Antimicrobial resistance and strategies for Gram-negative bacteria

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Epidemiology of antimicrobial resistance

- **Several bias**
  - → **Selection of participating centres**
    (bedsize,, activity, types of patients, pathologies, length of stay,…)
  - →**Wide variations in study designs**
    (many surveillance programs sponsored by industry)
  - →**Variability/modification of definitions/criteria**
  - →**Differences/changes over time of susceptibiltiy testing methods and/or antibiotics tested (lack of standardisation)**
- **Many « Snapshot » studies, few longitudinal, continous surveillance studies**
- **Studies more frequently focused on selected populations** (ICUs, Hematology,…) **or on selected antibiotics**

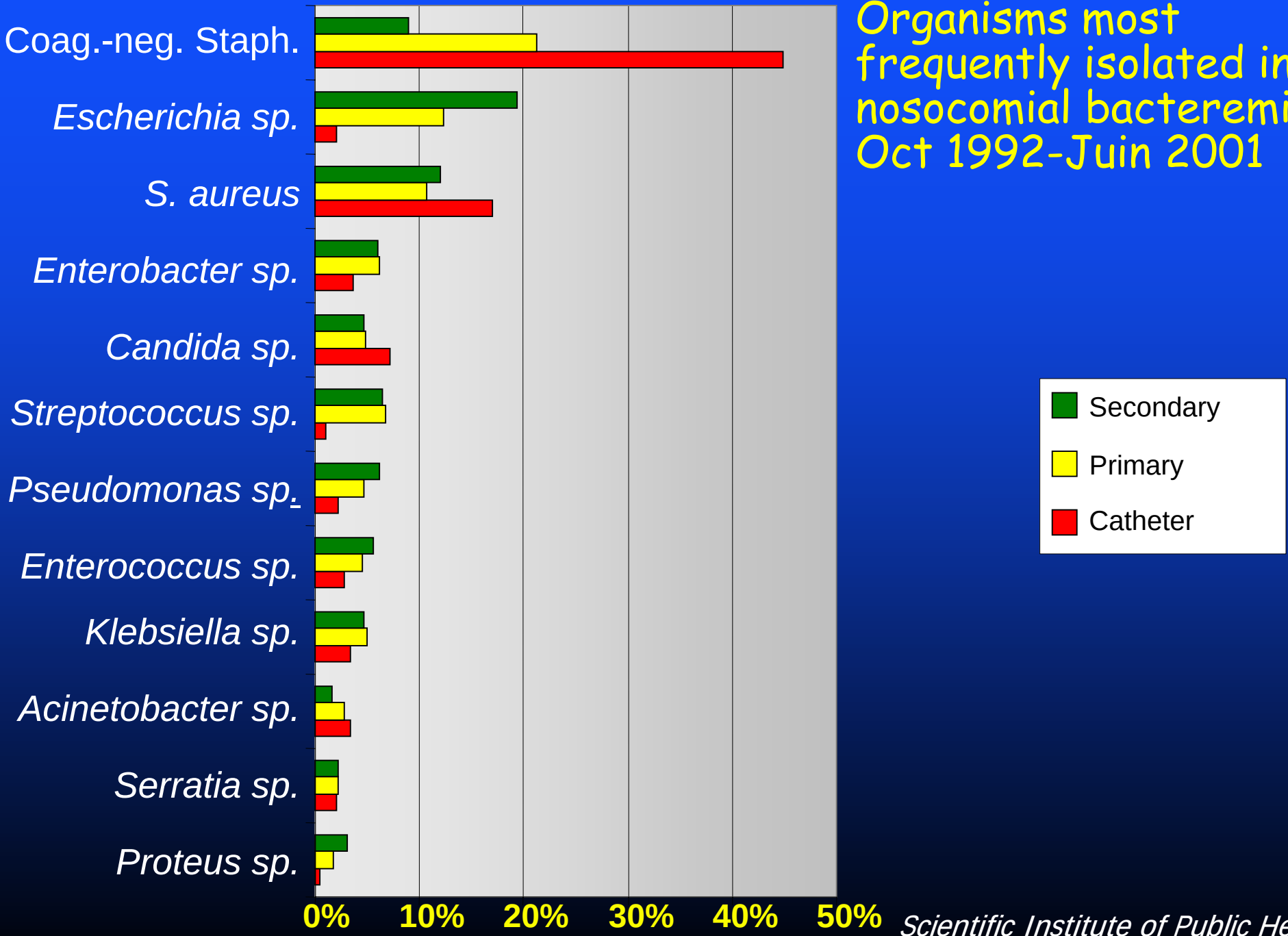
Surveillance studies on resistance among Gram-negative organisms

- **Community-acquired and nosocomial pathogens**
  - ***Enterobacteriaceae***
  - ***Pseudomonas aeruginosa***

- **Data gathered from local, Belgian multicentric studies (1995-2004)**
  - **NPRS program (1995-2001): ICU only (15-25 centres)**
  - **MYSTIC program (1998-2004); ICU, hematology, CF, general wards (8 centres)**
  - **EARSS (2001-2003); invasive *E. coli* infections, hospitalwide (27 centres)**
  - **Others**

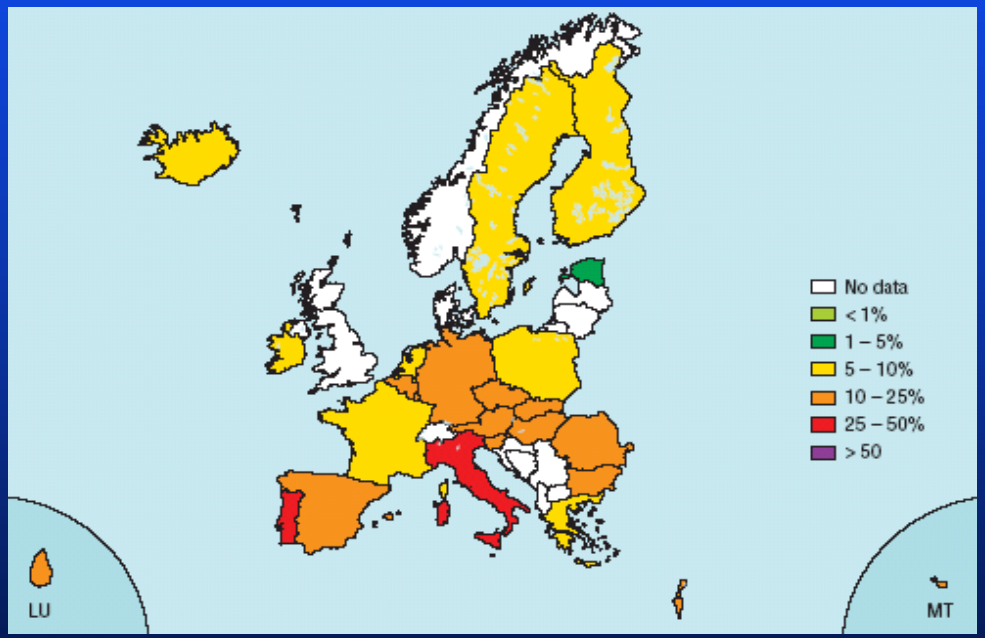
Escherichia coli

Organisms most frequently isolated in nosocomial bacteremia Oct 1992-Juin 2001

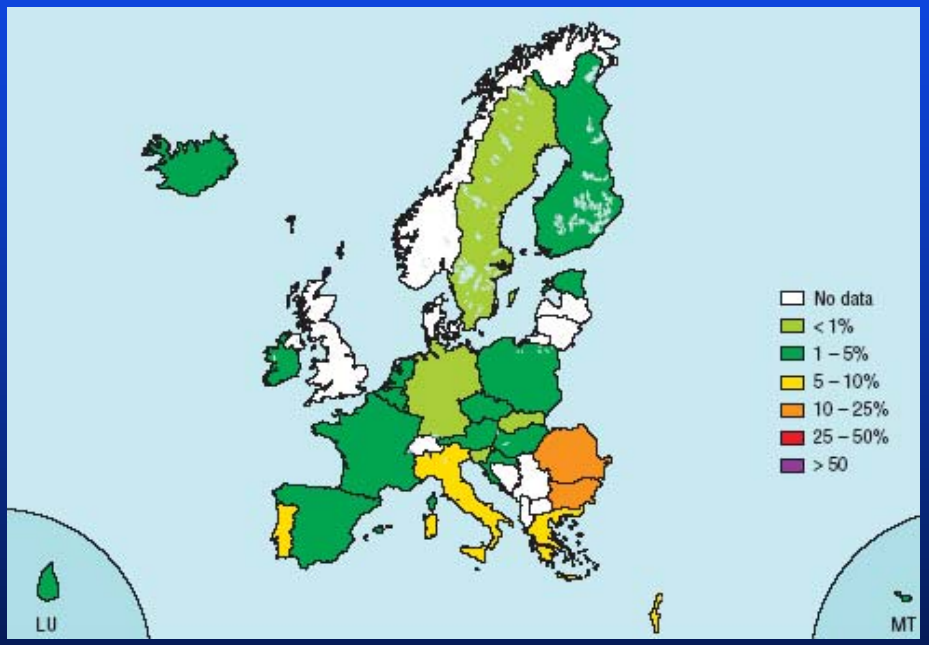


Antimicrobial resistance of *Escherichia coli* invasive isolates from blood

EARSS report- 2003



FQ-resistance

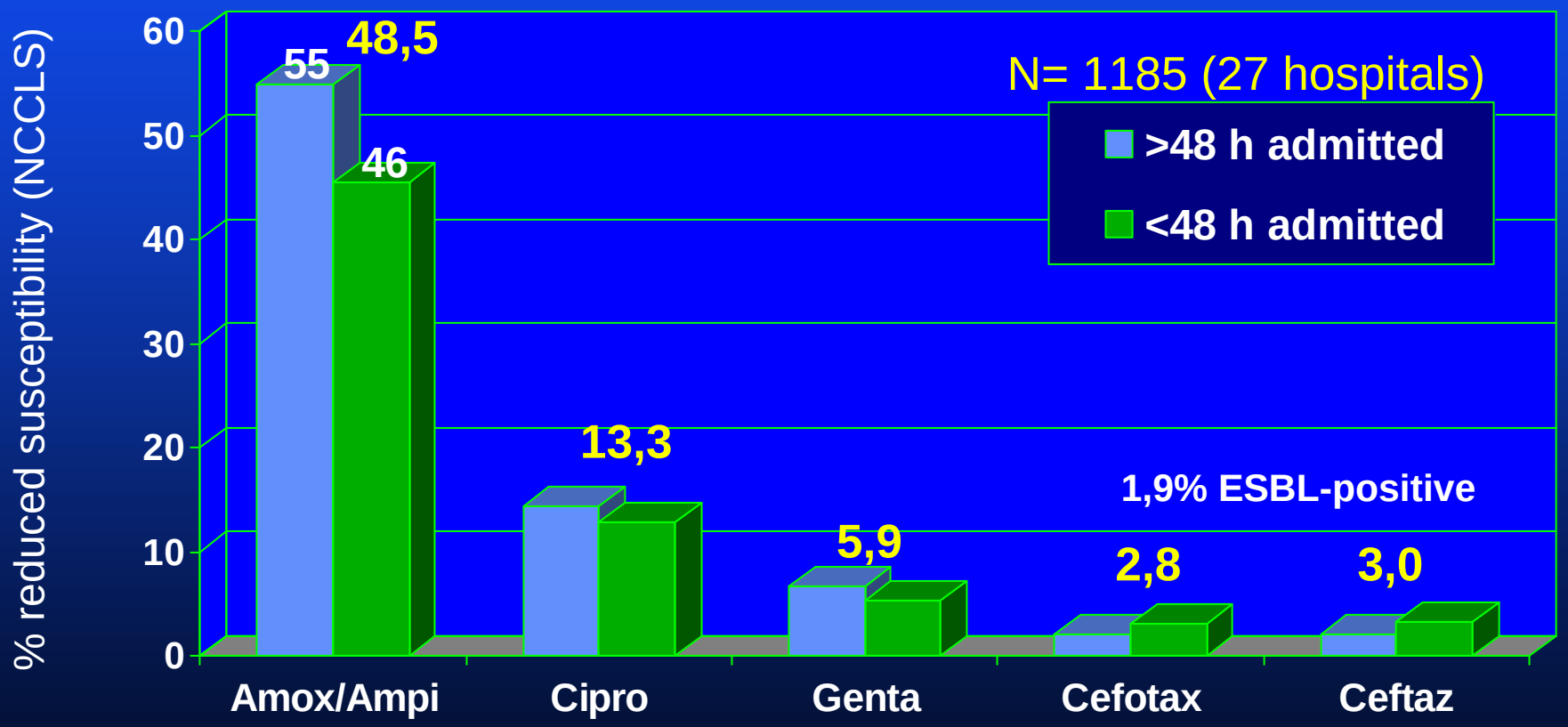


C3 G-resistance

http://www.earss.rivm.nl

Antimicrobial susceptibility in invasive *E. coli* isolates from bloodstream infections

(Belgium 2002 – EARSS Report)

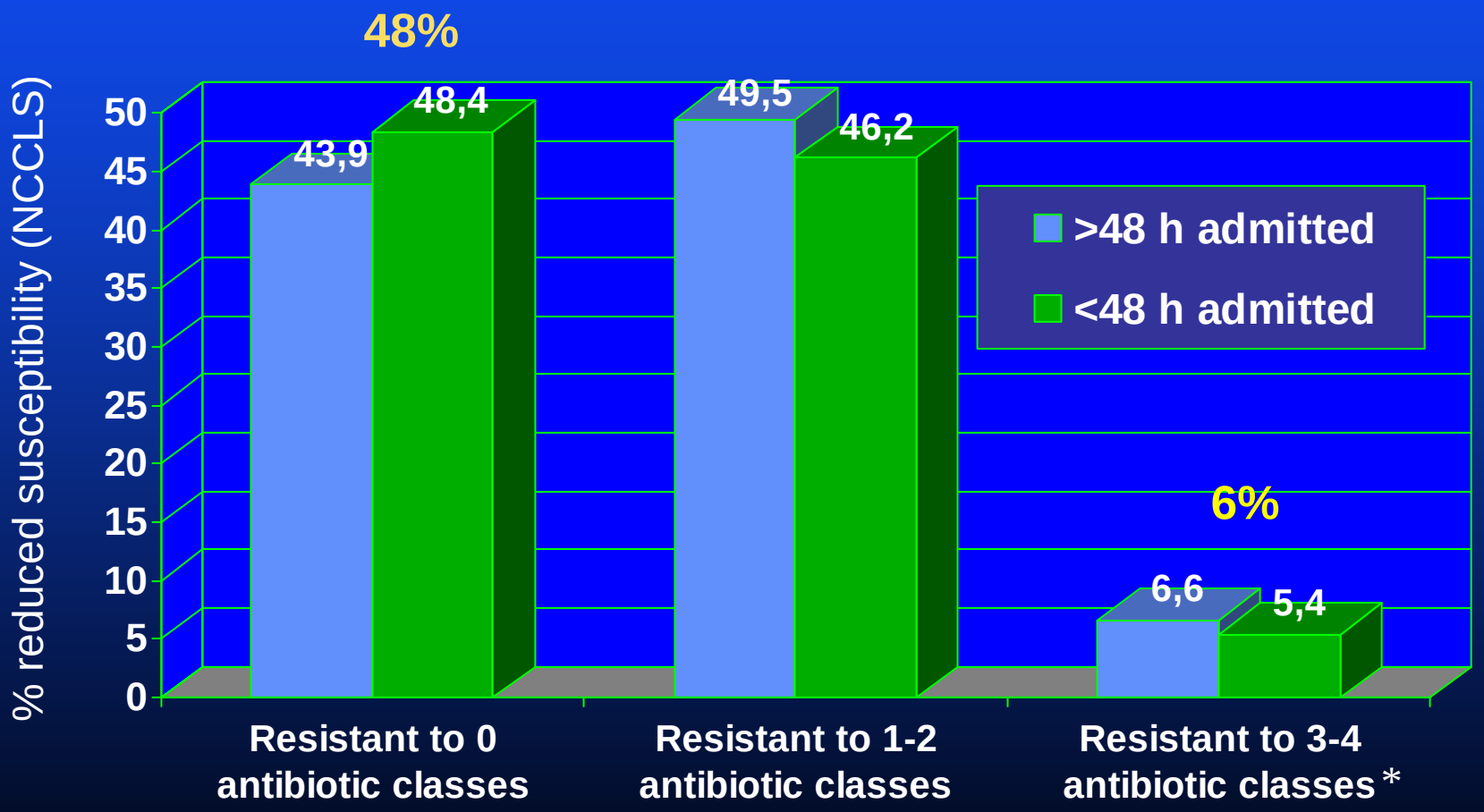


P < 0.005

Hendrickx & Pierard, ECCMID 2004

Multidrug resistance in *E. coli* blood or CSF isolates according to EARSS protocol

(Belgium 2002)

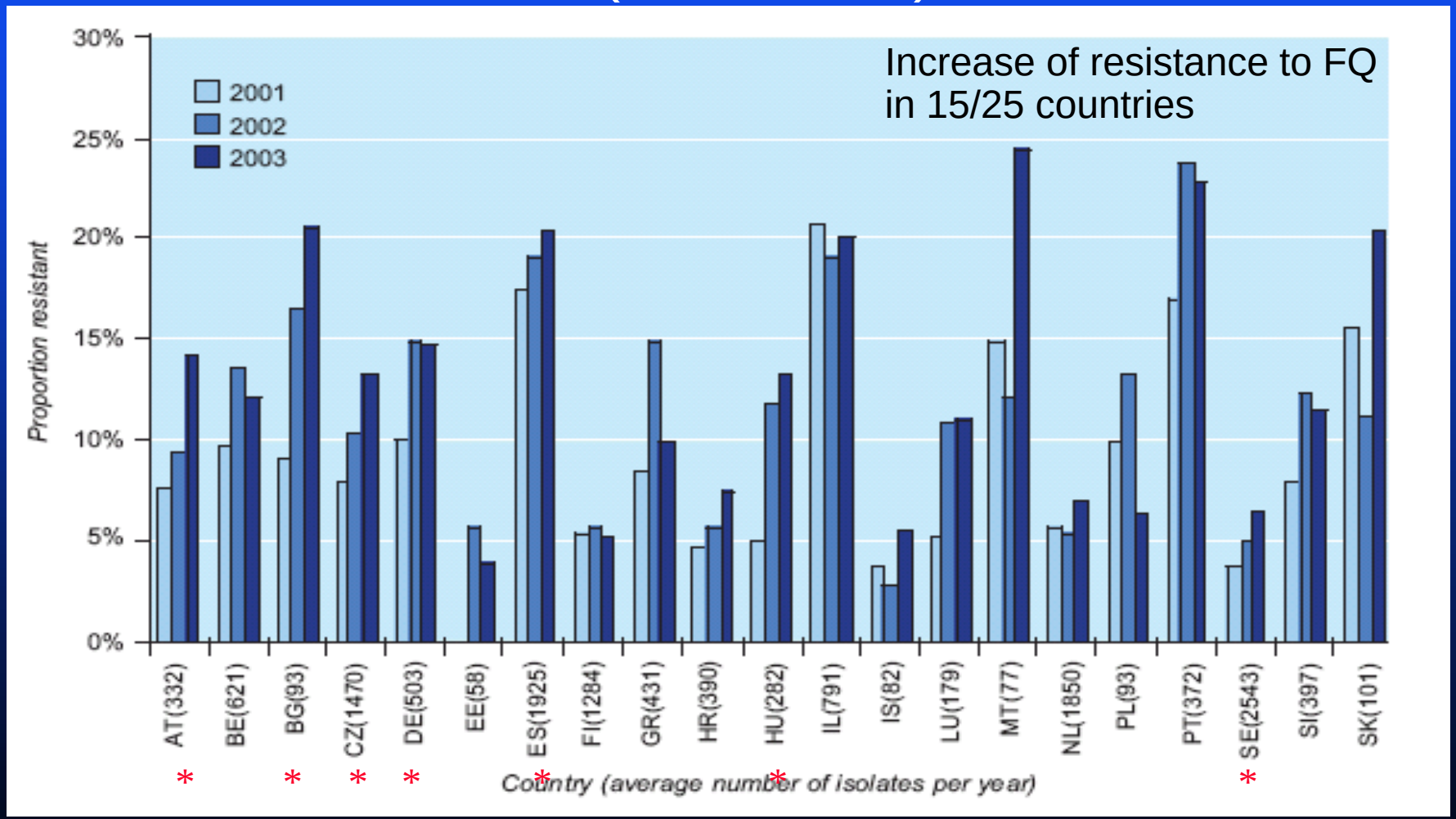


*aminopenicillins, C3G, aminoglycosides, quinolones

Hendrickx & Pierard, ECCMID 2004

E.coli invasive isolates resistant to fluoroquinolones

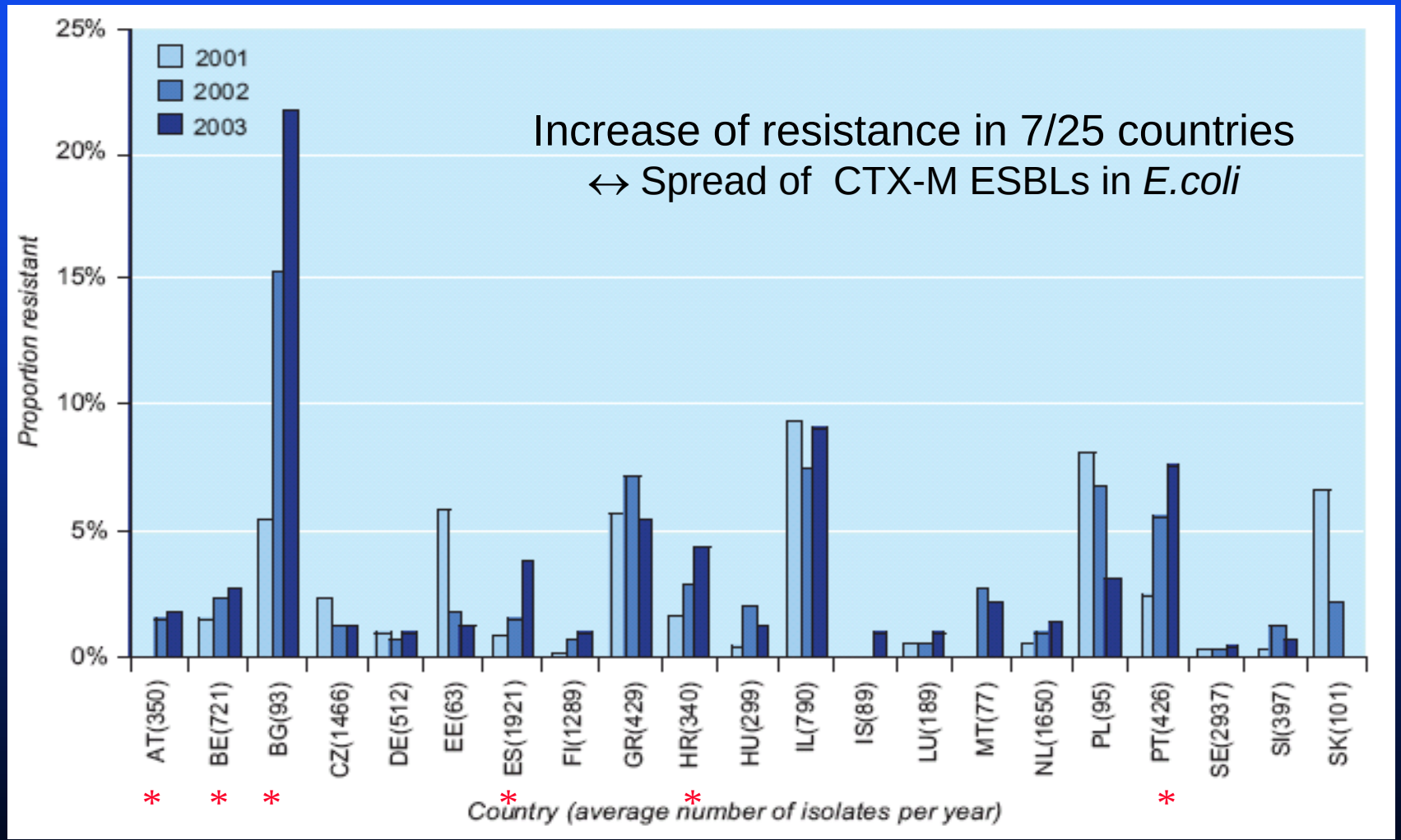
(2001-2003)



http://www.earss.rivm.nl

Escherichia coli invasive isolates resistant to 3rd gen. cephalosporins

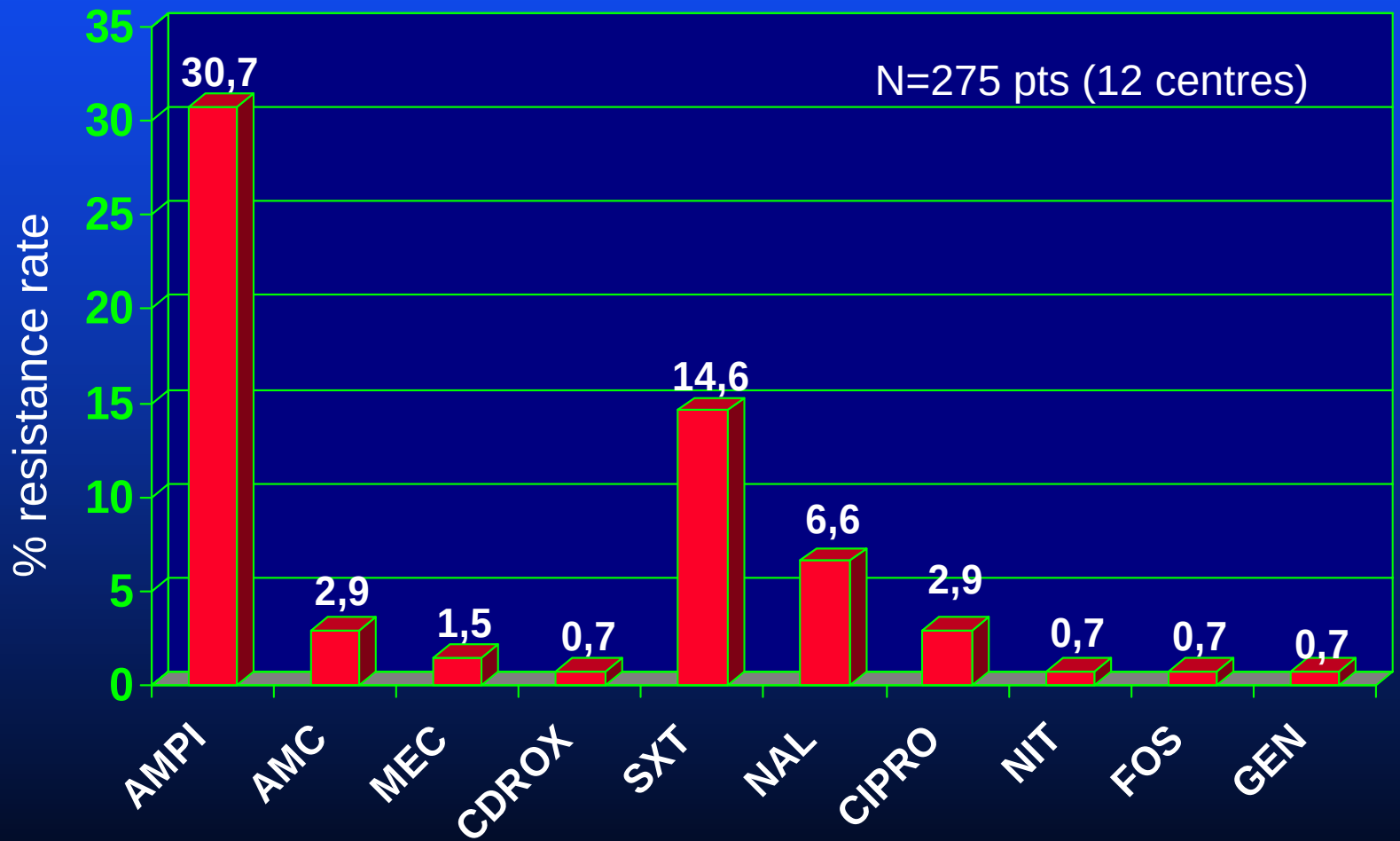
(2001-2003)



http://www.earss.rivm.nl

Antimicrobial susceptibility of *E. coli* from outpatients with uncomplicated UTI

-The ECO-SENS Project (1999-2000)-



Kahlmeter, JAC 2003; 51:69-76

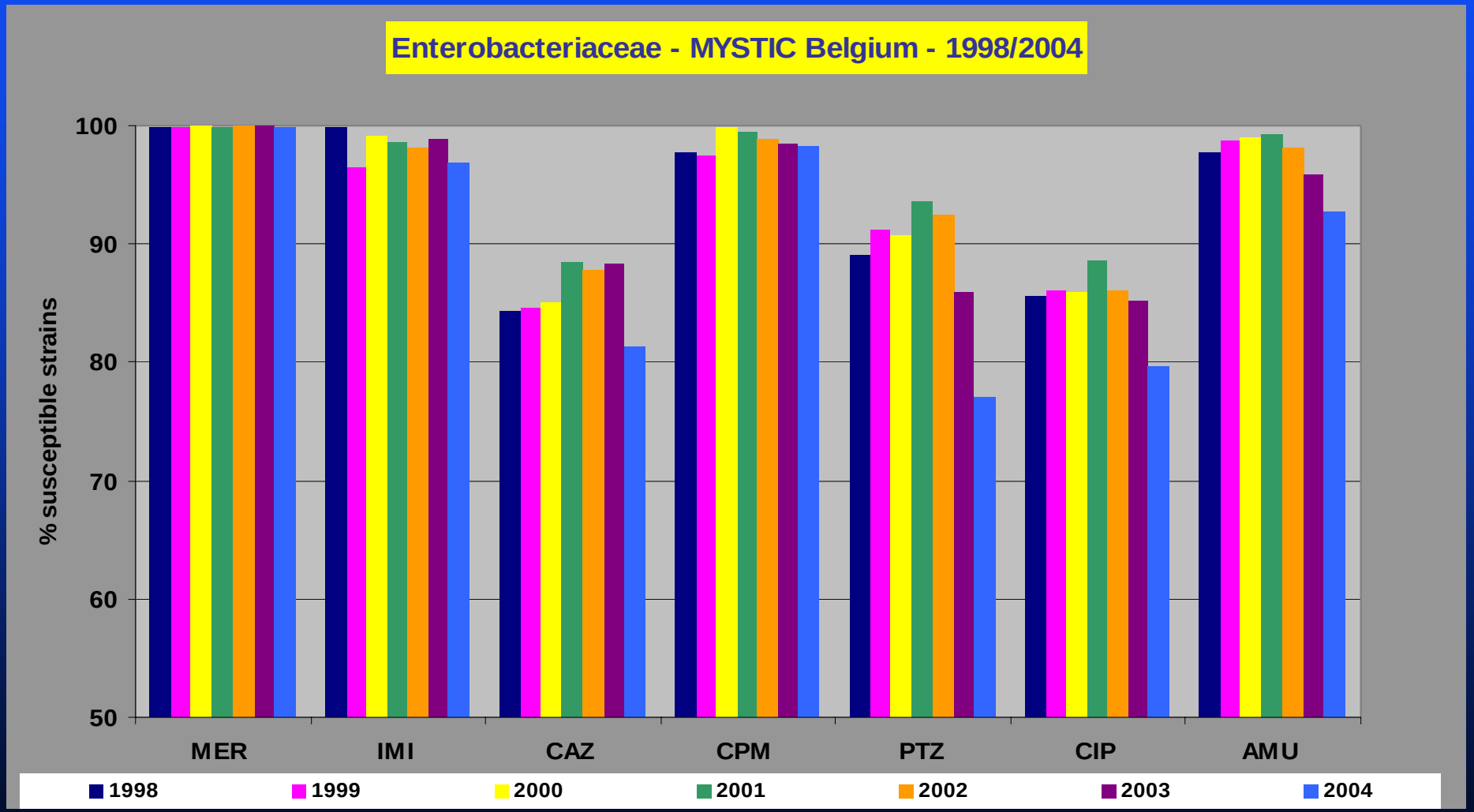
Enterobacteriaceae

Gram- Negative pathogens isolated from Belgian (8) ICUs from 1997-2000

Pseudomonas aeruginosa	383 (21,6%)
Escherichia coli	343 (19,4%)
Enterobacter cloacae	165 (9,3%)
Enterobacter aerogenes	137 (7,7%)
Proteus mirabilis	132 (7,5%)
Klebsiella pneumoniae	123 (6,9%)
Serratia marcescens	103 (5,8%)
Klebsiella oxytoca	88 (5,0%)
Acinetobacter baumanii	32 (1,8%)
Other	265 (15,0%)

MYSTIC Program, Belgium data
Goossens, JAC 2001

Activity vs Enterobacteriaceae



n=512 n=602 n=746 n=581 n=512 n=650 n=803

MYSTIC Program, Belgium data

Trends in Antimicrobial Spectrum and Potency for Enterobacteriaceae

Year	n	MIC_{90} (% susceptibility)			
		Agent			
		MEM	IMP	CAZ	CEP
1998	512	0.064 (99.8)	1 (98.8)	32 (84.4)	1 (97.7)
1999	602	0.125 (99.8)	2 (96.5)	32 (84.6)	2 (97.5)
2000	746	0.064 (100)	1 (99.1)	32 (85.1)	1 (99.8)
2001	581	0.064 (99.8)	1 (98.6)	16 (88.5)	0.5 (99.5)
2002	512	0.032 (100)	1 (98.1)	32 (87.7)	0.5 (98.8)
2003	650	0.064 (100)	1 (98.8)	16 (88.3)	1 (98.4)
2004	803	0.125 (99.8)	2 (96.8)	128 (81.3)	2 (98.3)

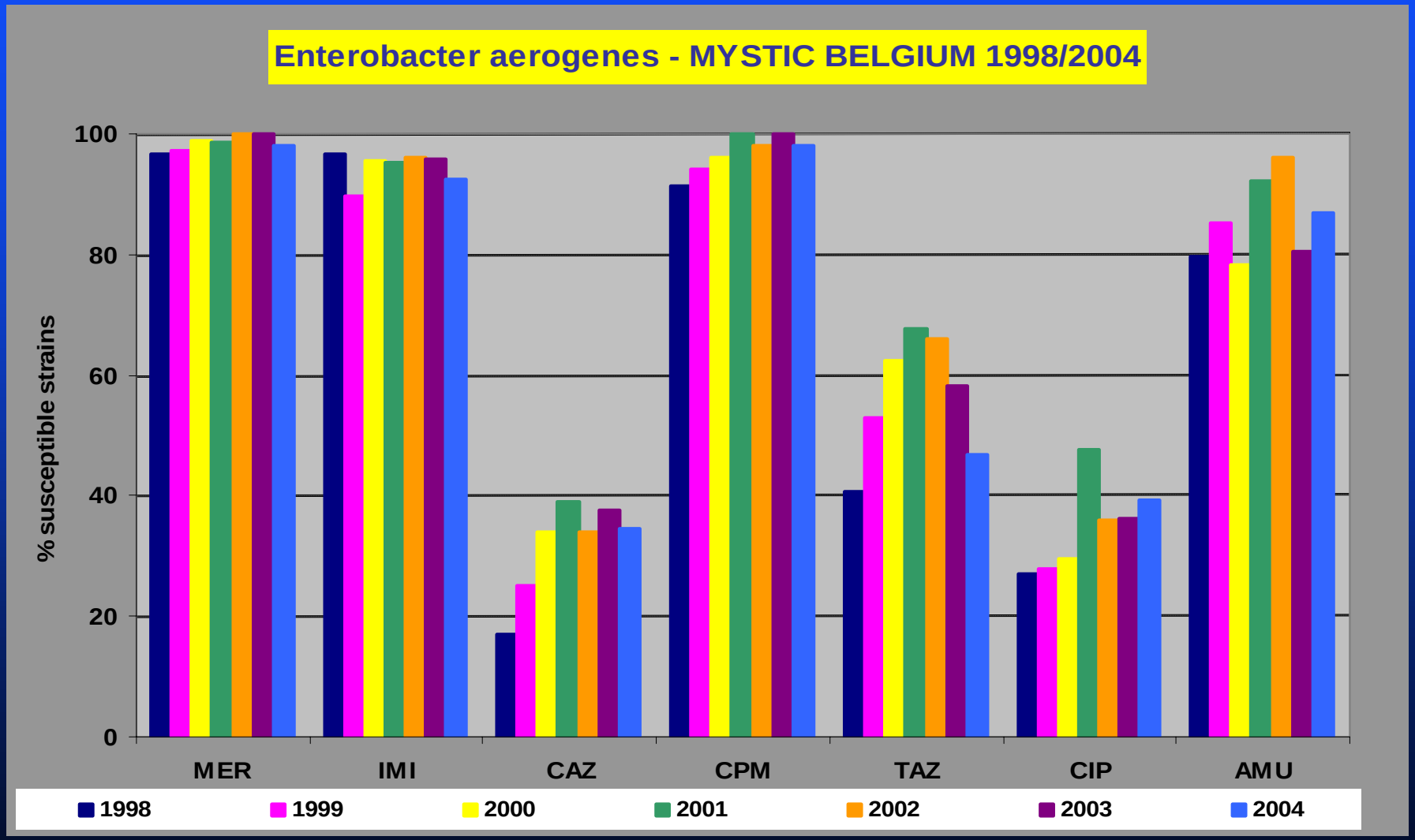
MYSTIC Program, Belgium data

Trends in Antimicrobial Spectrum and Potency for Enterobacteriaceae

Year	n	MIC_{90} (% susceptibility)		
		Agent		
		TAZ	AMI	CIP
1998	512	32 (89.1)	8 (97.7)	8 (85.6)
1999	602	16 (91.2)	4 (98.7)	4 (86.1)
2000	746	16 (90.8)	4 (99.0)	8 (85.9)
2001	581	16 (93.6)	4 (99.3)	2 (88.6)
2002	512	16 (92.4)	4 (98.1)	8 (86.1)
2003	650	32 (85.9)	8 (95.9)	8 (85.2)
2004	803	128 (77.1)	16 (92.8)	32 (79.6)

MYSTIC Program, Belgium data

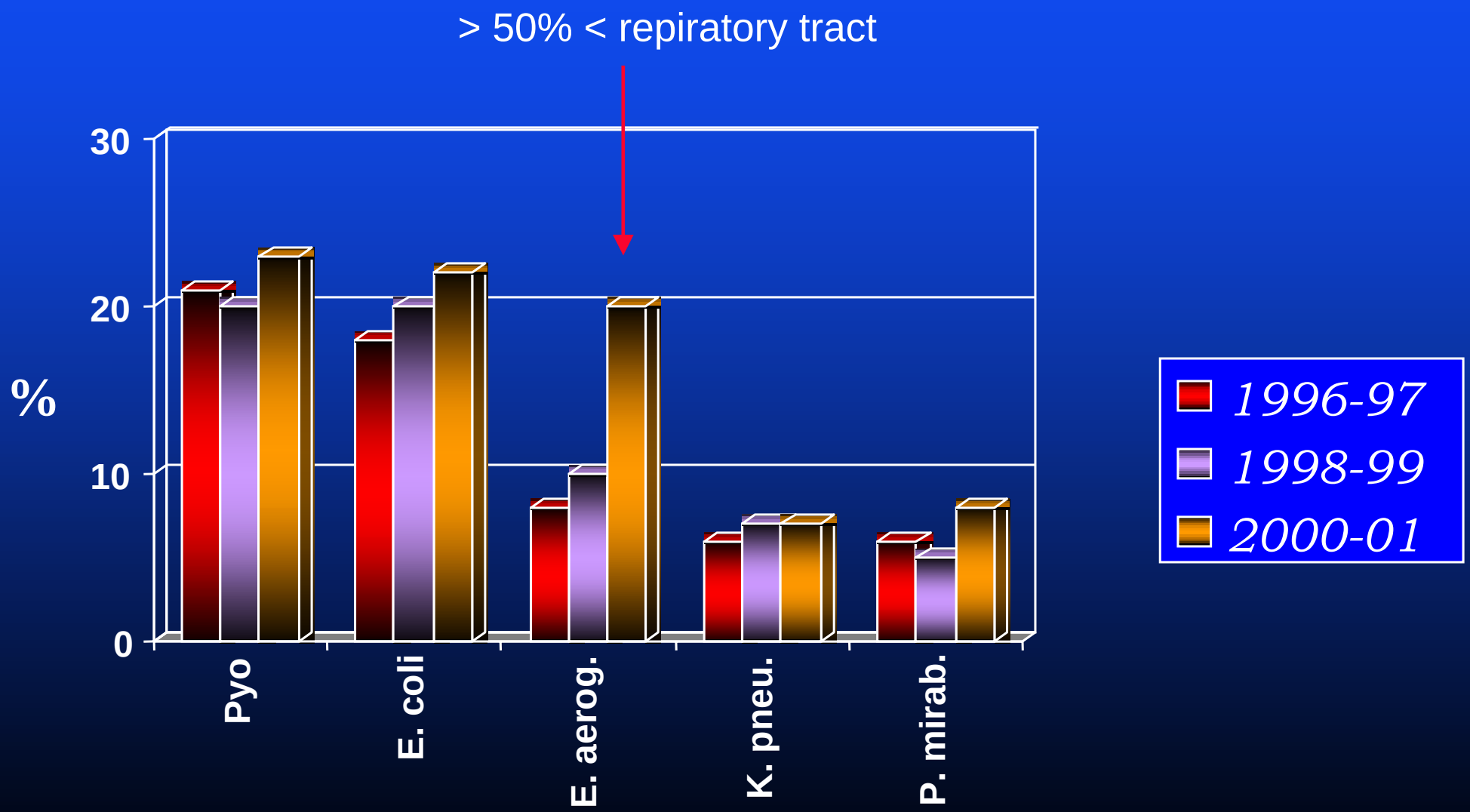
Trends over Time in Susceptibility of *Enterobacter aerogenes* to several antimicrobial agents



N=59 N=68 N=88 N=65 N=50 N=72 N=107

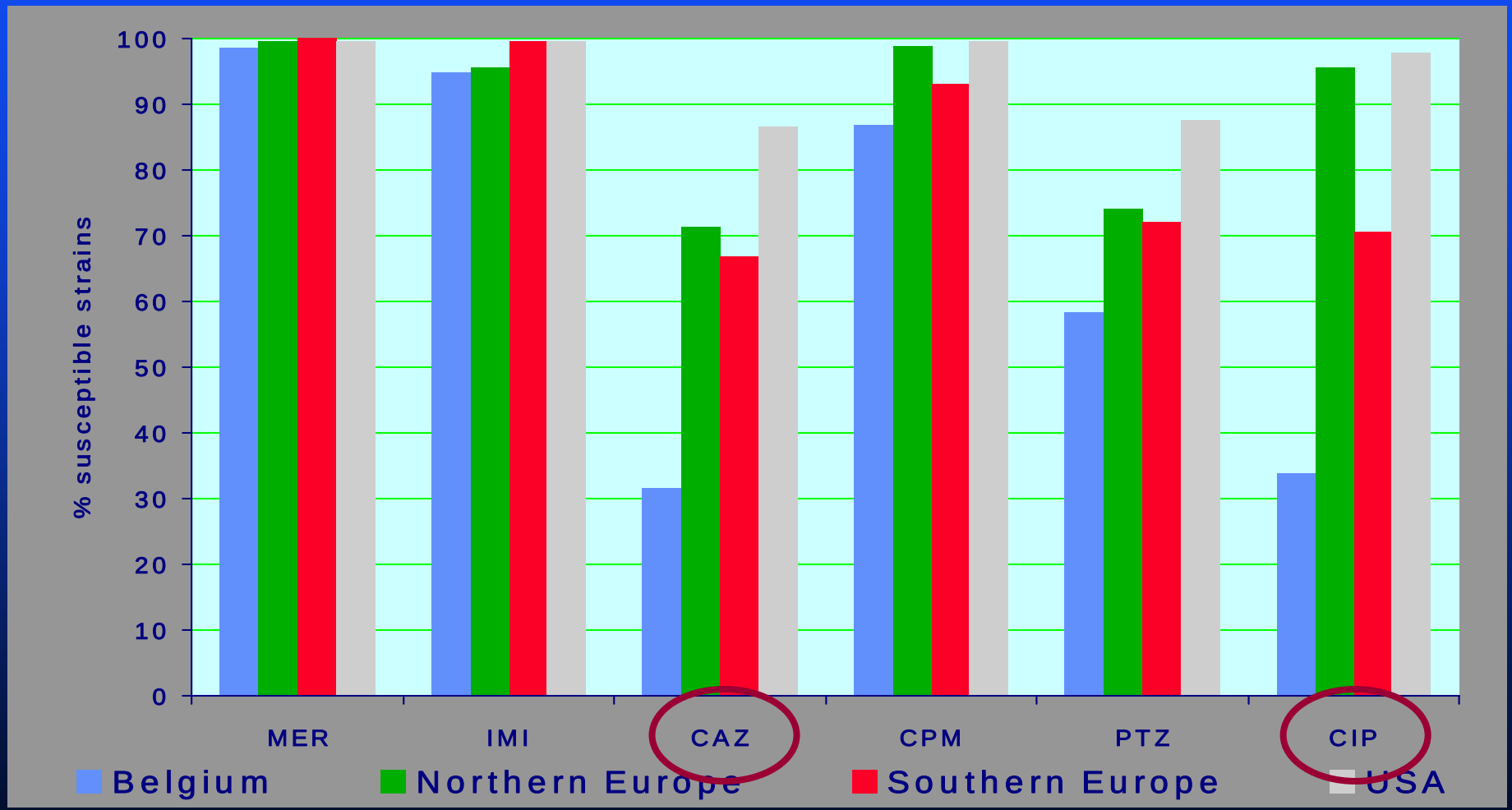
MYSTIC Program, Belgium data

Distribution of nosocomial Gram-negative bacteria isolated from ICU patients



Glupczynski, Acta Clin Belgica 2001

Trends in Antimicrobial Spectrum and Potency for *E. aerogenes* (up to 2003)



NE : Germany, UK,Finland,Sweden SE : Italy, Spain, Portugal, Greece, Malta

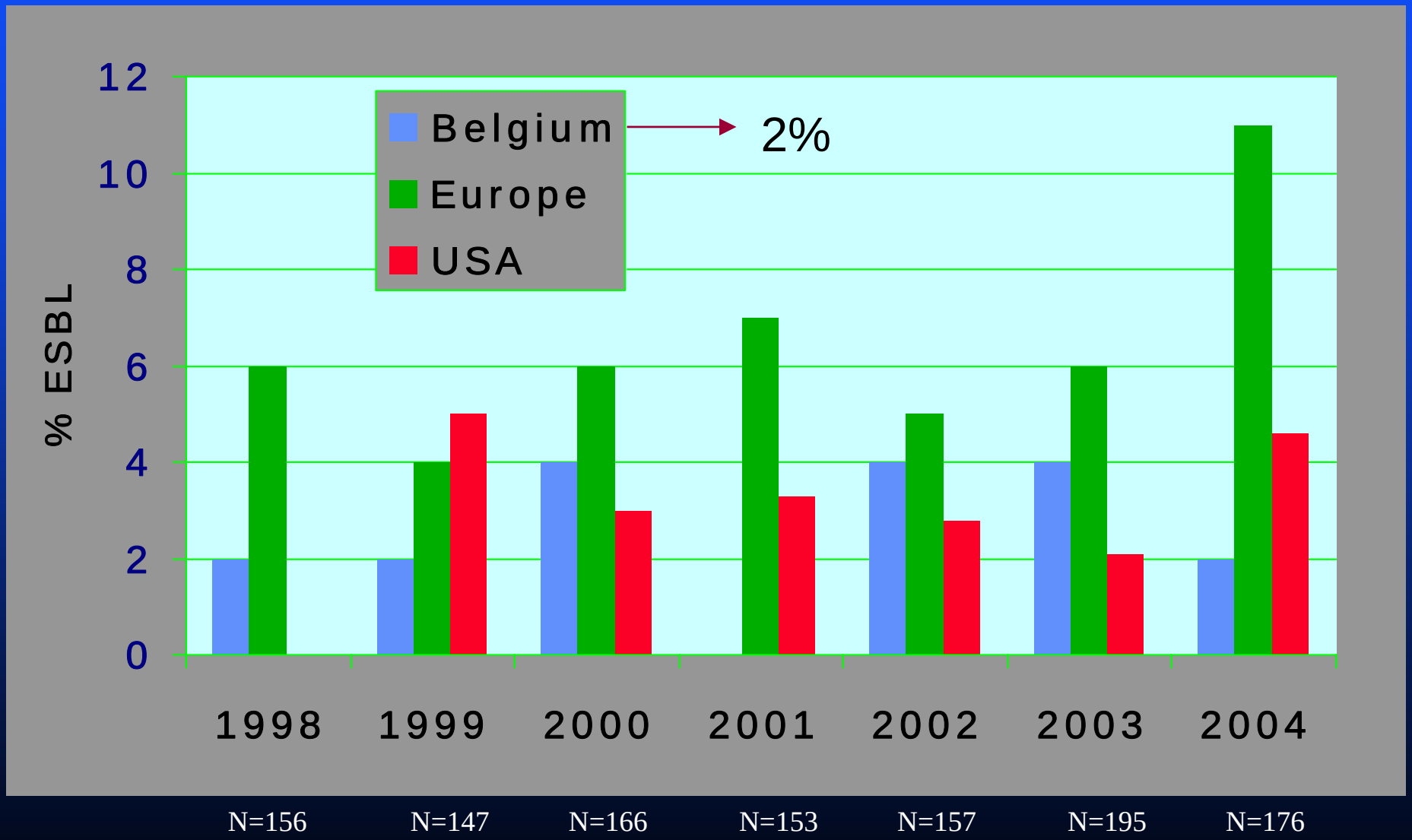
Extended-Spectrum ß-Lactamases (ESBL)

- TEM and SHV mutants (+ other emerging ESBLs; eg. CTX-M)
- Initially reported in *K. pneumoniae,* than spread to other *Enterobacteriaceae* species
- Plasmid-mediated
- Worldwide prevalent, especially in the ICU
- Risk factor for selection: ceftazidime
- Resistant to cephalosporins, aztreonam, piperacillin
- Therapeutic options :
  - carbapenems
  - others ? (cefepime, inhibitor combinations)

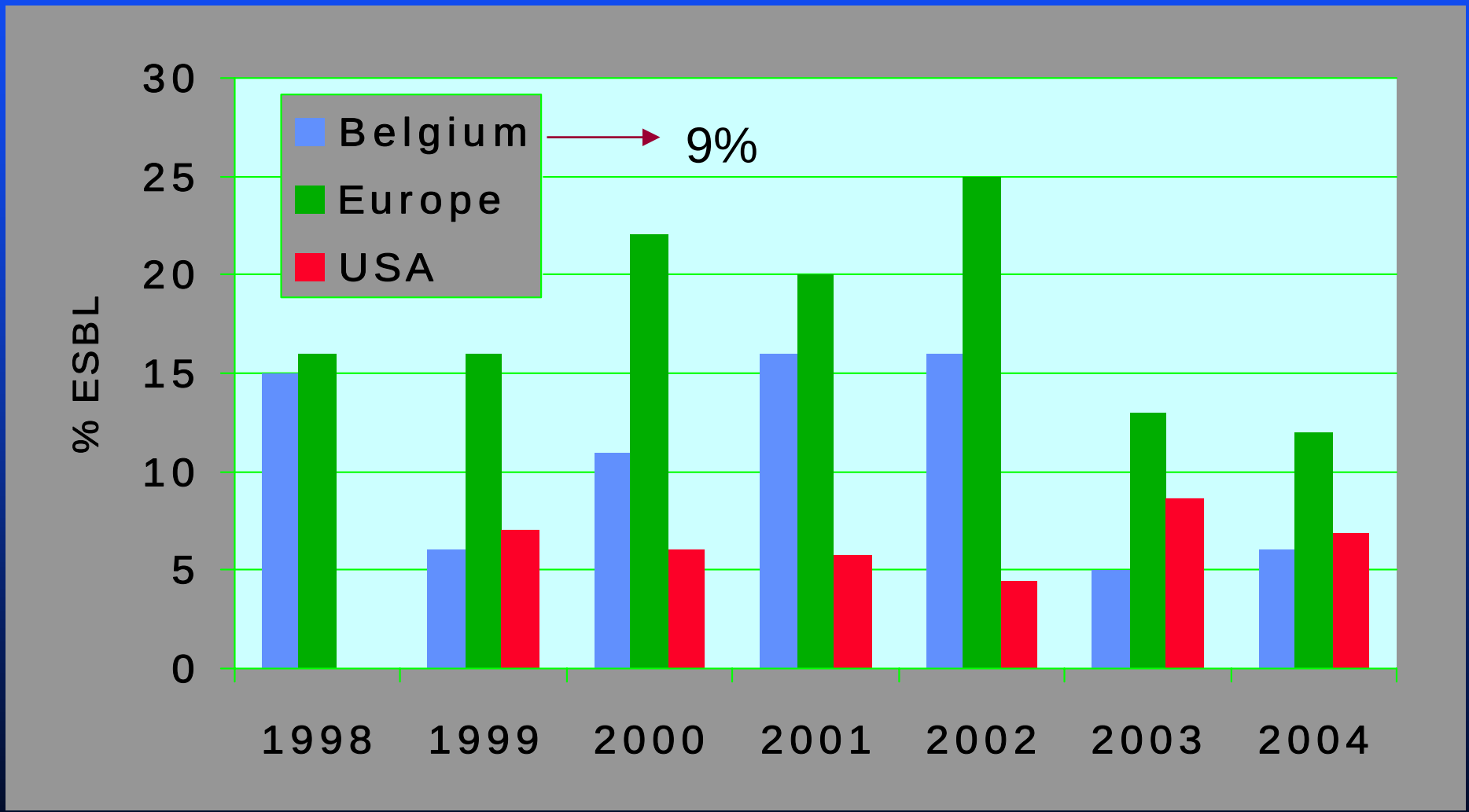
Prevalence of ESBL Producing *Enterobacteriaceae* in Europe

	% ESBL					
Country	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**
Russia	24	34	42	47	22	30
Poland	37	23	21	40	33	37
Turkey	-	-	23	40	21	26
Czech Republic	5	8	8	6	14	10
Italy	40	10	15	9	11	7
UK	5	7	22	7	6	11
Germany	2	3	1	5	2	3
Belgium	-	6	5	8	5	8

Trends in the Occurrence of ESBL Phenotype Strains of *E.coli*



Trends in the Occurrence of ESBL Phenotype Strains of *K.pneumoniae*



Activity of Meropenem and Comparator Agents against ESBL-and AmpC-producing Strains in Europe

Organism	No. ESBL-or AmpC-producing strains/ no. isolates tested (%)	MEM MIC_{90} (%S)[a]	IMP MIC_{90} (%S)	TAZ MIC_{90} (%S)	CIP MIC_{90} (%S)	GM MIC_{90} (%S)
ESBL producers:						
E. coli	338/5487 (6.2)	0.125 (100)	0.5 (99.4)	128 (69.5)	64 (37.6)	>128 (53.4)
K. pneumoniae	382/3004 (12.7)	0.125 (99.7)	0.5 (99.5)	>128 (48.8)	32 (63.7)	>128 (33.9)
AmpC-producers:						
C. freundii	107/414 (25.8)	0.25 (100)	2 (100)	>128 (27.4)	16 (74.8)	32 (84.3)
E. cloacae	557/2056 (27.1)	0.5 (98.7)	2 (98.7)	>128 (14.6)	16 (79.4)	128 (75.1)
S. marcescens	107/1011 (10.6)	1 (99.1)	4 (94.3)	>128 (33.0)	32 (54.2)	>128 (53.0)

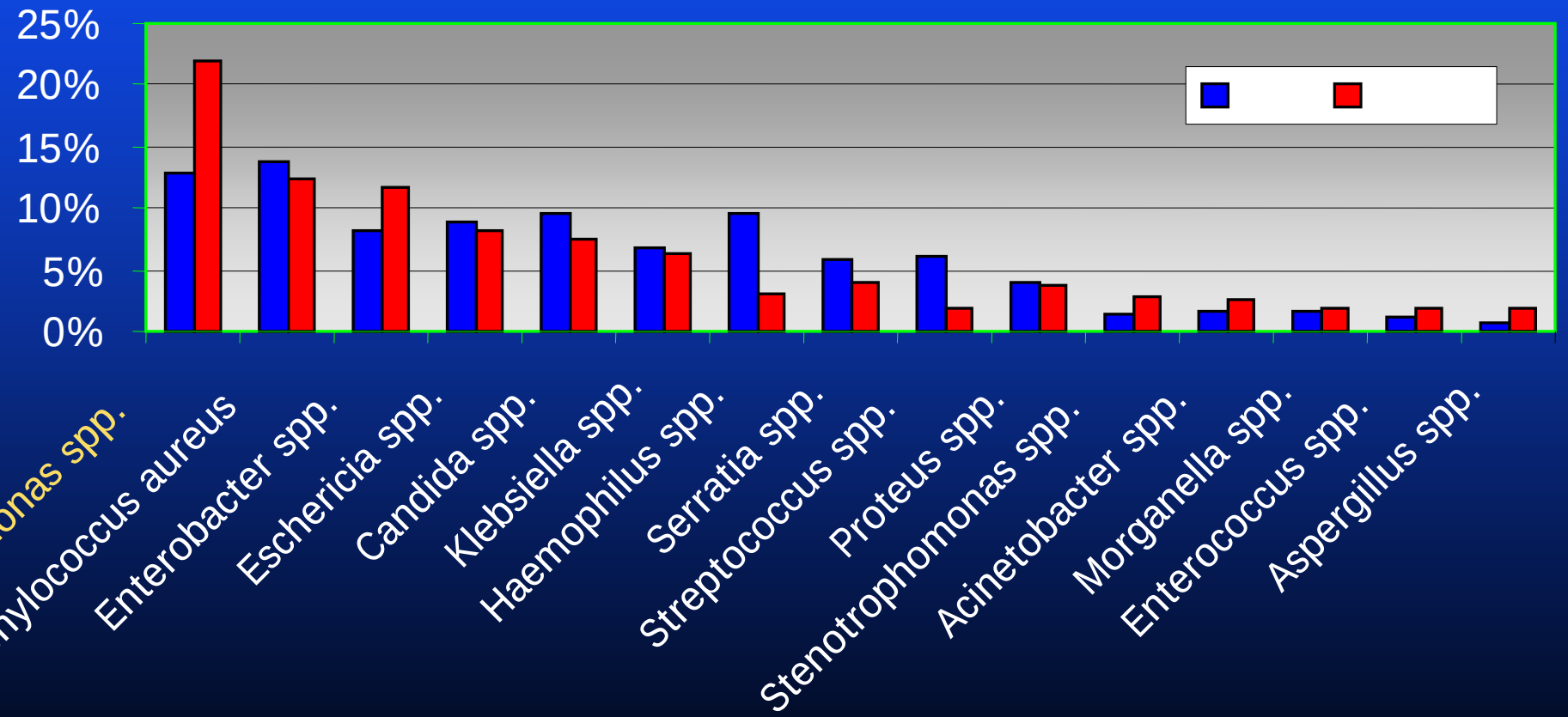
MEM=meropenem; IMP=imipenem; CAZ=ceftazidime; TAZ=piperacillin+tazobactam; CIP=ciprofloxacin; GM=gentamicin

[a]Susceptibility criteria of the NCCLS 2002

Pseudomonas aeruginosa

Most frequently isolated micro-organisms in early and late nosocomial pneumonia

1997-2002 (n=5119)



Antimicrobial susceptibility of *P. aeruginosa* isolates in Belgian hospitals

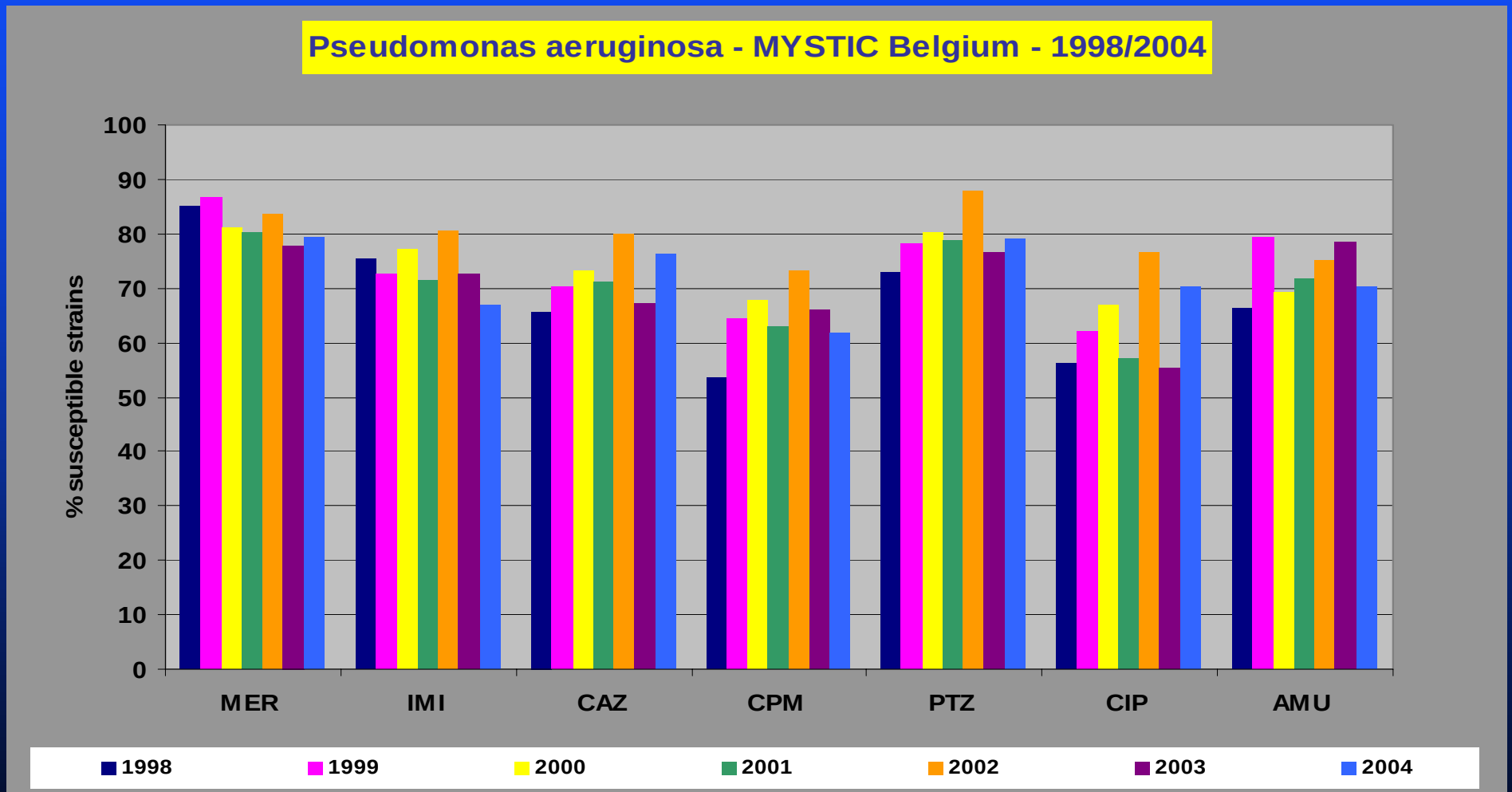
Table 1. Results of susceptibility testing

	Susceptible[a]	Intermediate[a]	Resistant[a]	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Gentamicin	67	9.5	23.5	4	256
Tobramycin	79.5	1	19.5	1	128
Amikacin	85	4.5	10.5	8	64
Isepamicin	81	7	12	8	64
Ofloxacin	49.75	12.5	37.75	4	128
Levofloxacin	61.5	11	27.5	2	64
Ciprofloxacin	71	5	24	0.5	32
Piperacillin	76	–	24	16	>256
Piperacillin/tazobactam	83	–	17.5	16	256
Ticarcillin/clavulanic acid	63	–	37	64	256
Aztreonam	17.75	26.75	55.5	32	256
Ceftazidime	59	12.5	28.5	8	64
Cefepime	50.5	20	29.5	8	64
Meropenem	81.5	9	9.5	2	8

[a]Percentage of all isolates.

Van Eldere, JAC 2003; 51: 347-52

Activity vs *Pseudomonas aeruginosa*



n=263 n=211 n=233 n=264 n=214 n=204 n=242

MYSTIC Program, Belgium data

Trends in Antimicrobial Spectrum and Potency for *Pseudomonas aeruginosa*

Year	n	MIC_{90} (% susceptibility)			
		Agent			
		MEM	IMP	CAZ	CEP
1998	263	32 (85.2)	64 (75.3)	128 (65.8)	128 (53.6)
1999	211	8 (86.7)	32 (72.5)	64 (70.1)	64 (64.5)
2000	233	32 (81.1)	64 (77.3)	64 (73.4)	64 (67.8)
2001	264	16 (80.3)	64 (71.5)	128 (71.2)	64 (62.9)
2002	214	8 (83.6)	32 (80.4)	64 (79.9)	32 (73.4)
2003	217	32 (76.5)	64 (71.0)	128 (65.9)	64 (64.2)
2004	242	64 (79.3)	64 (66.9)	64 (76.4)	64 (76.4)

MYSTIC Program, Belgium data

Trends in Antimicrobial Spectrum and Potency for *Pseudomonas aeruginosa*

Year	n	MIC_{90} (% susceptibility)		
		Agent		
		TAZ	AMI	CIP
1998	263	>128 (73.0)	128 (66.2)	64 (56.3)
1999	211	>128 (78.2)	64 (79.2)	16 (61.9)
2000	233	>128 (80.3)	128 (69.2)	64 (67.0)
2001	264	>128 (78.8)	128 (71.6)	64 (57.2)
2002	214	128 (87.9)	64 (75.2)	16 (76.6)
2003	217	>128 (76.5)	64 (76.8)	64 (55.8)
2004	242	>128 (78.9)	>128 (71.2)	32 (70.2)

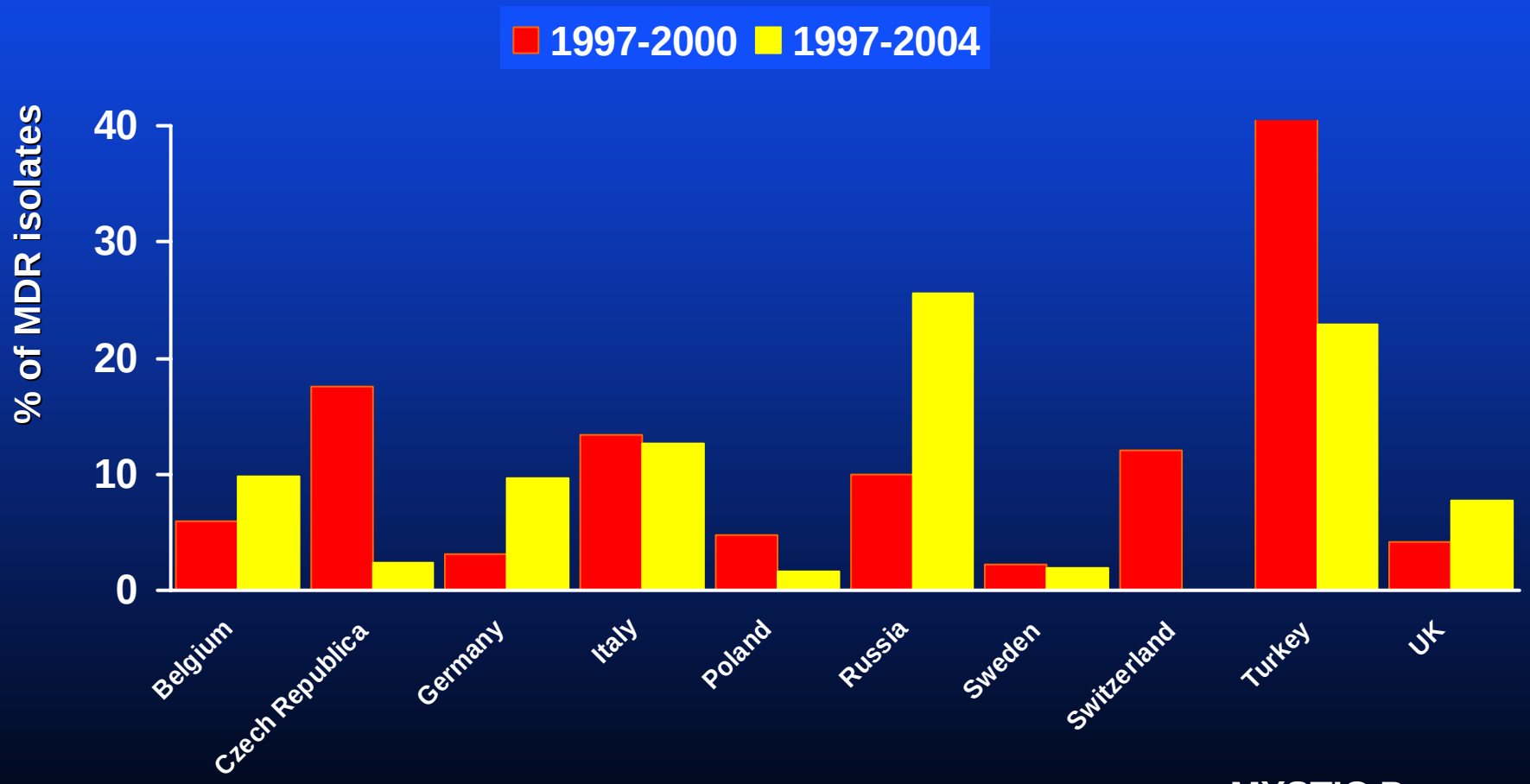
Multi Drug Resistant Isolates of *Pseudomonas aeruginosa* 1997 - 2004

Country	N° Centers	N° of isolates (%)	
		Ps.aeruginosa	MDR
Belgium	8	1613	157 (9.8)
Czech Republic	1	164	39 (2.4)
Germany	7	1799	172 (9.6)
Italy	3	1111	252 (22.7)
Poland	1	178	3 (1.7)
Russia	1	160	41 (25.6)
Sweden	4	267	5 (1.9)
Turkey	9	1280	383 (29.9)
UK	5	1056	82 (7.8)

Total MDR : 12.2% (2000) → 14.8% (2004) *P* = 0.002

Prevalence of MDR Isolates of *Ps. aeruginosa* by Country

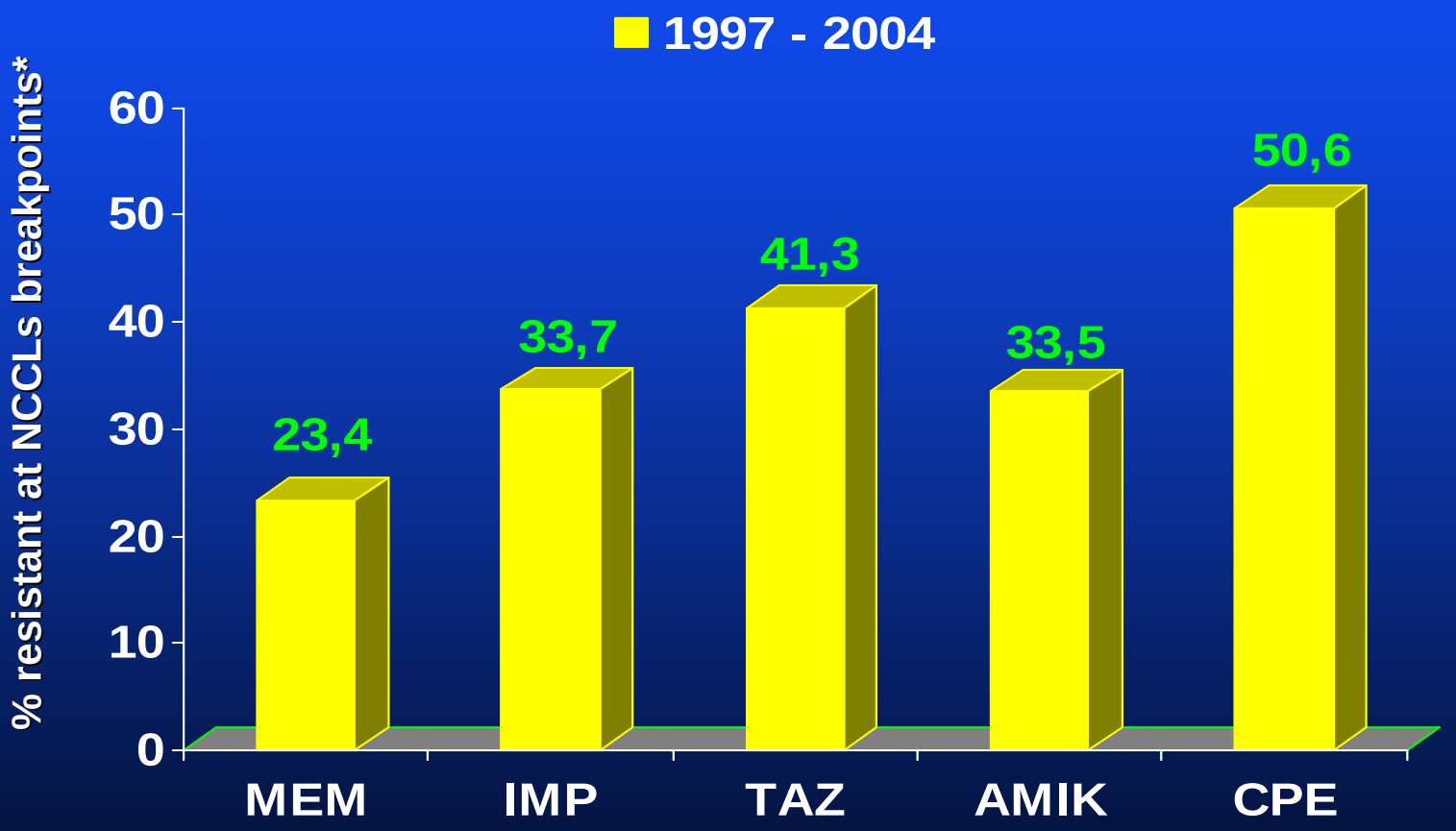
R to cefta (MIC ≥ 32 µg/ml); R to genta (MIC ≥ 16 µg/ml); R to cipro (MIC ≥ 4 µg/ml)



Total MDR : 12.2% (2000) → 14.8% (2004) *P* = 0.002

MYSTIC Programme Europe

Percentage Resistance of MDR *Pseudomonas aeruginosa*



*MEM / IPM = 16 mg/L AMK = 64 mg/L
TAZ = 128 mg/L CPE = 32 mg/L

MYSTIC Programme Europe

Conclusions by Organism and Antibiotic Class in Belgium

- Possible increase in resistance of *E. coli* to fluoroquinolones, and co-resistance to several classes of antimicrobials
- The occurence of ESBL-producing *E. coli* and *K. pneumoniae* seems stable and is significantly lower in Belgium comparing to the rest of Europe
- Higher incidence resistance in *E. aerogenes* in Belgium compared to other European countries and USA isolates (spread of ESBL-producing clones)

Conclusions by Organisms and Antibiotic Class in Belgium

- **Carbapenems retain activity against most ESBL-and AmpC-producing pathogens**
- **In general, carbapenems exhibit higher potency than other antibiotic agents against all Gram-negative organisms tested**
- **There is a clear tendency towards decreased susceptibility of *P. aeruginosa* for different antibiotics**
- **Pip/tazo and meropenem remain the most active agents against *P. aeruginosa***

→ ***Global trends towards higher rates of resistance and multi-resistant strains both in community-acquired and nosocomial pathogens***