

Séminaire de pathologie infectieuse
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Antibiotic Treatment of Community-acquired RTI

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Drugs for Which There is NO Resistance

A scanning electron micrograph (SEM) of Streptococcus pneumoniae bacteria. The image shows numerous spherical, Gram-positive cocci, many of which are arranged in pairs or small chains. The surface of the bacteria appears textured and slightly irregular. The background is a dark, uniform color, making the lighter-colored bacteria stand out.

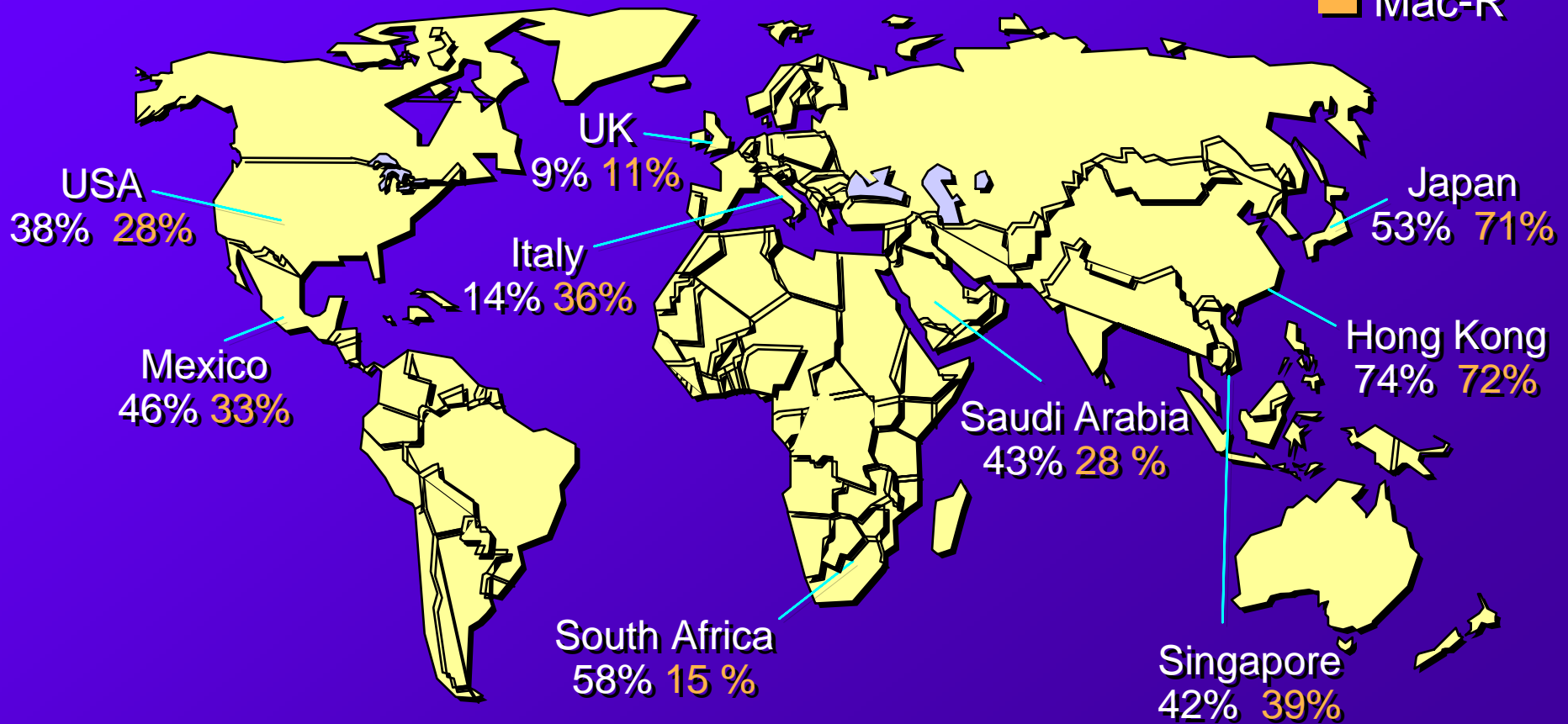
Streptococcus pneumoniae

... **typical Gram-positive
extracellular respiratory
pathogen**

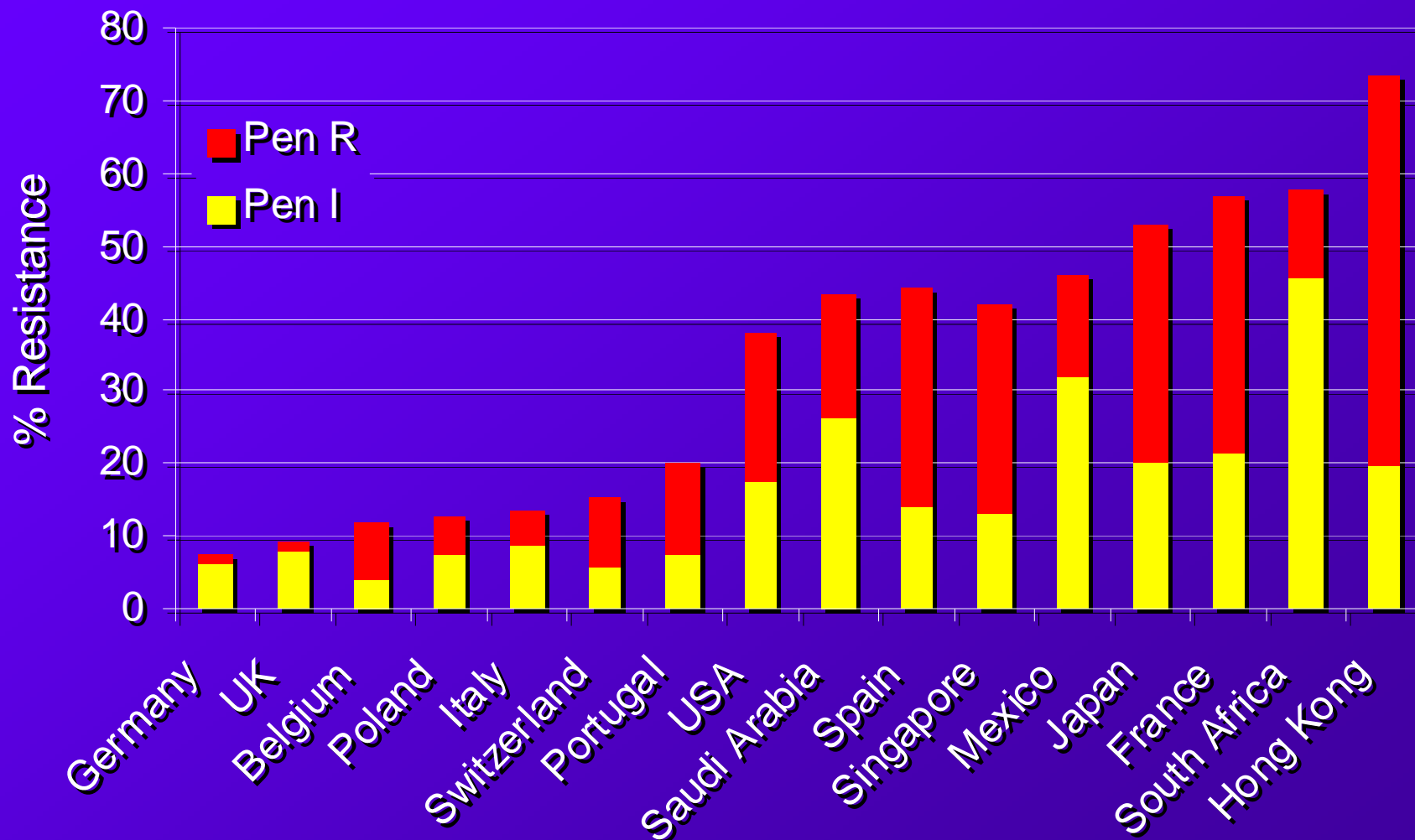
S. pneumoniae: prevalence of penicillin- and macrolide-resistant strains – 2001

Pen-I MIC 0.12–1 mg/l; Pen-R MIC ≥ 2 mg/l; Mac-R MIC ≥ 1 mg/l

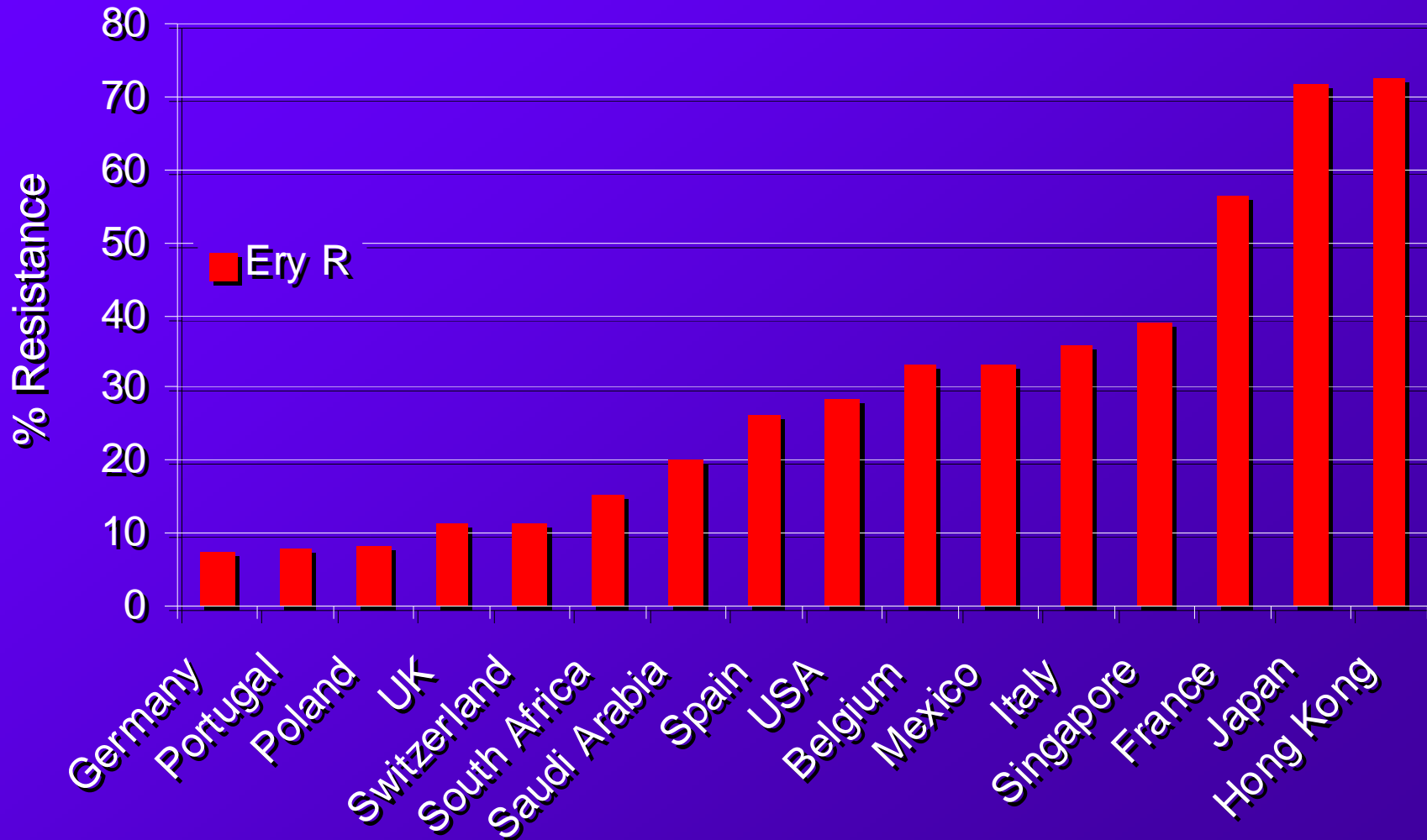
■ Pen-I+R
■ Mac-R



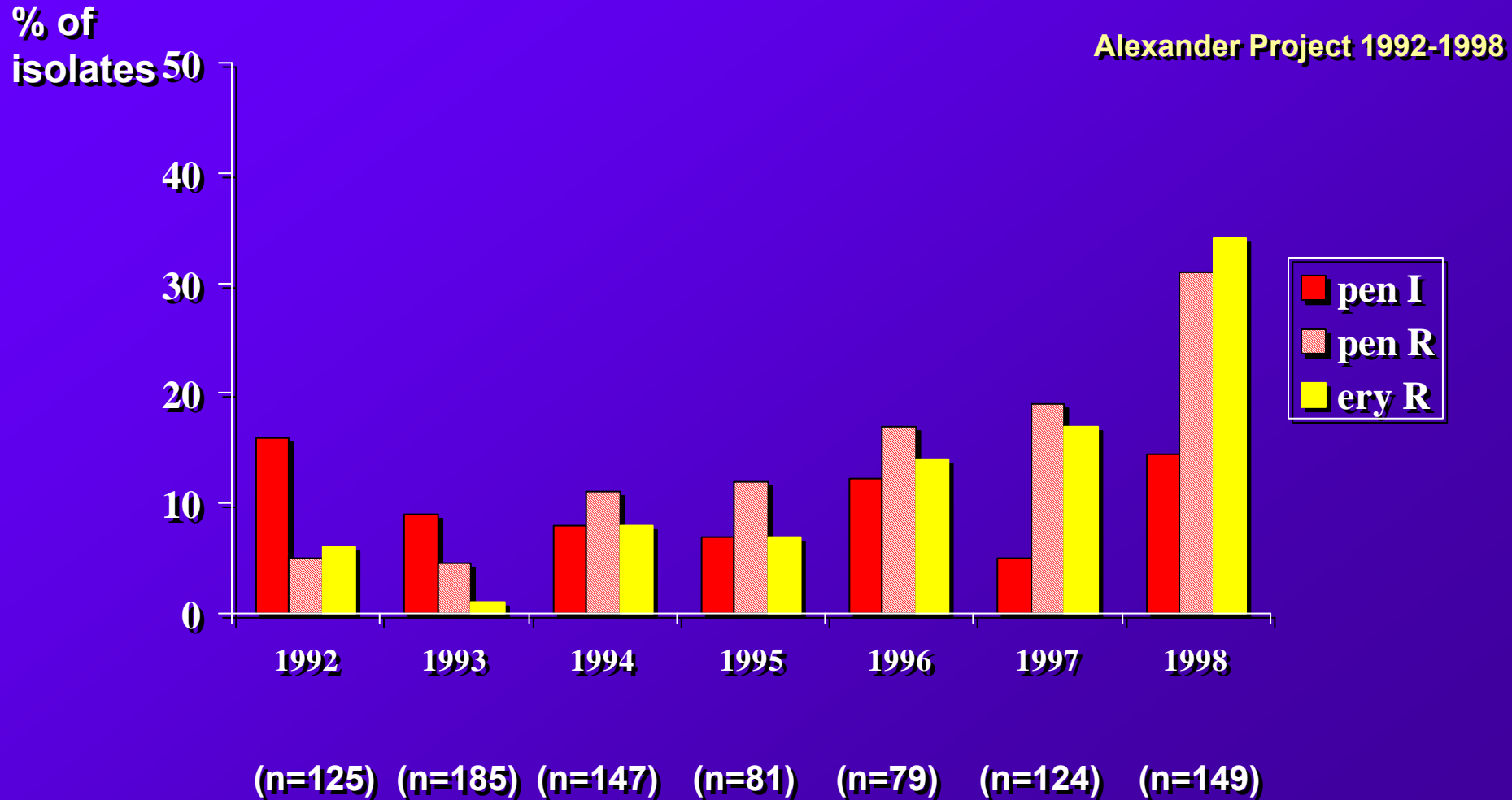
Penicillin resistance - *S. pneumoniae* Alexander Project 2001 (N=2482)



Macrolide resistance - *S. pneumoniae* Alexander Project 2001 (N=2482)



Penicillin and macrolide resistance in *S.pneumoniae* in USA 1992-1998

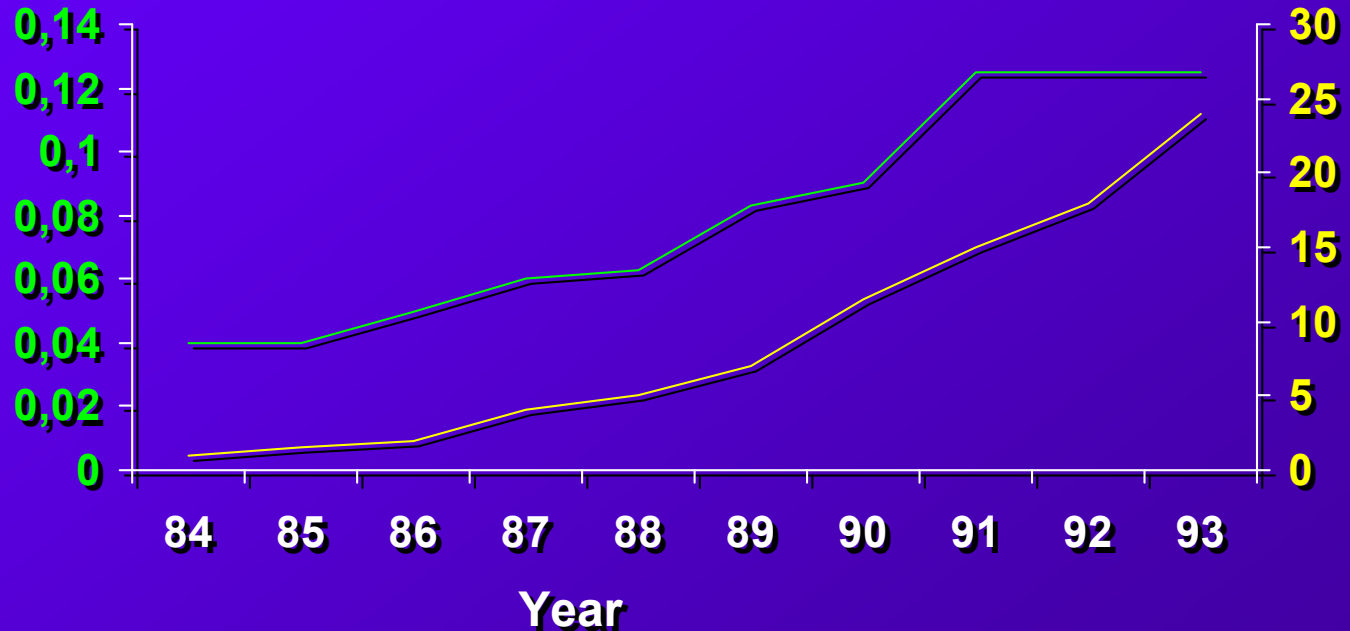


Resistance defined as erythromycin MIC \geq 1mg/L

β -lactam consumption and *S. pneumoniae* resistance – France

Ratio of cephalosporins:aminopenicillins

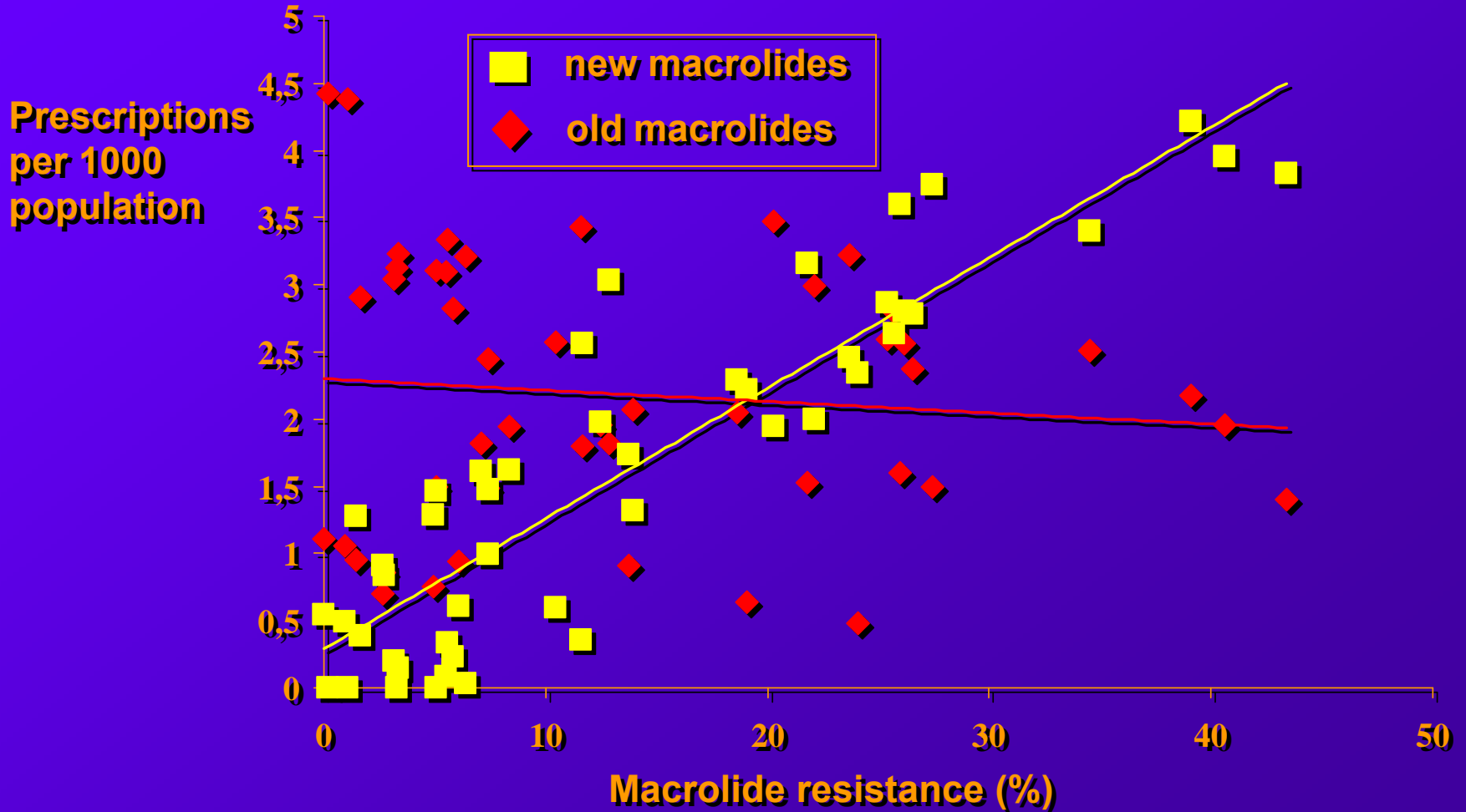
% of penicillin-resistant strains



Prescription ratio of cephalosporins:aminopenicillins in France (green) compared with the evolution of penicillin resistance in *S. pneumoniae* (yellow)

Prescribing and Resistance

Use of new macrolides correlates with increased resistance in *S.pneumoniae*



QUINOLONE RESISTANCE IN PNEUMOCOCCI

1) Very rare (<1%) in most countries

2) High incidences in Hong Kong, followed by Central and Eastern Europe (Croatia, Hungary), Spain, Canada.

3) Quinolone treatment of a patient carrying a pneumococcus carrying a silent parC has potential to select for pneumococci with more mutations in QRDR

Antibiotics can also select resistance to other antibiotic classes

- **Many strains of *S. pneumoniae* are resistant to multiple antibiotic classes (e.g. macrolide and penicillin resistance are often linked)**
- **Co-selection of resistance is a key contributor to the spread of antibiotic resistance**
- **Survival of the fittest clone => clonal spread of resistance**
- **Eradication is the best way to prevent the spread of resistant clones**
- **Eradication can only be achieved by appropriate prescribing**

EMERGENCE OF PAN-RESISTANT 19A

- Not included in the pediatric vaccine
- Resistant to all drugs approved by the FDA to treat otitis media
- 2003-2006: Among 1816 children with AOM 59 pneumococcal cases; 9 AOM caused by pan-R 19A
- Four children unsuccessfully treated by ≥ 2 antibiotics; 3 recurrent AOM; 2 with first AOM infection
- First 4 required tympanostomy after additional unsuccessful antibiotic therapy
- Other five cases treated with levofloxacin

Pichichero & Casey. JAMA 2008; 298: 1772-1778

RESISTANCE PHENOTYPE OF 19A

• Drug	MIC (µg/ml)
Penicillin G	8
Amoxicillin	8
TMP	>32
Macrolides	>32
Clindamycin	>32
Tetracycline	>16
Chloramphenicol	>2
All oral cephalosporins	>16
Ceftriaxone	6
Telithromycin	0.5
Vancomycin	0.25
Rifampin	<0.125
Cipro and levofloxacin	1

WHAT CAN BE USED TO TREAT THESE STRAINS?

- Nothing approved by the FDA

- Possibilities:

Faropenem (problems with the FDA)

Sulopenem (? Pneumococcal indication)

AR 709 (very early in development)

WIDESPREAD USE OF QUINONOLES IN BABIES IS TO BE DISCOURAGED!!!

***S. pneumoniae*: summary**

- **Percentage of penicillin- and macrolide-resistant strains is very high in many countries**
- **Strains often multi-resistant, for example, resistant to penicillin, macrolides, tetracycline and co-trimoxazole**
- **Quinolone resistance, although low, may increase in the future**
- **Amoxicillin/clavulanic acid is the most active oral agent tested**
- **The problem of non-vaccine pan-R 19A is very severe indeed: this strain will spread everywhere**



Haemophilus influenzae

... typical Gram-negative
extracellular respiratory
pathogen

β -Lactam Resistance in *H. influenzae*

Phenotype	Ampi	Amox/clav	Mechanism
BLP	R	S	TEM-1, ROB-1
BLNAR	R	R	PBP mutation
BLPACR*	R	R	Mutation in PBP3 and TEM or ROB No change in β-lactamase sequence

BLNAR and BLPACR strains were isolated in Japan. The incidence of BLNAR in Japan is approximately 30%.

***Matic V, et al. *J Antimicrob Chemother.* 2003;52:1018-1024.**

INCIDENCE OF BLNAR AND BLPACR IN FRANCE (2003)

- **β-LACTAMASE POSITIVE: 30%**
- **BLNAR: 16.2% (9.9% pure BLNAR, 6.3% BLPACR)**
- **MOST BLNAR AND BLPACR STRAINS SEEN IN ENT, BRONCHO-PULMONARY AND EYE**
- **USUALLY NONCAPSULATED**
- **FOUND IN CHILDREN AS WELL AS ADULTS**

H. Dabernat (personal communication)

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Percentage of *H. influenzae* isolates that were β -lactamase negative ampicillin-resistant (BLNAR)

Year of Isolation

1997/78

2002/03

Country	n	β -lactamase+	BLNAR	n	β -lactamase+	BLNAR
Austria	34	5.9	5.9	--	--	--
France	92	24.0	8.7	55	29.1	5.5
Germany	77	2.6	5.2	50	2.0	2.0
Italy	62	0.0	6.5	30	3.3	3.3
Netherlands	39	7.7	2.6	34	5.9	5.9
Poland	50	0.0	4.0	35	5.7	20

n, number of isolates

Fluit et al JAC 2005; 56 133-138

Percentage of *H. influenzae* isolates that were β -lactamase negative ampicillin-resistant (BLNAR)

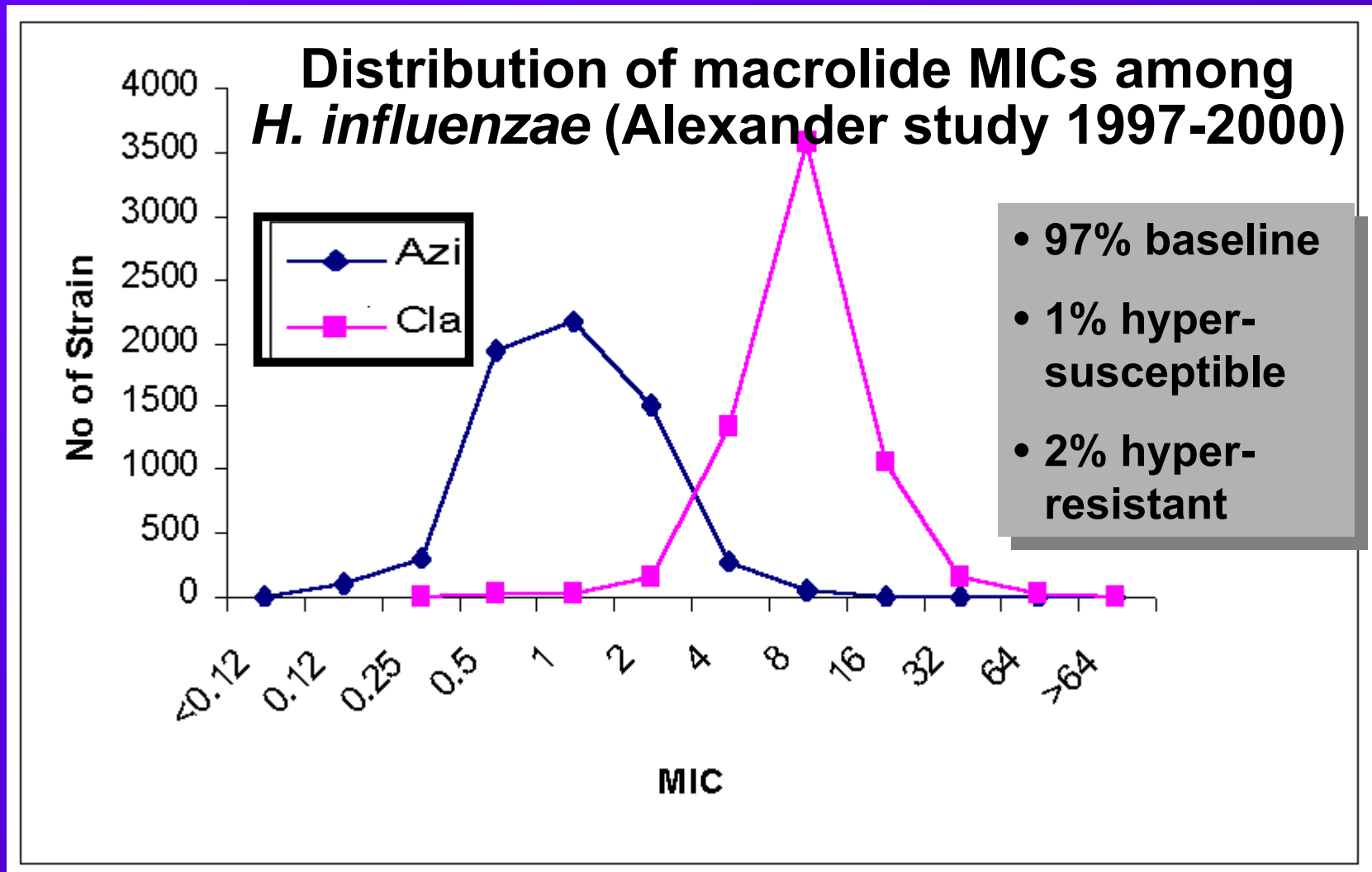
Year of Isolation

Country	1997/78			2002/03		
	n	β -lactamase+	BLNAR	n	β -lactamase+	BLNAR
Portugal	41	7.3	14.6	34	38.2	11.8
Spain	71	23.0	15.5	72	13.9	11.1
UK	33	21.2	18.2	33	21.2	18.2
Ireland	--	--	--	33	9.1	15.2
Turkey	--	--	--	40	5.0	7.5
Total	499	11.0	8.8	416	13.7	9.6

Fluit et al JAC 2005; **56** 133-138

n, number of isolates

Macrolide susceptibility of *H. influenzae*



Macrolide susceptibility

- Hypersusceptible strains

- Azithromycin <0.25 µg/ml (1.80%)
- Clarithromycin <2 µg/ml (0.58%)

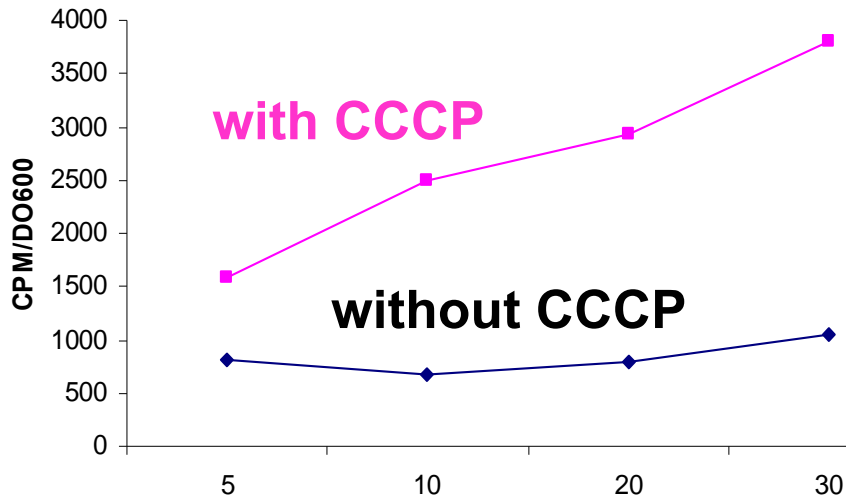
- Baseline strains

- Azithromycin 0.25-4 µg/ml (96.96%)
- Clarithromycin 2-16 µg/ml (96.66%)

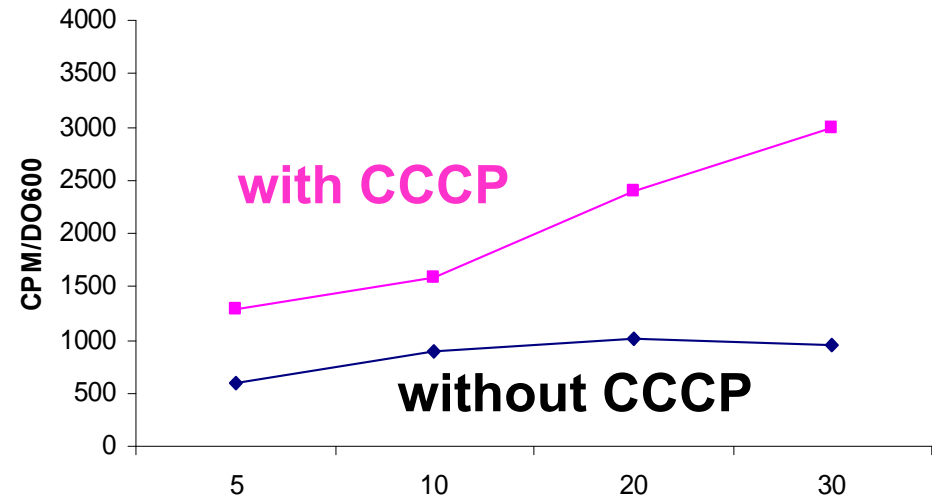
- High level resistant strains

- Azithromycin >4 µg/ml (1.28%)
- Clarithromycin >16 µg/ml (2.76%)

Baseline Strain

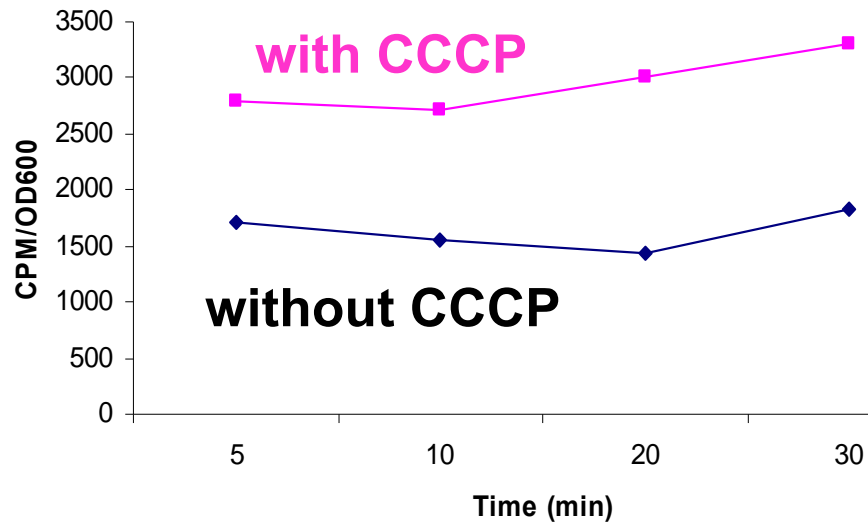


Clarithromycin accumulation

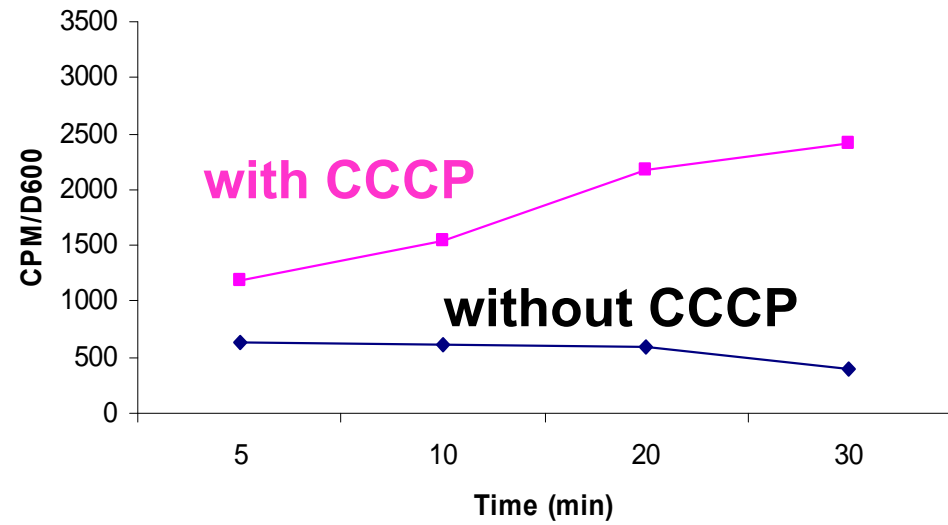


Azithromycin accumulation

High-Level Resistant Strain

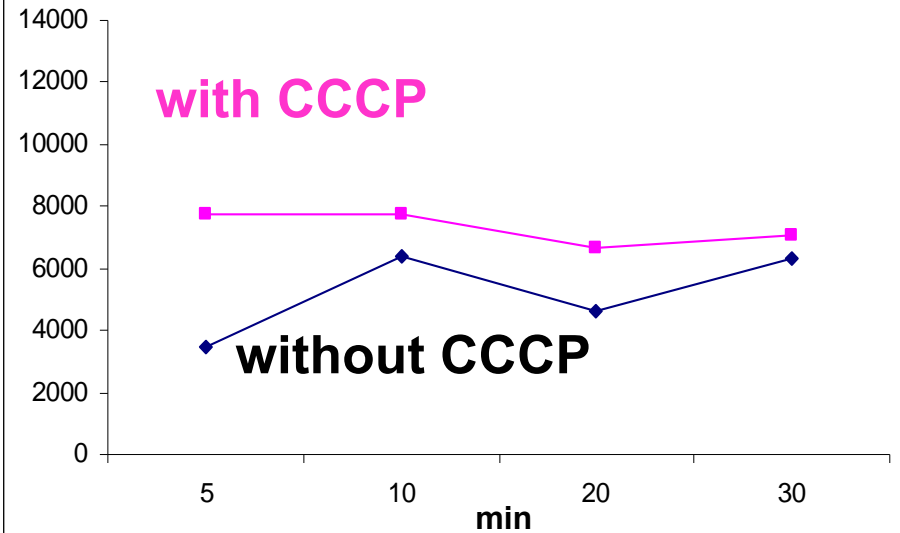
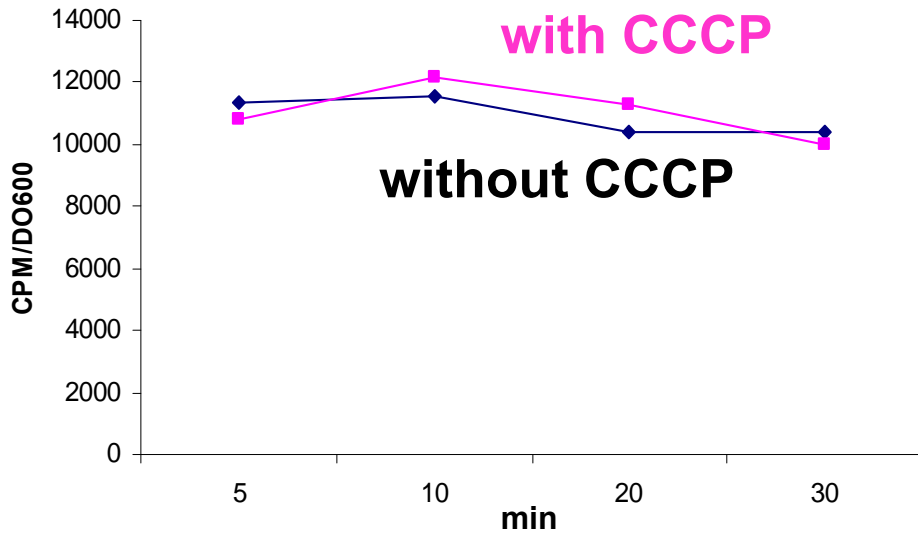


Clarithromycin accumulation



Azithromycin accumulation

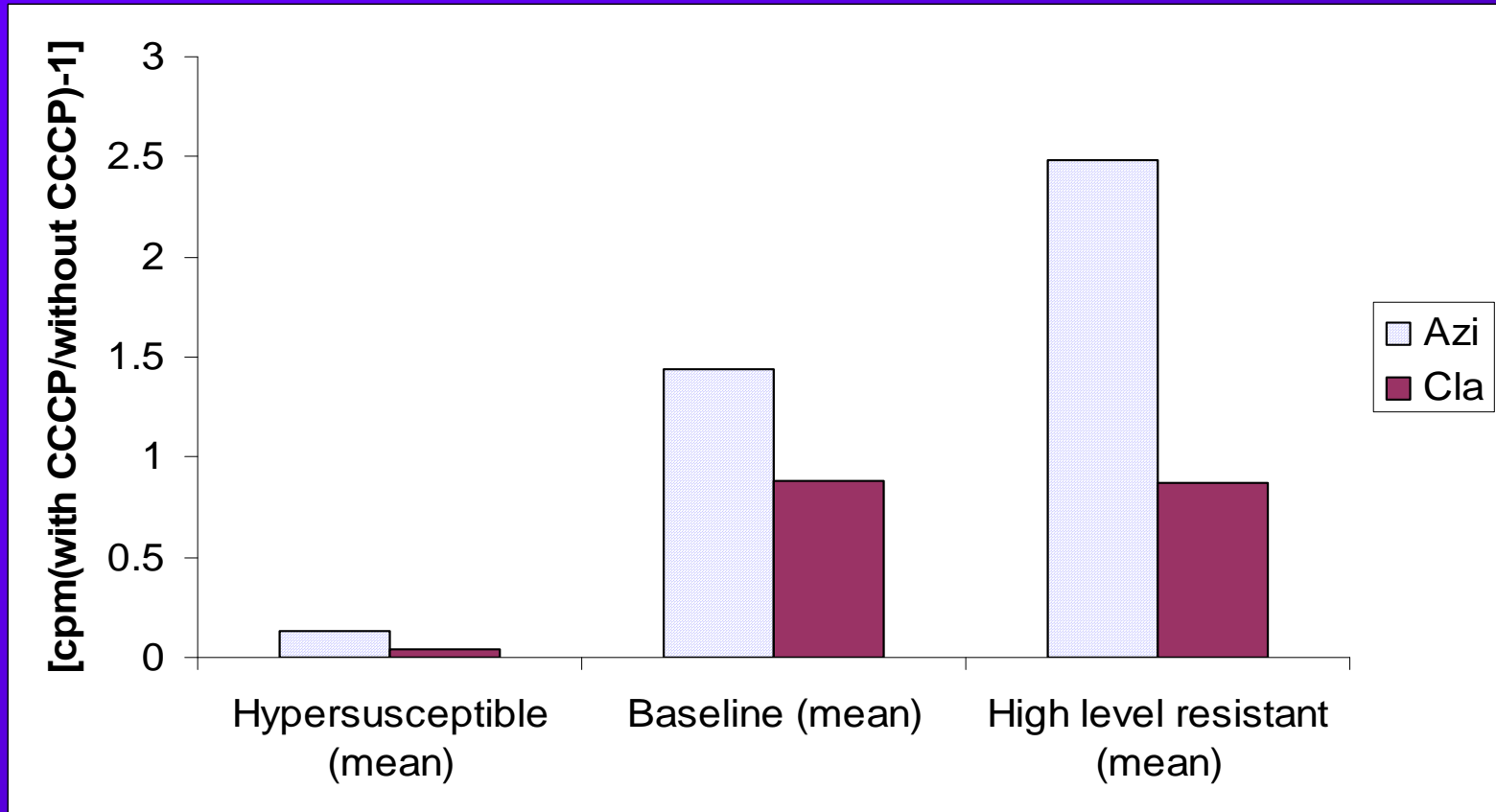
Hypersusceptible Strain



Clarithromycin accumulation

Azithromycin accumulation

Effects of Efflux Inhibitor on Accumulation



Mean values for 20 hypersusceptible, 20 baseline, and 20 resistant strains.

Conclusions

Resistance Mechanism

Strains

Efflux

Hypersusceptible strains

(-)

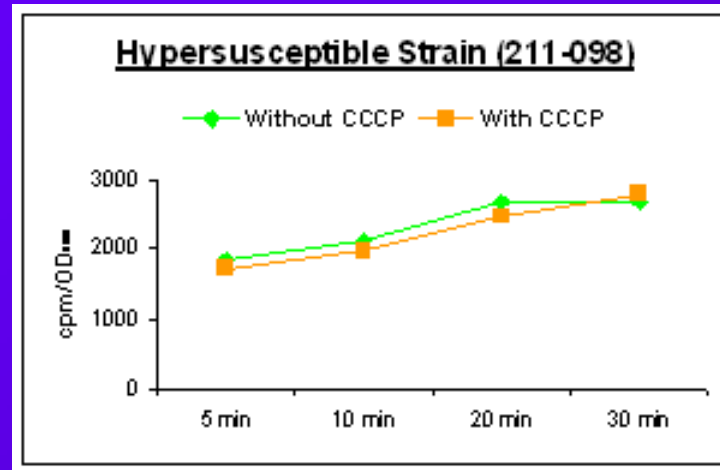
Baseline strains

(+)

High-level resistant strains

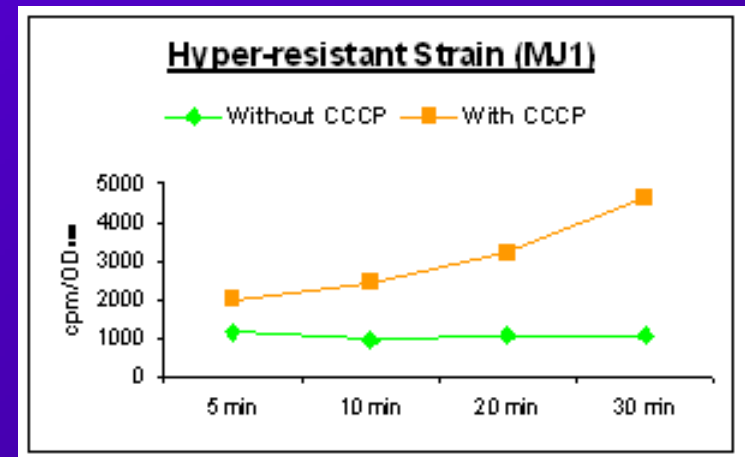
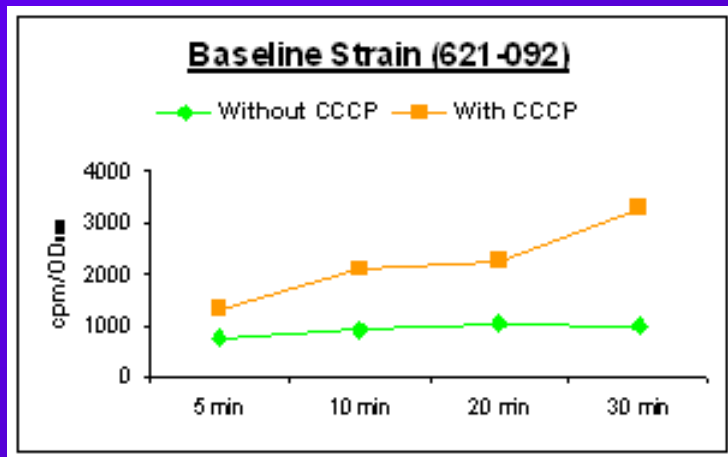
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Telithromycin Efflux in *H. influenzae*



↔ **No TEL Efflux**

↔ **No target modification (mutations)**



Telithromycin Efflux Study: SUMMARY

- *H. influenzae* with TEL MICs ≤ 0.25 $\mu\text{g/ml}$ lack TEL efflux and strains with TEL MICs ≥ 0.5 $\mu\text{g/ml}$ have efflux present
- TEL resistance mechanism (efflux pump) is present even among strains that are considered susceptible by CLSI
- Only TEL-Hypersusceptible strains have neither target modification nor efflux; they are also hypersusceptible to azithromycin and clarithromycin

Mechanisms of Resistance in Clinical *H. influenzae* With Elevated FQ MICs

<u>Strain</u>	<u>MIC (µg/mL)</u>			<u>Mutation</u>			
	<u>Gemi</u>	<u>Cipr</u>	<u>Lev</u>	<u>ParC</u>	<u>ParE</u>	<u>GyrA</u>	<u>GyrB</u>
1	0.03	0.5	0.5	S133A N138S	None	S84L	None
2	0.125	0.25	0.25	None	S458L	S84F	None
3	0.125	1	1	S84-I	None	S84L	None
4	0.25	1	0.5	D83N	Extra S	S84F, D88N	Q468R
5	0.25	1	1	E88K	G405S	S84Y	None
6	0.5	2	2	S84R	D420N	S84L, A117E	None
7	0.5	2	2	S84R	D420N	S84L, A117E	None
8	0.5	2	2	S84R	D420N	S84L, A117E	None
9	1	8	4	S84R N138S	S458A S474N	S84F, D88Y	None

***H. influenzae*: summary**

- **The proportion of β -lactamase-producing strains is relatively stable, but varies between countries**
- **Japan: 28.8% BLNAR; France: 16%; increasing elsewhere**
- **Activity of macrolides is questionable**
- **Quinolone resistance is extremely rare**
- **Co-trimoxazole resistance is as high as 40% in some areas, while tetracycline resistance is uncommon**

Overall conclusions

- **There is a worrying global trend of increasing resistance in respiratory tract pathogens**
 - ◆ **penicillin-resistant *S. pneumoniae***
 - ◆ **macrolide-resistant *S. pneumoniae* and *S. pyogenes***
 - ◆ **β -lactamase-producing *H. influenzae* and *M. catarrhalis***
- **Macrolides have limited activity against *H. influenzae***
- **Prescribing the right antibiotic is now more important than ever before**

Evaluating antibiotic efficacy using pharmacokinetics and pharmacodynamics

- Pharmacokinetics

- ◆ Serum concentration profile
- ◆ Penetration to site of infection

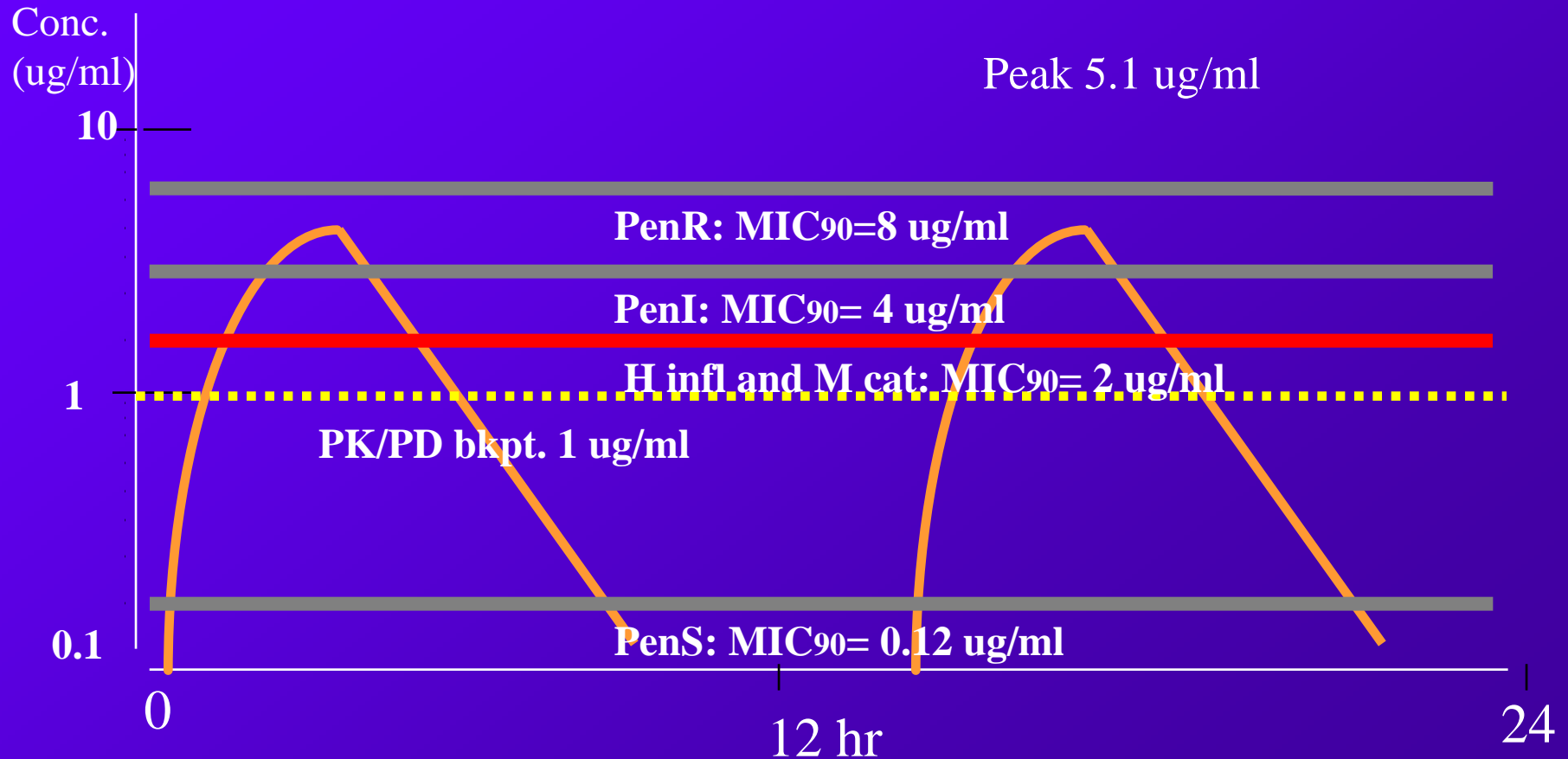
- Pharmacodynamics

- ◆ Susceptibility – MIC (potency)
- ◆ Concentration vs. time-dependent killing
- ◆ Persistent (post-antibiotic) effects (PAE)

Cefuroxime (Ceftin)

30 mg/kg/day (bid)

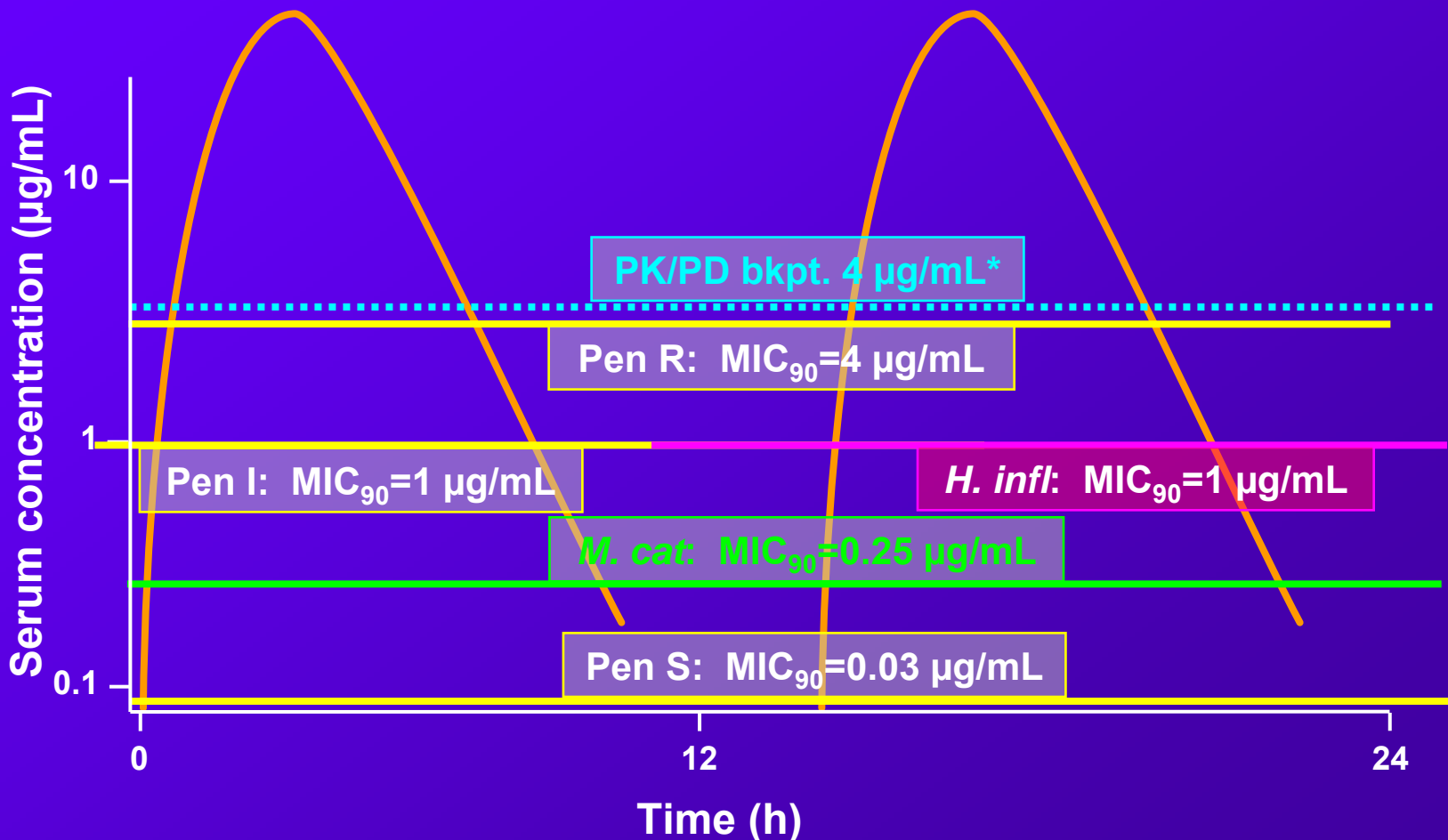
500 mg bid



Amoxicillin (*S. pneumoniae*)

Amox/clavulanate (*H. influenzae*, *M. catarrhalis*)

90 mg/kg/d (bid); (PEDIATRIC SUSPENSION)



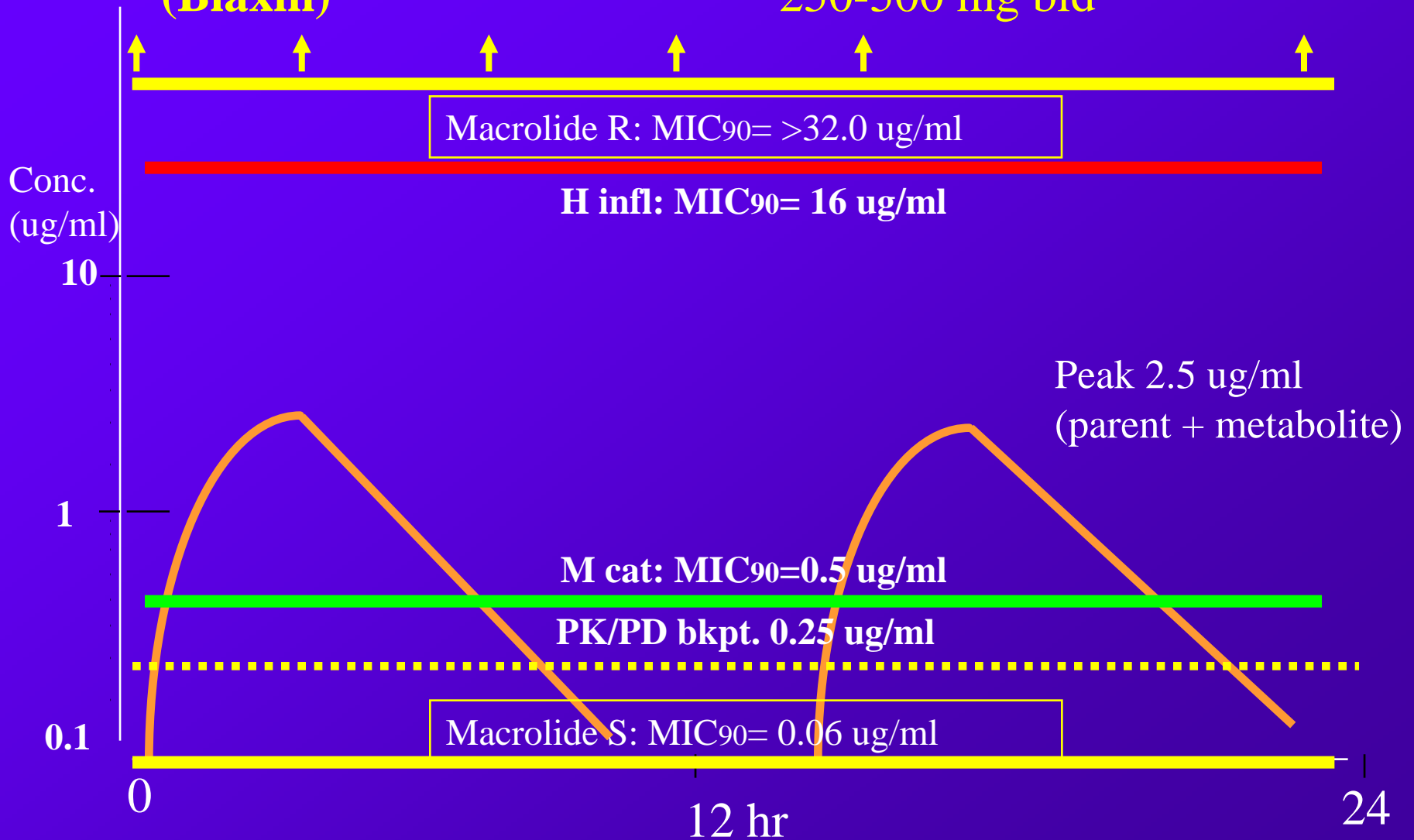
Adapted from Craig et al. *Pediatr Infect Dis J* 1996;15:944;
Jacobs et al. *Antimicrob Agents Chemother* 1999;43:1901.

Clarithromycin

15 mg/kg/day (bid)

(Biaxin)

250-500 mg bid

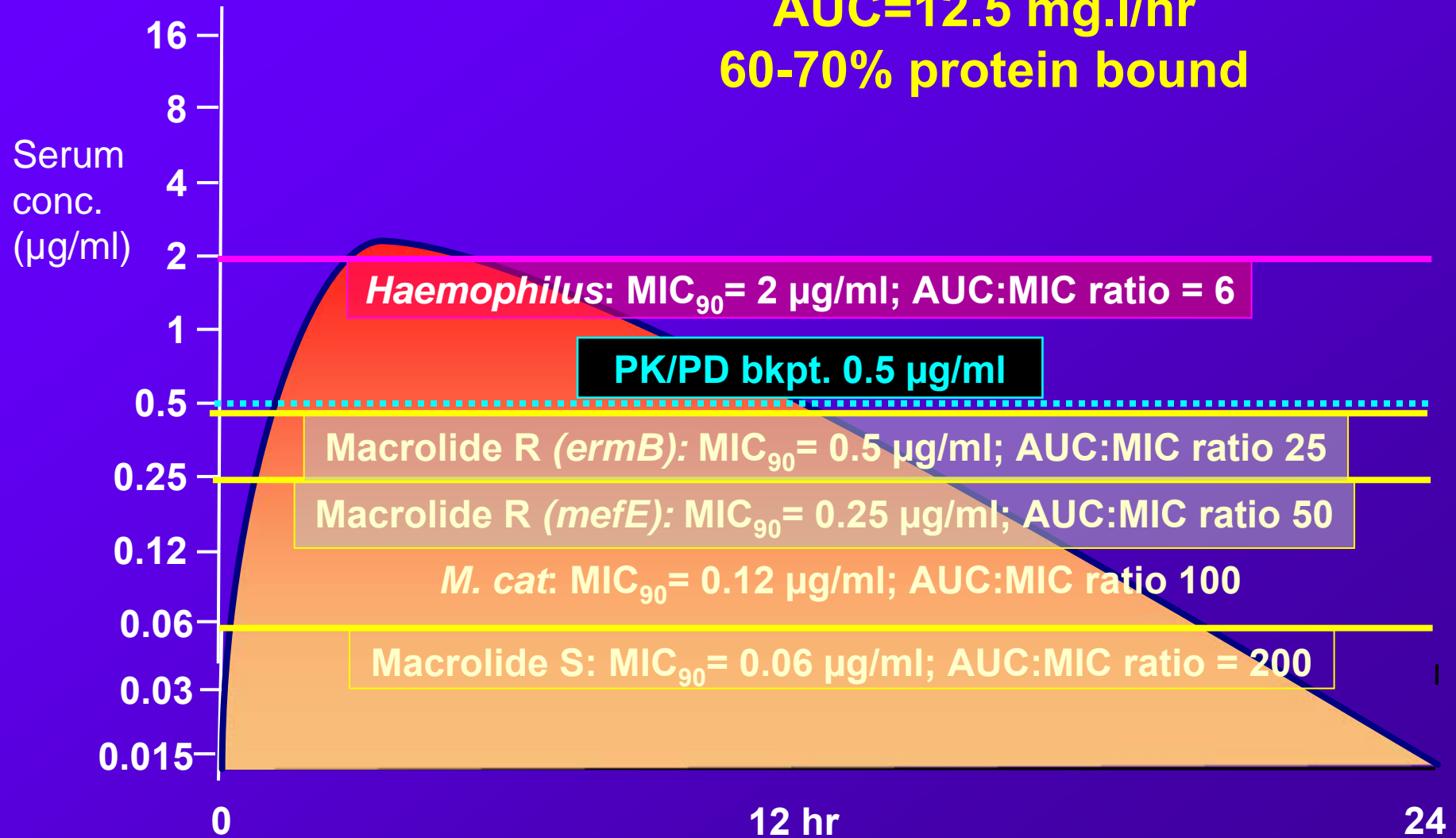


Adapted from: Schito GC et al. J Chemother 1997 (suppl n.3):18-28
and Jacobs, et al. AAC 1999,43:1901-1908

Telithromycin

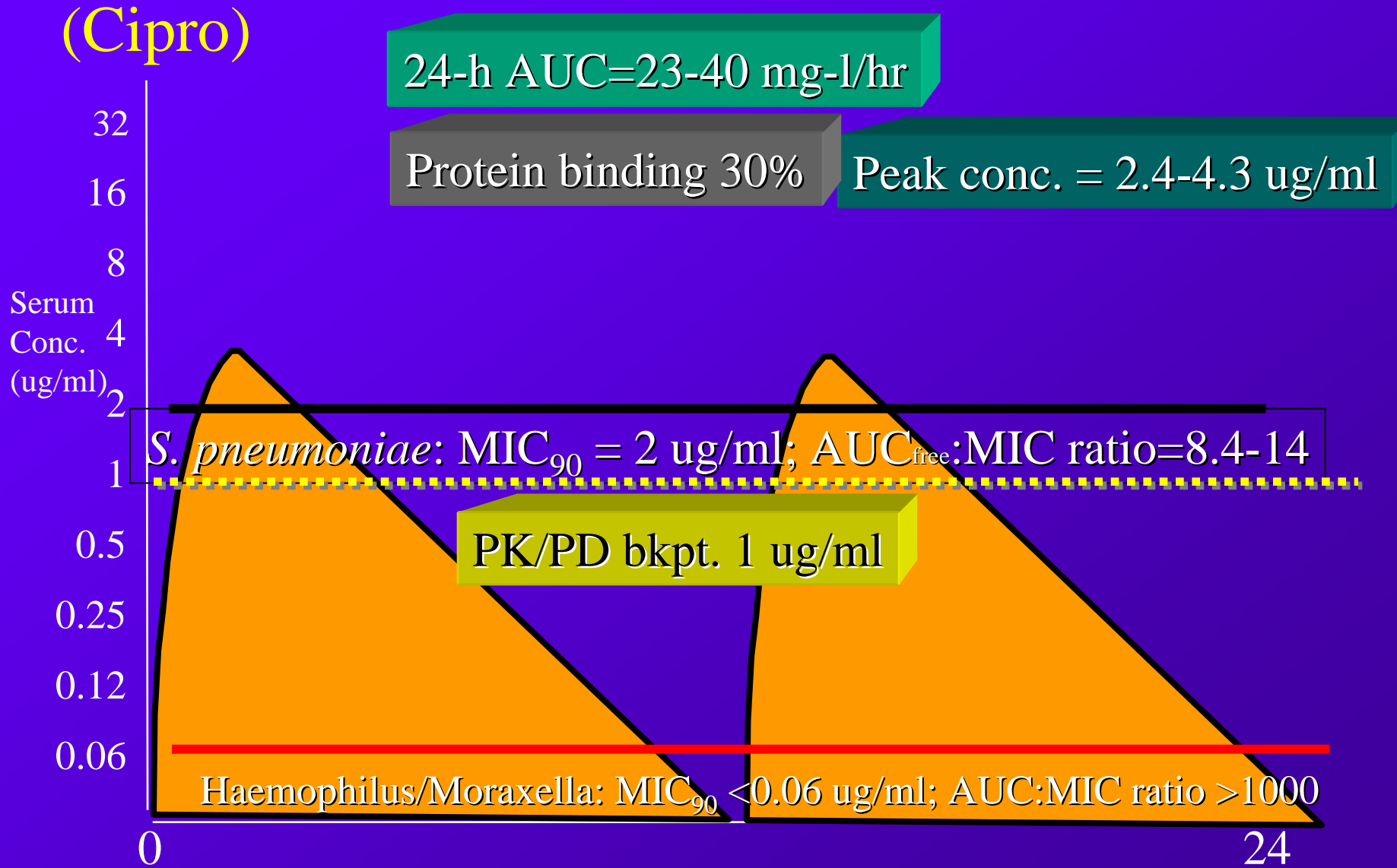
800 mg/day qd

AUC=12.5 mg.l/hr
60-70% protein bound



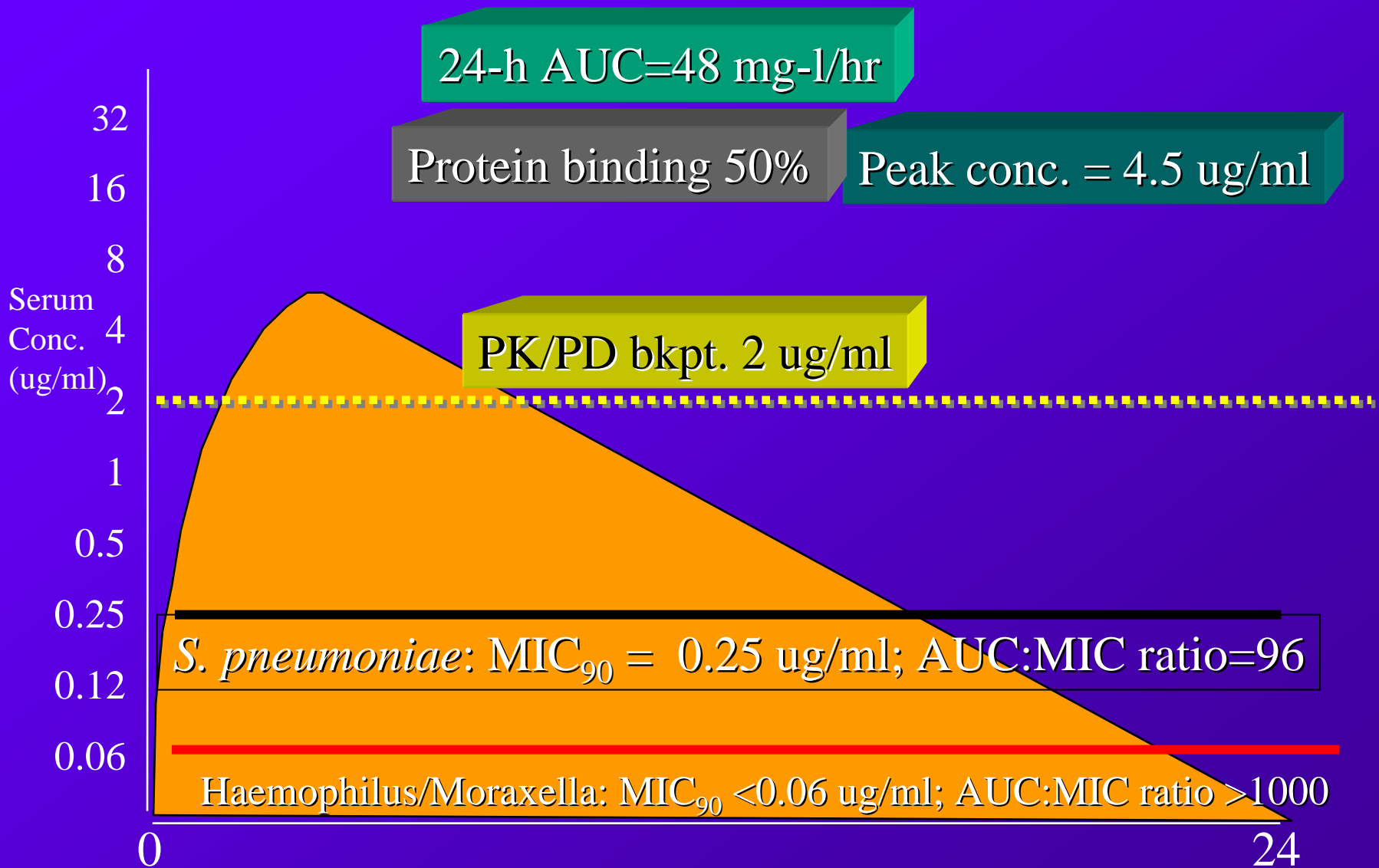
Adapted from FDA Anti-Infective Drugs Advisory Committee, 4/26/2001

Ciprofloxacin 500-750 mg bid



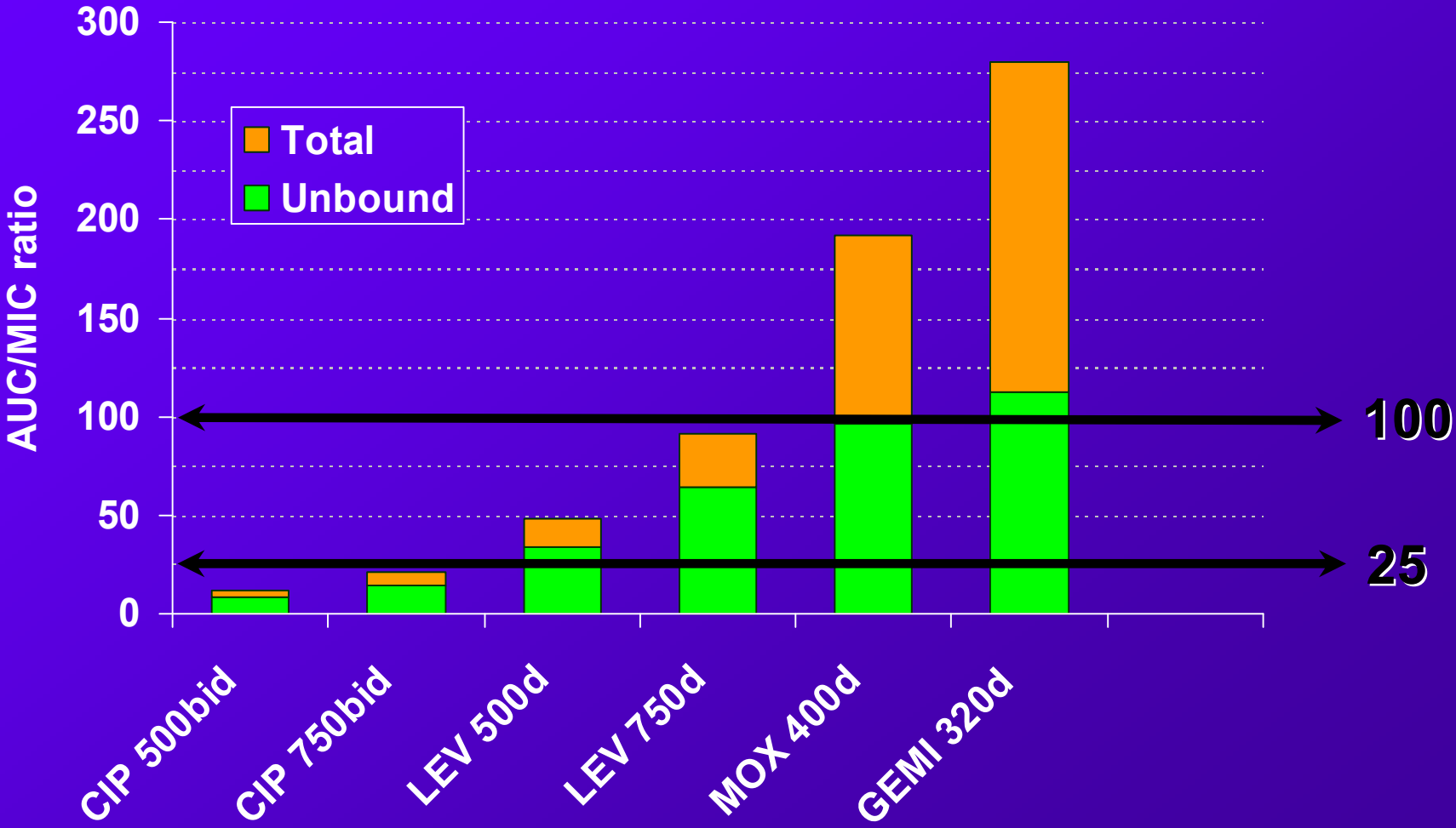
Adapted from Drusano G et al. J Chemother 1997 (suppl n.3);9:38-44 and Craig CID 1999

Moxifloxacin 400 mg qd



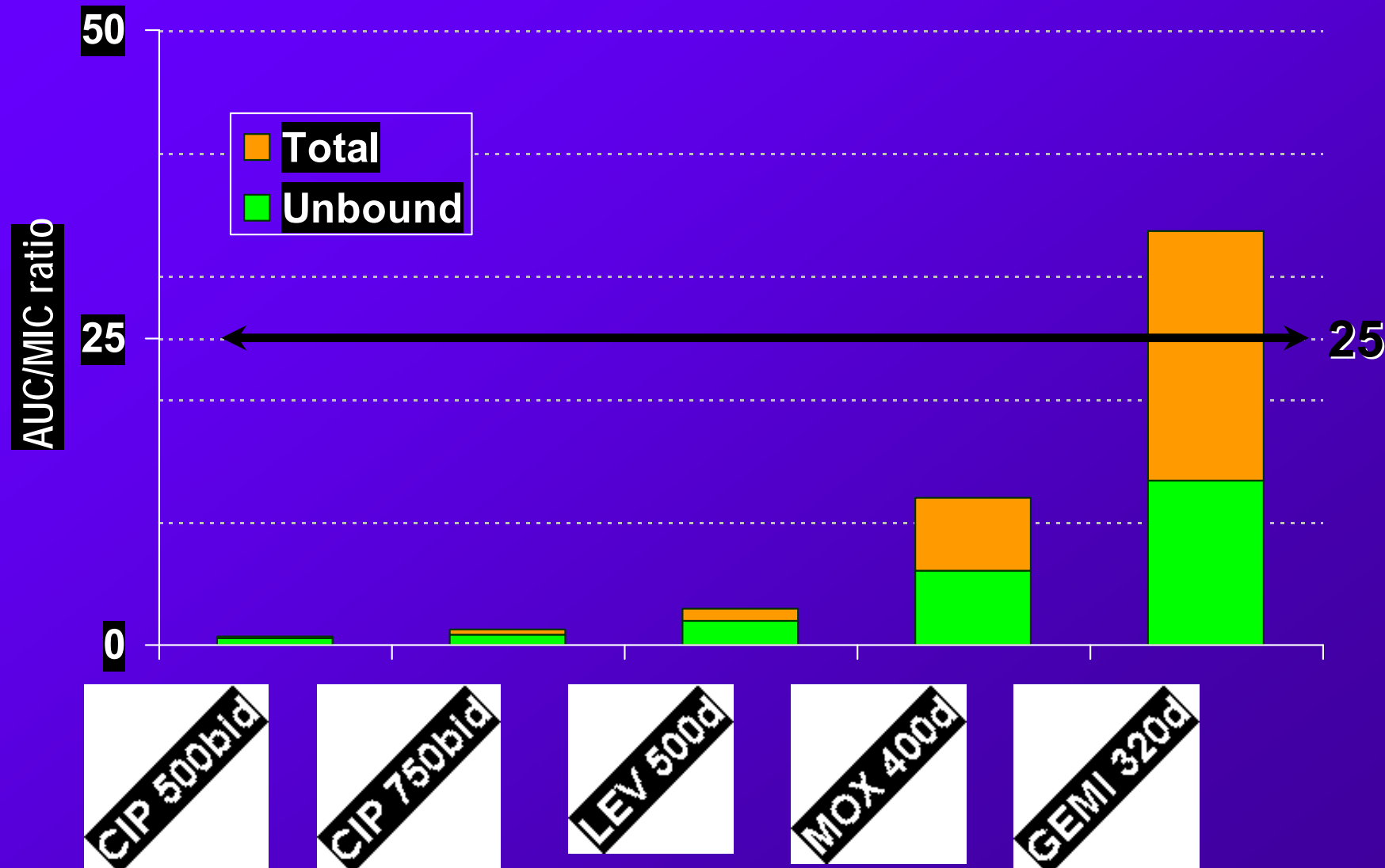
Adapted from Drusano G et al. J Chemother 1997 (suppl n.3);9:38-44 and Craig CID 1999

Fluoroquinolone AUC/MIC₉₀ ratios for *S. pneumoniae*



Adapted from Kelly et al. ICAAC 1998 abstract F-87; Turrnidge 1999 Drugs 38:supp 2: 29-36

AUC/MIC₉₀ Ratios for 75 Canadian fluoroquinolone resistant *S. pneumoniae*



*Ciprofloxacin MICs $\geq 4 \mu\text{g/mL}$. Adapted from Turnidge 1999 *Drugs* 38:S2:29-36, and Chen et al 1999 *N Engl J Med* 22:341-233-9

Conclusions

- **PK/PD parameters are useful for predicting antibiotic efficacy in respiratory infections**
- **Currently available antibiotics can vary significantly in their ability to achieve PK/PD parameter values necessary for bacterial eradication**
- **Prudent use of antimicrobials would include the choice of agents which can maximize bacteriologic and clinical cure and minimize the emergence and spread of resistant bacteria**

PAUL EHRLICH'S RECIPE FOR SUCCESS

- **GELD** (Money)
- **GEDULD** (Patience)
- **GESCHICK** (Fate)
- **GLUECK** (Luck)

Our Future Without New Antibiotics

