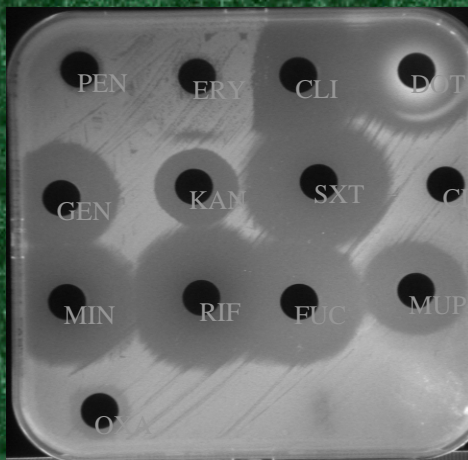


Antibiotic Resistance in Belgium : Current Situation 2005



Marc Struelens
Service de microbiologie
Hopital Erasme

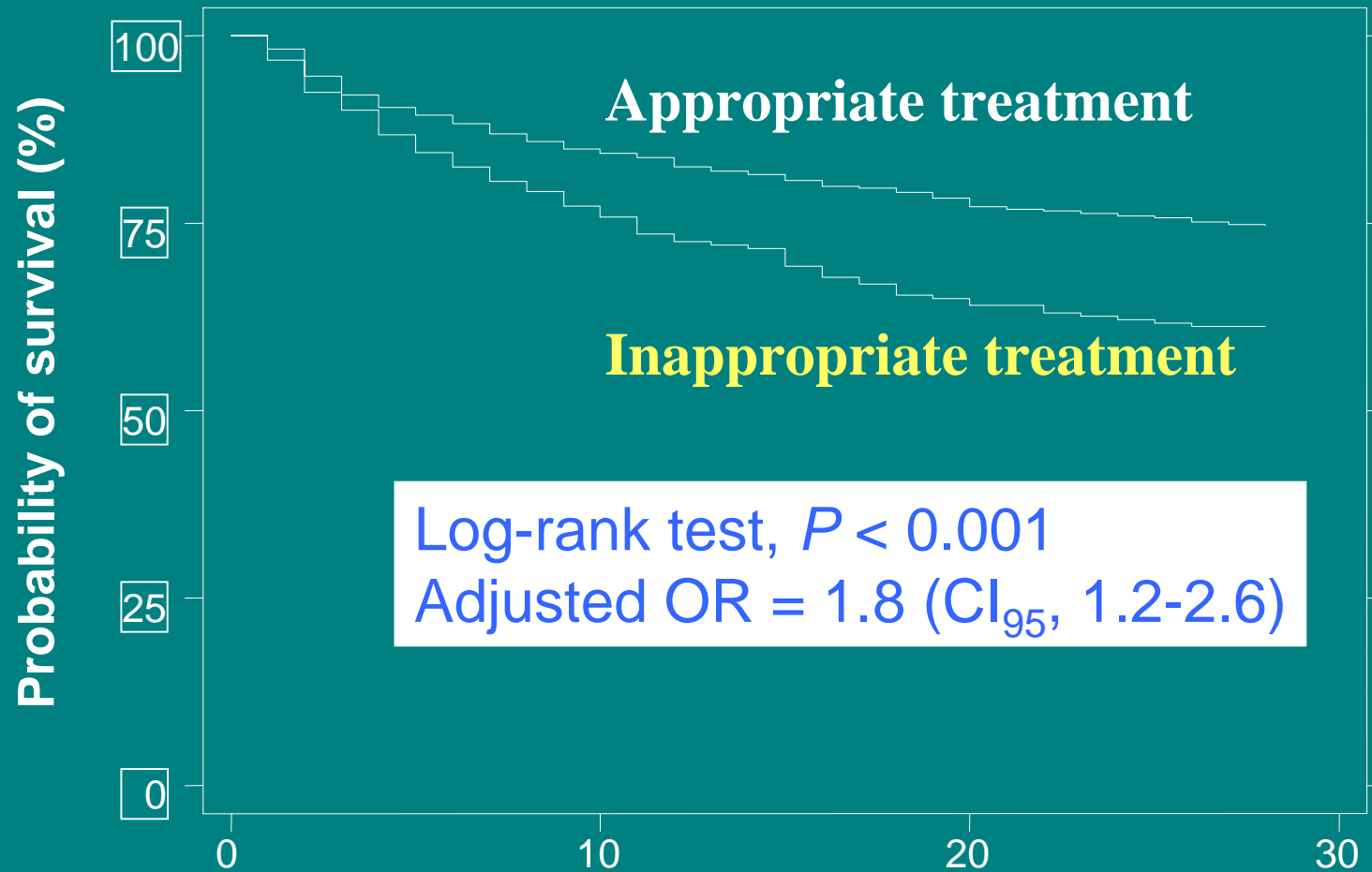


The Clinical Challenge of Antimicrobial Resistance

- Inappropriate antimicrobial therapy increases the mortality in severe infection
- Infection with antibiotic resistant bacteria increases the risk of inappropriate therapy
- Drug spectrum escalation drives excess medication costs & selective pressure

Impact of antimicrobial treatment appropriateness on patient outcome

(904 cases of microbiologically documented severe sepsis)



Microbial etiology and treatment appropriateness in severe sepsis

(904 cases of microbiologically documented severe sepsis)

	Inappropriate Antimicrobial Therapy (n = 211)	Appropriate Antimicrobial Therapy (n = 693)
- Adequately treated bacteria		
<i>Streptococcus pneumoniae</i>	7	130
<i>Escherichia coli</i>	47	176
Methicillin-sensitive <i>S. aureus</i>	36	105
- Inadequately treated bacteria		
MRSA	12	8
<i>Pseudomonas aeruginosa</i>	40	42
<i>Enterobacter</i> spp	24	32
<i>Acinetobacter</i> or <i>Stenotrophomonas</i>	28	11

The Public Health Challenge of Resistance



- Alert for transmissible resistance
 - Clonal spread
 - Gene epidemics
- Early detection enhances efficacy of infection control
- Reducing the antibiotic selective pressure by streamlining therapy

MRSA in the UK Press

TV uncovers hospital 'lethal superbugs'

HOW OUR HOSPITALS ARE LOSING WAR ON SUPERBUGS

THE FULL SHOCKING REPORT Pages 4&5

Secret probe reveals MRSA is out of control



DAILY EXPRESS

THE NORTHERN & SHELL BUILDING,
NUMBER 10 LOWER THAMES STREET, LONDON EC3R 6EN
Tel: 0871 434 1010 (outside UK: +44(0)870 062 6620)

Hospital superbug crisis is a national disgrace

THE MRSA superbug crisis infecting Britain's hospitals is a national scandal. The government admits that as many as 100,000 patients a year fall victim to poor hygiene in the wards. Up to 5,000 of them die as a result, according to official estimates. But independent watchdogs say these figures are a decade out of date and that the true death toll could be as high as 30,000 a year.

MRSA 'is winning'

HOSPITALS are losing the fight against the MRSA superbug, according to an undercover survey for ITV's Tonight show.

Reporters took swabs at six major hospitals and found traces of antibiotic resistant bugs on at least two per hospital.

All five samples from one hospital were infected.

The programme is to be shown on ITV1 tonight at 8pm.

Superbug spin doesn't wash

The Challenging Pathogens

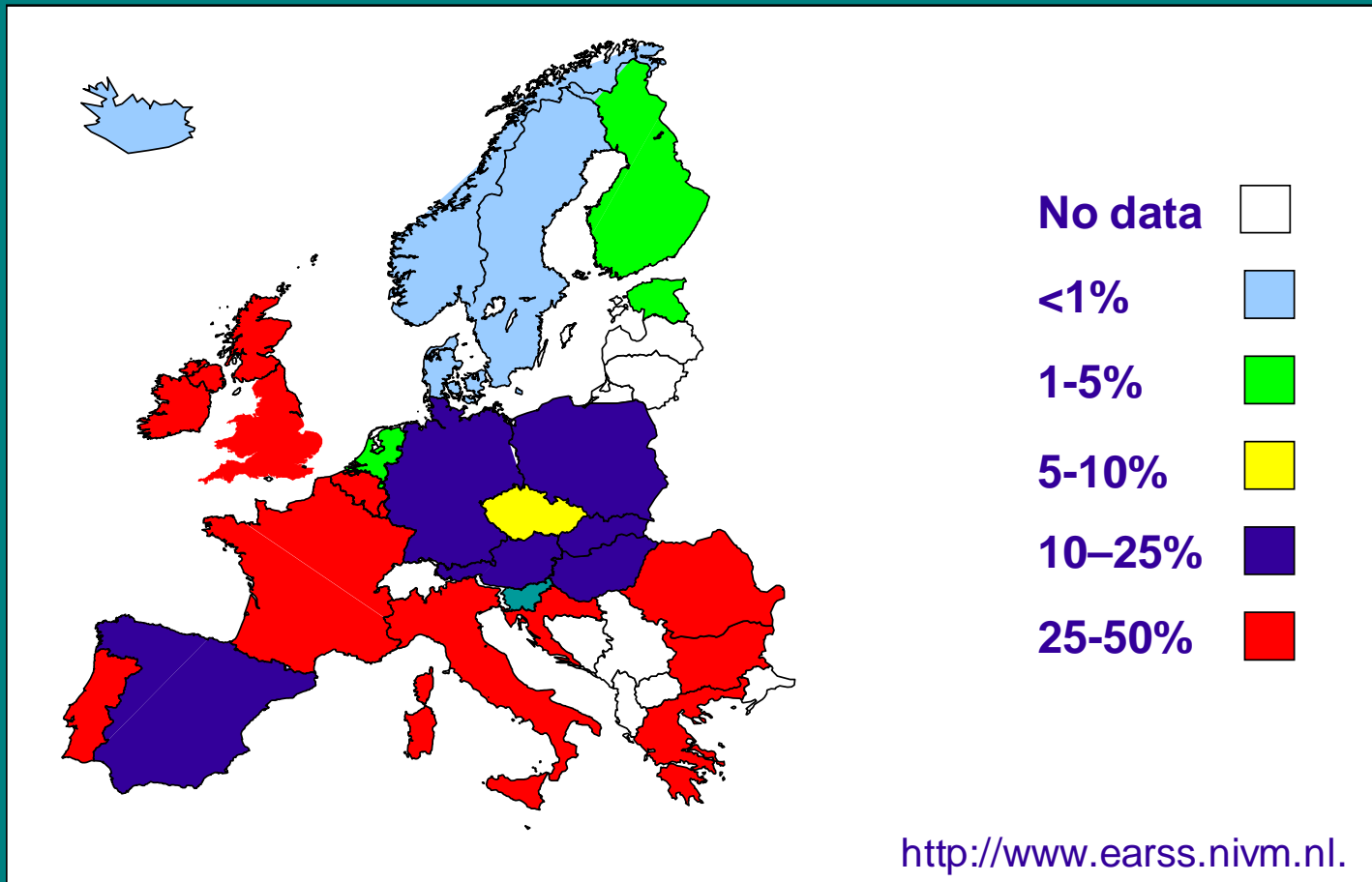
Healthcare

- *Staphylococcus aureus* (MRSA, GISA, GRSA)
- Enterococci (GRE)
- *Enterobacteriaceae* (ESBL, carbapenemase, FQ)
- MDR-*Pseudomonas aeruginosa*
- MDR-*Acinetobacter baumannii*

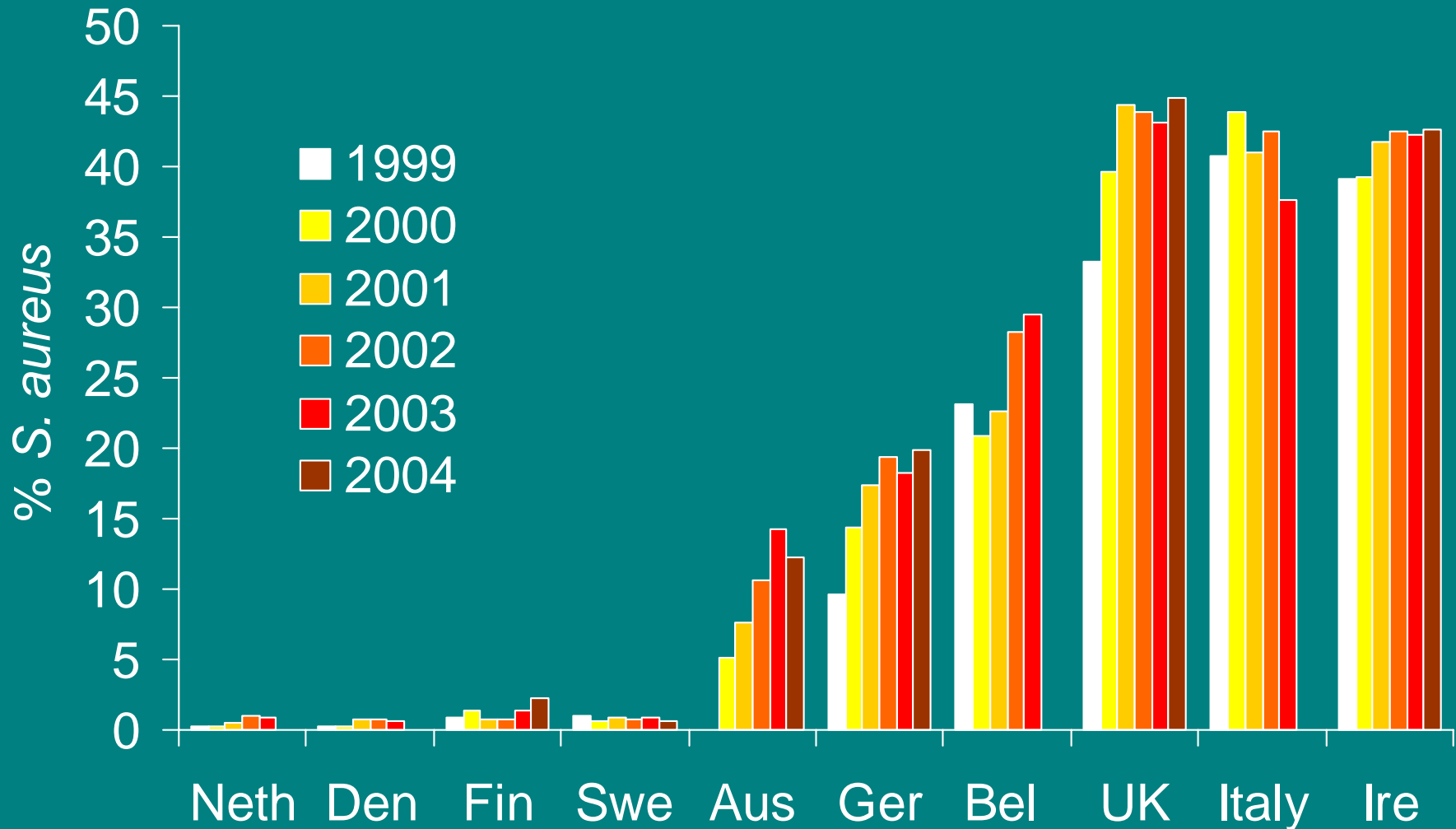
Community

- MDR- *Strep. pneumoniae*
- CA- MRSA
- Salmonella (ESBL, FQ)
- Campylobacter (FQ, Macrolides)
- *Helicobacter pylori*
- MDR-Tuberculosis

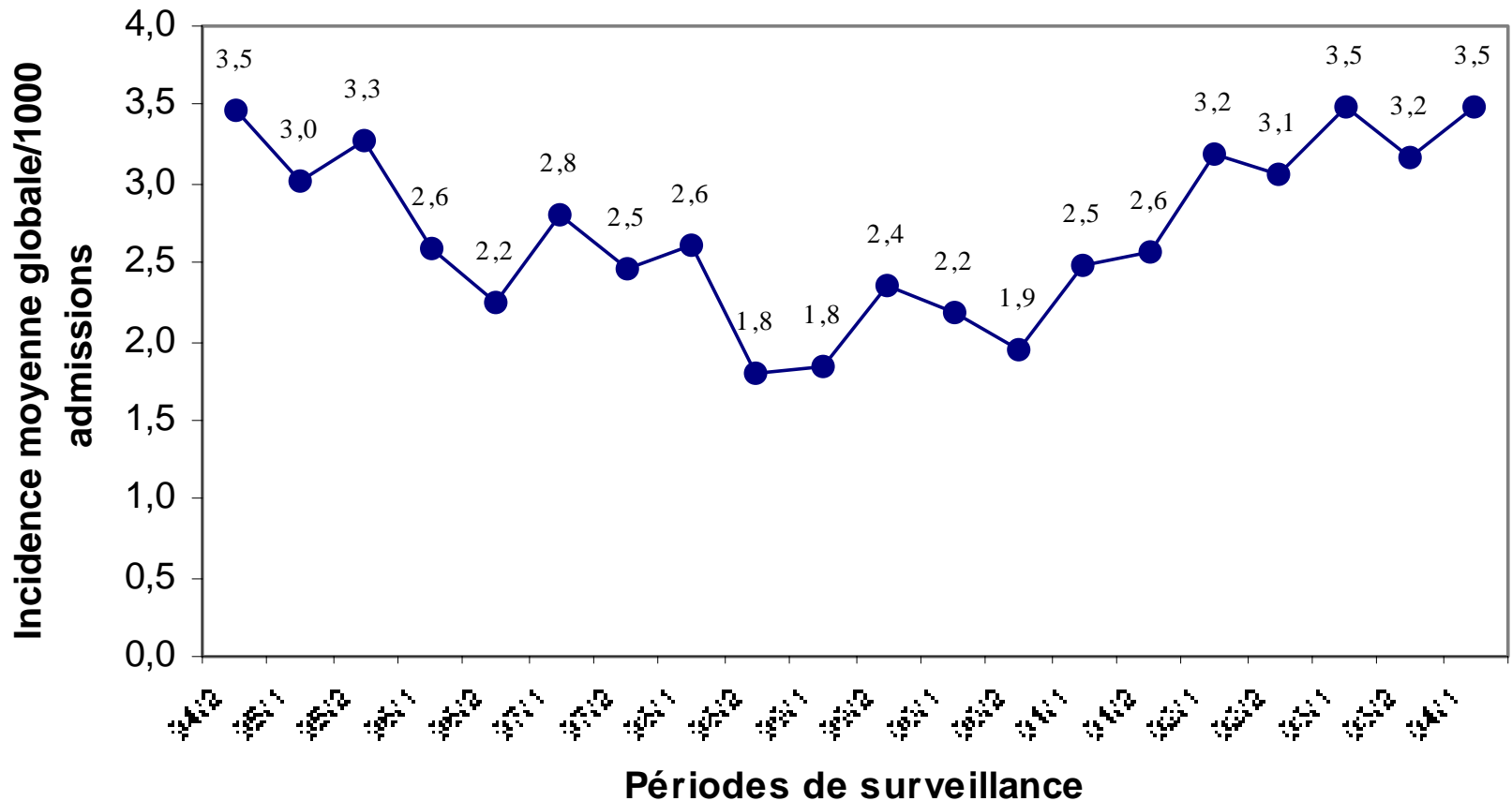
MRSA Proportion in *S.aureus* Bacteremia, EARSS 2003



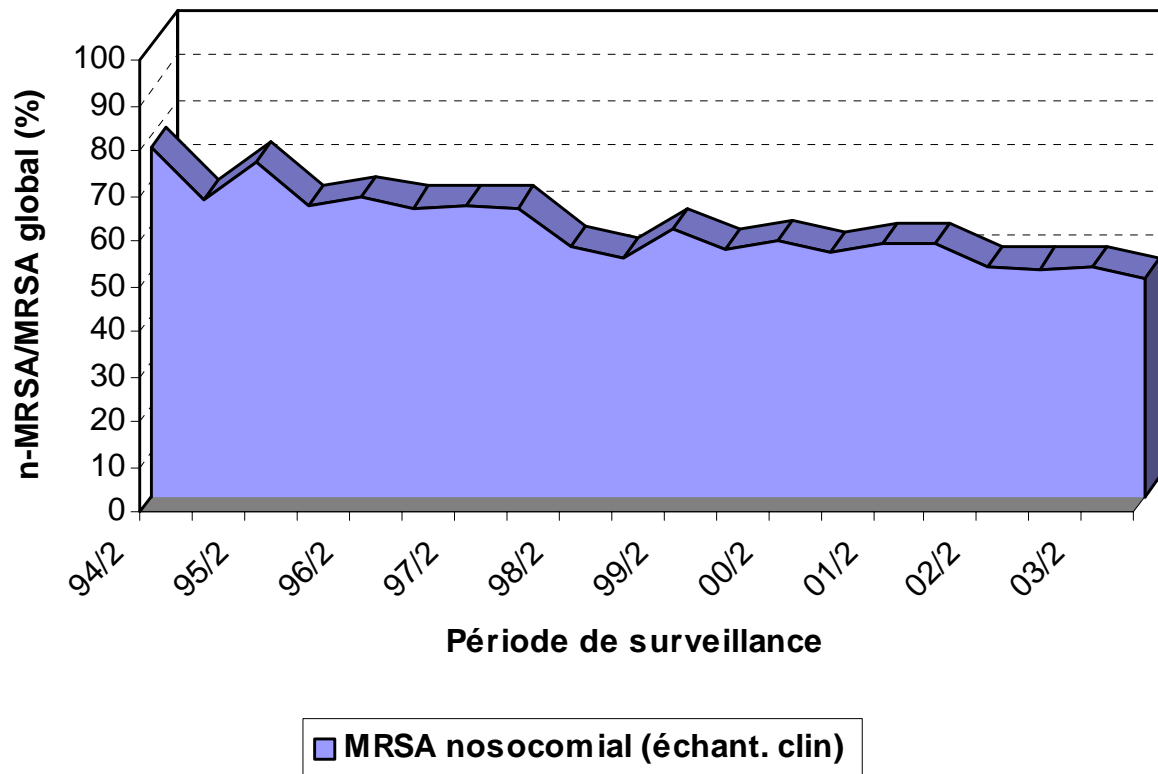
Trends in MRSA bacteraemia, EARSS, 1999-2004



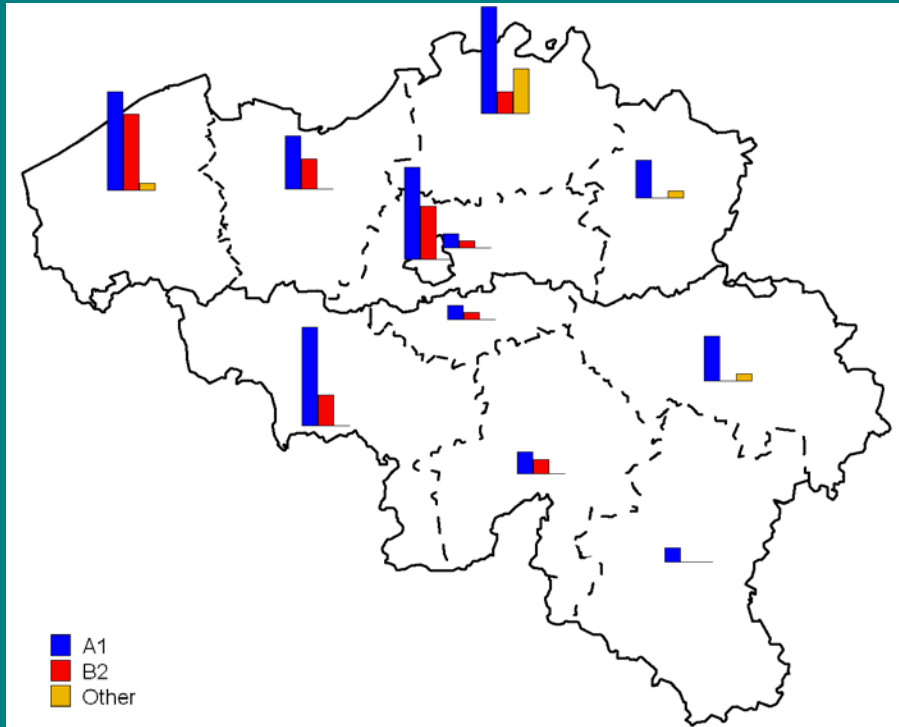
Incidence of Nosocomial MRSA Belgium, 1994-2004



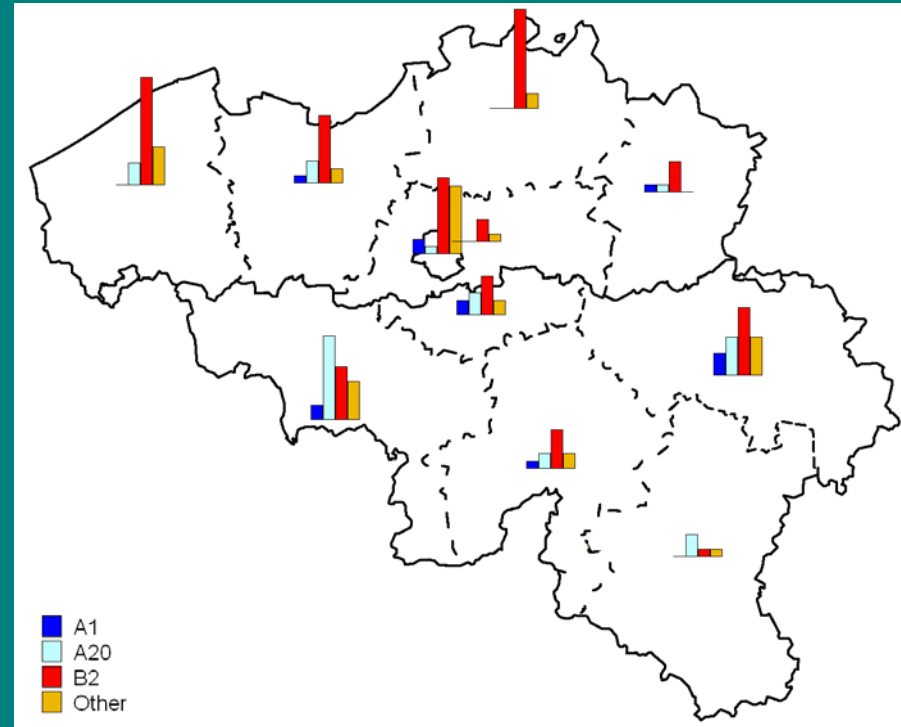
Decrease in nosocomial vs imported MRSA, Belgium, 1994-2004



Evolution of geographic distribution of epidemic MRSA PFGE types A1, A20, B2

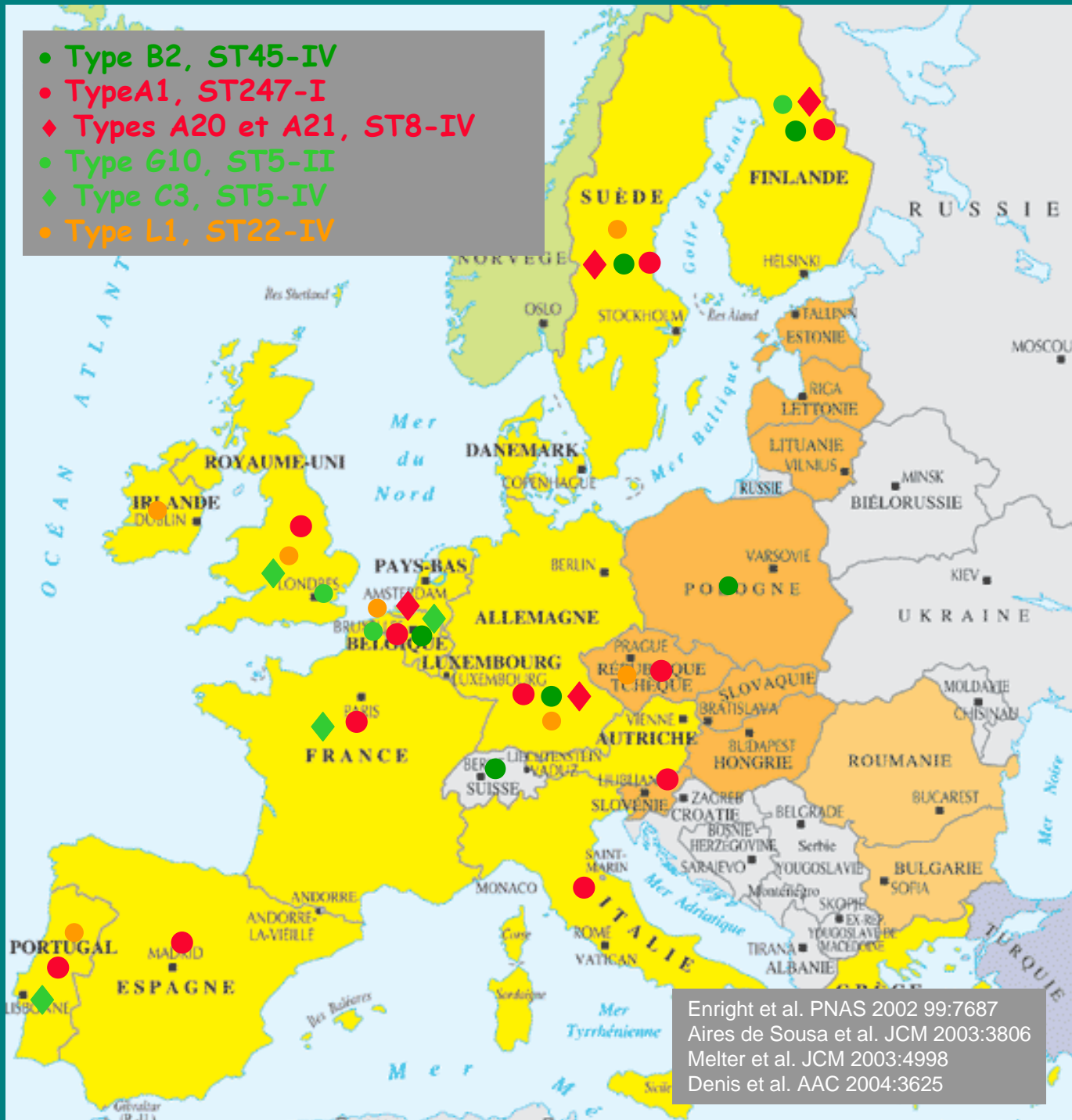


1995



2001

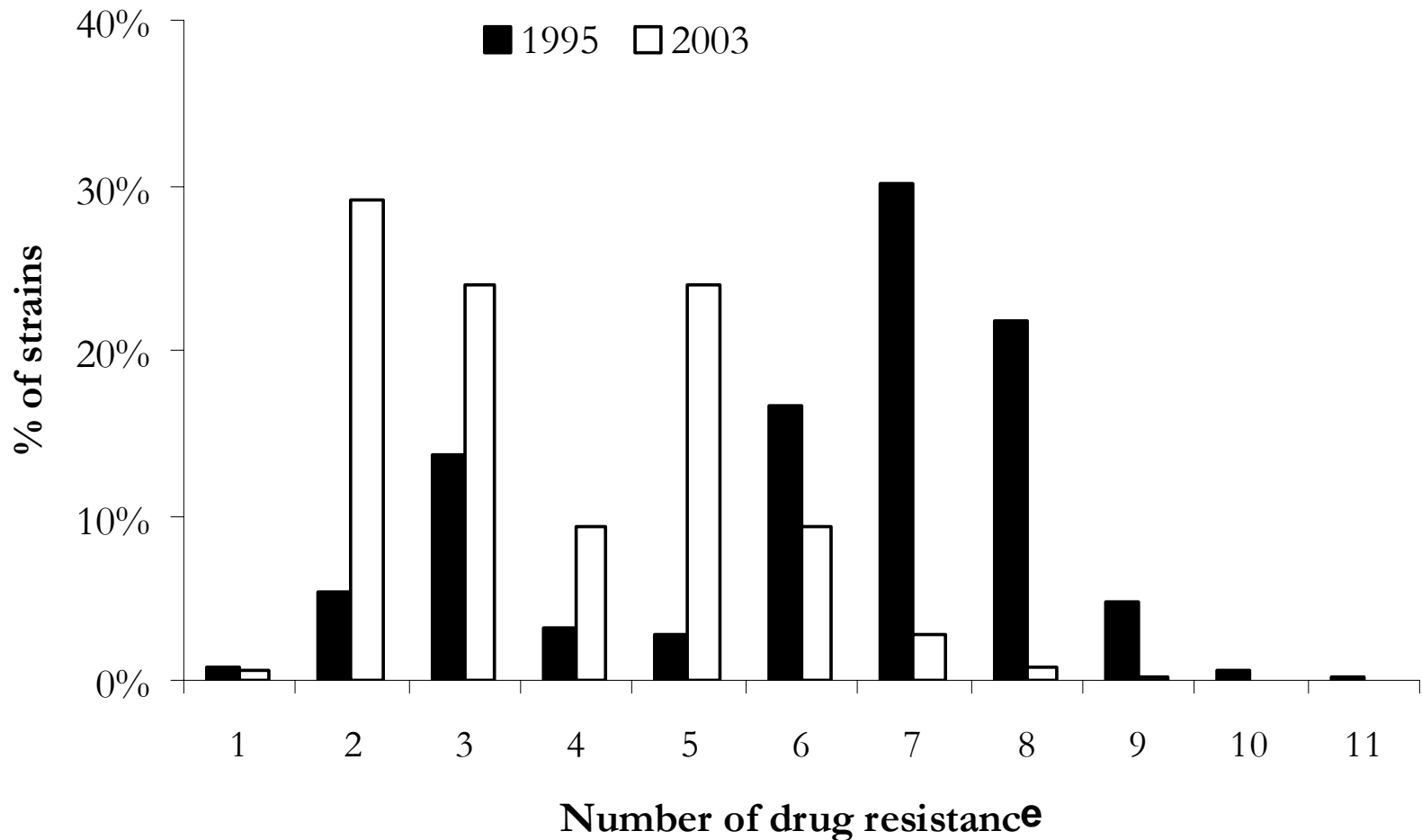
- Type B2, ST45-IV
- Type A1, ST247-I
- ◆ Types A20 et A21, ST8-IV
- Type G10, ST5-II
- ◆ Type C3, ST5-IV
- Type L1, ST22-IV



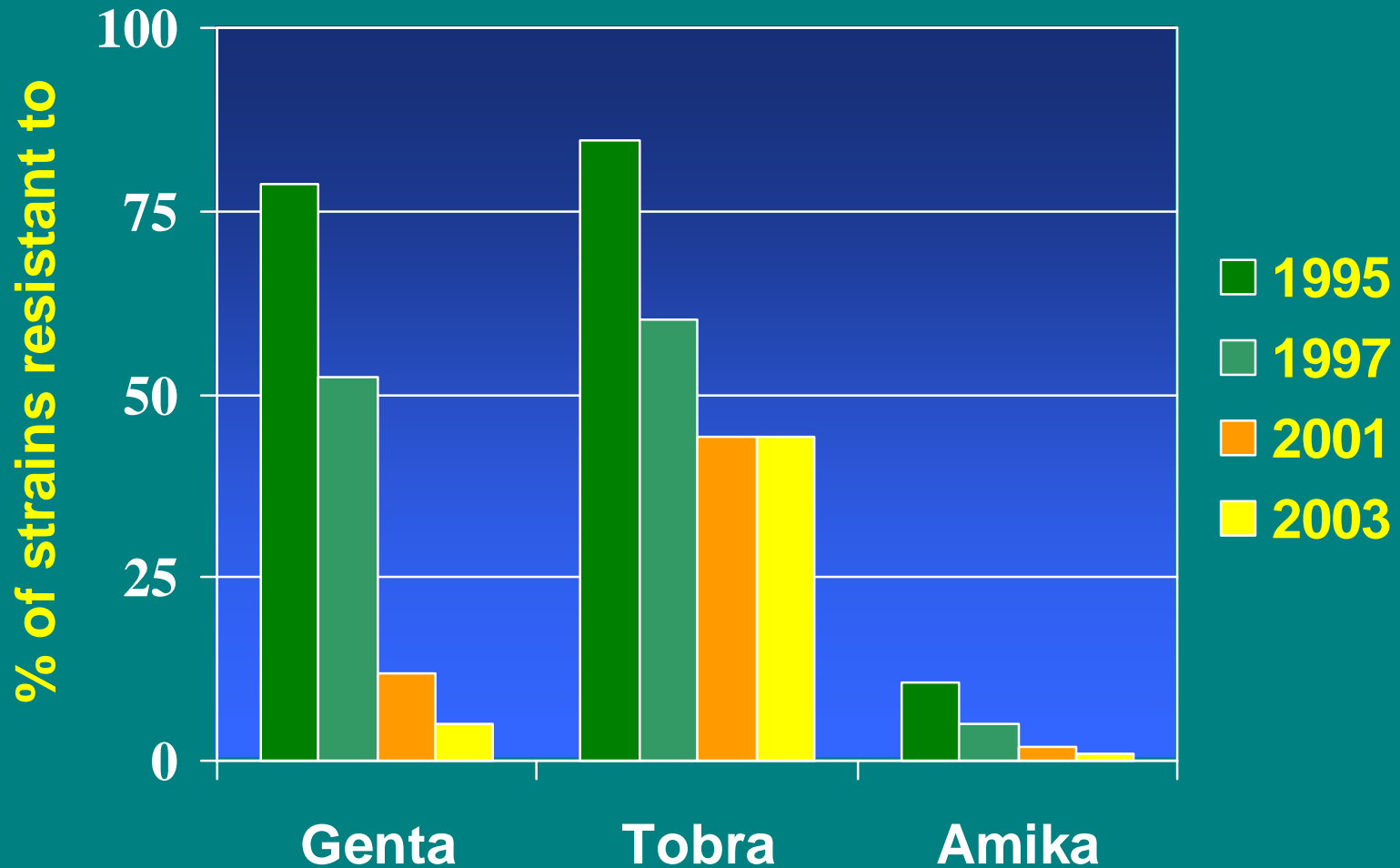
Enright et al. PNAS 2002 99:7687
 Aires de Sousa et al. JCM 2003:3806
 Melter et al. JCM 2003:4998
 Denis et al. AAC 2004:3625

MRSA Co-resistance to non β -lactams

Hospitalised patients, Belgium 1995-2003



MRSA resistance to aminoglycosides, *Belgium, 1995-2003*



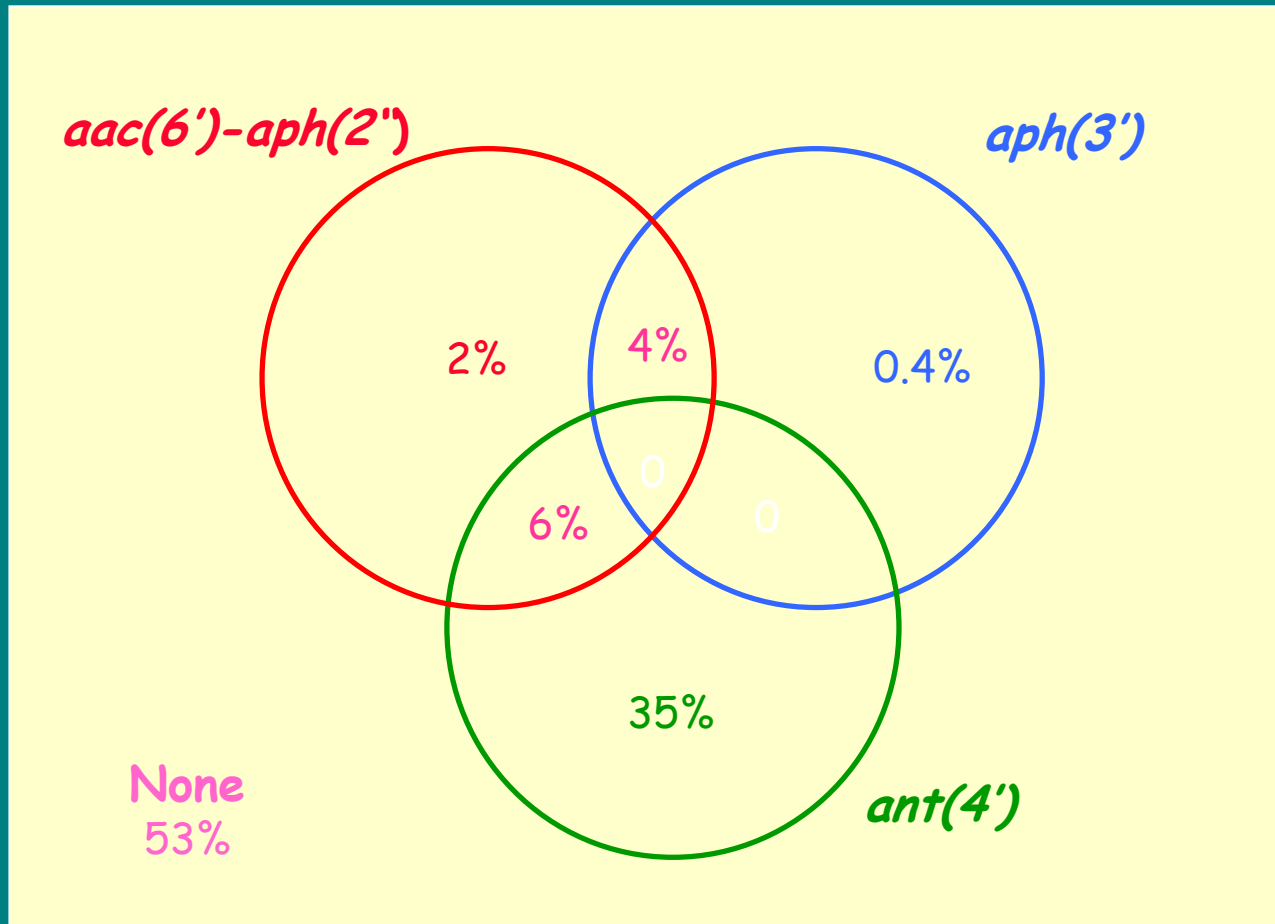
Denis O. et al. Microb Drug Resist. 2003;9:61

Denis O. et al. Antimicrob. Agents Chemother. 2004;48:3625

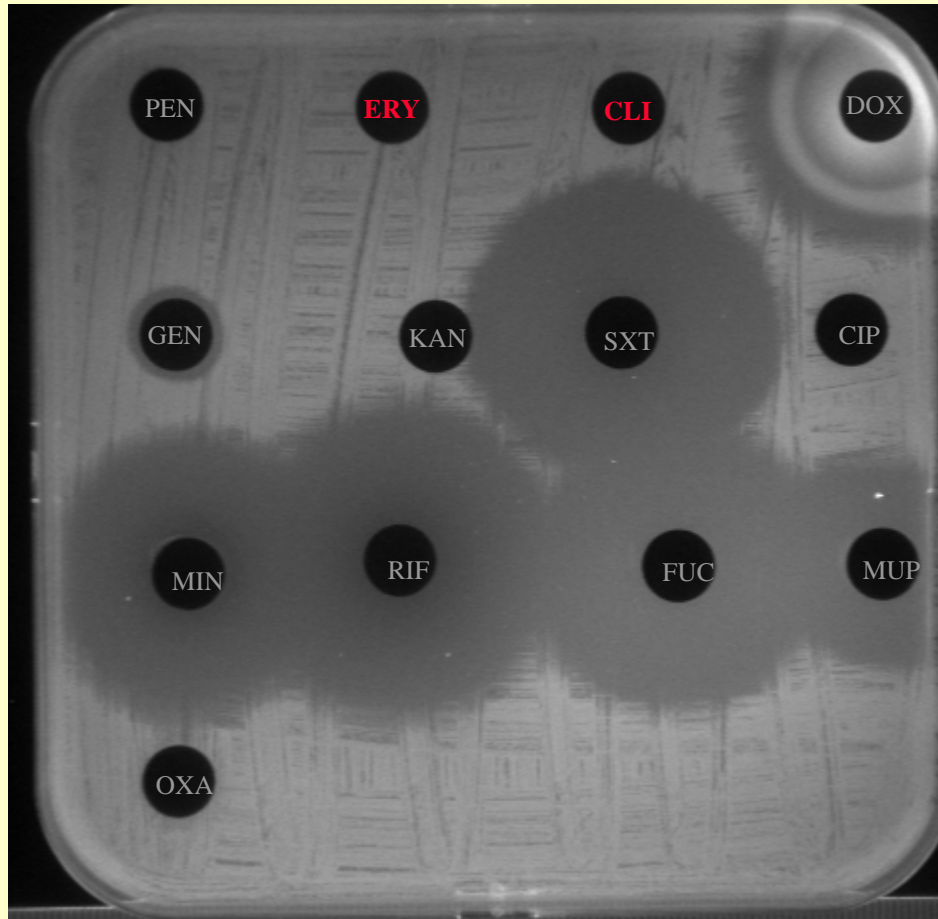
Denis O. et al. 15th ECCMID P1570; Copenhagen, Denmark

Proportion of MRSA strains carrying AME genes

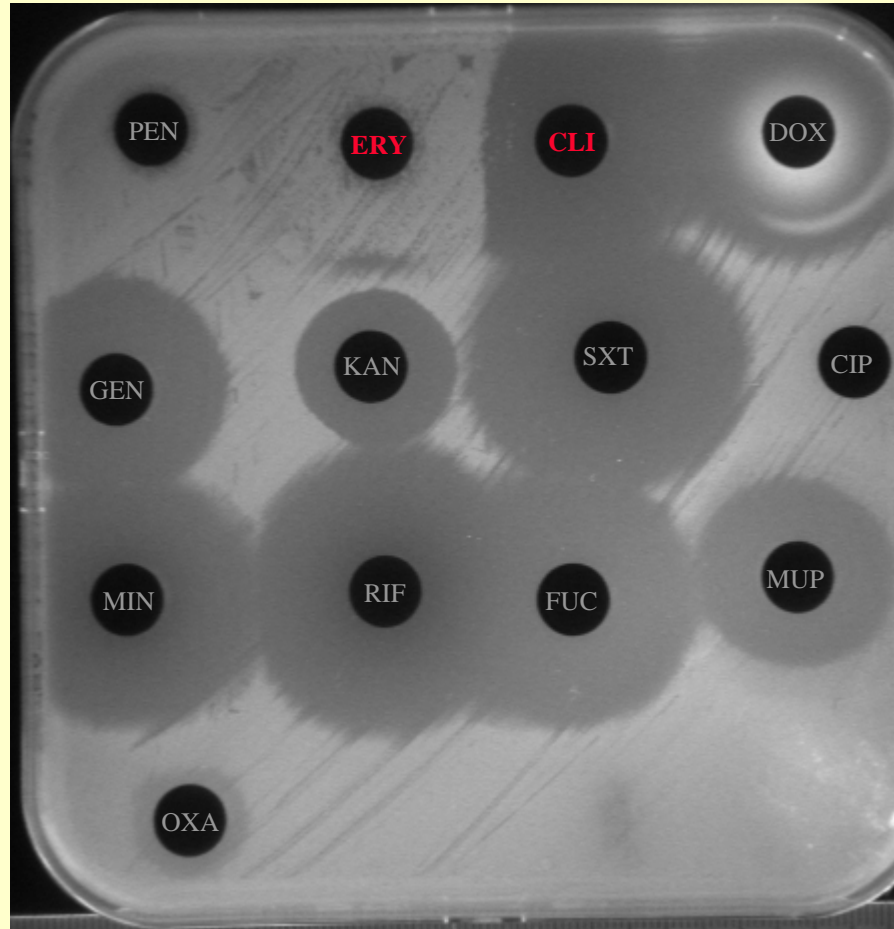
Belgium, National Survey 2001



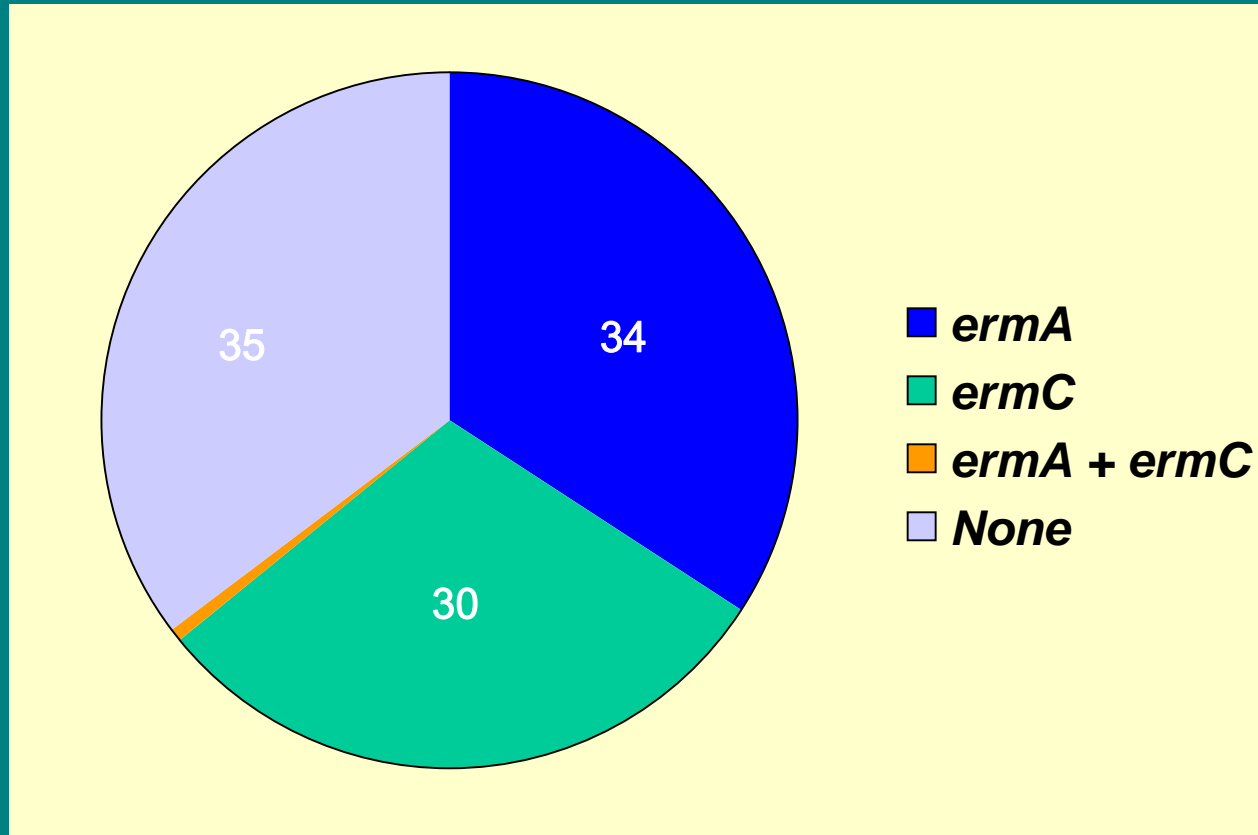
MLSb constitutive resistance phenotype



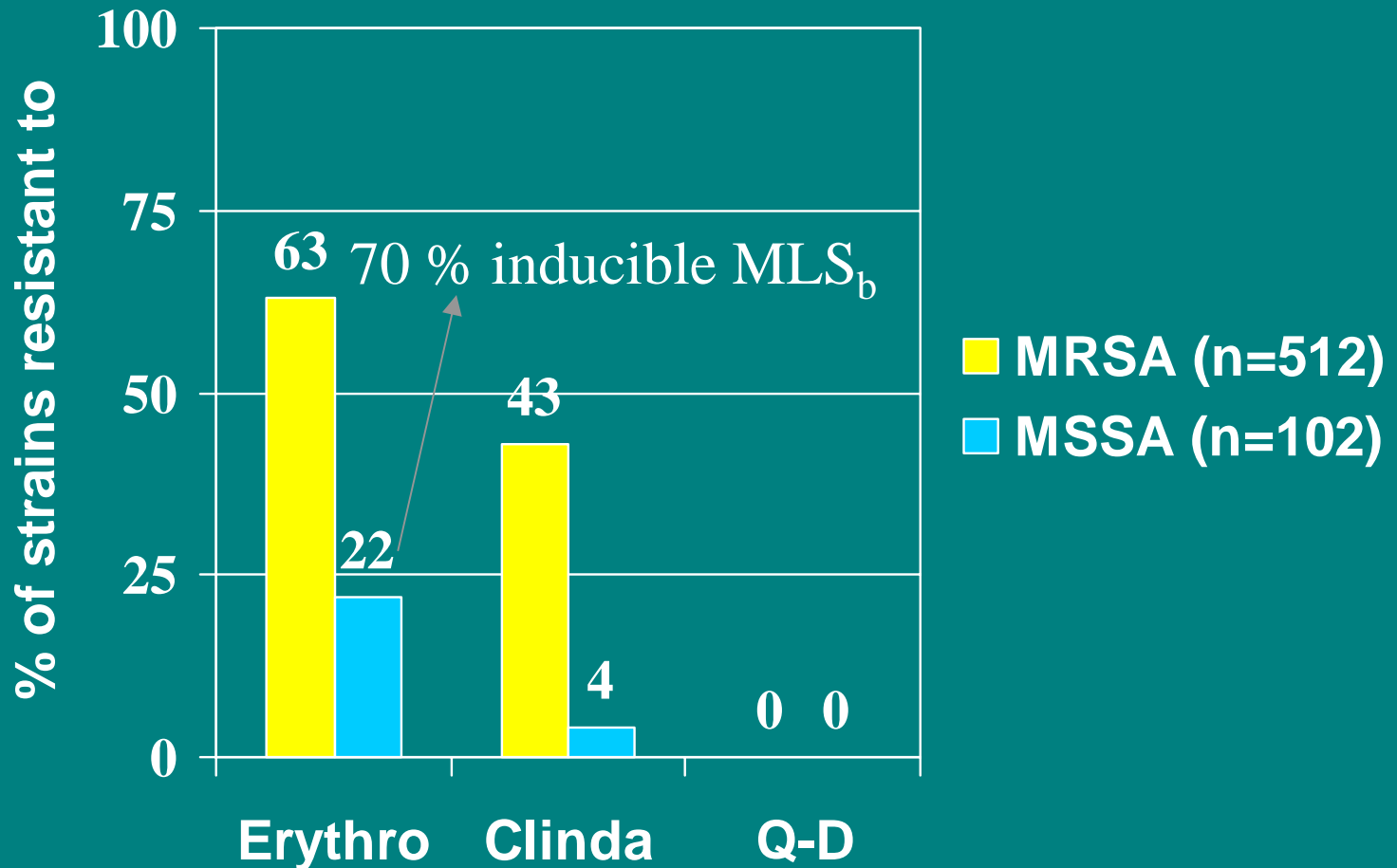
MLSb inducible resistance phenotype



Proportion of MRSA strains with MLS resistance genes, Belgium 2001

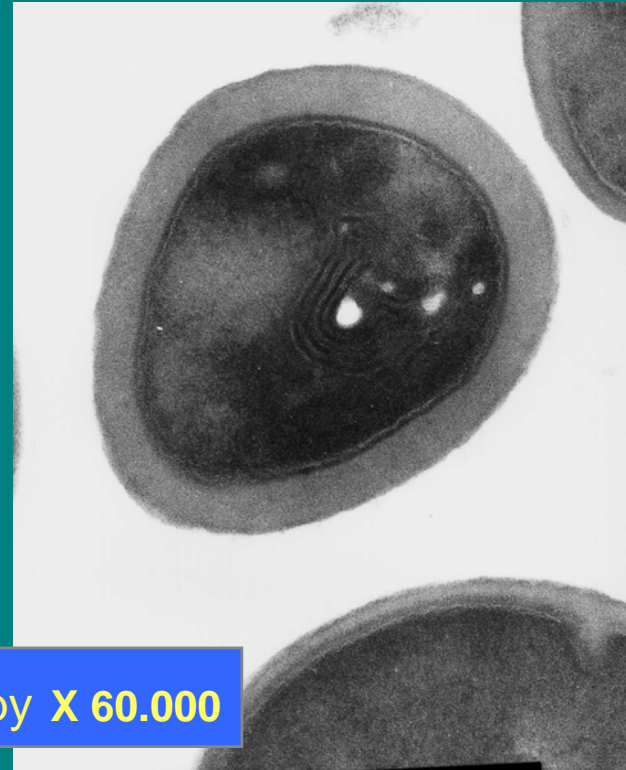
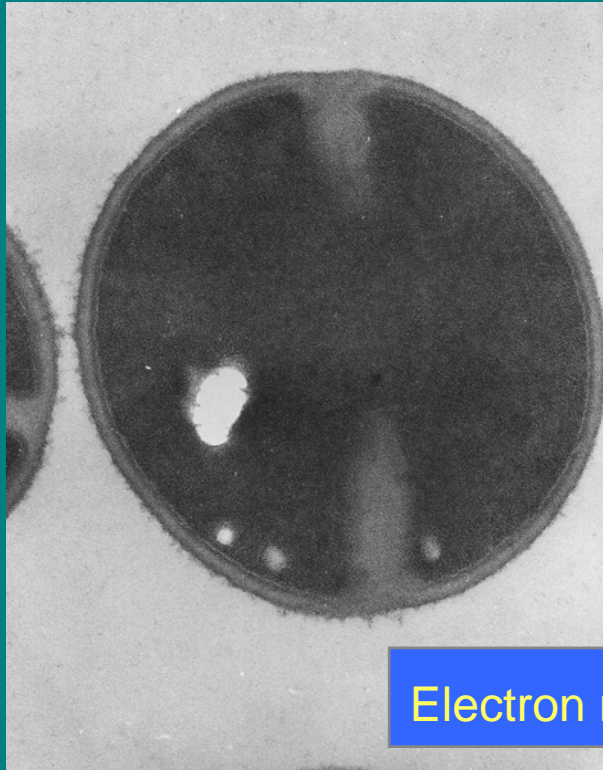


Macrolide-Lincosamide-Streptogramin Resistance in MRSA and MSSA isolates Belgium National Survey, 2003



The Shadow Mutant: Vancomycin Intermediate *S.aureus* / VISA

Denis *JAC* 2002;50:383



Electron microscopy X 60.000

S.aureus ATCC 29213

VISA strain - P1V44
Vancomycin MIC 8 mg/l

S.aureus Glycopeptide Resistance

- Definitions

- GISA : MIC > 4 µg/ml for vancomycin or > 8 µg/ml for teicoplanin
- Hetero-GISA : sub-population (10^{-6}) able to grow at ≥ 4 µg/ml vancomycin or at ≥ 8 µg/ml teicoplanin

- National surveys in Belgium

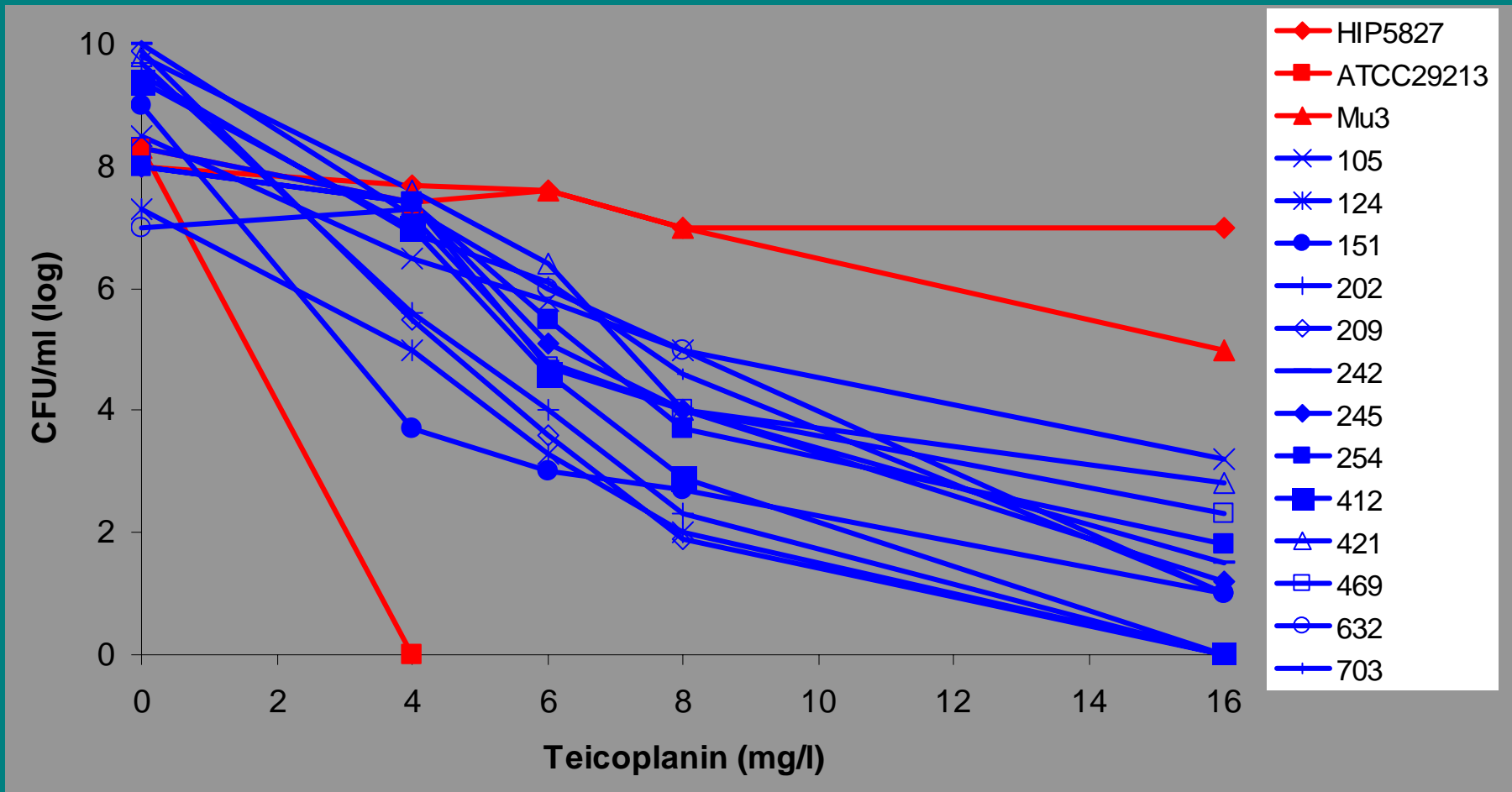
- (Denis Microb Drug Resist. 2003;9:61;Nonhoff CMI 2005;11:214)

- **Hetero-VISA : from 1.7H% in 1997 to 0.7% in 2001**
- **Hetero-TISA : 2.7% in 2001**
- PFGE group A (69%) and group D (31%)

- Local surveys in Belgium

- Van Eldere (37th ICAAC 1997) : Outbreak of TISA in ICU
- Denis (JAC 2002; 50:755) : First Belgian VISA infection
- Pierard (Pathol Biol 2004;52:486): **0.6 % hVISA**
- Glupczynski (ECCMID 2005 P870): **1.5 % hGISA**

Population analysis of MRSA isolates with decreased teicoplanin susceptibility, Belgium, 2001



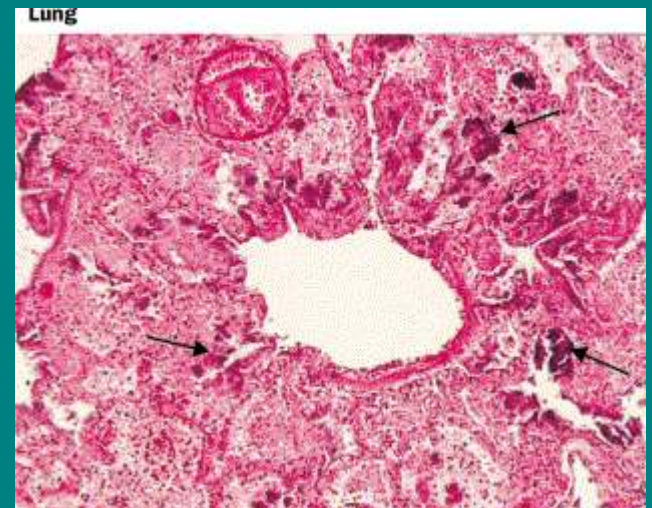
Community-Acquired PVL (+)-MRSA : Furunculosis & Necrotizing Pneumonia

Emergence since 1990s

Australia, USA, Asia, Europe

Healthy children & young adults

New disease



Demographic characteristics of 16 patients with PVL positive MRSA strains, Belgium

Denis ECCMID 2005

Median age (range)	24 (1-70) yrs
Sex	
Male	7
Female	9
Acquisition	
Community	15
Hospital	1
Previous beta-lactam therapy	5
Familial transmission	1
Travel abroad (Tunisia, Egypt, Ecuador)	3

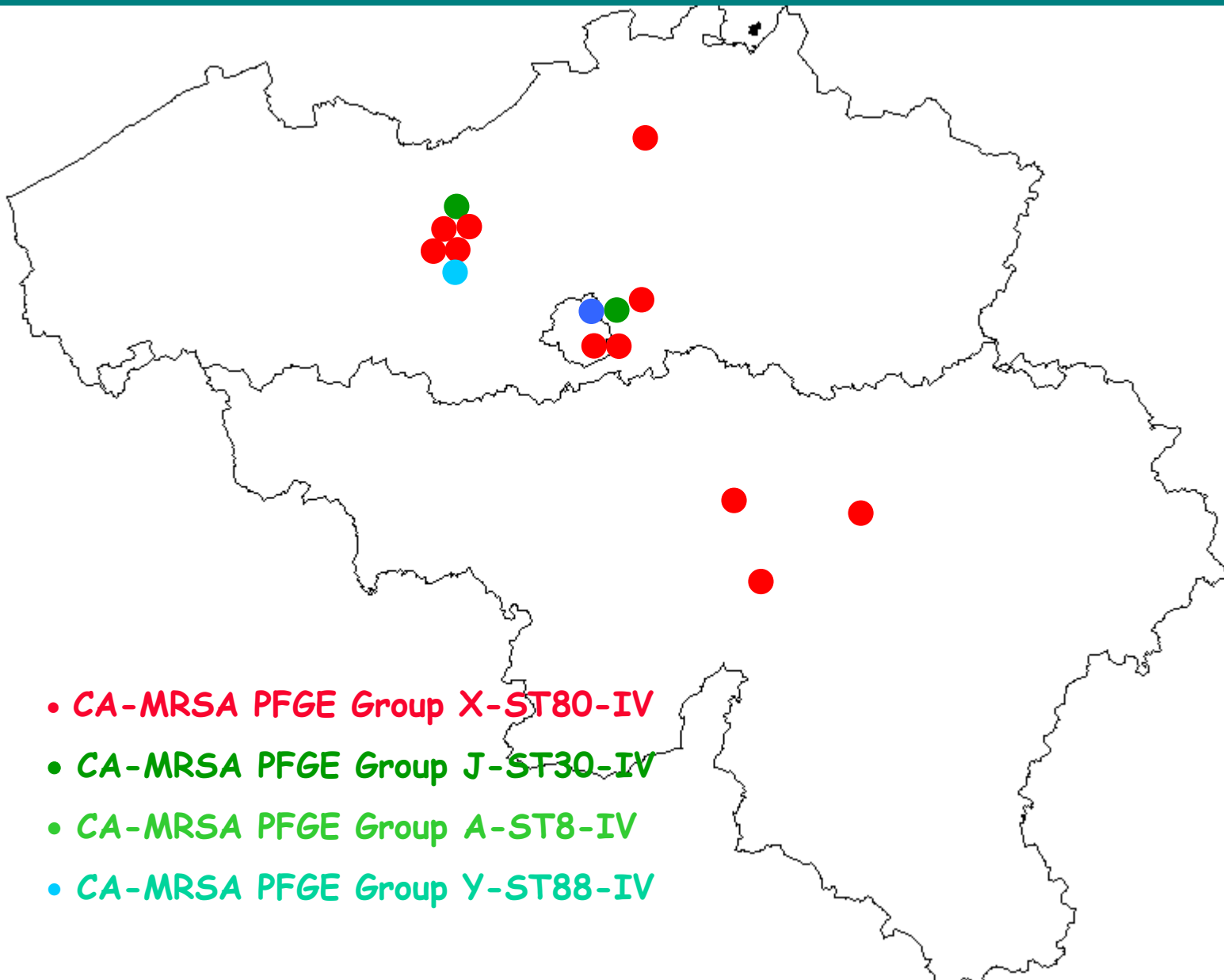
Clinical origin of 16 PVL positive MRSA strains from Belgium

Community-acquired infections (n = 15)

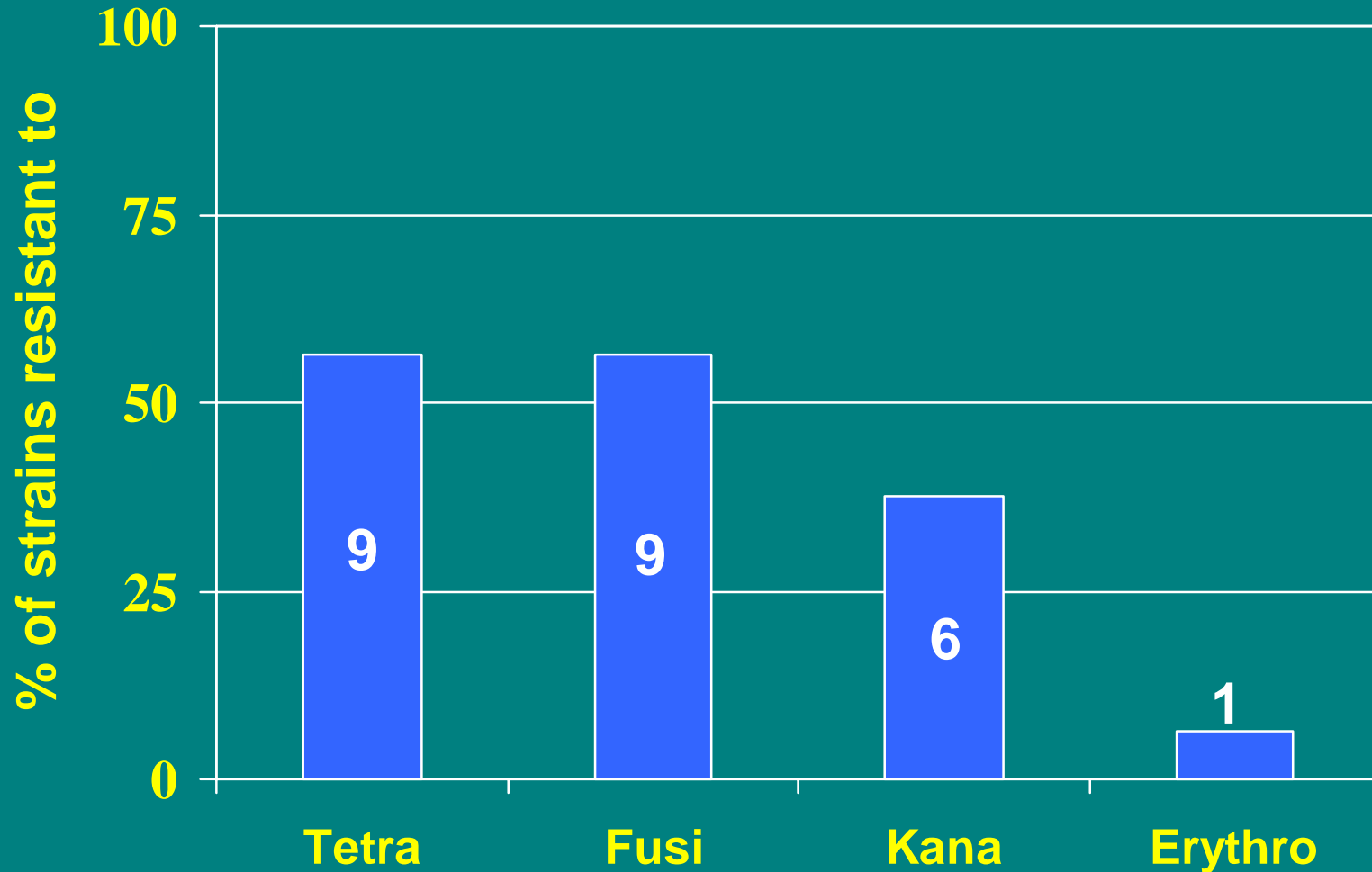
Skin and soft tissue abscesses	8
Furunculosis	3
Colonization	2
Wound infection	1
Cellulitis with bacteremia	1

Hospital-acquired infection (n = 1)

Post-surgical peritonitis	1
---------------------------	---



Antimicrobial resistance of PVL-positive MRSA strains



Molecular characteristics of PVL-positive MRSA strains, Belgium 2002-04

PFGE Group	MLST	SCC <i>mec</i>	<i>agr</i>	<i>spa</i>	No of strains
X	ST80	IV	3	t044	8
X	ST80	IV	3	t131*	1
X	ST153**	IV	3	t044	1
A	ST8	IV	1	t008	3
J	ST30	IV	3	t019	2
Y	ST88	IV	3	t186	1

* 1 repeat deletion from t044 , ** single allele variant of ST80

Methicillin-resistant *Staphylococcus aureus* Toxic Shock Syndrome

Sophie Jamart,* Olivier Denis,*
Ariane Deplano,*
Georgios Tragas,*
Alexandra Vandergheynst,*
David De Bels,*
and Jacques Devriendt*

*Université Libre de Bruxelles, Brussels,
Belgium

as previously described (3).

By molecular typing, the strain belonged to the epidemic MRSA pulsed-field gel electrophoresis clone G10 and carried the staphylococcal chromosome cassette *mec* (SCC*mec*) type II. This clone belongs to the sequence type (ST) 5-SCC*mec* II clone, formerly named “New-York/Japan clone,” which has been associated with neonatal TSS-like exanthematous disease in Japanese hospitals (4–6). This epidemic clone, which is widely disseminated in the

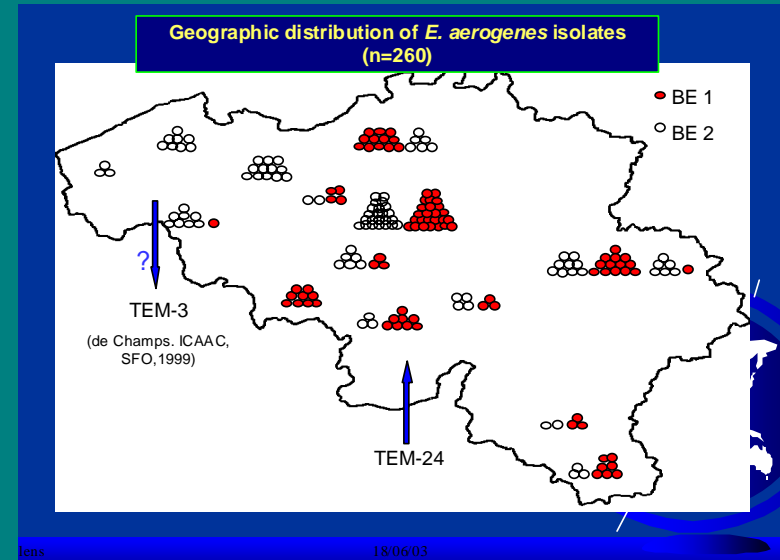
We would also like to emphasize the rising risk of TSS due to virulent MRSA strains outside Japan and particularly in Europe. The usual recommendations for the treatment of staphylococcal TSS do not consider this possibility and consist of a β -lactamase-resistant anti-staphylococcal agent and clindamycin in some cases (to decrease the synthesis of TSST-1) (9–11).

We immediately treated our patient with teicoplanin and clindamycin because we suspected a nosocomia

Epidemiology of ESBL-producing Enterobacteria

- Clonal outbreaks
inter-hospital epidemic spread by transfer of colonised patients (France, USA, Belgium,...)

- Plasmid epidemics

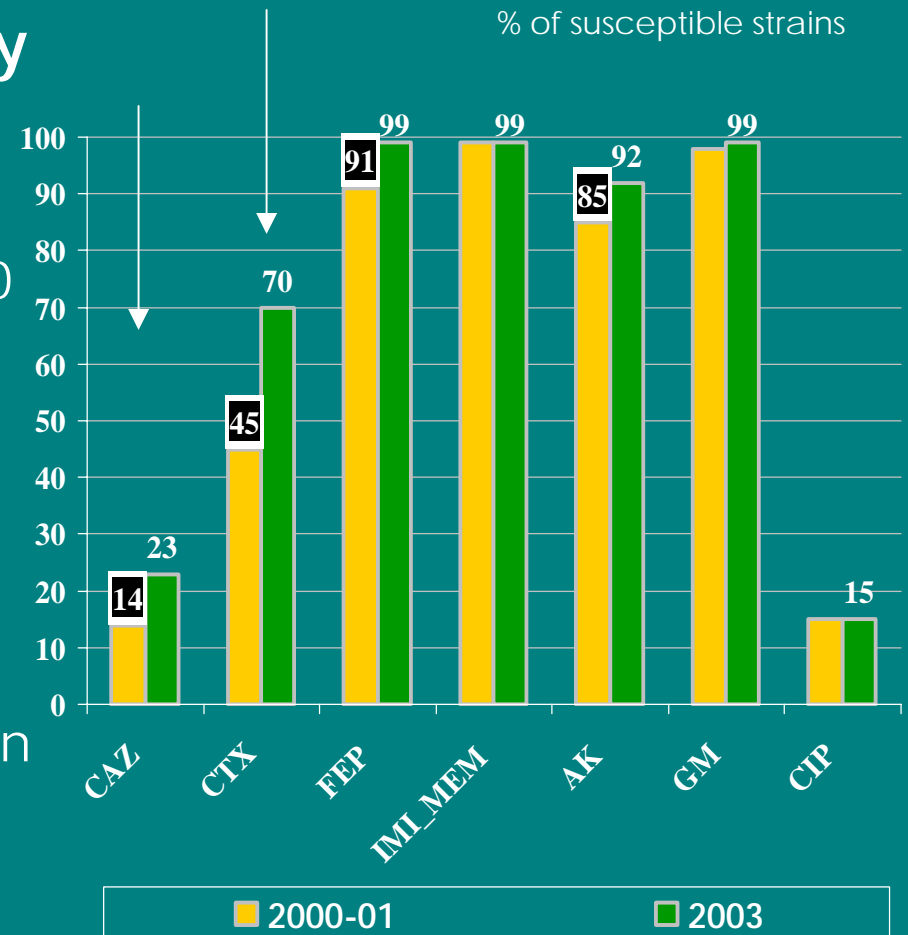


- ESBL-producing strains often co-resistant to fluoroquinolones, SXT and aminoglycosides

Enterobacter aerogenes

Persistence of multi resistant *E. aerogenes* in Belgium

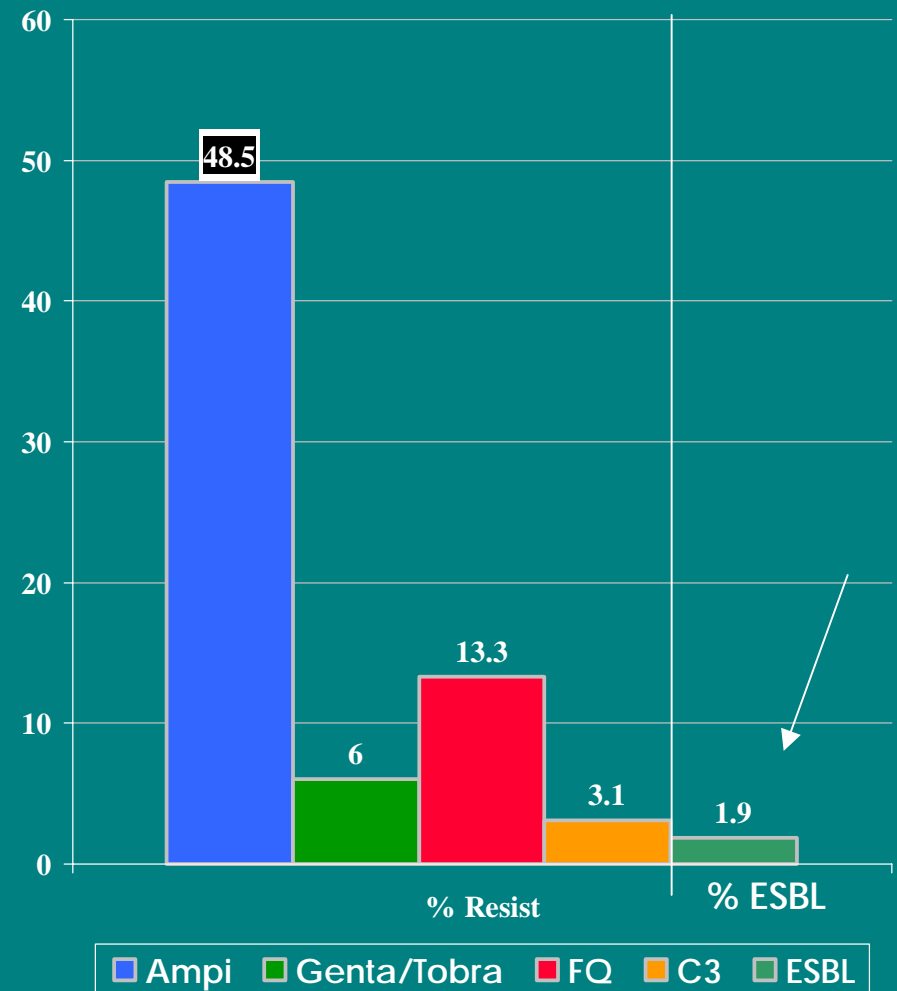
- **Second multicentric survey**
403 strains from 87 centres
 - Proportion of MREA: 60%
 - Incidence of MREA: 3.2/1000 admissions
- **stable proportion of ESBL-producing strains**
 - 61% in 2000, 54% in 2003
 - Co-resistance CAZ and CIP in 99%



Escherichia coli

EARSS surveillance in Belgium 2002

- n=1185 from blood or CSF
- Prevalence of ESBL: 1.9%

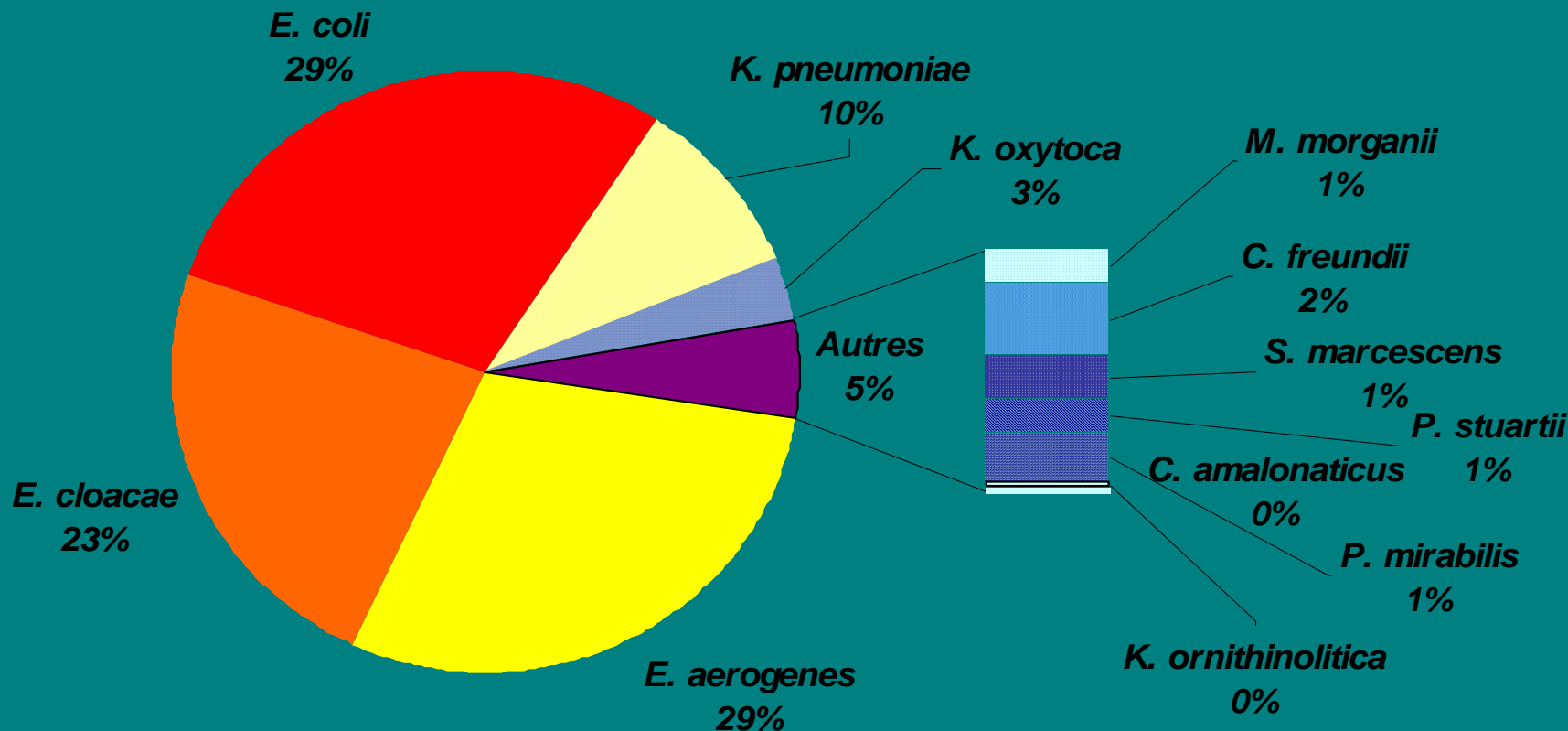


Hendrickx, ECCMID 2004, P1123

ESBL-producing *Enterobacteriaceae*

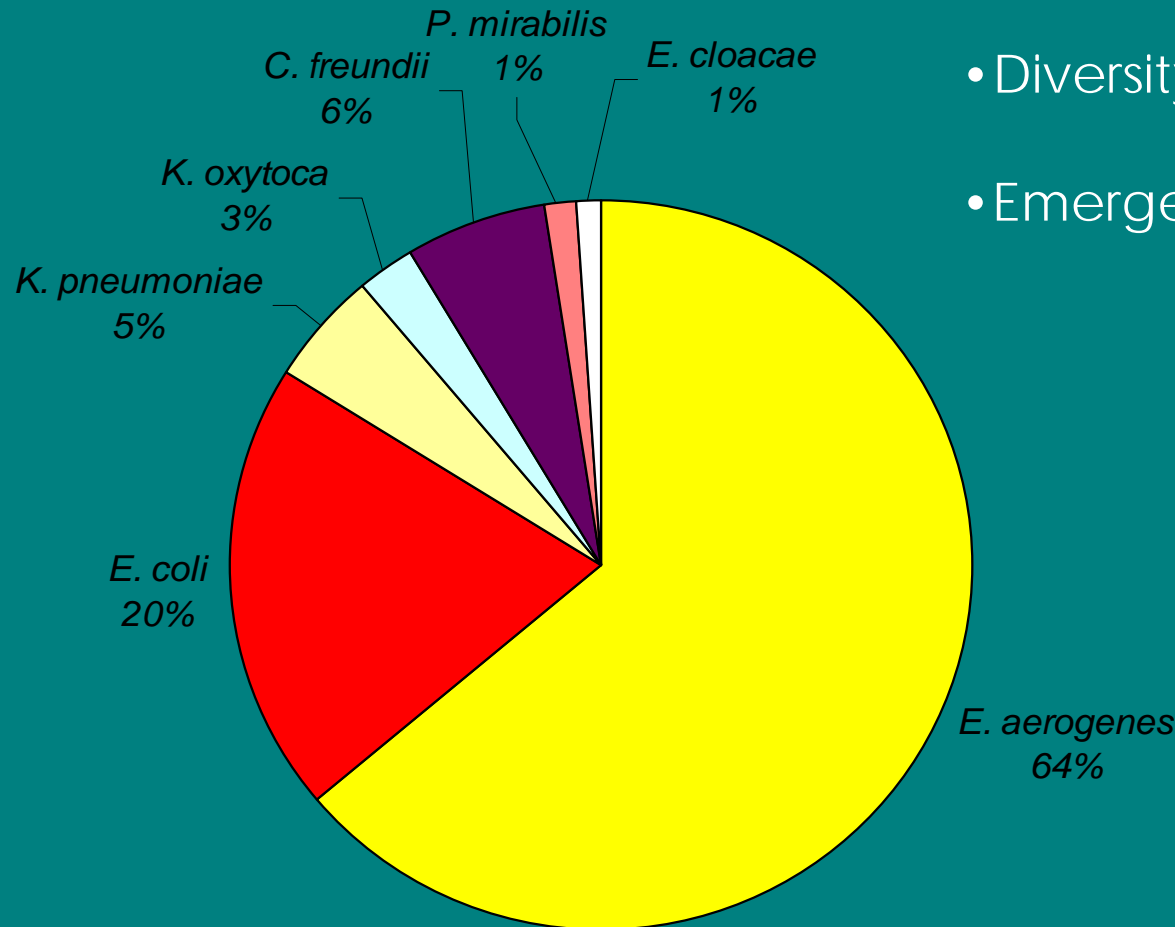
Hôpital Erasme-ULB 2000-2004

N= 847 ESBL-producing strains from 725 patients



ESBL-producing *Enterobacteriaceae* Hôpital Mont-Godinne-UCL 2003-2004

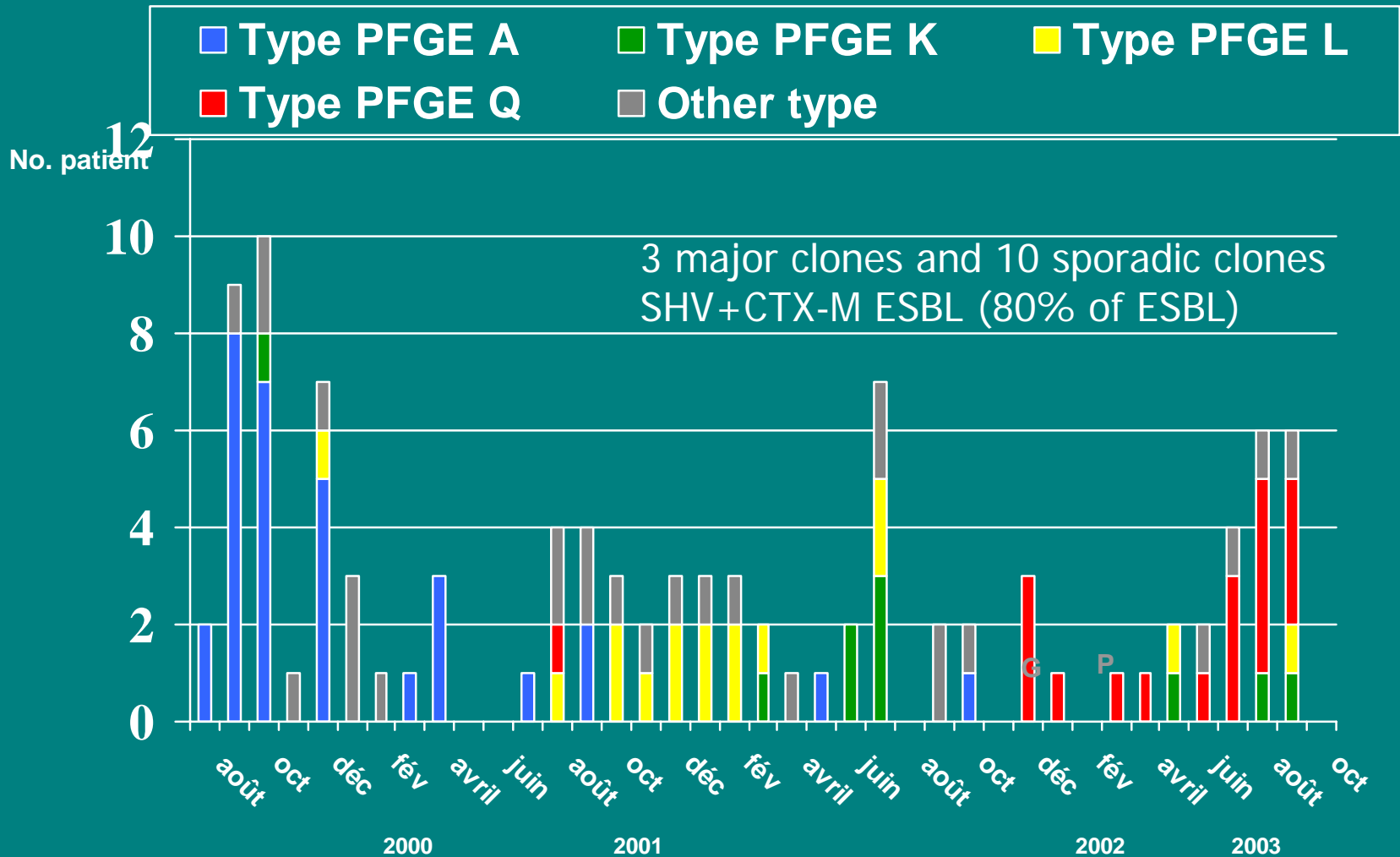
N=80 isolates (7% *Enterobacteriaceae*)



- Diversity of ESBL types
- Emergence of CTX-M group

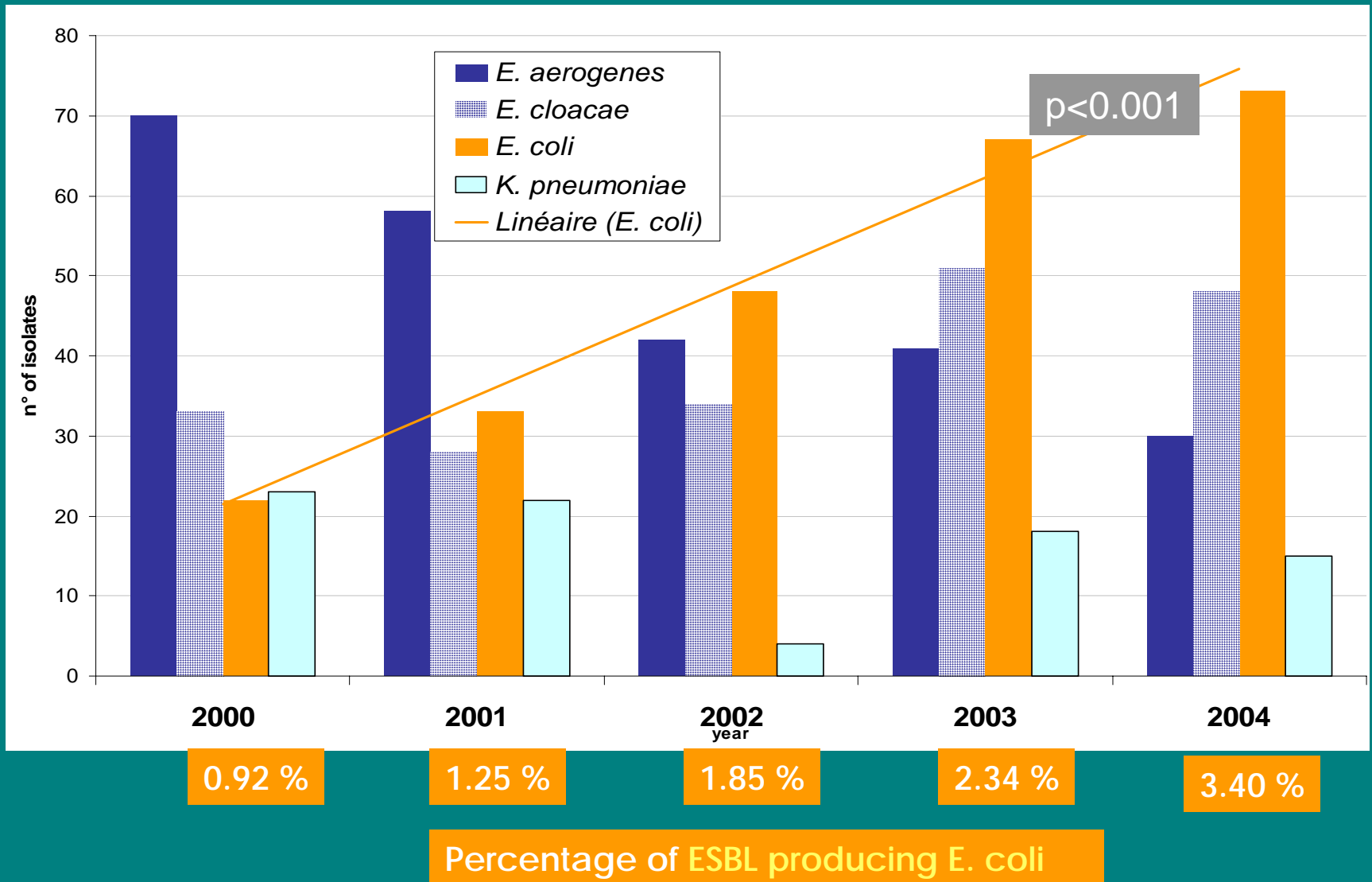
ESBL-producing *E. cloacae* in ICU pts by clone

Hôpital Erasme, 2000-03



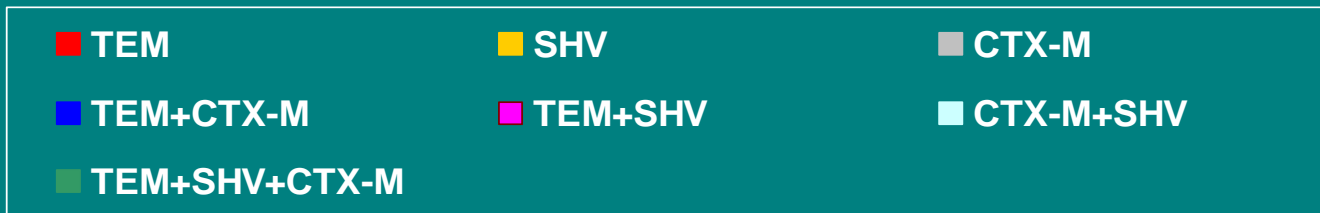
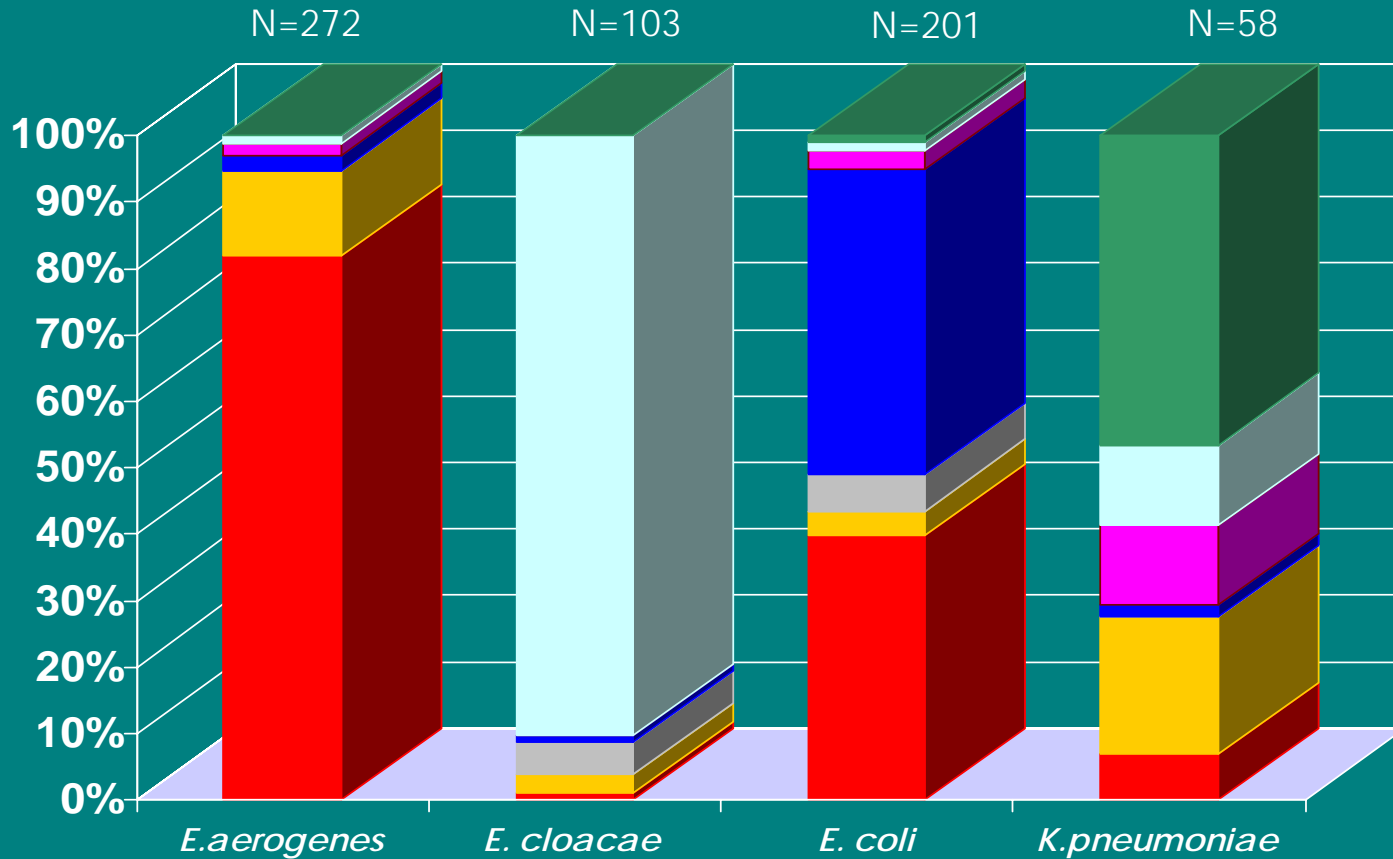
ESBL-producing *Enterobacteriaceae*

Prevalence by species, Hôpital Erasme-ULB, 2000-2004



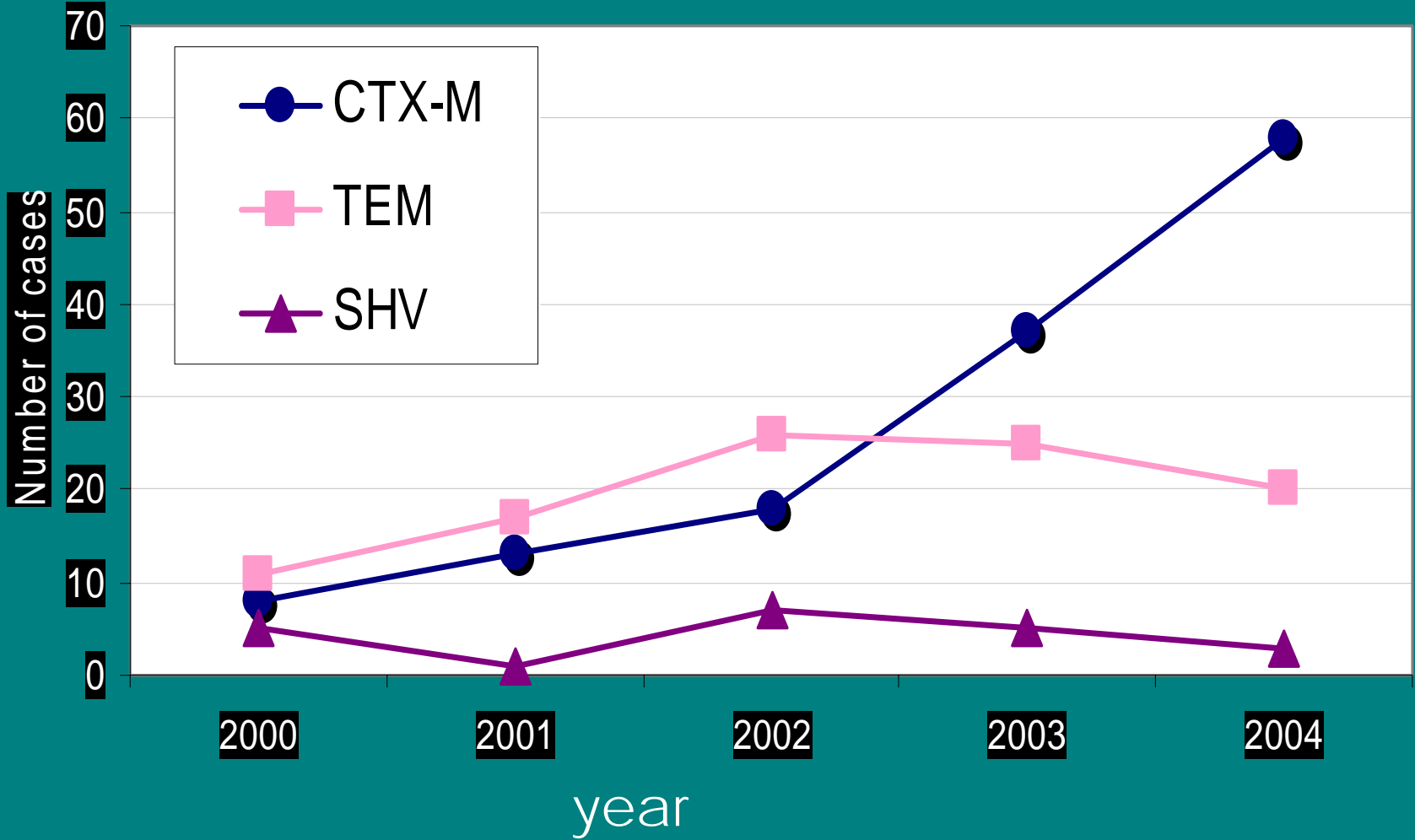
ESBL gene families by species

Erasme Hospital-ULB 2000-2003



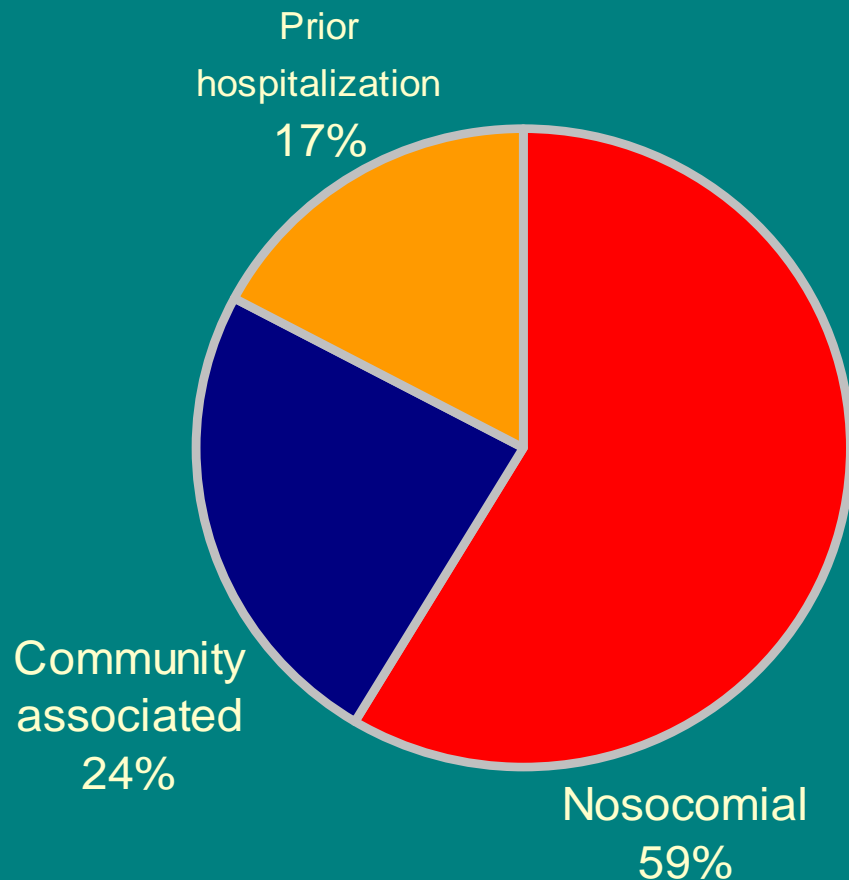
Increase of CTX-M enzymes among ESBL producing *E.coli*

Erasme Hospital – ULB, 2000-04

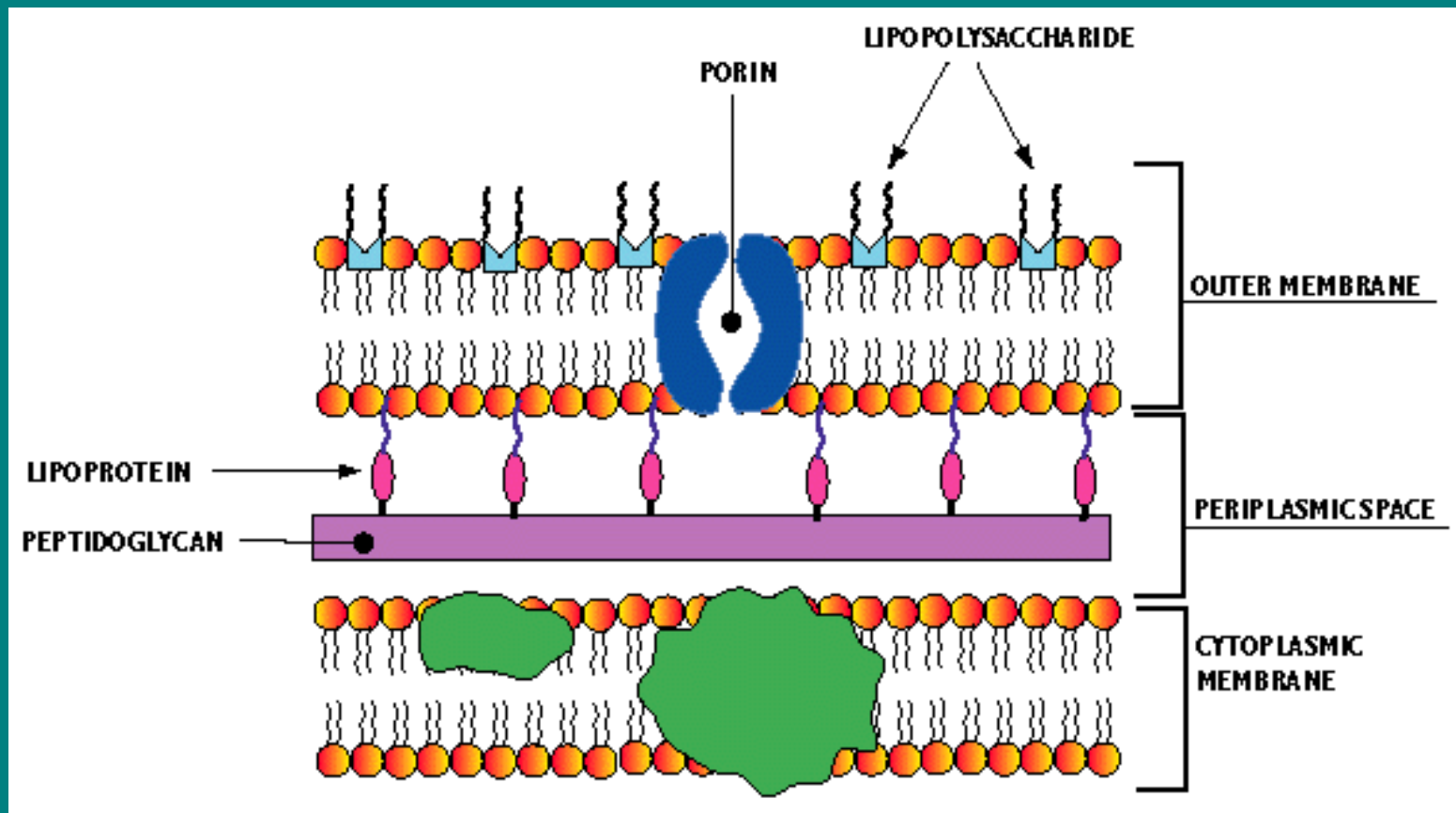


Community-associated emergence of CTX-M/TEM ESBL-producing *E.coli*

H. Rodriguez. Eurosurveillance Vol 10 .2005

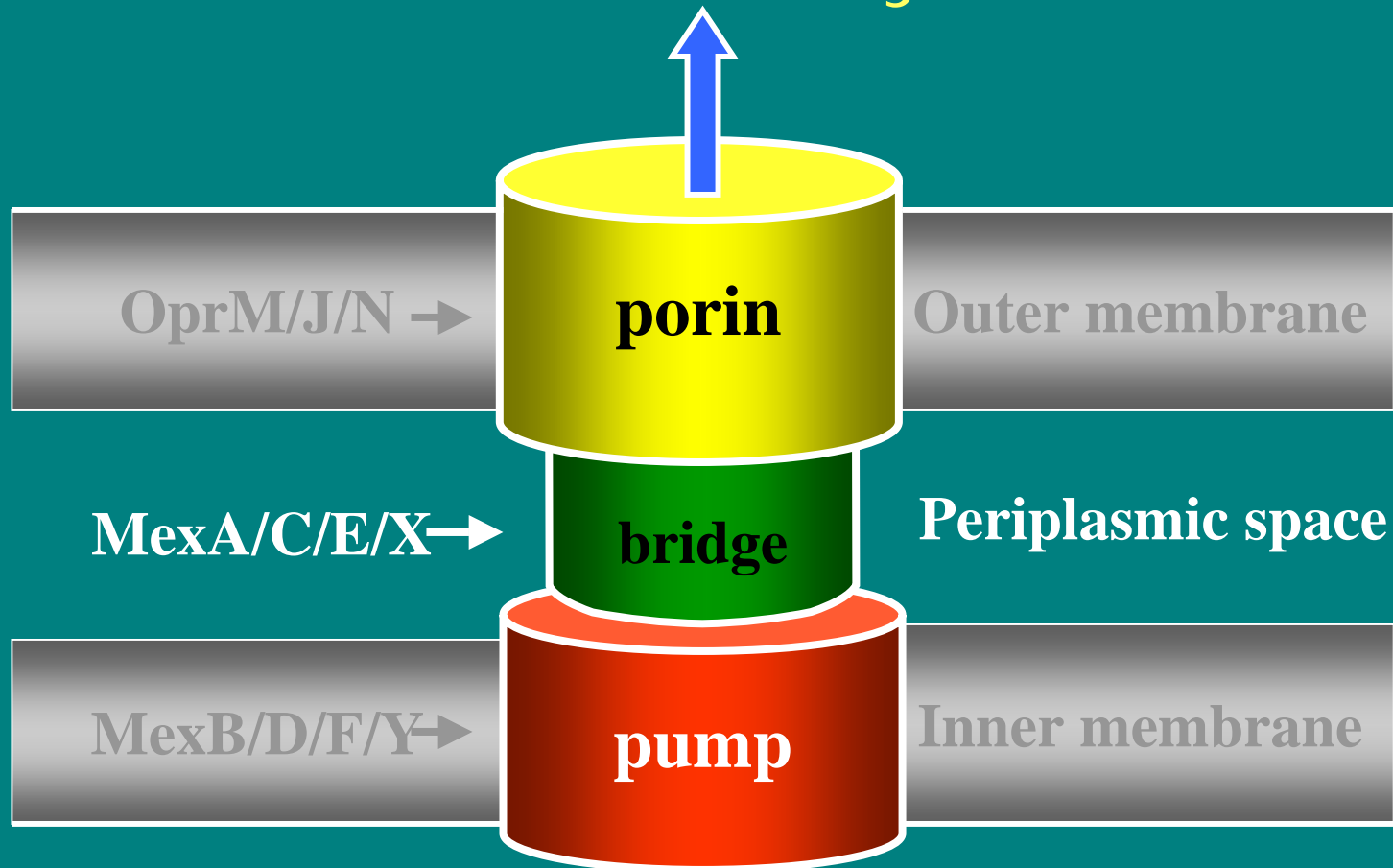


Antibiotic resistance in *P.aeruginosa*: reduced outer membrane permeability



Antibiotic resistance in *P.aeruginosa*:

Active efflux systems



Belgian national survey 2002: b-lactam resistance in *P.aeruginosa*

Van Eldere *JAC* 2003

Drug	S	I	R
Pip-tazo	82,5%		17,5%
Cefta	59,0%	12,5%	28,5%
Cefep	50,5%	20%	29,5%
Mero	81,5%	9%	9,5%

Molecular Characterization of an Epidemic Clone of Panantibiotic-Resistant *Pseudomonas aeruginosa*

A. Deplano,^{1*} O. Denis,¹ L. Poirel,² D. Hocquet,³ C. Nonhoff,¹ B. Byl,⁴
P. Nordmann,² J. L. Vincent,⁵ and M. J. Struelens¹

J Clin Microbiol 2005;43:1198

No. of patients

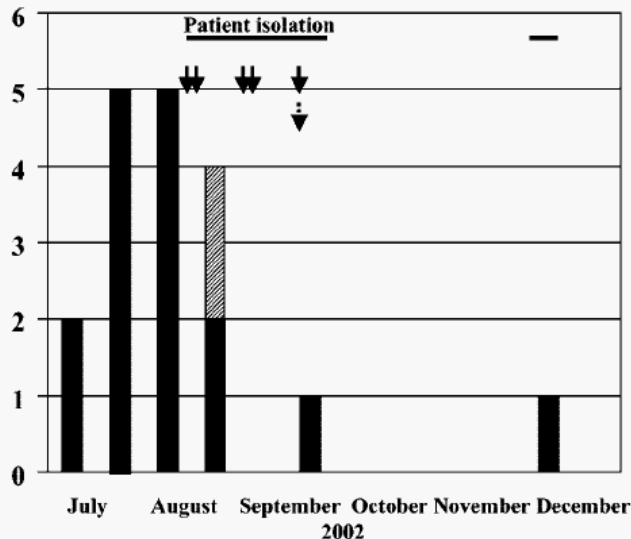


TABLE 2. Variations of resistance mechanisms in multiresistant *P. aeruginosa* isolates

Strain	β -Lactamase activity (nmol/min/mg of protein)	Expression ^a		Sequence of <i>mexZ</i> ^b
		<i>oprD</i>	<i>mexX</i>	
PAO1	72	1.00	1.00	
Positive control			>22 ^c	
PFGE type A1	5,100	0.02	49.4	GAC→G_C (164)
PFGE type K1	3,500	0.2	3.6	

Antibiotic Resistance Belgium

Current Situation 2005

- Major challenges:
 - MRSA, ESBL-Enterobacteriaceae, *P.aeruginosa*... & others!
- Blurring frontier between community and hospital reservoirs requires new studies
- Need for consolidation of initiatives by BAPCOC & federal platform for hygiene
- Need for concerted international action