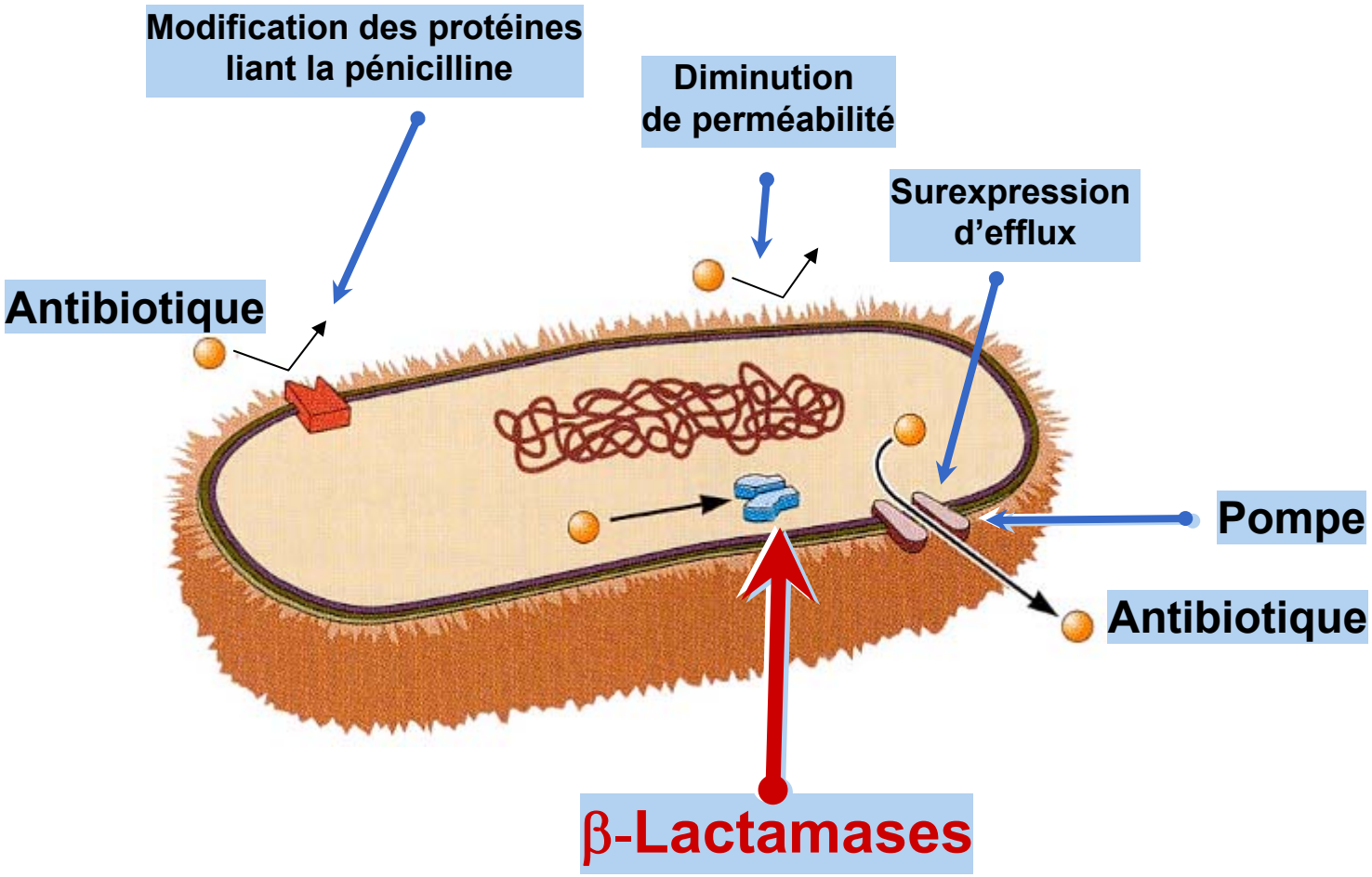
Antibiothérapie des infections à BGN résistants; BLSE émergentes chez les entérobactéries

Pr P. Nordmann

hôpital de Bicêtre, INSERM 914, Faculté et

Université Paris Sud, France

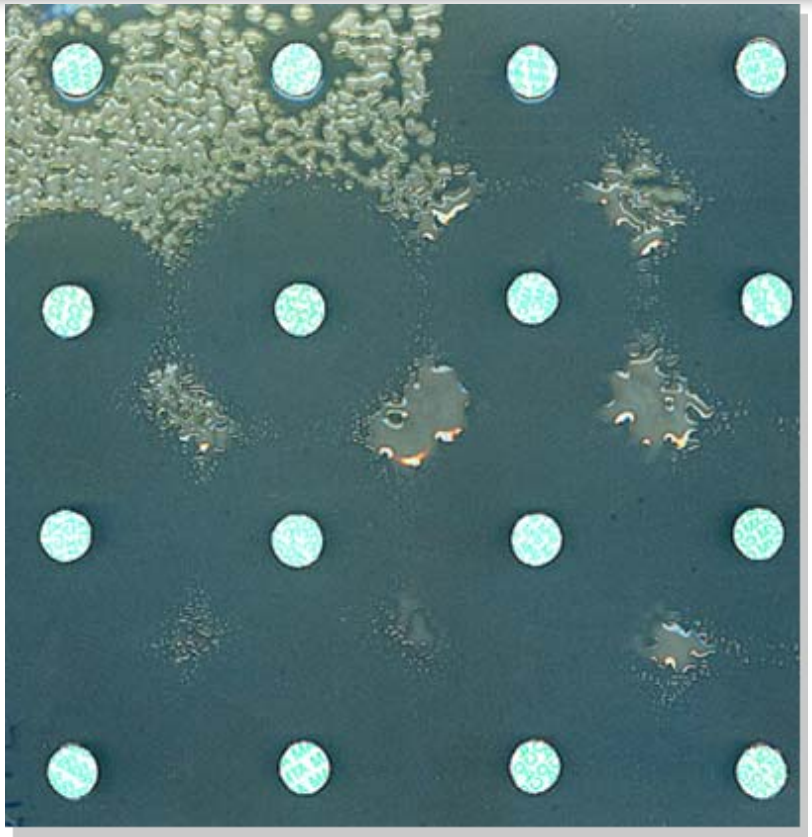
Résistance aux ß-lactamines chez les bacilles à Gram négatif

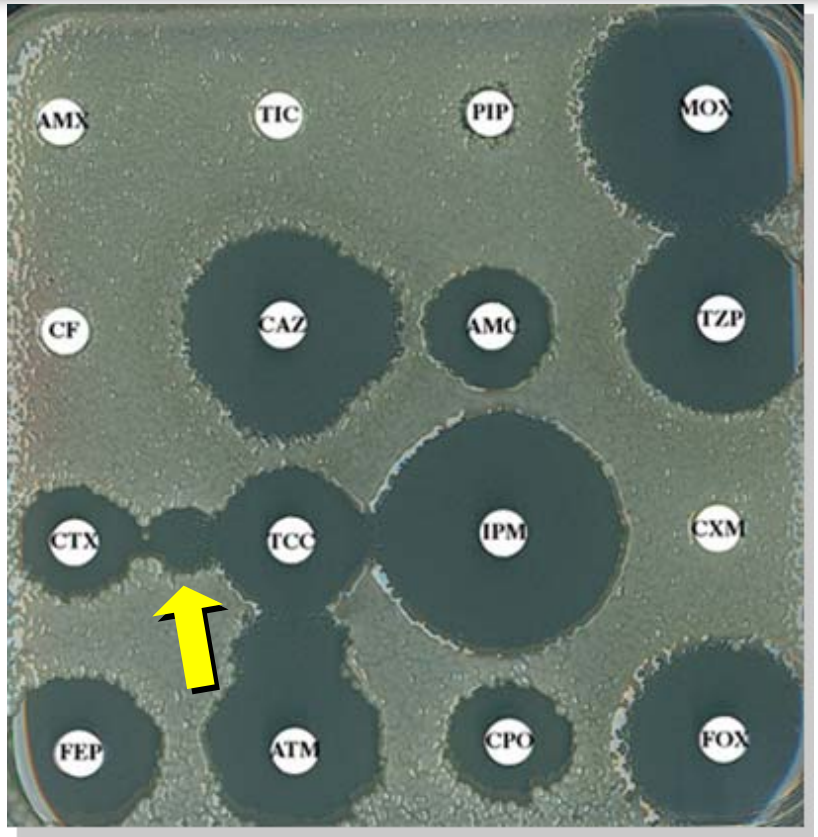


Définition d'une BLSE

- **ß-Lactamases le plus souvent d'origine plasmidique** qui hydrolysent les pénicillines, céphalosporines et l'aztréonam mais pas les céphamycines et les carbapénèmes
- **Leur activité est inhibée *in vitro*** habituellement par l'acide clavulanique, le sulbactam et le tazobactam

Sauvage *K. pneumoniae* TEM-4





AMX : amoxicillin, TIC : ticarcillin, PIP : piperacillin, MOX : moxalactam, CF : cefalotin, CAZ : ceftazidime, AMC : amoxicillin + clavulanic acid, TZP : piperacillin + tazobactam , CTX : cefotaxime, TCC : ticarcillin +clavulanic acid, IPM : imipenem, CXM : cefuroxime, FEP : cefepime, ATM : aztreonam, CPO : cefpirome, FOX : cefoxitin

BLSEs

- « classiques

1983 - SHV

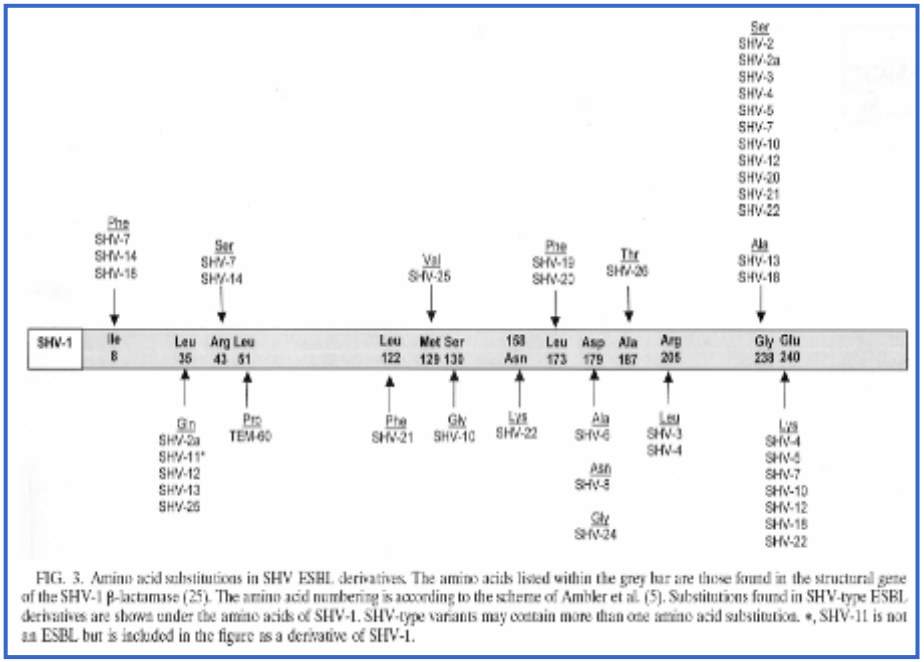


FIG. 3. Amino acid substitutions in SHV ESBL derivatives. The amino acids listed within the grey bar are those found in the structural gene of the SHV-1 β-lactamase (25). The amino acid numbering is according to the scheme of Ambler et al. (5). Substitutions found in SHV-type ESBL derivatives are shown under the amino acids of SHV-1. SHV-type variants may contain more than one amino acid substitution. *, SHV-11 is not an ESBL but is included in the figure as a derivative of SHV-1.

1985 - TEMs

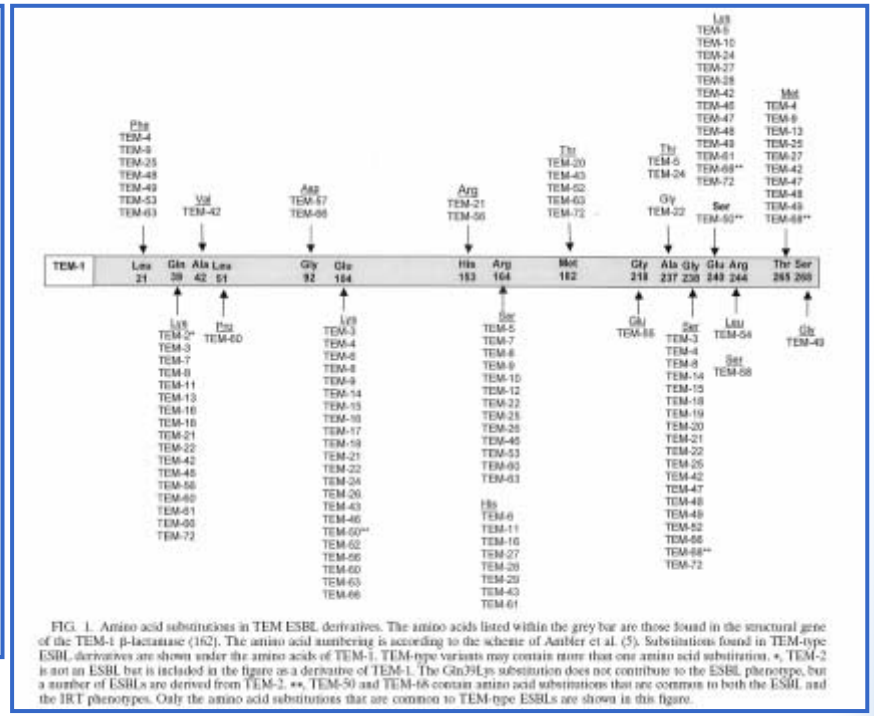


FIG. 1. Amino acid substitutions in TEM ESBL derivatives. The amino acids listed within the grey bar are those found in the structural gene of the TEM-1 β-lactamase (162). The amino acid numbering is according to the scheme of Ambler et al. (5). Substitutions found in TEM-type ESBL derivatives are shown under the amino acids of TEM-1. TEM-type variants may contain more than one amino acid substitution. *, TEM-2 is not an ESBL but is included in the figure as a derivative of TEM-1. The Gln39Lys substitution does not contribute to the ESBL phenotype, but a number of ESBLs are derived from TEM-2. **, TEM-50 and TEM-68 contain amino acid substitutions that are common to both the ESBL and the IRT phenotypes. Only the amino acid substitutions that are common to TEM-type ESBLs are shown in this figure.

••• **Rares** : PER, VEB, BES, SFO GES, TLA, IBC, …

BLSEs…

- **Epidémiologie**
  - épidémies hospitalières
  - très rarement isolées dans le communautaire
- **Prévalence**
  - *K. pneumoniae* (+++) ; *E. aerogenes*
  - rarement *E. coli*, *Salmonella* spp., *P. mirabilis*
  - variabilité de la prévalence selon le pays, l'hôpital et le type d'unité d'hospitalisation
- **Facteurs de risque**
  - admission en soins intensifs
  - chirurgie récente, cathéter urinaire ou veineux
  - hospitalisation prolongée et/ou répétée
  - utilisation d'antibiotiques : ß-lactamines, fluoroquinolones

2000;BLSEs… la fin de l'histoire…

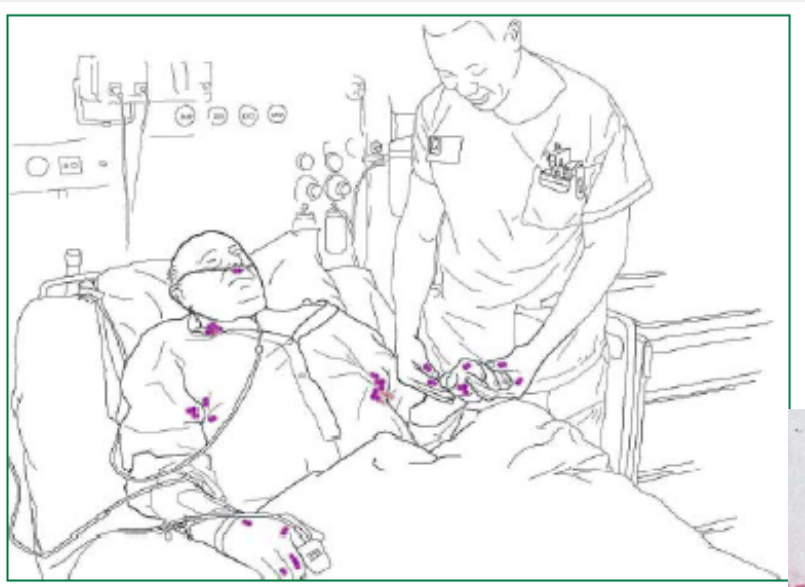
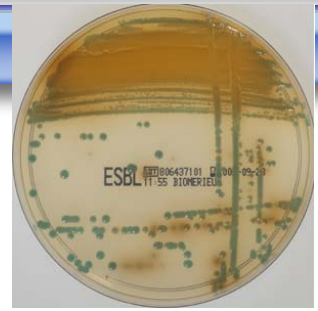
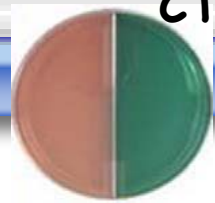


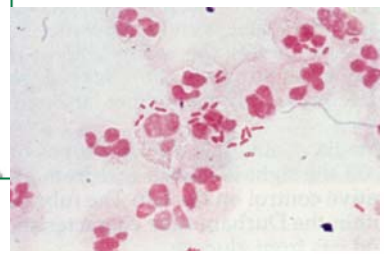
Figure 2: Organism transfer from patient to health-care worker's hands
Contact between the health-care worker and the patient results in cross-transmission of microorganisms. In this case, Gram-positive cocci from the patient's own flora.

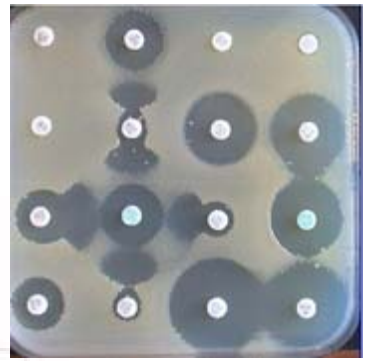


Drigalski
CTX 0.5 µg/ml



Mac Conkey
CAZ 2 µg/ml



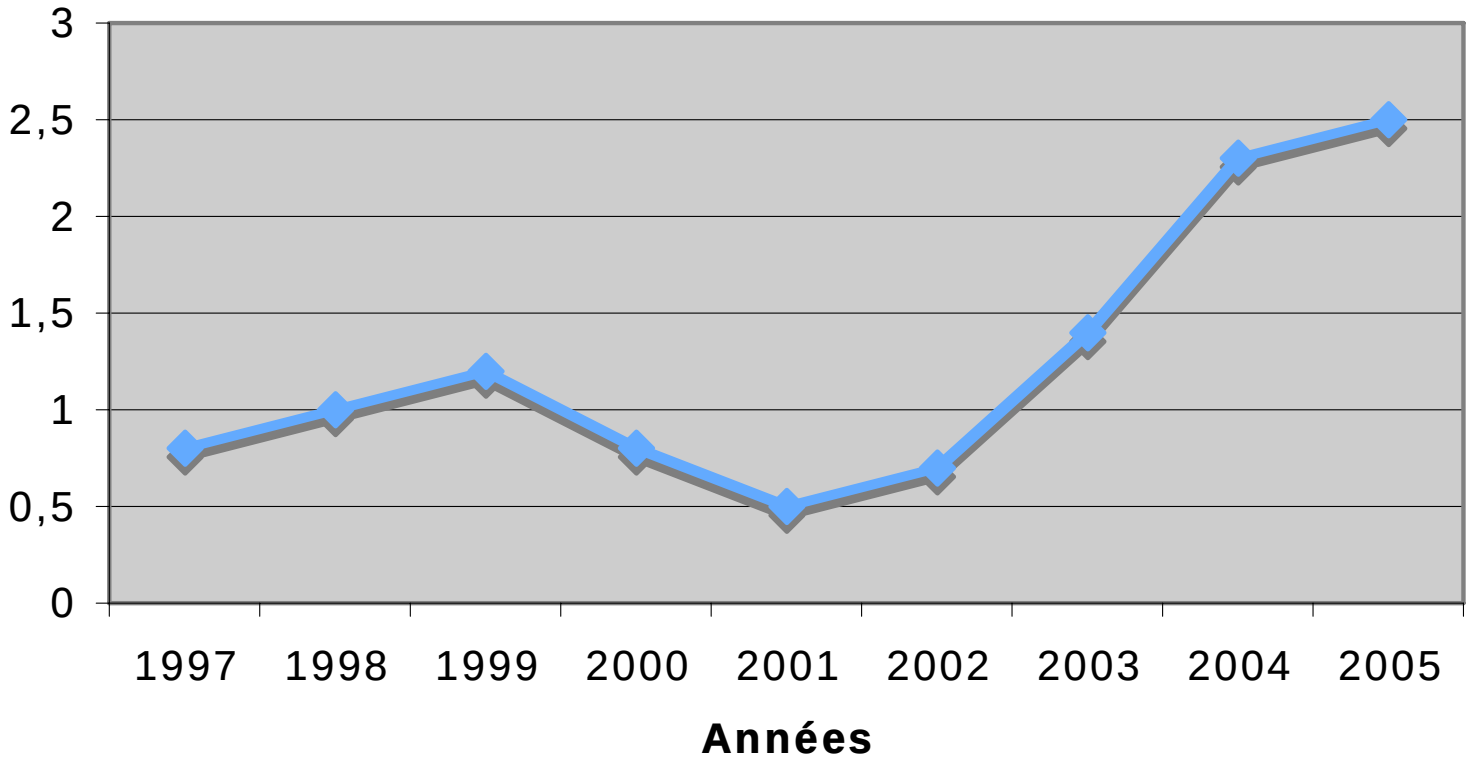


→ **Prevalence Kp BLSEs (+) Paris (AP/HP); 15-20% à 2-3%** de 1990 à 2000

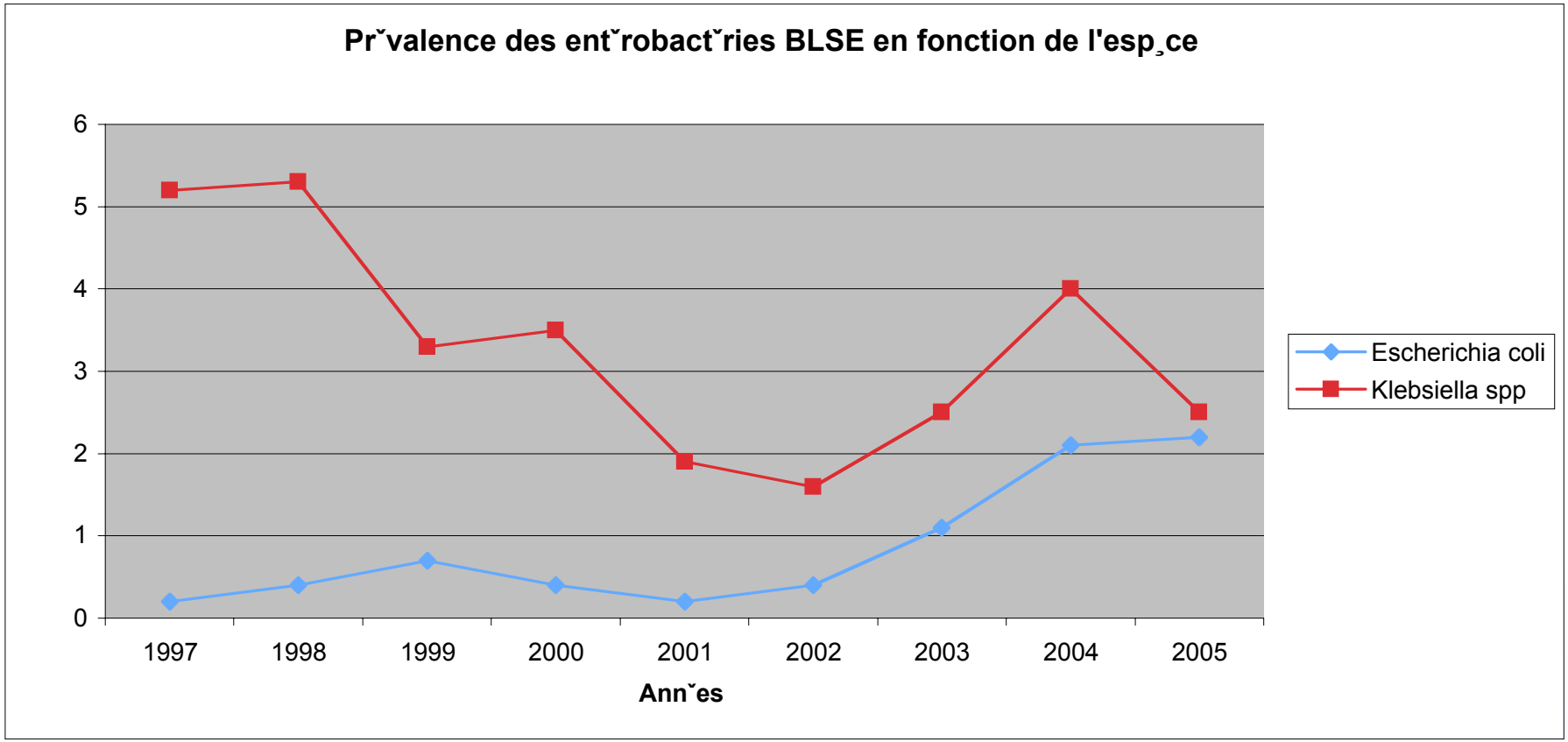
Réanimateurs dans les années 90

QuickTime™ et un
décompresseur TIFF (non compressé)
sont requis pour visionner cette image.

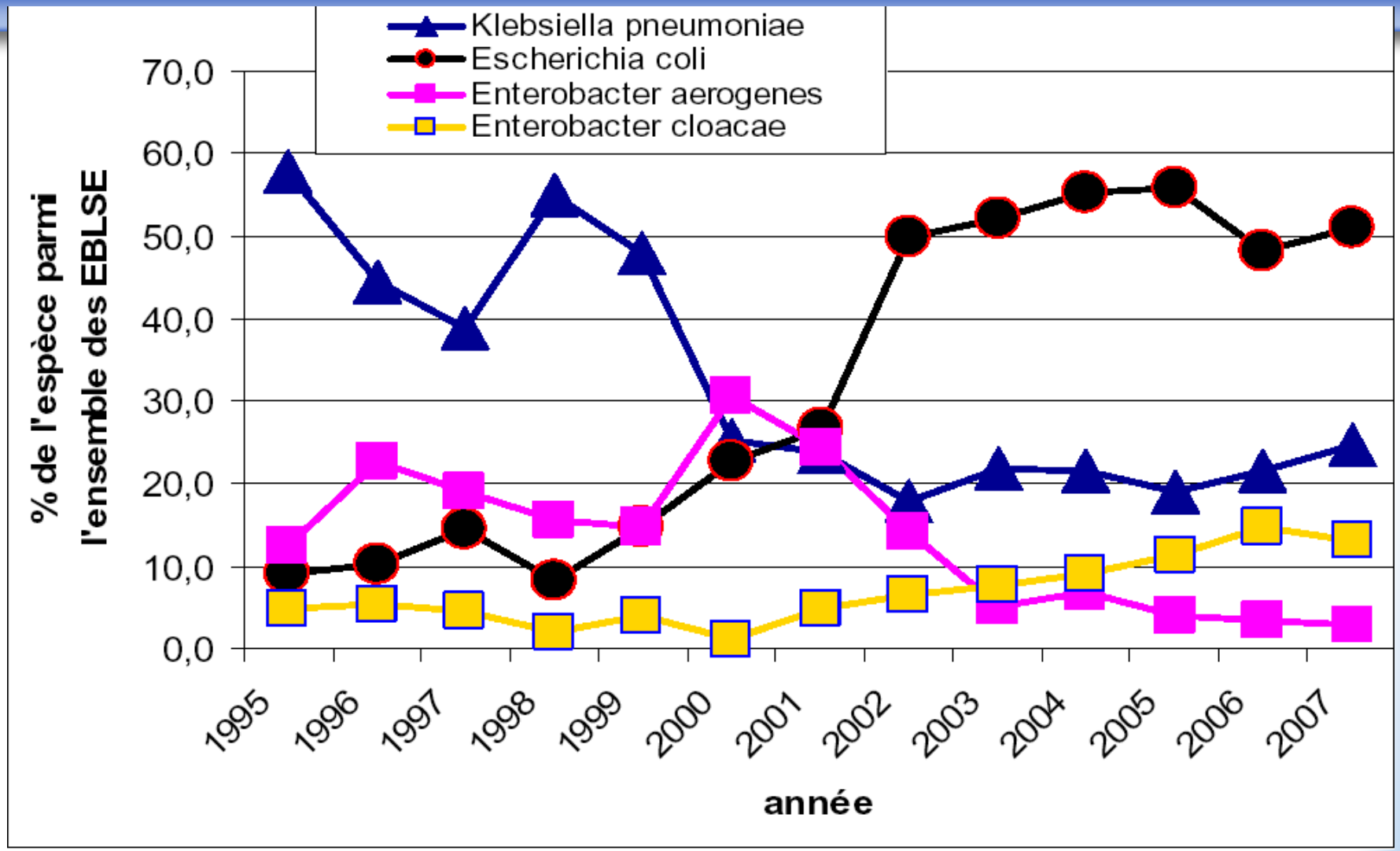
Prévalence des BLSEs chez les entérobactéries isolées de prélèvements à visée diagnostique chez les patients hospitalisés à l'hôpital de Bicêtre



Bicêtre

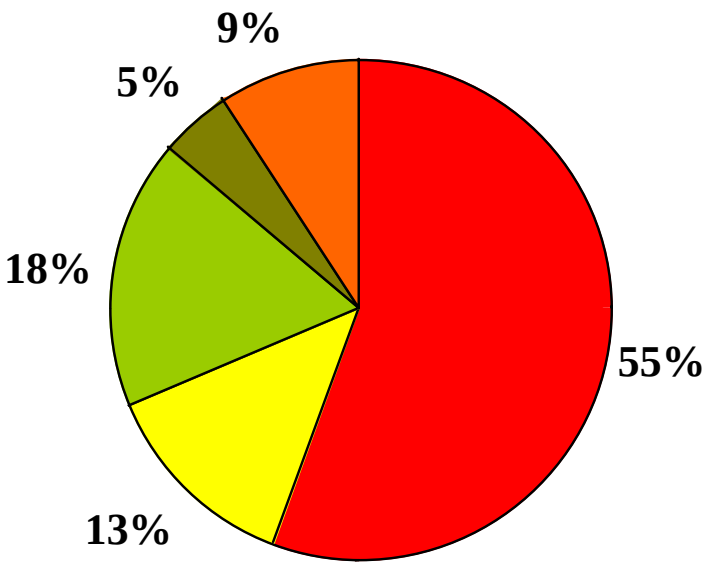

Pr˘valence des ent˘robact˘ries BLSE en fonction de l'esp¸ce
6
5
4
3
2
1
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
Ann˘es
Escherichia coli
Klebsiella spp

AP-HP


Klebsiella pneumoniae
Escherichia coli
Enterobacter aerogenes
Enterobacter cloacae
% de l'espèce parmi l'ensemble des EBLSE
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
année

BLSEs- distribution par espèce- Bicêtre

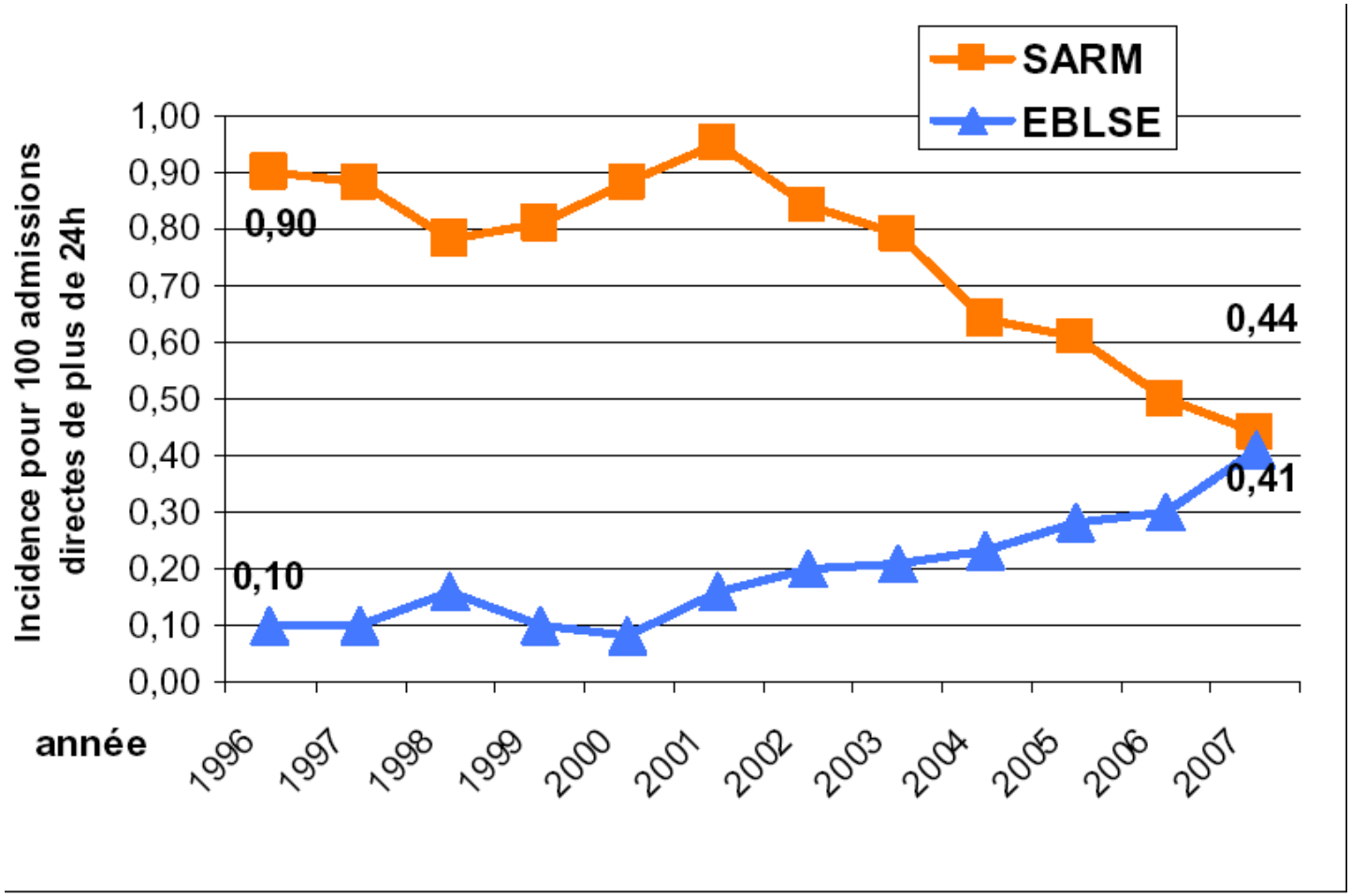
N= 111 ESBL



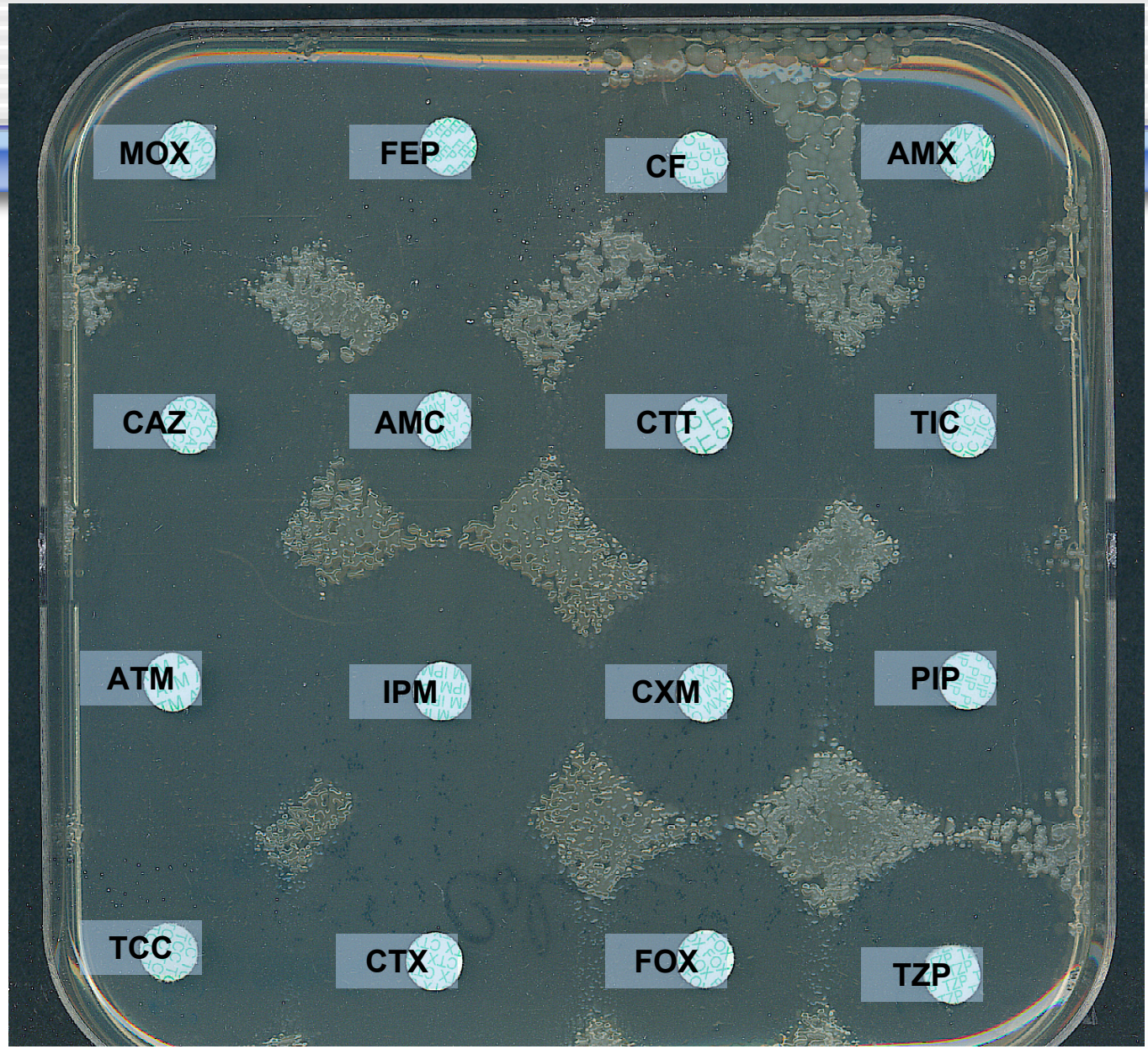
2006

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

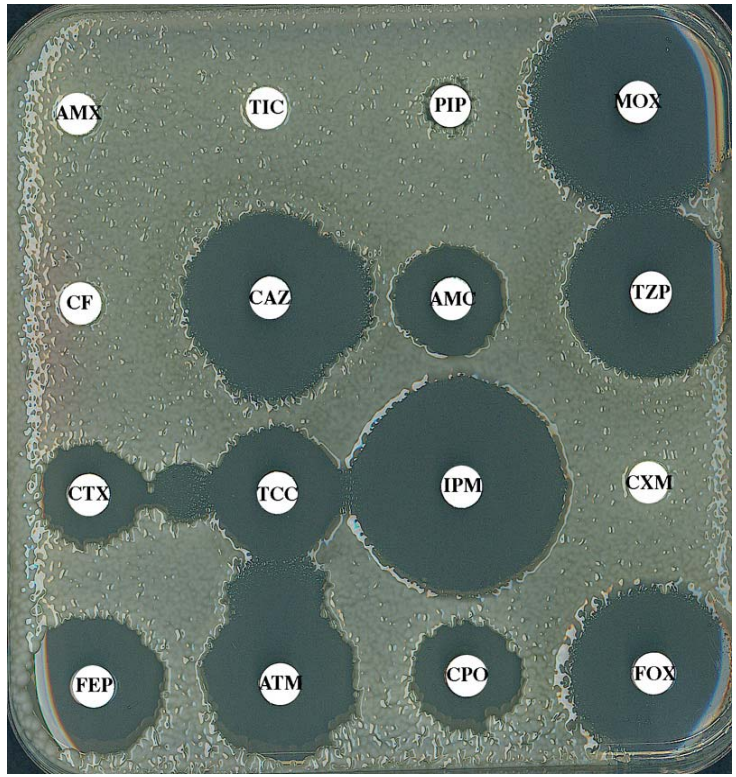
AP-HP



E. coli;
Le bon vieux temps…

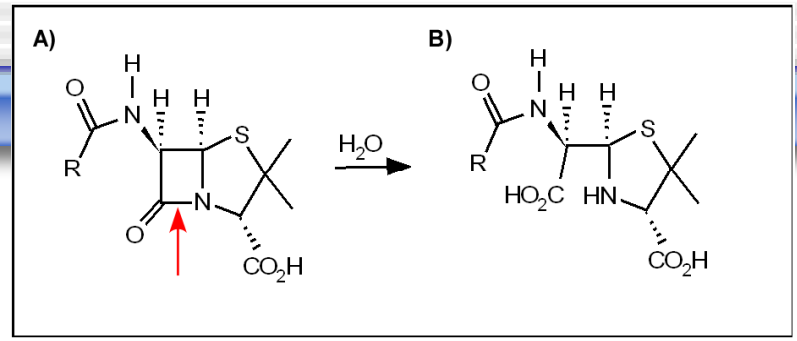


E. coli… 2009

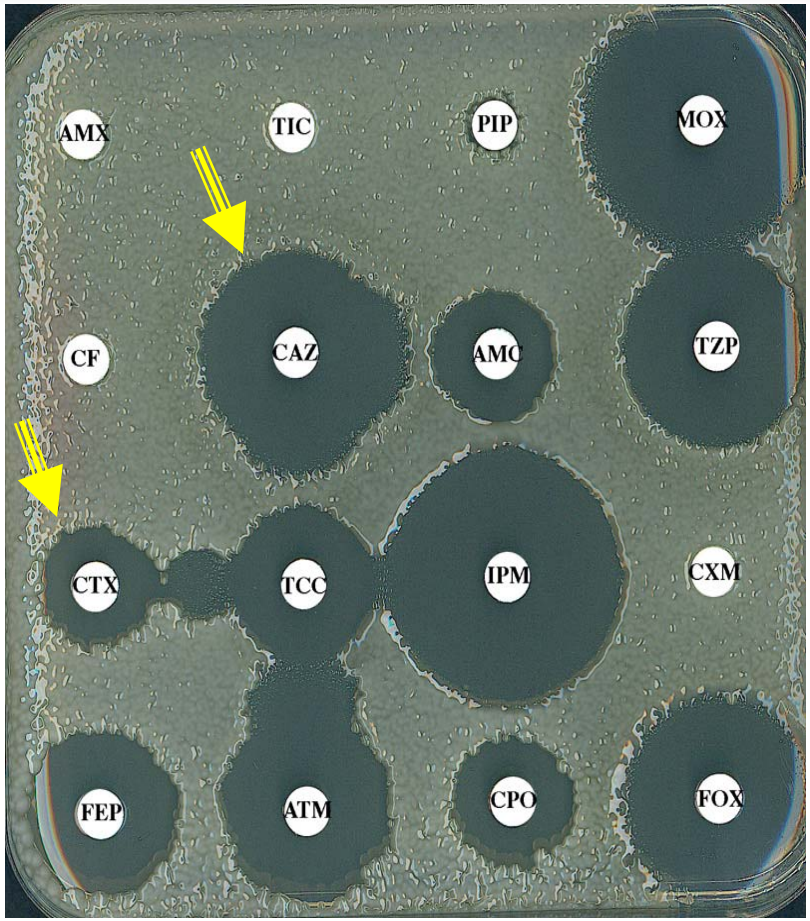


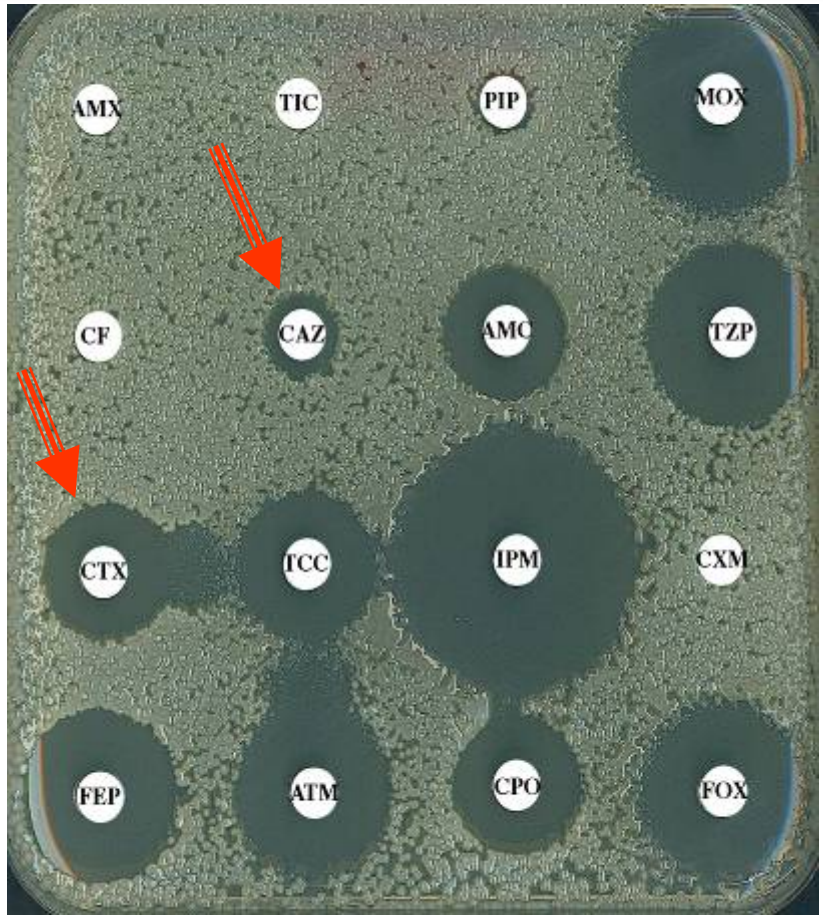
Ces nouvelles BLSEs…

TEM/SHV



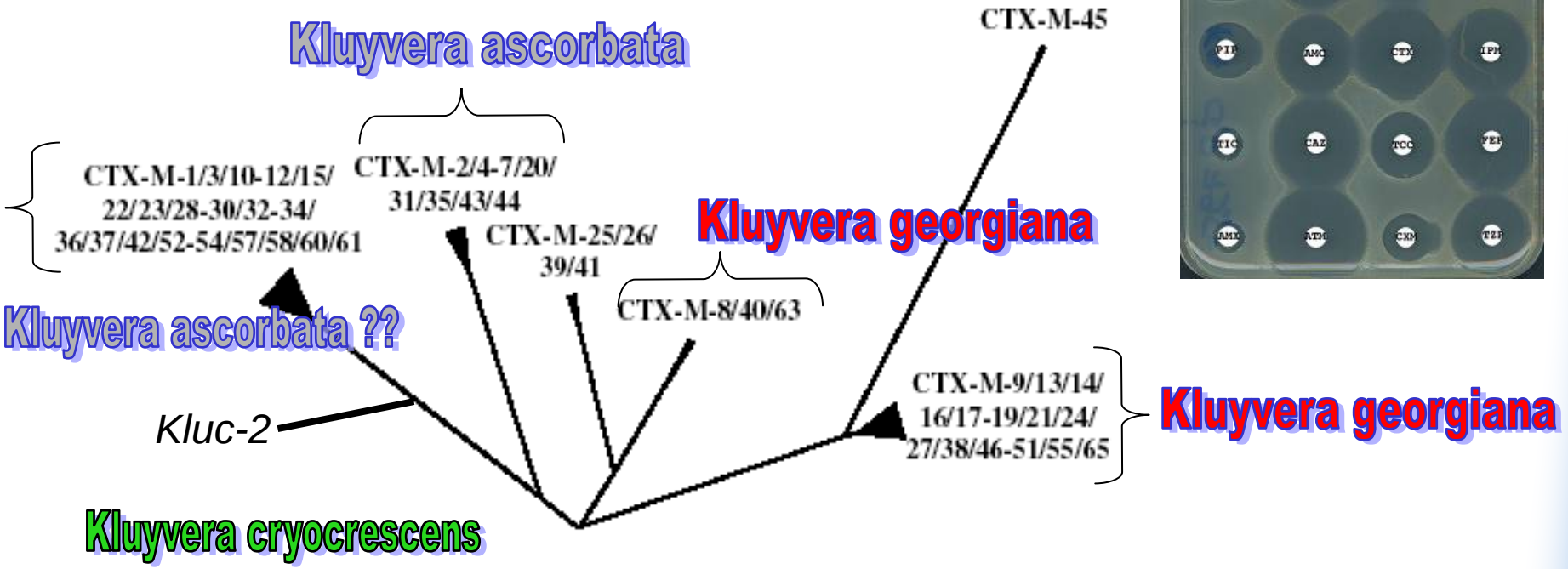
CTX-Ms: hydrolyse du cefotaxime… et de la ceftazidime

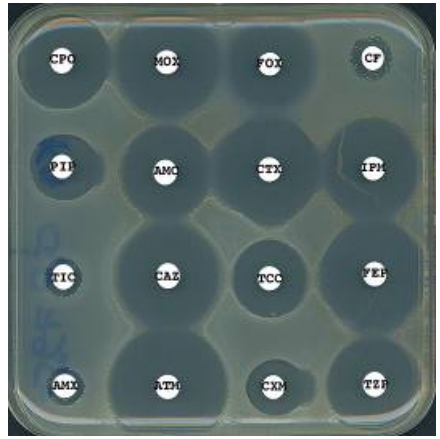




CTX-M-3 ***E. coli*** **CTX-M-15**

L'origine des CTX-Ms





BLSEs en France

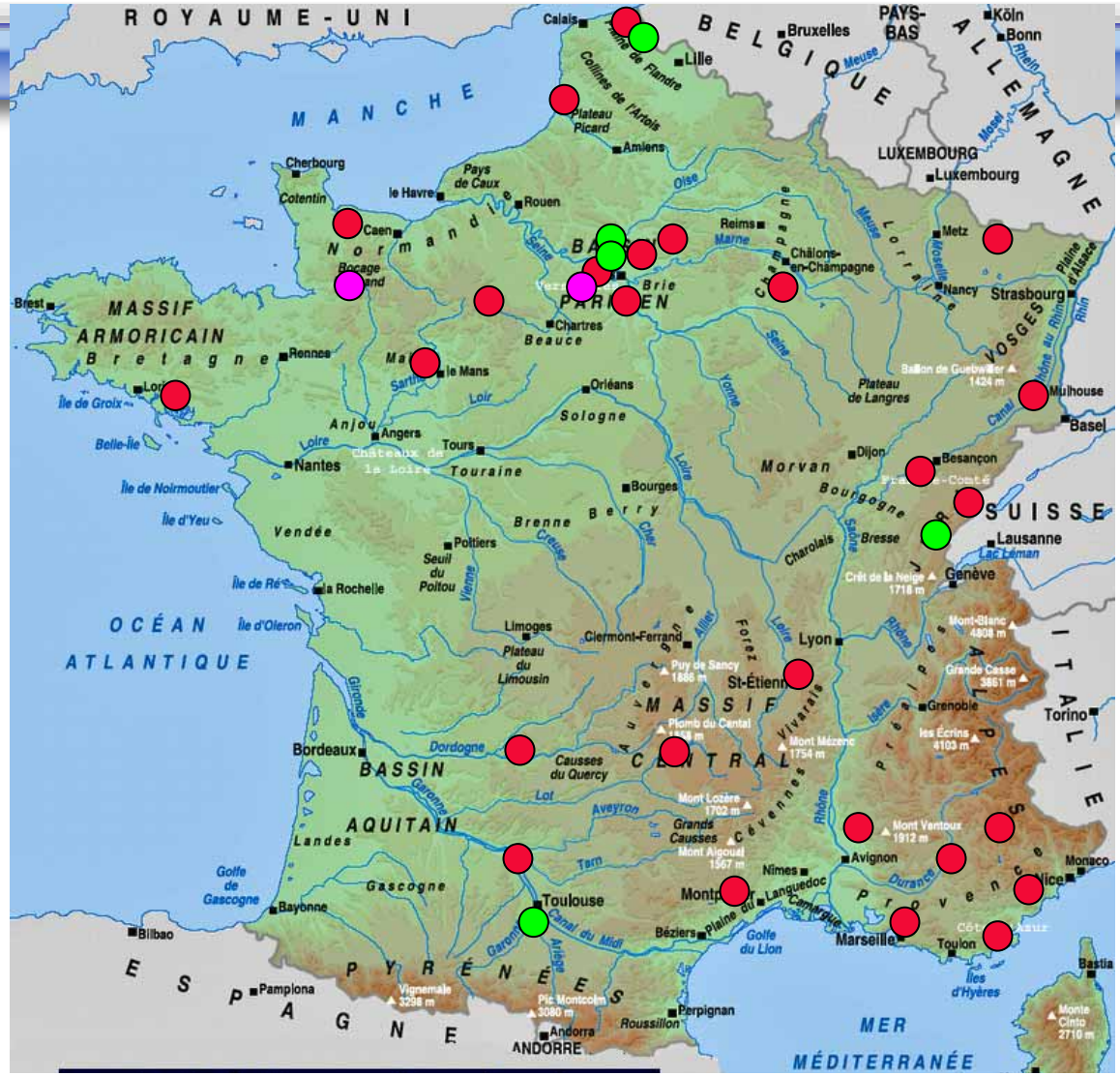
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2008, p. 786–789 Vol. 52, No. 2
0066-4804/08/$08.00+0 doi:10.1128/AAC.00906-07

Nationwide Study of the Prevalence, Characteristics, and Molecular Epidemiology of Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae* in France[▽]

Muriel Galas,[1] Jean-Winoc Decousser,[2,3]* Nelly Breton,[1] Thierry Godard,[1] Pierre Yves Allouch,[1] Patrick Pina,[4] and the Collège de Bactériologie Virologie Hygiène (ColBVH) Study Group†

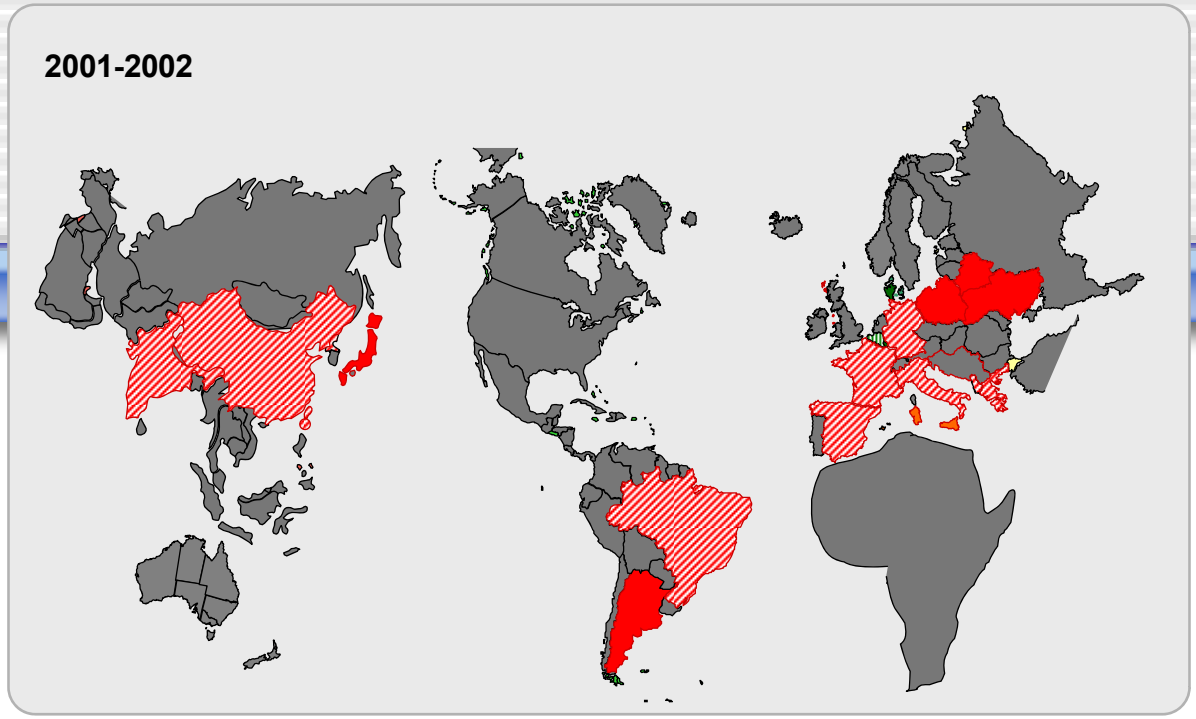
Among 10,872 isolates of *Enterobacteriaceae* from a nationwide study of 88 French hospitals in 2005, 169 (1.7%) expressed an extended-spectrum β-lactamase. The most prevalent species were *Escherichia coli* (48.5%), *Enterobacter aerogenes* (23.7%), and *Klebsiella pneumoniae* (14.8%). Molecular analysis underlined the polyclonal spread of CTX-M-expressing *E. coli*, primarily isolates of the CTX-M-1 subgroup.

CTX-Ms; distribution en France 2005



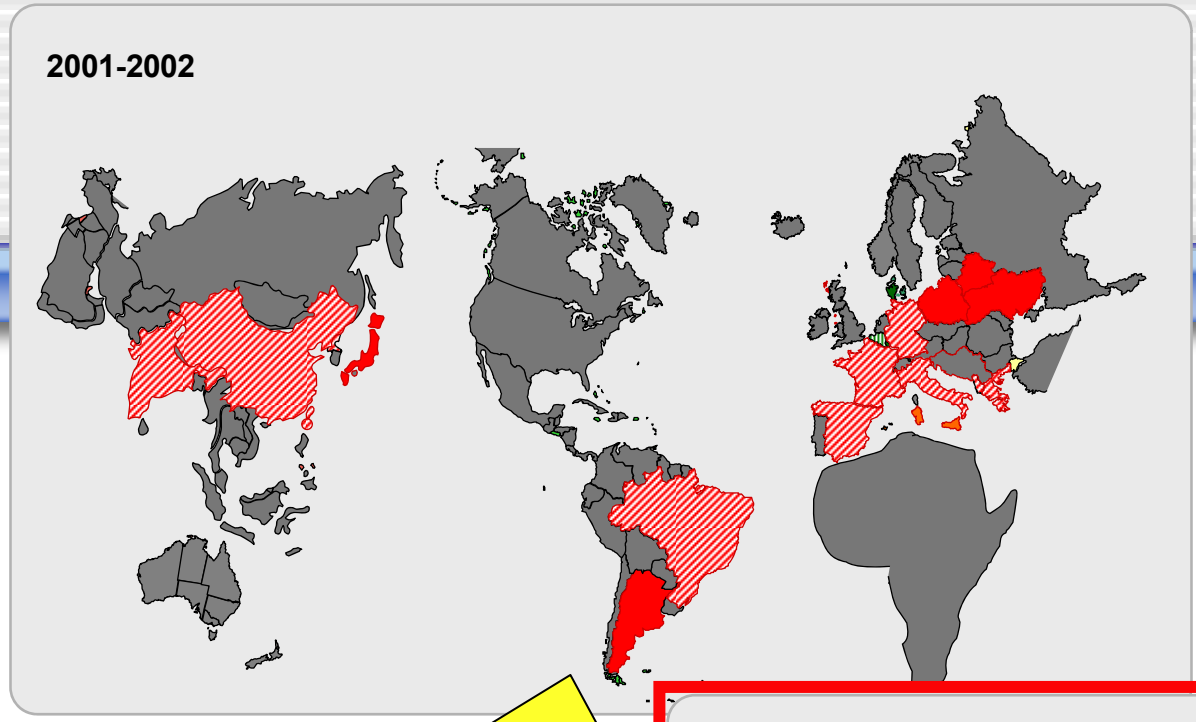
- CTX-M group-1
- CTX-M group-9
- Other CTX-M groups

Dissémination des CTX-Ms

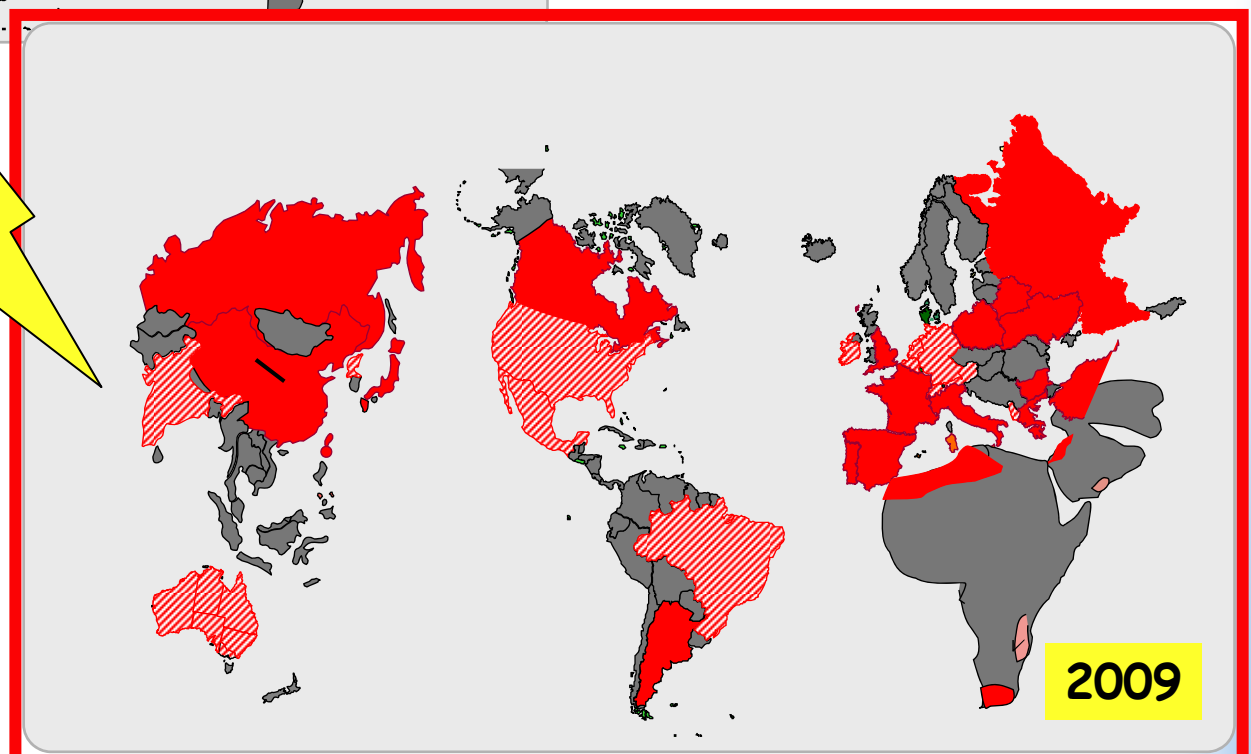


Adapté de Canton and Coque

Dissémination des CTX-Ms



Endemic Spordic reports



Adapté de Canton and Coque

Où sont ces souches CTX-Ms (+) ?

- **Infections communautaires**

- **Infections urinaires**

- ***E. coli* (+++; 2-4% ?),** *K. pneumoniae, Salmonella sp Shigella sp, Citrobacter sp, Enterobacter sp, Serratia sp…..*

Conséquences pour l'hôpital ; BLSE maintenant aux urgences, urologie, néphrologie, gastro-entérologie, médecine interne, gériatrie, maternité, pédiatrie….

Mais pas d'épidémies à *E. coli* BLSE ….!!!

CTX-M-15-producing *Escherichia coli* in fatal neonatal meningitis: failure of empirical chemotherapy

Sophie Boyer-Mariotte[1,2*], Pauline Duboc[1], Stéphane Bonacorsi[3], Jean-François Lemeland[1], Edouard Bingen[3] and Didier Pinquier[4]

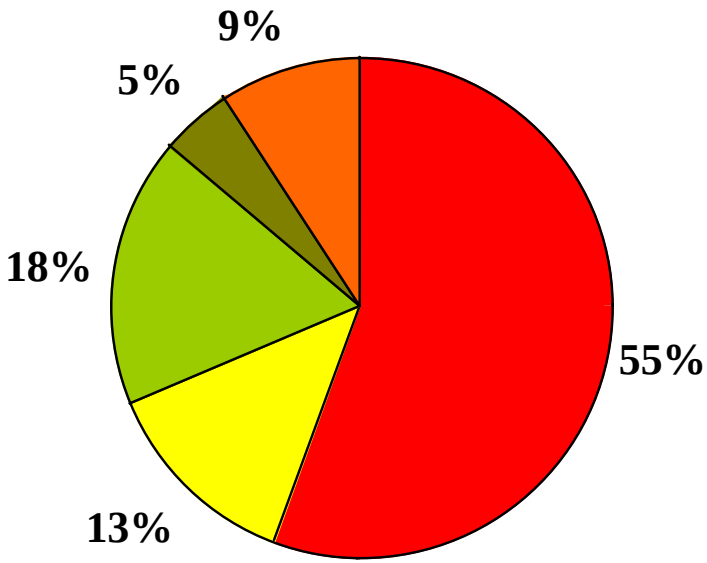
[1]Département de Microbiologie, CHU de Rouen, 1 rue de Germont, 76031 Rouen cedex, France; [2]EA2656 GRAM, IHURBM, Faculté de Médecine, Université de Rouen, Rouen, France; [3]Département de Microbiologie, Hôpital Robert Debré, 48 bd Sérurier, 75019 Paris, France; [4]Département de Néonatalogie, CHU de Rouen, 1 rue de Germont, 76031 Rouen cedex, France

Facteurs de risque d'acquisition de *E.coli* BLSE (+)

- **Infections récidivantes; hospitalisation antérieure**
- **Soins de suite -hospitalisation en longs séjours**
- **Diabète**
- **Pays de forte endémie: Grèce, Espagne, Italie, UK**
- **Traitement antibiotique antérieur;**
  - **penicillines, cefixime**
  - **fluoroquinolones**

K. pneumoniae BLSE (+) : le retour…

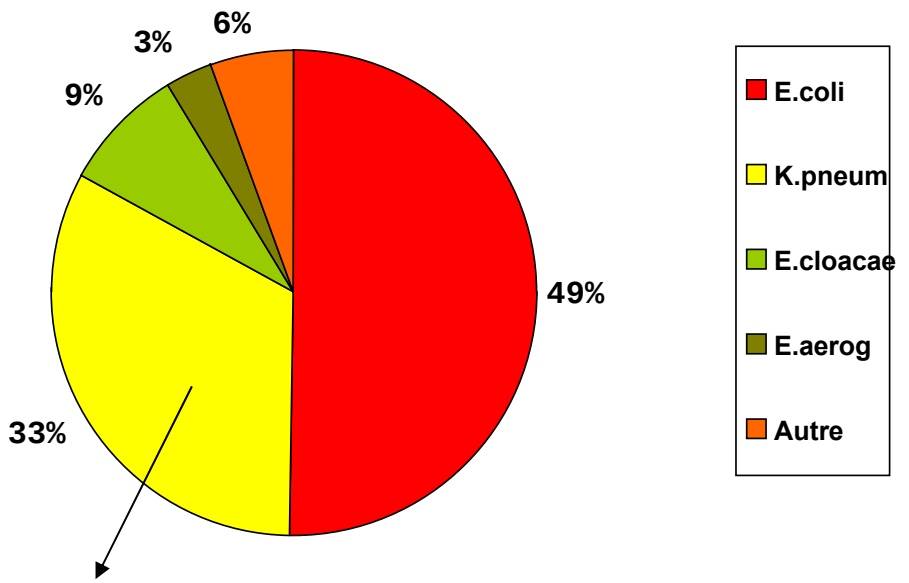
N= 111 BLSE



2006

Epidémie

N= 142 BLSE



2007

Epidémie; *K. pneumoniae* CTX-M (+)

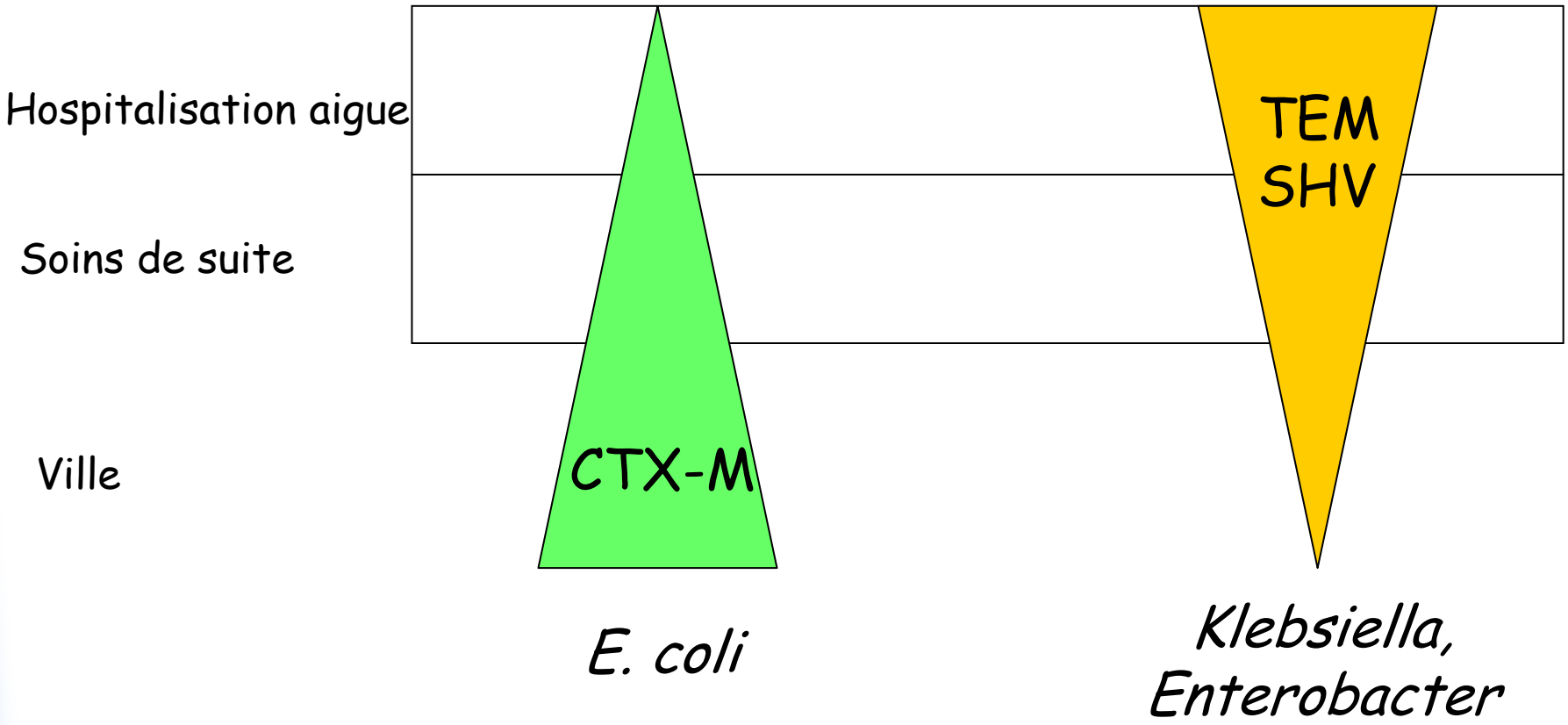
MICROBIAL DRUG RESISTANCE
Volume 15, Number 1, 2009

Outbreak of CTX-M-15-Producing Klebsiella pneumoniae in the Intensive Care Unit of a French Hospital

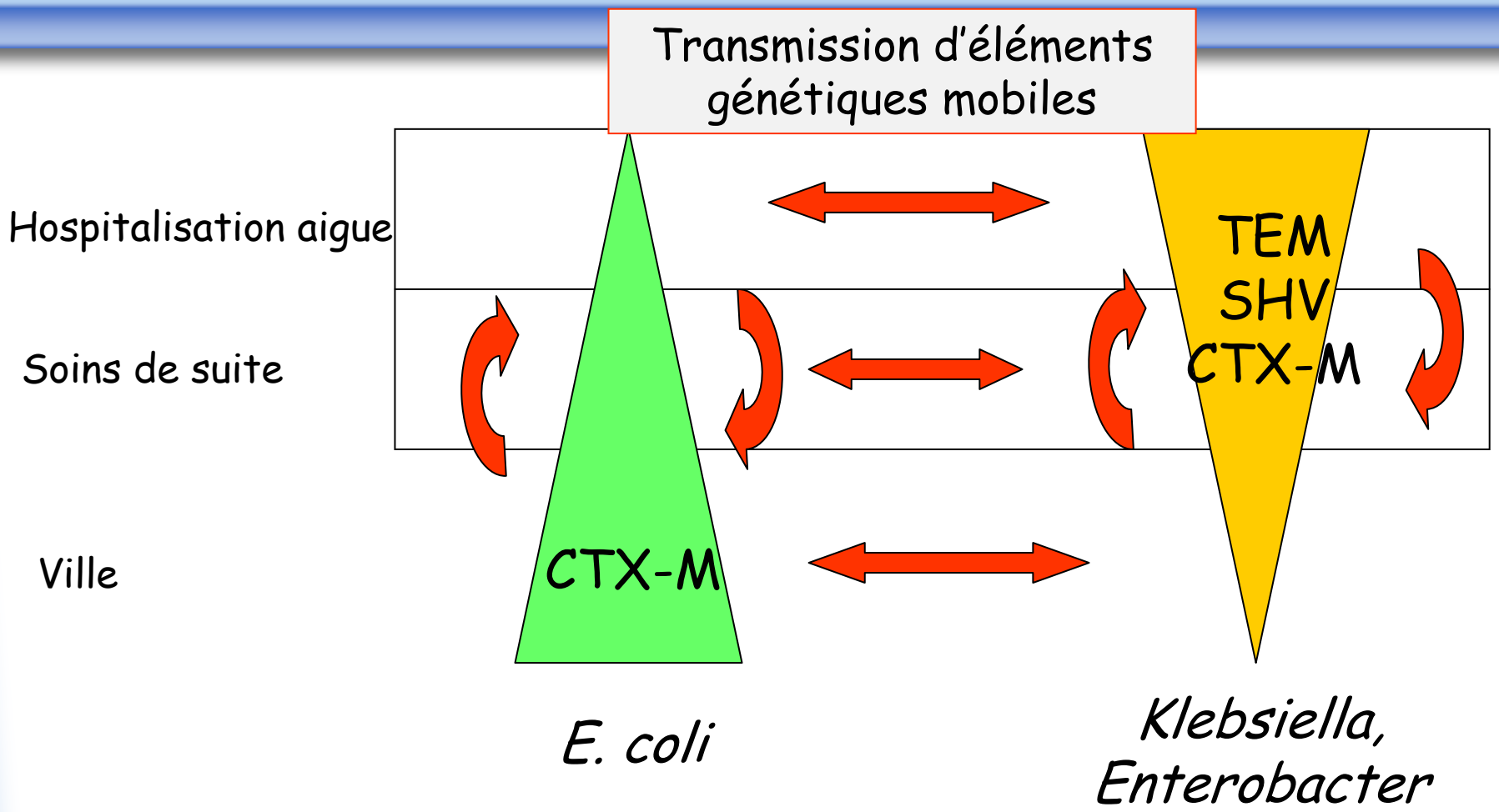
Amelie Carrer Ludovic Lassel, Nicolas Fortineau, Meriem Mansouri, Nadia Anguel, Christian Richard, and Patrice Nordmann

The CTX-M-15 extended spectrum b-lactamase (ESBL)-producing Klebsiella pneumoniae isolates were identified in 36 patients hospitalized from December 2006 to September 2007 in the medical intensive care unit (ICU) of the Bicêtre hospital, South Paris, France. The incidence of colonization and=or infection was 4.8%. Eighty-nine percent of the ESBL-producing K. pneumoniae isolates were acquired in the ICU, and only 8.3% of the patients were infected. Pulsed field gel electrophoresis (PFGE) analysis of the isolates showed that 32 isolates were clonally related and contained a 160-kb plasmid carrying the blaCTX-M-15, blaOXA-1, blaTEM-1, and aac6o -Ib-cr genes. CTX-M-15-producing Escherichia coli isolates collected in the ward during the same period of time contained distinct plasmids and were not clonally related. This study highlights the possible occurrence of outbreaks due to CTX-M-producing K. pneumoniae within hospital settings, whereas CTX-Ms are mostly reported in E. coli in community-acquired infections.

Dissémination des BLSES



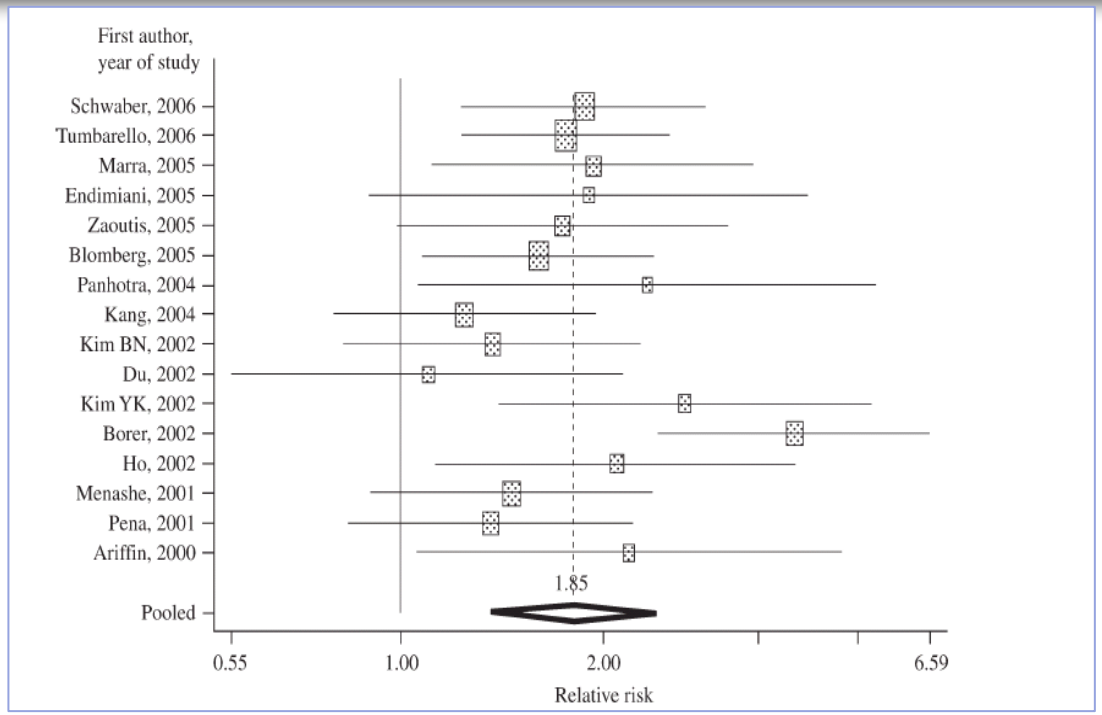
Dissémination des BLSES



Quel est le problème avec ces BLSE (+)?

- **Mortalité associée aux BLSE (+)**
- Traitement des infections à BLSE (+)

Meta-analysis: ESBL bloodstream infections and mortality; *Mortality ESBL: (34%) vs. Non-ESBL: (20%)*



Schwaber and Carmeli, JAC, 2007

ESBL: n= 519
Non-ESBL: n=1091

Relative Risk: 1,85 (95% CI 1.39-2,47)

Potential causes of excess mortality in ESBL infections:

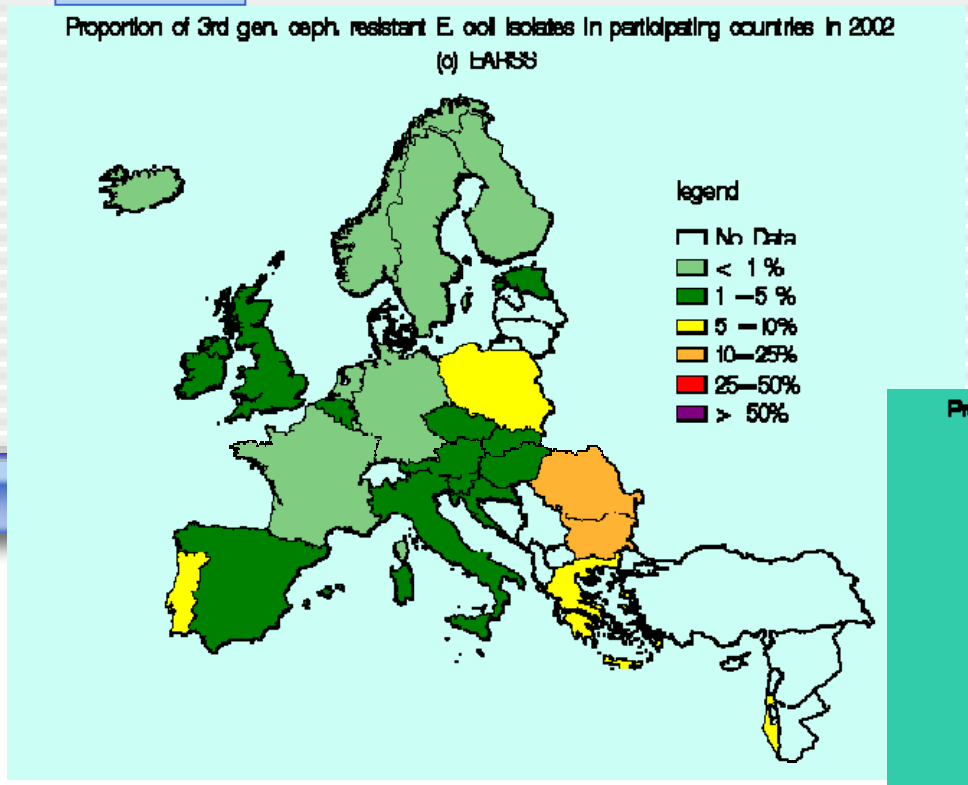
- -Selection bias (i.e. risk-factors for ESBL are also risk-factors for mortality)
- -ESBL is associated with virulence genes
- **-Delay in effective therapy**

Quel est le problème avec ces BLSE (+)?

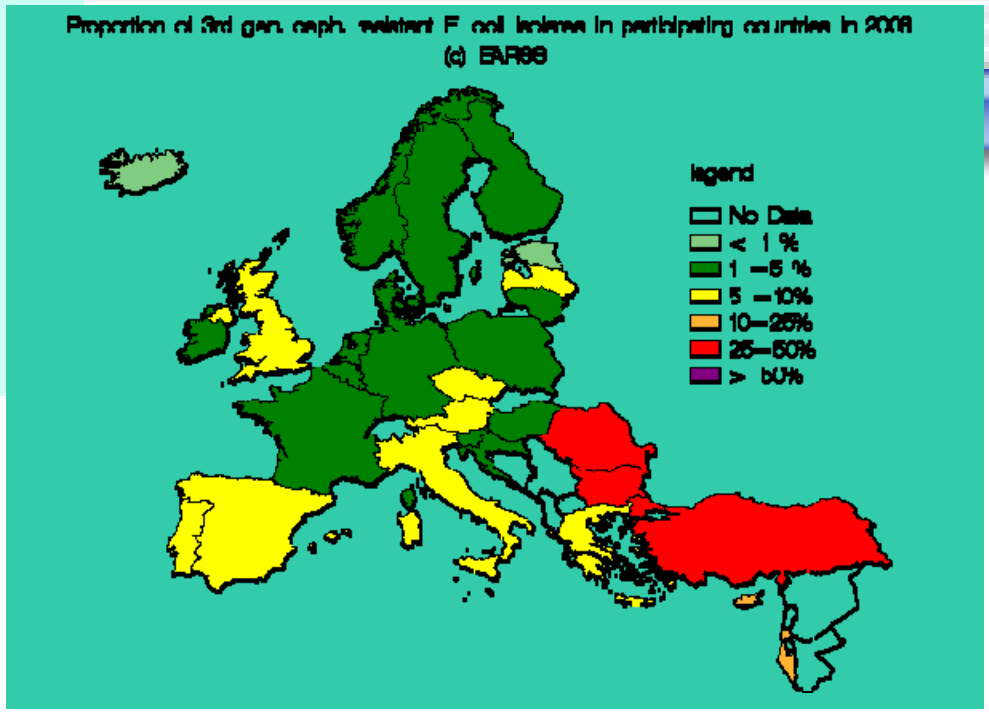
- Mortalité associée aux BLSE (+)
- **Traitement des infections à BLSE (+)**

Résistance aux cephalo III

2002



2006



Traitement des infections à *E. coli*

	Infections Urinaires basses (per os)	Sepsis (abdominal, urinaire…)(IV)
Amino, ureidopencillines		
Amoxicilline/a .clavulanique		
Pipéracilline/Tazobactam		
Cephalosporines 3/4 ème génération		
Carbapénèmes		
Aminoglycosides		
Quinolones/Fluoroquinolones		
Trimethoprime/Sulfamethoxazole		
Colistine		
Tigécycline		
Fosfomycine/Nitrofuarantoine		

Traitement des infections à *E. coli*: BLSE

spectre d'activité in vitro

	Infections Urinaires basses (per os)	Sepsis (abdominal, urinaire…)(IV)
Amino, ureidopencillines		
Amoxicilline/a .clavulanique		
Pipéracilline/Tazobactam		
Cephalosporines 3/4 ème génération		
Carbapénèmes		
Aminoglycosides		
Quinolones/Fluoroquinolones		
Trimethoprime/Sulfamethoxazole		
Colistine		
Tigécycline		
Fosfomycine/Nitrofuarantoine		

B-Lactamines et assocation ß-lactamines/inhibibiteurs; effet inoculum

Inoculum (CFU/ml) (n) and antibiotic	MIC[a] (µg/ml) 90%	% Susceptible[b,c]
10^5 CFU →		
10^5 (19)		
Meropenem	0.03	100
Cefoteten	1	100
Cefotaxime	64	79
Ceftazidime	256	32
Ceftriaxone	128	79
Cefepime	16	79
Aztreonam	128	47
Pip-Tazo[d]	8	95
10^7 CFU →		
10^7 (19)		
Meropenem	0.12	100 (1/19)
Cefoteten	4	100 (4/19)
Cefotaxime	>1,024	21 (17/18)
Ceftazidime	>1,024	5 (11/16)
Ceftriaxone	>1,024	5 (18/19)
Cefepime	>128	5 (18/18)
Aztreonam	>1,024	16 (16/19)
Pip-Tazo	1,024	58 (8/19)

CFU's in vivo: 10^9 - 10^{10} per gram tissue[2,3]

1: Thomson et al, AAC, 2001
2: Bingen et al., AAC, 1994
3: Korzeniowski, Infect. Dis, 1998

Traitement des infections à *E. coli*: BLSE

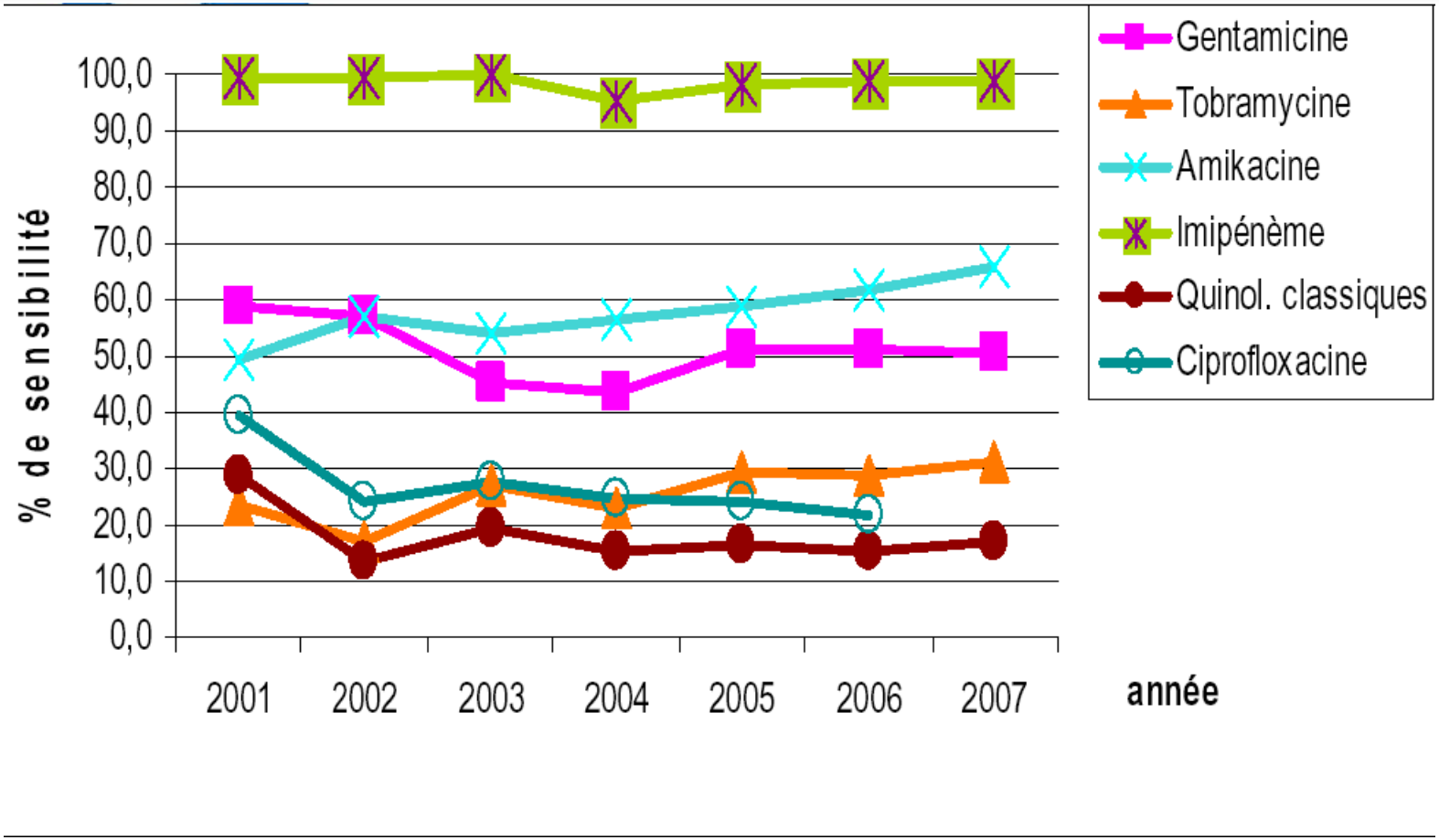
spectre d'activité in vitro + effet inoculum

	Infections Urinaires basses (per os)	Sepsis (abdominal, urinaire…)(IV)
Amino, ureidopencillines		
Amoxicilline/a .clavulanique		
Pipéracilline/Tazobactam		
Cephalosporines 3/4 ème génération		
Carbapénèmes		
Aminoglycosides		
Quinolones/Fluoroquinolones		
Trimethoprime/Sulfamethoxazole		
Colistine		
Tigécycline		
Fosfomycine/Nitrofuarantoine		

Co-resistances
ESBL - Bicetre -*E.coli* - 2007 (n=71)

	% résistance
Gentamicin	39
Tobramycin	51
Amikacin	27
Netilmicin	47
Tetracycline	58
Trimethoprim/Sulfamethoxazole	63
Nalidixic acid	79
Ciprofloxacin	72
Colistin	0
Fosfomycin	0
Ertapenem/Imipenem	0
Tigecycline	0

Co-resistances- BLSE-APHP

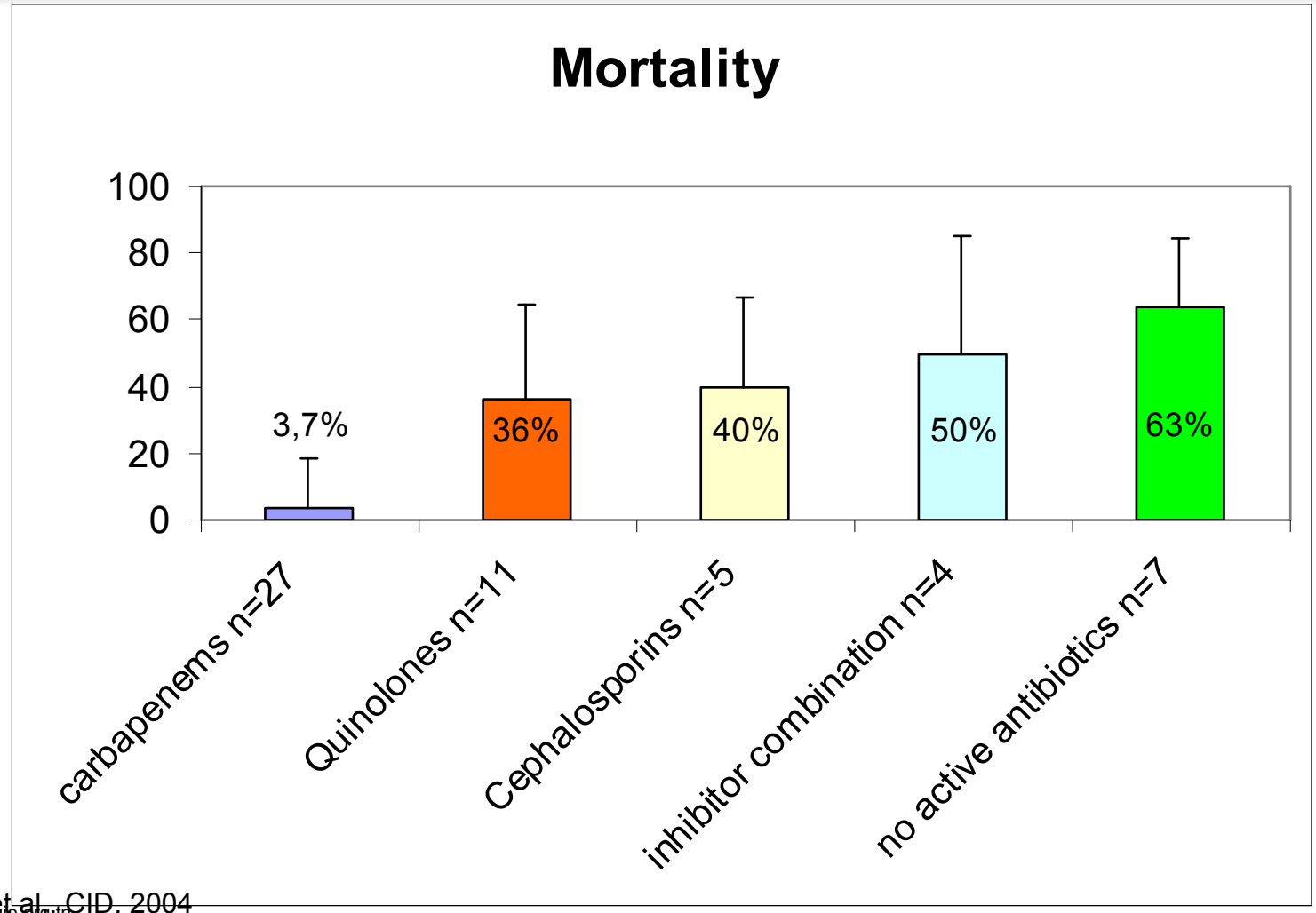


Traitement des infections à *E. coli*: BLSE

spectre d'activité in vitro + effet inoculum + co-résistances

	Infections Urinaires basses (per os)	Sepsis (abdominal, urinaire…)(IV)
Amino, ureidopencillines		
Amoxicilline/a .clavulanique		
Pipéracilline/Tazobactam		
Cephalosporines 3/4 ème génération		
Carbapénèmes		
Aminoglycosides		
Quinolones/Fluoroquinolones		
Trimethoprime/Sulfamethoxazole		
Colistine		
Tigécycline		
Fosfomycine/Nitrofuarantoine		

Mortalité à 14 jours par classe d'antibiothérapie



Paterson et al., CID, 2004

90's

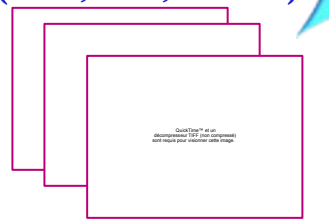
K. pneumoniae (TEM, SHV)

QuickTime™ et un
décompresseur TIFF (non compressé)
sont requis pour visionner cette image.

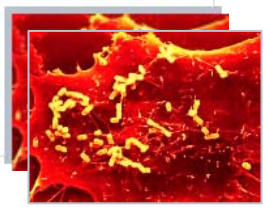
H

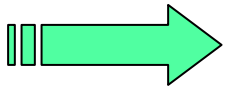
2000's

K. pneumoniae
(TEM, SHV, CTX-M)



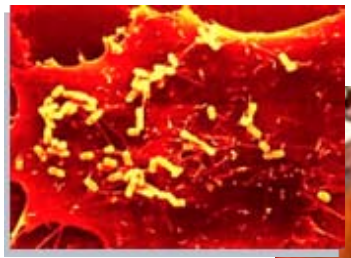
E. coli (CTX-M)





E. coli (CTX-M)

H



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Addressing the challenge of extended-spectrum β-lactamases

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During the last decade, community-acquired extended-spectrum β-lactamase (ESBL)-producing bacteria, and in particular Escherichia coli producing ESBLs of the CTX-M-type, have spread worldwide. These organisms are most often isolated from the urinary tract, but have also been isolated from bacteria in the blood. Cephalosporin- and fluoroquinolone-containing treatments are the two most common risk factors identified in patients with ESBL producers. In addition, associated resistance to other classes of antimicrobial agents are often observed in CTX-M producers, limiting the availability of therapeutic options. Carbapenems should be considered as the drug of choice for treating serious systemic infections caused by ESBL-producing bacteria, but preventing the spread of and appropriately managing these infections remains difficult.

Screening

Table 1: **Proposal for controlling spread of ESBL-producing *Enterobacteriaceae* in hospital**

1-Screen patients admitted from other hospitalization units (ICU, surgery), from other hospitals or long term facilities
2-Screen patients previously colonized/infected with ESBL producing bacteria within on e year after discharge from the hospital
3-Take standard precautions when ESBL-positive *K. pneumoniae, Enterobacter spp, Serratia spp.* are detected. Isolation measures for ESBL-positive *E. coli* isolates are debatable in the absence of identification of an outbreak.
4-In case of epidemic situation think about cohorting

Traitement

Table 2: **Proposals for the first line treatment of urinary tract infections in the era of ESBL-producing *Enterobacteriaceae***

Cystitis

First episode, no history of antibiotic therapy: trimethoprim-sulfamethoxazole or fluoroquinolones History of antibiotic therapy or multiples episodes: fosfomycin trometanol

Community acquired pyelonephritis or prostatitis

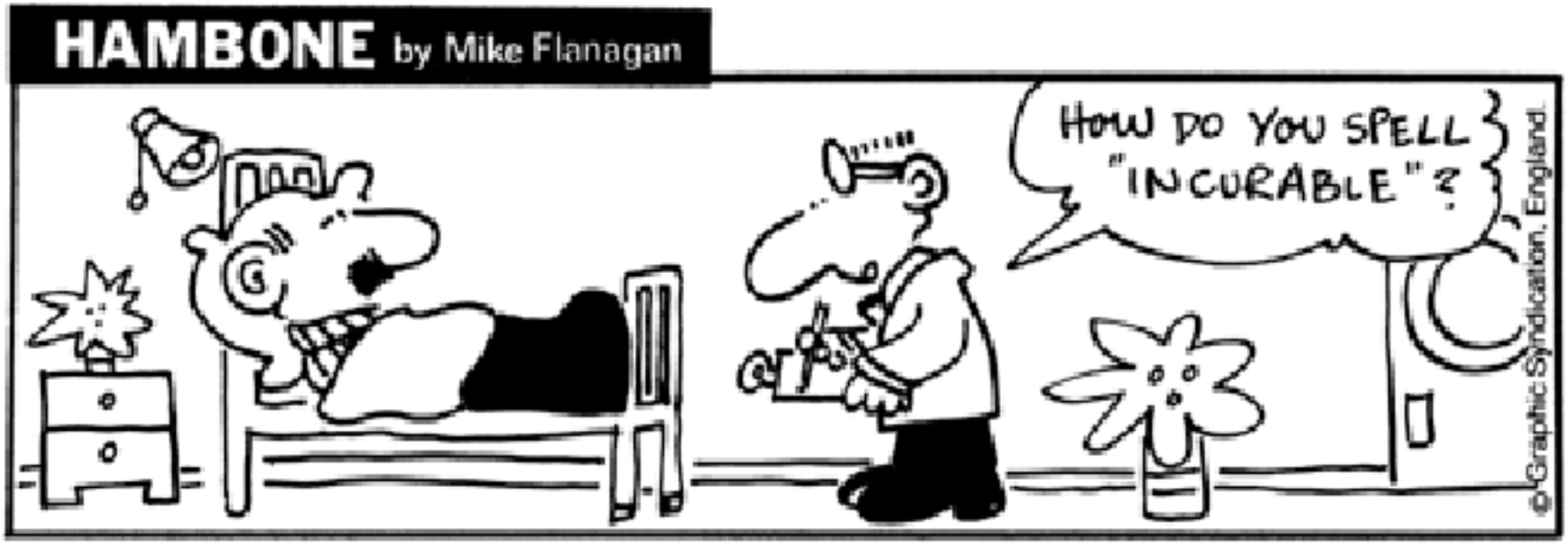
A-Patient living in Europe* without any risk factors for ESBL producers, no history of antibiotic therapy, no sepsis or septic shock: expanded-spectrum cephalosporins B-Patient living in Europe *with no risk factors for ESBL producers, no history of antibiotic therapy, with severe sepsis or septic shock: Expanded-spectrum cephalosporin plus aminoglycoside C- Patient coming from a country with high prevalence of ESBL producers: C1-without risk factors for ESBL producers and no sepsis or septic shock: Expanded-spectrum cephalosporin plus aminoglycoside C2-sepsis or septic shock or risk factors for ESBL producers Carbapenem plus aminoglycoside

*Current situation may vary significantly among European countries with increasing spread of CTX-M producers at least in the UK, Italy, and Spain.

Questions d'avenir

- Augmentation de la prévalence des BLSEs dans le communautaire, jusqu'à quel niveau? Quand doit-on changer guidelines des traitements de ville ?
- Importance du réservoir (environnement, animaux, portage sain, distribution géographique… ?
- Origine des éléments génétiques qui sont à l'origine de la dissémination?
- Les antibiotiques sélecteurs? Lesquels ? Où ?

Treatment regimens for multi-resistant Gram-negative organisms



- No new drugs expected for the coming years
- Resistance will get worse not better