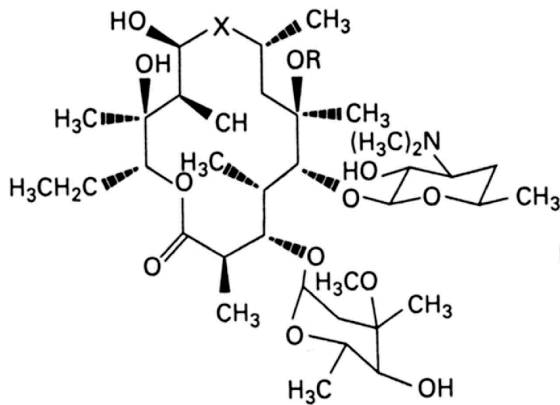


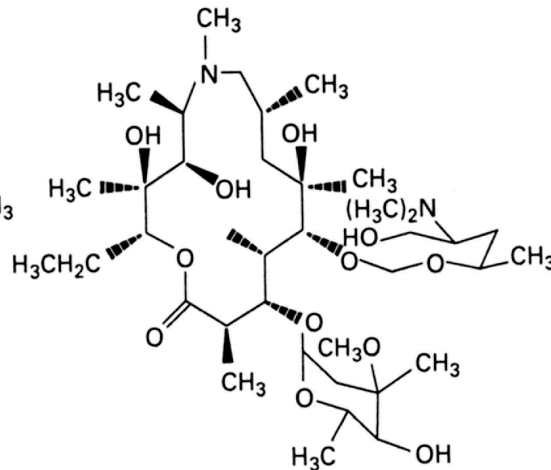
Macrolides

The macrolide family ...

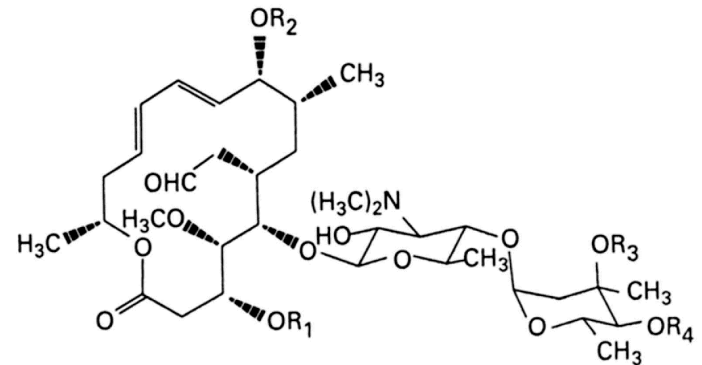
14-Membered



15-Membered



16-Membered



erythromycin

- roxithromycin
- clarithromycin
- dirithromycin

azithromycin

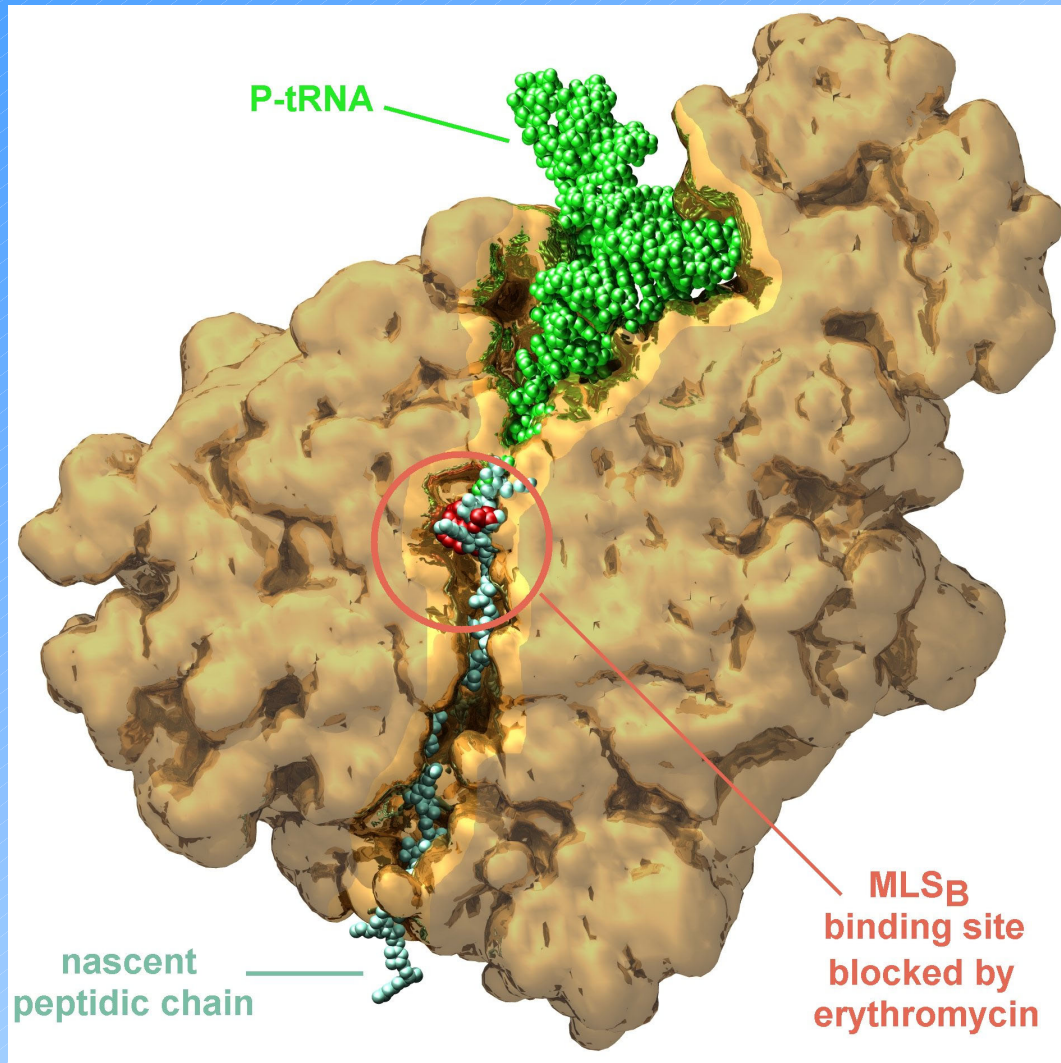
- telithromycin

josamycin

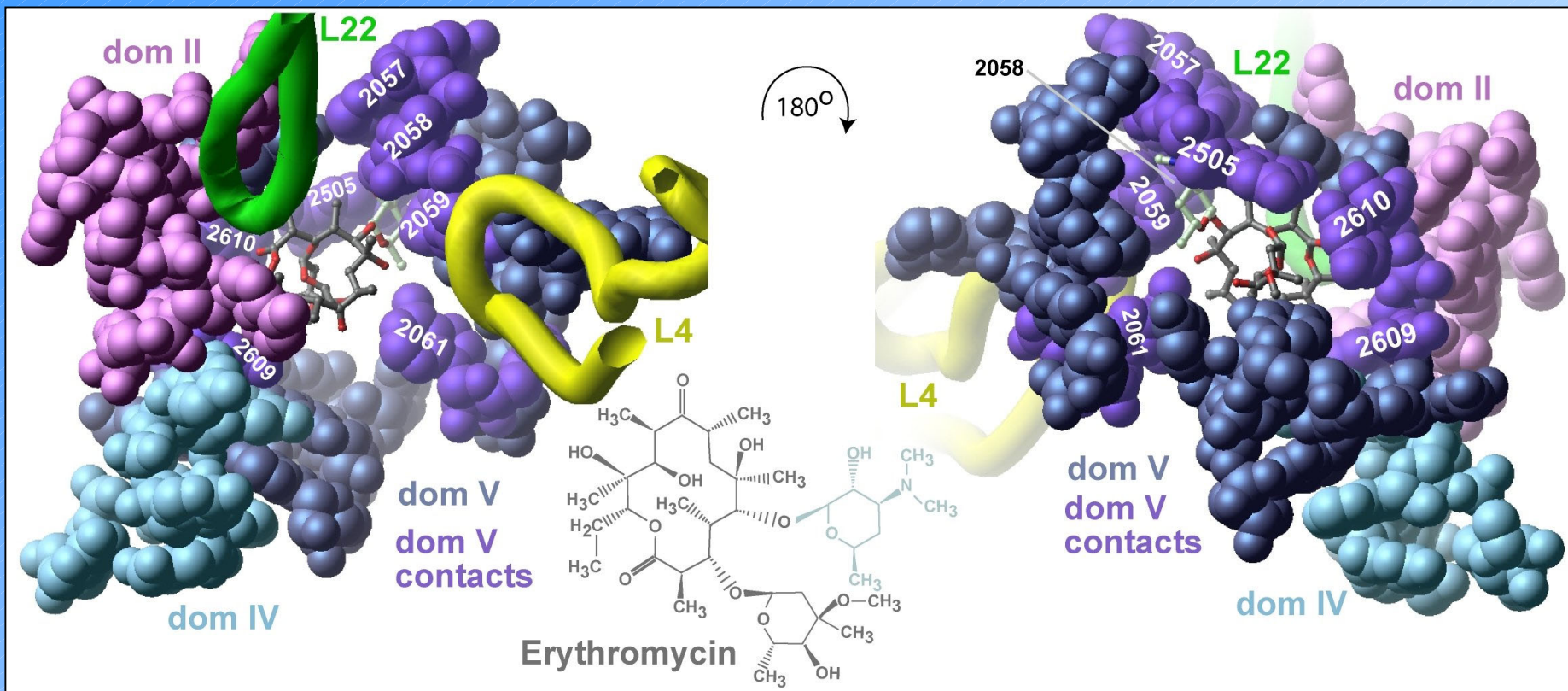
spiramycin
miocamycin

Coming soon !!

Erythromycin: mode of action



Erythromycin: mode of action



Erythromycin: spectrum of activity

Erythromycin A : mostly Gram (+) organisms

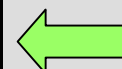
Plus:

- ***Legionella p.***
- ***Chlamydia spp.***
- ***Mycoplasma spp.***
- ***Mycobacterium avium***

Erythromycin - MIC distributions of isolates that lack resistance mechanisms

Mg/L	.004	.008	.016	.032	.064	.125	.25	.5	1	2	4	8	16	32	≥64
S.aureus					●	●	●	●							
Coag-neg staph				●	●	●									
S.saprophyticus				●	●	●									
Streptococcus_A				●	●	●									
Streptococcus_B				●	●	●									
Pneumococci				●	●	●									
Strept misc			●	●	●	●									
Enterococcus						●	●	●	●	●					
Listeria						●	●	●							
Corynebacteria				●	●	●									
Bacillus spp				●	●	●									
H.influenzae								●	●	●	●	●			AST
M.catarrhalis					●	●	●								
B.pertussis						●	●	●	●						
P.multocida											●	●	●		
L. pneumophila						●	●	●	●						
Camp. jejuni						●	●	●							
N.gonorrhoeae			●	●	●	●									
N.meningitidis					●	●	●	●							
M.pneumoniae	●	●	●	●											
Borr. burgdorferi				●	●	●									

+



SRGA and SRGA- M, 1998-04-13, 2001-11-11

G Kahlmeter & B.Olsson-Liljequist

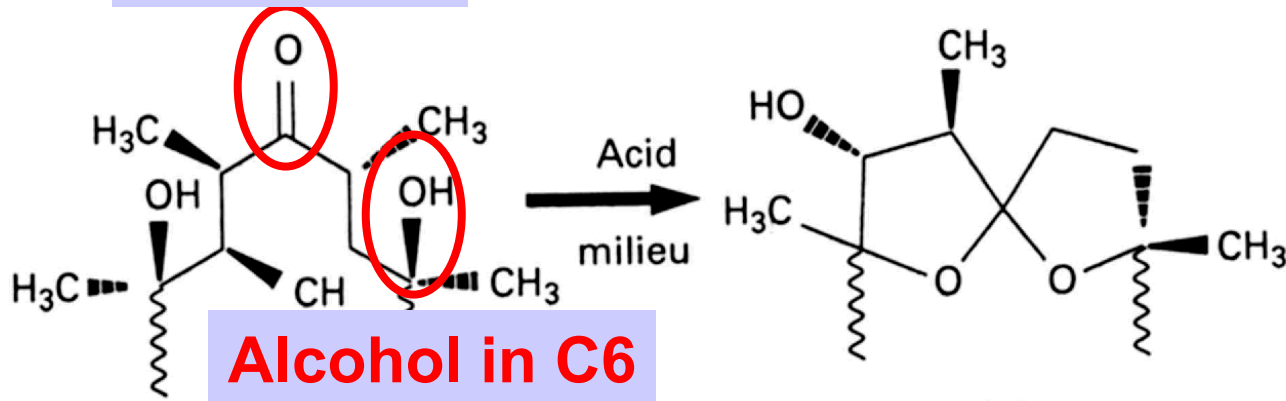
Erythromycin: the problems

Erythromycin A

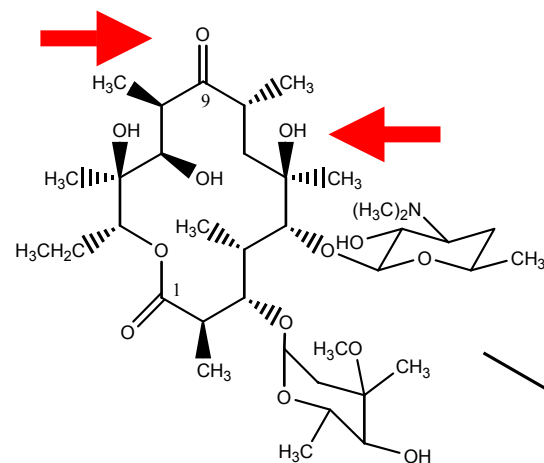
14 atoms

Instability in acid media

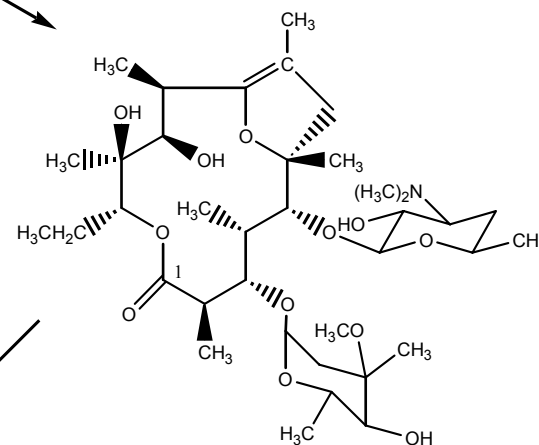
Keto in C9



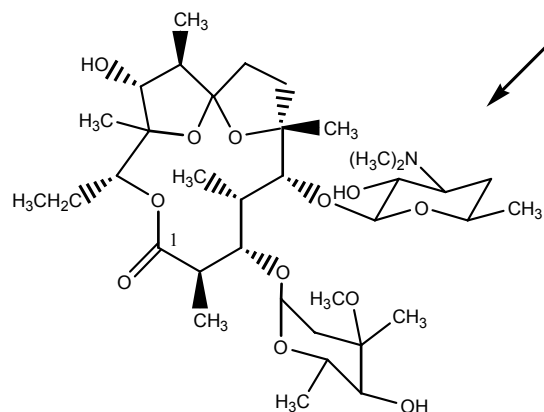
Erythromycin: details of acid the degradation



ERYTHROMYCIN

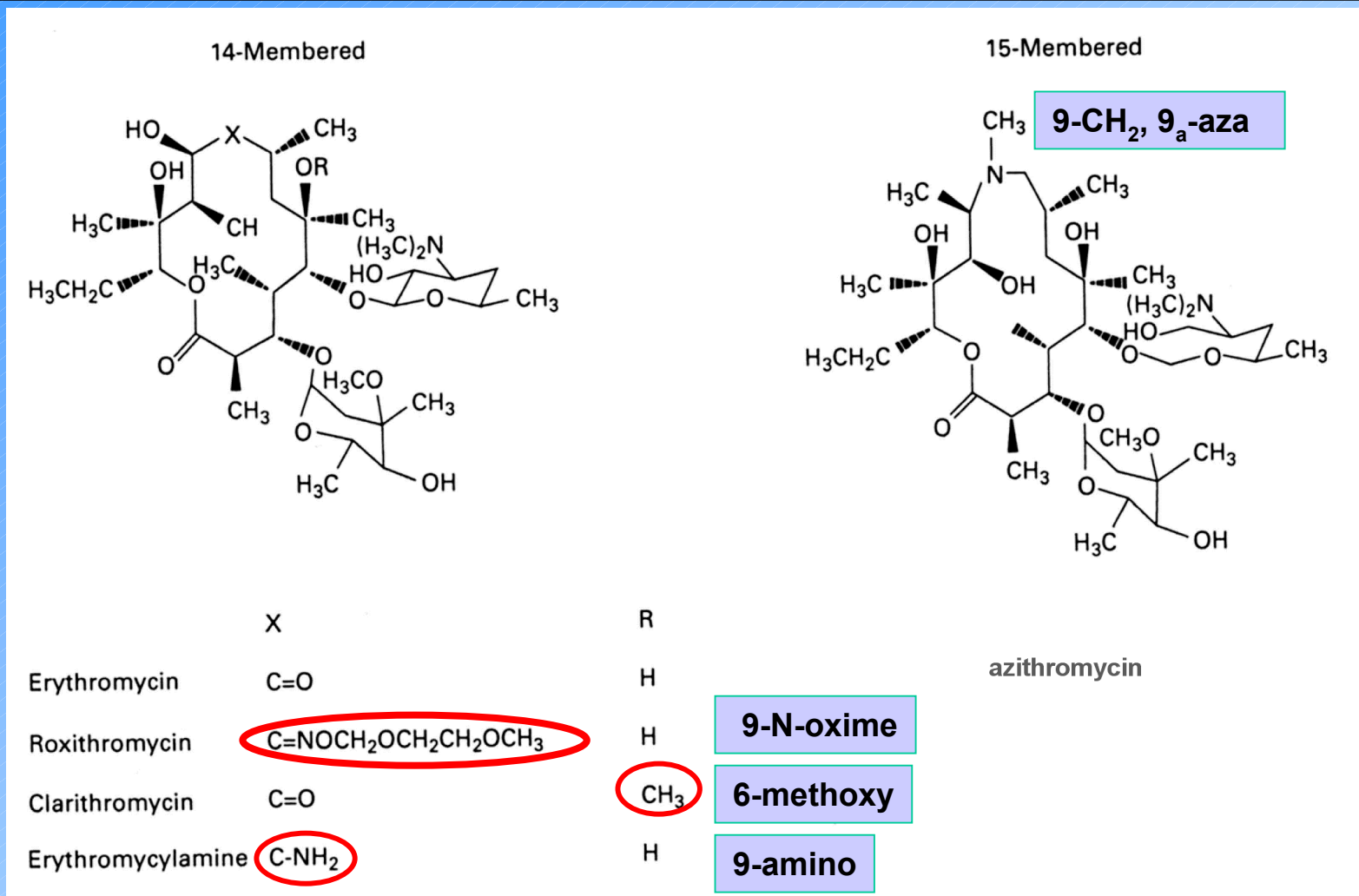


8,9-anhydroerythromycin-6,9-hemi ketal

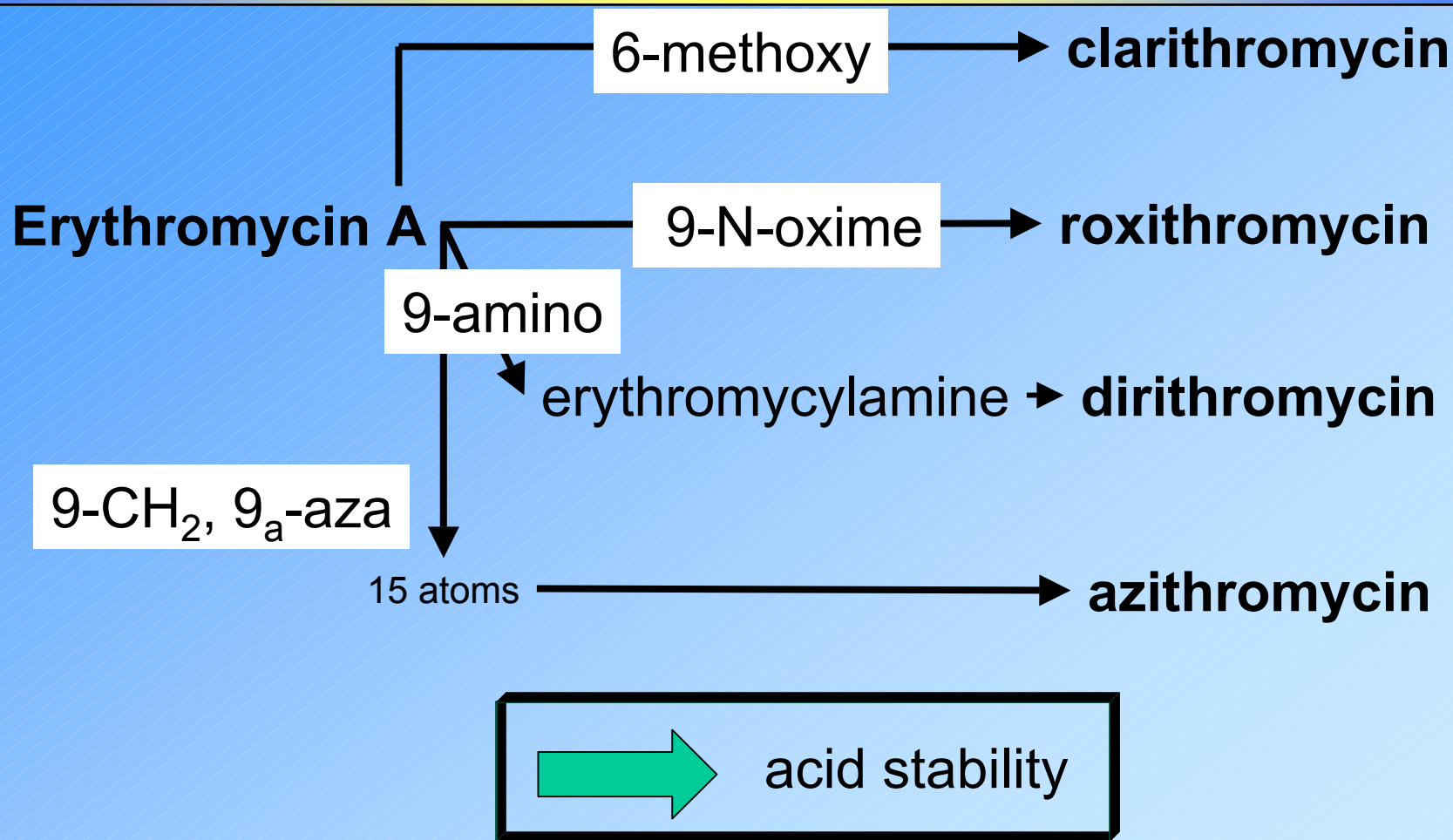


**erythromycin-6,9;9-12
-spiroketal**

What have the chemists done to avoid acid-instability ?



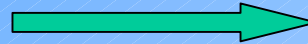
What have the chemists done to avoid acid-instability ?



Did these modifications change anything else in PK ?

clarithromycin

roxithromycin



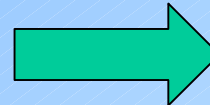
higher tissue
accumulation

dirithromycin

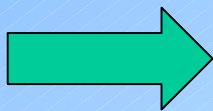
azithromycin



dibasic



**much
higher tissue
accumulation**



pharmacokinetic differentiation

Did these modifications change anything else ?

Cytochrome P₄₅₀ interactions

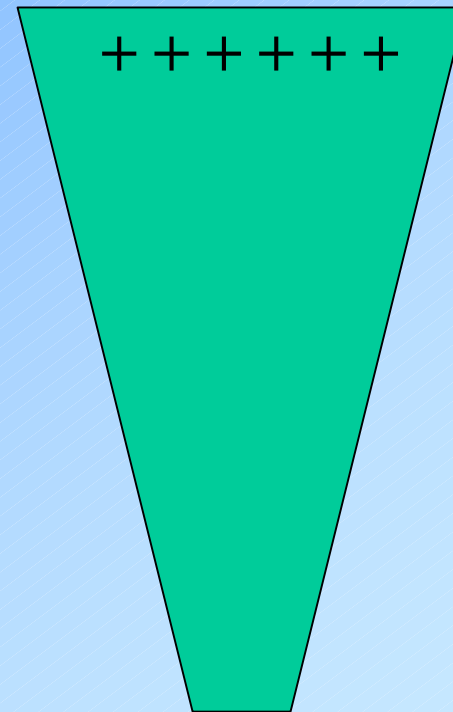
erythromycin A

clarithromycin

roxithromycin

dirithromycin

azithromycin



Drug interactions with macrolides

- The main problem due to interactions between some macrolides and the cytochrome P 450 system, especially the CYP3A subclass of enzymes
- Finally results in lowered metabolism of CYP3A-dependent drugs

drug	azi	clari	diri	ery	josa	mid	roxi	spira
théophyllin	0	0	0	++	+	ND	0/+	0
ciclosporin	ND	ND	ND	+++	+++	+++	+	0
carbamazepin	ND	0/+	ND	+++	+	+	0/+	0/+
midazolam	0	++	ND	++	ND	ND	+	ND
warfarin	0	ND	ND	+	ND	ND	0	ND
terfenadin	0	++	ND	+++	0/+	ND	0	ND
cisapride	ND	++	ND	++	++	ND	ND	0

From Petitjean et al.

N=undocumented

Mainly considered as a class-effect, resulting from what is known for erythromycin, except for spira and azithromycin

Basic indications of (classical) macrolides in a world of no resistance

erythromycin

clarithromycin

roxithromycin

dirithromycin

azithromycin

Respiratory tract infections

- pharyngitis
- otitis
- sinusitis
- acute exacerbations of chronic bronchitis
- community acquired pneumonia
- legionellosis
- *C. pneumoniae*
- *Mycobacterium avium* (AIDS)

Genital/Ocular infections

- chlamydiosis (*C. trachomatis*)
- syphilis
- donovanosis
- gonorrhea

Gastric ulcer (*H. pylori*)

Which is the best ?

erythromycin

clarithromycin

roxithromycin

dirithromycin

azithromycin



But what has been the problem ?

erythromycin

clarithromycin

roxithromycin

dirithromycin

azithromycin



Emergence of resistance

Target modification: erm

Efflux: Mef

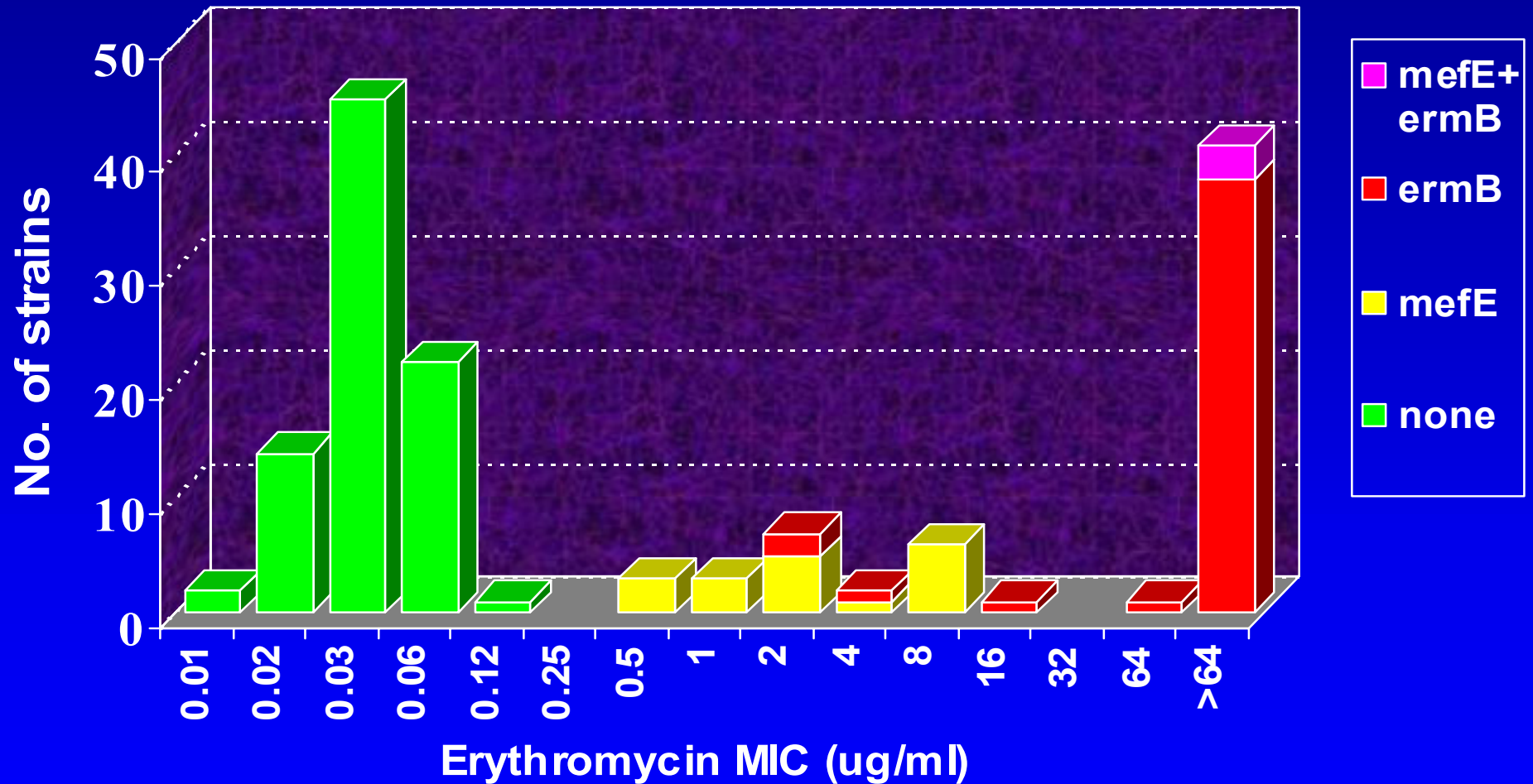


All are similarly affected

Mechanisms of macrolide resistance

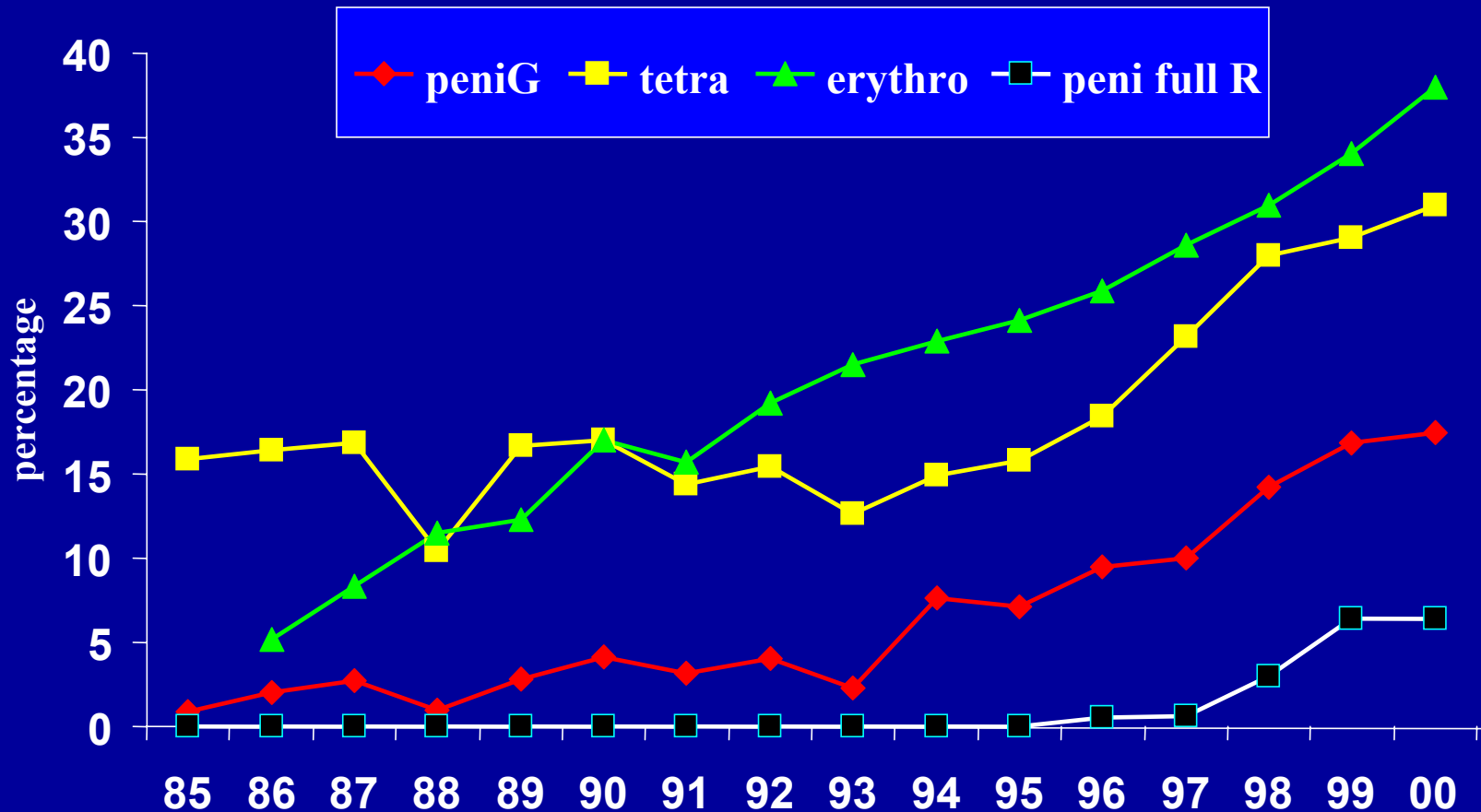
- **Ribosomal modification by methylase (*erm* genes)**
 - *S. pneumoniae*: *erm*(B) 75-100% of Ery-R strains in Europe
 - *S. pyogenes*: *erm*(B) generally <50% of Ery-R strains
erm(A)
- **Ribosomal modification by mutation (rRNA, proteins)**
 - Occasional in Ery-R *S. pneumoniae*
 - Rare in Ery-R *S. pyogenes* (up to 18% in Eastern Europe)
 - The only mechanism or highly prevalent in *H. pylori*,
Campylobacter, *M. avium*
- **Drug efflux (*mef* genes)**
 - <25% in Ery-R *S. pneumoniae*
 - >50% in Ery-R *S. pyogenes* (up to 95%)

Correlation between erythromycin MICs and resistance mechanisms



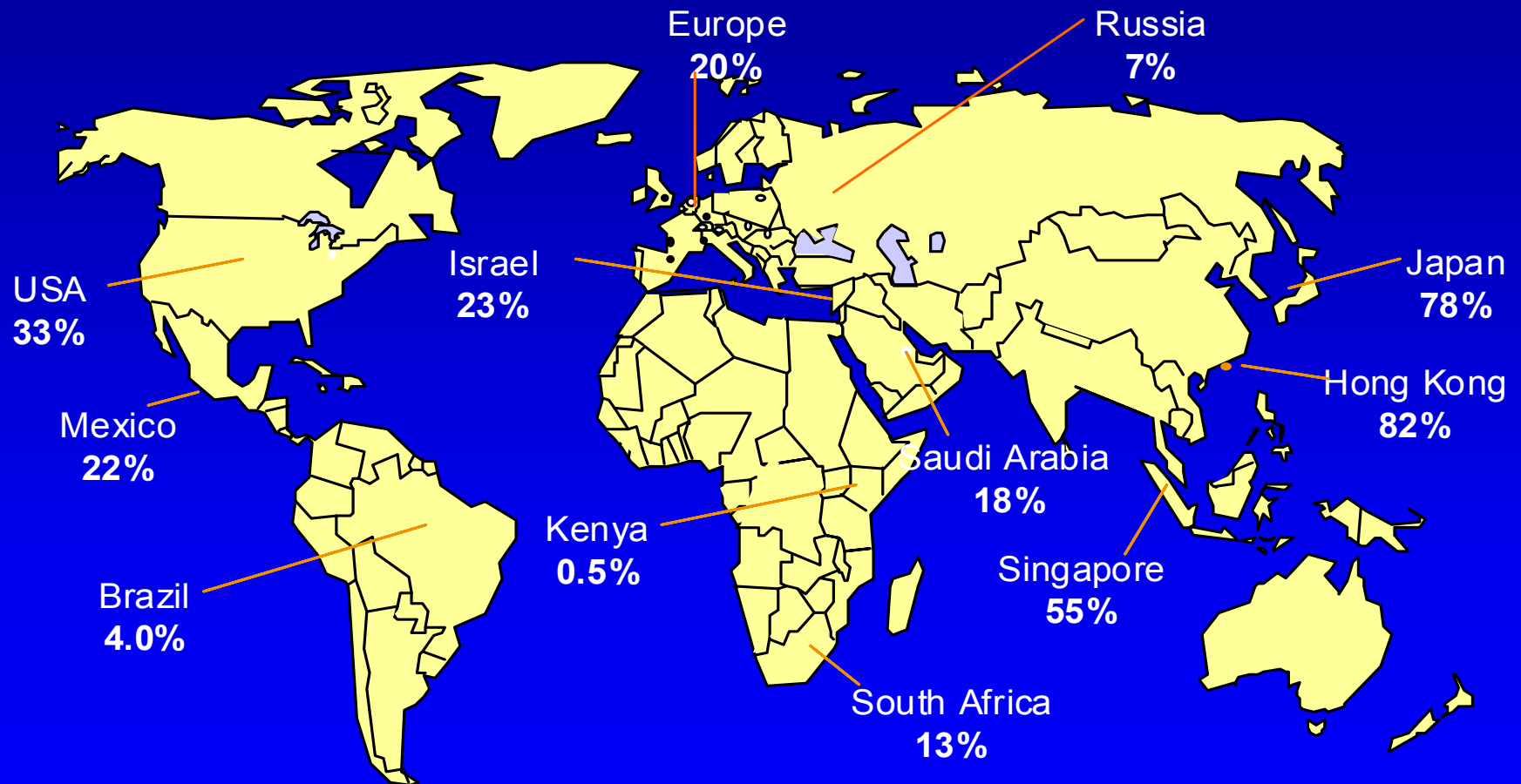
Nagai ICAAC 2000, abstr # 892

One example: the evolution of *S. pneumoniae* resistance in Belgium between 1985 and 2000



J. Verhaegen, Central Pneumococci Reference Laboratory, Louvain

The Alexander Project 1999: *S. pneumoniae*, Macrolide Resistance



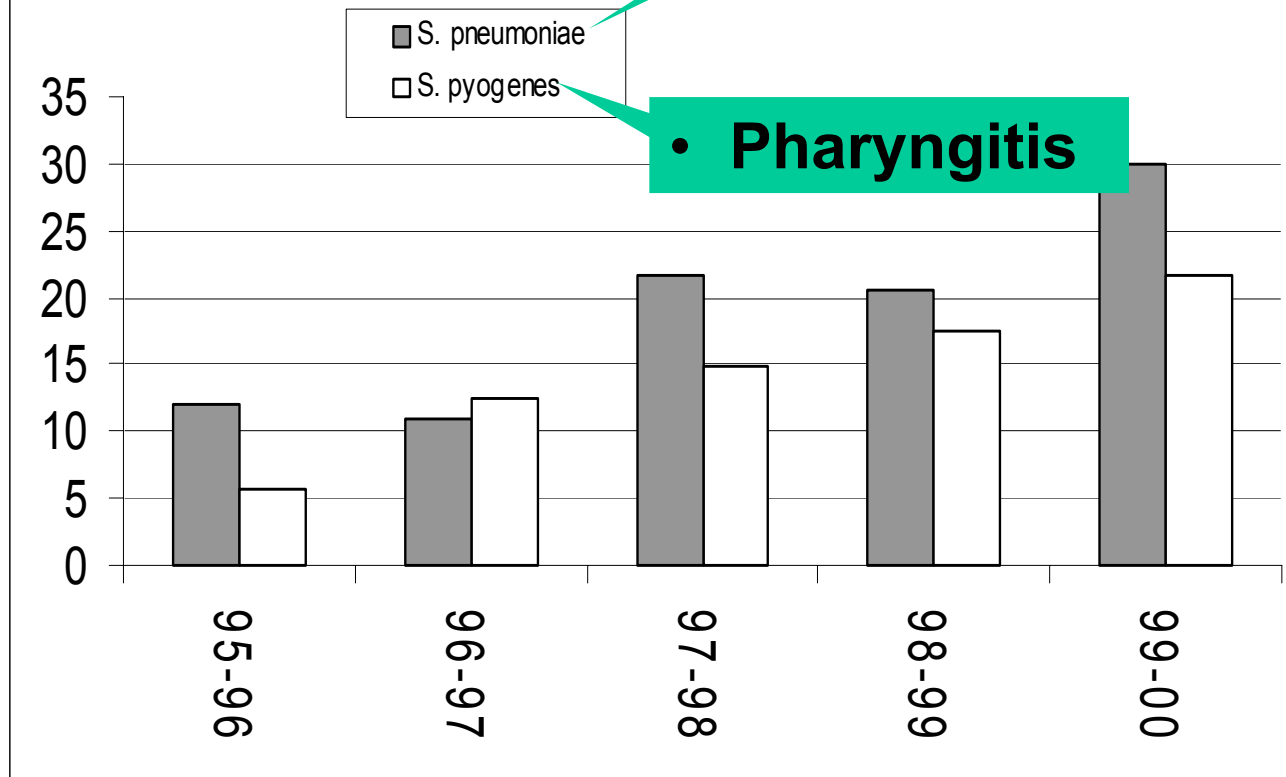
Resistance defined as erythromycin MIC ≥ 1 mg/L

Distribution of erythromycin-resistance phenotypes among pneumococci from 8 different European countries (1998-2000)

Country (total N of isolates)	ref	overall % of erythromycin-resistance	distribution of resistance phenotype		
			MLS _B	M	other
Belgium (59)	1	31	91.5	8.5	0
Finland (651)	2	11.2	71	21	11.2
France (48)	3	53	100	0	0
Germany (102)	4	10.6	74	22.5	3.5
Greece (140)	5	18	67.9	29.2	3.6
Italy (85)	6	31.7	76.5	23.5	0
Norway (8)	7	4.5	75	25	0
Spain (109)	8	36.1	84	15	1

- Bronchitis
- pneumonia
- sinusitis
- otitis

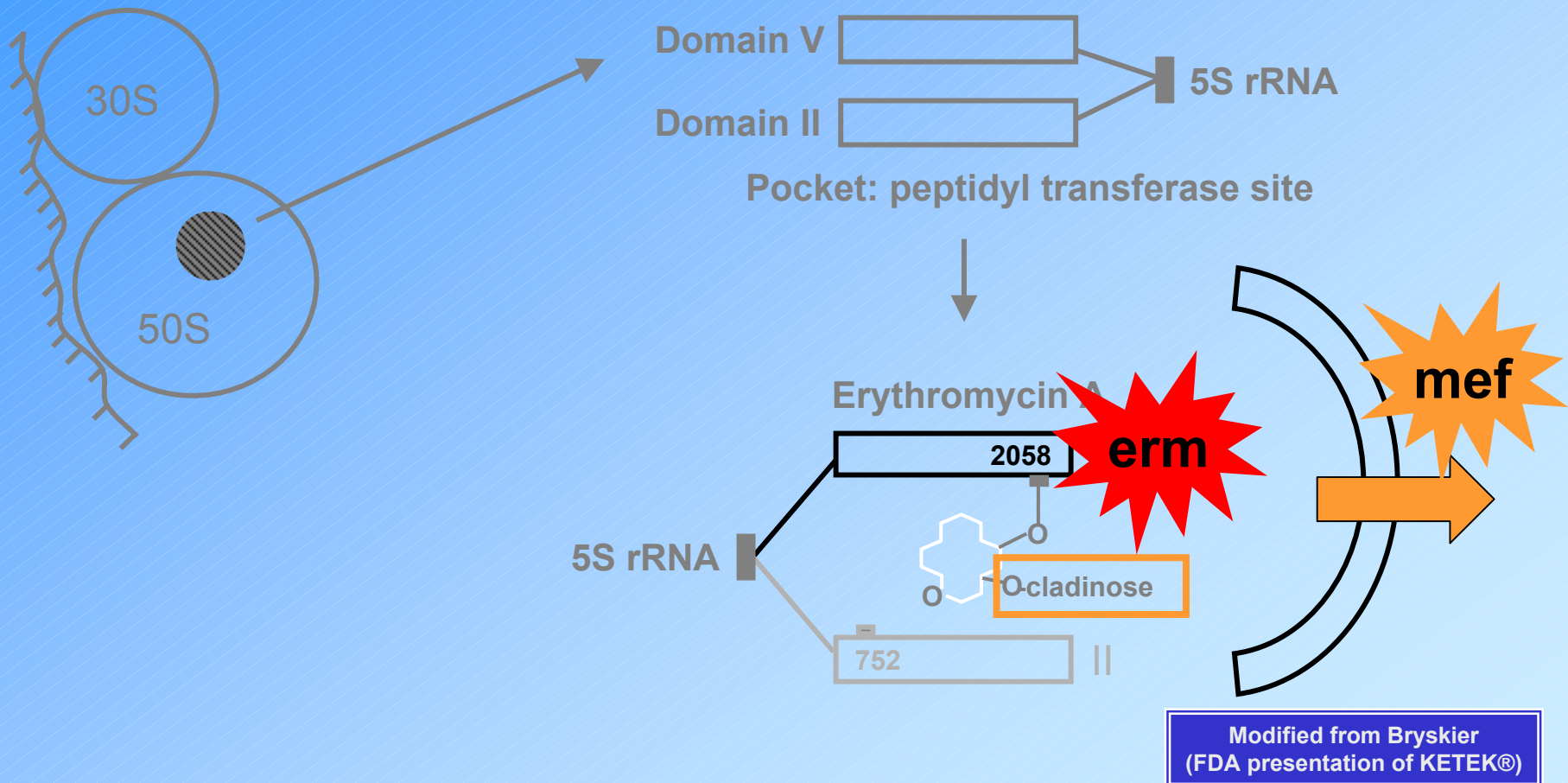
Resistance to macrolides in Greece

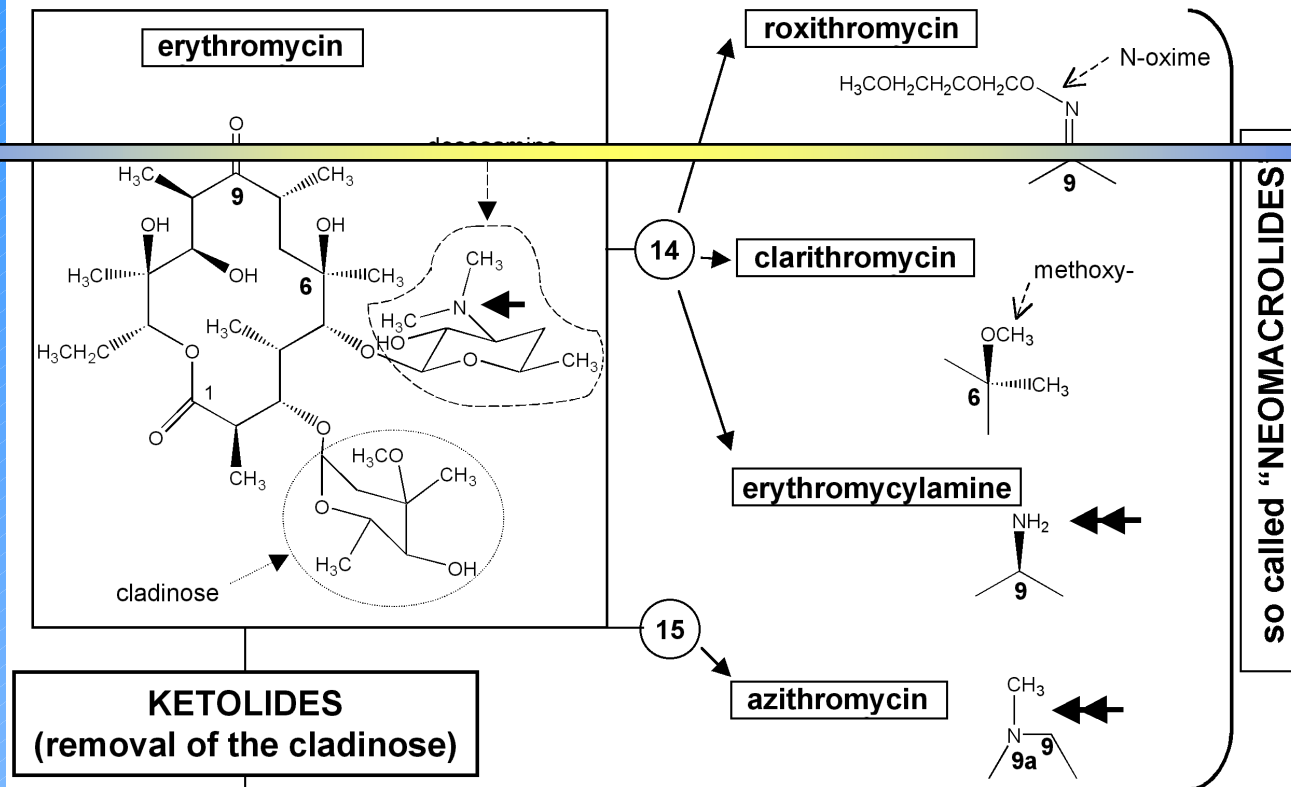


- Pharyngitis

Inhibition of Protein Synthesis (1)

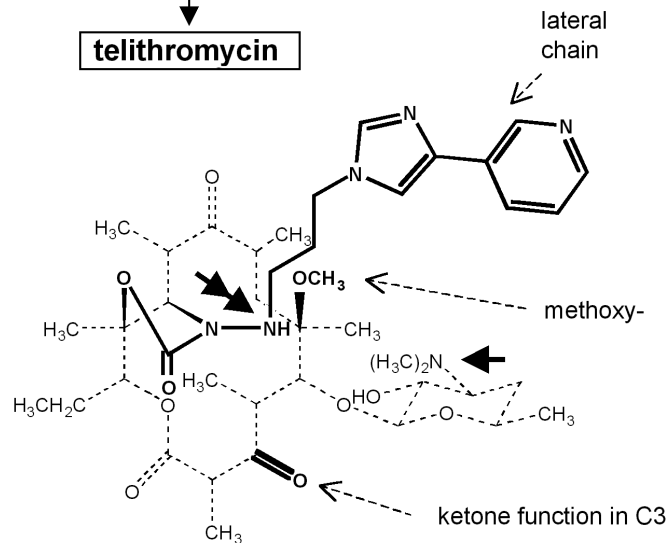
- Inhibition of peptidyl transferase activity



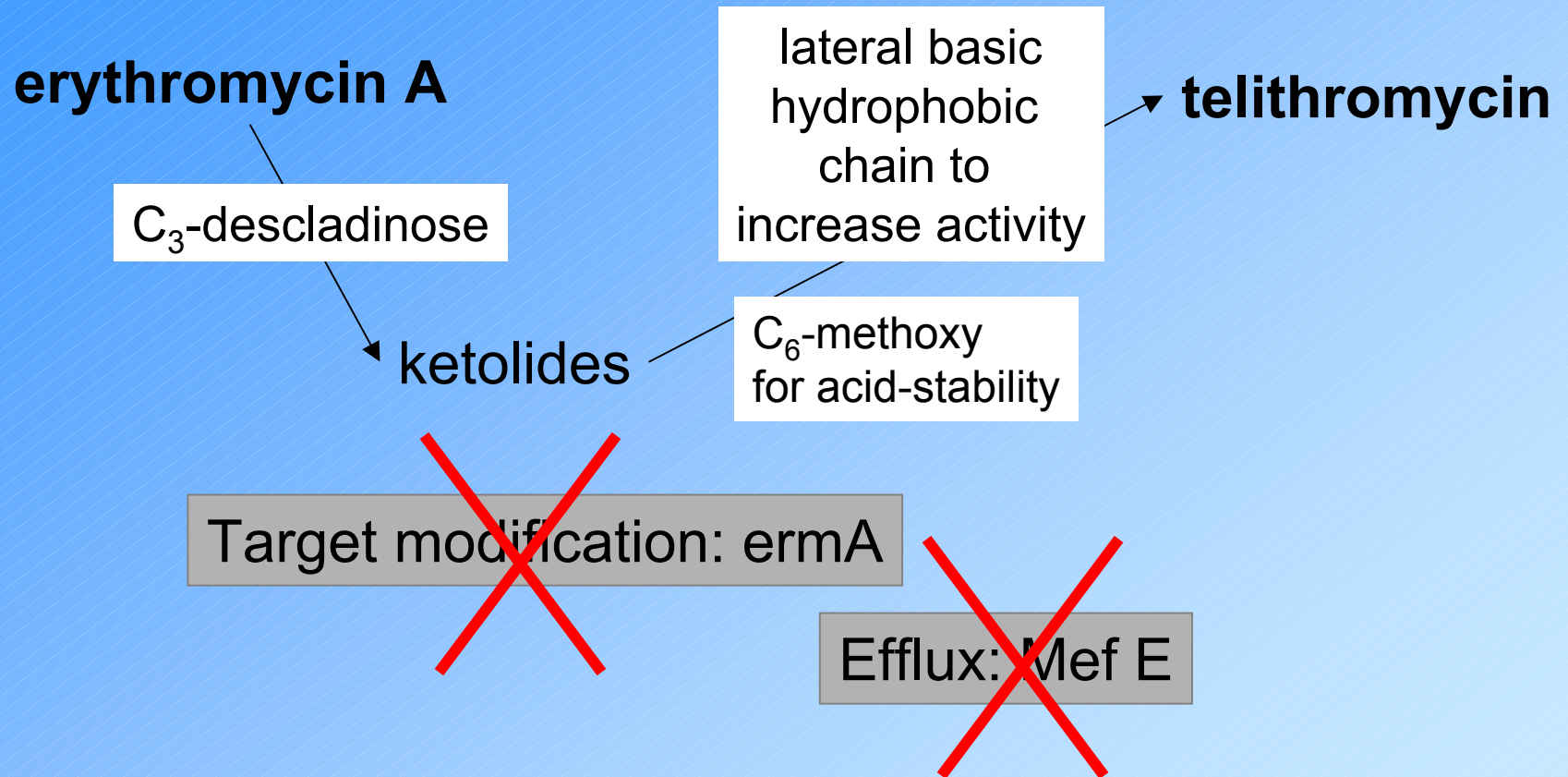


KETOLIDES
(removal of the cladinose)

telithromycin

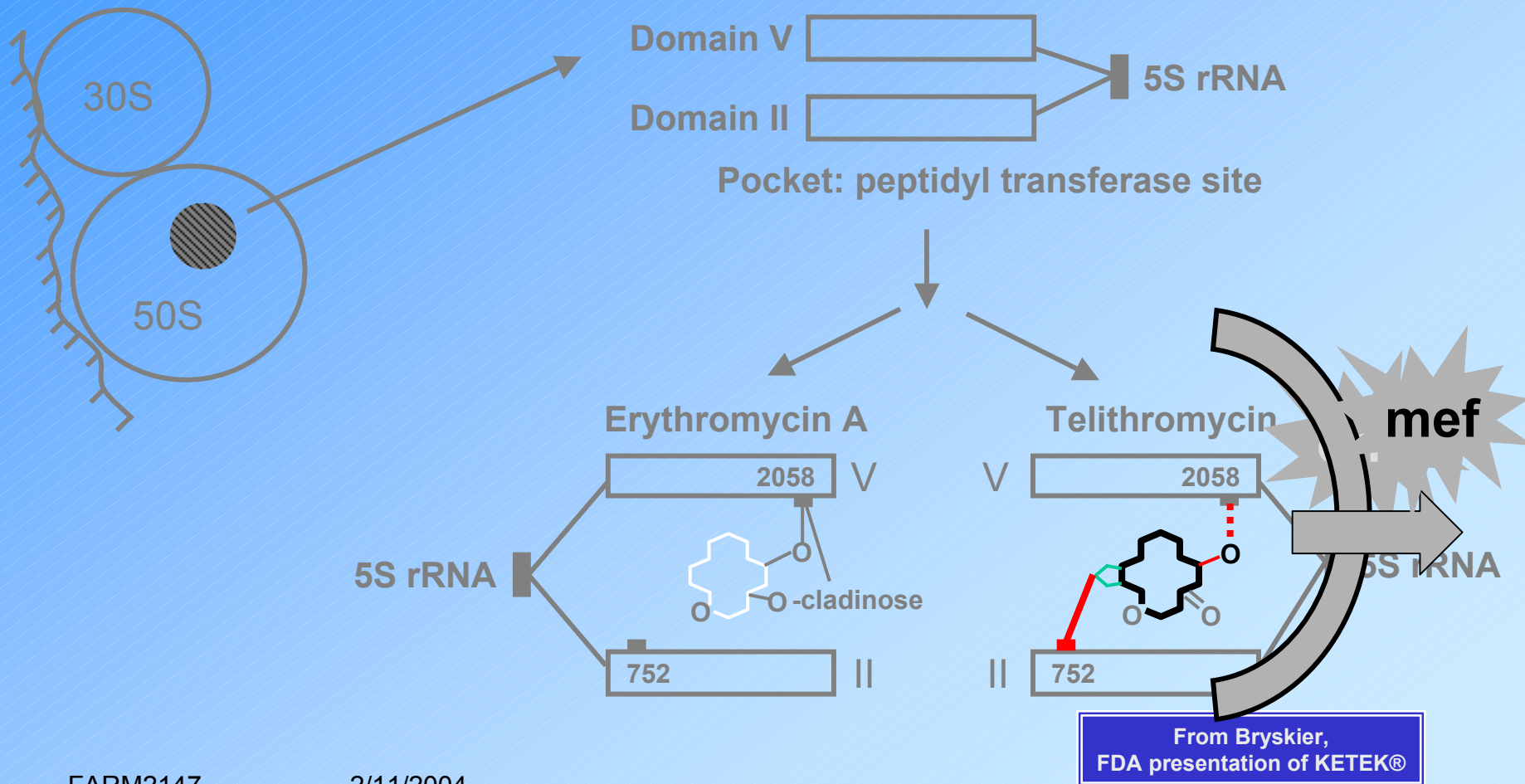


Resistance: a semi-rational answer ...



Inhibition of Protein Synthesis (2)

- Inhibition of peptidyl transferase activity



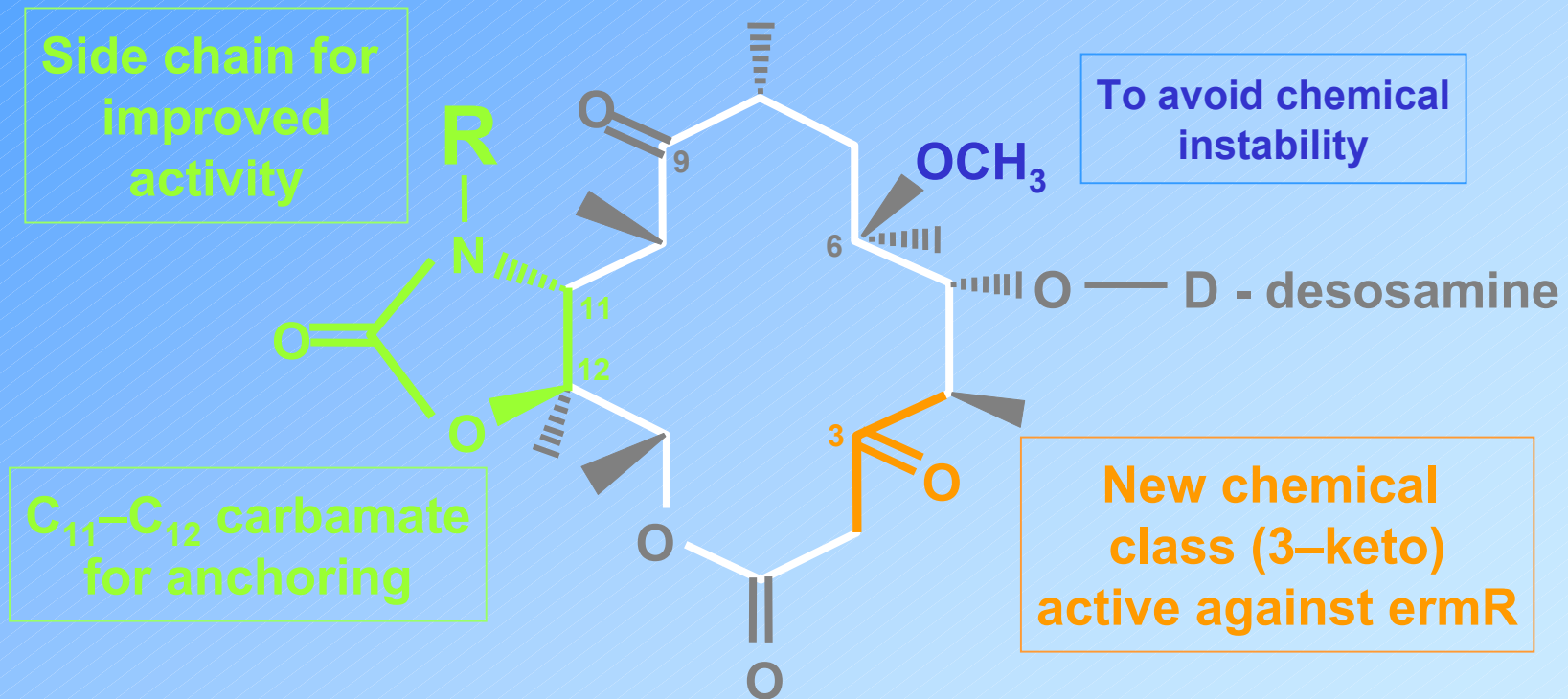
MIC₅₀ [μg/ml] of wild type and mutant strains

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



Telithromycin

- Telithromycin, the first ketolide, was designed to overcome erythromycin A resistance within Gram (+) positive cocci and take advantage of PK improvements of clarithromycin



Pharmacokinetics of telithromycin

(as submitted to the FDA; april 2001)

	800 mg (single dose)	800 mg (7 days)
C_{\max} (mg/L)	1.9 (42)	2.3 (31)
C_{24h} (mg/L)	0.03 (45)	0.07 (72)
AUC_{24h} (mgxh/L)	8.3 (31)	12.5 (43)
$t_{1/2}$ (h)	7.2 (39)	9.8 (20)

**The company has declared
that activity of telithromycin is
driven by C_{\max} /MIC and by
 AUC_{24h} /MIC ratios**

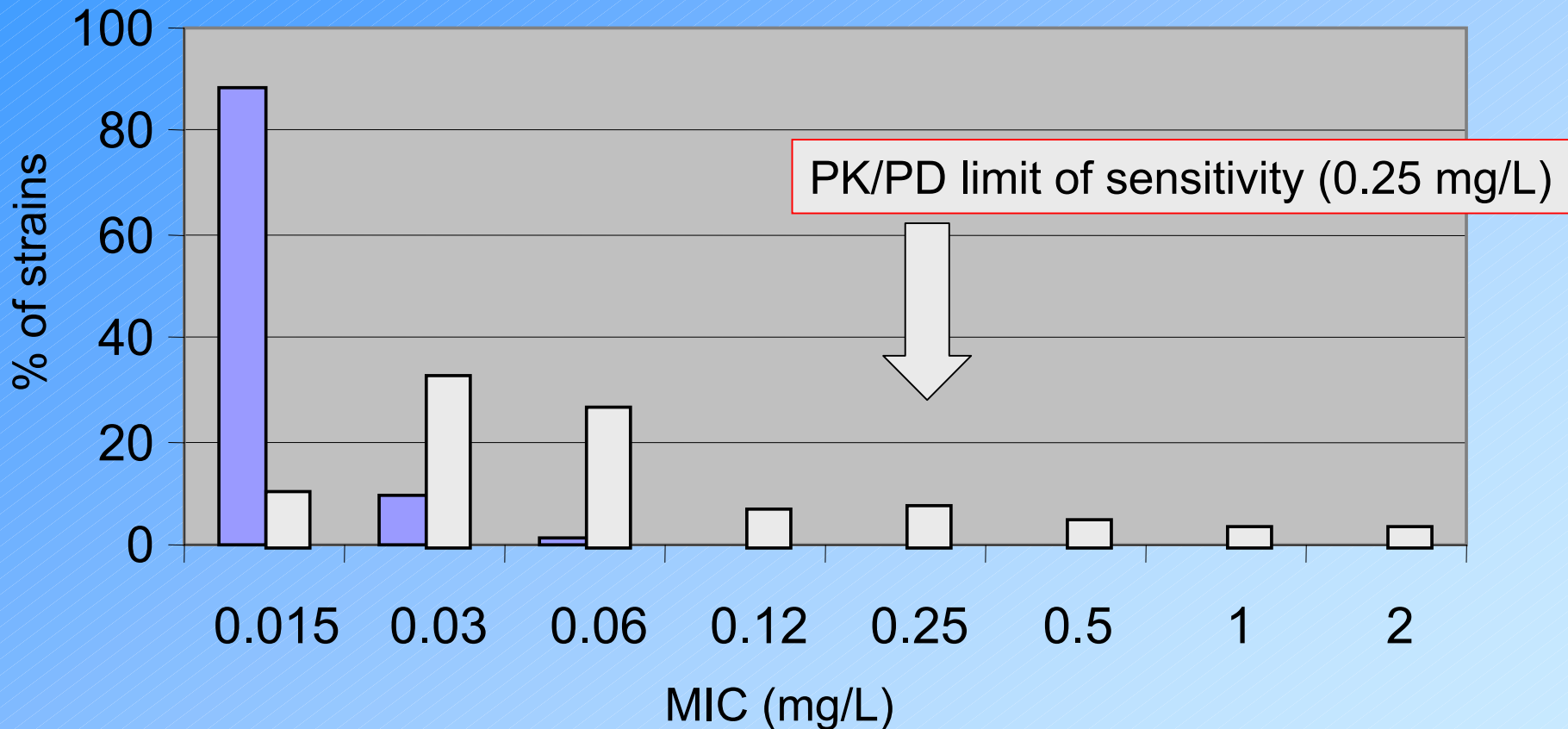
Pharmacodynamics of telithromycin (as based on FDA submission; april 2001)

Organism	MIC ₉₀	C _{max} /MIC _{90max}	AUC _{24h} /MIC _{90max}
S. pneumoniae	< 0.008 - 0.25	7.6	33.2
S. pyogenes	< 0.015 - 0.06	31.6	138
H. influenzae	2.0 - 4.0	0.475	2.075
M. catarrhalis	0.12	15.8	69.1
L. pneumophila	0.03 - 0.12		
C. pneumoniae	0.03 - 2		
M. pneumoniae	0.25		

Activity will be good for MIC ≤ 0.25 mg/L, but may become problematic for higher MICs

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

■ Ery-S ■ Ery-r



MIC₉₀ for Ery-s strains: < 0.06 ...

But MIC₉₀ for Ery-r strains: 0.25-0.5 ...

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

Macrolides: the 16 atoms family

Erythromycin A

14 atoms



Instability in acid media

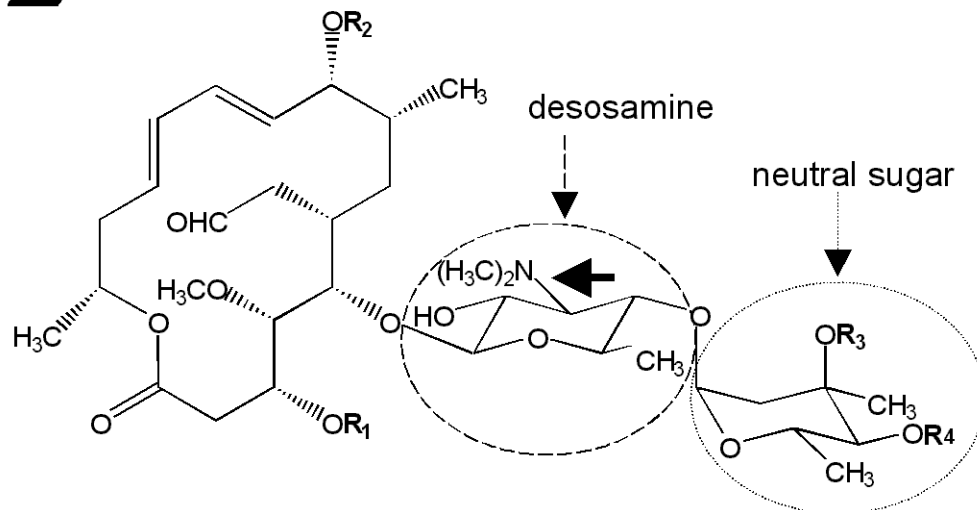
Carbomycin A / Spiramycins

16 atoms

**Intrinsically
acid-stables**

Macrolides: the 16 atoms family

► 16 ATOMS



josamycin

$R_1 = \text{COCH}_3$ / $R_2 = \text{H}$ / $R_3 = \text{H}$ / $R_4 = \text{COCH}_2\text{CH}(\text{CH}_3)_2$

miocamycin

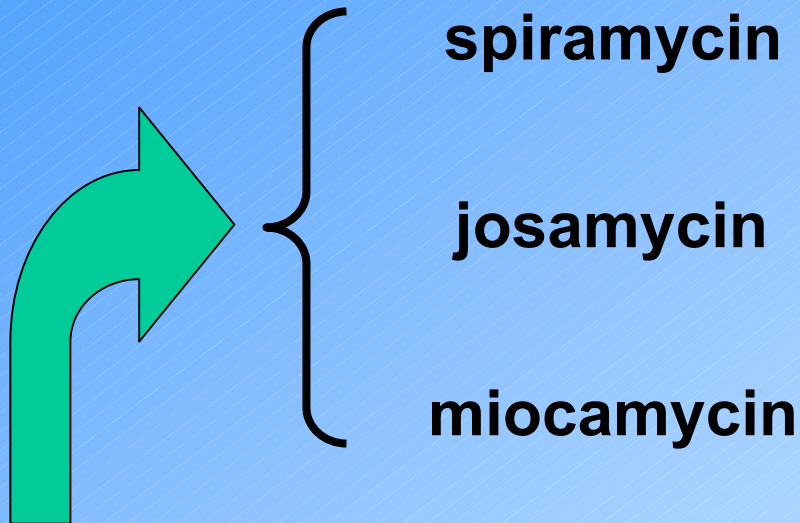
$R_1 = \text{COCH}_2\text{CH}_3$ / $R_2 = \text{COCH}_3$ / $R_3 = \text{COCH}_3$ / $R_4 = \text{COCH}_2\text{CH}_3$

spiramycin

$R_1 = \text{H}$ / $R_2 = \text{CO}(\text{CH}_2)_2\text{CHCHOHCH}_3$ / $R_3 = \text{H}$ / $R_4 = \text{H}$



Properties of the 16 atoms family



Low cyt P450 interactions

Non ermB inducers

Non mefE substrates

Intrinsically acid-stables

Carbomycin A / Spiramycins

16 atoms

But, usually, lower intrinsic activities

Macrolides: the present family picture

