

FDA Advisory Committee

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KETEK[®] (telithromycin)

sanofi-aventis US

Postapproval Microbiology

Stephen Jenkins, PhD

**Professor of Pathology
Professor of Medicine
Mount Sinai School of Medicine
Director, Clinical Microbiology Laboratories
Mount Sinai Medical Center
New York, NY**

Postapproval Microbiology Studies

Primary Objectives

- Follow-up data on the activity of telithromycin against key respiratory pathogens
 - focused on *S. pneumoniae* and *H. influenzae*
 - compared findings to those for other antibacterial agents used for treatment of RTIs
- Monitor the epidemiology of *S. pneumoniae* resistance
 - trends in mechanisms of resistance (phenotypes, genotypes)
 - impact of PCV 7 vaccine (serotypes)

Methodology of Microbiologic Surveys

PROTEKT* Studies

- Longitudinal surveillance studies
- Consecutive collection of RTI isolates
- PROTEKT Global
 - ongoing since 1999
 - 35 countries / 116 sites in the 6th year of study (2004-2005)
 - central laboratory, GR Micro (London) for MICs** (CLSI*** methodology), genotyping, serotyping
- PROTEKT US
 - ongoing since 2000
 - 191 sites in the 5th year of study (2004 - 2005)
 - central laboratories, CMI (Portland, OR) for MICs** (CLSI methodology) and GR Micro (London) for genotyping, serotyping

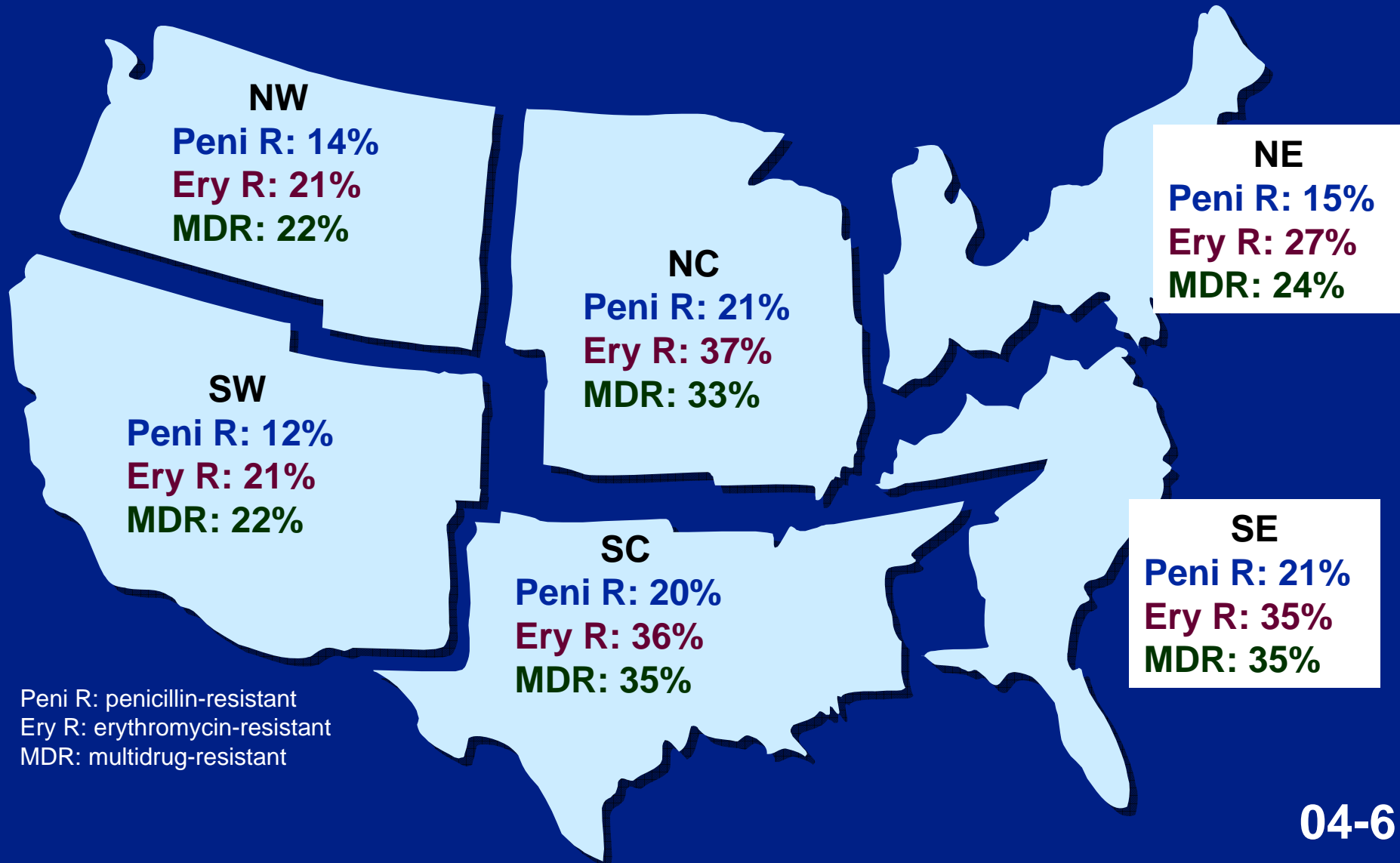
* Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin

** Minimal Inhibitory Concentration; ***Clinical Laboratory Standard Institute

PROTEKT United States

- Epidemiology by geographic area
- *In vitro* activity of telithromycin versus other antibiotics
 - *S. pneumoniae*
 - overall population
 - by age group
 - by genotype
 - *H. influenzae*

PROTEKT US Year Five: Prevalence of Resistance by Region



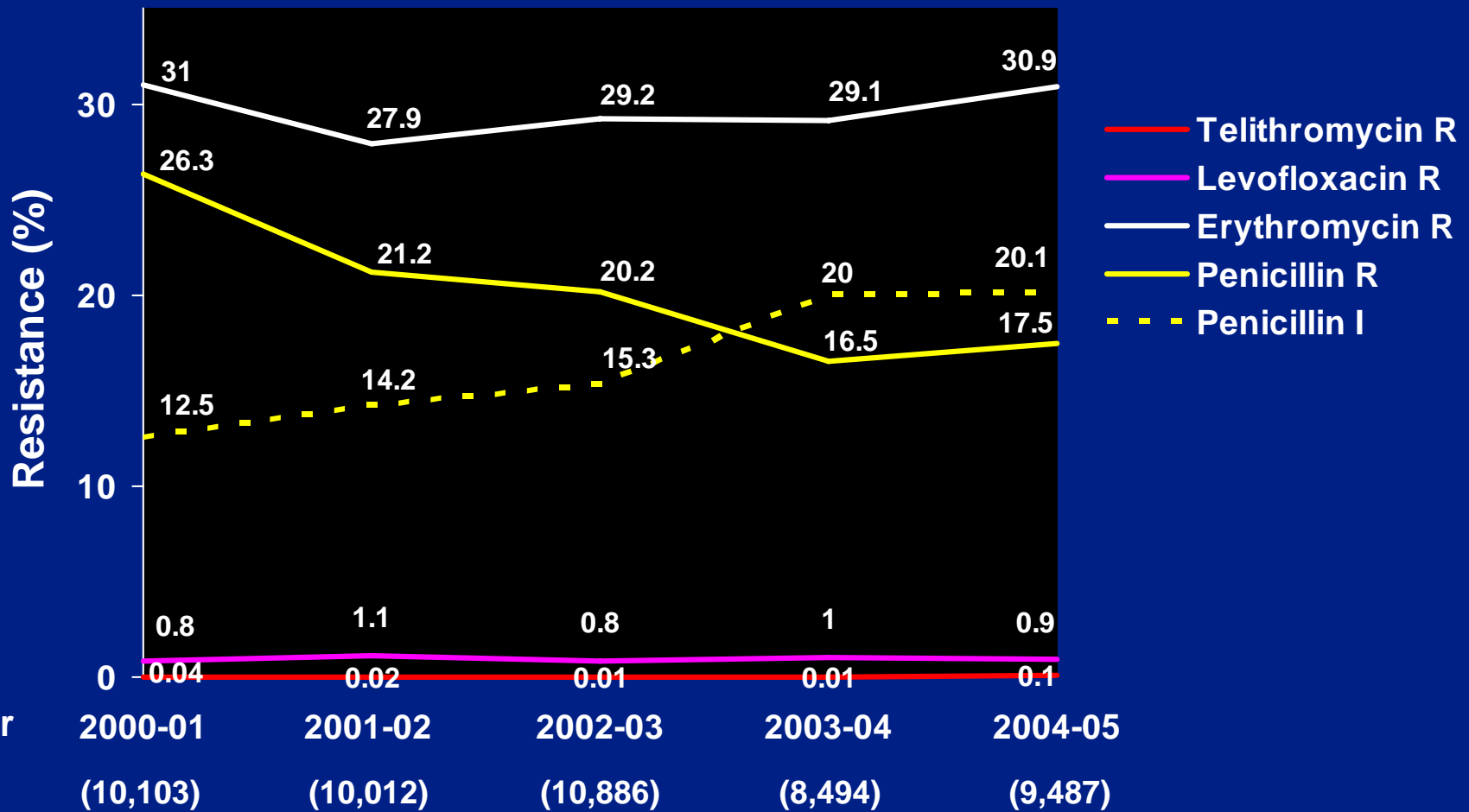
PROTEKT US Year Five: *S. pneumoniae* Phenotype Distribution and Antibiotic Activity

	N	% vs total	Resistance %				
			TEL	AZI	AMC	CXM	LEV
Total	9487	100	0.1	30.8	5.5	19.9	0.9
Penicillin resistant	1658	17.5	0.4	76.4	31.6	99.4	1.6
Erythromycin resistant	2927	30.9	0.3	99.6	17.5	47.9	1.3
Multi-drug resistant (≥ 2 classes*)	2765	29.1	0.4	83.4	19	65.6	1.8
Extended-drug resistant (≥ 5 classes*)	781	8.2	0.5	99.7	54.8	100	2

TEL: telithromycin, AZI: azithromycin, AMC: amoxicillin-clavulanic acid, CXM: cefuroxime axetil, LEV: levofloxacin

*Among penicillin, cefuroxime axetil, erythromycin, tetracycline, trimethoprim - sulfamethoxazole, levofloxacin

PROTEKT US (Years 1-5): Trends in Antibiotic Resistance Among *S. pneumoniae* Isolates



PROTEKT US Year Five: *S. pneumoniae* Antibiotic Resistance by Age Group

Resistance %

Age (Y)	N	PEN	ERY	TEL	AZI	AMC	CXM	LEV
≤ 2	1140	31.6	47.0	0.1	46.7	14.9	35.6	0.1
3-14	1149	18.8	32.7	0.1	32.7	7.2	20.7	0.1
15-64	4151	13.8	26.4	0.1	26.4	3.2	16.0	0.8
>64	2576	14.8	28.2	0.1	28.1	3.3	16.8	1.6

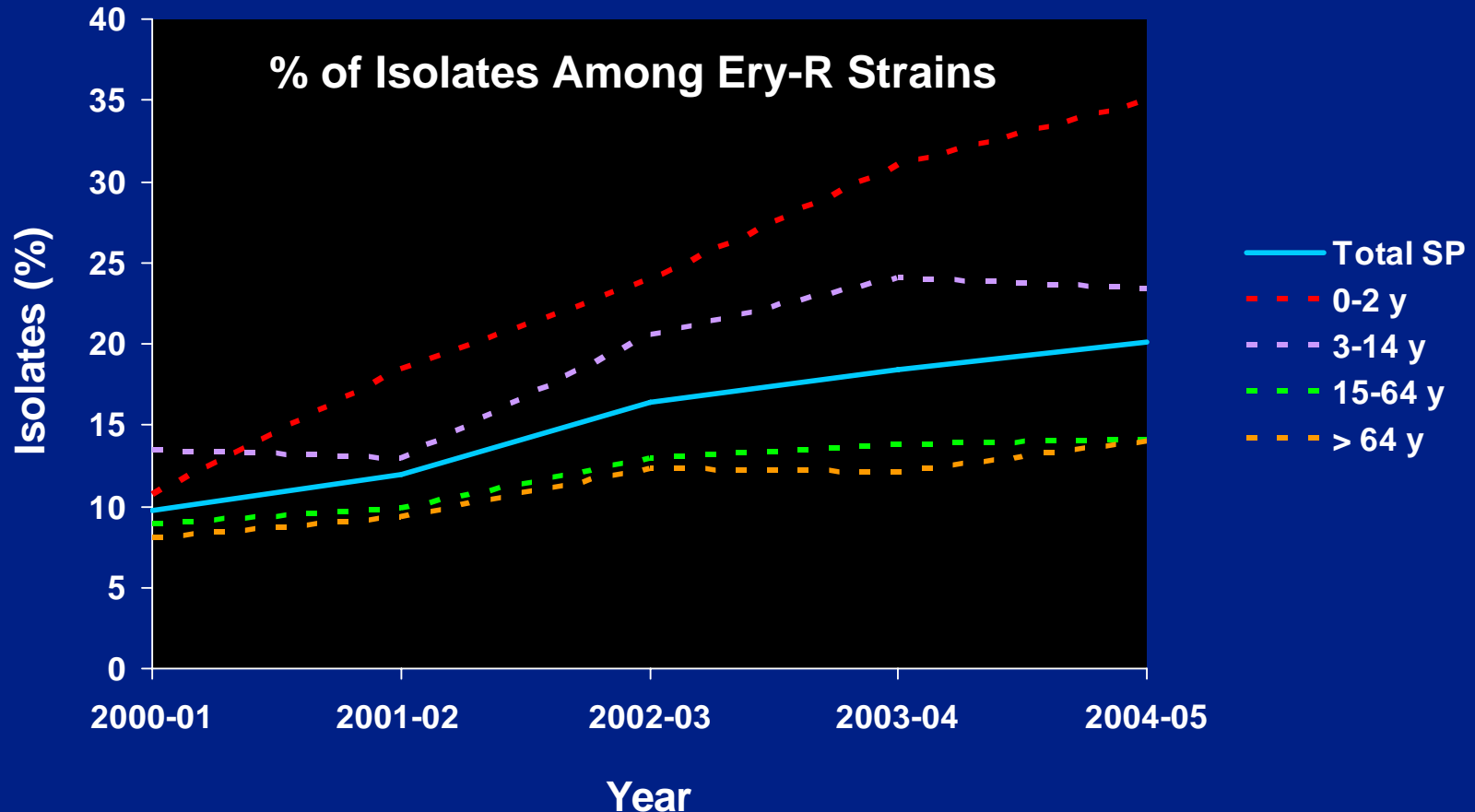
PEN: penicillin, ERY: erythromycin, TEL: telithromycin, AZI: azithromycin,
AMC: amoxicillin-clavulanic acid, CXM: cefuroxime axetil, LEV: levofloxacin

PROTEKT US Year Five: Activity of Telithromycin and Macrolides Against *S. pneumoniae* by Macrolide Resistance Genotype

Genotype	N	TEL		ERY		AZI		CLA	
		MIC ₉₀ (µg/mL)	R%	MIC ₉₀ (µg/mL)	R%	MIC ₉₀ (µg/mL)	R%	MIC ₉₀ (µg/mL)	R%
<i>erm</i> (B)	505	0.25	0.6	≥256	99.4	≥256	99.4	≥256	99.4
<i>mef</i> (A)	1768	0.5	0.1	32	99.8	32	99.4	16	99.1
<i>erm</i> (B)+ <i>mef</i> (A)	588	1	0.7	≥256	100	≥256	100	≥256	100

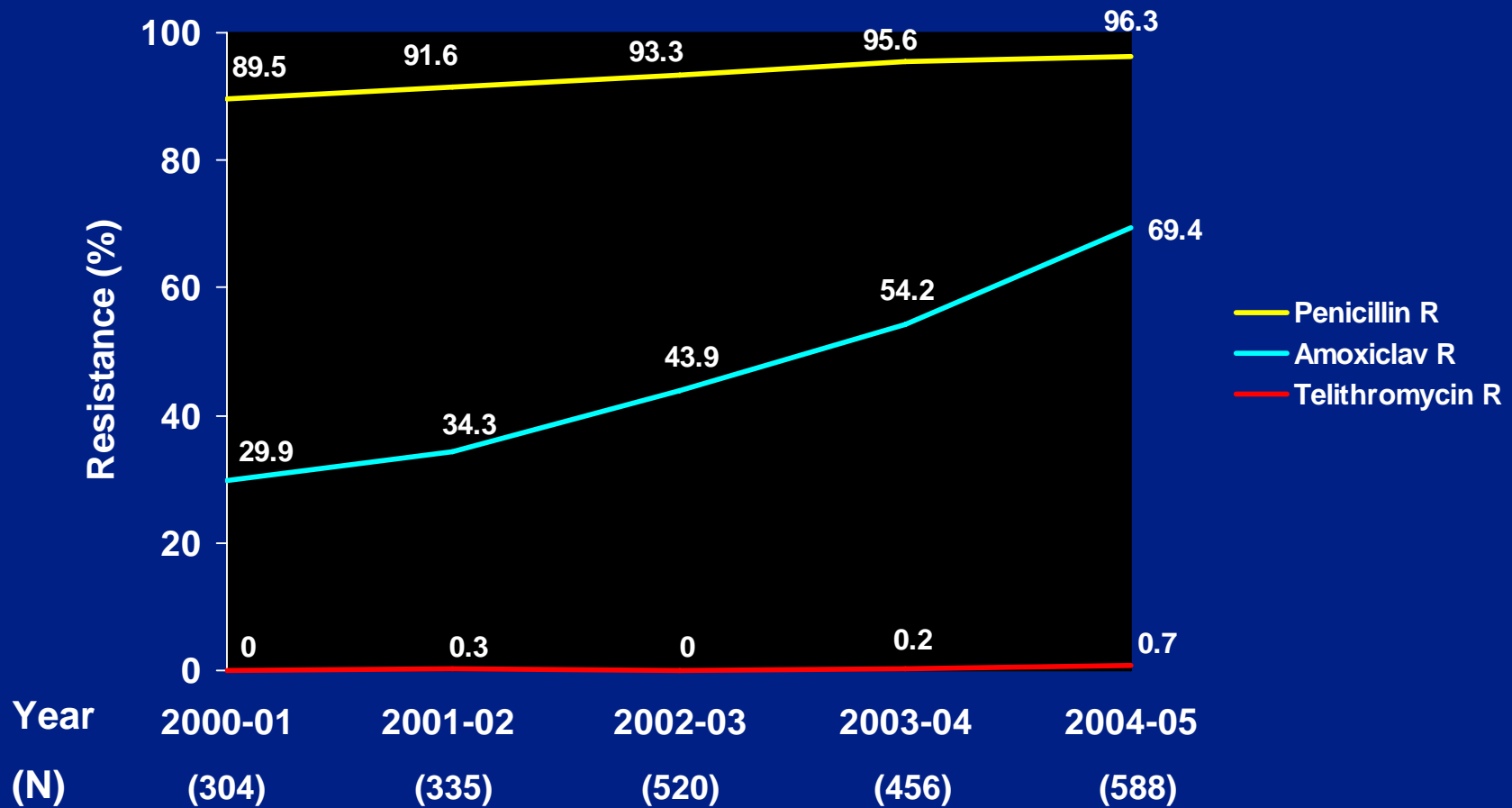
TEL: telithromycin, ERY: erythromycin AZI: azithromycin, CLARI: clarithromycin

PROTEKT US (Years 1-5) : Increase in *erm*(B) + *mef*(A) Isolates

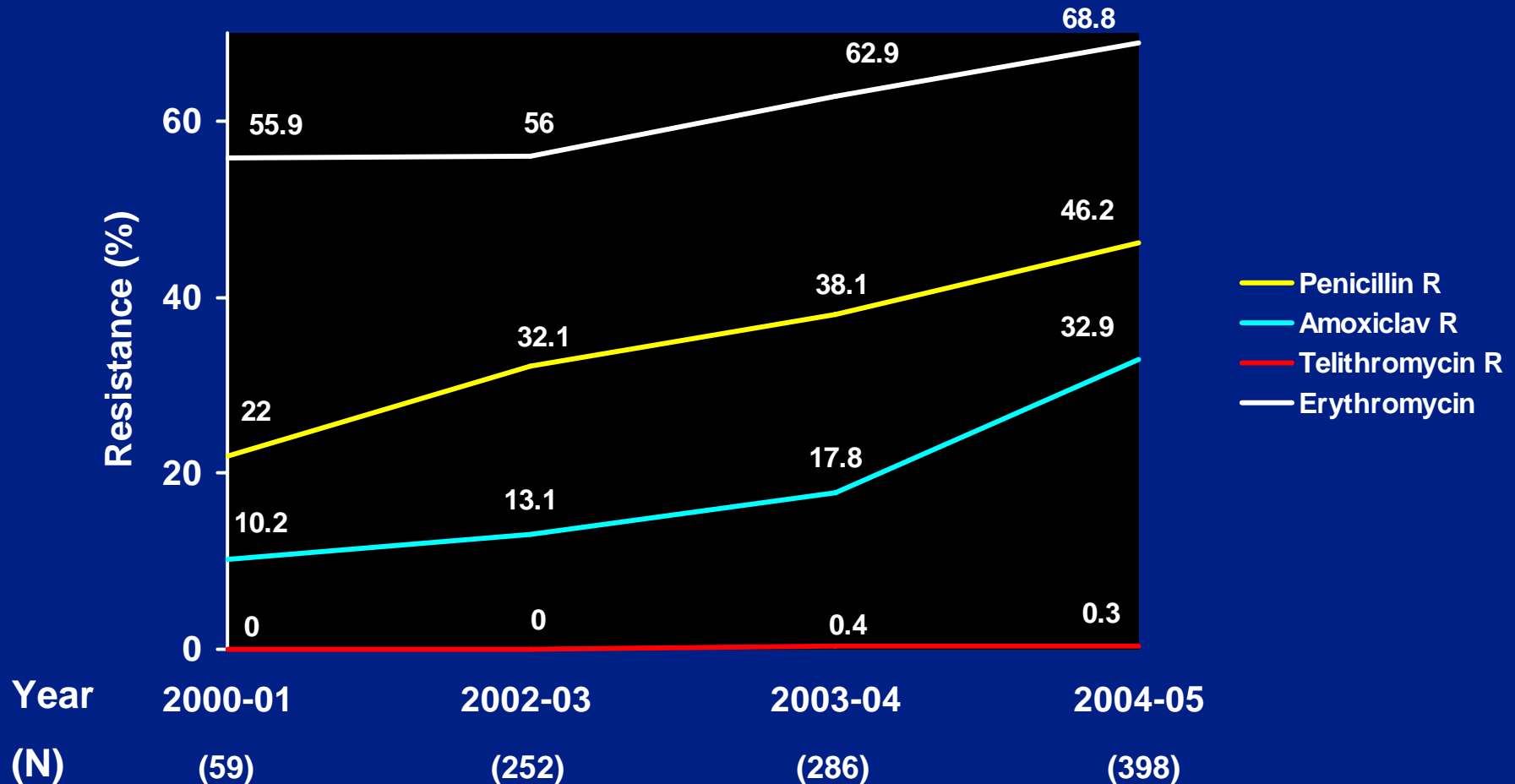


95% of the strains are clonal complex 271, mostly serotypes 19A and 19F, and multidrug resistant

PROTEKT US (Years 1-5): Increase in Amoxicillin-clavulanic Acid Resistance Among Macrolide Resistant Isolates of *S. pneumoniae* of the *erm(B) + mef(A)* Genotype



PROTEKT US (Years 1-5): Evolution of Resistance among Serotype 19A Isolates of *S. pneumoniae* in Children 0-2 Years of Age



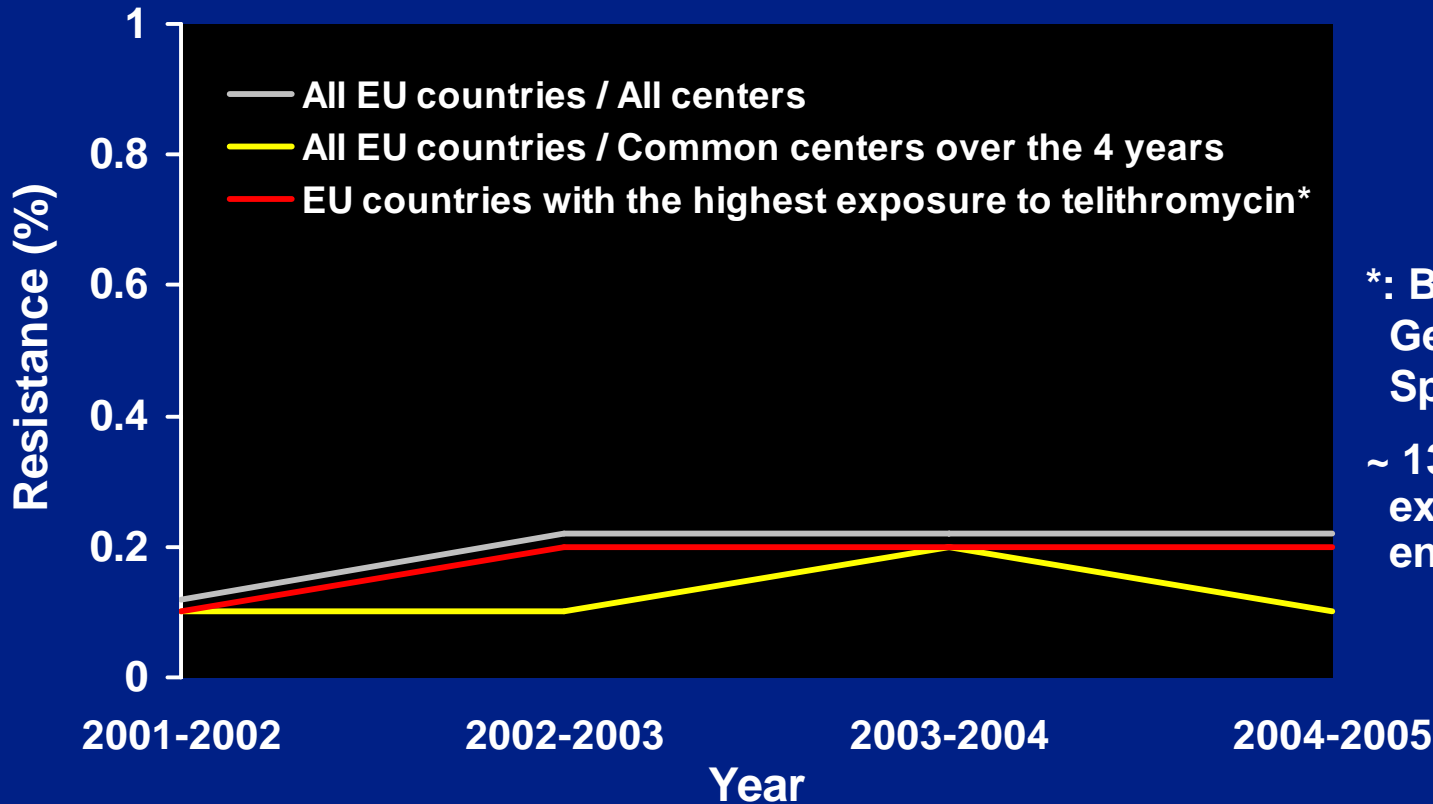
PROTEKT Global Year Six: *S. pneumoniae* Phenotype Distribution and Antibiotic Activity

	N	% vs Total	TELITHROMYCIN R %
Total	6395	100	0.2
Penicillin resistant	1233	19.3	0.7
Erythromycin resistant	2234	34.9	0.5
Multi-drug resistant (≥ 2 classes*)	2360	36.9	0.5
Extended-drug resistant (≥ 5 classes*)	551	8.6	0.2

* Among penicillin, cefuroxime axetil, erythromycin, tetracycline, trimethoprim - sulfamethoxazole, levofloxacin

PROTEKT Global: Telithromycin *in vitro* Activity in Europe

Telithromycin resistance (%)



*: Belgium, France, Germany, Italy, Spain, Turkey

~ 13 Million exposures by end of 2005

First launched in Germany: Oct 2001

Antibiotic Activity vs *H. influenzae*

	PROTEKT US		PROTEKT Global	
	Year 1	Year 5	Year 1	Year 5
Number of Isolates	2706	3,529	2986	2834
β -lactamase + (%)	28.3	27.3	16.4	13.1
TELITHROMYCIN				
MIC ₉₀ (μ g/mL)	4	4	2	2
Resistance (%)	0.6	0.6	0	0.1
AZITHROMYCIN				
MIC ₉₀ (μ g/mL)	4	2	2	2
Resistance (%)	0.6	1	0.2	0.3
AMOX-CLAV				
MIC ₉₀ (μ g/mL)	1	1	1	2
Resistance (%)	0.3	0.3	0.1	3.6
CEFUROXIME AXETIL				
MIC ₉₀ (μ g/mL)	4	4	2	4
Resistance (%)	0.5	0.5	0.1	5
LEVOFLOXACIN				
MIC ₉₀ (μ g/mL)	0.06	0.06	0.015	0.03
Resistance (%)	0.4	0.3	0	0

Summary

- Telithromycin's activity against *S. pneumoniae* remains high in the US and worldwide (resistance rate ~ 0.1%)
 - no signal of increased resistance
 - no indication of clonal spread of resistance
- Telithromycin maintains activity against increasingly common, highly antibiotic-resistant strains of *S. pneumoniae*
 - *erm(B)* + *mef(A)* strains
 - 19A serotype (not included in the PCV7 vaccine);
- Activity remains stable against *H. influenzae*