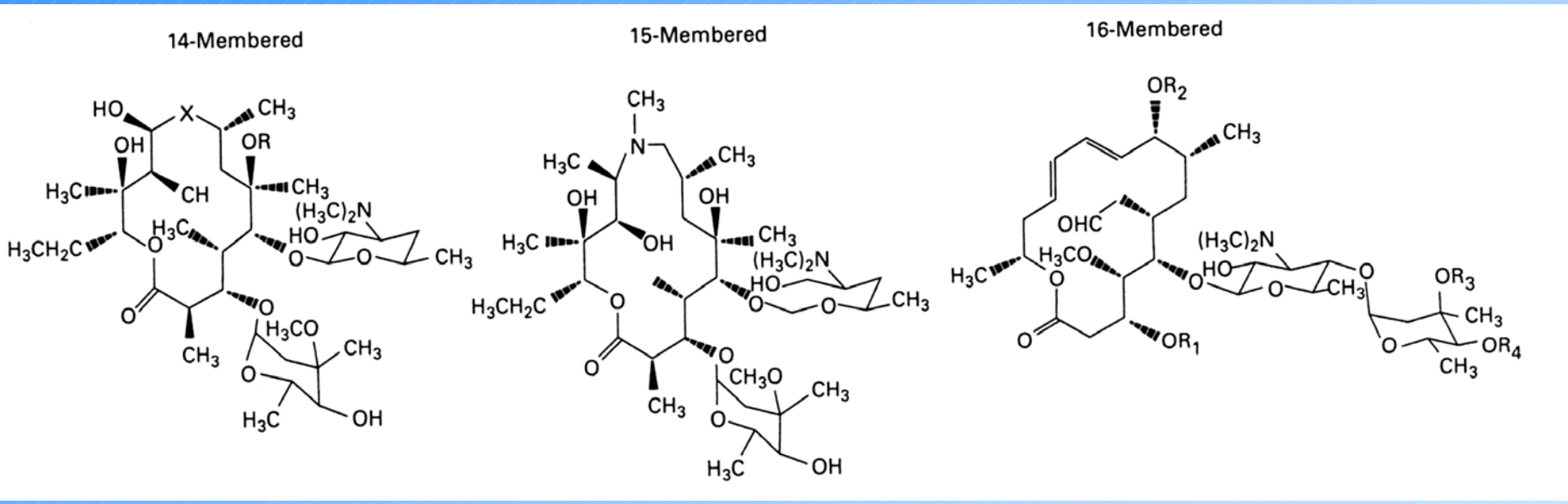
Macrolides

The macrolide family ...



erythromycin
- **roxithromycin**
- **clarithromycin**
- **dirithromycin**

azithromycin

josamycin
spiramycin
miocamycin

- **telithromycin**

Erythromycin: 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

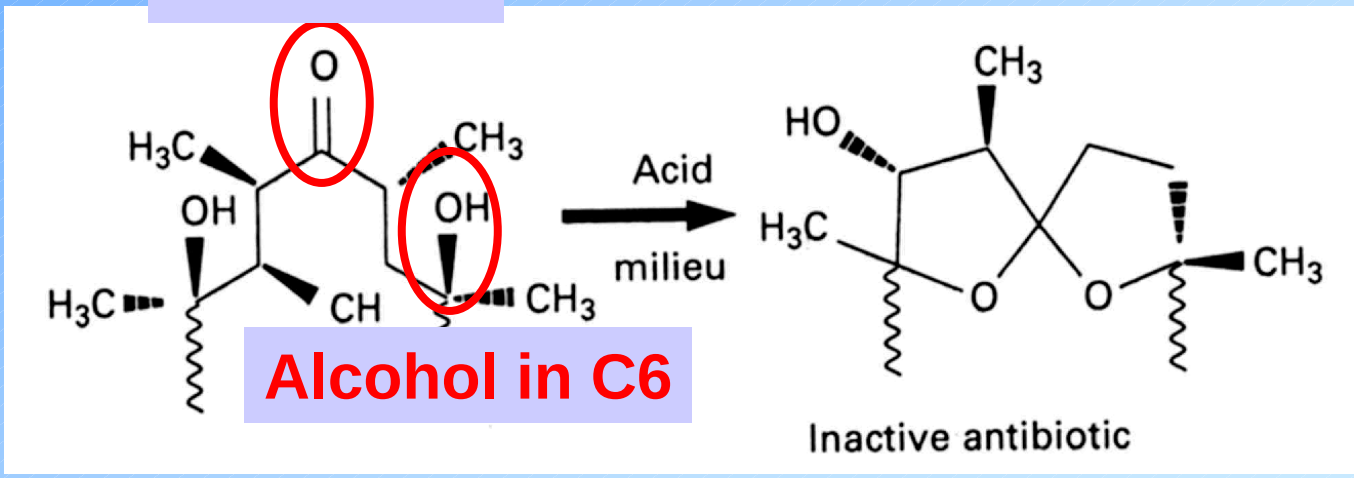
Erythromycin: the problems

Erythromycin A

14 atoms

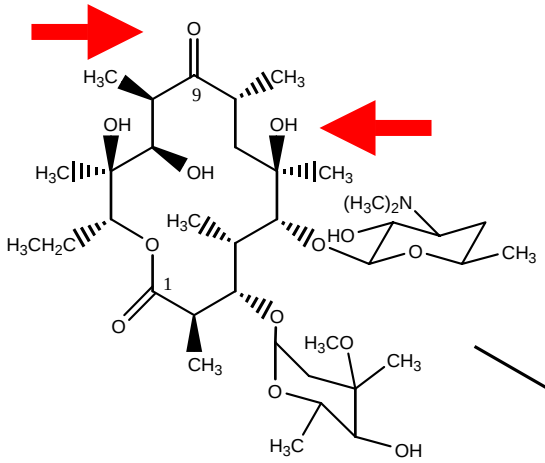
Instability in acid media

Keto in C9

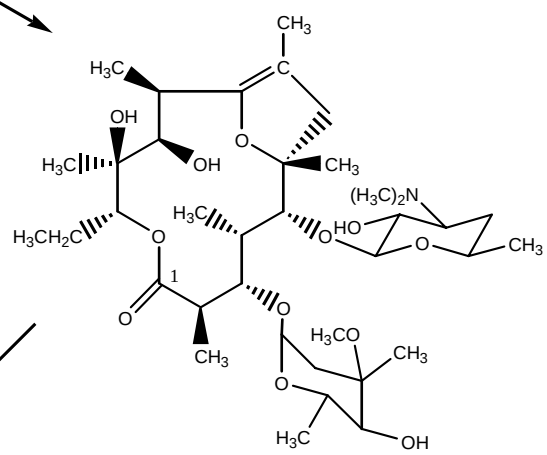


Alcohol in C6

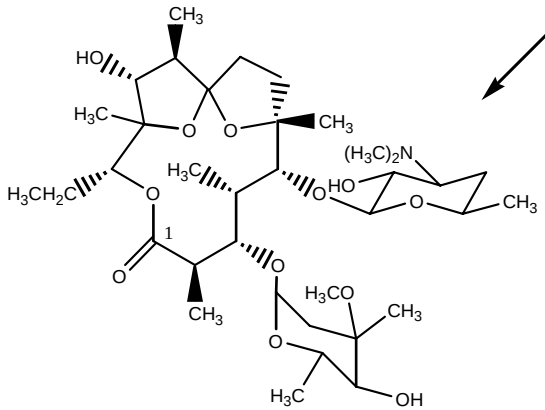
Erythromycin: details of acid the degradation



ERYTHROMYCIN



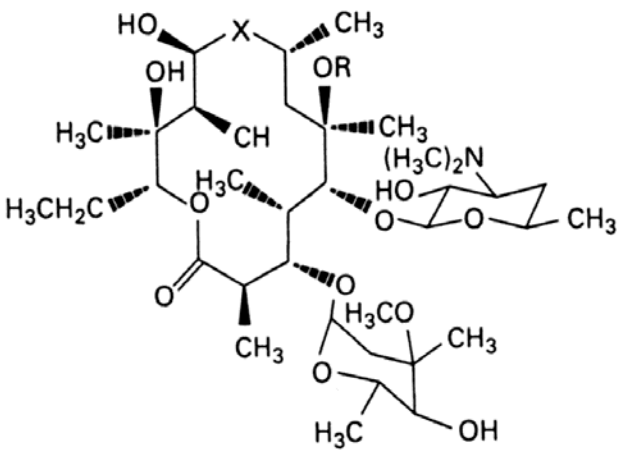
8,9-anhydroerythromyin-6,9-hemi ketal



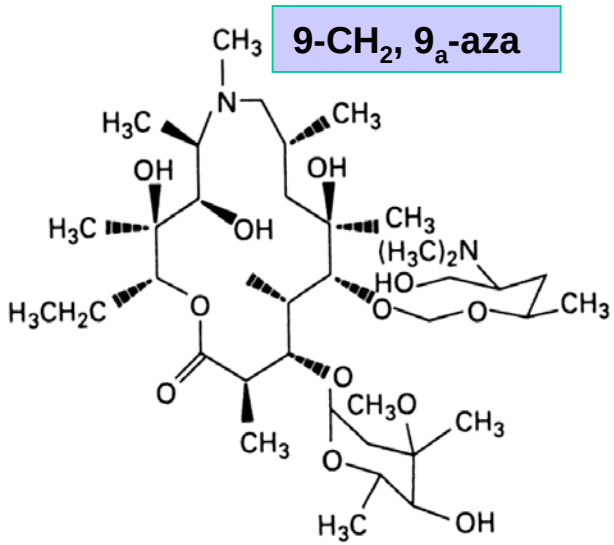
erythromyin-6,9;9-12 -spiroketal

What have the chemists done to avoid acid-instability ?

14-Membered



15-Membered

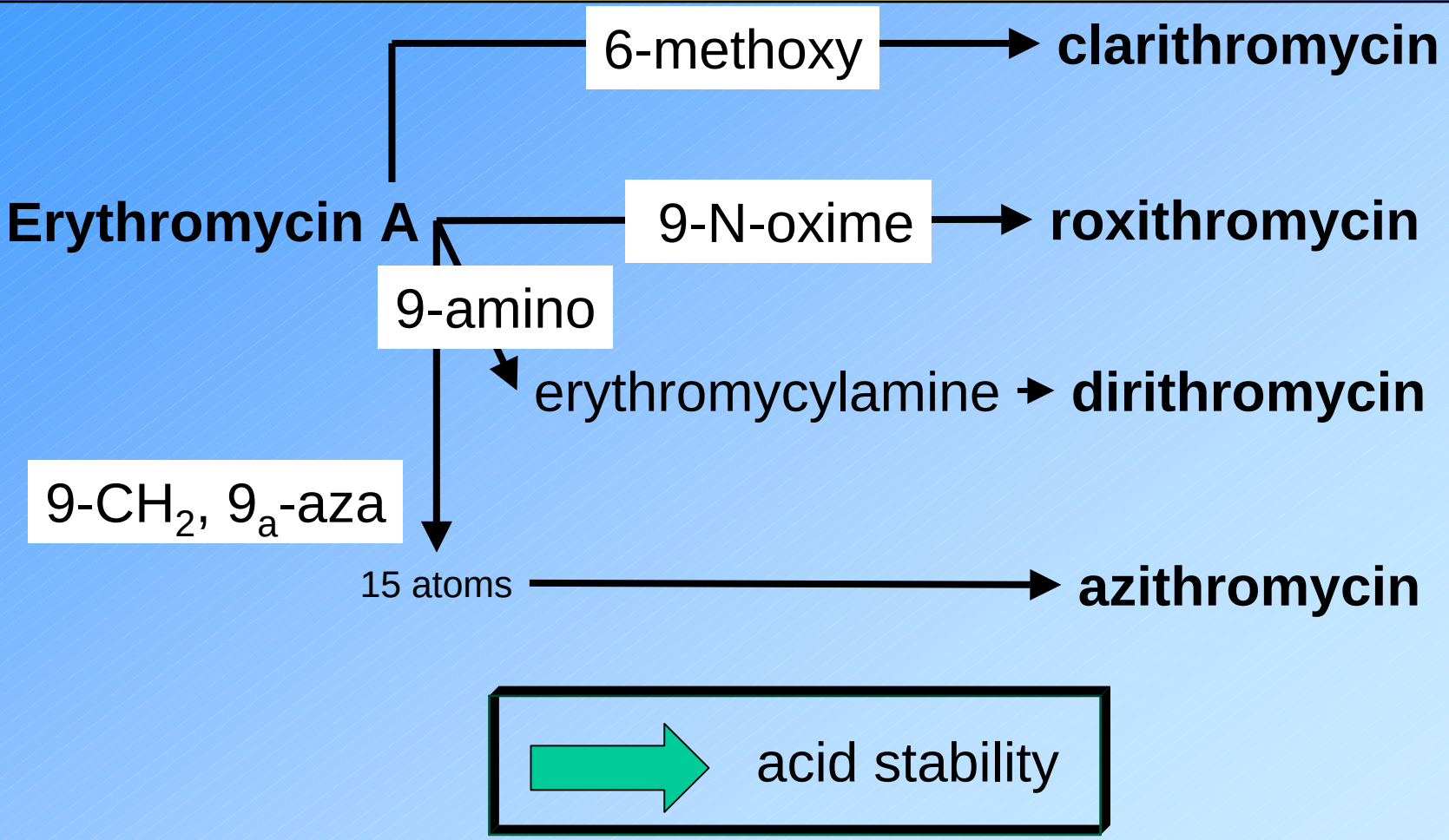


9-CH_2, 9_a-aza

azithromycin

	X	R	
Erythromycin	C=O	H	
Roxithromycin	$C{=}NOCH_2OCH_2CH_2OCH_3$	H	9-N-oxime
Clarithromycin	C=O	CH_3	6-methoxy
Erythromycylamine	$C\text{-}NH_2$	H	9-amino

What have the chemists done to avoid acid-instability ?



Did these modifications change anything else in PK ?

clarithromycin

roxithromycin

→ **higher tissue accumulation**

dirithromycin

azithromycin

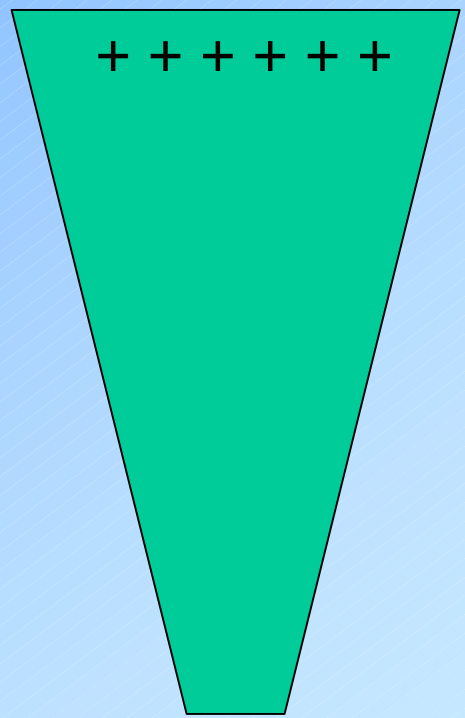
dibasic → **much higher tissue accumulation**

→ **pharmacokinetic differentiation**

Did these modifications change anything else ?

Cytochrome P_{450} 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**
- **gonorhhea**

Gastric ulcer (H. pylori)

Which (who ...) is the best ?

erythromycin

clarithromycin

roxithromycin

dirithromycin

azithromycin

But was has been the problem ?

erythromycin

clarithromycin

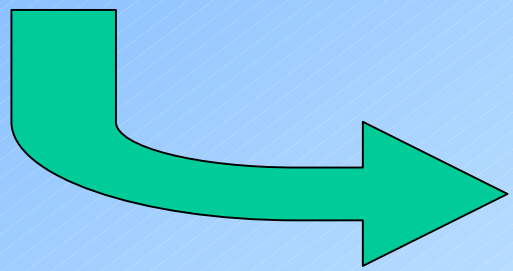
roxithromycin

dirithromycin

azithromycin

Target modification: erm

Efflux: Mef

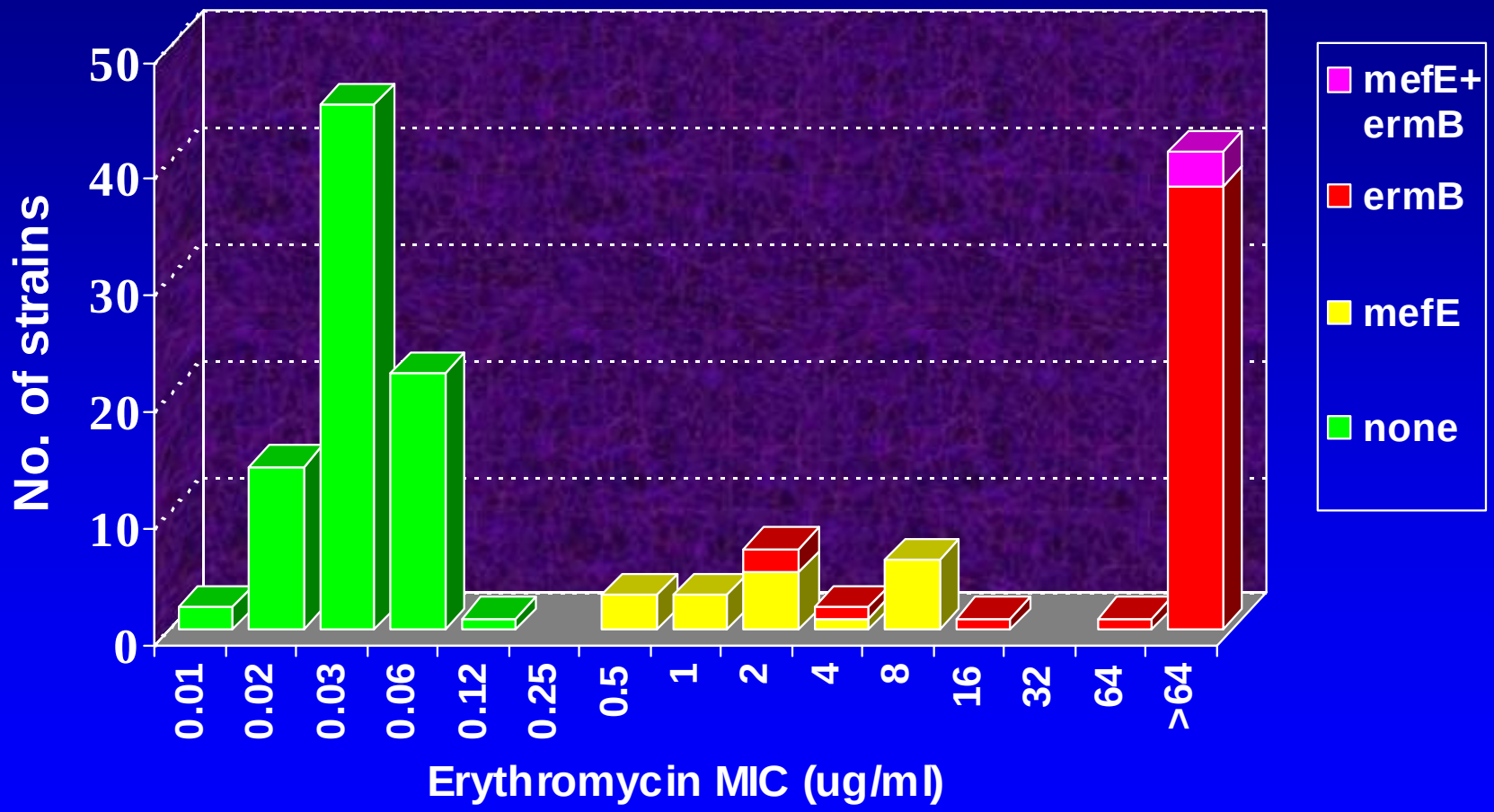


All are similarly affected

Mechanisms of macrolide resistance

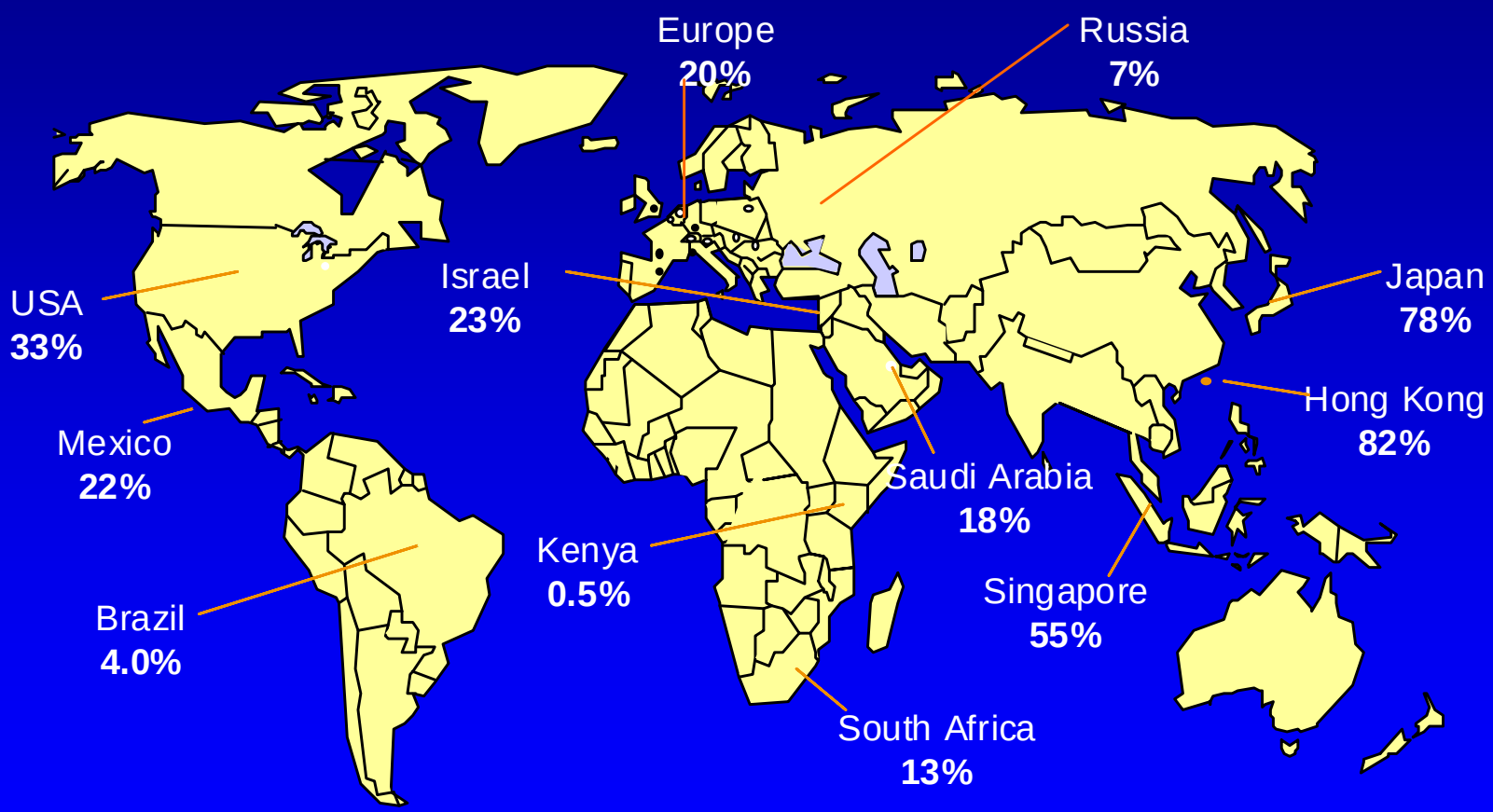
- **Ribosomal modification by methylase (*erm* genes)**
  - *S. pneumoniae*: *erm*(B) 75-100% of Ery-R strains in Europe
  - *S. pyogenes*: *erm*(B) generally <50% of Ery-R strains
    erm(A)
- **Ribosomal modification by mutation (rRNA, proteins)**
  - Occasional in Ery-R *S. pneumoniae*
  - Rare in 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

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

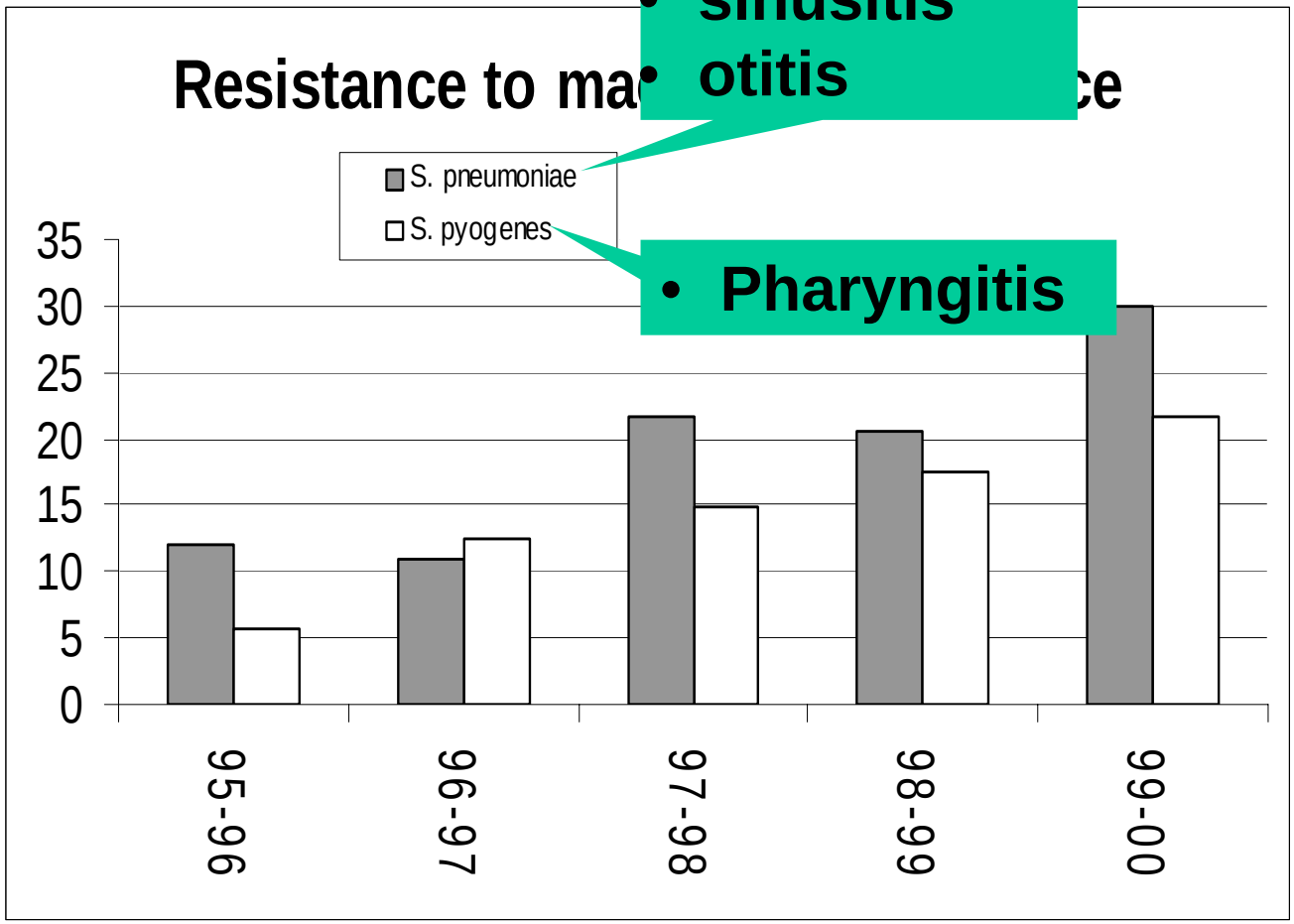


Resistance defined as erythromycin MIC ≥1mg/L

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

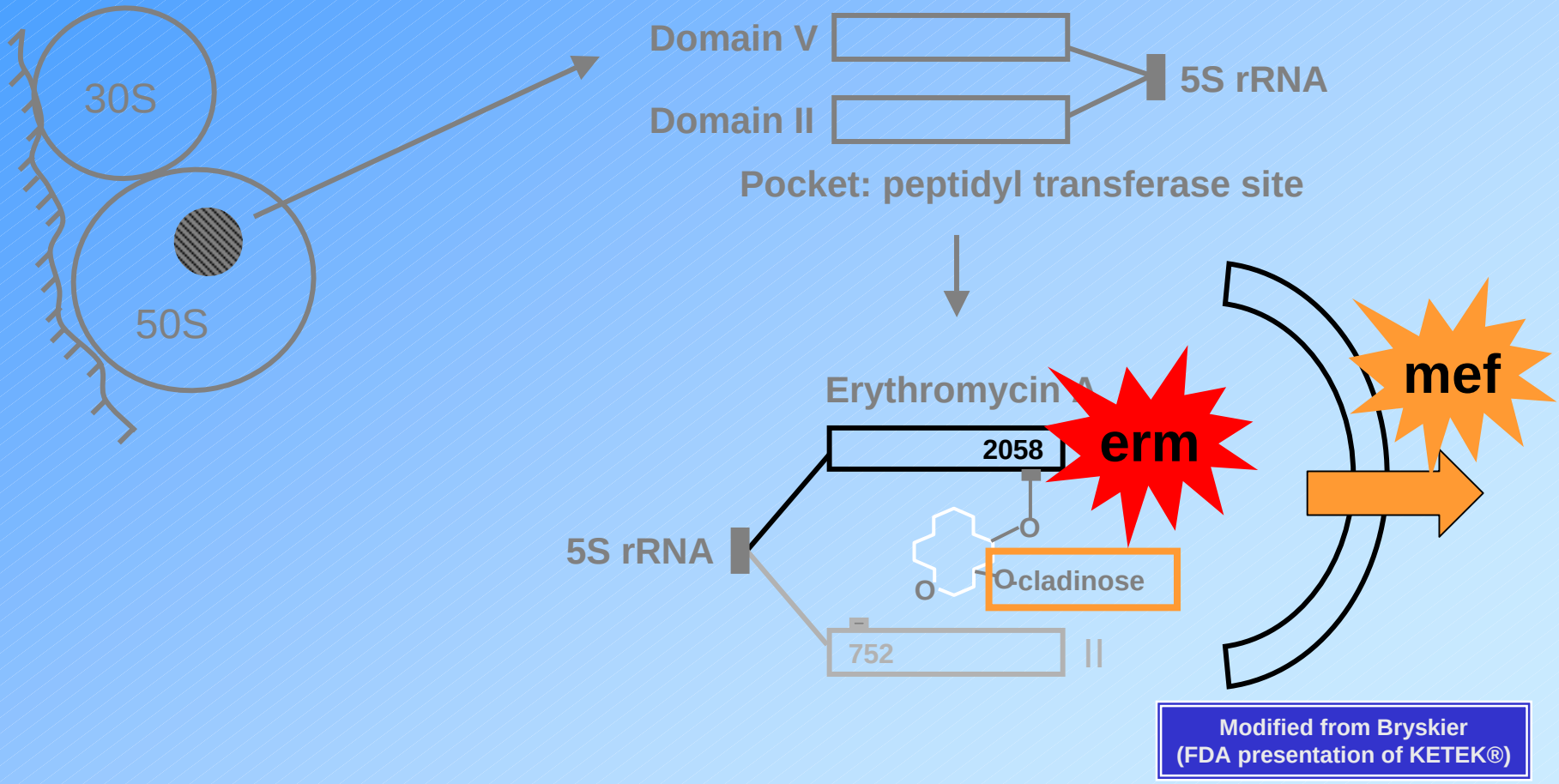
- **Bronchitis**
- **pneumonia**
- **sinusitis**
- **otitis**



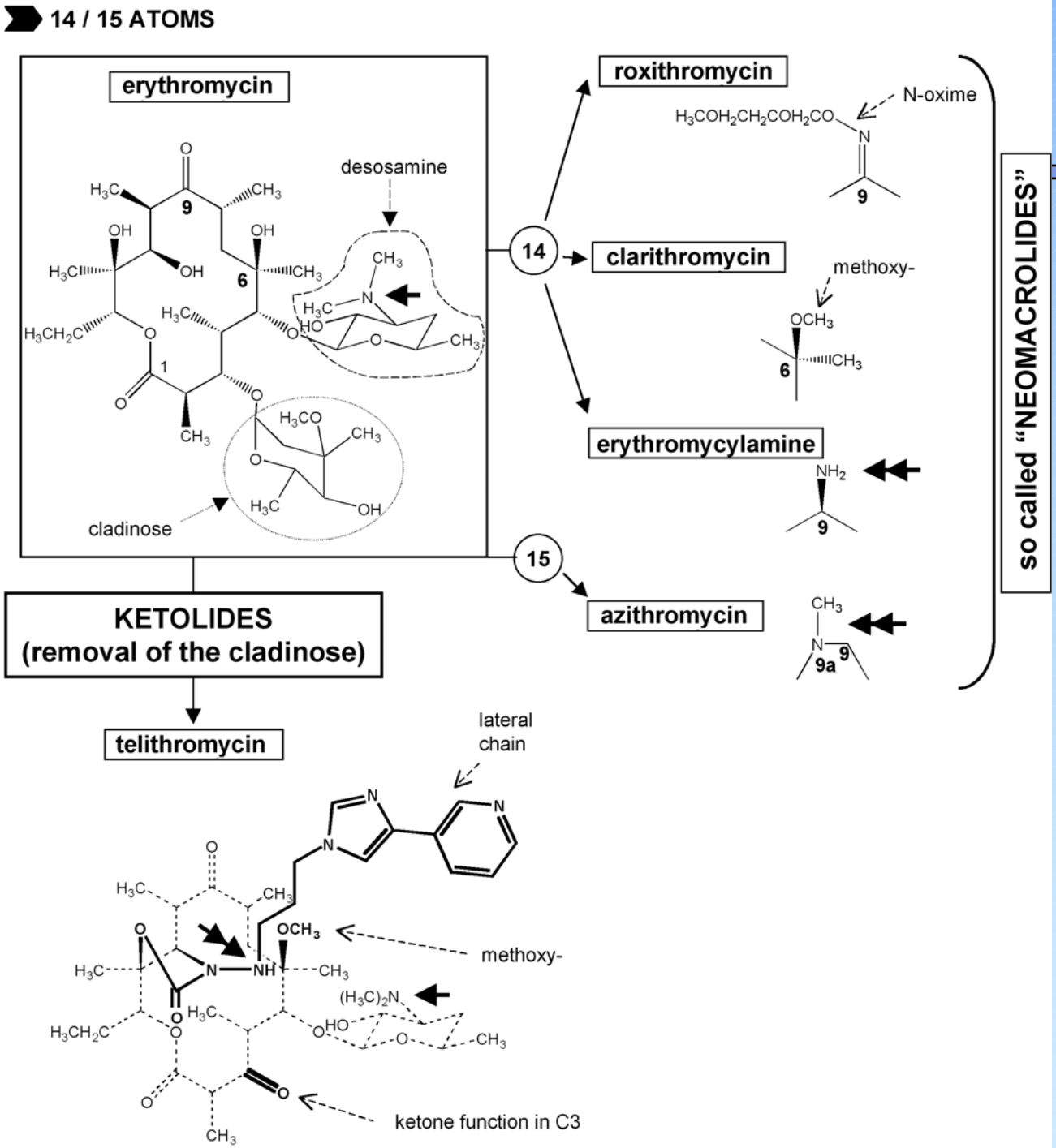
- **Pharyngitis**

Inhibition of Protein Synthesis (1)

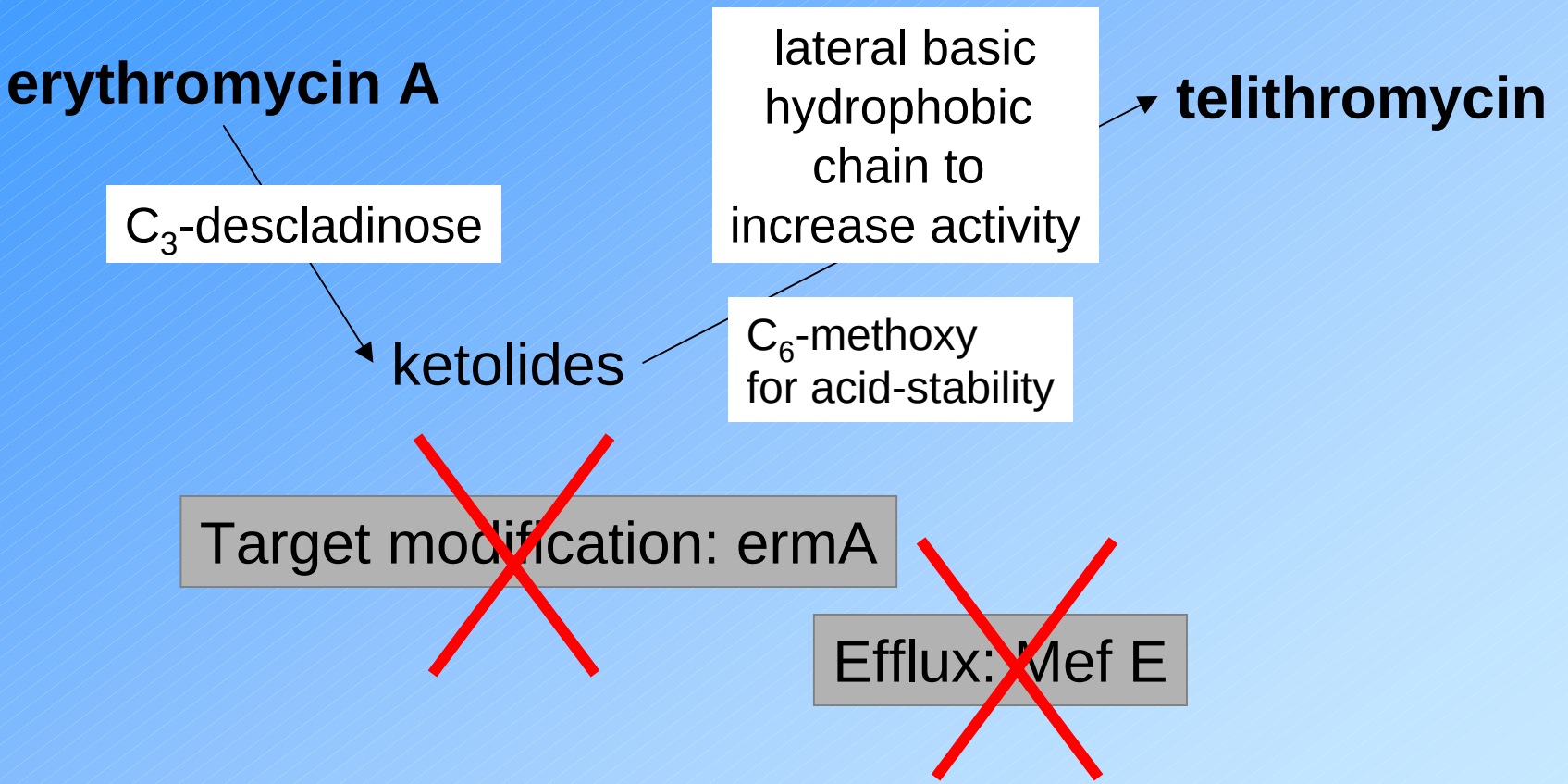
- Inhibition of peptidyl transferase activity



Modified from Bryskier
(FDA presentation of KETEK®)

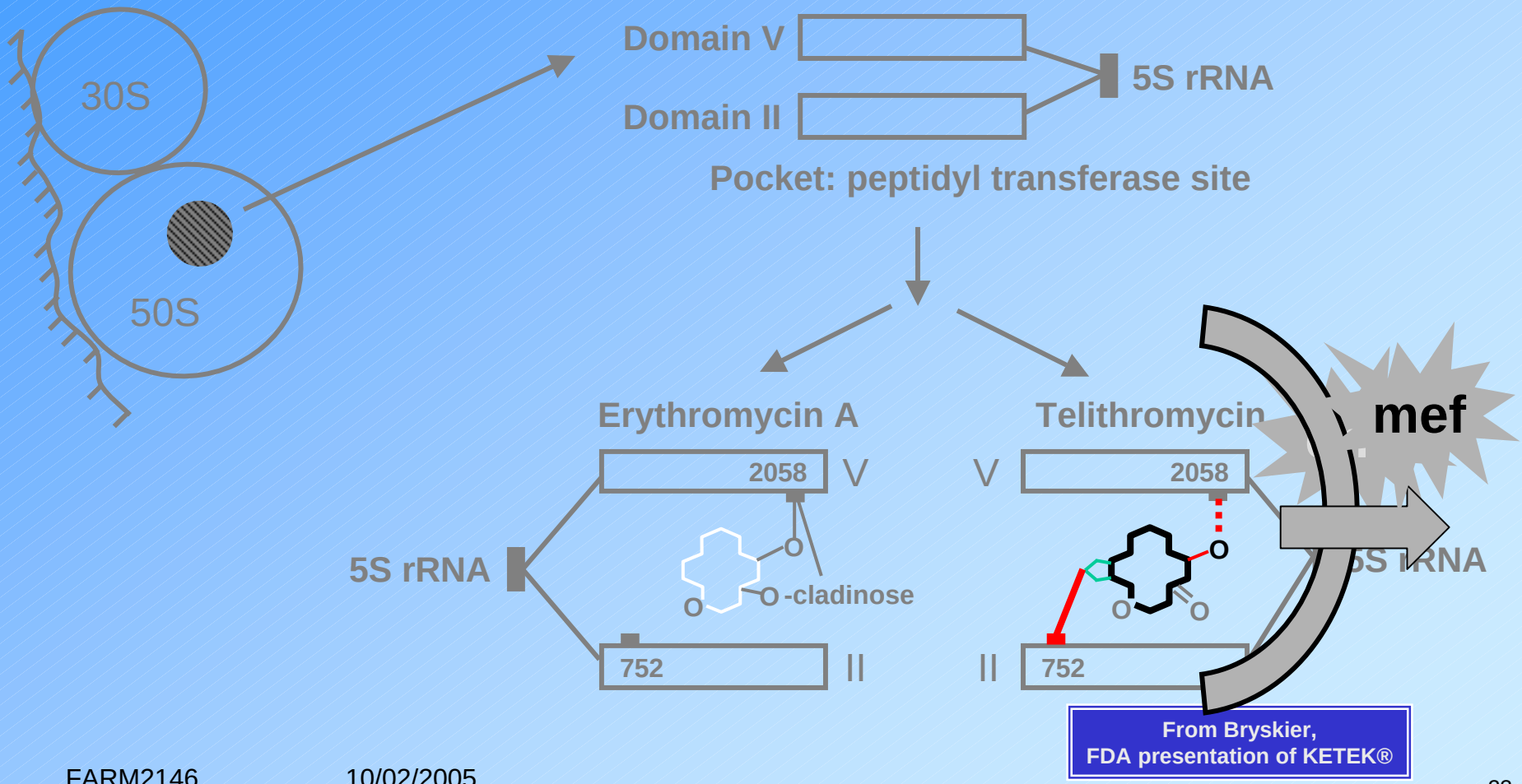

14 / 15 ATOMS
erythromycin
desosamine
cladinose
14
15
roxithromycin
N-oxime
clarithromycin
methoxy-
erythromycylamine
azithromycin
so called "NEOMACROLIDES"
KETOLIDES
(removal of the cladinose)
telithromycin
lateral
chain
methoxy-
ketone function in C3

Resistance: a semi-rational answer ...



Inhibition of Protein Synthesis (2)

- Inhibition of peptidyl transferase activity

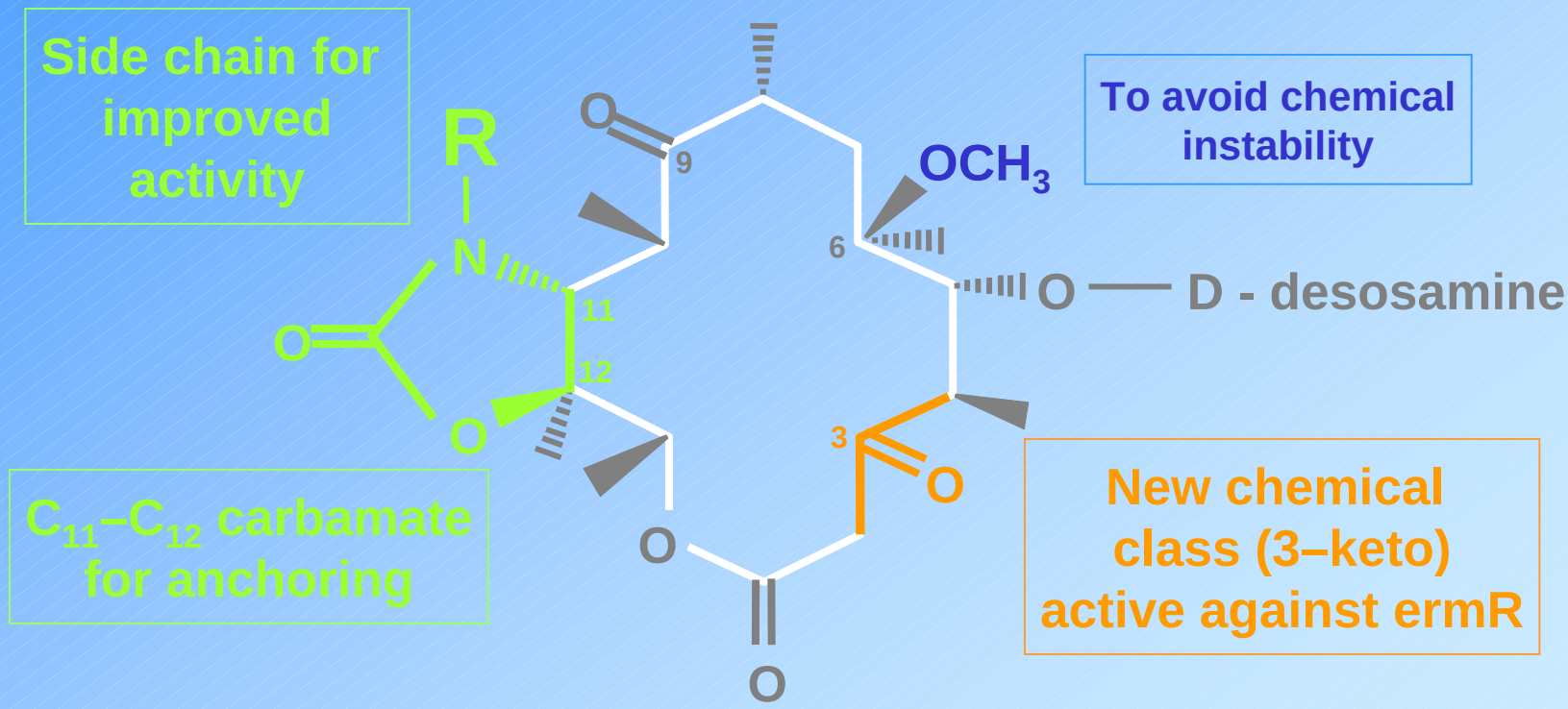


MIC_{50} [µg/ml] of wild type and mutant strains

		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

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

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/

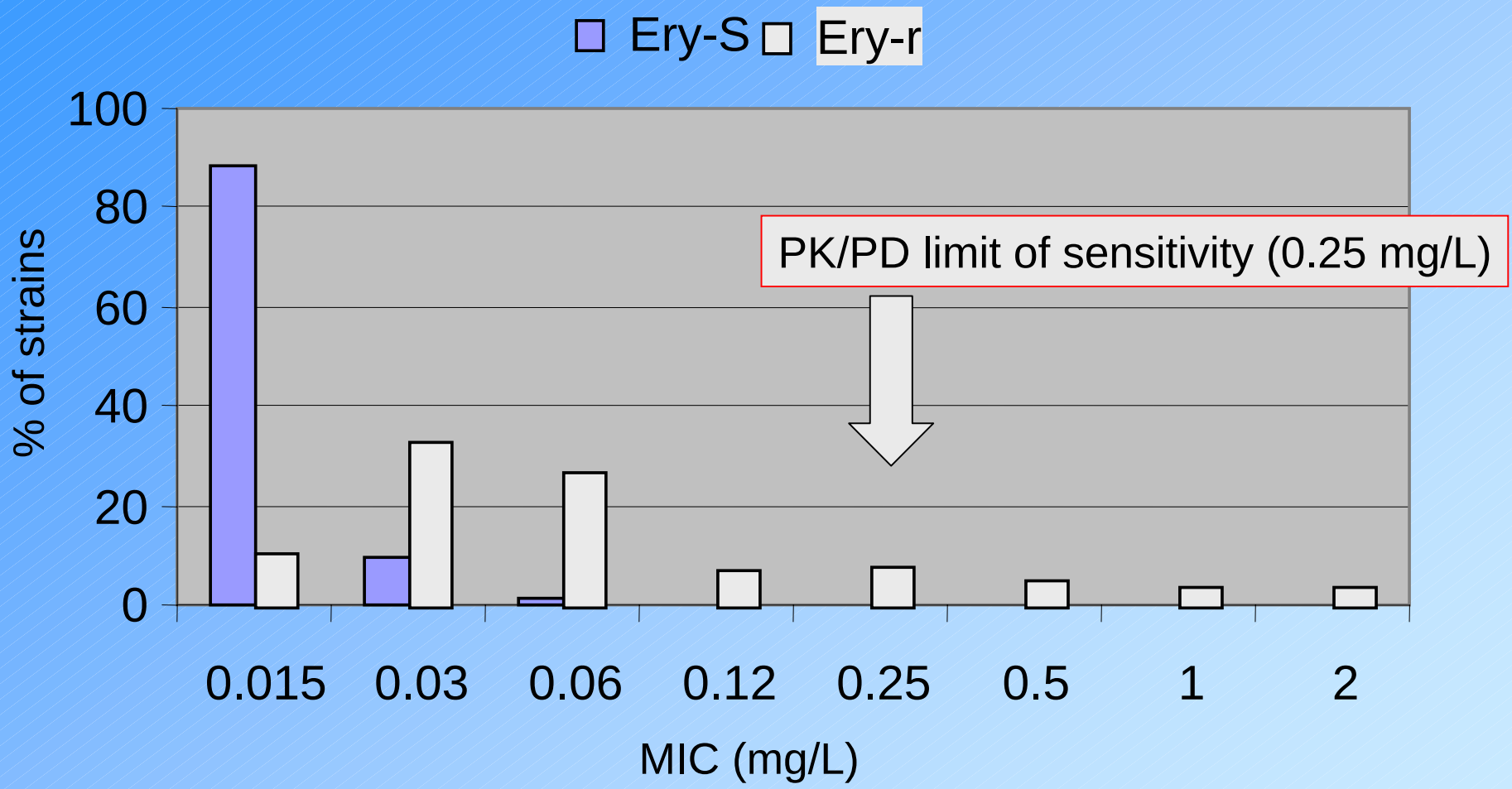
Pharmacodynamics of telithromycin (as based on FDA submission; april 2001)

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

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/

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



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

But MIC_{90} 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

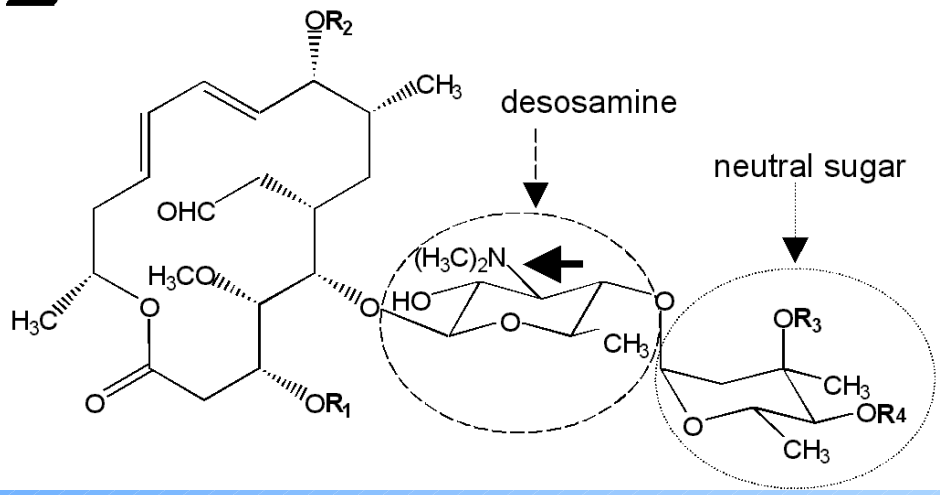
Carbomycin A / Spiramycins

16 atoms

Intrinsically acid-stables

Macrolides: the 16 atoms family

16 ATOMS



josamycin

R1 = $COCH_3$ / **R2** = H / **R3** = H / **R4** = $COCH_2CH(CH_3)_2$

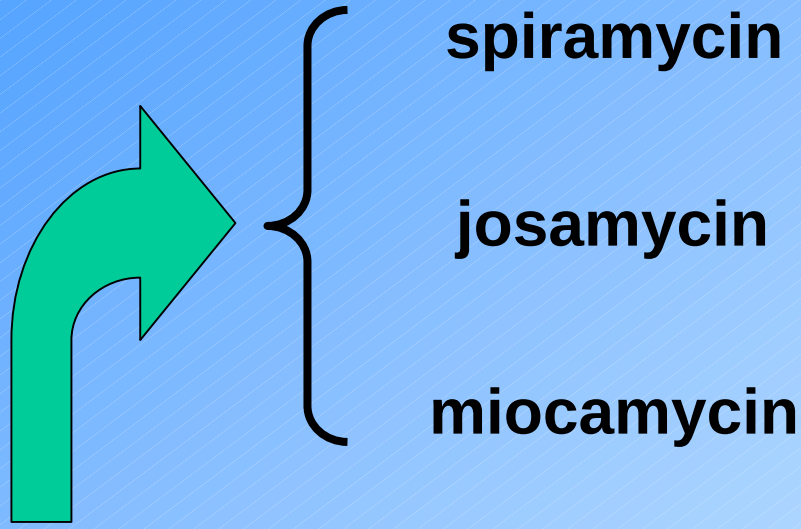
miocamycin

R1 = $COCH_2CH_3$ / **R2** = $COCH_3$ / **R3** = $COCH_3$ / **R4** = $COCH_2CH_3$

spiramycin

R1 = H / **R2** = $CO(CH_2)_2CHCHOHCH_3$ / **R3** = H / **R4** = H

Properties of the 16 atoms family



spiramycin

josamycin

miocamycin

Carbomycin A / Spiramycins

16 atoms

But, usually, lower intrinsic activities

Low cyt P450 interactions

Non ermB inducers

Non mefE substrates

Intrinsically acid-stables

Macrolides: the present family picture