What's new with antibiotics, 2005

David Livermore

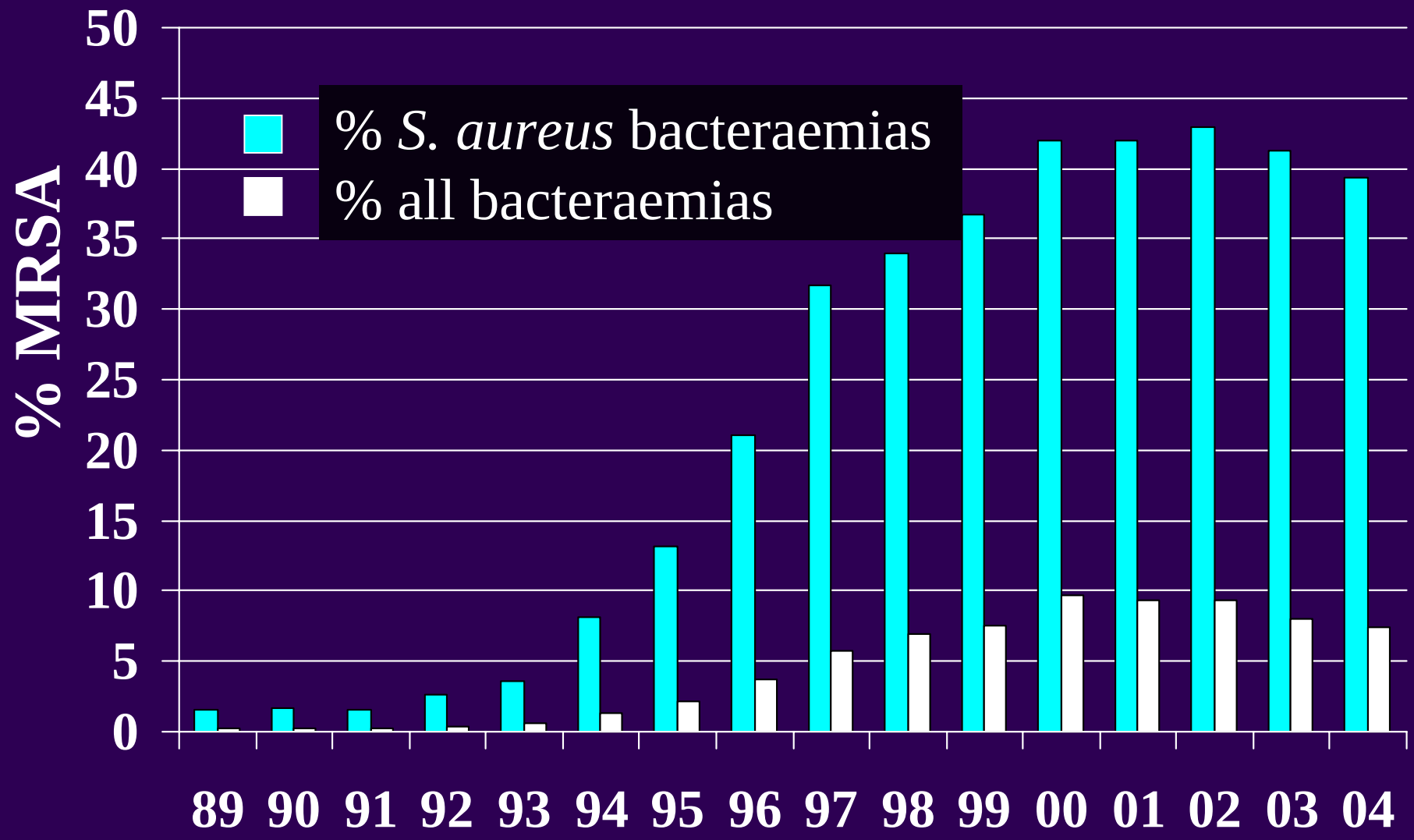
Health Protection Agency,

Colindale, London

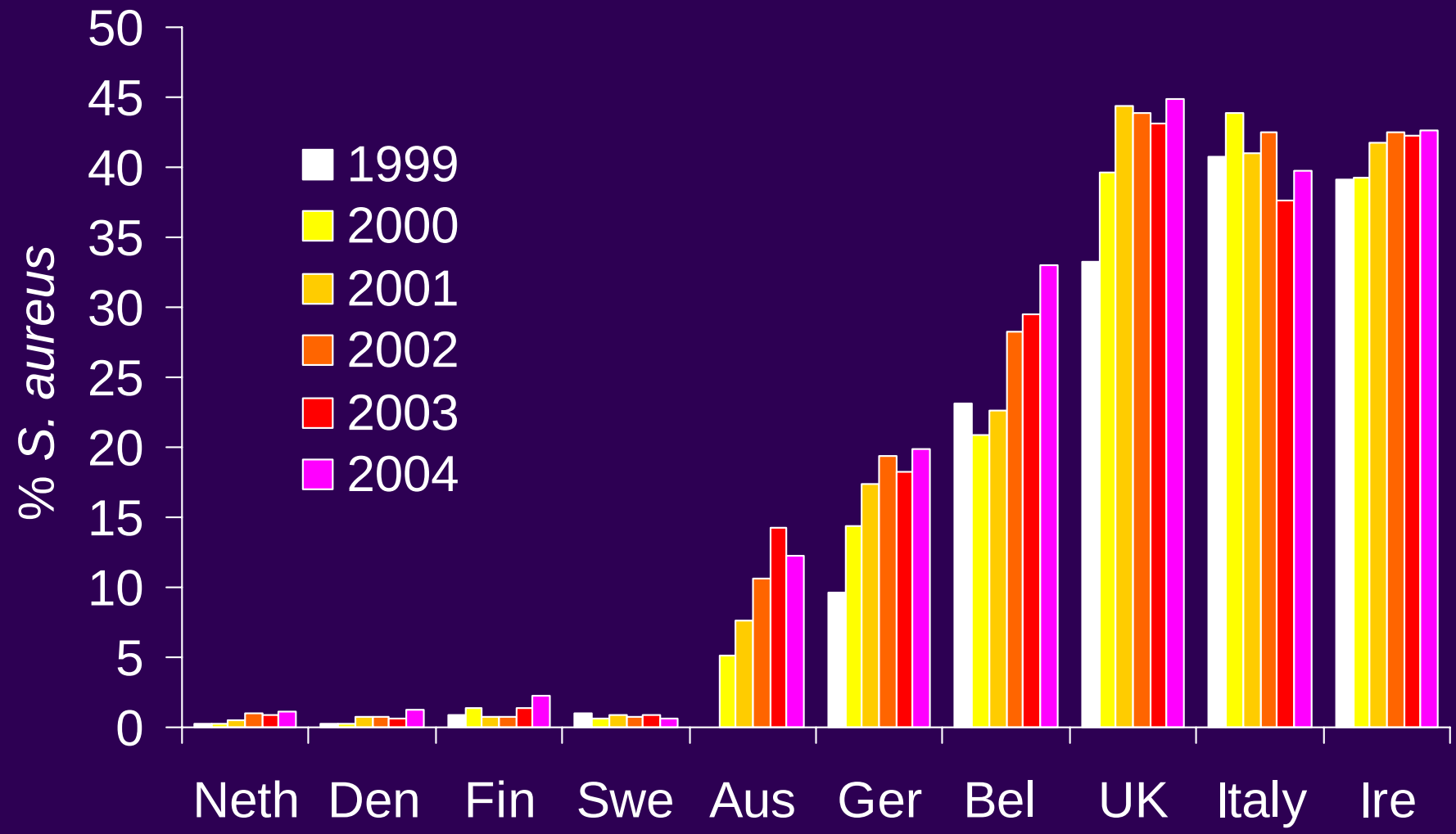
Big developments 1998-2005

- Rise of MRSA
- Ciprofloxacin resistance
- *E. coli* turning nasty
- Pan-resistant non-fermenters
- Failure to control resistance of any wide scale
- Decline of antimicrobial research

MRSA bacteraemia, England & Wales

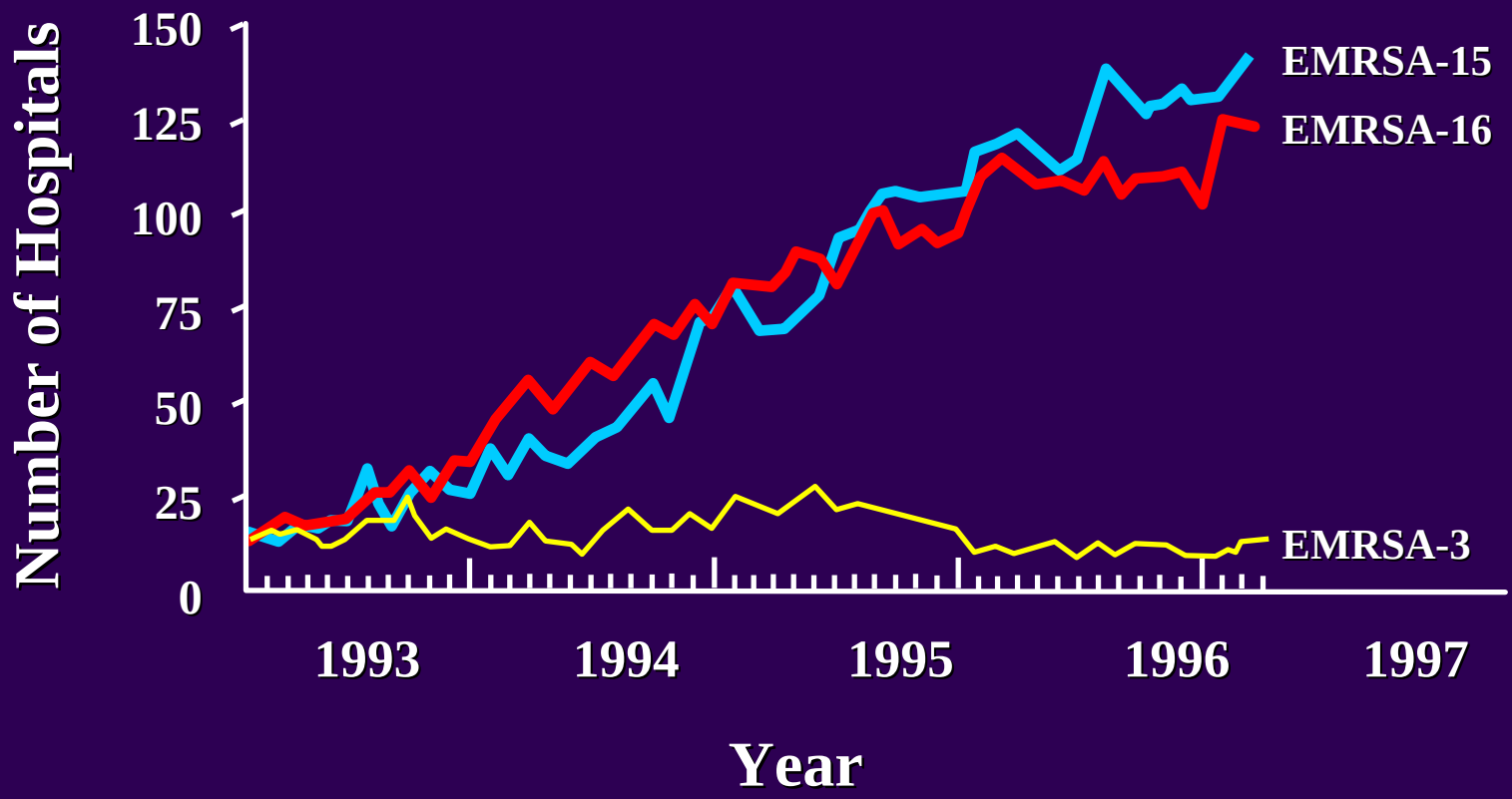


MRSA in bacteraemia: EARSS



http://www.earss.rivm.nl

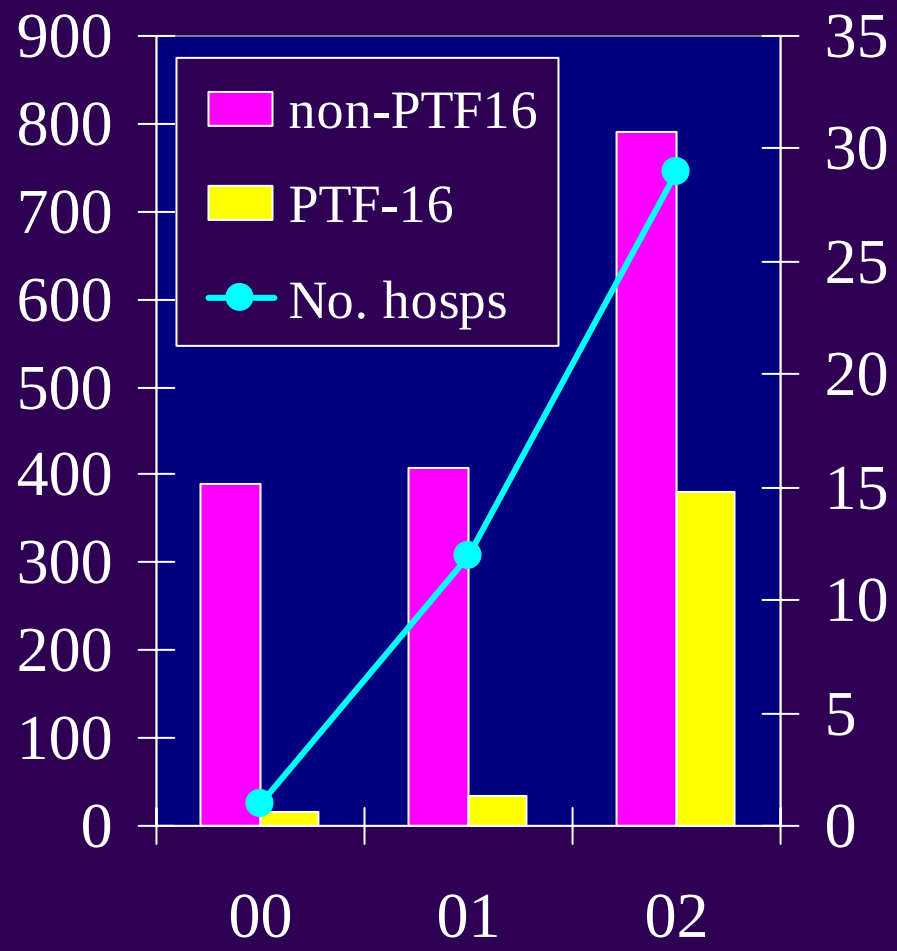
Hospitals affected by EMRSA-3, -15, & -16



Data CPHL-Laboratory of Hospital Infection

Netherlands- selection of difficult-to-detect MRSA

- Effective search & destroy vs. MRSA
- Rates generally <1%
- Rise of PTF-16 in 2001
- Oxacillin MICs 8-32 mg/L
- Missed by diagnostic labs



Wannet *et al. JCM* 2004, **42**, 3077

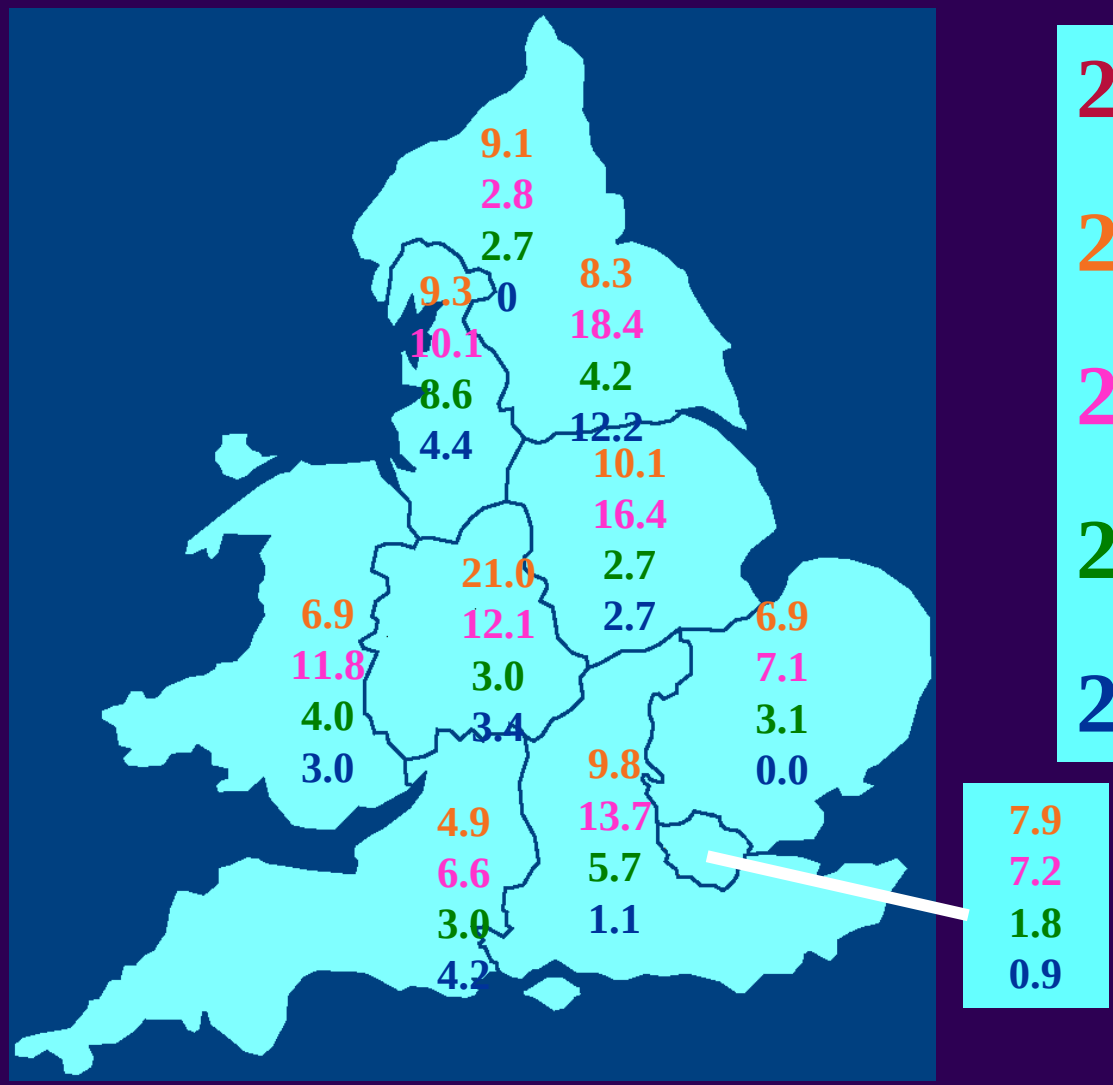
Community MRSA

- New acquisition of SCC*mec*IV by *S. aureus*
- In US: ST5 & ST8, mostly R only to β-lactams
  - –Outbreaks linked to contact sports, prisons, bath-houses
- In Europe: ST80, R also to tetracyclines & fucidin
  - –Infrequent but increasing scatter of reports, few outbreaks
- US & European strains often have Panton-Valentine leukocidin

Why fluoroquinolone resistance seemed unlikely

- Starting MICs for enterobacteria & gonococci <0.01 mg/L
- Resistance needs 3-4 separate mutations; ……probability $<10^{-21}$
- No plasmid mediated resistance had been found to nalidixic acid

Cipro resistance (MIC ≥1 mg/L), N. gonorrhoeae-GRASP, 2000-02



2004, 15%

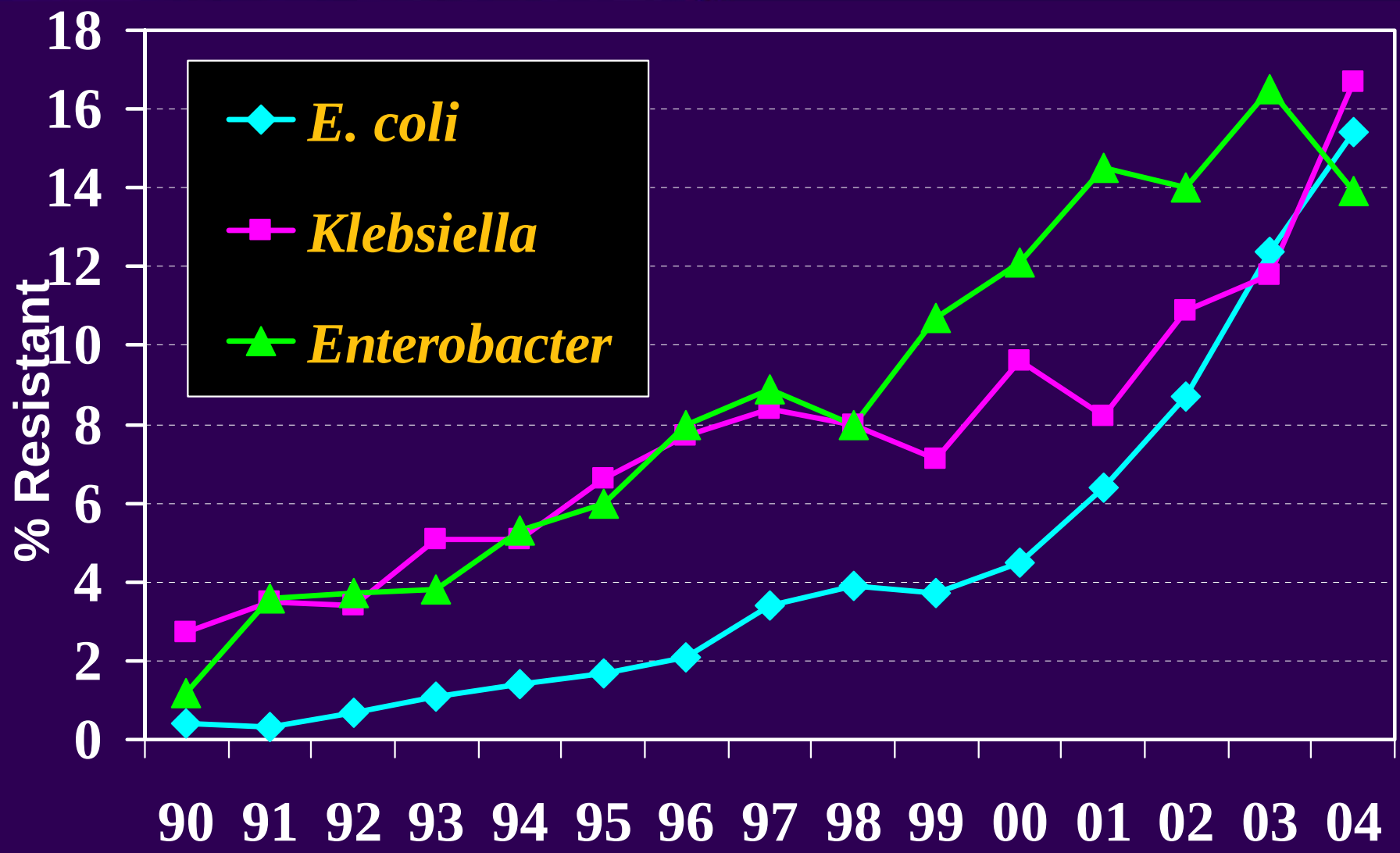
2003, 9%

2002, 10%

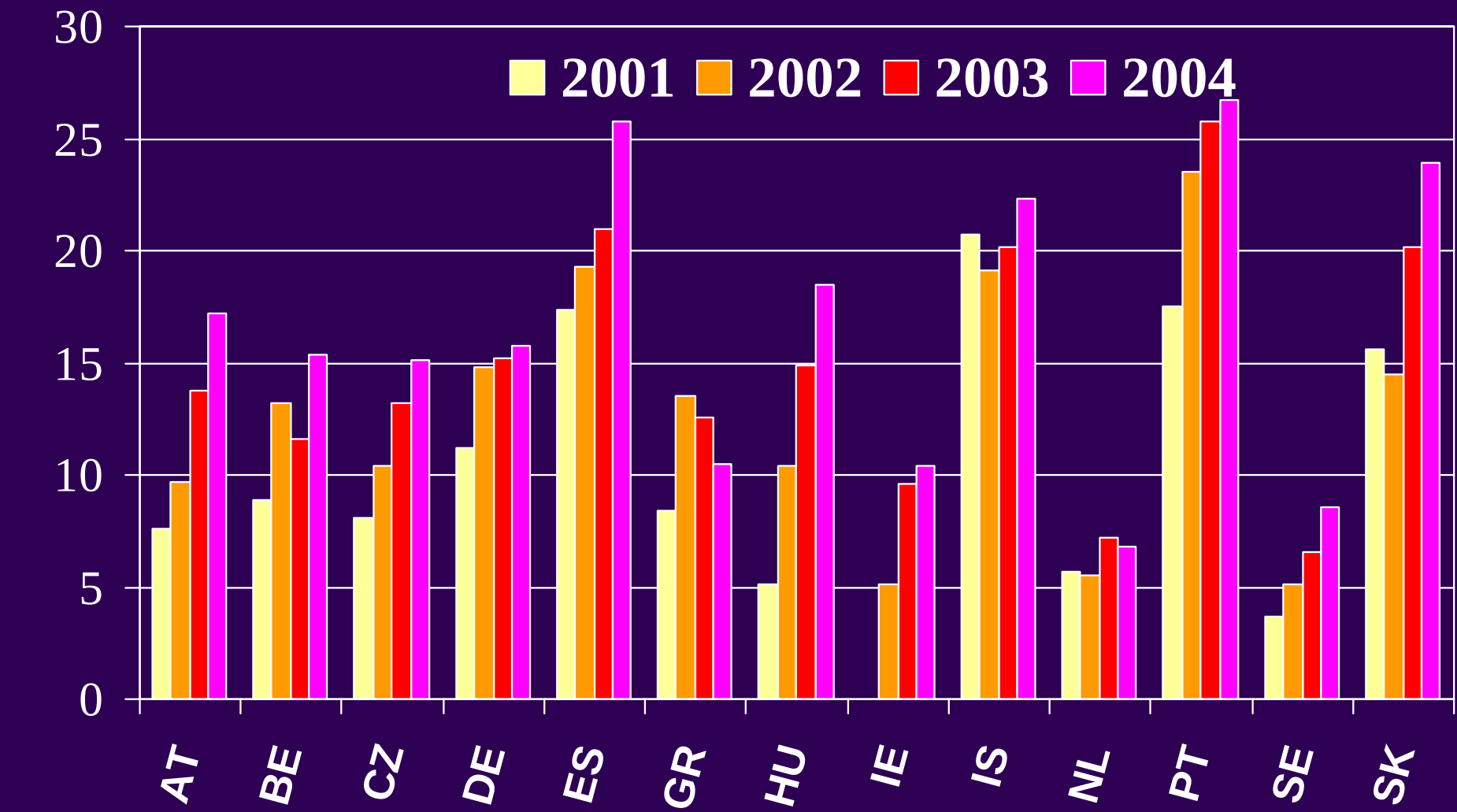
2001, 3%

2000, 2%

Cipro^{R} : blood & CSF isolates



Quinolone^{R} E. coli, *EARSS*



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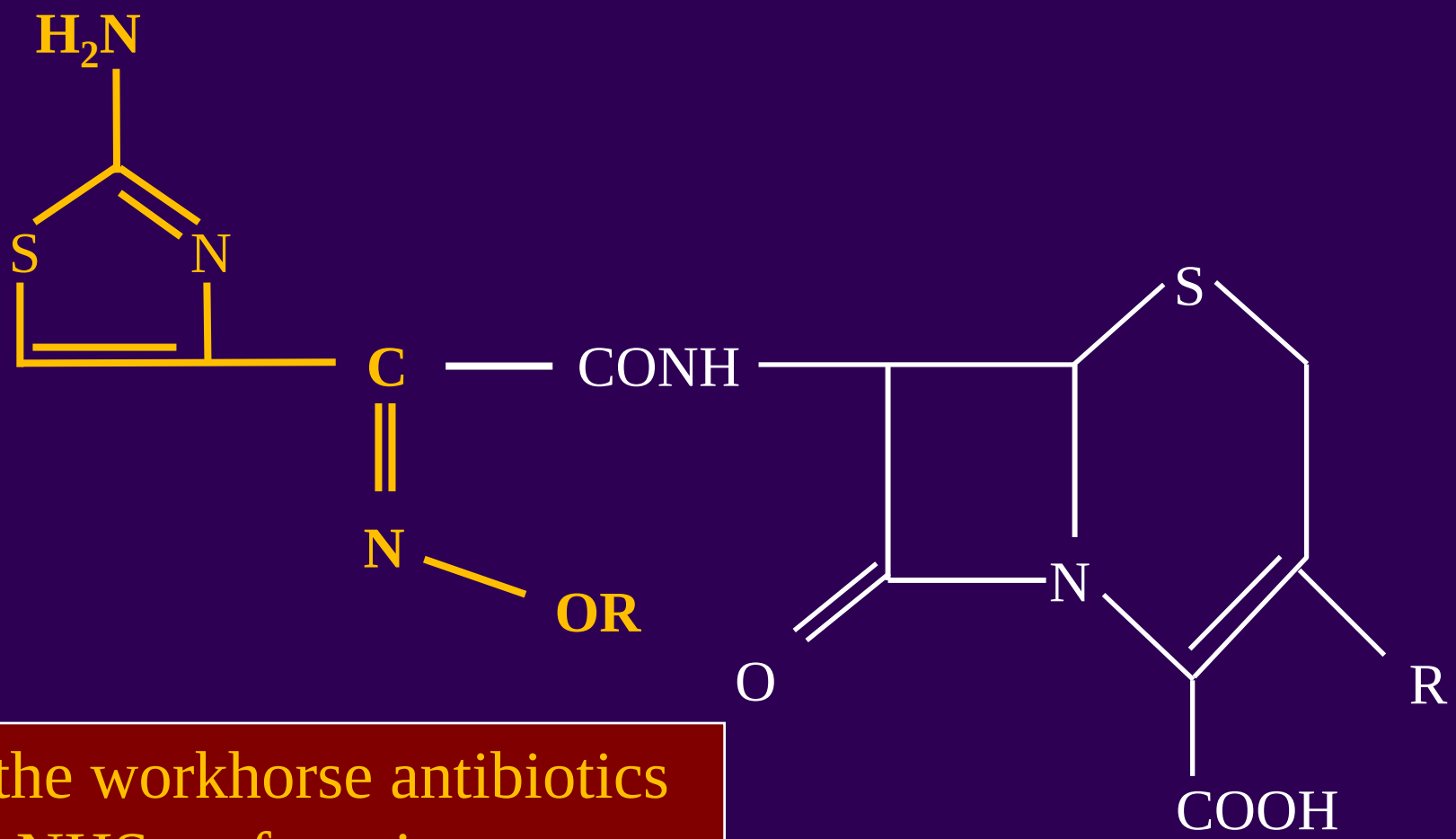
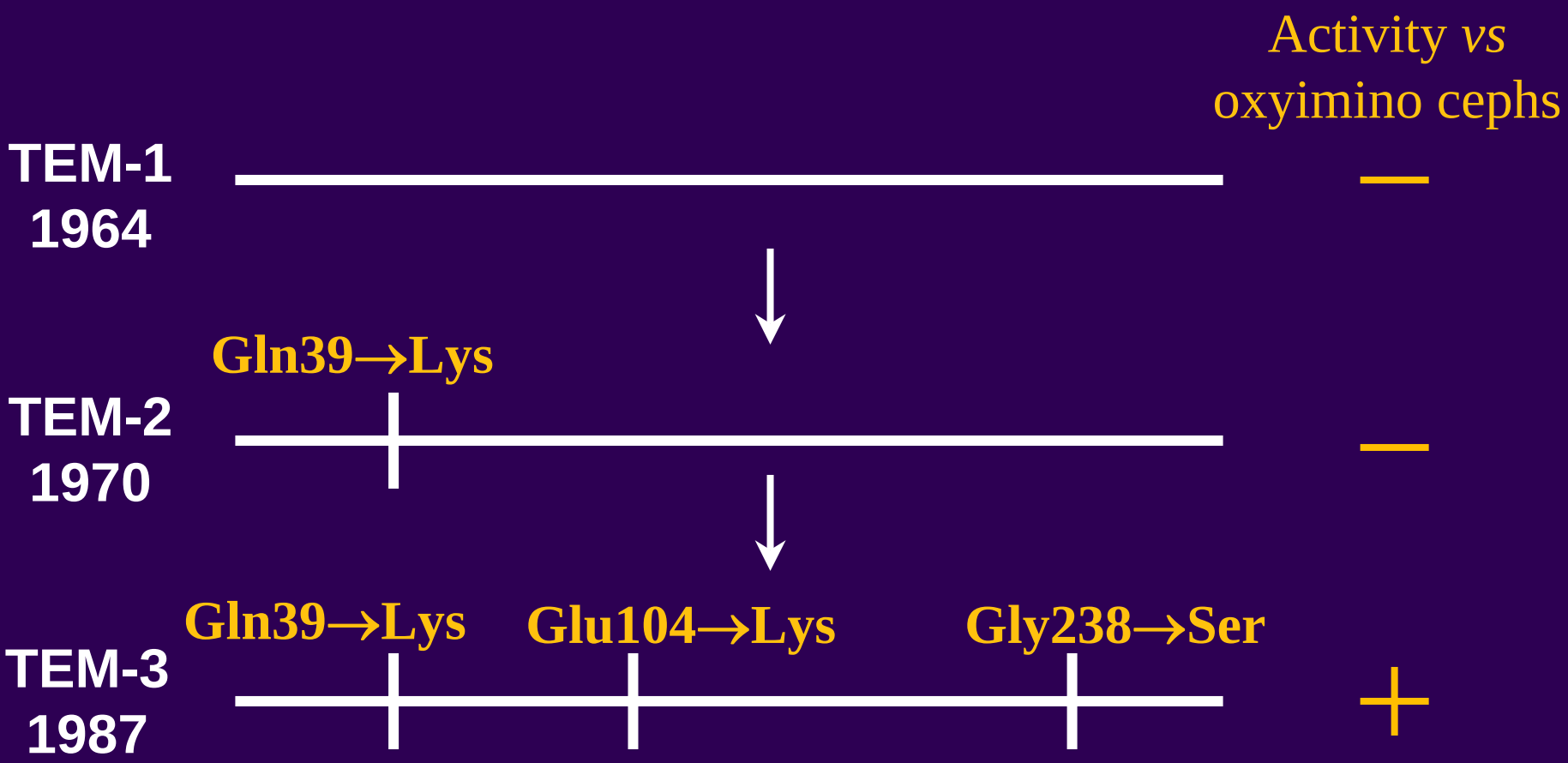
β-Lactamase-stable cephs



Now the workhorse antibiotics of the NHS- cefuroxime, cefotaxime *etc.*

Evolution of extended-spectrum β-lactamases (ESBLs)



Epidemiology of ESBL production, UK

Pre –2000

- Mostly *Klebsiella* spp.
  - *–sticky, survives well on fingers*
- Nosocomial, often ICU
- Occasional outbreaks
- c. 5% of *Klebsiella* spp.; <2% *E. coli*

2003 –repeated phone calls

‘We’ve got these ESBL producers from GP patients. About 20 or 30. Do you want them?’

“The patient hasn’t been in hospital…”

“We don’t get bacteria like this from this sort of patient”

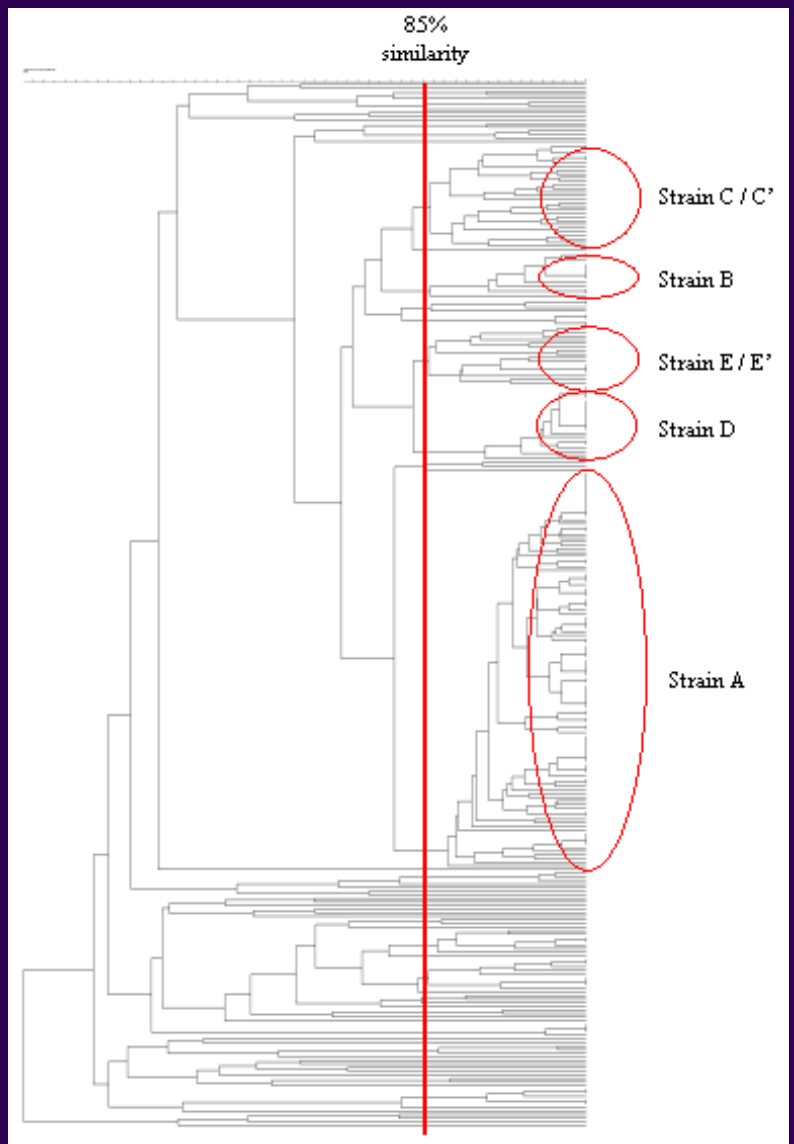
‘What do we use?- It’s got an ESBL & it’s trim and cipro resistant. We don’t want to have to admit the patient for i.v. therapy.’

UK, 2003-4: CTX-M-15 E. coli

- >1000 isolates from >100 UK labs referred
- Mix of hospital and ‘community’ isolates
- Mostly UTI; several bacteraemias from community
- Most age >65; underlying medical problems

Woodford *et al.* 2004 *JAC* **54,** 735

PFGE: CTX-M +ve E. coli

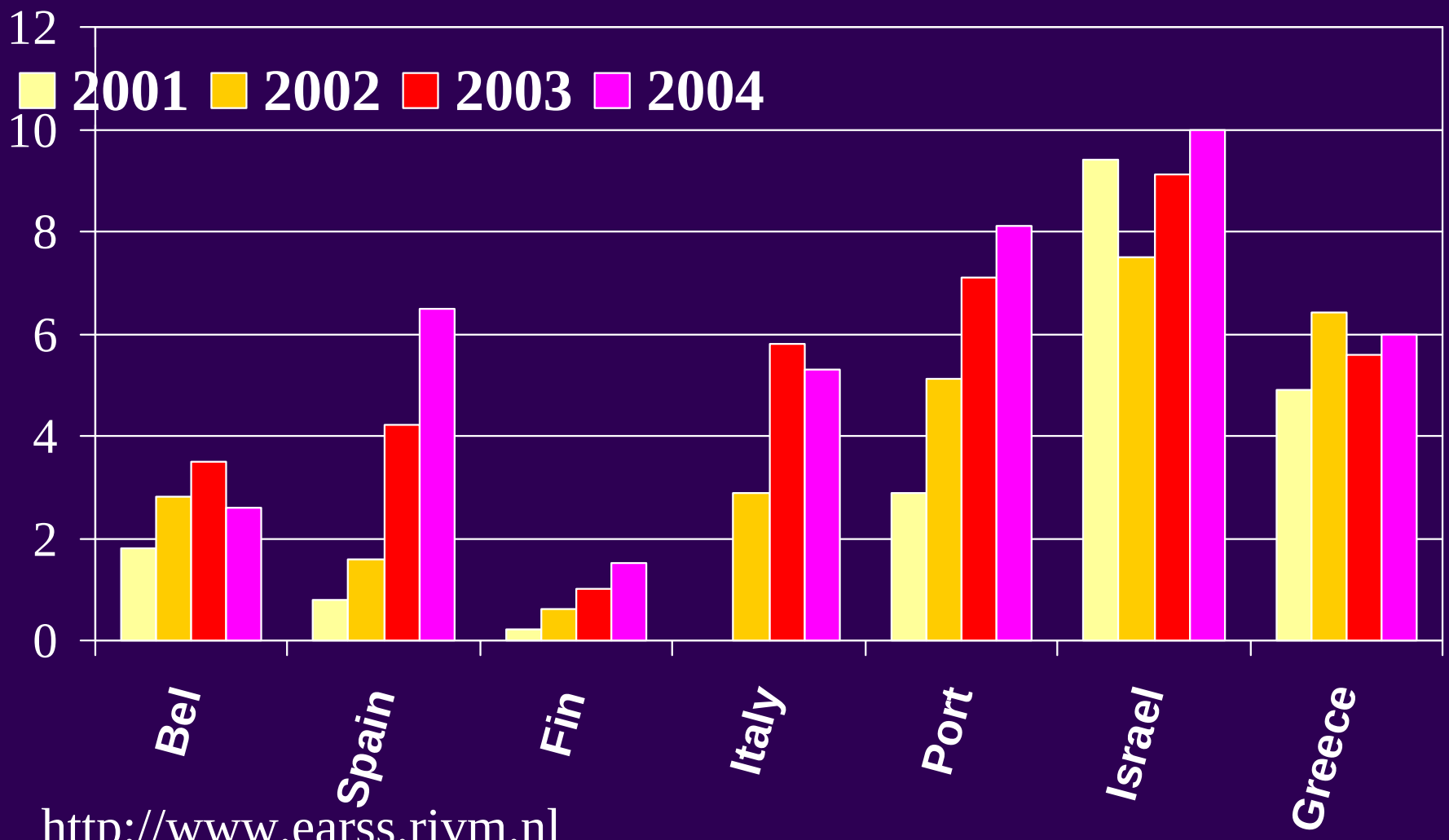


- 5 Major strains, A-E
  - –May share evolutionary history
- Strain A dominant in
  - –Shropshire, S. Coast, N. Ireland
- B-E locally prevalent
  - –e.g. D in Shropshire
- Many diverse producers too
  - –SE London/NE Surrey

Geom. mean MICs, (mg/L) CTX-M-15 +ve E. coli

	‘Epidemic A’	Other major	Minor
Cefotaxime	37.3	93.2	73.0
Ceftazidime	2.9	23.0	37.9
Pip/taz	20.1	13.2	14.7
Imipenem	**0.2**	**0.2**	**0.3**
Ciprofloxacin	17.5	6.7	6.1
Trimethoprim	256	9.6	45.3
Gentamicin	**1.1**	28.6	12.2
Amikacin	9.0	18.2	9.3
Nitrofurantoin	**8**	**7.3**	**22.6**

3-gen ceph^{R} *E. coli*, EARSS



http://www.earss.rivm.nl

CTX-M in the UK; clinical impact

Shrewsbury & Telford NHS Trust

- 326 new cases 1/03 to 8/04
- 28 deaths among first 105 patients; many with underlying disease
- 10 attributable deaths in 54 cases reviewed
- Changes to antibiotic reporting and policy

Warren, Harvey; pers. comm

17th July 2004: CTX-M on Fleet St.

Health Protection Agency

Scientists fear 28 people killed by new superbug

James Meikle
Health correspondent

Scientists are urgently assessing the threat from new superbugs that are wrecking antibiotic treatments for hundreds of patients and may have killed 28 people in Shropshire in the year to March.

Laboratories have reported a surge in the number of urinary tract infections such as cystitis and cases of blood poisoning caused by strains of the E coli bug resistant to most antibiotics.

The bugs, represented by an increasingly dreaded acronym ESBL, are not only striking in hospitals, but also turning up in GP surgeries, and only one class of antibiotic to which they have not developed resistance is available in tablet form.

They are still not as prevalent as the notorious MRSA family but over the last 12 months the Health Protection Agency has been sent more than 400 samples from 60 labs across Britain. The agency is assessing these results and will report next month.

It may prove difficult to be specific on how many people have died as a result of the bug, or where it was a contributory factor. Patients may have had underlying medical conditions or been receiving other hospital treatment.

One of the problems for the scientists is that there is no mandatory reporting system, unlike for MRSA. Yesterday Michael Gwynne, coroner for Telford and the Wrekin in Shropshire, said there had been 200 clinical infections in the county over 12 months, and among the first 105 cases, 28 had died.

The outbreak started in March 2003, but coroners found out only when Shrewsbury and Telford Hospital NHS Trust sought advice on referring deaths of patients who had died from extended spectrum beta lactamases (ESBLs). These are enzymes produced by E coli bacteria which are resistant to two classes of antibiotics, penicillins and cephalosporins.

Mr Gwynne said: "I think it is alarming to say the least. The steps I have taken and agreed with o… this county is … related death … to the corone… cide individu… have an inque…

He is planni… inquest on a … cause he has … death was attr…

Pat Troop, c… the Health Pr… said GPs had … send samples … patients did … conventional … ments and the … consulting sp… the world to a…

Superbug deaths

A hospital superbug may have killed up to 28 people in an outbreak in the Telford area, a coroner said yesterday. Michael Gwynne, coroner for Telford and Wrekin, demanded tougher action to control a highly resistant strain of *E coli*.

…, 2004 THE DAILY TELEGRAPH

Coroner fears new superbug outbreak

By Roger Highfield
Science Editor

A CORONER called yesterday for greater efforts to deal with antibiotic-eating bacteria, a different kind of superbug to MRSA, which had been linked to 28 deaths in the past year in his area.

Prompted by his concerns, the Health Protection Agency admitted there had been an increase in urinary tract infections and blood poisoning caused by antibiotic-digesting strains of the gut bacterium *E coli*.

Risk factors for infection with ESBL producers outside hospital

Factor	Odds ratio
R_x 3 gen ceph	15.8
R_x 2 gen ceph	10.1
Hospital in last 3 months	8.95
R_x quinolone	4.1
R_x penicillins	4.0
Antibiotic R_x in last 3 months	3.23
Age >60 years	2.65
Diabetes	2.57
Male	2.47

Colonder *et al EJCMID* 2004 **23,** 163.

Options vs. multi-resistant *E. coli*

Carbapenems

- *Ertapenem-least pressure on non-fermenters; resistance in Klebsiella with ESBL & impermeability*
- *Imipenem/meropenem- most reliable activity vs. ESBL producers; more pressure of non-fermenters*

Temocillin

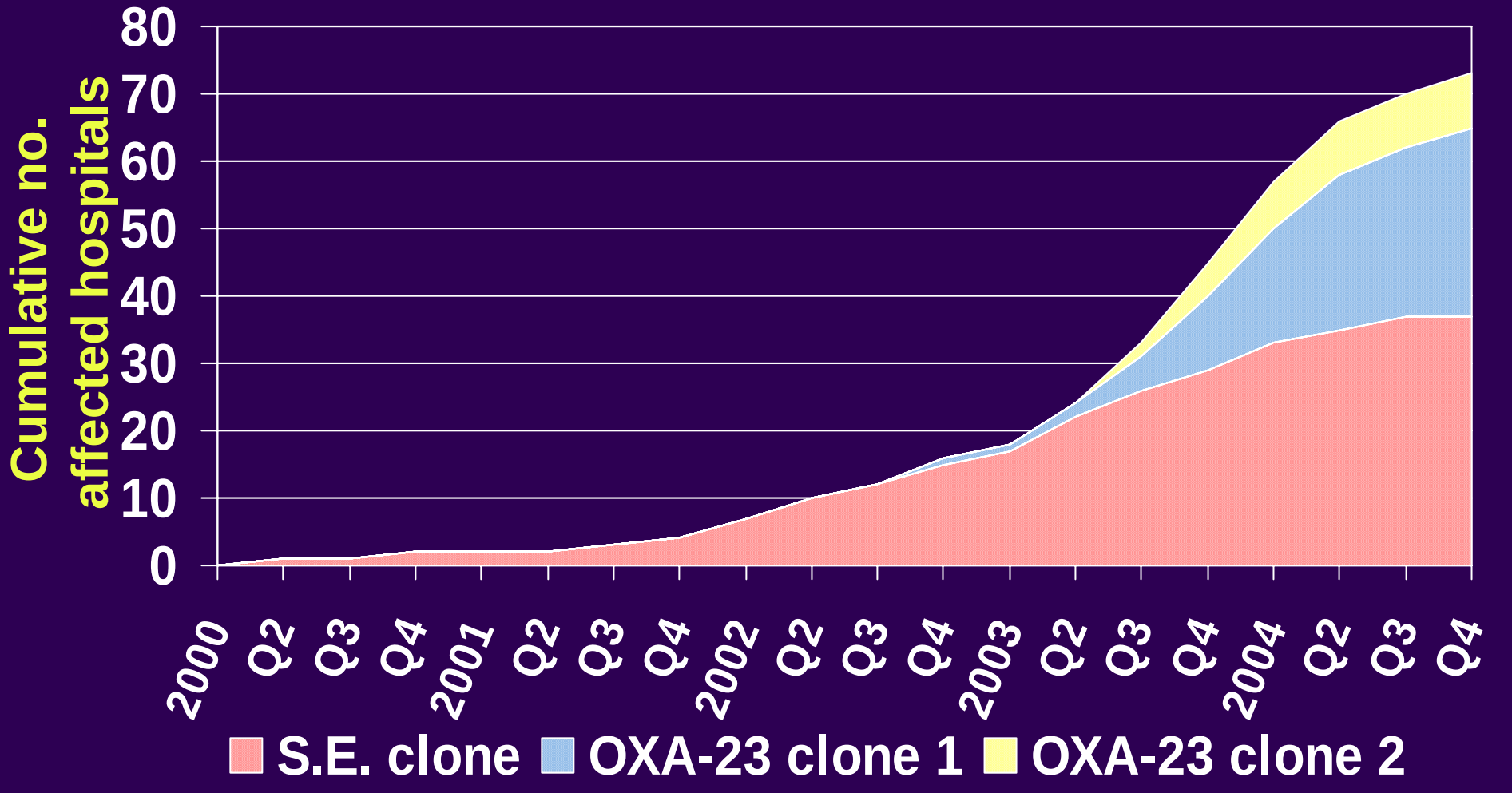
Oral *vs.* lower UTI, nitrofurans, fosfomycin

Acquired carbapenemases

- Class B - IMP, VIM & SPM metallo β-lactamases
- Class D - OXA-23, -40 & -58 related
- Class A – KPC, SME & NMC/IMI

Still rare, but increasing esp., in non-fermenters

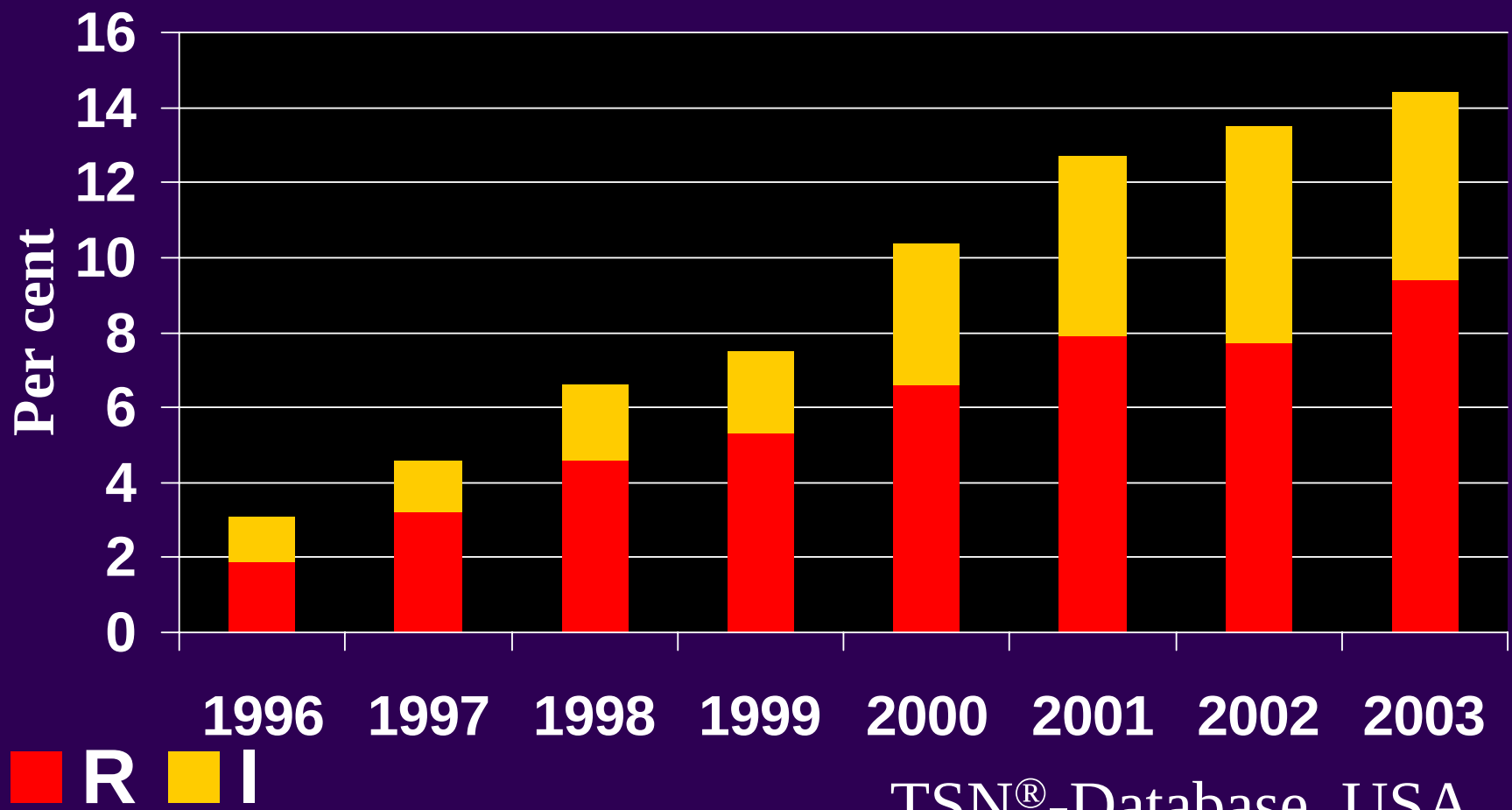
OXA Carbapenemases in *Acinetobacter*



OXA c'penemase +ve *Acinetobacter*, London, Geom. mean MICs (mg/L)

Clone	Amik	Gent	Cip	C'tax	C'taz	Imp	Mero	Ptaz	Mino	Poly
1 OXA-23 &- 51	128	64	16	128	99	39	32	128	5.3	**0.3**
2 OXA-23 & -51	**2.4**	53	16	128	128	17	17	128	**1.1**	**0.3**
SE OXA-51	v	32	>32	256	256	2.6	7.4	256	ND	**0.5**

Imipenem-resistant *Acinetobacter* Jan ’96- Dec ‘03, USA



TSN®-Database, USA

Therapy *vs.* multi-resistant *Acinetobacter*

Carbapenem MIC 2-4 mg/L):

- ? Still use carbapenem

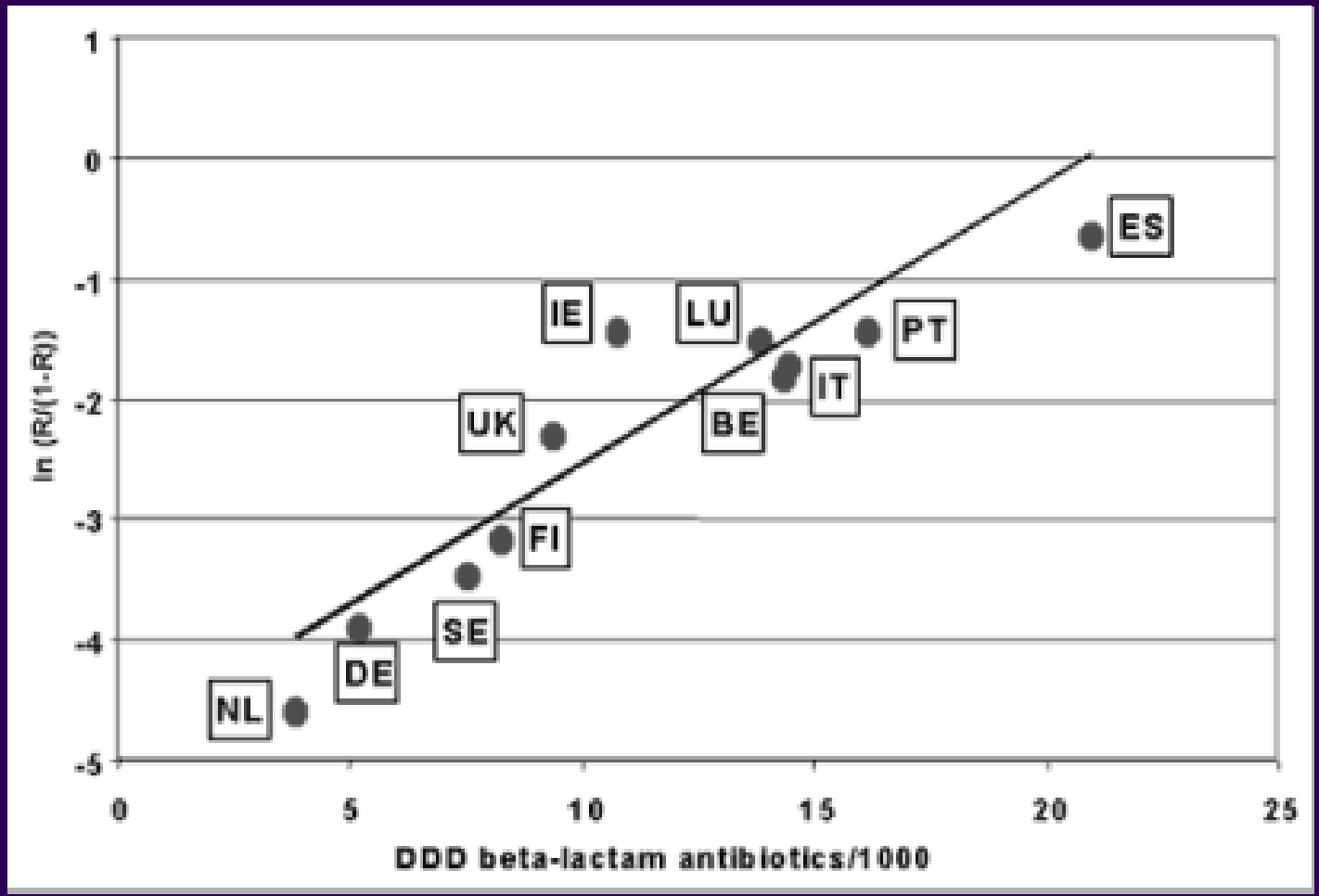
If carbapenem MICs >4 mg/L:

- ? Colistin i.v. +/- nebulised colistin
- ? Role of tigecycline

A depressing question

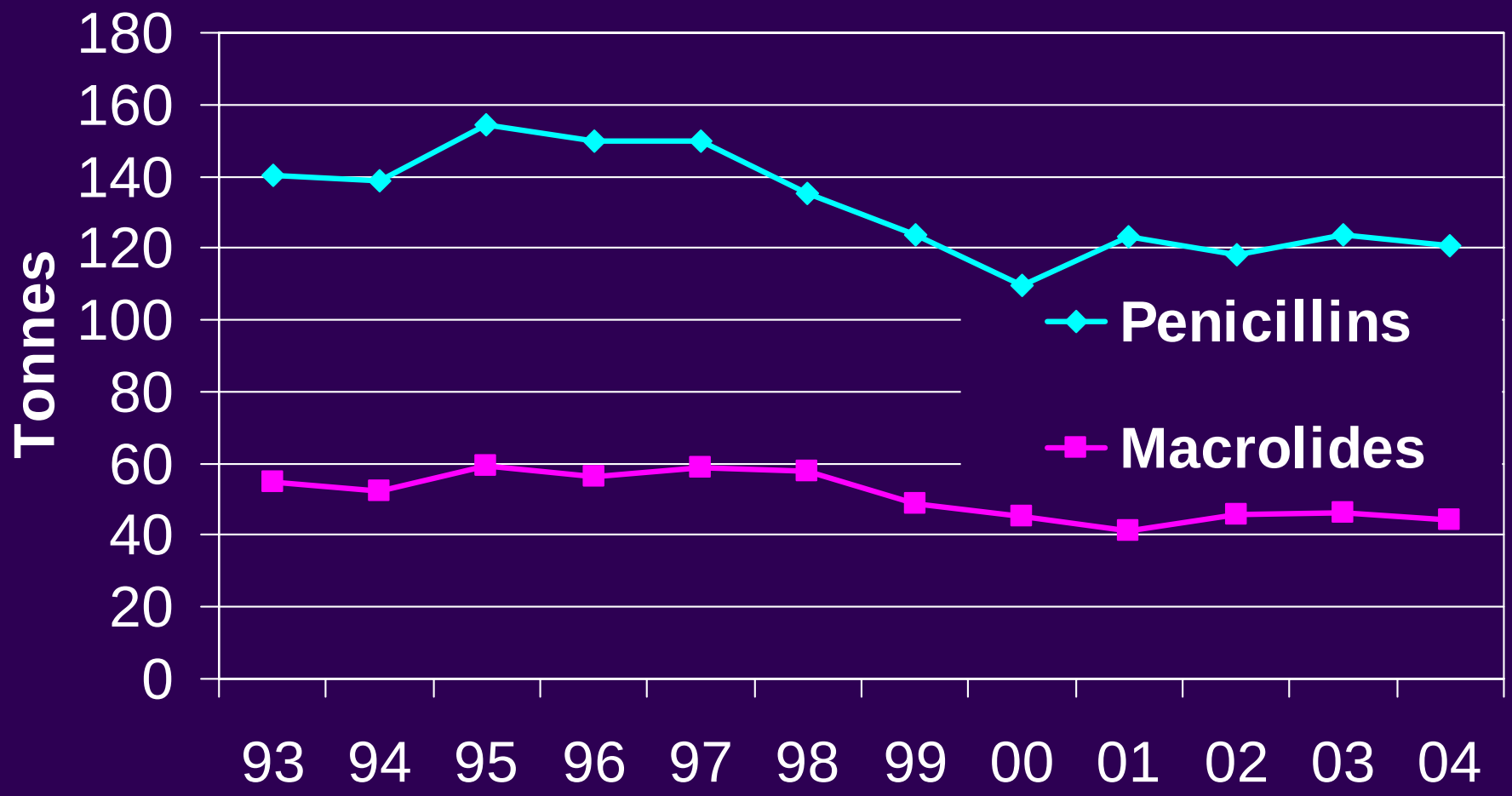
Has nothing been achieved by all the pressure to reduce prescribing?

β-Lactam use & resistance in *S. pneumoniae*

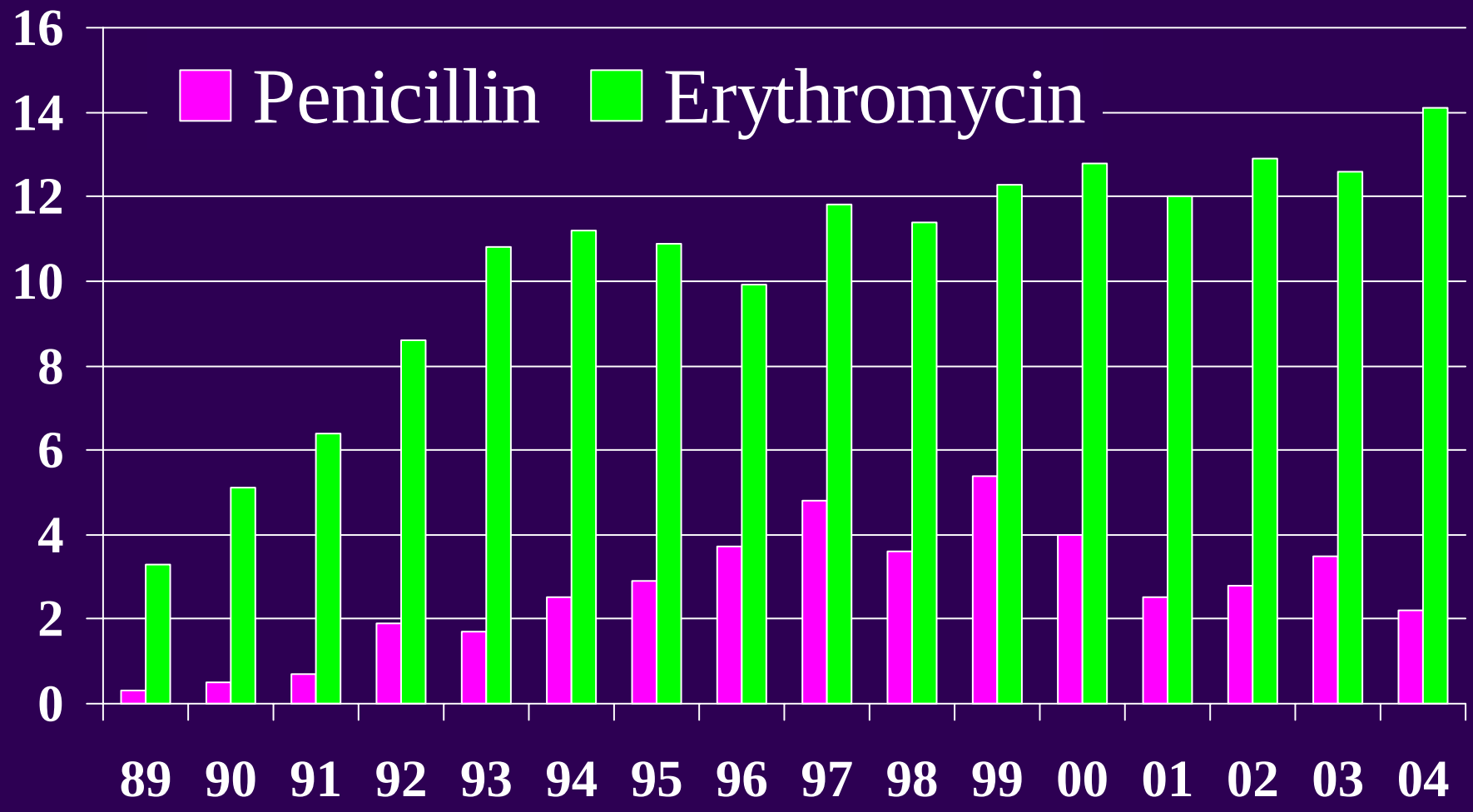


Bronzwaer et al *Emerg Infect Dis*. 2002; **8:**278-82

Reduced sales to pharmacies, UK



Resistance (%) pneumococci Blood & CSF



New antibiotics, C21

* microbiological advance

Anti-gram+ve

Linezolid*

Quinu/dalfo*

Daptomycin*

Dalbavancin

Telavancin*

Anti-PBP2’ cephs*

Respiratory

Ketolides*

Quinolones

PDF inhibitors*

Iclaprim*

Broad spectrum

Tigecycline*

Ertapenem

Doripenem

Why worry?

- Lack of new agents *vs.* Gram-negatives &, especially, non-fermenters
- Big pharma abandoning antibiotic R&D
- Ability of small pharma to develop antibiotics

Big pharma; dropping antibiotic discovery

- Worldwide mkt $24 bn; $8 bn in hospitals
- Big pharma seeks $1 bn p.a. turnover

But

  - Likely to be reserved/restricted
  - Likely to select resistance = bad press
  - Used in short courses
  - Small markets where medical need greatest

Can small pharma fill the gap?

- Many biotechs interested in antibiotics
- Cubist brought daptomycin to market

BUT

  - –Huge barriers to entry
  - –Venture capital, no sales income
  - –Seek liaison with big pharma…. Who are losing interest
  - –Moving from discovery to developing big pharma cast-offs

Where do we stand?

- Resistance situation worsening *vs* G-ves
- Undoubted medical need for new agents
- New antibiotics are still being launched
- Good ideas out there... & advances in drug design
- Big pharma's interest declining
- Huge barriers to entry for small pharma