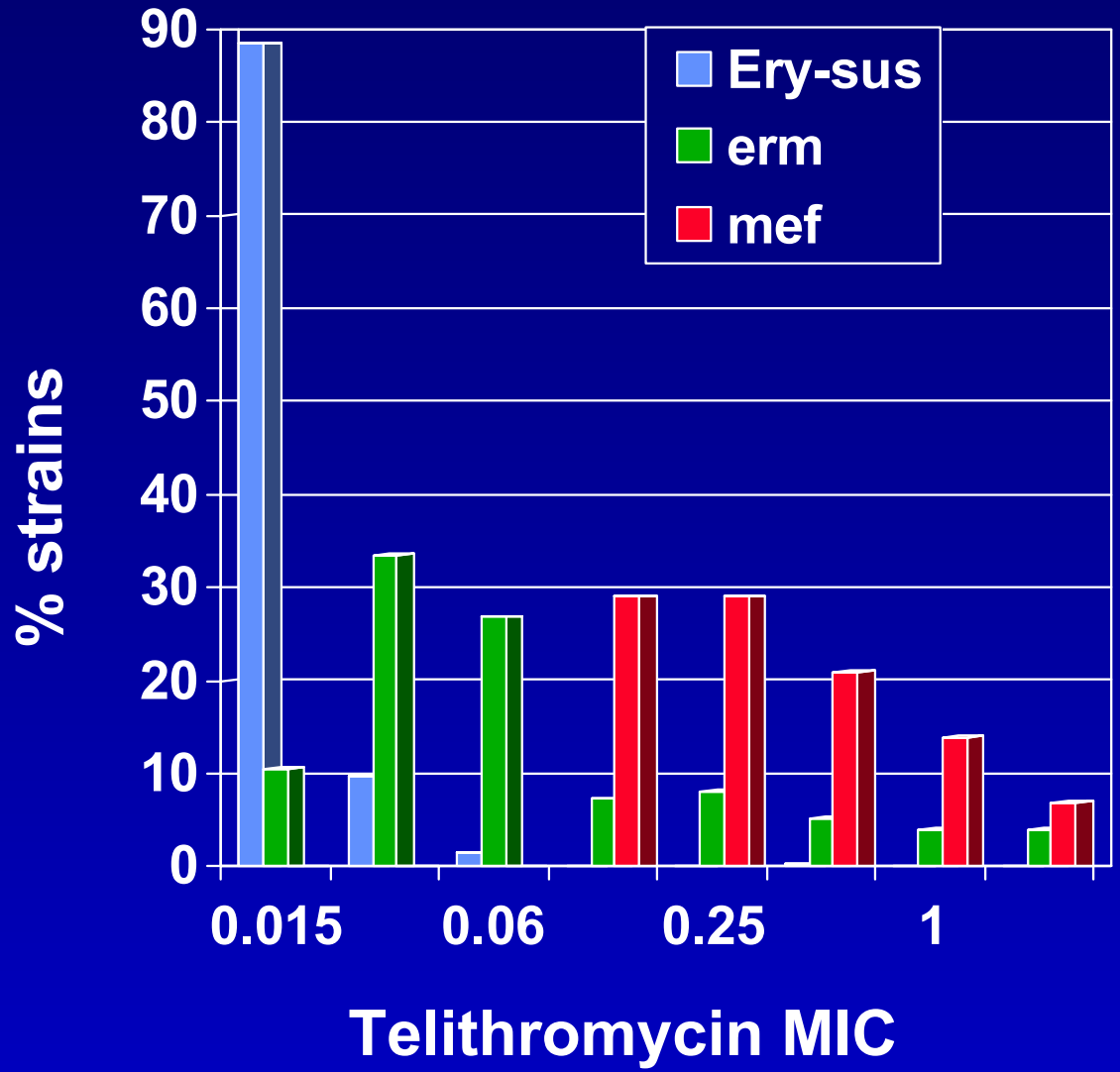
- Target modification
  - Ribosomal modification via inducible or constitutive methylation (*erm* genes)
    - Most frequent mechanism in *S. pneumoniae*, less frequent in *S. pyogenes*
  - Ribosomal modification via point mutations
    - Rare in streptococci, most frequent in *H. pylori, Campylobacter, M. avium*
- Drug efflux (*mef* genes)
    - Most frequent mechanism in *S. pyogenes*, less frequent in *S. pneumoniae*

# Mechanisms of action and resistance

| gene | Phenotype acronym | Phenotype 14-15 macrolides | Phenotype 16 macrolides | Phenotype ketolides |
|---|---|---|---|---|
| *erm* | $MLS_B$ | R | R | S |
| *mef* | M | R | S | S |

# Mechanisms of action and resistance: telithromycin activity in Belgian pneumococci

- 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



# In vitro activity of telithromycin

| | Erythro $MIC_{90}$ | Telithro $MIC_{90}$ | $AUC_{24h}/MIC_{90}$ |
|---|---|---|---|
| *S. pneumoniae* Pen S | 0.06 | 0.015-0.03 | 276-416 |
| *S. pneumoniae* Pen I / R | 16-32 | 0.12-0.5 | 17-25 |
| *H. influenzae* Bla + and - | 4-8 | 2-4 | 2-3 |
| *M. catarrhalis* Bla + and – | 0.25 | 0.06-0.12 | 69-104 |
| *Legionella* spp. | 0.12-2 | 0.03-0.06 | |
| *M. pneumoniae* | <0.01 | 0.06 | |
| *C. pneumoniae* | 0.012-0.25 | 0.25 | |
| *S. pyogenes* | 0.12 | 0.015-0.03 | |

Felmingham, 97, Schülin, 98, Roblin, 98, Barry, 98, Hoban, 99, Pankuch, 98, Reinert, 98, Hamilton-Miller, 98, Karlowsky, 99, Torres, 98

# In vitro activity of telithromycin

| | Erythro $MIC_{90}$ | Telithro $MIC_{90}$ |
|---|---|---|
| *S. aureus* (methi-S) | 2 | 0.12 |
| *S. aureus* (methi-R) | >128 | >128 |
| *E. faecalis* | >128 | 2-4 |
| *E. faecium* | >64 | 8 |
| *Listeria monocytogenes* | 0.5 | 0.06 |
| *U. urealyticum* | 4 | 2 |

Felmingham, 97, Schülin, 98, Roblin, 98, Barry, 98, Hoban, 99, Pankuch, 98, Reinert, 98, Hamilton-Miller, 98, Karlowsky, 99, Torres, 98

# Pharmacokinetics and pharmacodynamics of telithromycin

| | 800 mg (single dose) | 800 mg (7 days) |
|---|---|---|
| $C_{max}$ (mg/L) | 1.9 | 2.3 |
| $C_{24h}$ (mg/L) | 0.03 | 0.07 |
| $AUC_{24h}$ (mg.h/L) | 8.3 | 12.5 |
| $T_{½}$ (h) | 7.2 | 9.8 |

Aventis, 2001

# Pharmacokinetics and pharmacodynamics of telithromycin

| Tissue | Subject | Mean concentration (mcg/mL) | | | | |
|---|---|---|---|---|---|---|
| | | 2-3 h | 6-8 h | 12 h | 24 h | 48 h |
| Epithelial lining fluid | Healthy | 5.4[a] | 4.2[d] | - | 1.17 | 0.30 |
| | RTI patients | 4.9[a] | - | 3.27 | 0.84 | - |
| Alveolar macrophages | Healthy | 65[a] | 100[d] | - | 41 | 2.15 |
| | RTI patients | 69[a] | - | 318 | 162 | - |
| Bronchial tissue [e] | Healthy | 0.68[a] | 2.2[d] | - | 3.5 | LOQ |
| | RTI patients | 3.88[a] | - | 1.41 | 0.78 | - |
| Tonsils [e] | Tonsilitis | 3.95[b] | - | 0.88 | 0.72 | - |
| WBC (Day 5) | Healthy | 64.6[a] | 72.1[c] | 39.4 | 14.1 | - |
| (Day 10) | Healthy | 83[a] | 60.9[c] | 40.6 | 20.9 | 8.9 |

[a]2h, [b]3h, [c]6h, [d]8h, [e] concentrations in mcg/g
LOQ = Below the lower limit of quantification; - = No data collected

*Aventis, data on file*

# Breakpoints for telithromycin (MIC)

| species | susceptible | intermediate | resistant |
|---|---|---|---|
| *S. pneumoniae* | ≤ 1 | 2 | ≥ 4 |
| *S. aureus* | ≤ 1 | 2 | ≥ 4 |
| *H. influenzae* | ≤ 4 | 8 | ≥ 16 |

# CAP clinical studies: efficacy of telithromycin against *S. pneumoniae*

| Telithromycin MIC | N | (presumed) eradicated % | Clinical cure % |
|---|---|---|---|
| 0.004 | 4 | 100 | 100 |
| 0.008 | 125 | 98.4 | 96.8 |
| 0.015/0.016 | 113 | 96.5 | 93.8 |
| 0.3 | 23 | 91.3 | 91.3 |
| 0.6 | 6 | 100 | 100 |
| 0.12 | 6 | 66.7 | 66.7 |
| 0.25 | 1 | 100 | 100 |
| 0.5 | 3 | 100 | 100 |
| 1 | 5 | 100 | 100 |
| total | 286 | 96.5 | 94.8 |

Aventis, 2003

# CAP clinical studies: efficacy of telithromycin against *H. influenzae*

| Telithro MIC | N | (presumed) eradicated % |
|---|---|---|
| 0.002 | 1 | 100 |
| 0.12 | 1 | 100 |
| 0.25 | 3 | 100 |
| 0.5 | 5 | 60 |
| 1 | 47 | 87.2 |
| 2 | 96 | 89.6 |
| 4 | 40 | 87.5 |
| 8 | 11 | 100 |
| total | 204 | 88.7 |

Clinical cure: 90.2%

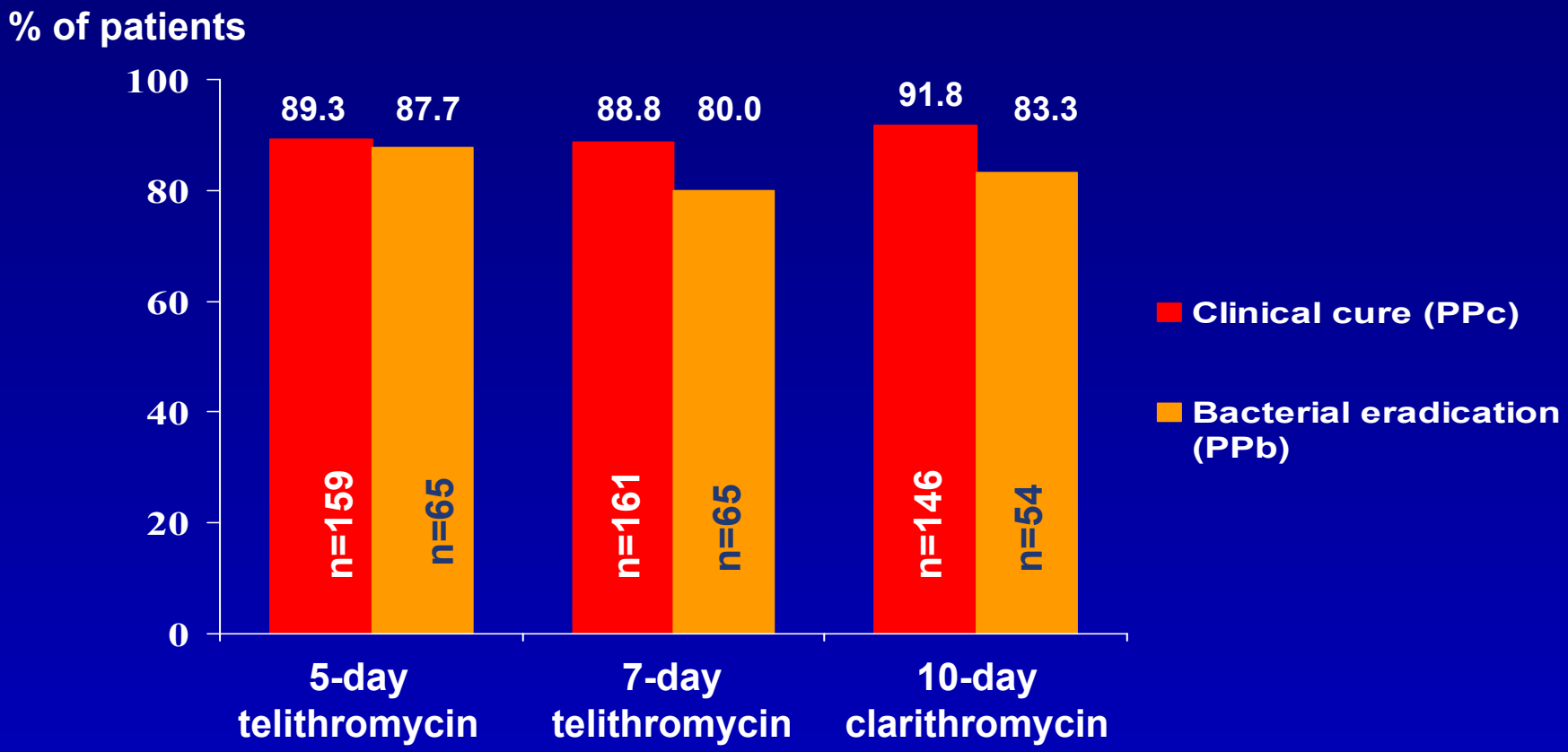
Aventis, 2003

# Summary of telithromycin efficacy in CARTIs from Phase IIIa studies

- Efficacy results consistent across all populations in all studies in four indications
- 5-day treatment effective in AECB, AMS, and tonsillitis/pharyngitis vs 10-day treatment with comparators
- 7- to 10-day treatment effective in CAP vs 10-day treatment with comparators
- Effective in infections caused by penicillin- and/or erythromycin-resistant *S. pneumoniae*

Balfour JA and Figgit DP. Drugs 2001; 61(6):815-29

# Efficacy of short-course telithromycin in treatment of CAP




Tellier et al. 42nd ICAAC San Diego. Abstract
Pullman et al. 42nd ICAAC San Diego. Abstract

# summary

- telithromycin offers alternative to existing therapies in RTI but additional data on activity against *H. influenzae* needed
- telithromycin still active on erythromycin-R streptococci, although MIC's are increased
- No significant resistance to telithromycin reported yet and potential for resistance selection *in vitro* lower than macrolides but long half-life is known to predispose to resistance development in macrolides

# contents

- Ketolides
- Fluoroquinolones
  - The fluoroquinolone family
  - Mechanisms of action and resistance
  - In vitro activity
  - Pharmacokinetics and pharmacodynamics
  - Clinical trials
- Treatment of RTI and place of ketolides and FQ's

# The fluoroquinolone family

| | | |
|---|---|---|
| GROUP I | oral<br>limited to UTI | Norfloxacin |
| GROUP II | broad<br>systemic use | Ciprofloxacin<br>Ofloxacin<br>Pefloxacin |
| GROUP III | improved vs.<br>Gram-pos.<br>atypicals | Levofloxacin<br>Sparfloxacin<br>Grepafloxacin |
| GROUP IV | improved vs.<br>Gram-pos.<br>atypicals<br>anaerobes | Gatifloxacin<br>Trovafloxacin<br>Moxifloxacin<br>Clinafloxacin |

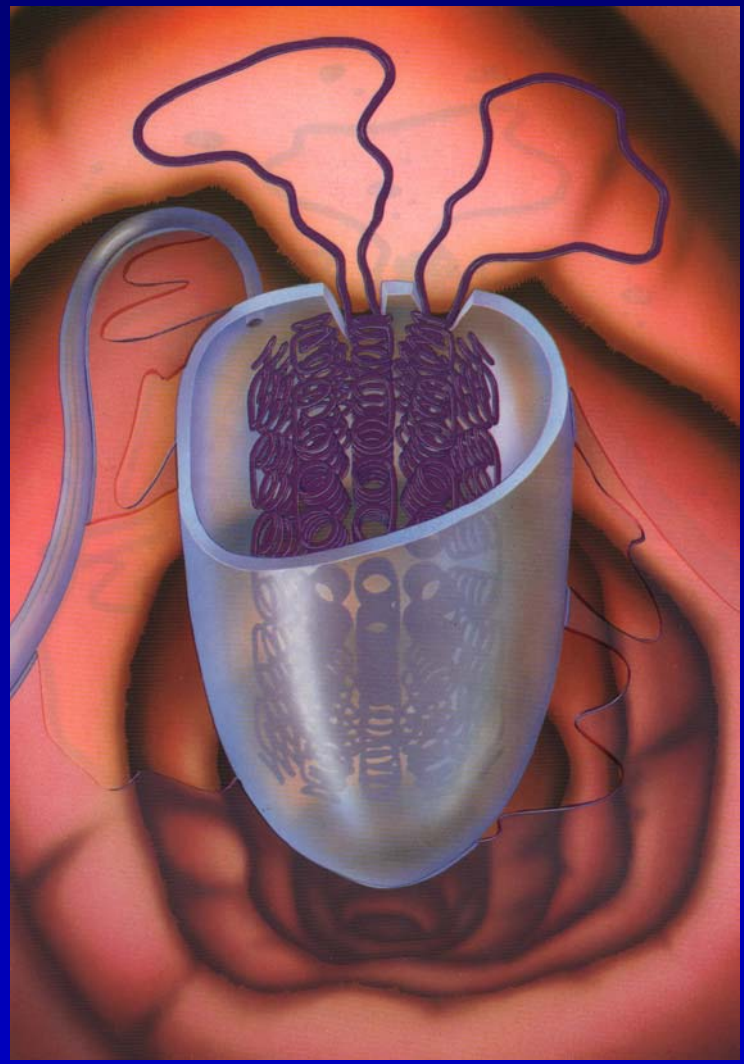
Int J Antimicrob Ag 1998;10:255-257

# Mechanisms of action and resistance

- all FQ's kill bacteria rapidly by binding to enzymes that are needed to wind or unwind DNA
  - ➡ topoisomerase II or gyrase
    - encoded by *gyrA* and *gyrB*
  - ➡ topoisomerase IV
    - encoded by *parC* and *parE*

# Mechanisms of action and resistance

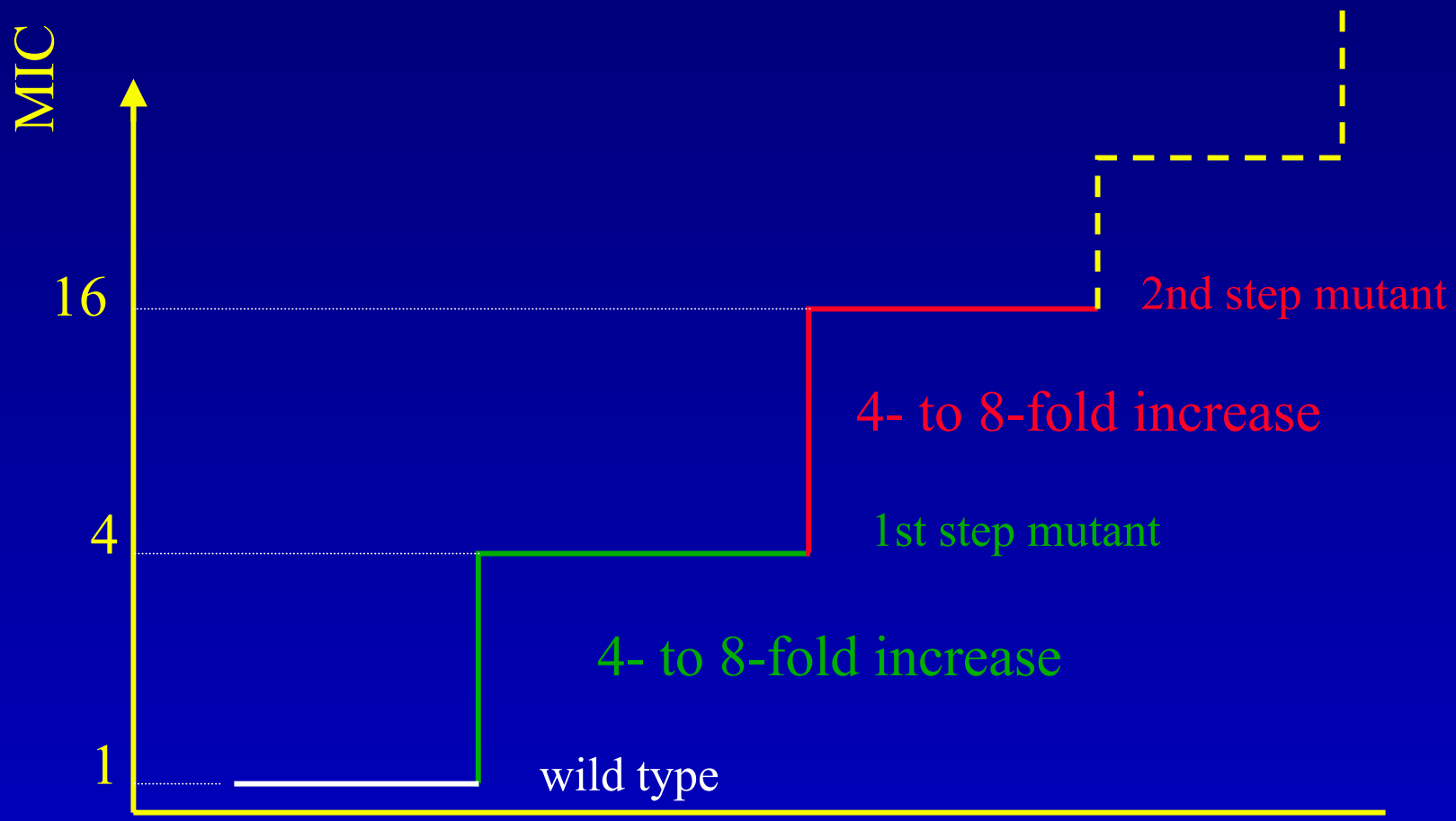
## DNA is supercoiled



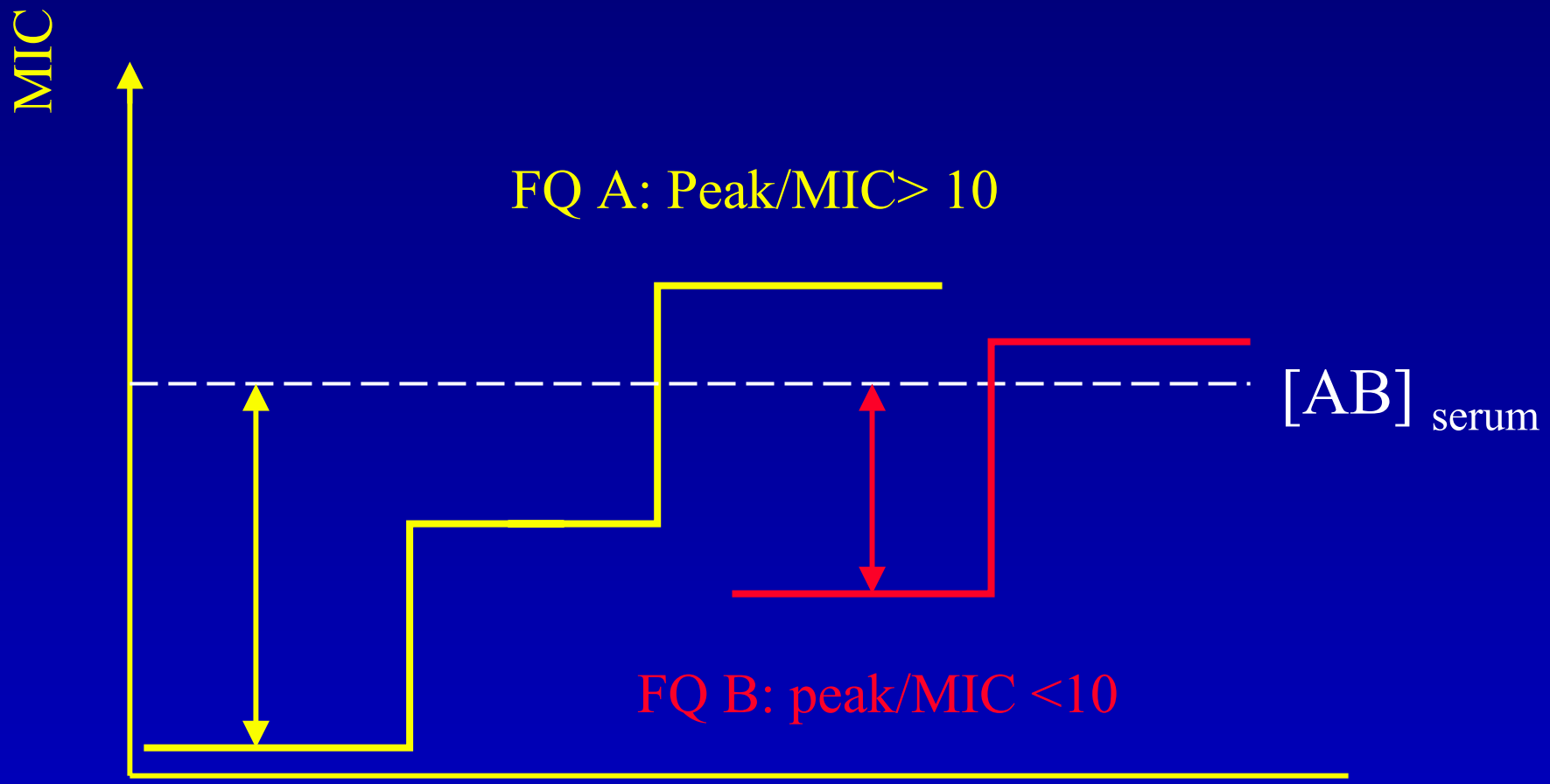
# Mechanisms of action and resistance

- 1) target modification
  - most common mechanism of resistance to FQ's
  - due to point mutations in 'hot spots' (**Q**uinolone **R**esistance **D**etermining **R**egions) mostly of *gyrA* and *parC*
  - spontaneous mutations in these regions appear with constant frequency during bacterial cell division
    - 1 per $10^6$ to 1 per $10^9$ cell divisions
- 2) efflux

# resistance development & selection: stepwise increase



# resistance development & selection: risk of emergence of resistance



# resistance development & selection: effect of specific mutations

| | cipro | levo | moxi |
|---|---|---|---|
| wild-type | 0.5* | 0.5* | 0.12* |
| *gyrA* mutant | 2* | 2* | 0.25* |
| *gyrA* + *parC* mutant | 16* | 16* | 2* |

*: MIC in mg/L for *S. pneumoniae* R6

Hartman-Neuman et al, AAC, 2001

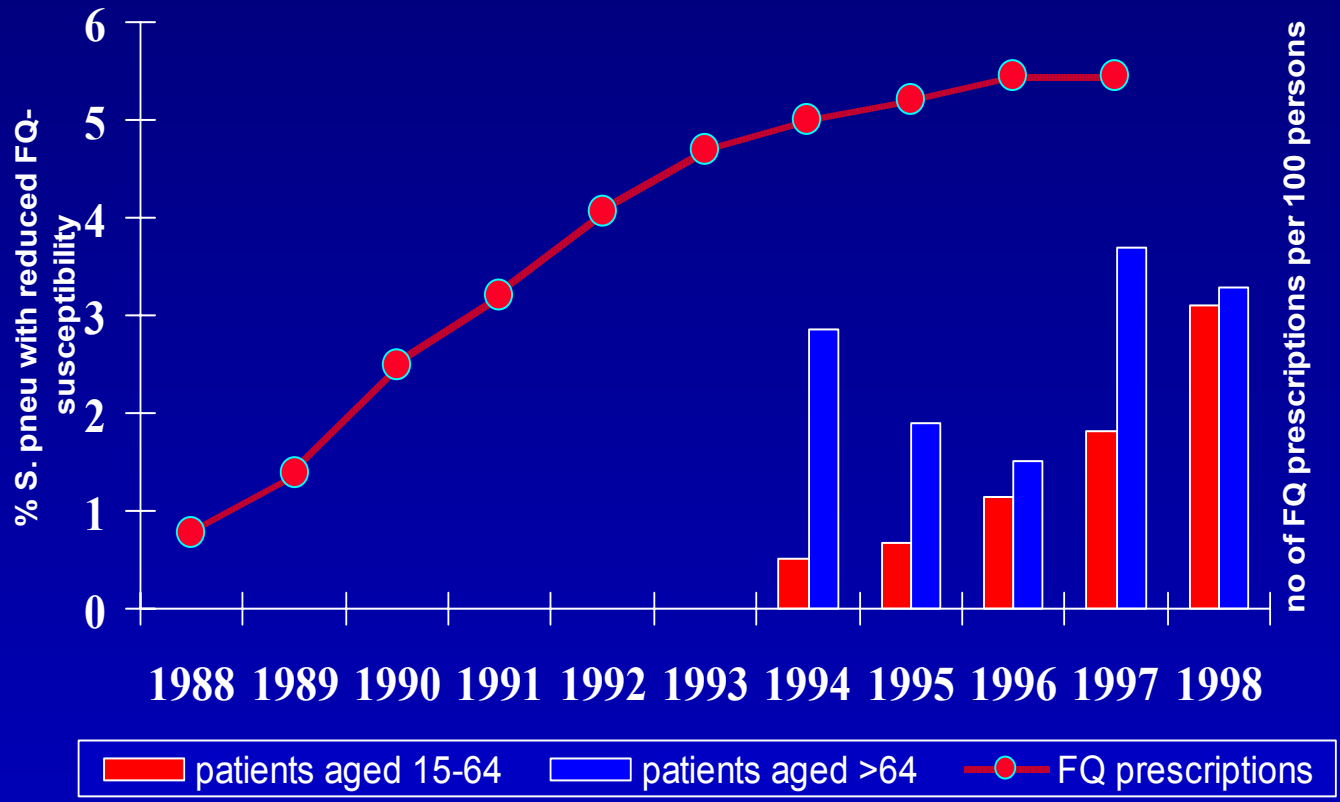
# resistance development & selection: peak concentration / MIC

| | $MIC_{90}$ *S. pneumoniae* | Peak serum value Single unit dose |
|---|---|---|
| cipro | 1(-2) | 3-4 |
| oflox | 2 | 4-5 |
| levo | 1 | 5 |
| moxifloxacin | 0.12 | 4-5 |

Bivemox, 2001
Fung-Tomc et al , AAC, 2000

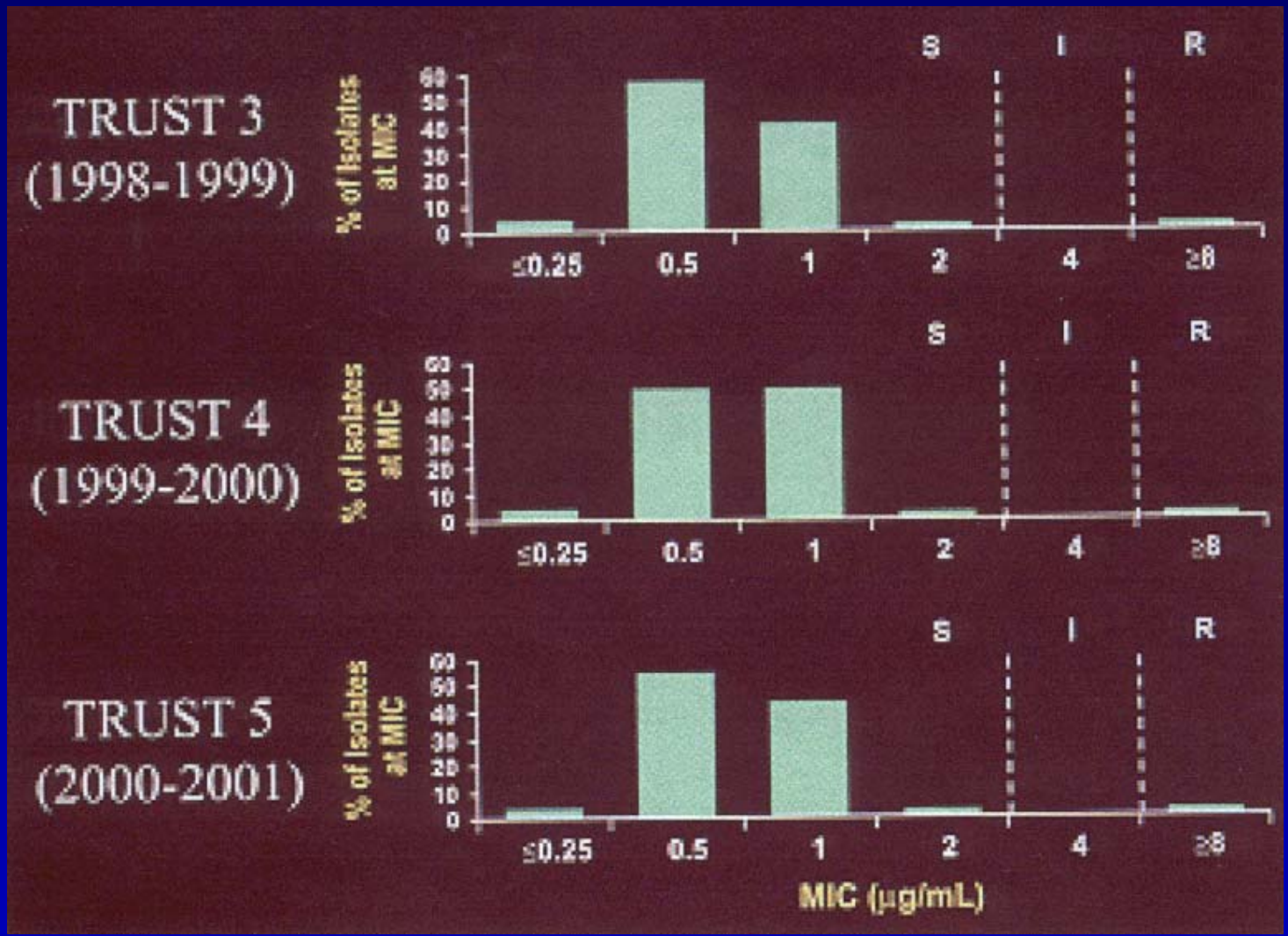
# epidemiological data on FQ resistance development

*decreased FQ-susceptibility in S. pneumoniae in Canada*




Chen et al. NEJM '99

# Epidemiological data – USA




levofloxacin MIC distribution for S. pneumoniae

TRUST study

# Clinical data on resistance development

**TABLE 1.** MICROBIOLOGIC CHARACTERISTICS OF *STREPTOCOCCUS PNEUMONIAE* ISOLATED BEFORE, DURING, OR AFTER THERAPY WITH ORAL LEVOFLOXACIN FROM FOUR PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA.*

| PATIENT NO. | SOURCE AND TIME OF CULTURE | SEROTYPE | PFGE PATTERN† | SUSCEPTIBILITY TO LEVOFLOXACIN‡ | MINIMAL INHIBITORY CONCENTRATION§ | | | AMINO ACID SUBSTITUTION | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | LEVOFLOXACIN | MOXIFLOXACIN | GATIFLOXACIN | IN PARC | IN GYRA |
| | | | | | μg/ml | | | | |
| 1 | Sputum, before treatment | 23F | A | S | 1 (S) | 0.12 (S) | 0.25 (S) | — | — |
| | Sputum, after treatment | 23F | A | R | 8 (R) | 1 (S) | 2 (I) | S79F | S81F |
| 2 | Sputum, before treatment | 6A | B | S | 4 (I) | 0.25 (S) | 0.5 (S) | S79F | — |
| | Sputum, during treatment | 6A | B | R | 16 (R) | 4 (R) | 4 (R) | S79F | S81F |
| 3 | Blood, before treatment | 14 | C | R | 16 (R) | 4 (R) | 2 (I) | S79F | S81Y |
| | Pleural fluid, during treatment | 14 | C | R | 16 (R) | 4 (R) | 2 (I) | S79F and D83Y | S81Y |
| 4 | Sputum, during treatment | ND | ND | R | 16 (R) | 4 (R) | 8 (R) | S79Y | E85K |

*PFGE denotes pulsed-field gel electrophoresis, S susceptible, R resistant, I having intermediate susceptibility, and ND not done. Dashes indicate that no mutation was found.

†Unique PFGE patterns are designated by arbitrary single letters.

‡Susceptibility was tested by the disk-diffusion method.

§The degree of susceptibility is indicated in parentheses.

Davidson, N Eng J Med, ’02, 346, 747

# resistance development & selection:

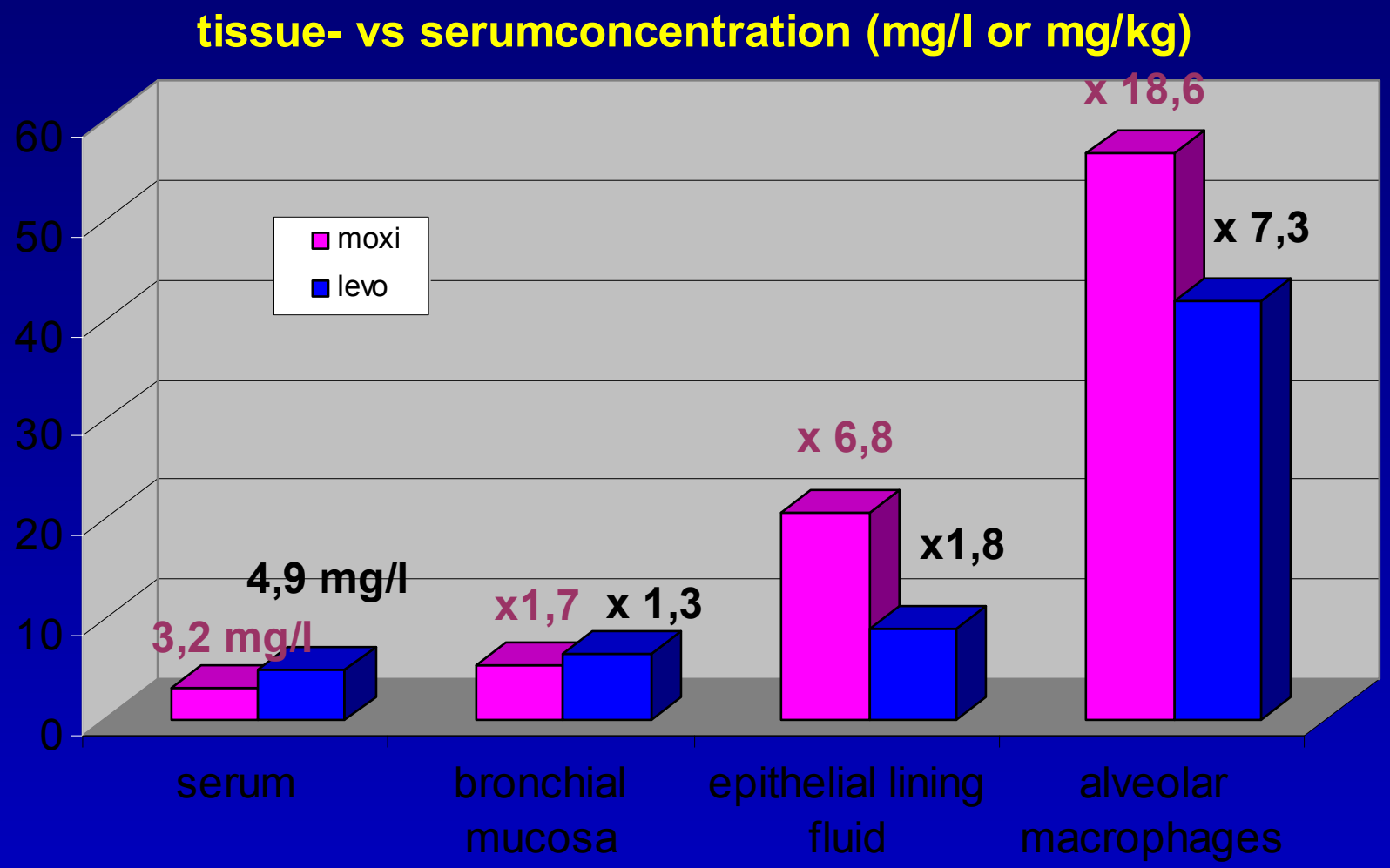
- peak/MIC > 10 prevents resistance development
- less potent FQ's will select first step mutants that will compromise more potent FQ's
- resistance mutations affect all FQ's, but to different extents
- differences in FQ resistance development are the result of different targets and different susceptibilities to efflux
- more potent FQ's select less resistance than less active FQ's

# In vitro activity

| | Cipro $MIC_{90}$ | levo $MIC_{90}$ | moxi $MIC_{90}$ |
|---|---|---|---|
| *S. pneu* – Peni S | 1-2 | 1 | 0.12 |
| *S. pneu* - Peni I or R | 1-2 | 1 | 0.12 |
| *H. influenzae* Bla + and - | 0.015 | 0.03 | 0.03 |
| *M. catarrhalis* Bla + and - | 0.015 | 0.12 | 0.12 |
| *Legionella spp.* | 0.12 | 0.015 | 0.015 |
| *M. pneumoniae* | 0.5-8 | 0.5 | 0.12 |
| *C. pneumoniae* | 1-2 | 0.12 | 0.12 |
| *S. pyogenes* | 1-2 | 1 | 0.12 |

Blondeau, Miravitlis, Fuchs, Adis, Verhaegen

# Pharmacokinetics and pharmacodynamics : tissue penetration



# Summary of moxifloxacin efficacy in CARTIs from Phase III studies

- 5 days treatment effective in AECB vs 7 – 10 days treatment with comparators; more rapid reduction of symptoms compared to macrolides
- 10 days treatment with 400 mg moxi PO effective in CAP vs 10 days treatment with comparators
- TARGET study: switch from IV to PO moxi in CAP more effective clinically/bacteriologically than co-amoxyclav +/- clarithro IV to PO
- 7 and 10 days moxi effective in AMS vs 10 days treatment with comparators

# Treatment of RTI and place of ketolides and FQ's : Key issues

- CAP
  - *S. pneumoniae* is the most frequent pathogen in CAP and must be covered in all patients
  - *S. pneumoniae* resistance in Belgium is predominantly of the intermediate type and can be effectively treated with adequately dosed β-lactams.
  - Conflicting evidence regarding presence and pathogenic role of atypical bacteria in CAP. No effect on outcome in CAP I, II and III if not covered empirically
  - β-lactams remain preferred treatment for CAP

# Treatment of RTI and place of ketolides and FQ's : Key issues

- AECB
  - ➡ Limited number of studies available
  - ➡ Antibiotics probably effective in severe patients

    Cost-effective ?
  - ➡ Type of AB :
    - shift in bacterial resistance
    - consequence for patients and community
  - ➡ Alternative approaches

# Telithromycin: indications in Belgium

- CAP:
  - alternative treatment in CAP I in case of IgE-mediated allergy or intolerance to β-lactams
  - more data needed on activity against *H. influenzae* in CAP II

# Telithromycin: indications in Belgium

- AECB:
  - further studies needed to confirm activity against *H. influenzae* in severe cases, to evaluate impact on infection-free interval and long term post-therapy costs
- AMS/ pharyngitis-tonsillitis:
  - no indications; existing treatment options suffice

# Fluoroquinolones: indications in Belgium

- CAP:
  - alternative treatment in CAP I in case of IgE-mediated allergy or intolerance to β-lactams
  - alternative treatment in CAP II in case of IgE-mediated allergy or intolerance to β-lactams or if no improvement after 3 days of β-lactams
  - Preferred treatment In CAP III when oral treatment possible and alternative treatment in CAP III in case of IgE-mediated allergy or intolerance to β-lactams or if no improvement after 3 days of β-lactams

# Fluoroquinolones: indications in Belgium

- AECB:
  - Alternative treatment in severe AECB in case of IgE-mediated allergy or intolerance to β-lactams or in case of clinical failure with first-line antibiotics (β-lactams)
- AMS/ pharyngitis-tonsillitis:
  - no indications; existing treatment options suffice