

Bactéries multirésistantes (BMR)
Bactéries hautement résistantes
émergentes (BHRe) :
épidémiologie et contrôle

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Bactériologie-Hygiène

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Délégué aux infections nosocomiales

Direction de la Politique Médicale, AP-HP

BMR et BHRe

BMR

- accumulation de mécanismes de **résistance à plusieurs antibiotiques majeurs**
- **difficultés thérapeutiques**
- **déjà établies**

BHRe

- étape supplémentaire dans la résistance
- presque **l'impasse thérapeutique**
- non encore établies : **émergentes**

BMR et BHR_e : choix des cibles

Bactéries commensales (composantes de nos flores), responsables d'infections nosocomiales et communautaires (risque de diffusion dans la population générale)

BMR

- Staphylocoques dorés : **SARM**
- Enterobactéries : **EBLSE** (R à C3G, aminosides ± quinol.) *

BHR_e

- Enterobactéries : **EPC** (R à C3G, carbapénèmes, aminosides ± quinolones) *
- Entérocoques : **ERV** (R aux glycopeptides) *
- * résistance transférable à d'autres bactéries

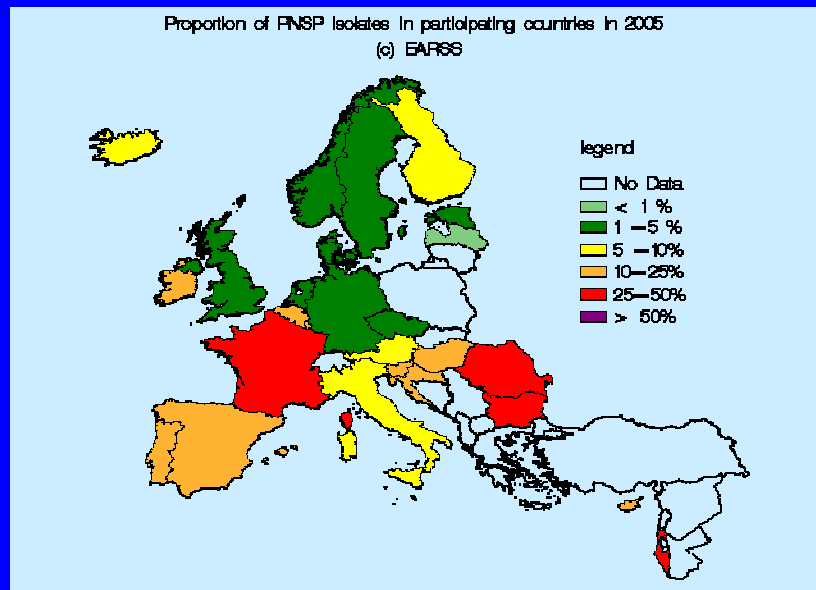
% MRSA in *Staphylococcus aureus*
in Europe 1990-1991
(43 hospitals, 7.354 strains)

Pays	%	Pays	%
Denmrk	0,1	Austria	21,6
Sweden	0,3	Belgium	25,1
Netherland	1,5	Spain	30,3
Switzerland	1,8	France	33,6
Germany	5,5	Italy	34,3

Voss ICAAC anaheim 1992 Eur J Clin Microbiol Infect Dis 1994

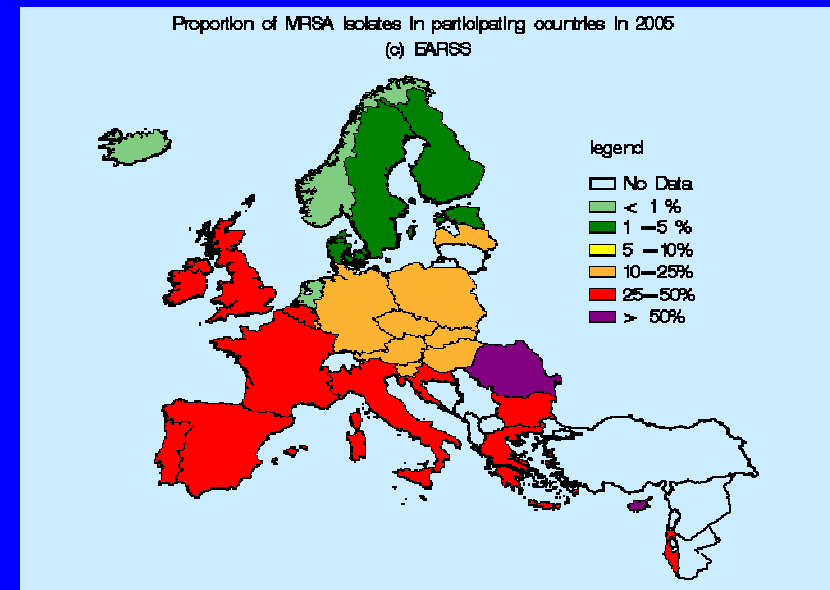
Taux de résistance de deux pathogènes majeurs en Europe au début des années 2000 (bactériémies)

S. pneumoniae et penicilline G



Souches de sensibilité diminuée ou résistantes

S. aureus et méticilline



Souches résistantes

Antibiotic consumption in Europe - Community - ESAC 2002

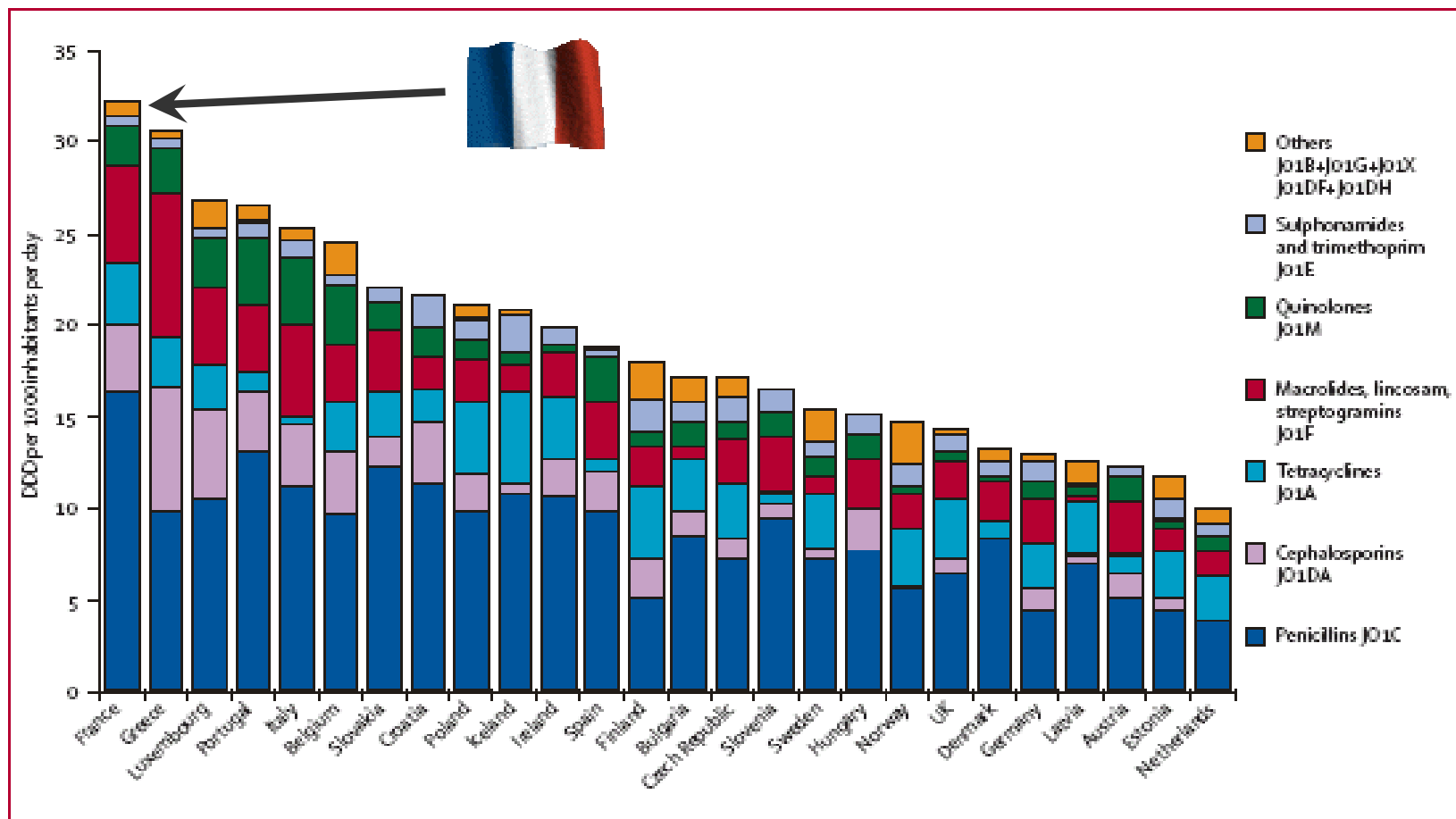
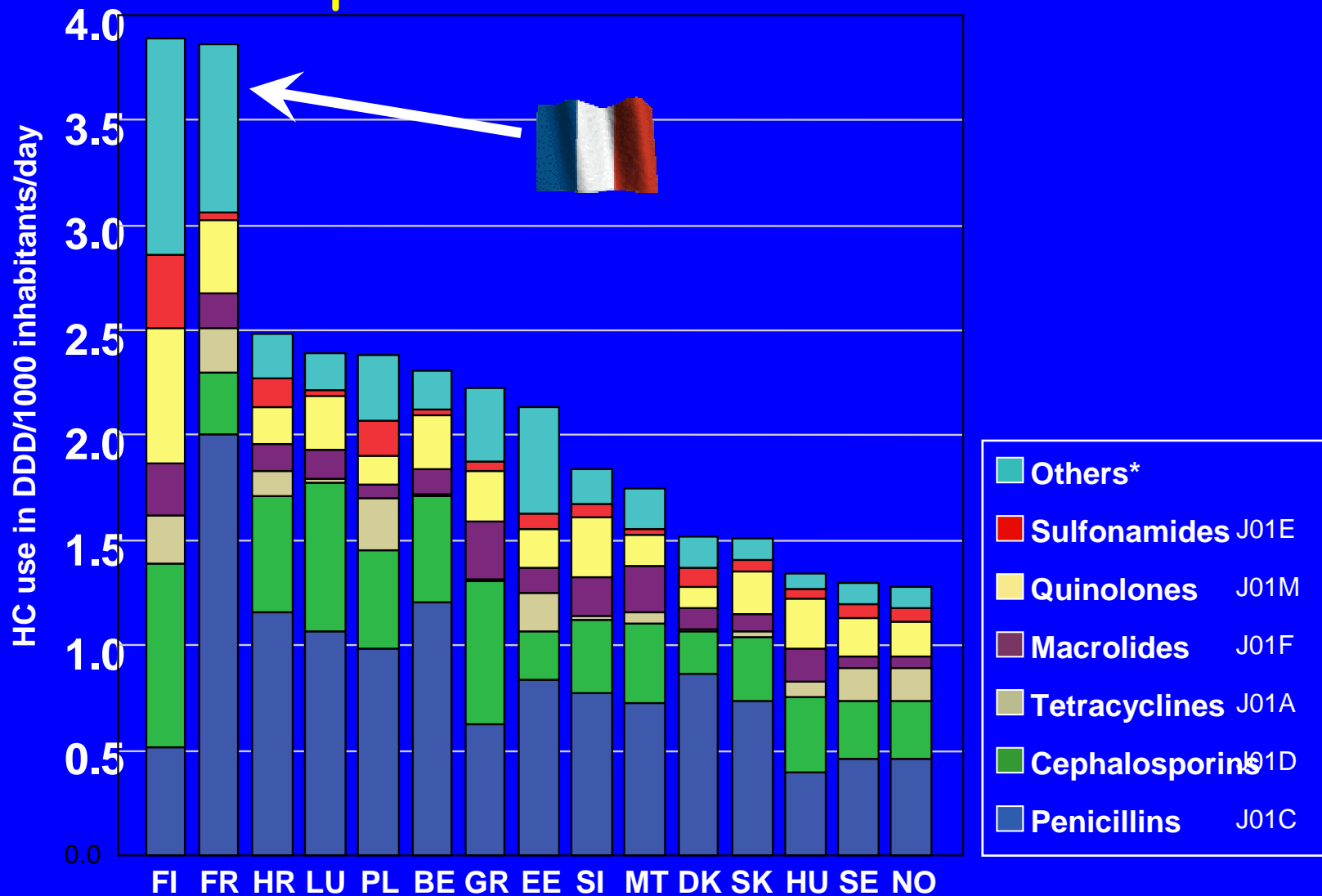
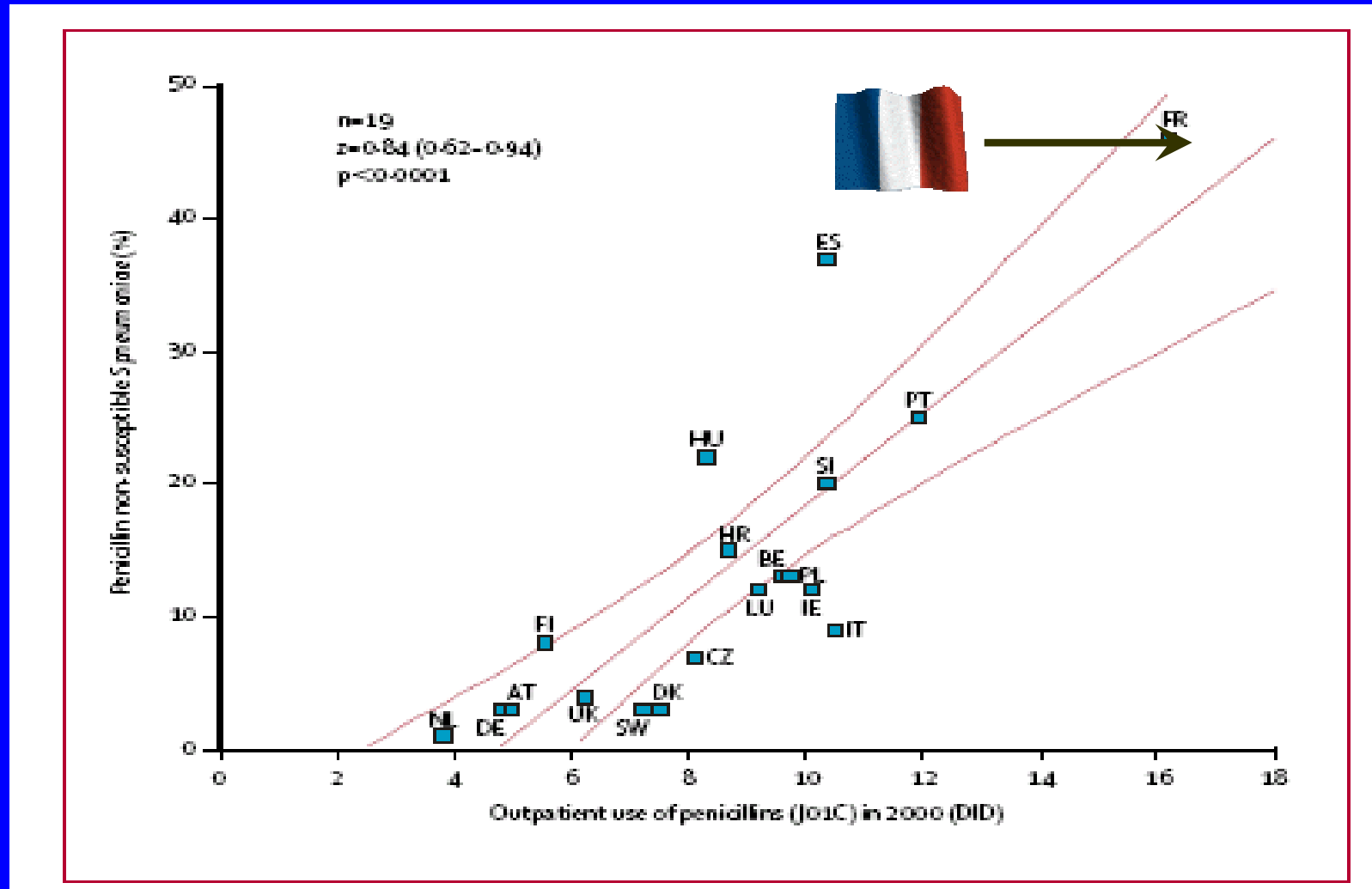


Figure 1: Total outpatient antibiotic use in 26 European countries in 2002

Antibiotic consumption in Europe - Hospital - ESAC 2002



Resistance to penicillin in *S.pneumoniae* in Europe



Control programs to curb resistance

Cross-transmission

Paris area
(AP-HP)
1993



National
1999



ABHR
AP-HP
2001



Antibiotic pressure

CNAM
2001-08



AP-HP
2006-10



BMR :
quels indicateurs ?

L'exemple des SARM

Proportion (%)
de SARM
chez *S.aureus*

*% des SARMchez Staphylococcus aureus
en Europe
1990-1991 (43 hôpitaux, 7.354 souches)*

Pays	%	Pays	%
Danemark	0,1	Autriche	21,6
Suède	0,3	Belgique	25,1
Hollande	1,5	Espagne	30,3
Suisse	1,8	France	33,6
Allemagne	5,5	Italie	34,3

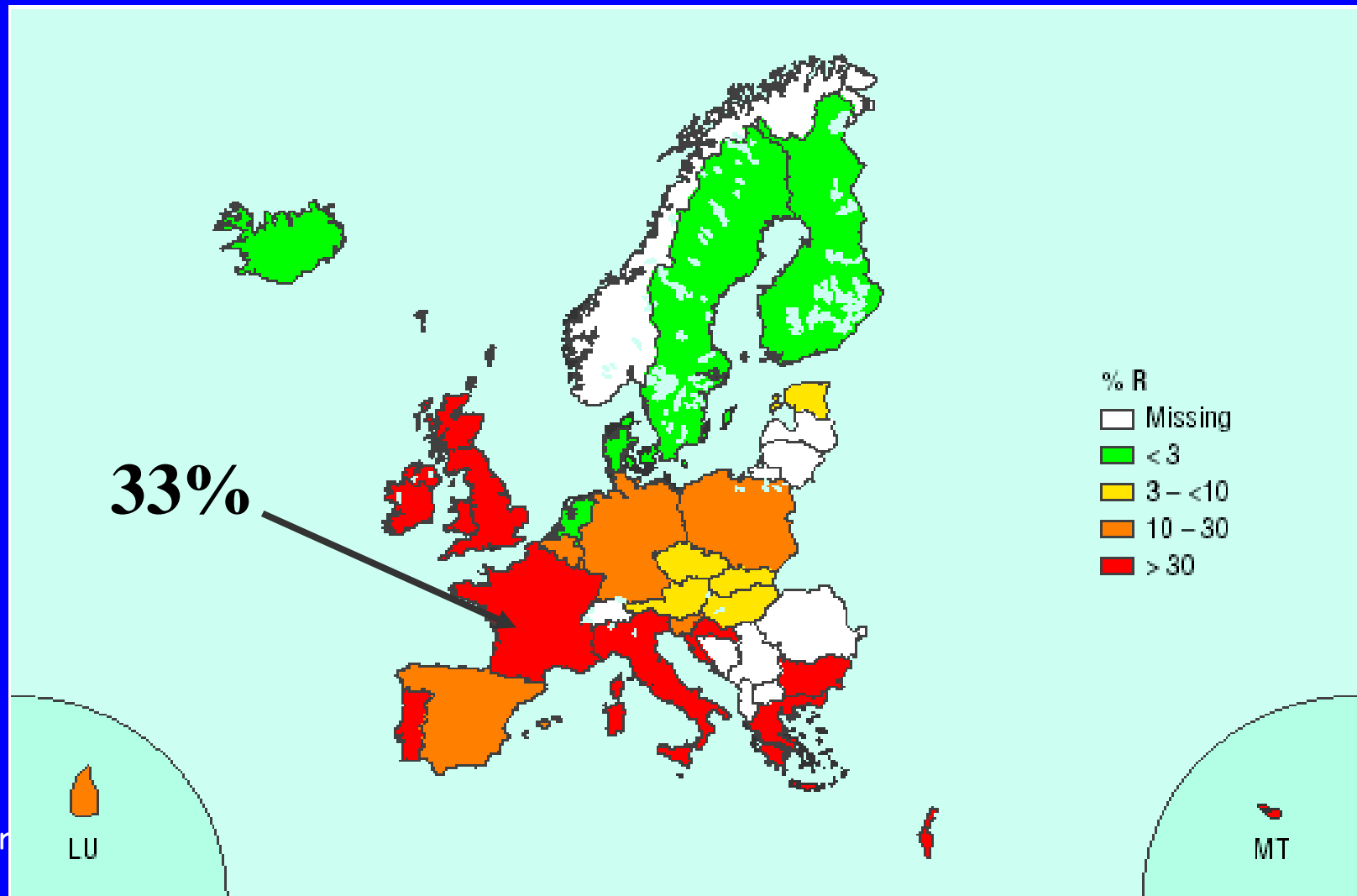
% SARM chez *S.aureus* dans les hôpitaux français, 1991-94

Réseau	Année	N.Hôpitaux	% chez <i>S.aureus</i> global hémocultures	
France (a)	1991	4	34	-
C.CLIN S.Ouest (b)	1993	44	38	37
AP-HP (c)	1993	44	42	46
Franc-Comtois (d)	1994	12	41	-

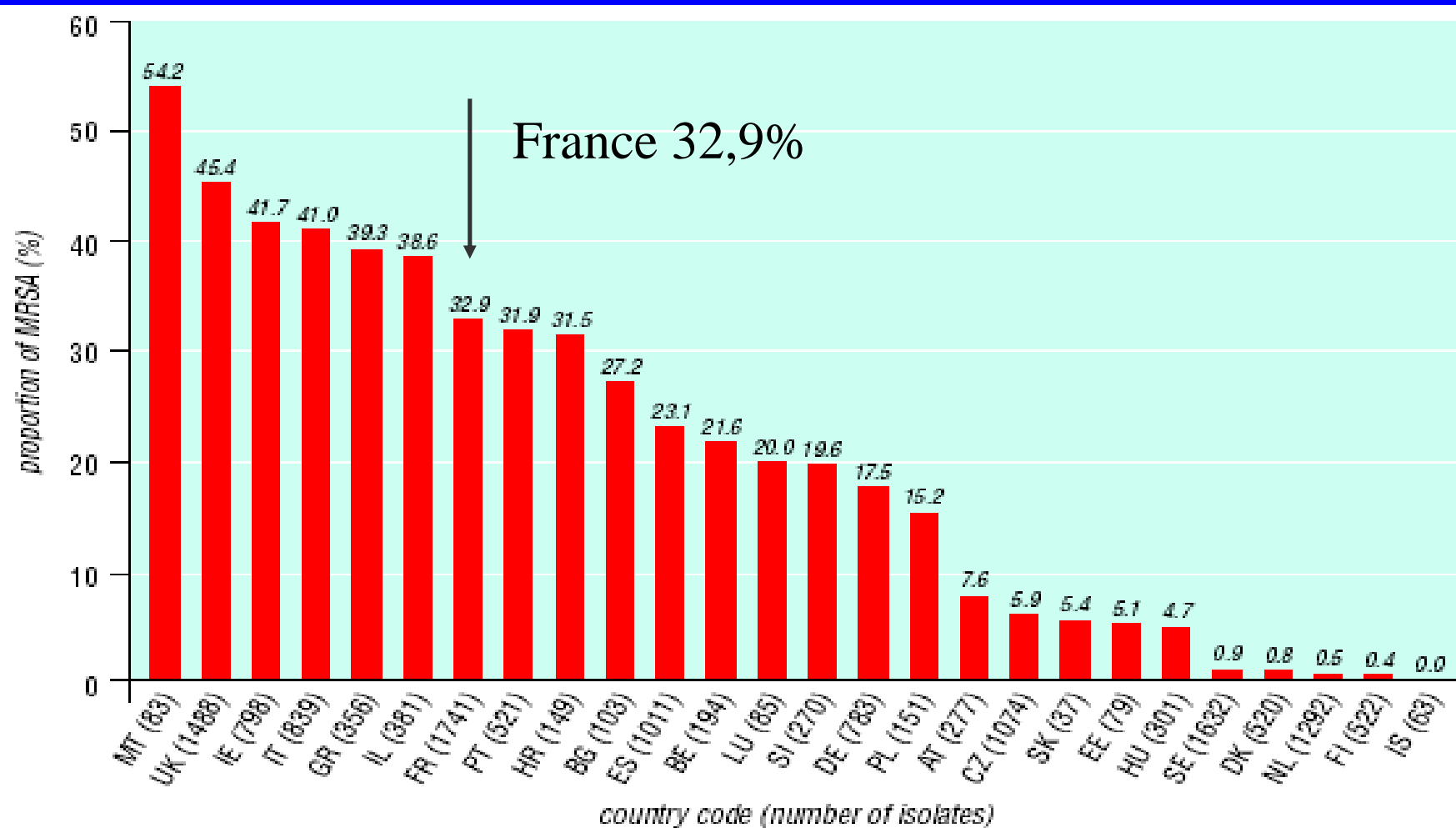
a : ref. 9 ; b : Malavaud et Didier BEH 1995, 13 : 59 ;

c : Marty et Jarlier BEH 1998, 10 : 41 ; d : Cailleaux Med Mal Inf 1996, 26 : 475

SARM dans les bactériémies en Europe (% chez *S.aureus*) EARSS 2001



SARM dans les bactériémies en Europe 2001 EARSS



Taux d'incidence des SARM

Taux d'attaque pour 100 admissions de l'isolement de SARM (prélèvements à visée diagnostique) dans les hôpitaux français, 1994-96

Réseau	Année	N Hôp (CHU)	Inc /100 admis	
			Globale	Court-S
Pays de loire	1994	19 (2)	0,45	
C.CLIN Est	1994-5	21 (4)	0,98	
Col-BVH	1995	95 (-)	0,72	
C.CLIN P.Nord	1996	35 (3)		0,79
AP-HP	1996	44 (44)		0,99

Estimation nombre de cas SARM en France/an

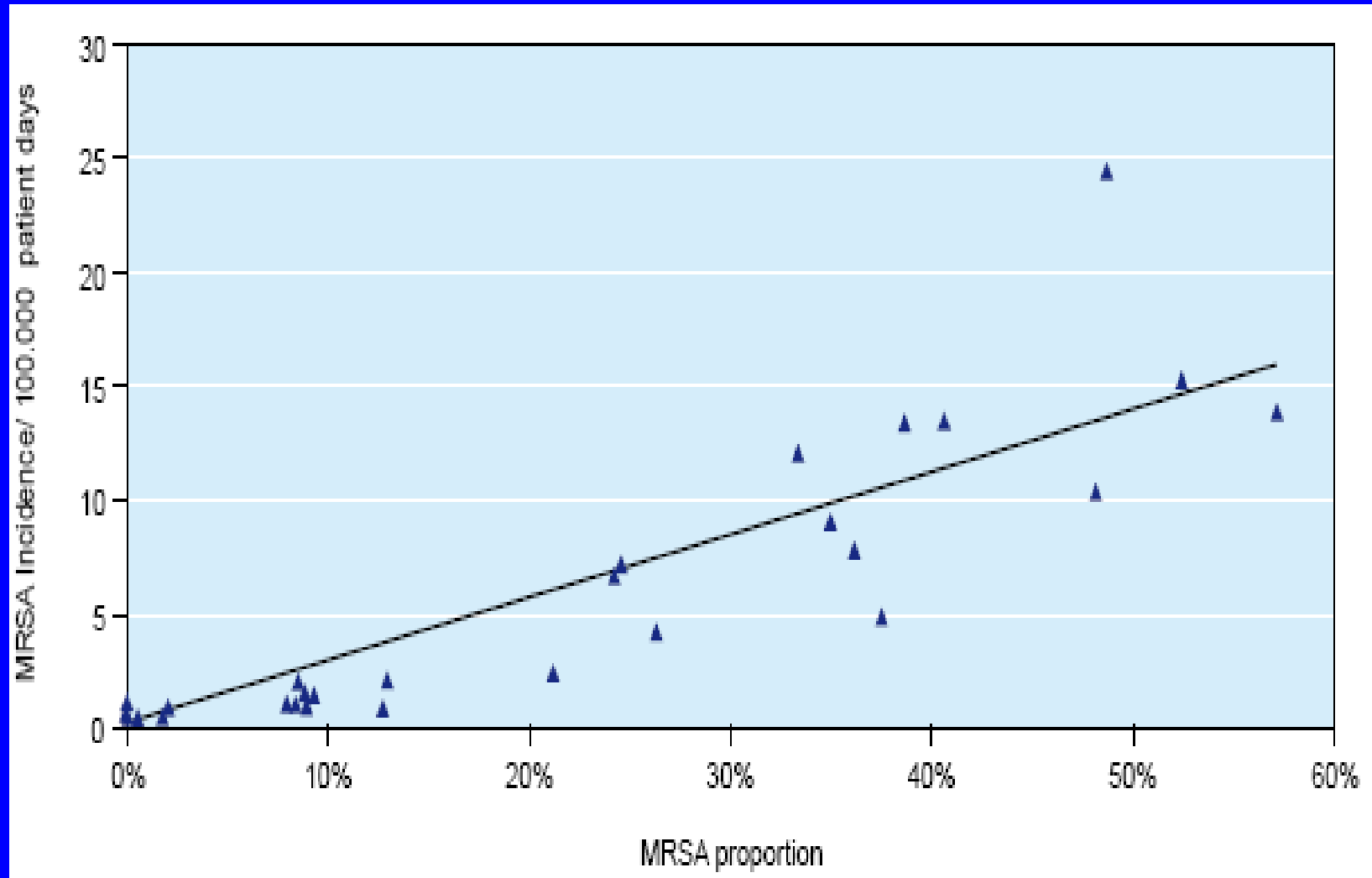
Tous prélèvements : 49 770 cas

Bactériémies : 2 990 à 3 980 cas

SARM dans les hôpitaux français en 1999 :
% chez *S.aureus* et densité d'incidence pour
1000 journées d'hospitalisation (JH)

C.CLIN	N Hôpitaux	% SARM	‰ JH
Paris-nord	95	39	0,92
AP-HP	44	35	0,88
Est			
Ch. Ardennes	16	34	0,63
Fr. Comté	30	30	0,72
Sud-Ouest (1998)	36	41	0,92
Sud-Est	126	26	0,84
Total	345	33^a	0,87^b

SARM : % chez *S.aureus* vs. incidence /100.000 JH (bactériémies, EARSS, 2007)



SARM dans les
infections nosocomiales
documentées :
les enquêtes
quinquennales
1996.....

SARM dans les infections nosocomiales (enquêtes nationales prévalence IN France)

- **1996**
 - SARM chez S.aureus : **57%**
 - Incidence infections SARM : **0,6 p. 100 admis**
- **2001**
 - SARM chez S.aureus : **64 %**
 - Incidence infectionne SARM : **0,7 p. 100 admis**

Indicateurs SARM : choix Ministère de la Santé (2004)

Densité d'incidence
pour 1000 JH

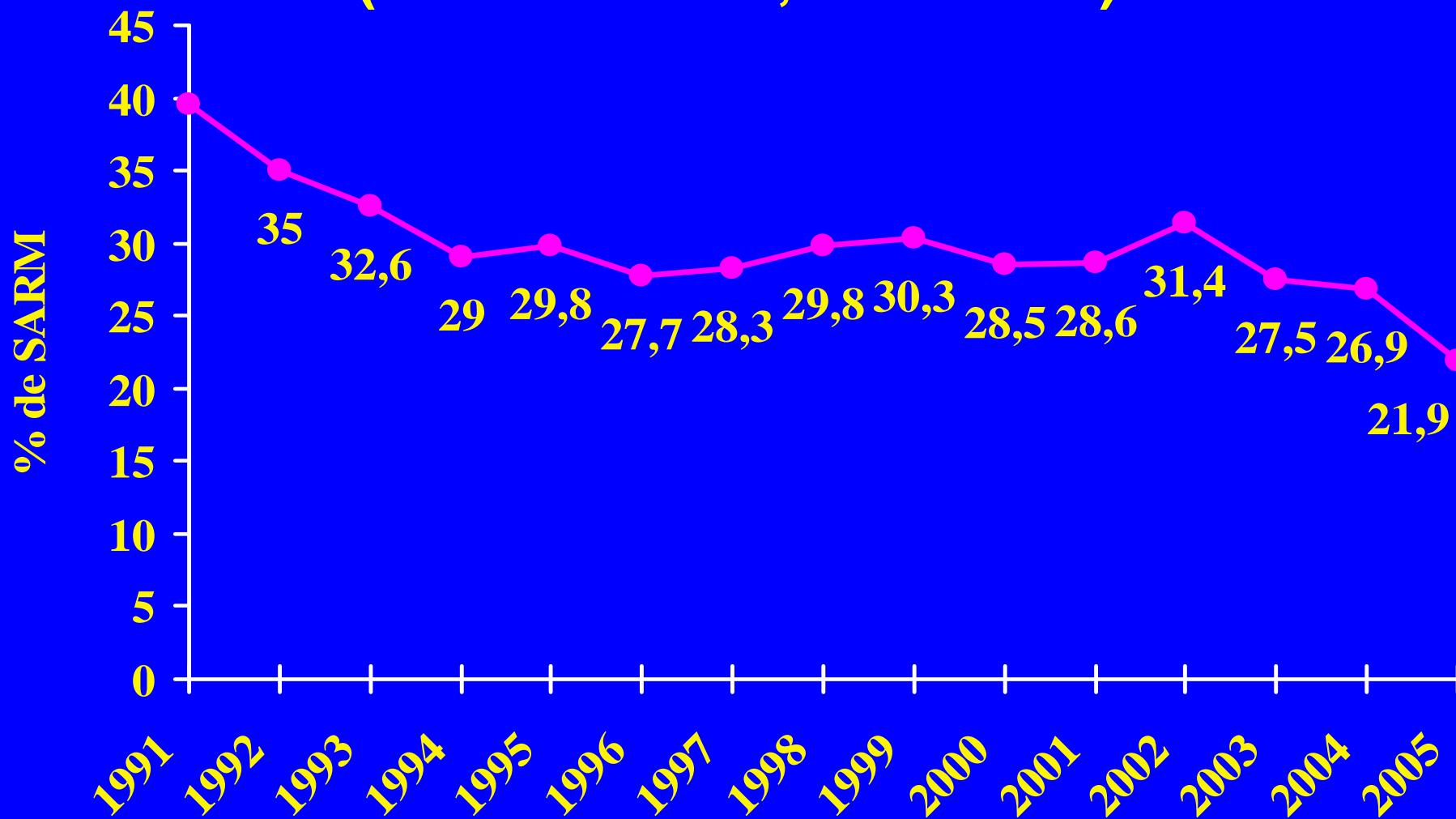
Control of "established" multiresistant bacteria in health care institutions

MRSA

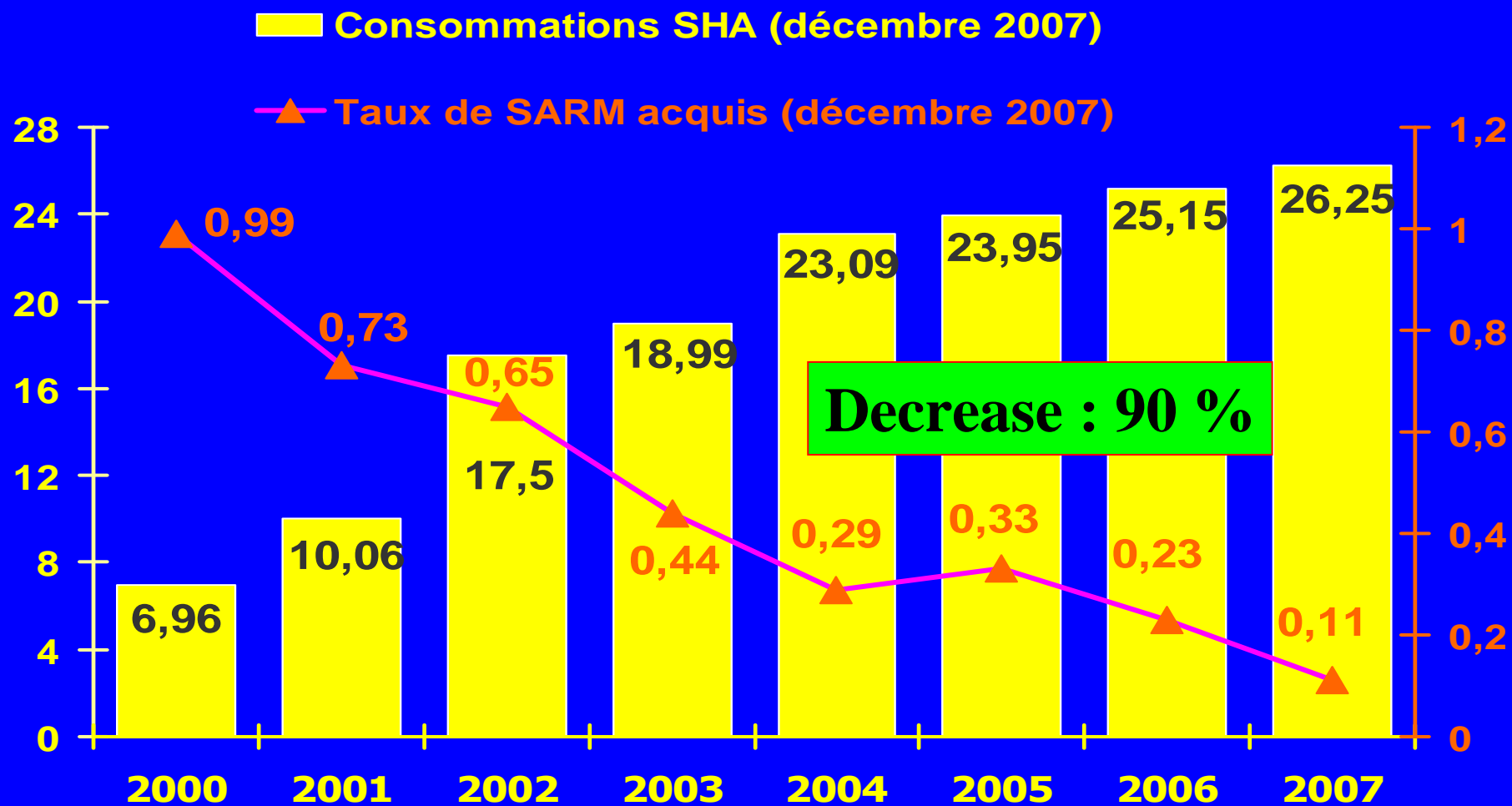
Resistance genes on chromosome

Local level

% de SARM chez *S. aureus* BICHAT - CLAUDE BERNARD 1991-2005 (A. Andremont, J.C. Lucet)

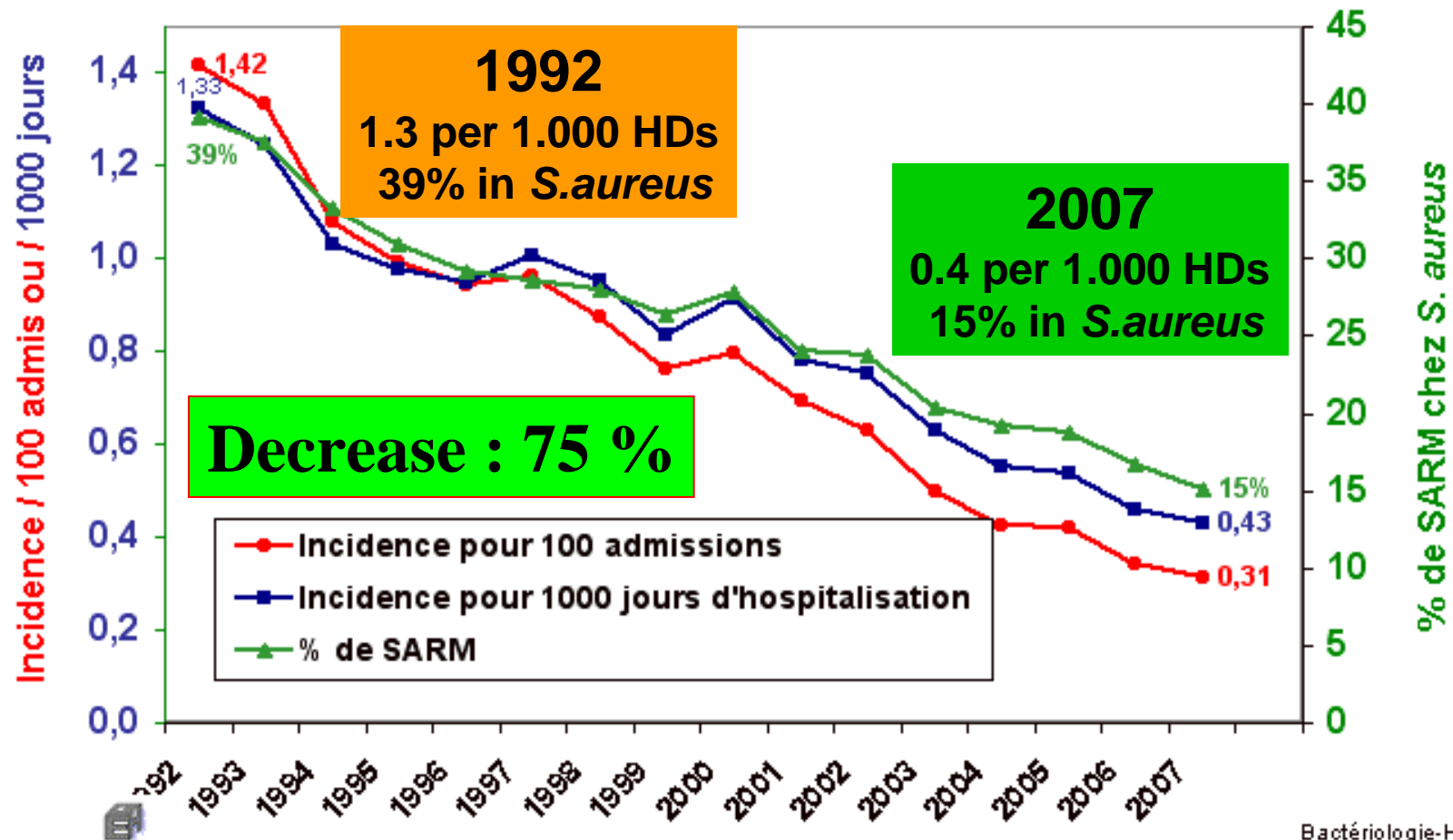


MRSA : incidence/ 1000 DHs Hôpital St Joseph, Paris 2000-2006 Acquired MRSA and consumption of ABHRs

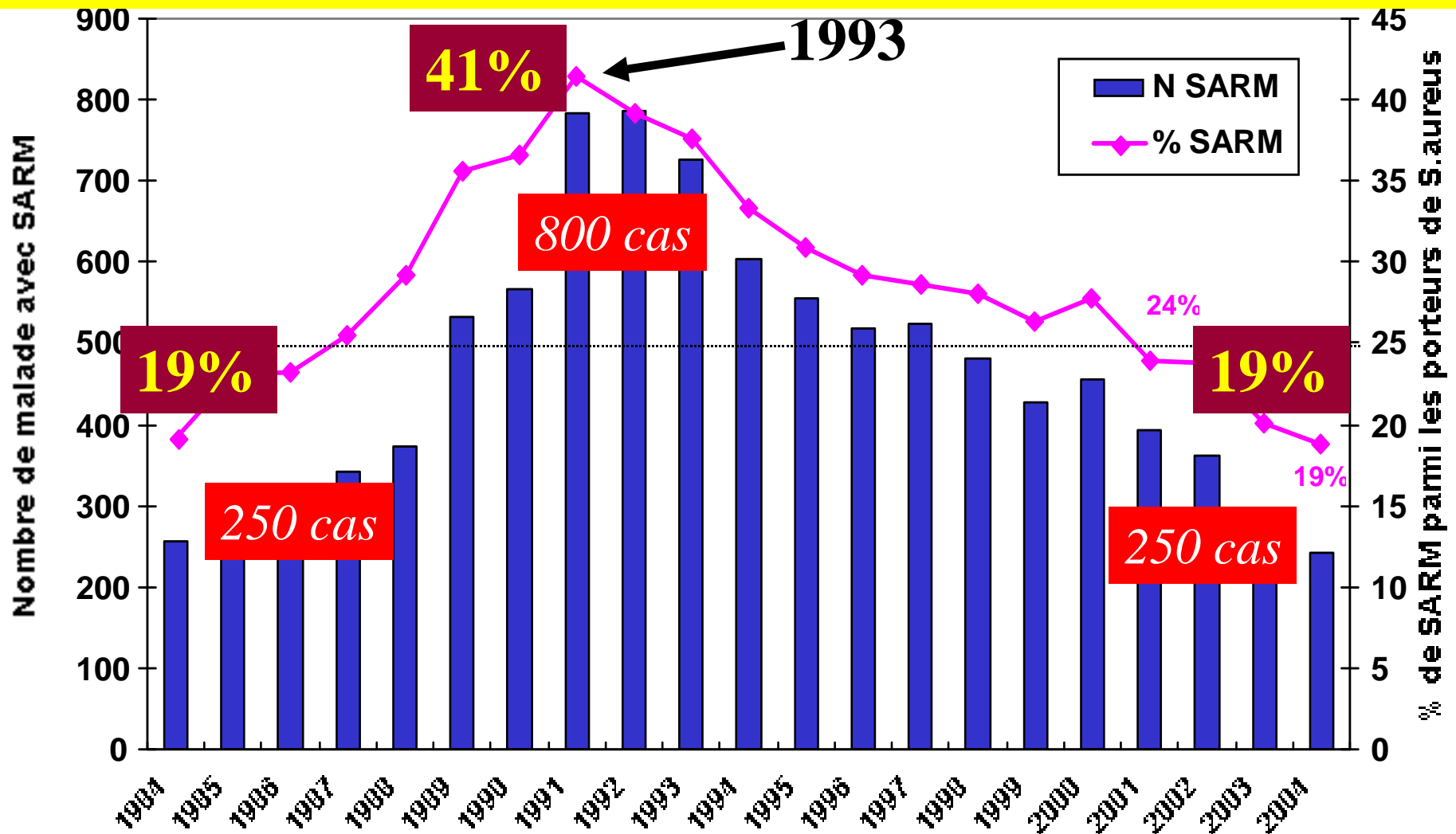


MRSA at the Pitié-Salpêtrière hospital in Paris (% in *S.aureus*, incidence rates) 1992-2007

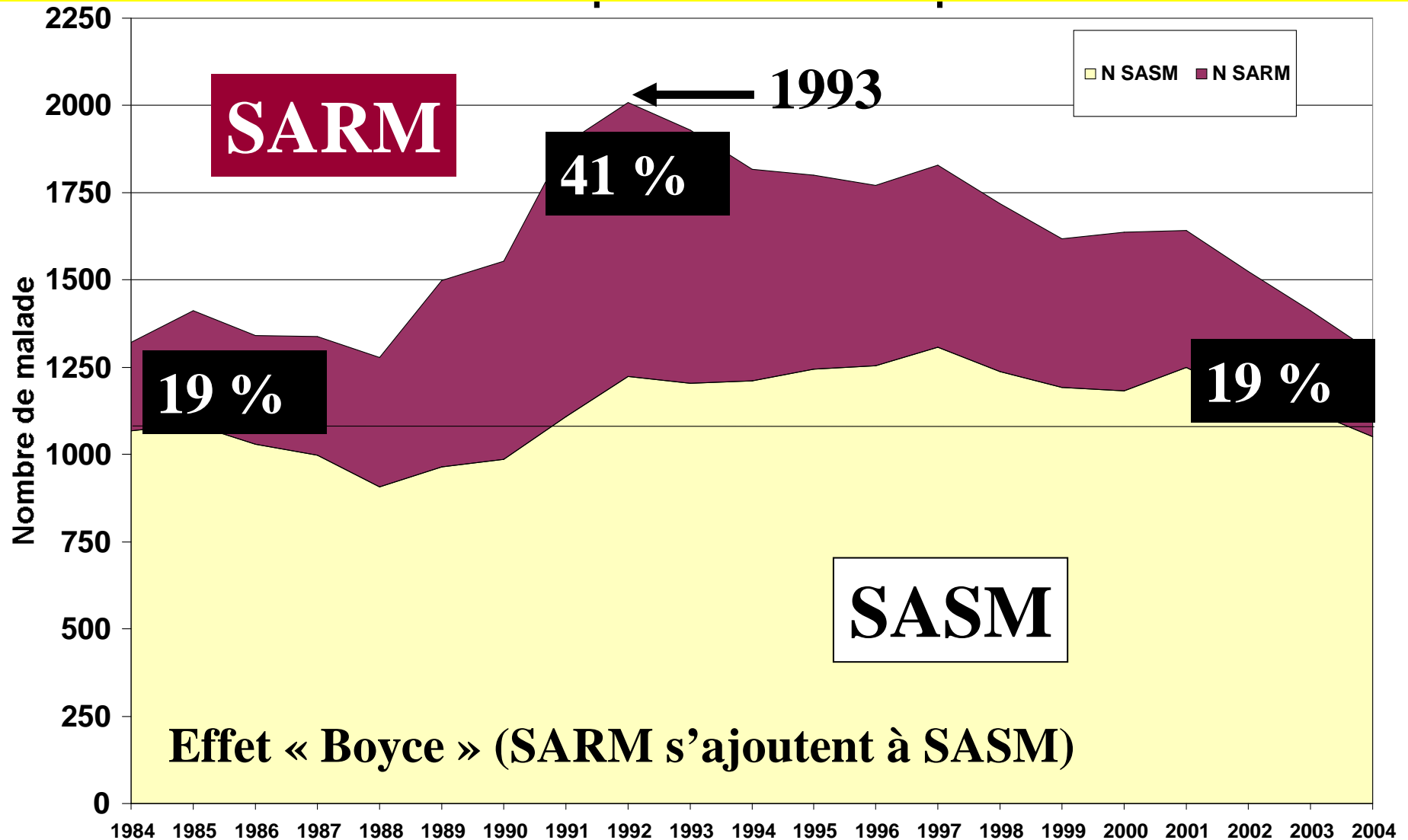
Evolution de *Staphylococcus aureus* résistant à la méticilline (SARM) à la Pitié-Salpêtrière - 1992-2007
(prélèvements à visée diagnostique)



SARM hôpital Pitié-Salpêtrière 1984-2004

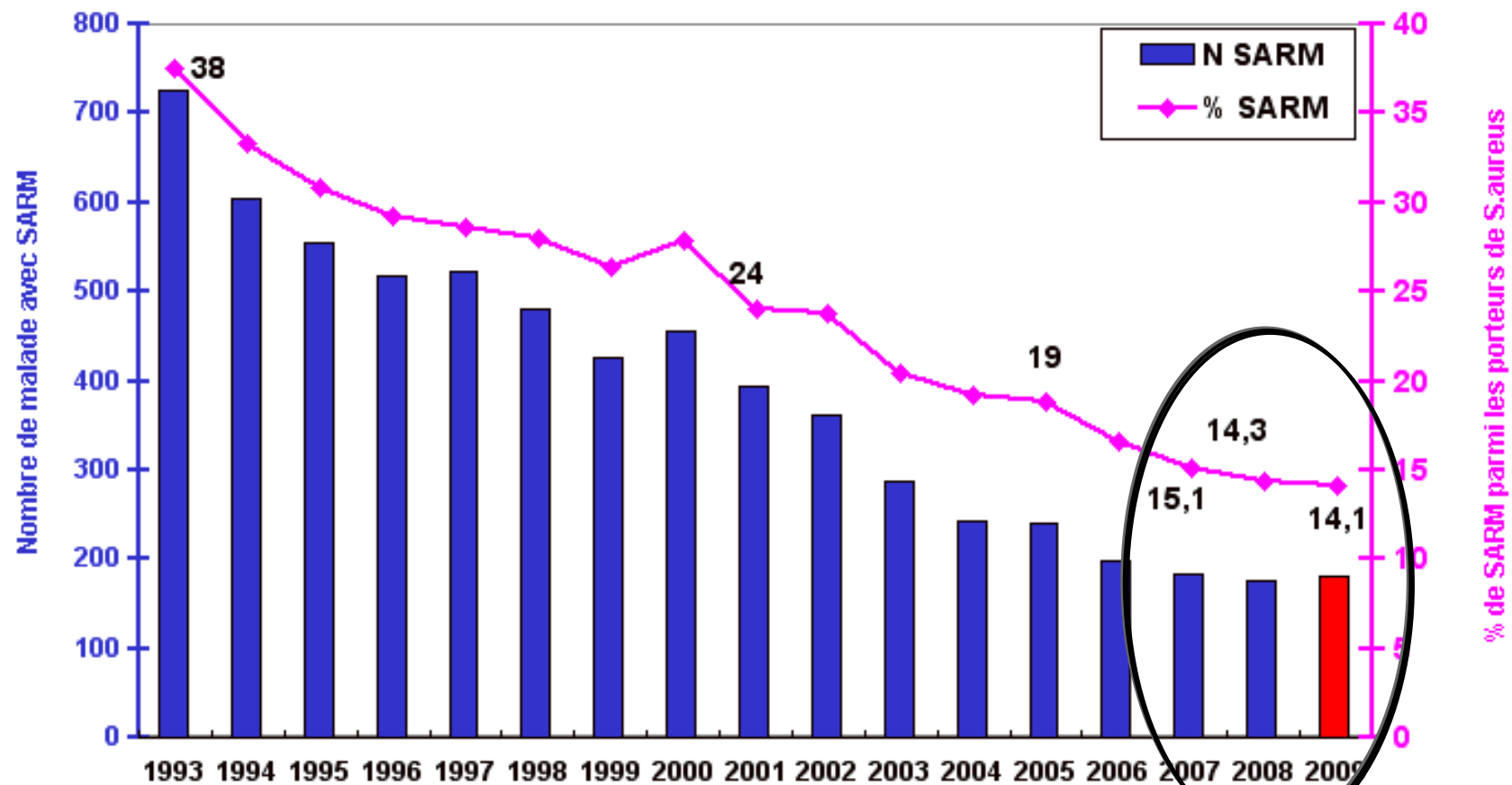


SARM hôpital Pitié-Salpêtrière 1984-2004



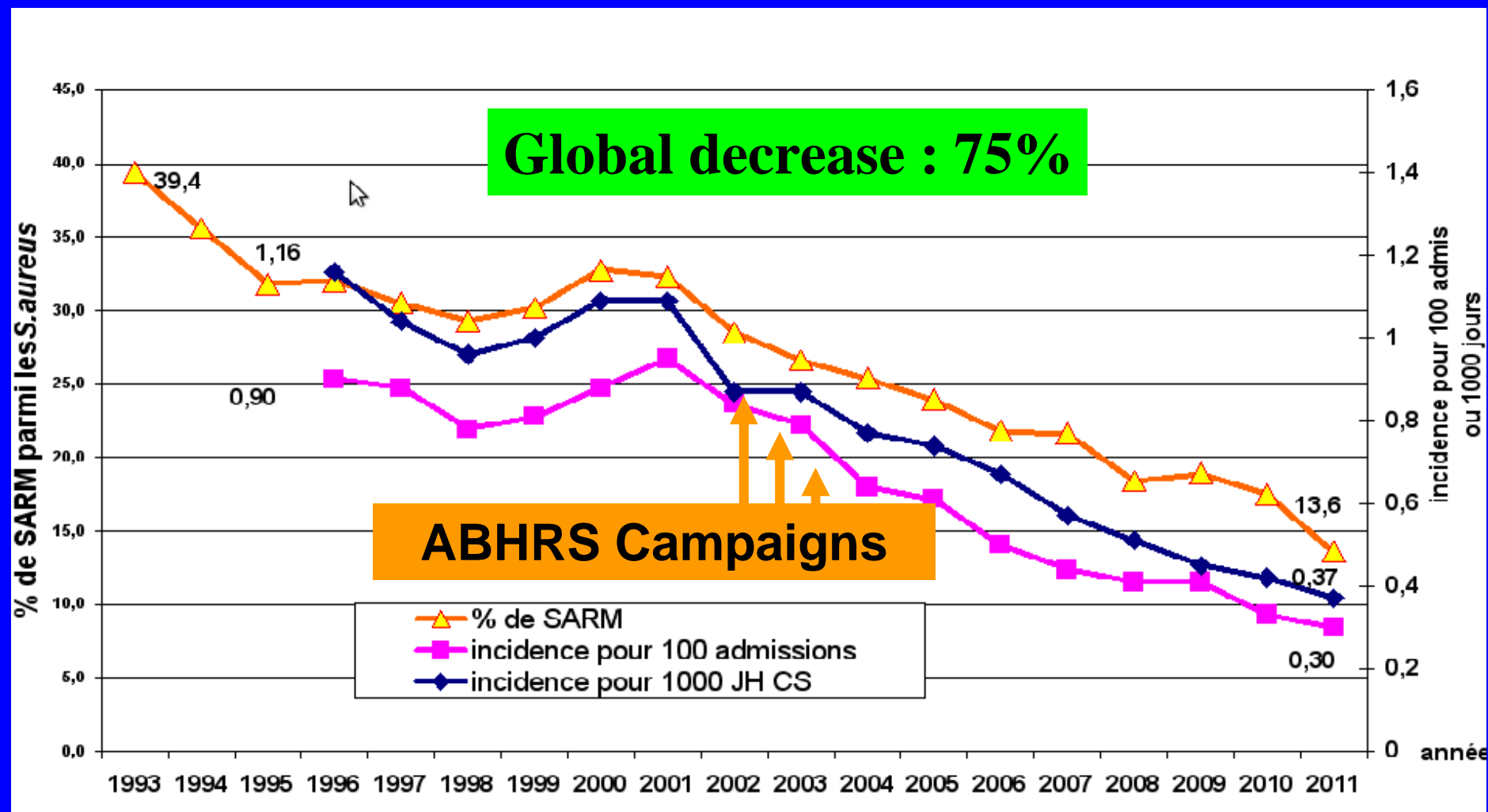
MRSA at Pitié-Salpêtrière hospital 1993-2009

Nombre et pourcentage de malades ayant une souche de *S. aureus* résistant à la méticilline (SARM) dans un prélèvement à visée diagnostique

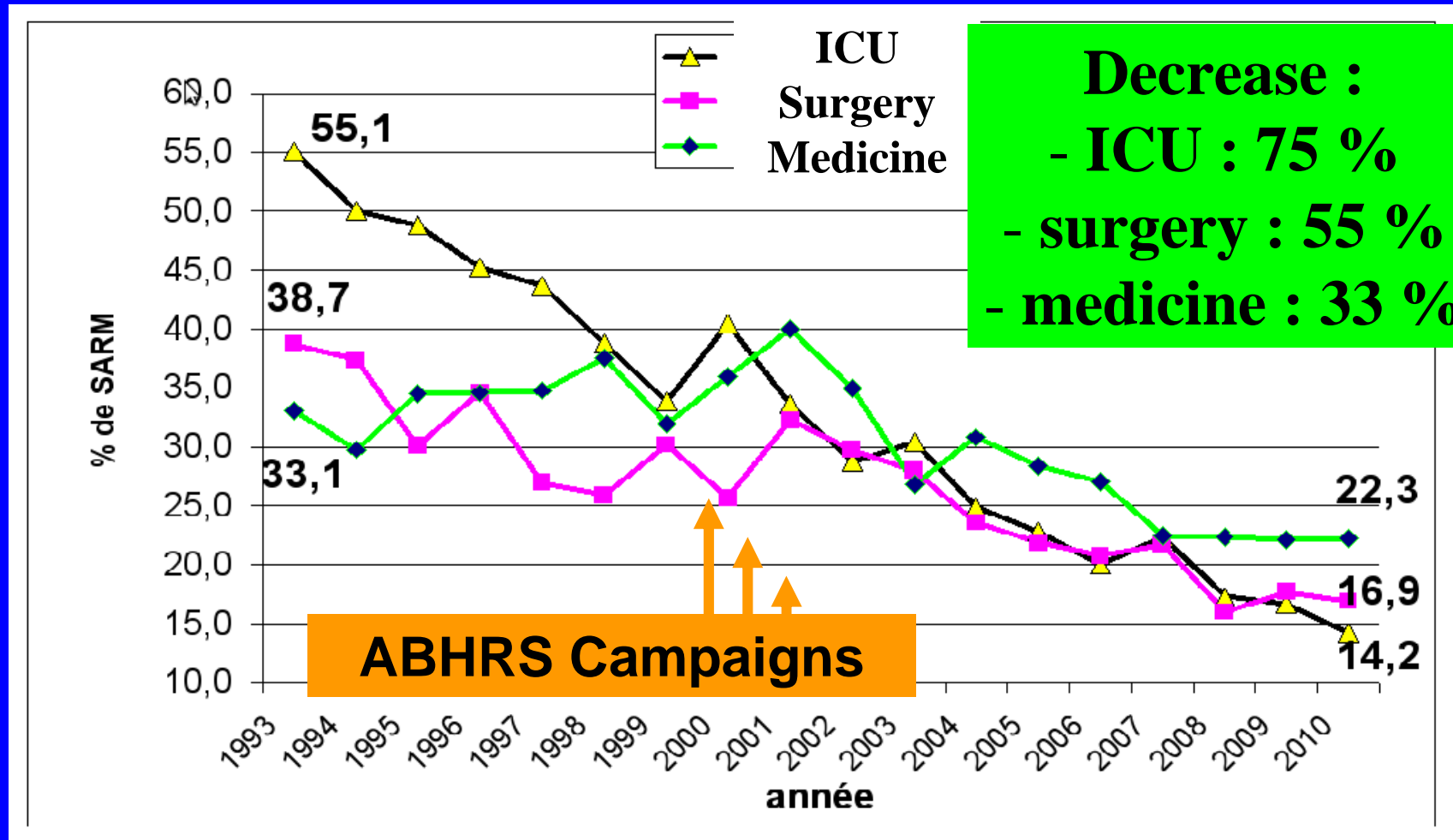


Regional level

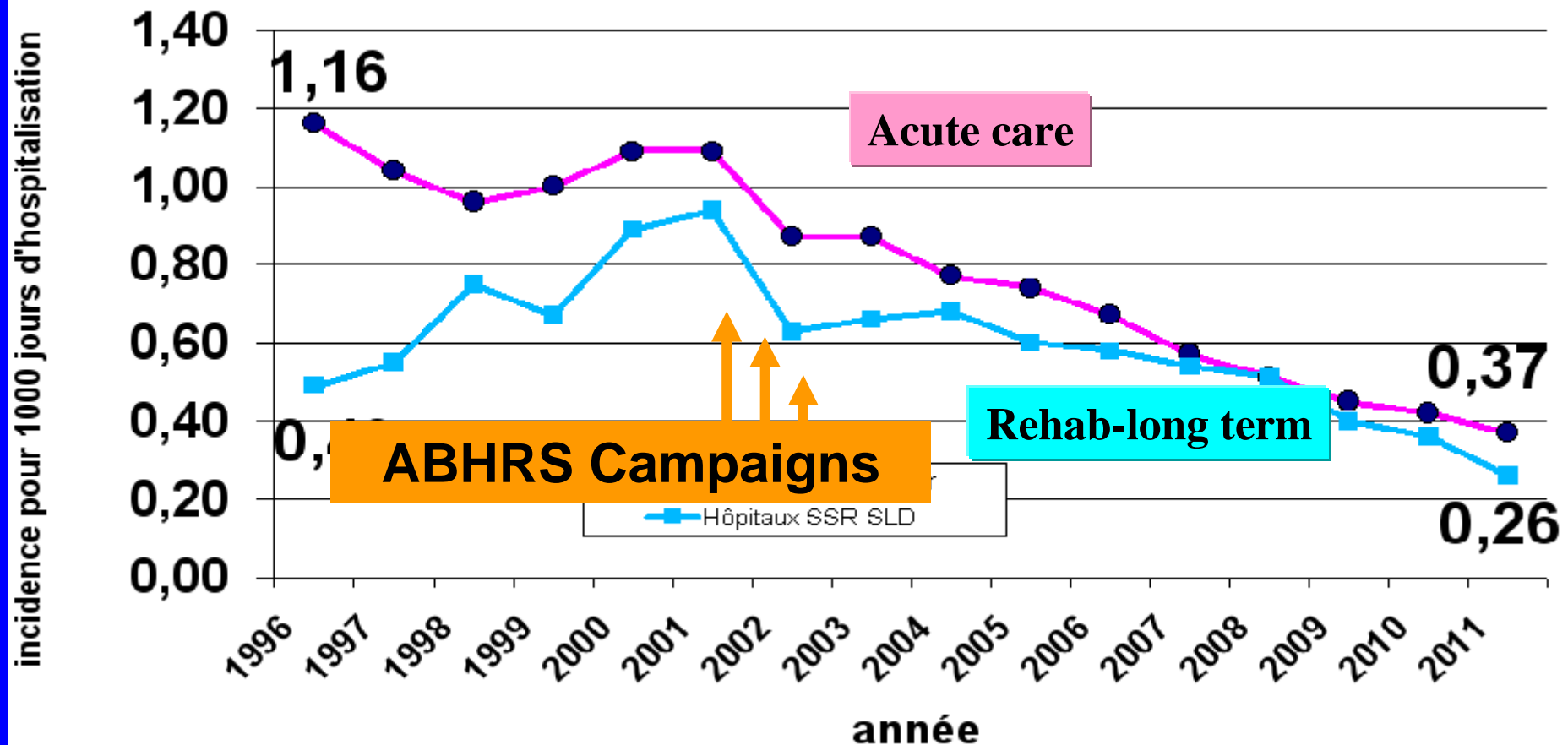
% MRSA in *S.aureus* and MRSA incidence Acute care hospitals of Paris area (AP-HP) (n=38) 1993-2011



% MRSA in *S. aureus* in acute care Acute care hospitals of Paris area (AP-HP) (n=38) 1993-2010



% MRSA in *S.aureus* in rehabilitation and long term care, hospitals of Paris area (AP-HP) (n=38) 1993-2010

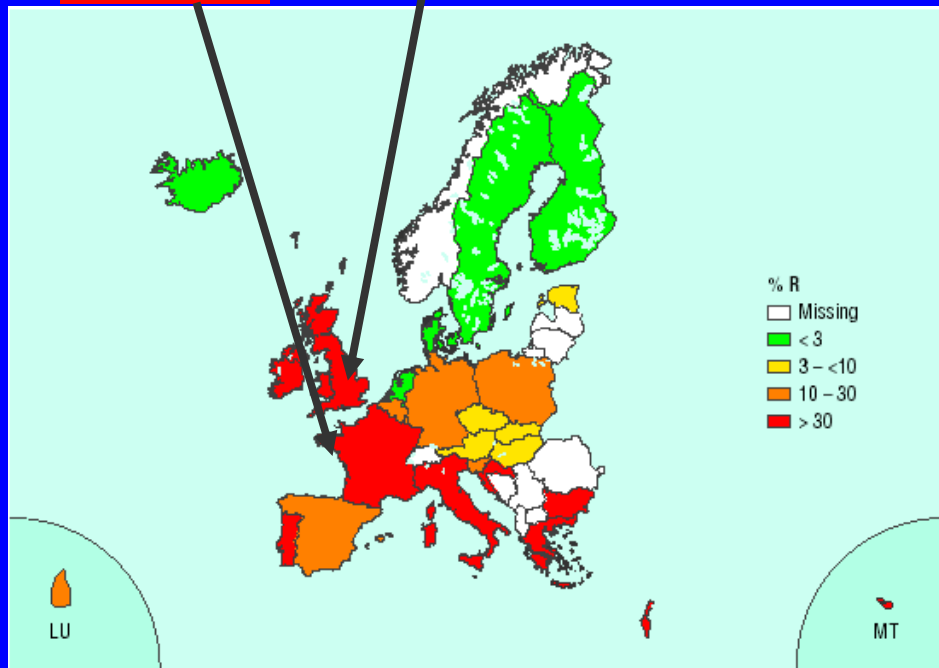


National level

MRSA in Europe (% in *S. aureus*) in bacteremias EARSS 2001-2011

33%

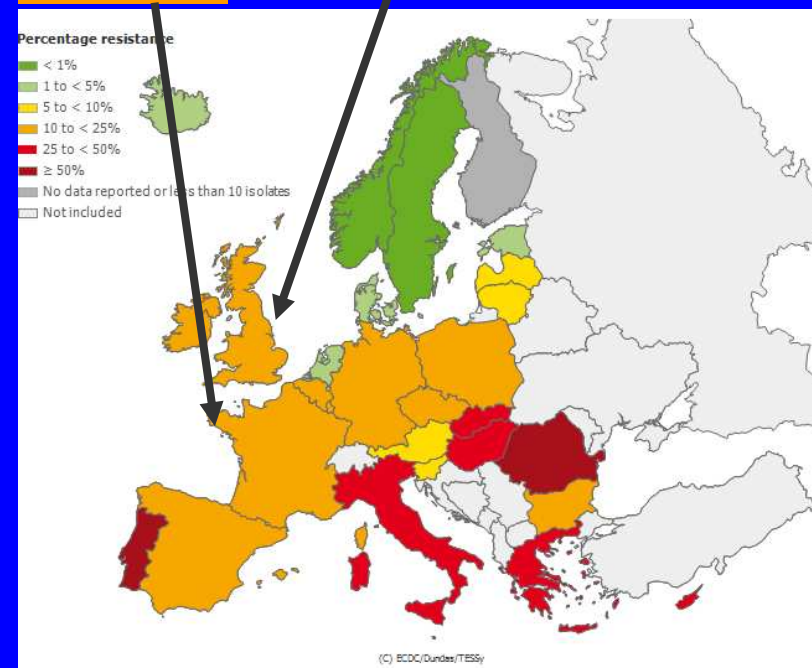
45%



2001

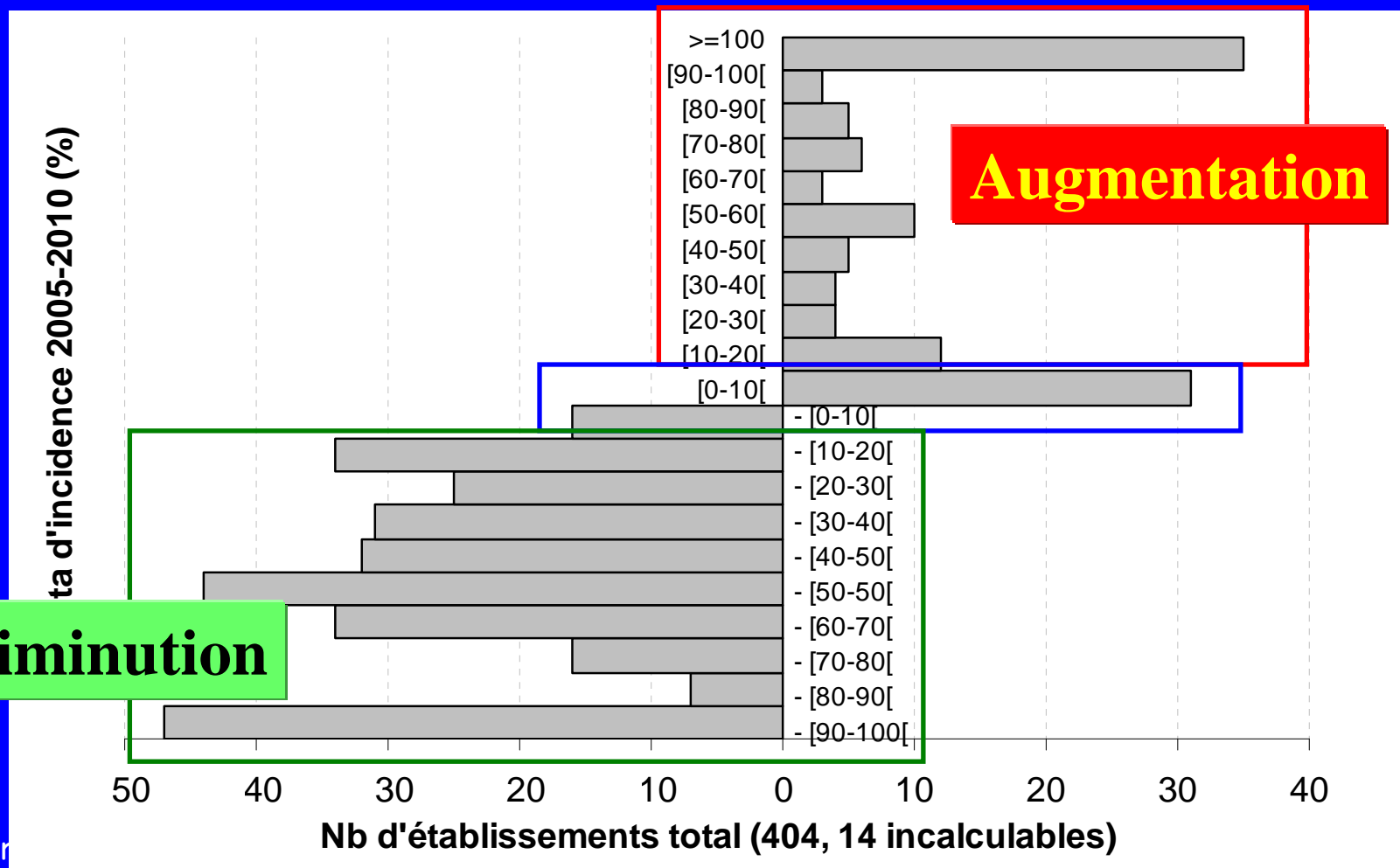
20%

14%



2011

Delta d'incidence des SARM par ES 2005-2010 (nb = 404)



Diminution

Augmentation

SARM dans les infections nosocomiales (enquêtes nationales prévalence IN France)

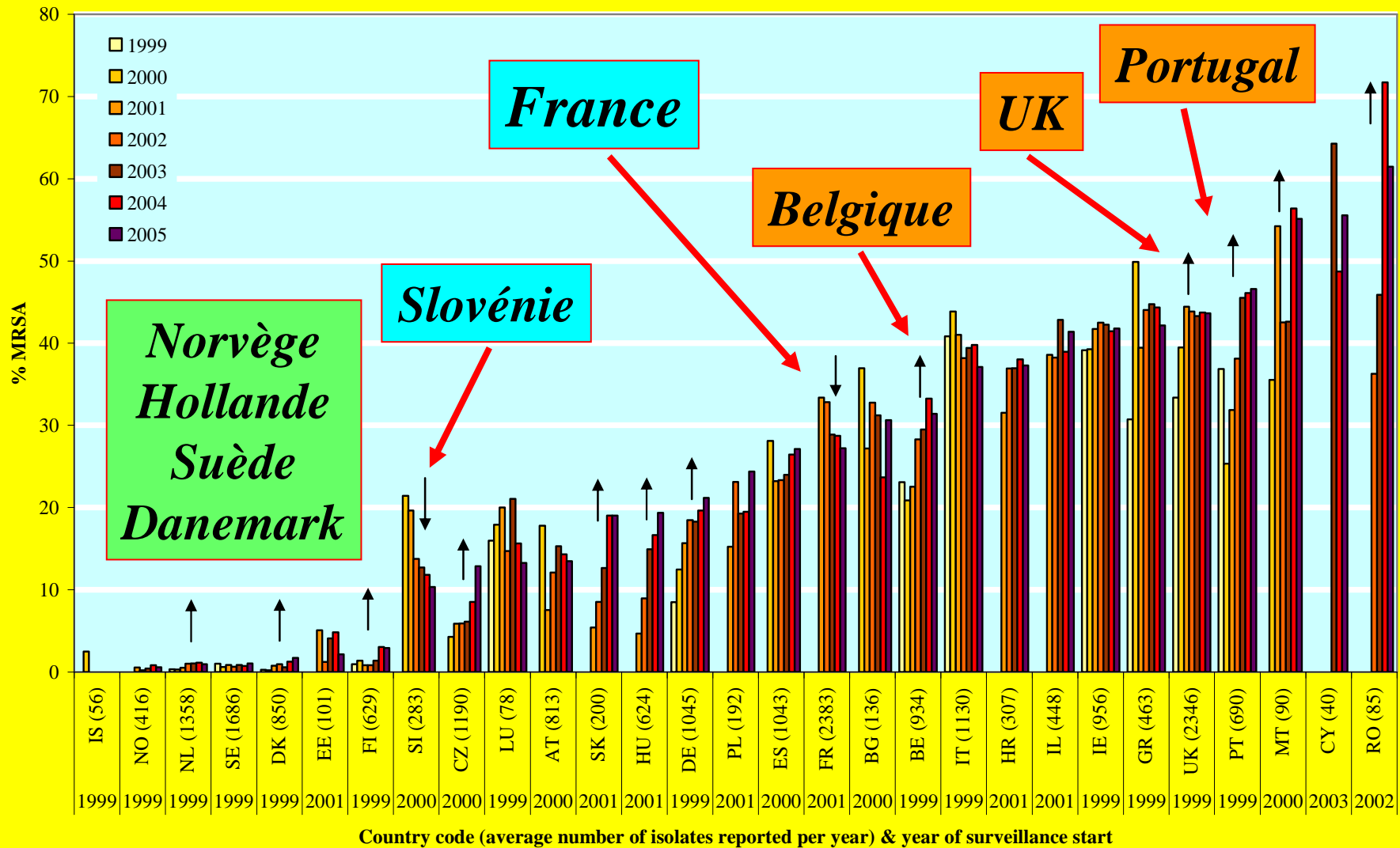
- **1996**
 - SARM chez S.aureus : **57 %**
 - Incidence infections SARM : 0,6 p. 100 admis
- **2001**
 - SARM chez S.aureus : **64 %**
 - Incidence infections SARM : 0,7 p. 100 admis
- **2006**
 - SARM chez S.aureus : **52 %**
 - Incidence infections SARM : 0,5 p. 100 admis

SARM en France en 2011

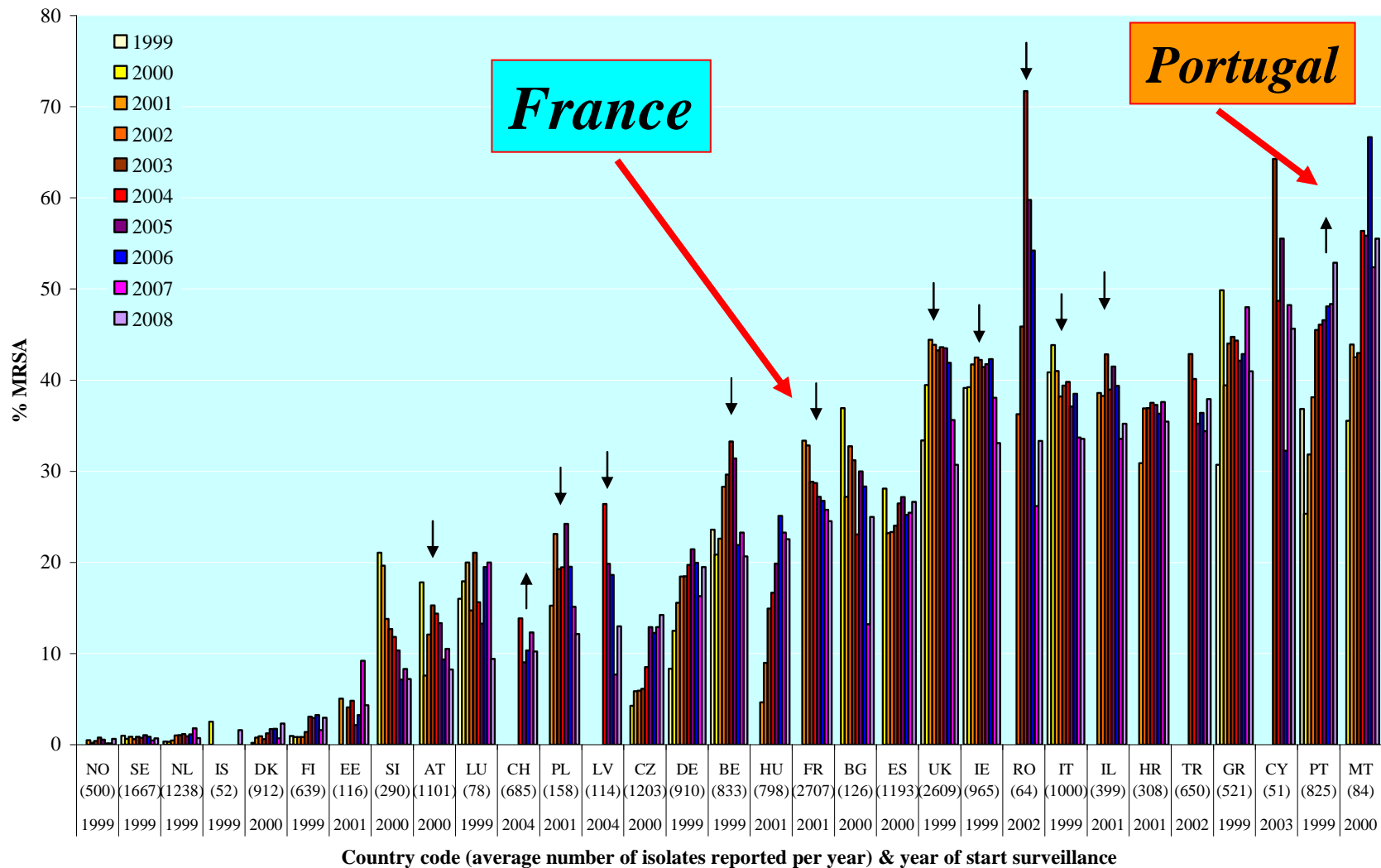
- Moyenne 0,4 cas / 1000 admissions
- Encore ~ 40 000 cas d'infections / an
- Encore ~ 4 000 bactériémies / an

In Europe ?

SARM dans les bactériémies en Europe (% chez *S.aureus*) EARSS : évolution 1999-2005



SARM dans les bactériémies en Europe (% chez *S.aureus*) EARSS : évolution 1999-2008



% MRSA in *S.aureus* in Europe Bacteremias, EARSS 2001-2011

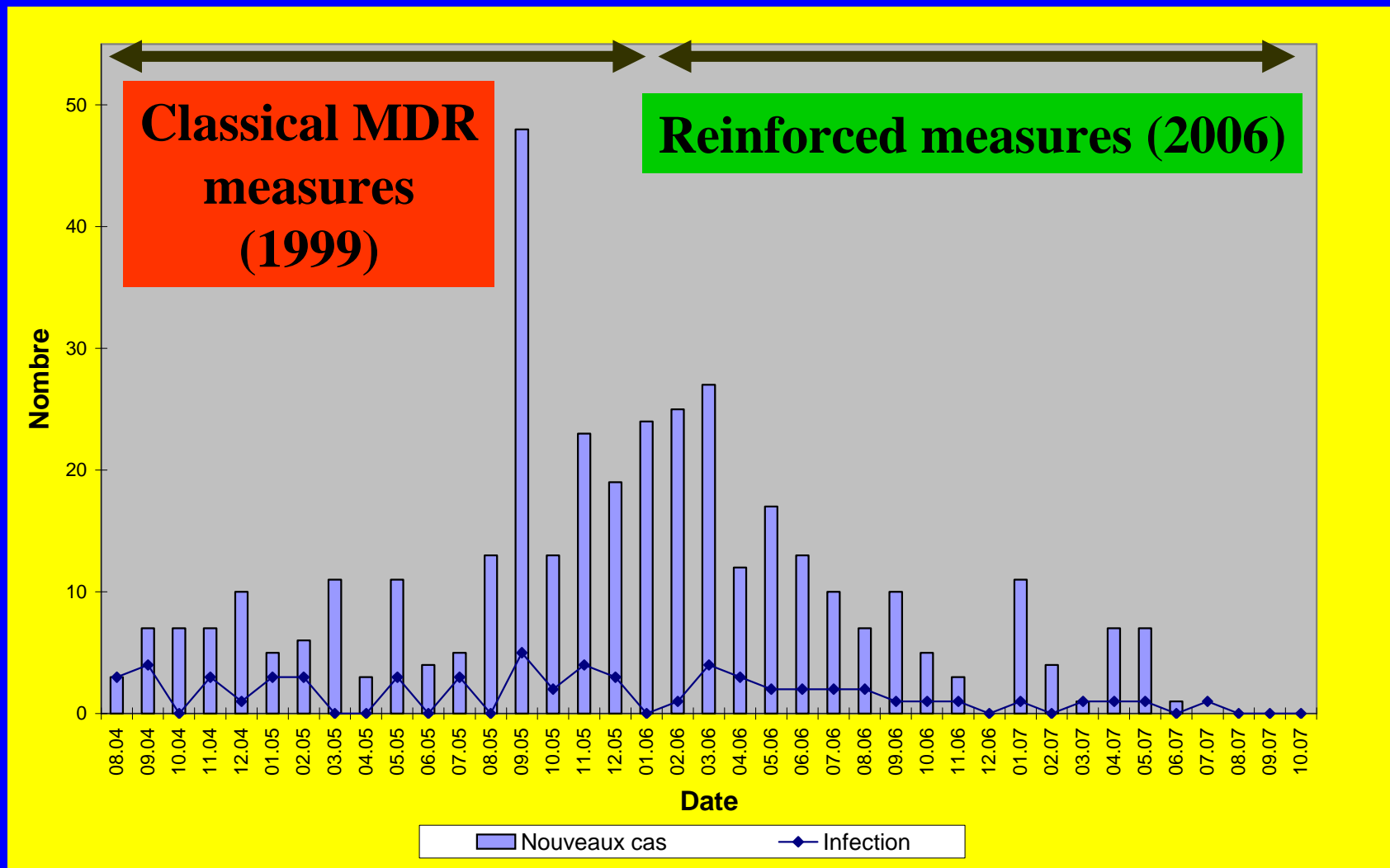
Country	~ number/year	% 2001	% 2011
Czek Rep	1500	6	15
Germany	1000-1900	17	16
Hungary	1000	5	26
Italy	1200-1500	41	38
Portugal	1000	32	55
Spain	1400-1900	23	23
Poland	150-800	15	24
Greece	350- 750	39	39

Control of "emerging" multiresistant bacteria in health care institutions

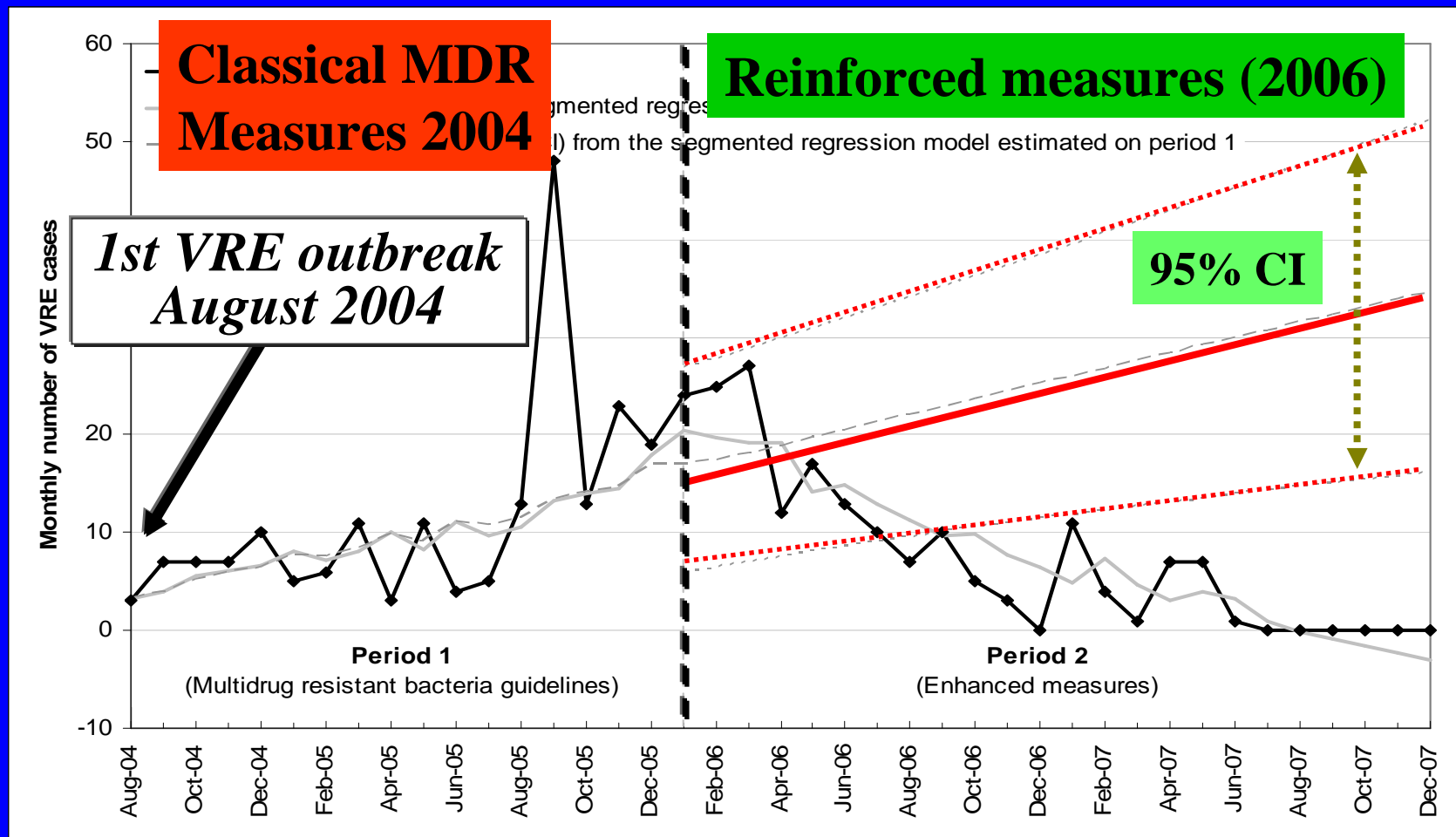
- Enterococci (VRE)
- Enterobacteria R to penems
 - Resistance genes
on mobile genetic elements
 - Digestive tract driven

VRE 2004-2010

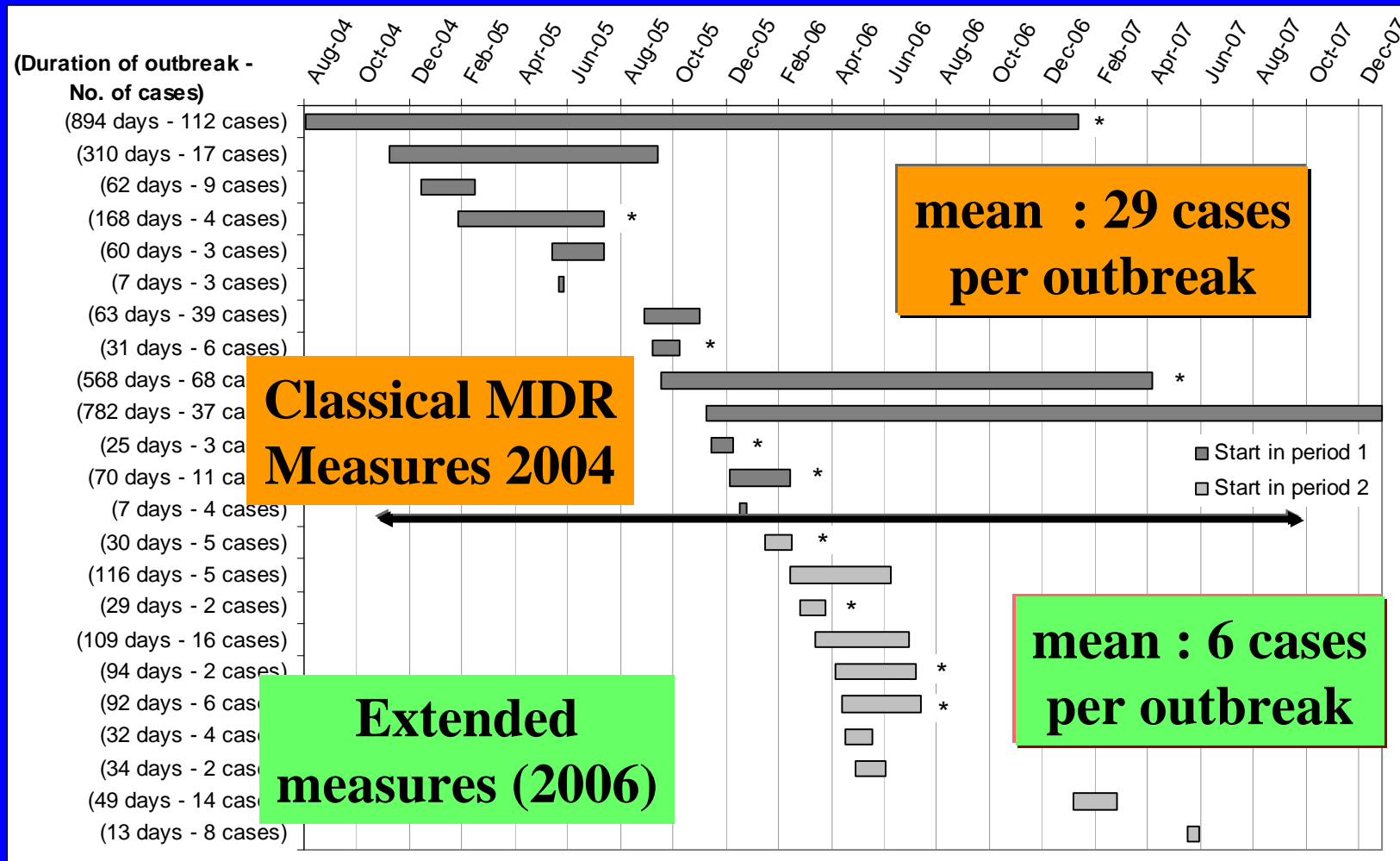
VRE cases per month 39 univ. hosp. Paris area (AP-HP) 2004-2007



VRE cases per month in the 38 hospitals of Paris area (AP-HP), time series analysis 2004-2007



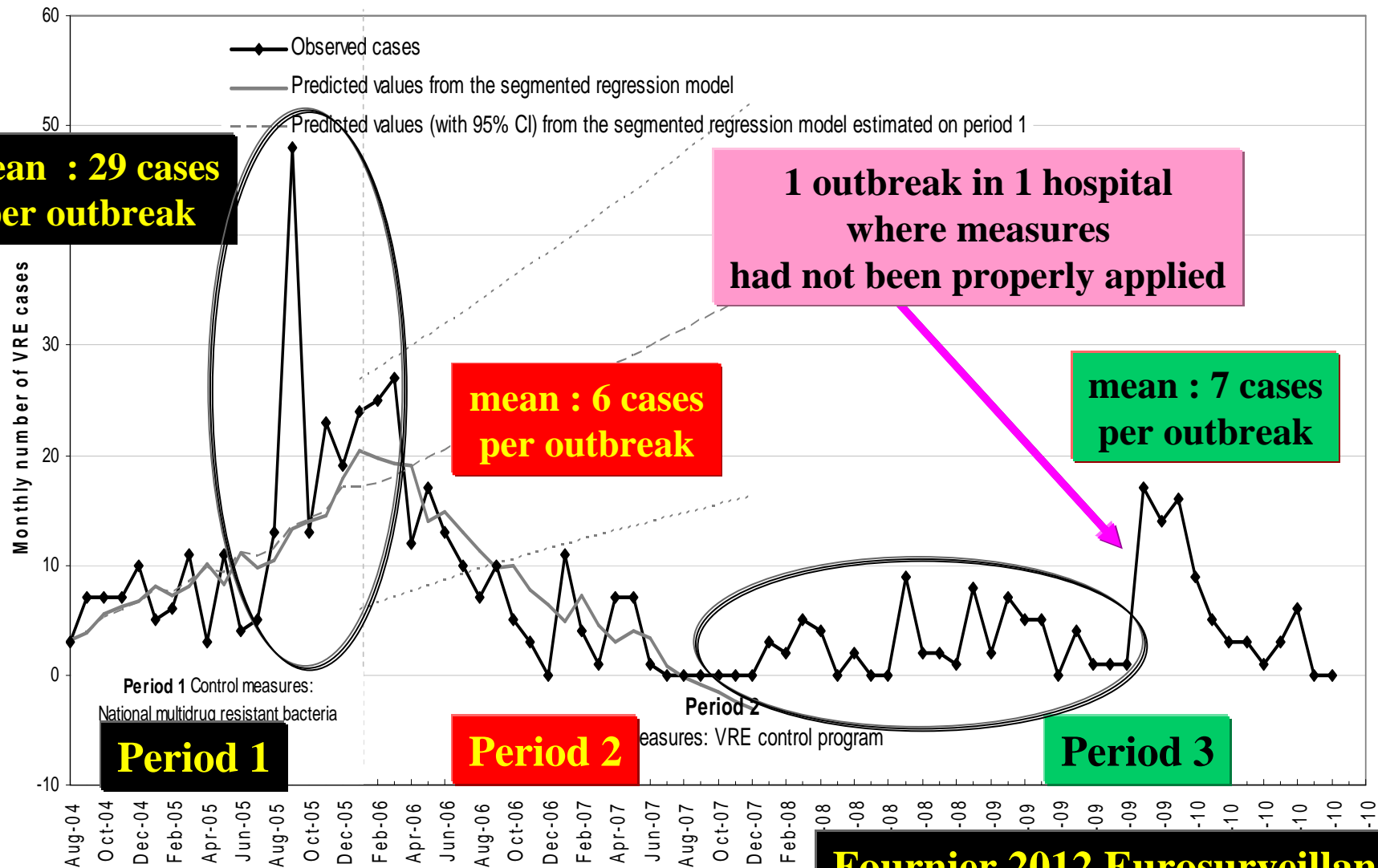
Length and size of VRE outbreaks in the 38 AP-HP hospitals 2004-2007



Mesures de contrôle « BMR émergentes » EOH-CLIN AP-HP 01/2006 - DGS 2006-2010

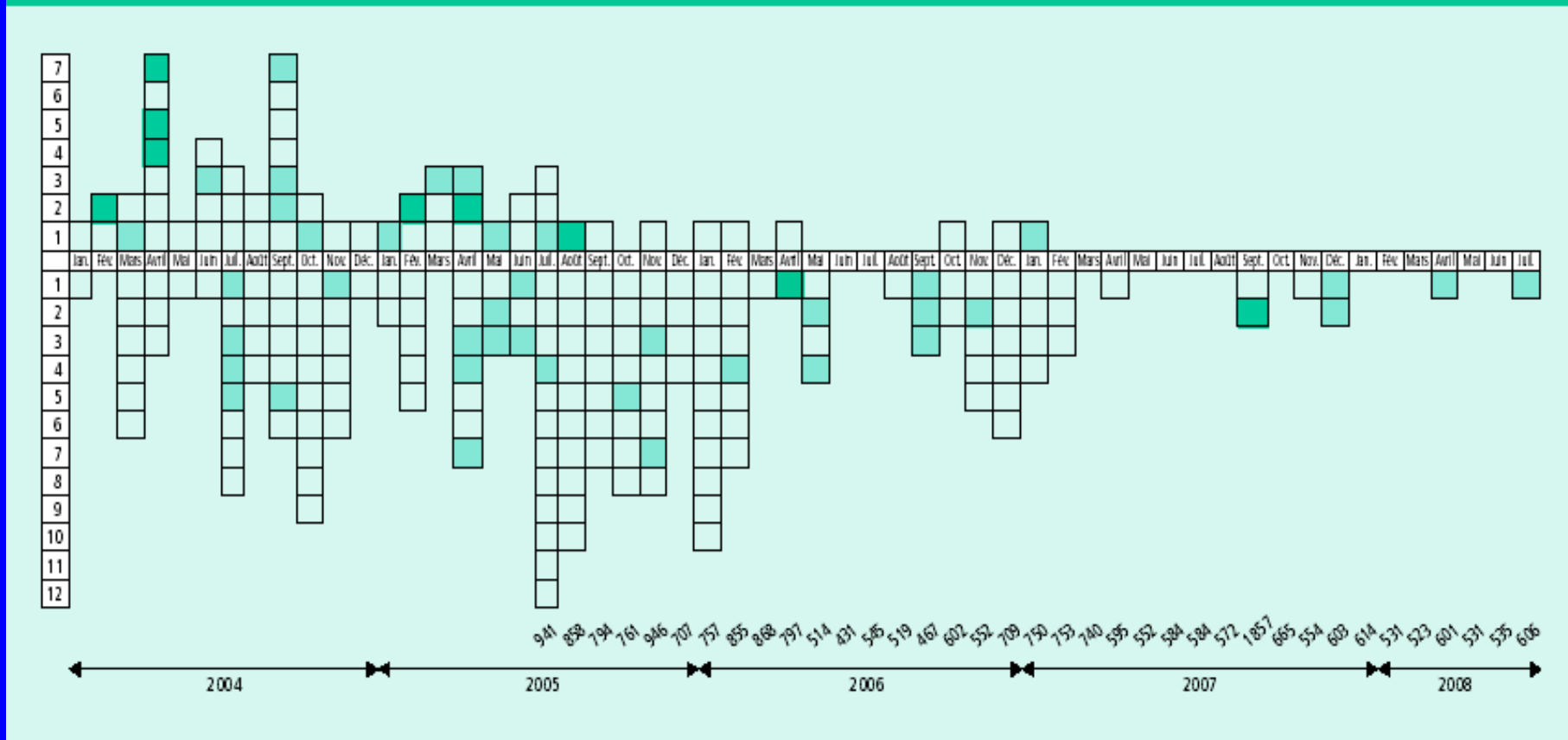
- Arrêter les transferts des patients porteurs et des patients contact
- Screening des patients contacts (1/semaine) jusqu'à leur sortie
- Sectoriser les patients avec du personnel dédié
 - Secteur des porteurs
 - Secteur des contacts
 - Secteur « indemne »
- Si pas personnel dédié : « marche en avant »
- Identifier les cas et les contacts sortis lors de leur réadmission
- Politique antibiotiques
- Signalement aux autorités sanitaires

Control of the 44 outbreaks of VRE in the 39 univ. Hosp. Paris area (AP-HP) 2004-2010



VRE cases per month Clermont Ferrand hospital (Auvergne) 2004-2008

Figure Patients colonisés par *Enterococcus faecium* résistant aux glycopeptides (ERG) et patients porteurs d'ERG de janvier 2004 à août 2007, France
 Figure Patients colonised by glycopeptides-resistant *Enterococcus faecium* (GRE) and patients carriers of GRE from January 2004 to August 2007, France

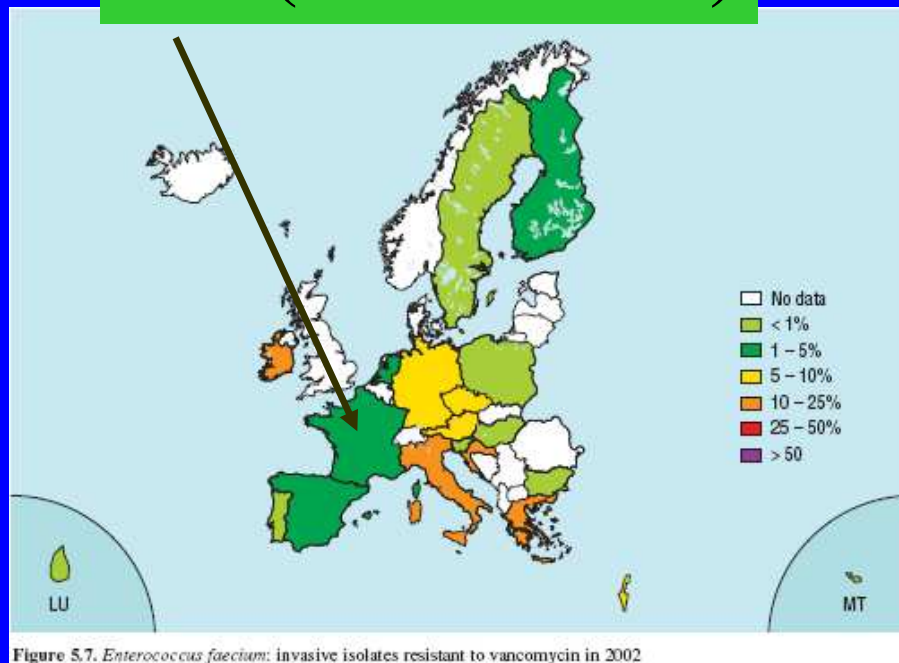


Link between MRSA and VRE rates in European countries Bacteremia EARSS 2011

	MRSA rate		
VRE rate	low	medium	high
low	5		3
medium	2	5	4
high			3

% VRE in *E. faecium* in bacteremias in Europe - EARSS 2002-11

2% (5% in 2004)



2002

1%



2011

EARSS-France résultats 2011

- *S.aureus* 2001-2011

SARM : 33% → 20% (20^{ème} → 15^{ème})

- *S.pneumoniae* 2001-2011

IR péni : 46% → 24% (26^{ème} → 24^{ème})

- *E.faecium* 2005-2011

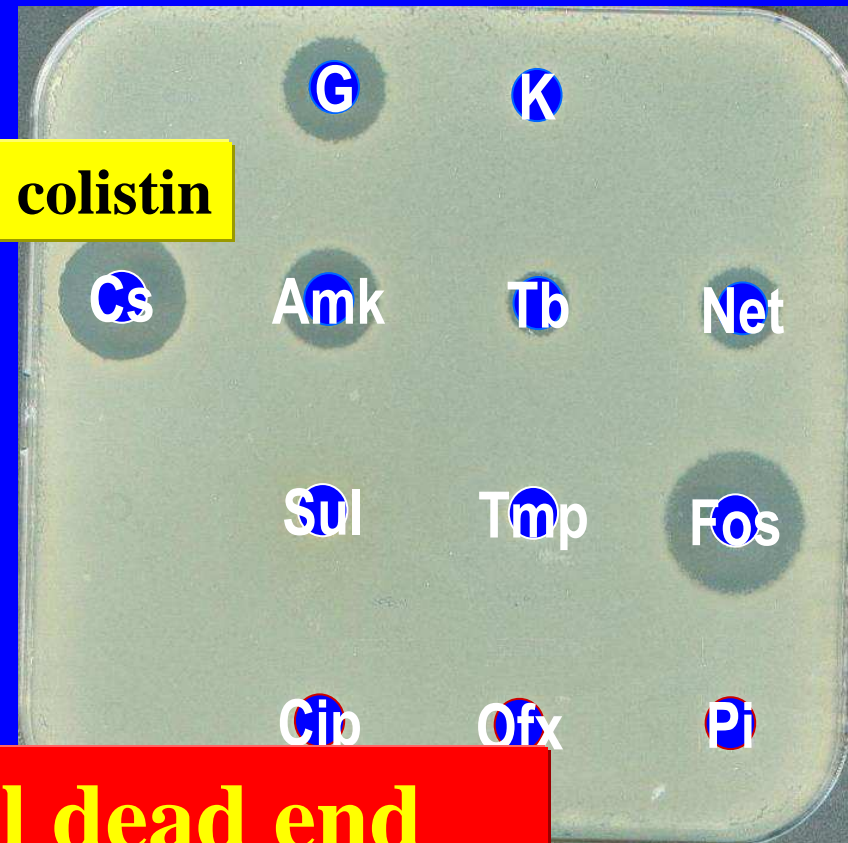
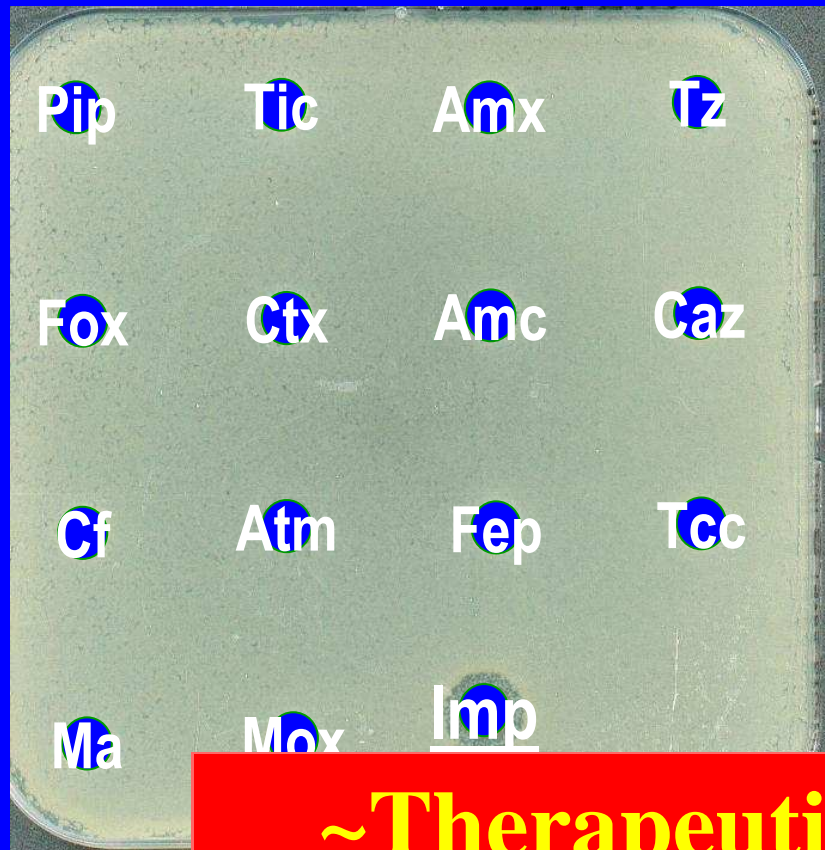
R vanco : reste ≤ 1% (avec 10 autres pays)

Enterobacteria carbapemense - producing :

first experience 2004

Paul Brousse hospital (Paris) 2004

Klebsiella pneumoniae VIM-1 + SHV-5
(index case : transfer from Athens)



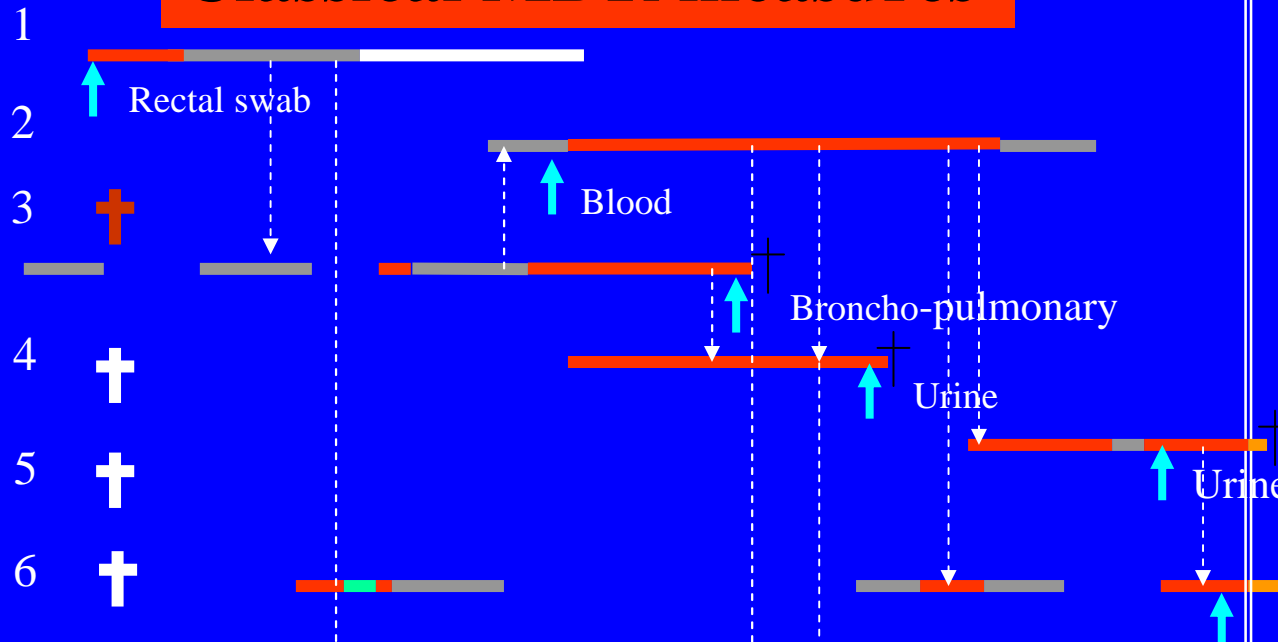
~Therapeutical dead end

MIC : imipenem 32 mg/l ; gentamicin 8 mg/l

Paul Brousse Hospital, 2004

December | January | February | March | April | May | June | July | August

Classical MDR measures



— ICU
— 4th floor
— 3rd floor
 VJarlier 2013
— Medicine unit

↑ First isolation of KP
+ No link + link

Kassis-Chikani
Eurosurveillance
2010

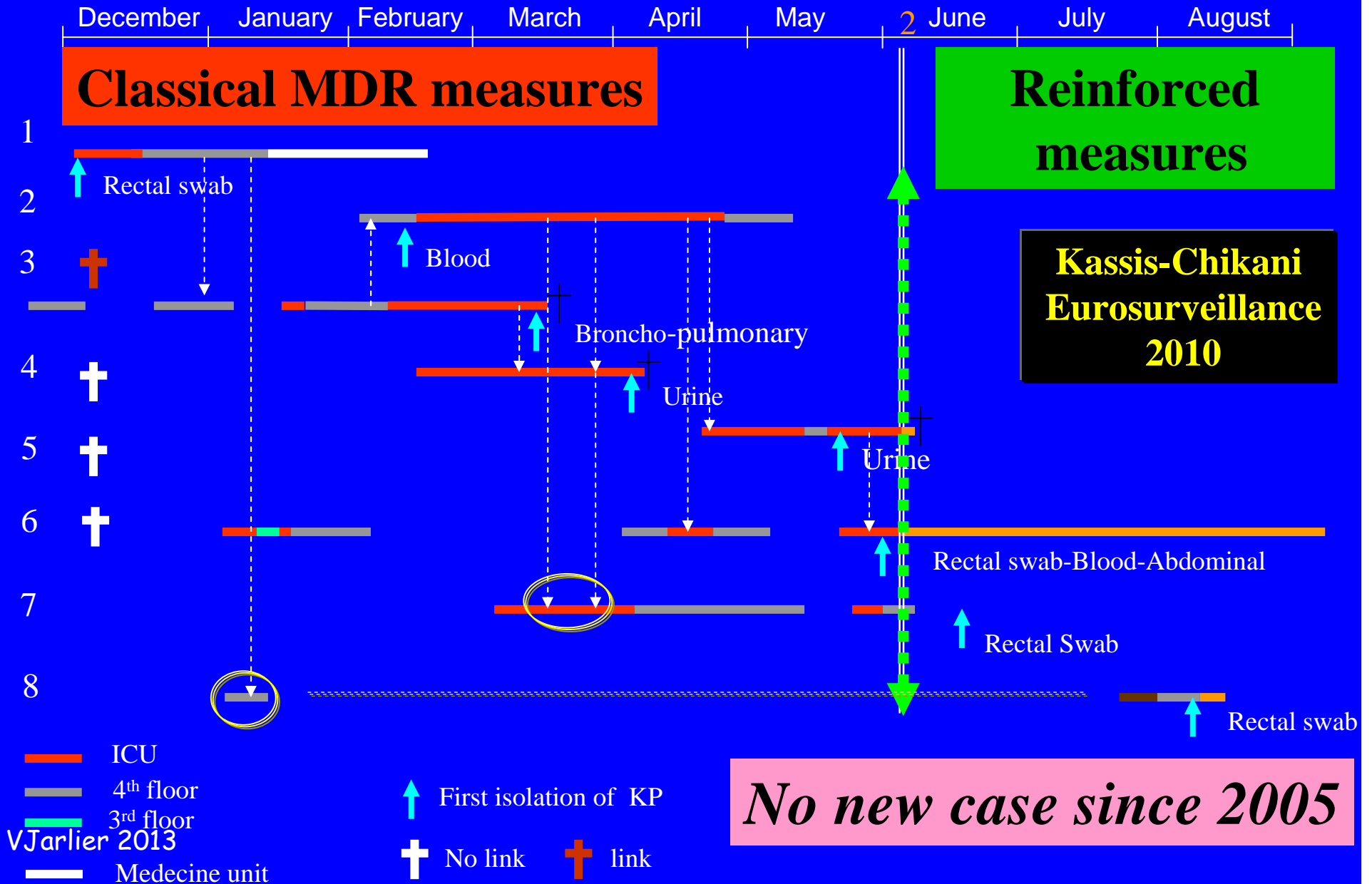
Reinforced control measures June 2004 (1)

- ICU divided in 2 distinct sections
 - 1 for CPE-Kp carriers
 - 1 for the new patients
- Conventional ward divided in 2 distinct sections :
 - 1 for contact patients (at risk to become carrier)
 - 1 for new patients (not at risk)
- Nurse staff dedicated to each section: cohorting

Reinforced control measures June 2004 (2)

- **Limit patient transfers** to other wards & care centers
- Screening all contact patients till discharge and **resume screening if readmitted**
- Inform contact patients who have been discharged at the beginning of the outbreak without being screened : letter to GPs, help line with 2 MDs during 2 weeks (MOH decision)

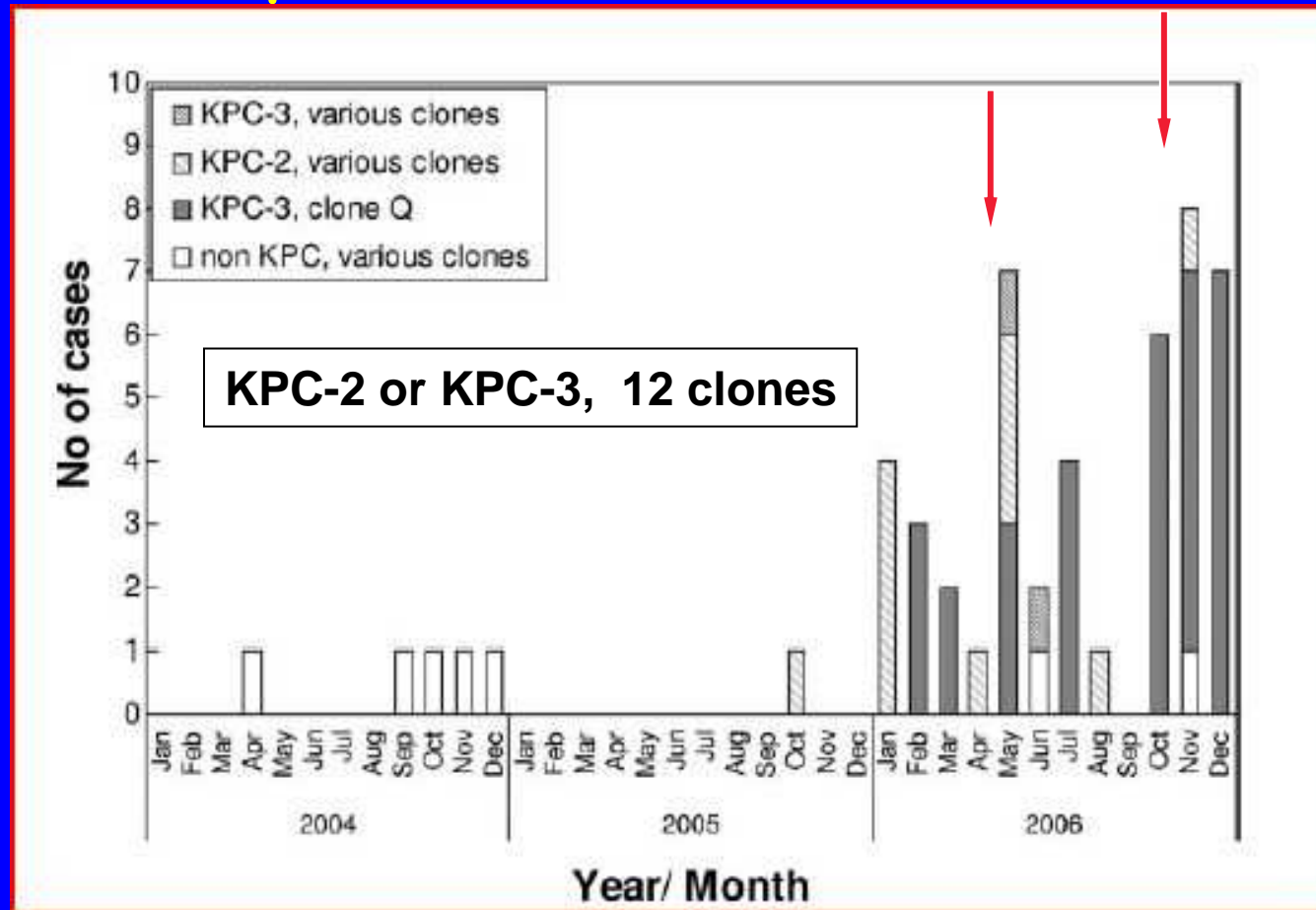
Paul Brousse hospital 2004



French national guidelines (MOH)
for emerging MDROs control
(VRE, CPE),
based on AP-HP experiences

2006, 2010
→ new edition 2013

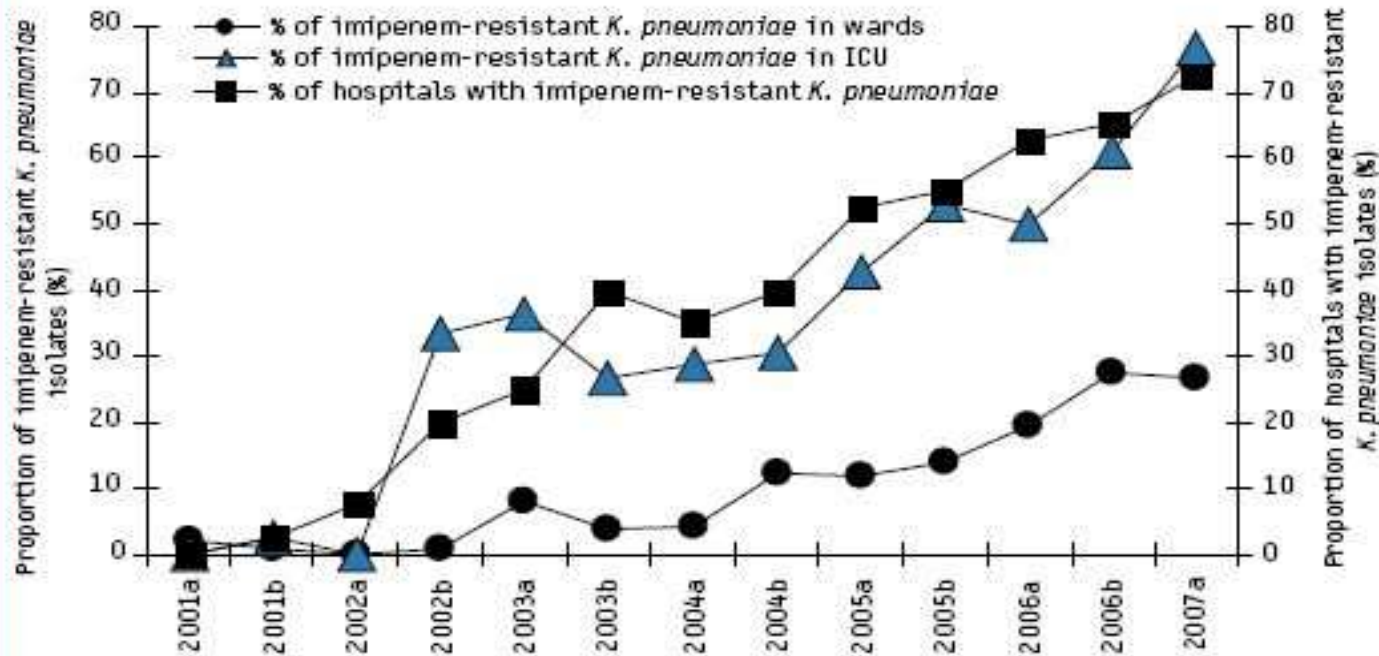
K.pneumoniae IMP-R in Tel Aviv hospitals (Israel) 2004-06



K.pneumoniae IMP-R in Greek hospitals 2001-07

FIGURE 2

Trends in proportion of imipenem-resistant *Klebsiella pneumoniae* isolates in hospitals in Greece, 2000-2006



Data from the Greek System for the Surveillance of Antimicrobial Resistance (<http://www.mednet.gr/whonet>)

As soon as identification of the 1st case (expedite this identification)

- Isolate the patient in a single bedroom
- Alert hospital direction & Infection control team
- Stop transfers of case & contact patients to other units or hospitals for containing spread
- Screen contact patients till discharge

The two days following the identification

- Identify contact patients who have been already transferred at the time of detection of the index case
- Screen them
- Re-enforce hand hygiene (ABHRS)
- Identify antibiotics that could be used in case of serious infection with the strain

During the entire period of the outbreak

- Cohort patients in 3 distinct sections with dedicated staff
 - case patients (« **case section** »)
 - contact patients ("**contact patient section** ")
 - newly admitted patients ("**free section** ")
- Screen 1/week all contact patients till discharge
- after 3 neg. screenings, contact patients can be transferred
but continue to isolate and screen them
- Strengthen survey of contact patients if receiving antibiotics
- Restrict antibiotics use
- Set up an information system allowing to identify cases and contact patients if re-admitted

Control of a KP-KPC2 outbreak in 7 hospitals September-December 2009

- 1 source case (from Greece)
- 7 2ary cases linked with duodenoscopy
- 5 2ary cases linked with cross-transmission through care

Total : 13 cases

Haute-Normandie

Ile-de-France

Centre

Screened contacts : 341

A: 87

B: 208

C: 25

D: no contact

E: no contact

F: 3

G: 18

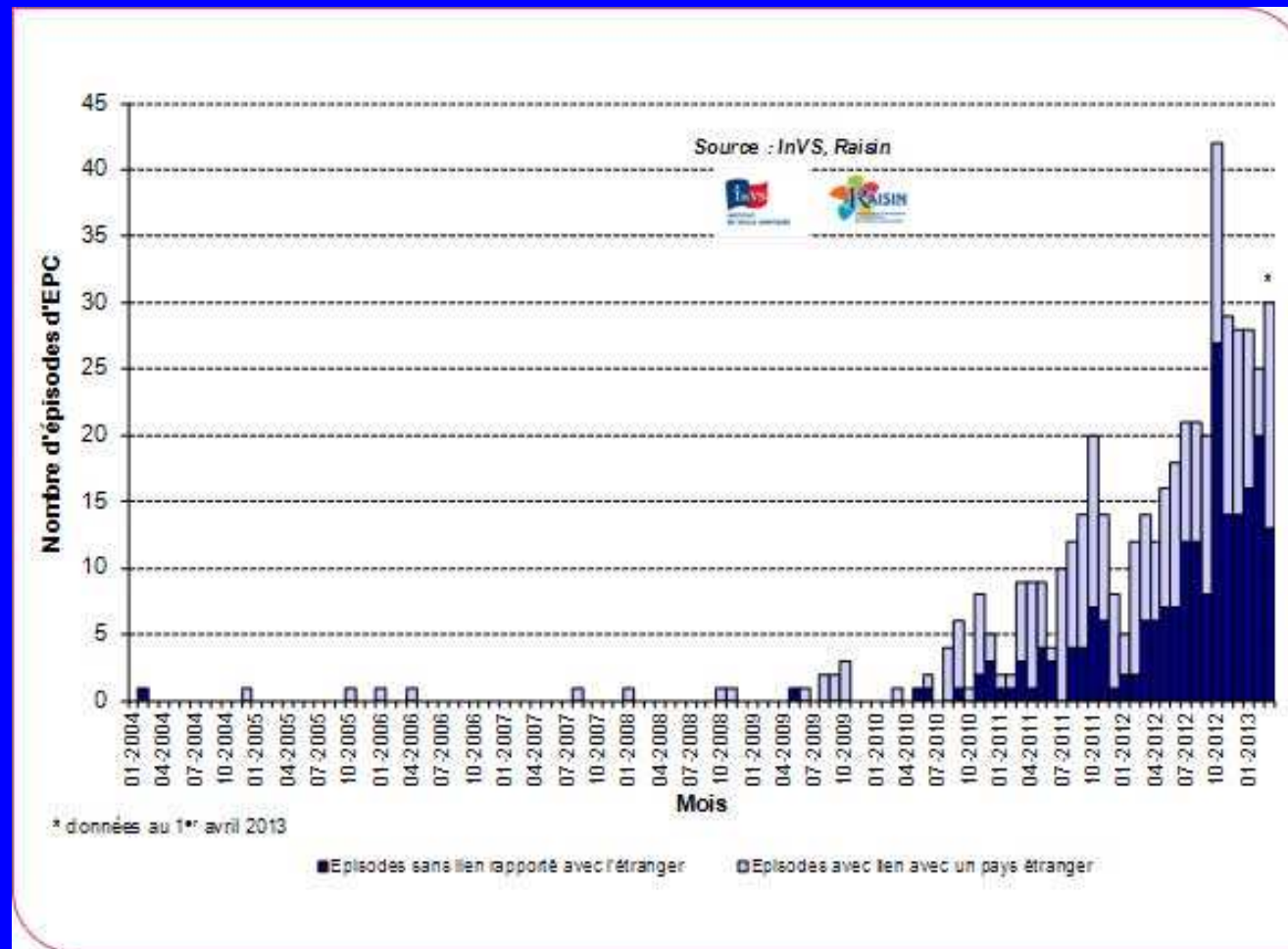
No new case since December 2009

- Transfer of case
- Hospitals where cross-transmission
- Hospitals where cases were transferred (no further cross-transmission)

Carbonne
Eurosurveillance
2010

CPE episodes in France :
a programme
for exhaustive survey at
national level
(2004-2013)

Nombre d'épisodes impliquant des EPC en France signalés à l'InVS entre janvier 2004 et le 1er avril 2013, (N=482).



Distribution (%) of EPC cases France 2004-13 (n = 482)

<i>Kpneumoniae</i>	60	OXA-48	67	Paris – Nord	61
<i>Ecoli</i>	21	KPC	14	Sud-Est	26
<i>E.cloacae</i>	11	NDM	12	Est	5
<i>Citrobacter</i>	3	VIM	6	Sud-Ouest	5
<i>E.aerogenes</i>	2	IMI	<1	Ouest	4
autres	2	autres	<1		

Controlling further CPE

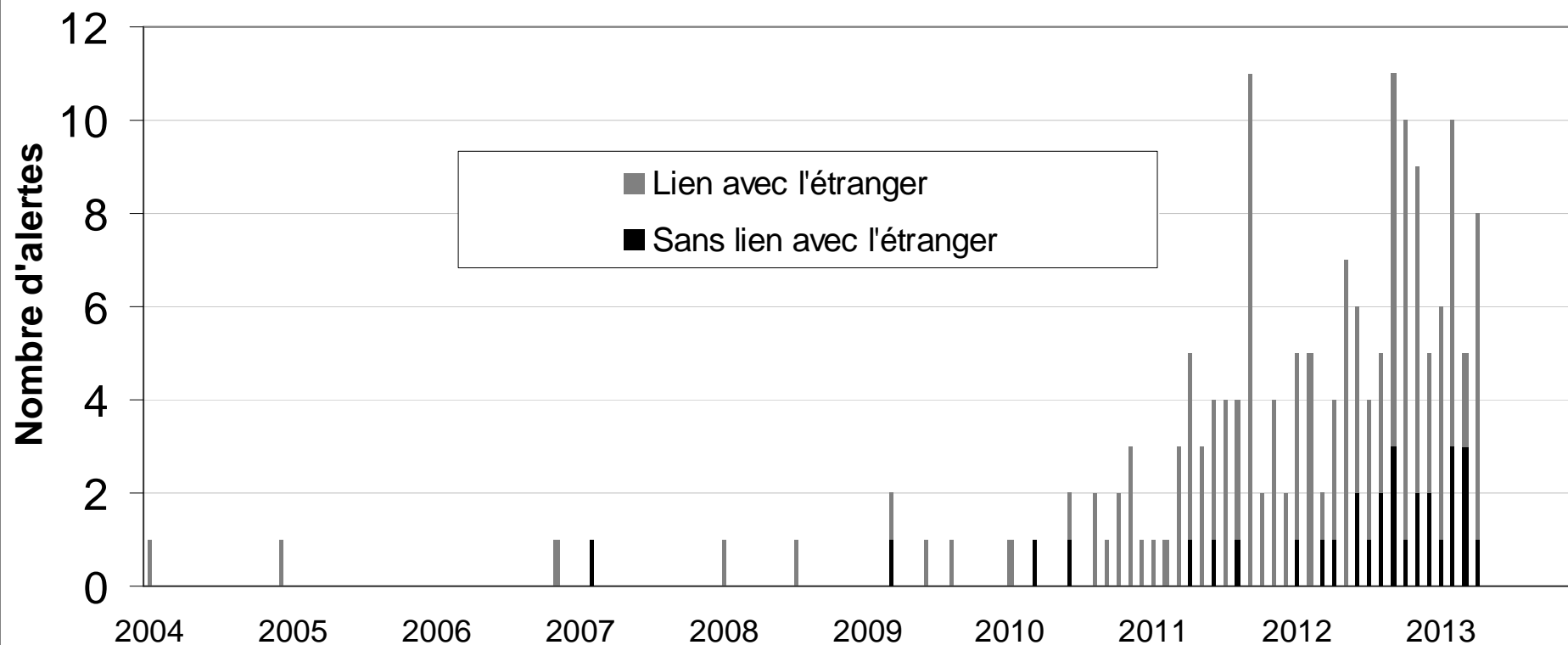
in the 38 hospitals of Paris area (AP-HP)
applying the "Emerging MDRO control national
guidelines"

- . Long lasting institutional infection control and antibiotic stewardship programme
- . Central infection control team (4 persons) following up all CPE (and VRE) episodes and helping local infection control teams to implement guidelines

EPC à l'APHP : nombre mensuel de signalements

2004- avril 2013 N=169

- **Lien étranger : 82% (2012: 78%, 2013: 72%)**
 - Grèce, Maghreb, Portugal, Inde ...
 - Rapatriés 59%
 - Hospitalisation 19%
 - Séjour 14%



**AP-HP recommendations to isolate and screen
for emerging MDROs (VRE, CPE) patients
transferred from hospitals of foreign countries:
October 2008**

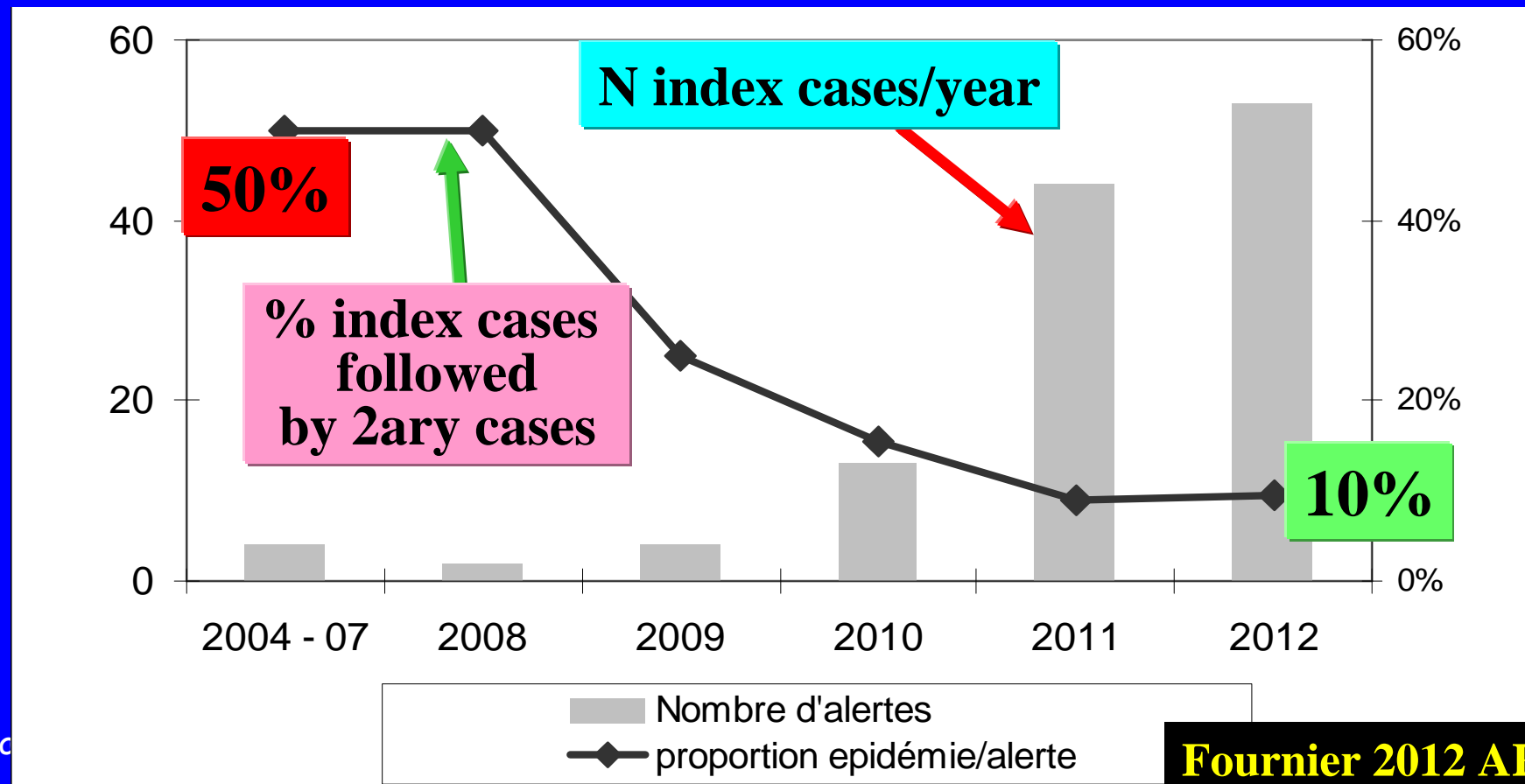


**Patient en provenance d'un hôpital d'un pays
à prévalence élevée de BMR émergentes**

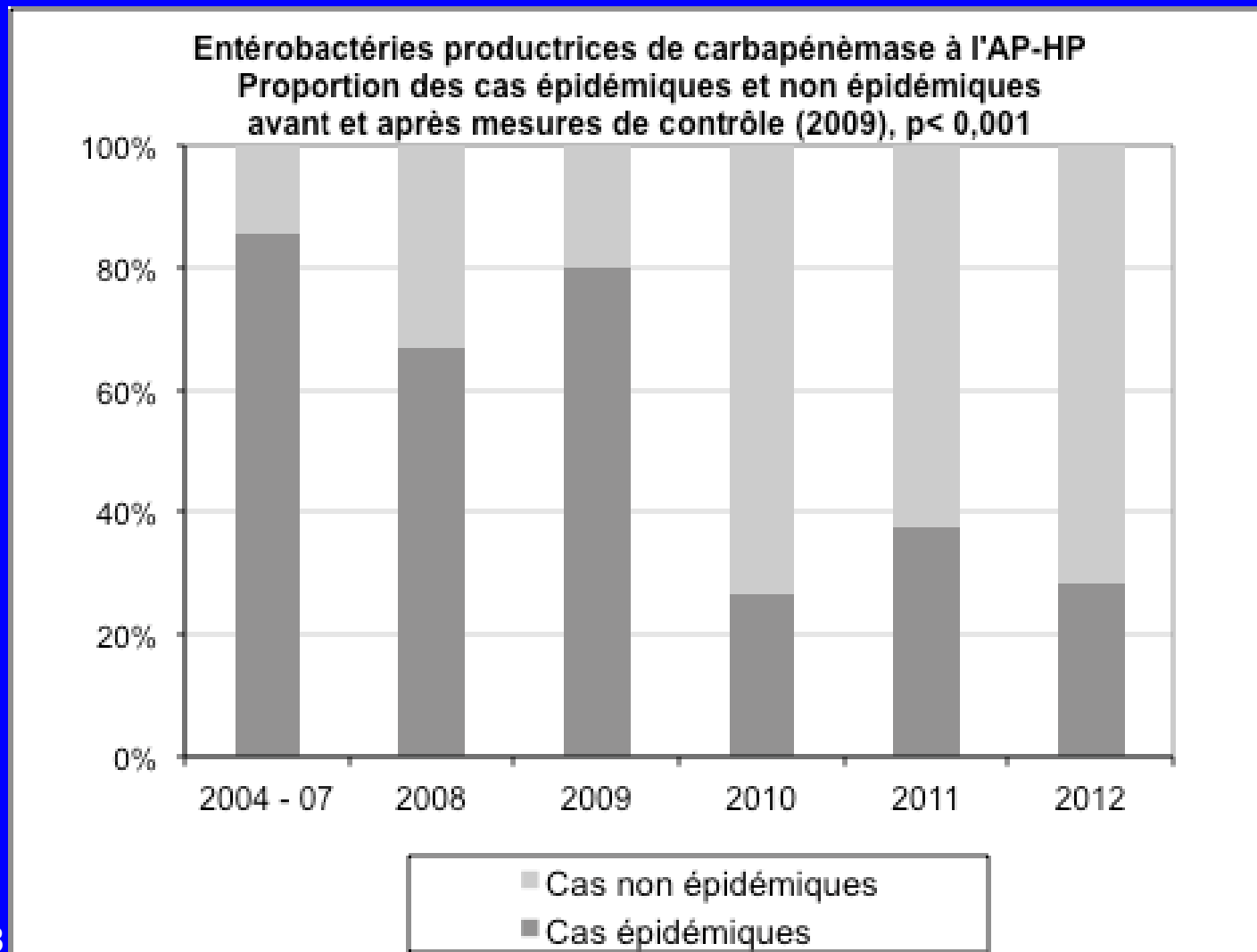
Recommandations du 20/10/2008

Control of Carbapenemase producing enterobacteria in 38 hospitals of AP-HP 2004-2012

120 index cases, 4/5 links with transfer from or previous stay in abroads hospitals



Control of Carbapenemase producing enterobacteria in 38 hospitals of AP-HP 2004-2012



épidémies d'EPC de l'AP-HP 2004-2012

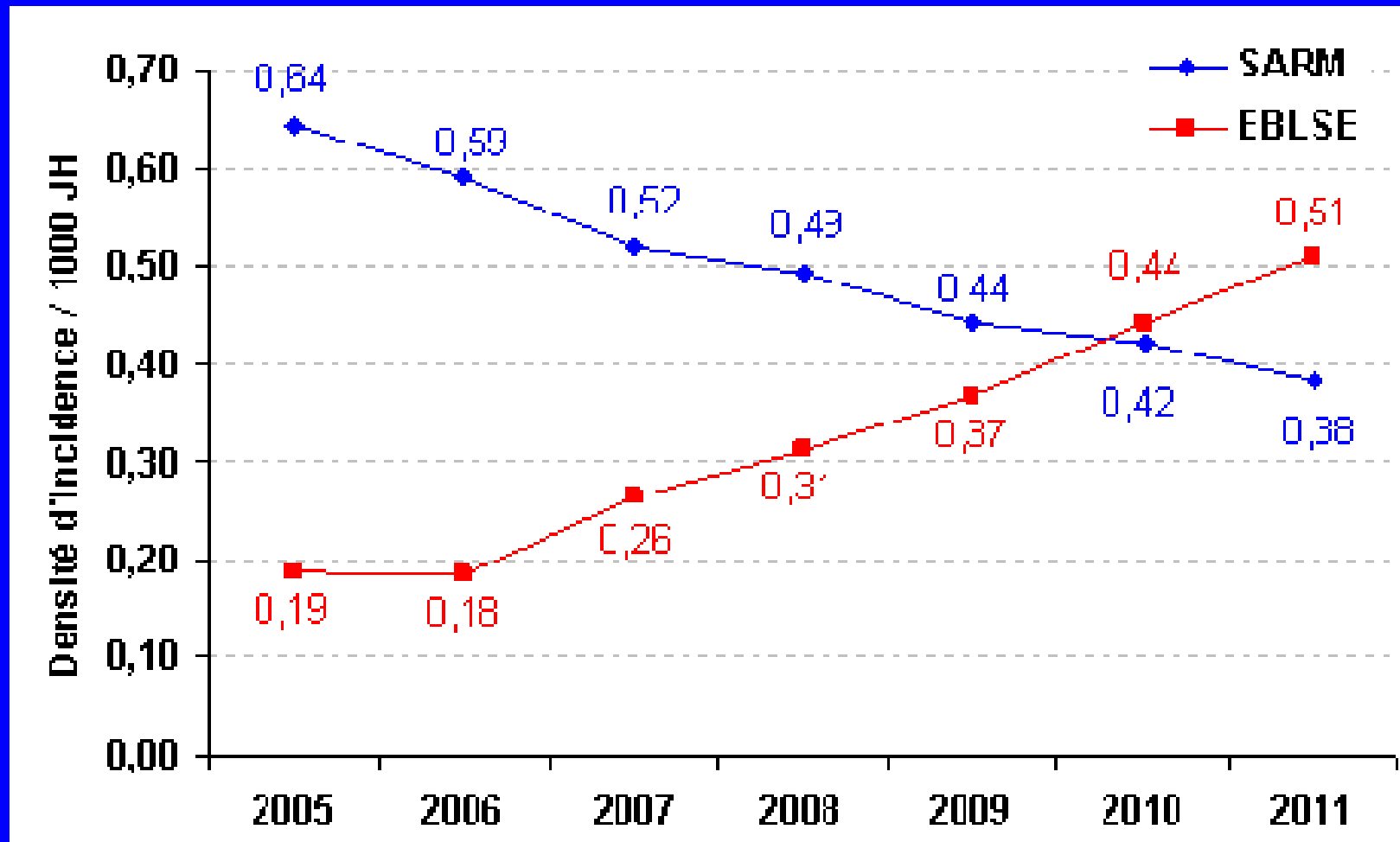
- Lien étranger du patient index : 15 épidémies
- Nombre de cas par épidémie : 2 à 14, moyenne 5, médiane 2
- Durée des épidémies : 0 à 8 mois, moyenne 2, médiane 1

Mesures mises en place dans les 2 jours suivant l'admission

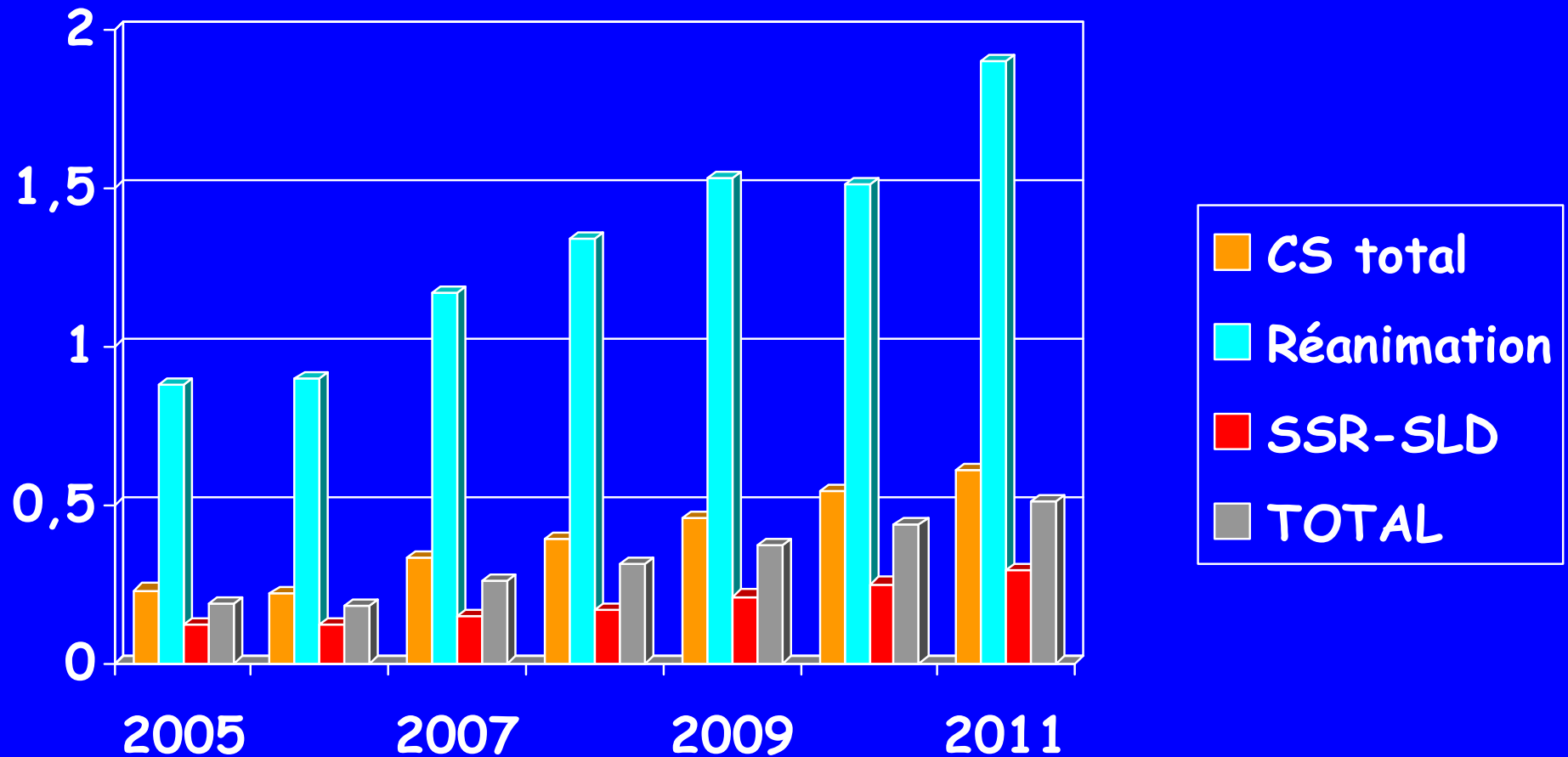
	Personnel dédié	Isolement en précautions contact	Retard à l'isolement	
N total d'alertes	18	55	67	
N épidémies	0 (0%)	6 (11%)	11 (16%)	P = 0.17
N cas totaux	18	74	108	
N cas 2aires	0 (0%)	19 (26%)	41 (38%)	P = 0.001

ESBL and
Carbapenemases :
« the infernal circle »

Incidence des SARM et EBLSE /1000 JH cohorte de 292 établissements « constants » RAISIN 2002-2011



incidence EBLSE 1,000 JH RAISIN 292 hôpitaux 2005-2011



Distribution (%) des cas EBLSE RAISIN 2011

	méd	chir	réa	Ped-GynObs	Ssr-Sld
Nord					
hors AP	34	16	18	4	18
APHP	27	16	18	7	20
Est	44	22	10	4	14
Ouest	43	22	18	5	18
Sud Est	34	22	6	3	21
S.Ouest	38	22	11	3	17
TOTAL	36	20	13	4	18

Distribution (%) des cas EBLSE RAISIN 2011

	Hémocultures	Pus-séreuses	Urines
Nord			
Hors APHP	7	5	65
APHP	8	7	66
Est	10	6	66
Ouest	6	5	76
Sud Est	9	5	65
Sud Ouest	9	5	66
TOTAL	8	6	67

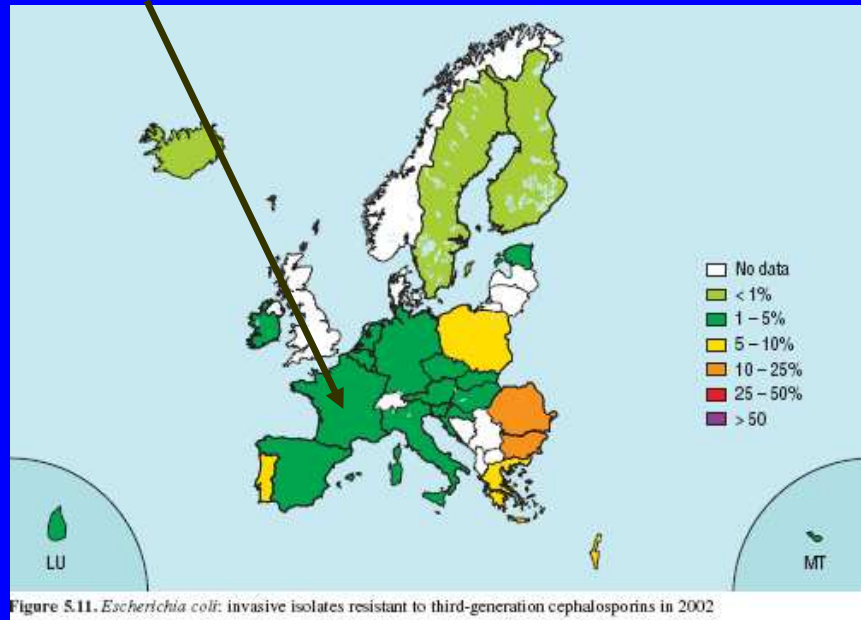
Distribution (%) des cas EBLSE RAISIN 2011

	<i>E.coli</i>	<i>K.pneumoniae</i>	<i>E.cloacae</i>
Nord			
Hors APHP	60	19	11
APHP	51	25	16
Est	61	20	7
Ouest	68	11	12
Sud Est	57	21	9
Sud Ouest	58	20	12
TOTAL	59	20	11

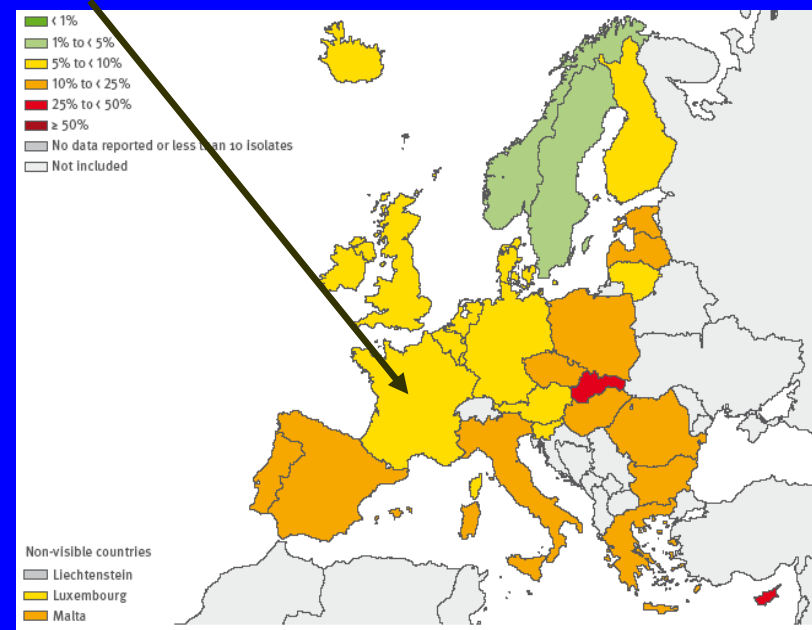
EARS-net : E.coli resistant to 3rd gen. cephalosporins (%) in bacteremias

1%

8% (6% ESBL)



2002

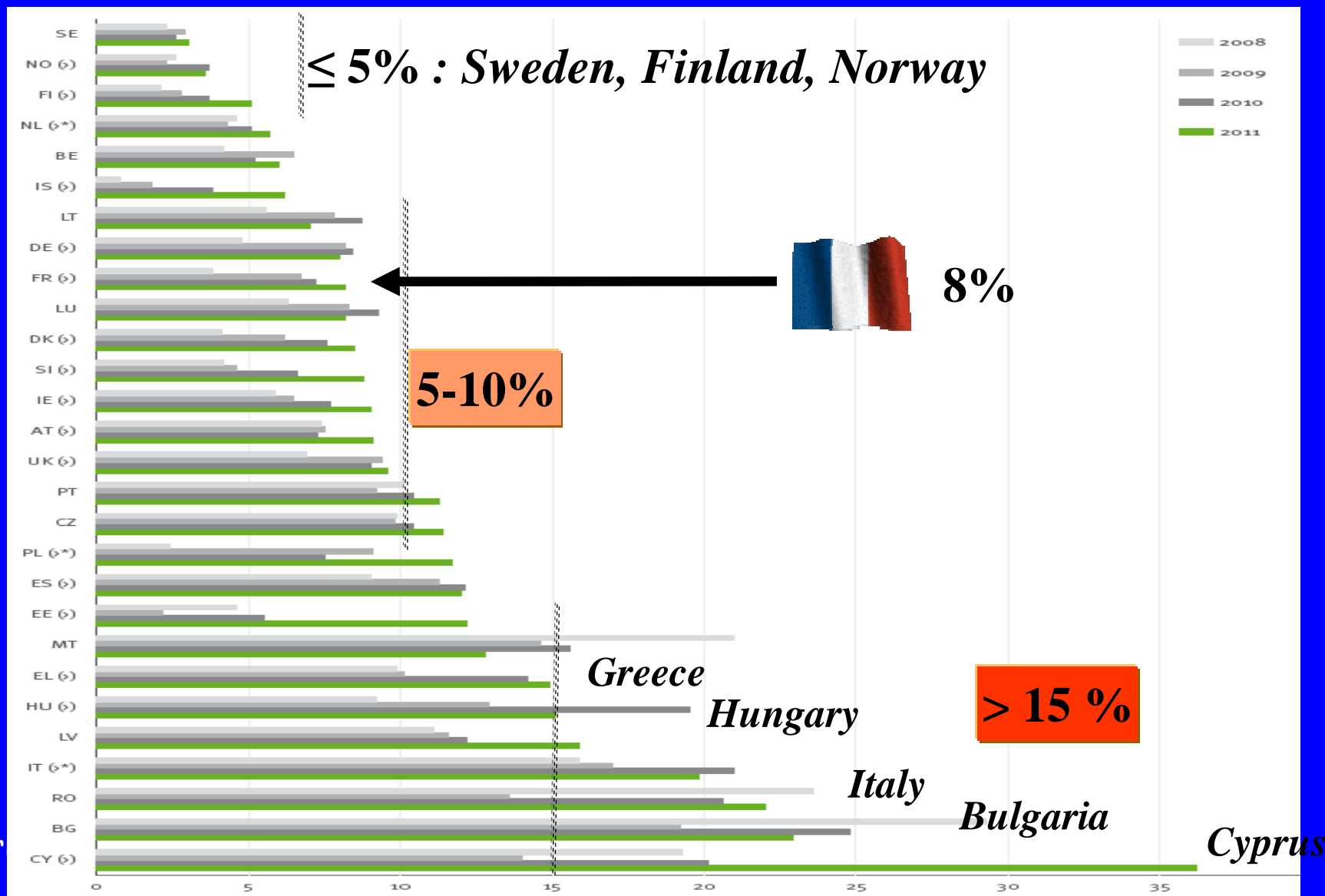


2011

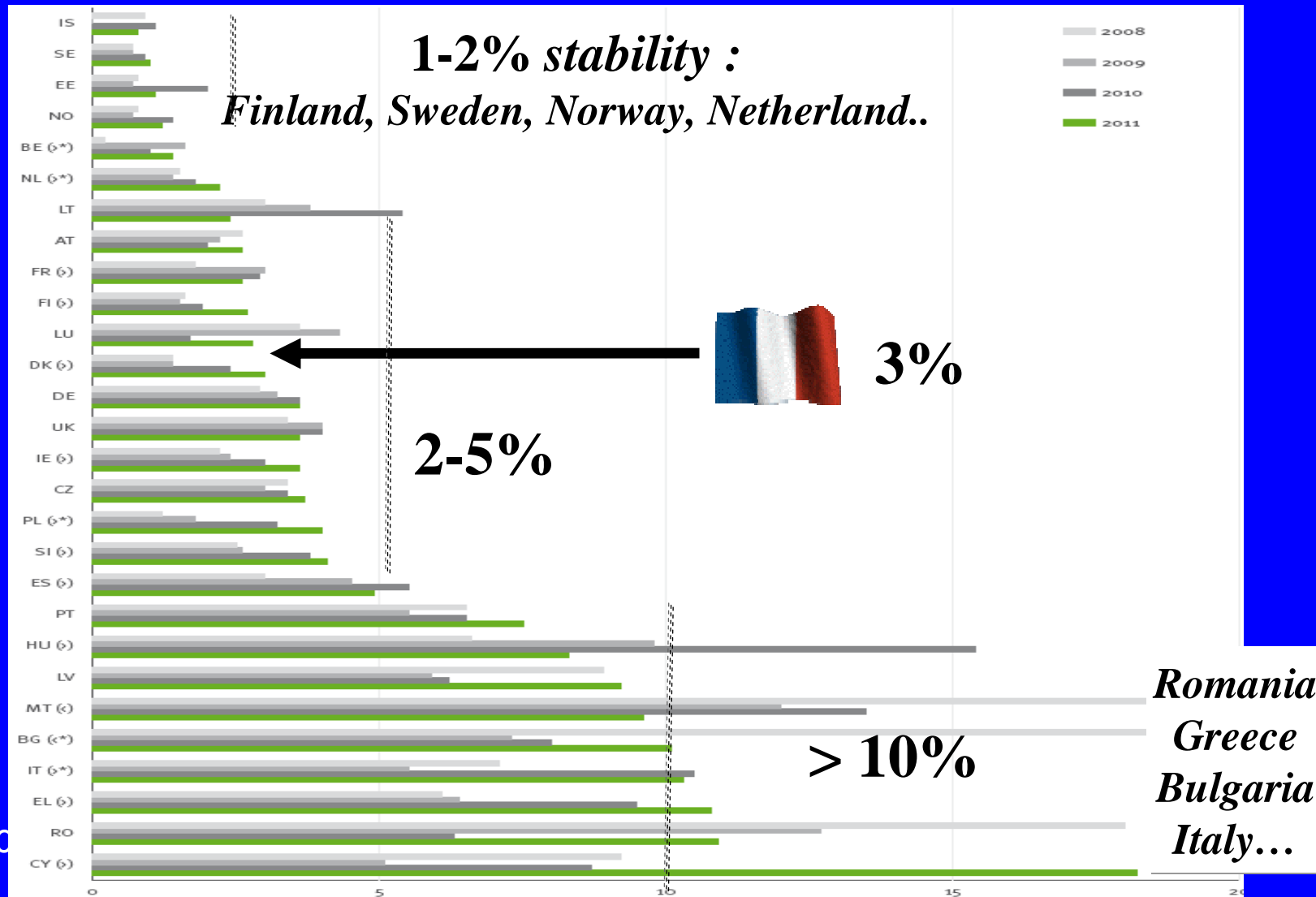
(~9,000 cases)

Extrapolation : ~2,500 ESBLcases /year in France in 2011

% R 3rd gener. Cephalosporins in *E.coli* bacteremias (ESBL~70-80%) in Europe, EARS-net 2008-11



% R 3rd gener. Cephalosporins + FQ + aminoglycosides in *E.coli* bacteremias in Europe, EARS-net 2008-11

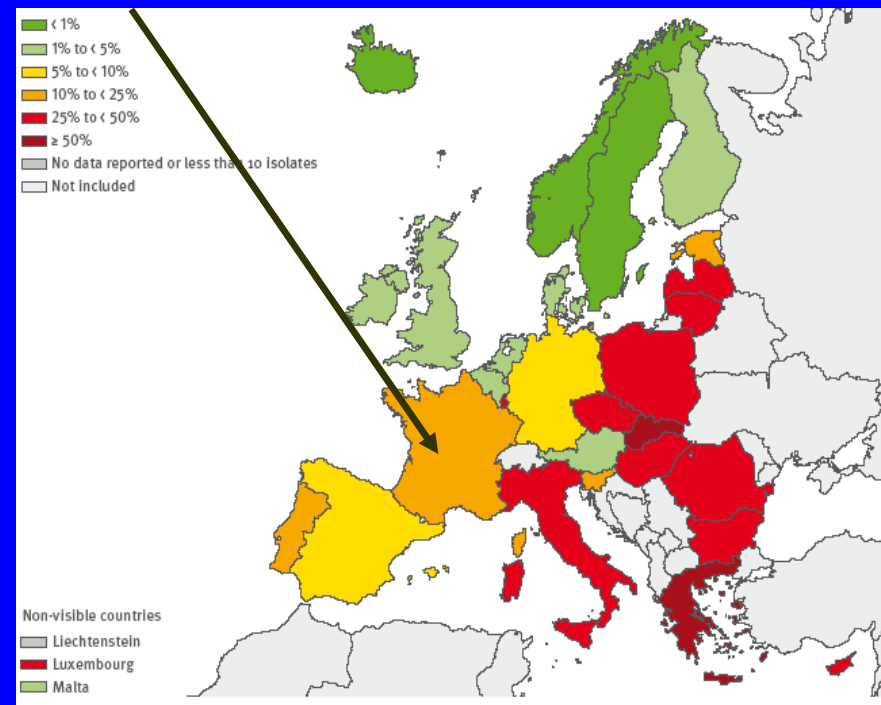
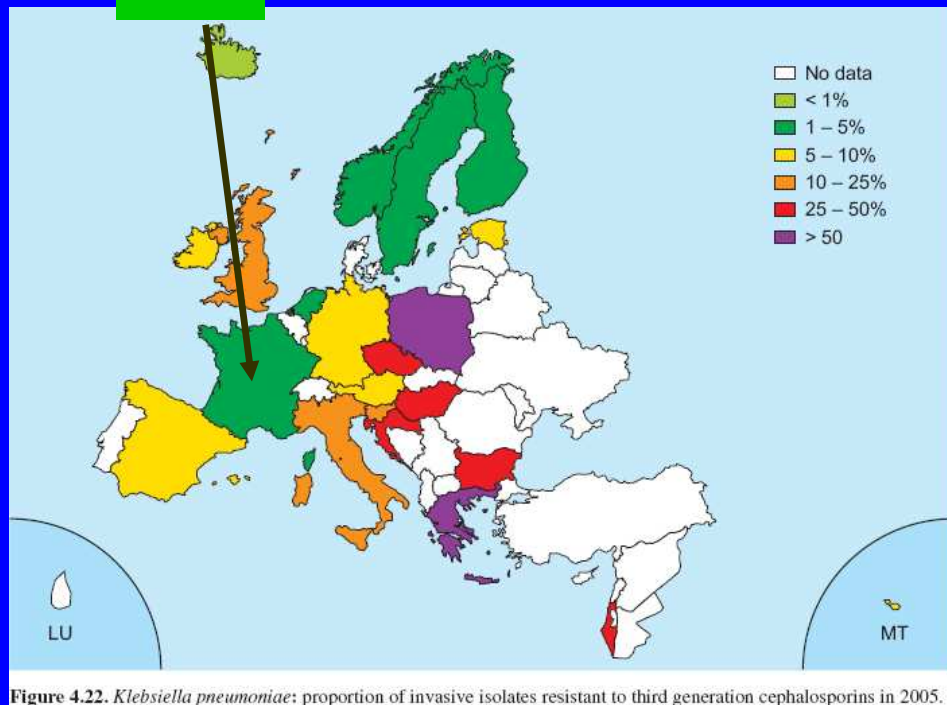


EARS-net : K.pneumoniae resistant to 3rd generation cephalosporins in bacteremias

4%

25%

~24% ESBL

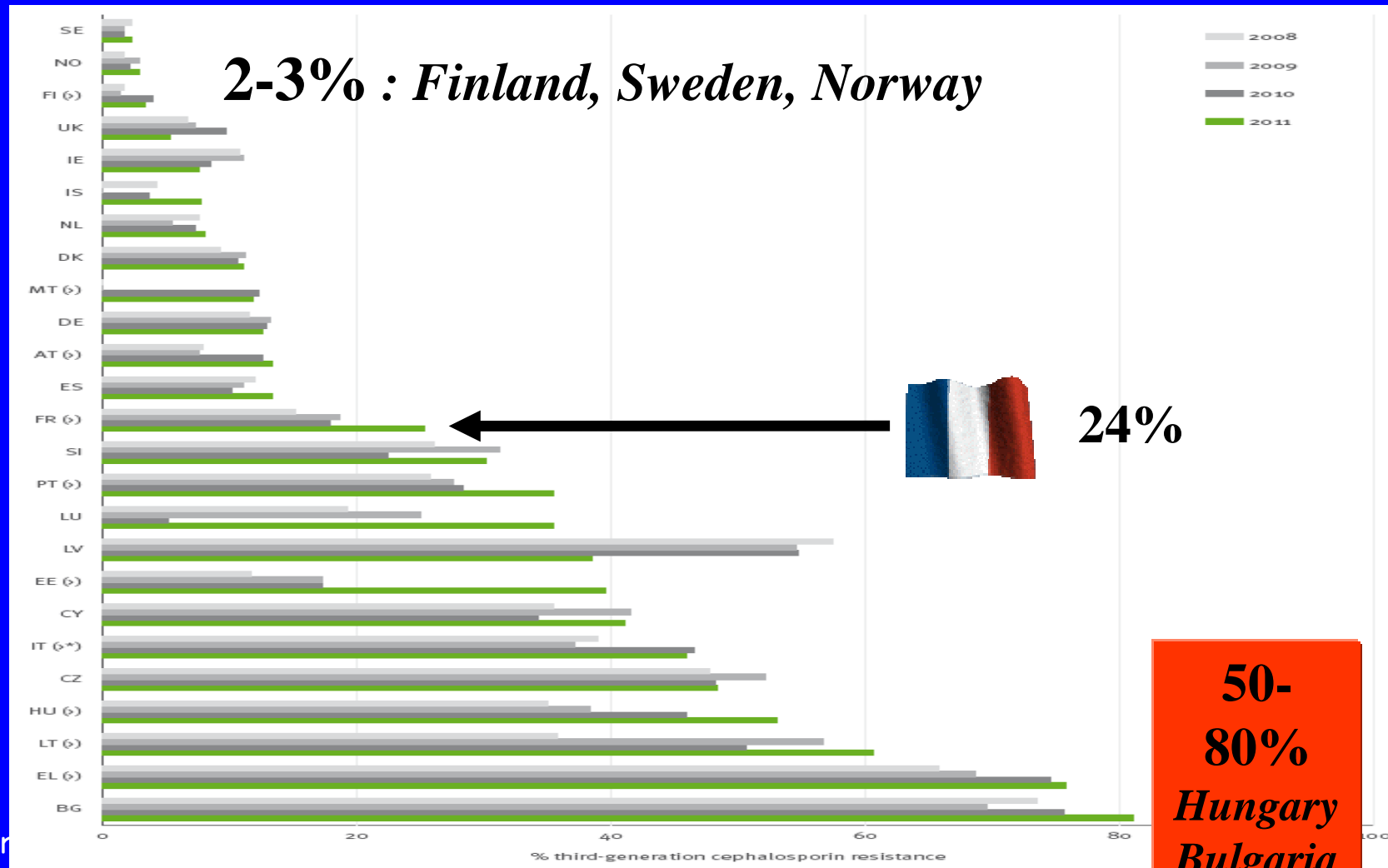


2005

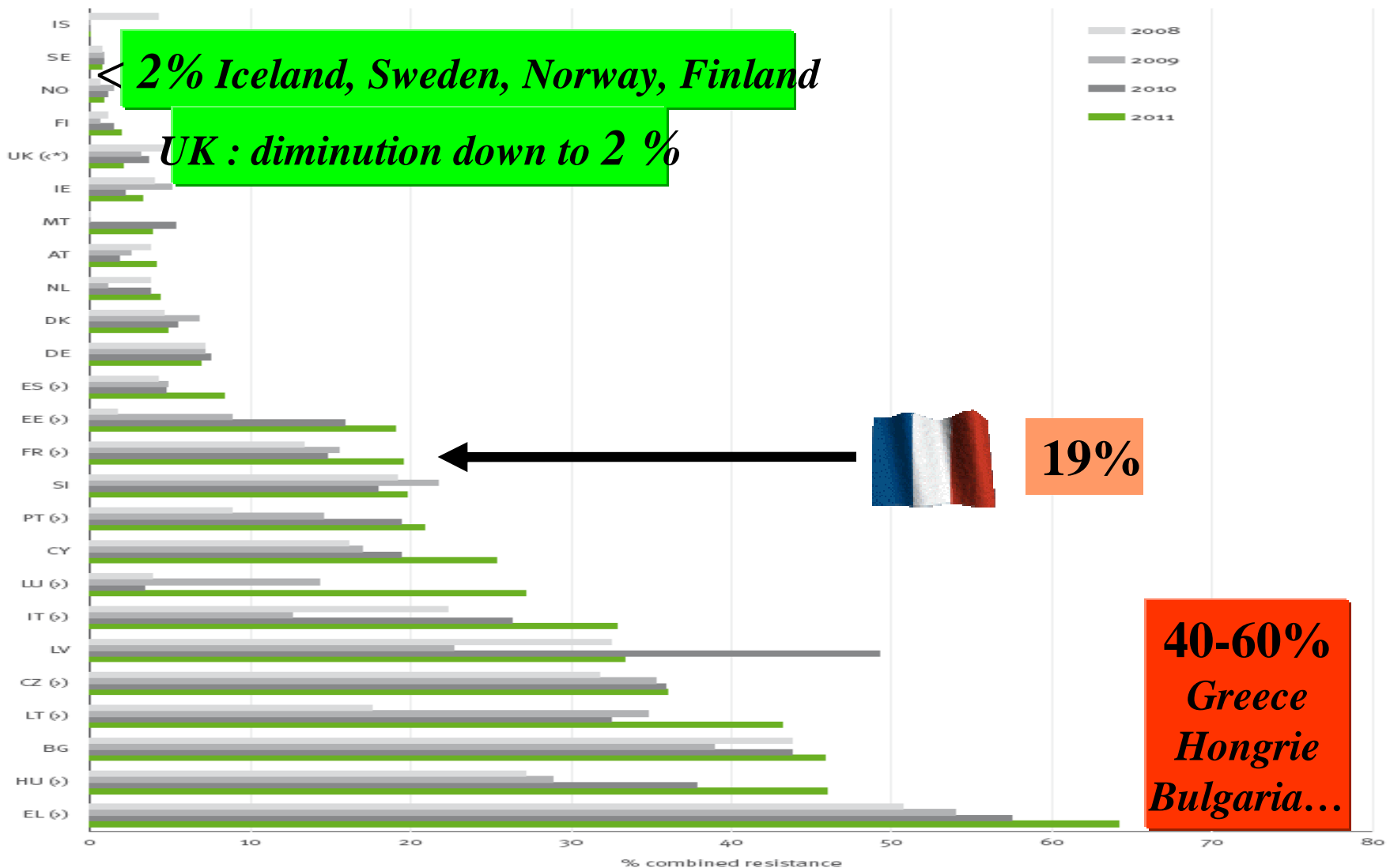
2011

(~1.600 cases)

% R 3rd gener. Cephalosporins in K.pneumoniae bacteremias in Europe, EARS-net 2008-11



% R 3rd gener. Cephalosporins + FQ + aminoglycosides in *K. pneumoniae* bacteremias in Europe, EARSS 2008-11



EARSS-France résultats 2011

- *E.coli* 2001-2011

R C3G : 1% → 8% (7^{ème} → 9^{ème})

- *K.pneumoniae* 2005-2011

R C3G : 4% → 25% (5^{ème} → 14^{ème})

- *P.aeruginosa* 2005-2011

R C3G : 9% → 16% (10^{ème} → 20^{ème})

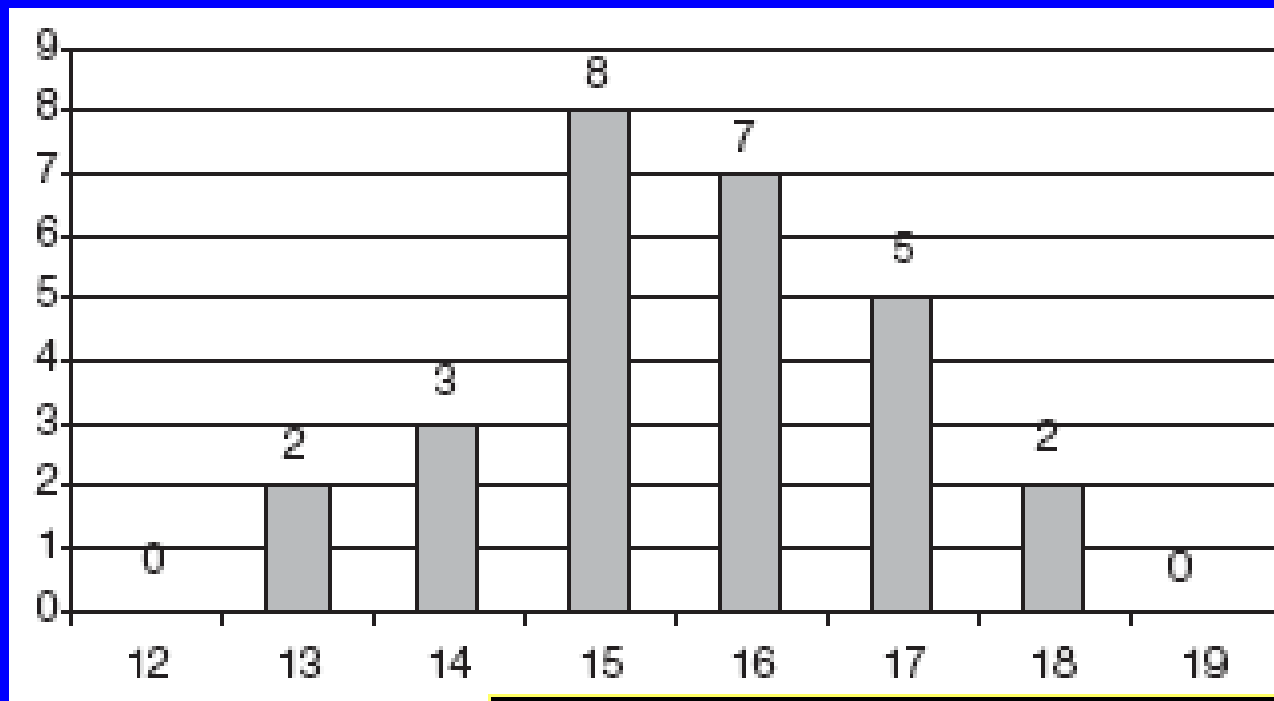
R Imip : 14% → 18% (8^{ème} → 18^{ème})

ESBL *E.coli* in recent years :

- hospital vs. community ?
- importation vs. acquisition ?
- role of animals, food and environment ?

Epidémie *E.coli* BLSE Hôpital Trousseau 2009

- Epidémie de 27 cas en 6 semaines
- Taux d'attaque 46 %
- 2 infections dont 1 méningite
- souches **clonales** TEM-52



Patient's Origin and Lifestyle Associated with CTX-M-Producing *Escherichia coli*: A Case-Control-Control Study

Marie-Hélène Nicolas-Chanoine^{1,2,3*}, Vincent Jarlier^{4,5}, Jérôme Robert^{4,5}, Guillaume Arlet⁶, Laurence Drieux^{5,7}, Véronique Leflon-Guibout¹, Cédric Laouénan^{8,9}, Béatrice Larroque¹⁰, Valérie Caro¹¹, France Mentré^{8,9}, and the study Group Coli β

Odds ratio (p) ESBL *E.coli* in hospitalized patients (multivariate) Compared to non ESBL *E.coli*

- Country of birth out Europe 2.4 (0.004)
- Recurrent UTI or chronic SSTI 2.9 (0.01)
- Hospitalised < 6 months 2.0 (0.01)
- ICU since admission 2.3 (0.03)
- Antibiotic <1 month 2.0 (0.04)

Compared to no positive samples

- Country of birth out Europe 3.1 (0.005)
- Female gender 2.5 (0.02)
- Functionally dependent before hosp 7.0 (0.002)
- Recurrent UTI or chronic SSTI 8.7 (0.005)
- Urine drainage < 6 months 4.4 (0.003)
- ≥ invasive device since admission 4.2 (0.003)
- Antibiotic since admission 3.3 (0.003)

FQ-R / ESBL-*E. coli* in nursing homes in North Ireland

- Prevalence:
 - 40 % (119/294) carrying FQ-R-ESBL *E. coli* in feces
 - 1/2 of strains = clonal O25:H4-ST131-*bla*CTX-M-15
 - 1/2 carriers had history of recent hospital admission
- Risk factors :

Characteristic	Multivariate analysis:	
	OR (95% CI)	P value
Days of fluoroquinolone use	1.33 (1.04-1.69)	0.02
History of UTI	2.56 (1.37-4.78)	0.003

Intrafamilial transmission of ESBL-producing *E. coli* and *S. enterica* in families of adopted children

- French study: 24/25 adoptees (Mali) positive for ESBL-producing *Enterobacteriaceae* (E-ESBL)
- Transmission of E-ESBL demonstrated for 5/22 (22%) families in which at least one family member other than the adoptee was found positive for E-ESBL

β -Lactam resistance genes	ESBL-producing <i>Enterobacteriaceae</i> :	
	<i>E. coli</i> , n (%)	<i>Salmonella spp.</i> , n (%)
CTX-M-15	6 (12.2)	-
CTX-M-15/TEM-1	36 (73.5)	-
SHV-12/TEM-1	4 (8.2)	4 (100.0)
SHV-2/TEM1	1 (2.0)	-
Unknown*	2 (4.1)	-
TOTAL	49 (100.0)	4 (100.0)

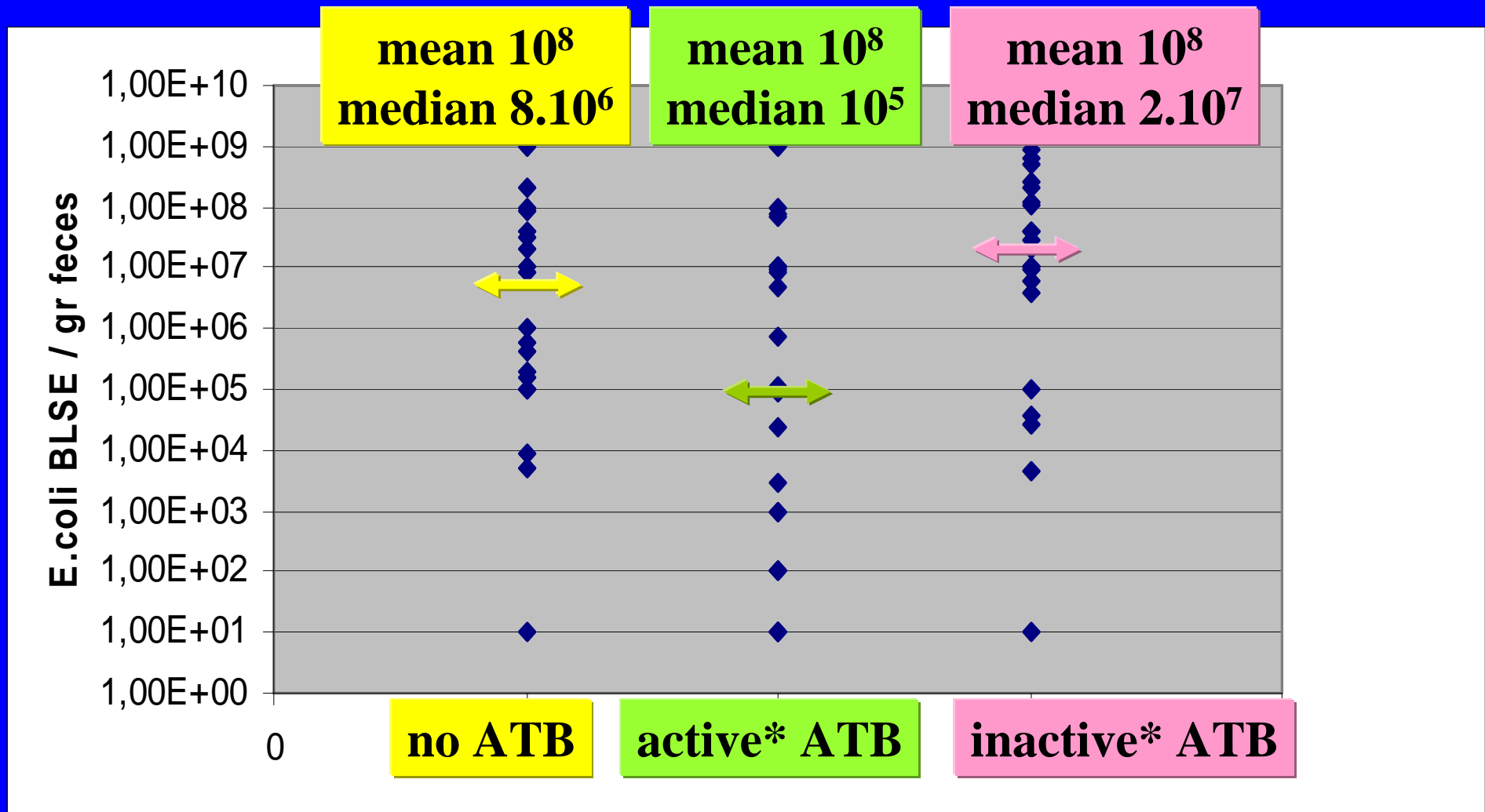
*: Isolates could not be recultured

Excretion of bacteria (and mobile elements)

~ 10^{10} ESBL *E.coli* per carrier (feces)
and **per day**

~ 10^9 ESBL *E.coli* per UTI and **per day**

Quantification (per gr of feces) of ESBL *E.coli* in carrying patients



Transmission of ESBL *E. coli* strains or plasmids within families

- Molecular analysis of ESBL dissemination in *E. coli* within families:
 - 19 families of patients with UTI, caused by ESBL-producing *E. coli*, where at least one other faecal carrier within each family was identified
 - 19 patients with UTI + 23 relatives

9 relatives (39%) from 7 families (37%):

- the same pulsotype
- the same ESBL

**Transmission of
same strain
(37%)**

10 families (53%):

- different pulsotypes
- the same ESBL

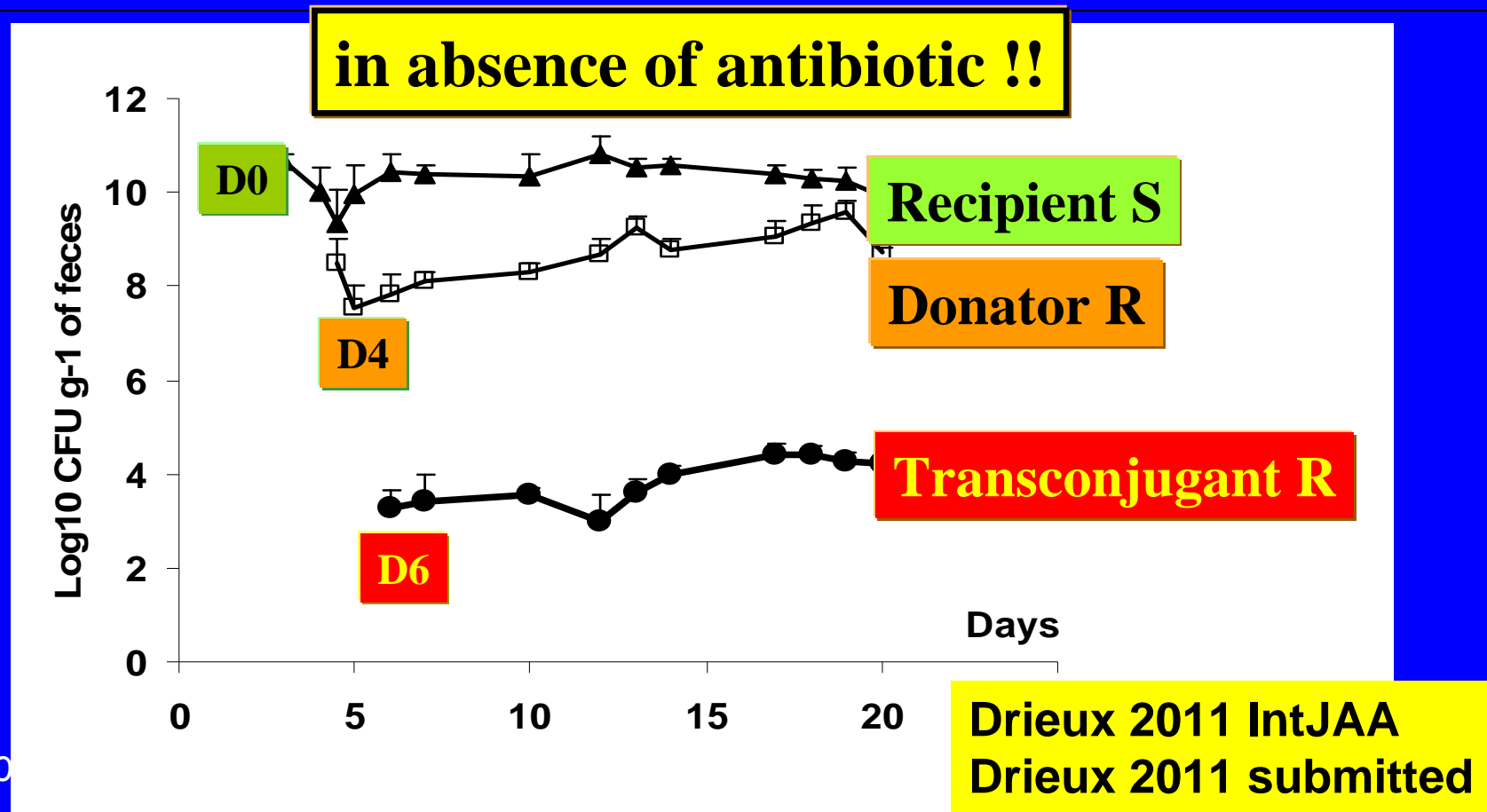
5 families (26%):

- ESBL located in similar RFLP plasmidic patterns
- 3 with CTX-M-14 and 2 with SHV-12

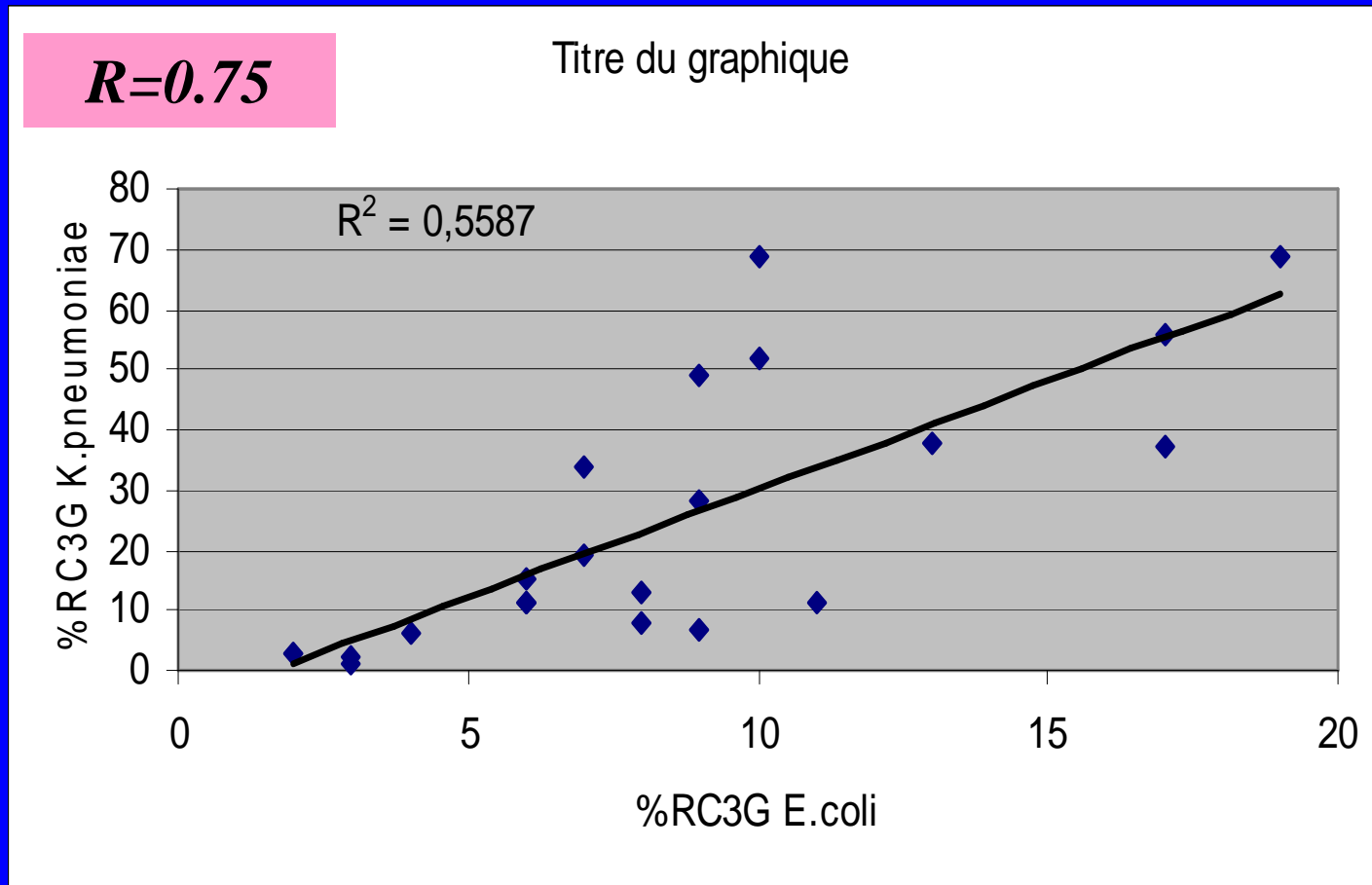
**≠ strain, same plasmid
(26%)**

In vivo exchange of plasmid carrying β -mases

- Several reports suggest in vivo transfer of ESBL or carbapenemase genes between strains or species in humans
- **in vivo transfer in the mouse : VIM-1 or CTX-M15**



Relation 3rd Gen Cephalosporin-Resistance *E.coli* vs. *K.pneumoniae* EARSS 2009



ESBL *E. coli* and animal farming : chicken meat as a potential source of ESBL-producing *E. coli* in UK?

ESBL *E. coli* from chicken, by country of origin :
mainly CTX-M-2 and CTX-M-14

Origin	Total positive/ total tested	CTX-M gene present:			
		CTX-M-1	CTX-M-2	CTX-M-8	CTX-M-14
UK	1/62	1	0	0	0
Ireland	0/3	0	0	0	0
Brazil	4/10	0	4	0	0
Brazil/Poland/France	3/4	0	3	0	0
Poland	0/4	0	0	0	0
The Netherlands	2/2	0	2	0	0
Spain, France, Denmark and Germany	0/4	0	0	0	0
Unknown	7/40	0	1	1	5
Total	17/129	1	10	1	5

Almost no CTX-M-15 found in chickens,
though this ESBL predominates in humans

10-Fold increase (2006–11) in the rate of healthy subjects with extended-spectrum β -lactamase-producing *Escherichia coli* faecal carriage in a Parisian check-up centre

Marie-Hélène Nicolas-Chanoine^{1-3*}, Coraline Gruson³, Suzanne Bialek-Davenet¹⁻³, Xavier Bertrand⁴, Frédérique Thomas-Jean⁵, Frédéric Bert¹, Mati Moyat¹, Elodie Meiller¹, Estelle Marcon¹, Nicolas Danchin⁵, Latifa Noussair¹, Richard Moreau³ and Véronique Leflon-Guibout¹

- Mean 56 years, 61% male
- **21/347 *E.coli* ESBL (6%)**
- CTX-M1, **7 CTX-M15**, 4 CTX-M-4, 4 SHV12
- When non dominant *E.coli* : \neq phylogenic group from dominant

- Travel abroad < 6 months 43 vs 36 %
- hospitalization < 6 months 14 vs 7 %
- Antibiotic(s) <1 month 14 vs 12 %
- Occupation in healthcare setting 5 vs 2 %
- Birth in metropolitan France 57 vs 69 %

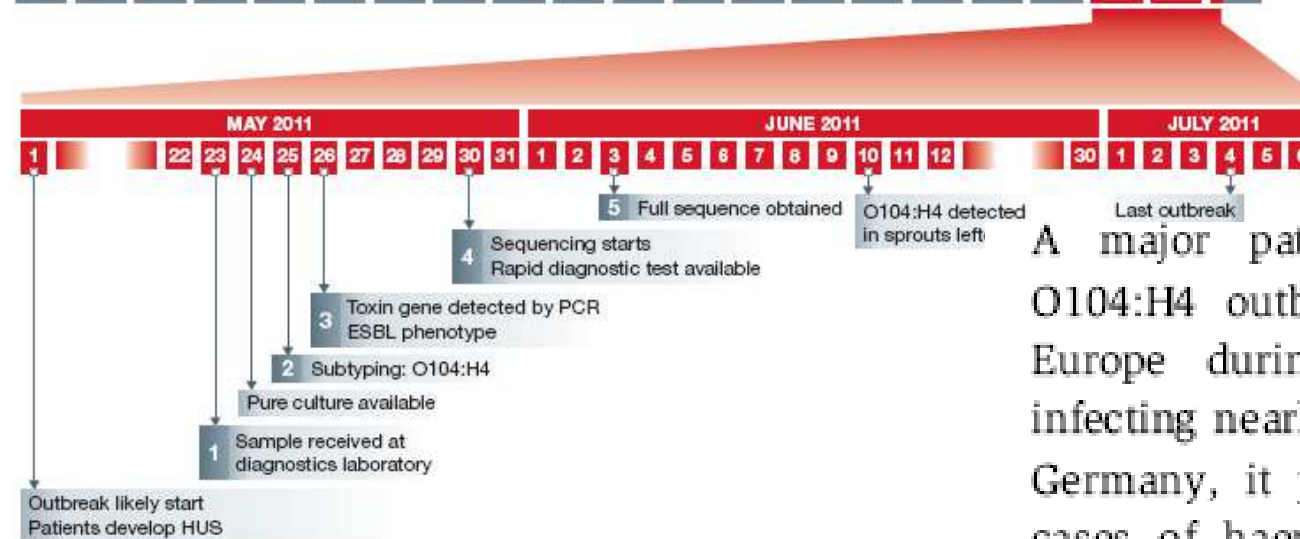
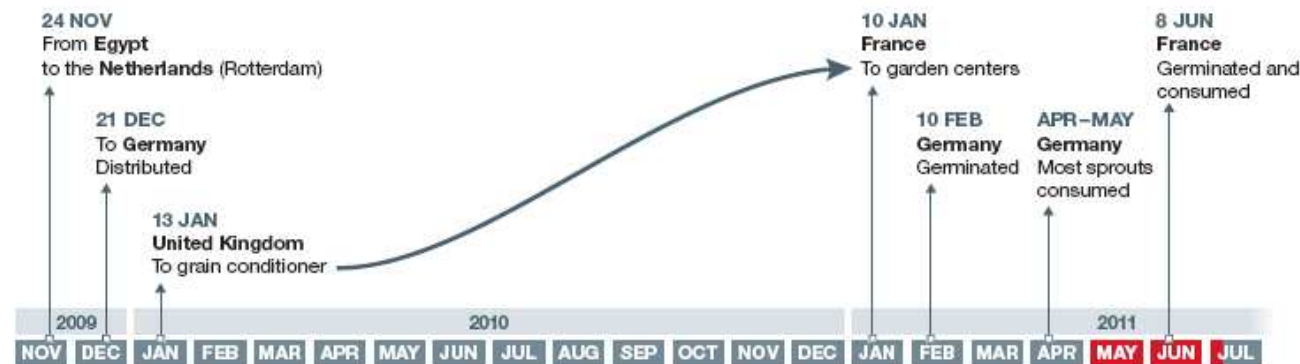
→ no statistical differences

ESBL colonization in Travellers

- **32 %** of Swedish carry ESBL-*Enterobacteriaceae* after travelling in foreign countries (**73 / 231**)
- Highest rate when travel in India (82%) and Egypt (57%)
- 79 % of cases associated with abdominal symptoms (ie: diarrhea)

The enemy within us: lessons from the 2011 European *Escherichia coli* O104:H4 outbreak

Helge Karch¹, Erick Denamur², Ulrich Dobrindt¹, B. Brett Finlay³, Regine Hengge^{4†}, Ludgers Johannes⁵, Eliora Z. Ron^{6†}, Tone Tønjum^{7†}, Philippe J. Sansonetti^{8†}, Miguel Vicente^{9*,†}



Souche multirésistante : BLSE...

A major pathogenic *Escherichia coli* O104:H4 outbreak occurred in central Europe during late spring of 2011, infecting nearly 4000 persons mainly in Germany, it produced more than 900 cases of haemolytic uremic syndrome (HUS) resulting in 54 deaths. In addition,

A dreadful result of resistance evolution:
epidemic EHEC O104:H4, Germany
May-June 2011

Resistance of the strain involved

- ESBL (CTX-M)
- Cefpodoxime
- Cephamycins (cephalosporinase overproduction?)
- Quinolones
- Cyclines
- Cotrimoxazole

Pathogenicity markers

- *stx1*

- *aggR*

VJc

When, where and how this monster has been created ?

Challenges in controlling "digestive tract driven" MDROs such as ESBL and Carb-R *Enterobacteriaceae*

- Bacterial (and mobile elements) excretion
 - ~**10¹⁰** per carrier (feces) and **per day**
 - ~**10⁹** per UTI and **per day**
- **Wastes** (feces and urines)
 - environment

ESBL in hospital wastewater Brazil

Detection of extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* in effluents and sludge of a hospital sewage treatment plant

T. Prado¹, W.C. Pereira¹, D.M. Silva¹, L.M. Seki², A.P.D'A. Carvalho² and M.D. Asensi²

1 Department of Sanitation and Environmental Health – Public Health National School, Oswaldo Cruz Foundation – Rio de Janeiro (RJ), Brazil

2 Department of Bacteriology – Oswaldo Cruz Institute, Oswaldo Cruz Foundation – Rio de Janeiro (RJ), Brazil

Letters in Applied Microbiology 2008

ESBL in hospital wastewater France

- Pitié-Salpêtrière - C.Foix hospital (Paris)
- December 2010
- Long term care facility
- ESBL *E.coli* in wastewater : $\sim 10^6$ /liter
- Same enzymes and identical strains as in patients carrying ESBL *E.coli* present at the same period in the hospital

ESBL in wastewater Portugal

**Leakage into Portuguese aquatic environments
of extended-spectrum- β -lactamase-producing
Enterobacteriaceae**

Elisabete Machado^{1,2}, Teresa M. Coque³⁻⁵,
Rafael Cantón³⁻⁵, João Carlos Sousa², Diana Silva¹,
Mayra Ramos¹, Joana Rocha¹, Helena Ferreira¹ and
Luísa Peixe^{1*}

J Antimicrob Chemother 2009

ESBL genes in wastewater treatment plant (Bielefeld, 320.000 inh. Westphalia, Germany, 2006)

Detection of 140 clinically relevant antibiotic-resistance genes in the plasmid metagenome of wastewater treatment plant bacteria showing reduced susceptibility to selected antibiotics

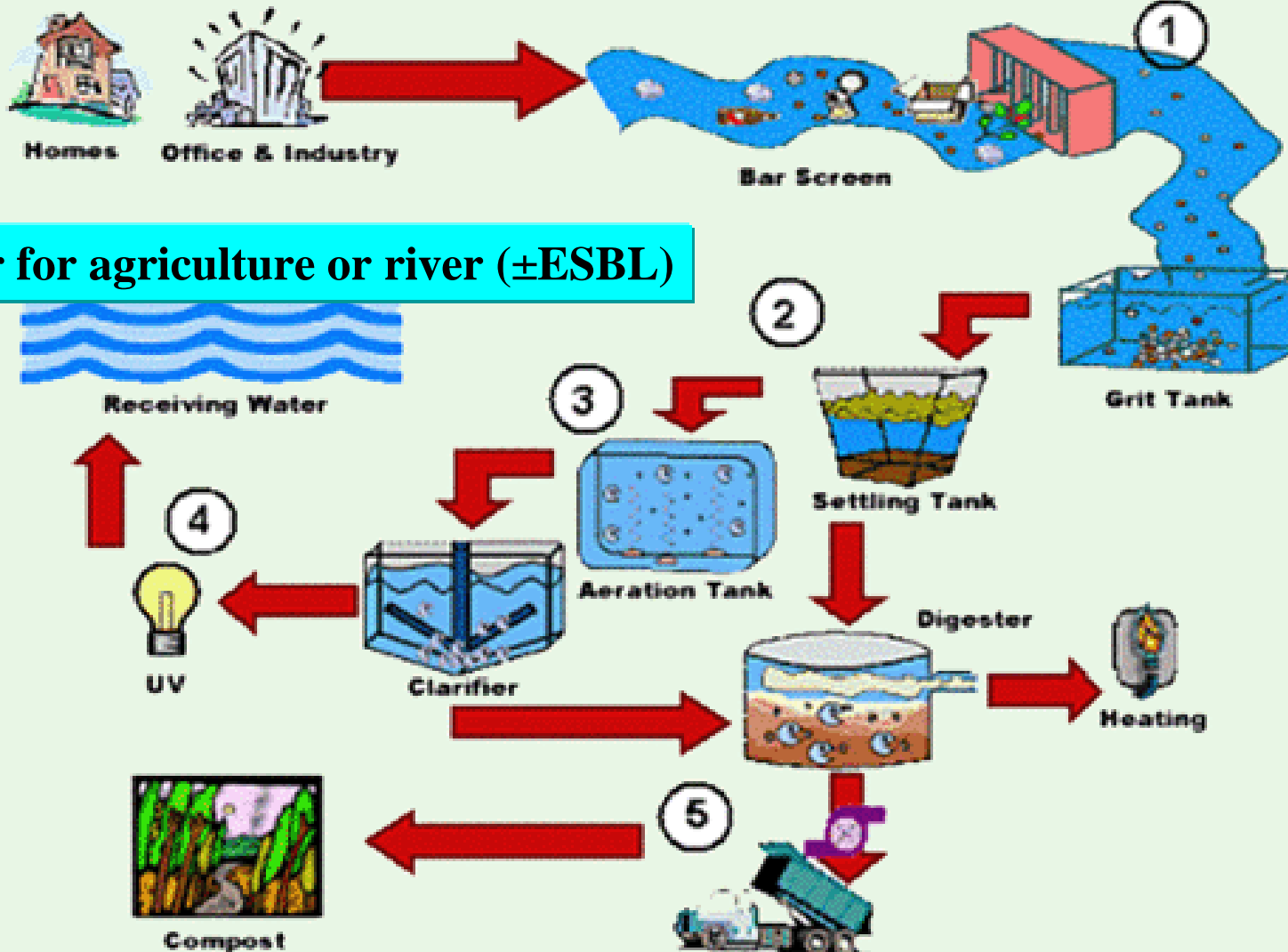
Rafael Szczepanowski,¹ Burkhard Linke,² Irene Krahn,¹
Karl-Heinz Gartemann,³ Tim Gützkow,¹ Wolfgang Eichler,⁴ Alfred Pühler¹
and Andreas Schlüter¹

Microbiology 2009

Gene name [†]	Gene product	Amplicon size (bp)	Resistance to/ function [‡]	Detected in activated sludge	Detected in the final effluents
<i>ctx-m-4</i>	Class A β -lactamase	155	Amp, Ctx, Cxm, Atm	+	+
<i>ctx-m-27</i> ‡	Class A β -lactamase	158	Caz, Ctx, Amo, Tic, Prl, Kf, Cxm, Cpo, Atm	+	+
<i>ctx-m-32</i> ‡	CTX-M, SHV, PER	156	Amo, Ctx, Caz, Fep, Prl, Kf, Fox, Cxm	+	+
<i>ges-3</i> ‡		181	Tetracycline, Prl, Caz, Ctx, Atm, Ipm	+	+
<i>per-2</i>	Class A extended-spectrum β -lactamase	198	Oxyiminocephalosporins, Atm, Cft	+	–
<i>shv-34</i>	Class A β -lactamase	200	Caz, Ctx	+	+
<i>bla_{TEM-1}</i>	Class A β -lactamase	167	Amp, Pen-G	+	+

Wastewater treatment plant

HOW IT WORKS



Water for agriculture or river (\pm ESBL)

Compost for agriculture (\pm ESBL)

ESBL in drinking water in Nepal

Serotyping, PCR, phage-typing and antibiotic sensitivity testing of *Salmonella* serovars isolated from urban drinking water supply systems of Nepal

D.R. Bhatta^{1,2}, A. Bangtrakulnonth³, P. Tishyadhigama³, S.D. Saroj⁴, J.R. Bandekar⁴, R.S. Hendriksen⁵ and B.P. Kapadnis¹

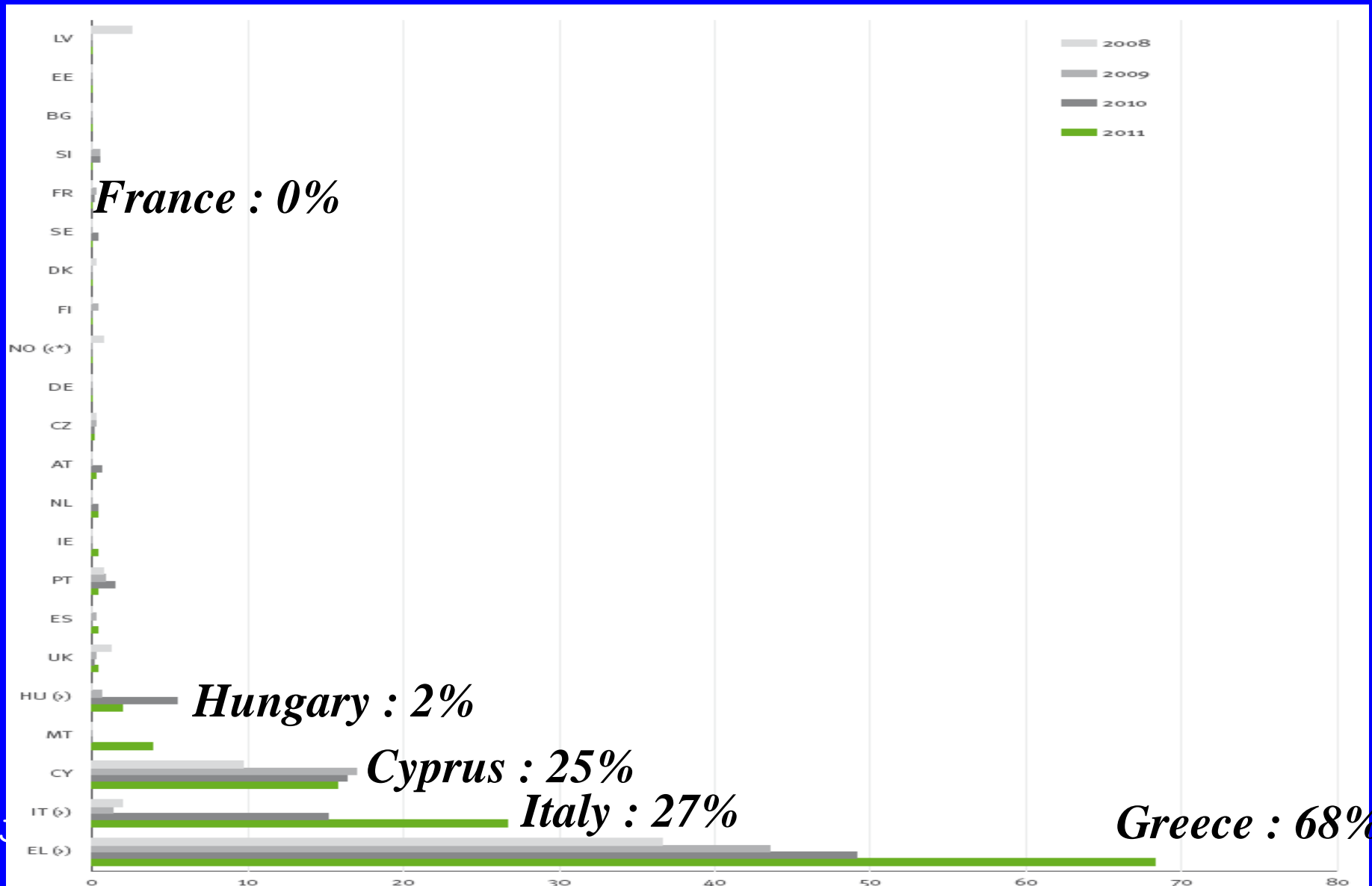
Letters in Applied Microbiology 2007

Link between the rates of
 ESBL *E.coli* and Carb-R *K.pneumoniae*
 in European countries
 Bacteremia EARSS 2011

	ESBL <i>E.coli</i>		
Carb-R <i>Kp</i>	low	medium	high
none	9	2	1
low	4	4	1
medium		2	
high		1	2

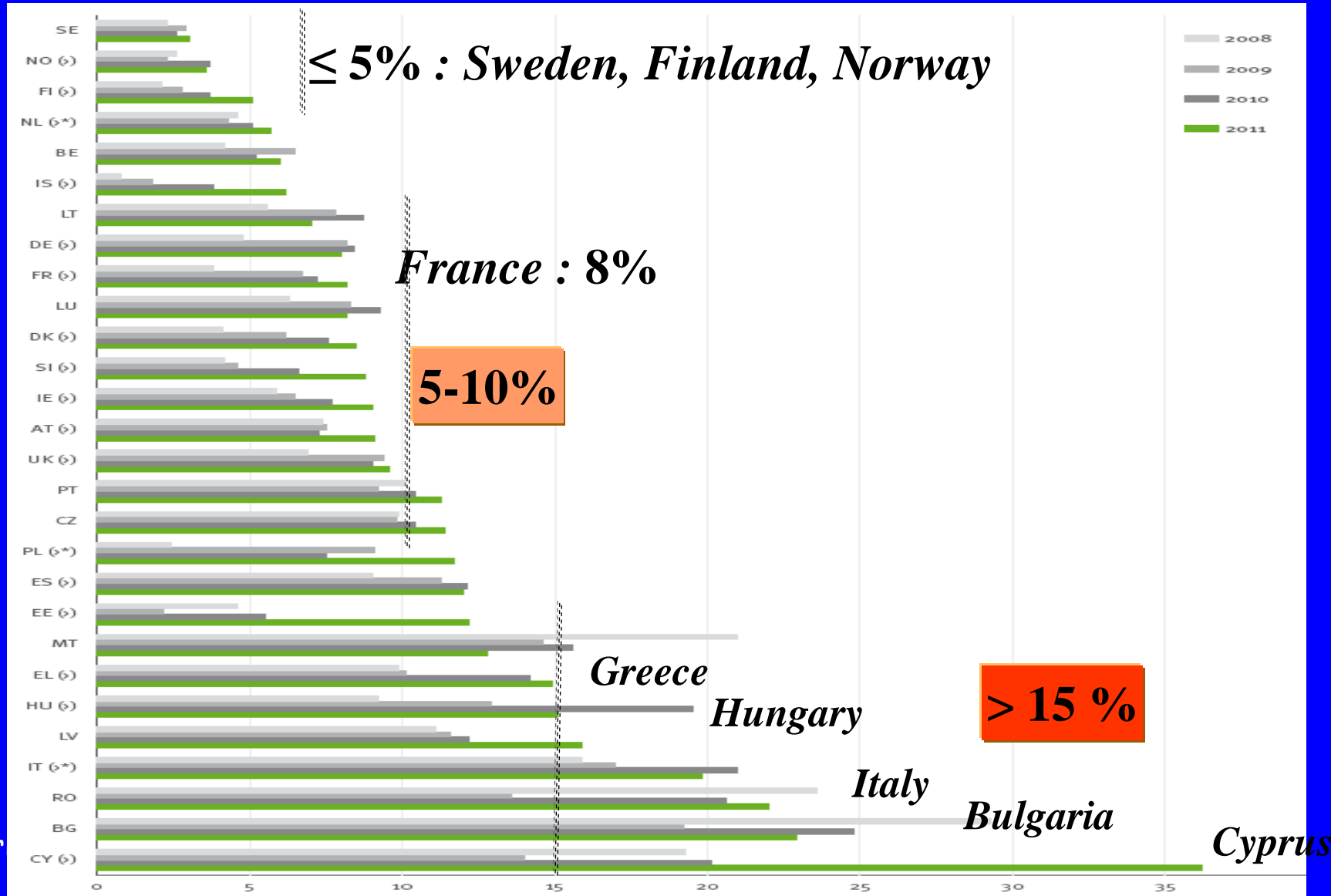
ESBL and
Carbapenemases :
break
« the infernal circle »

Bacteremias due to CPE *Klebsiella pneumoniae* (%) EARS-net 2008-2011



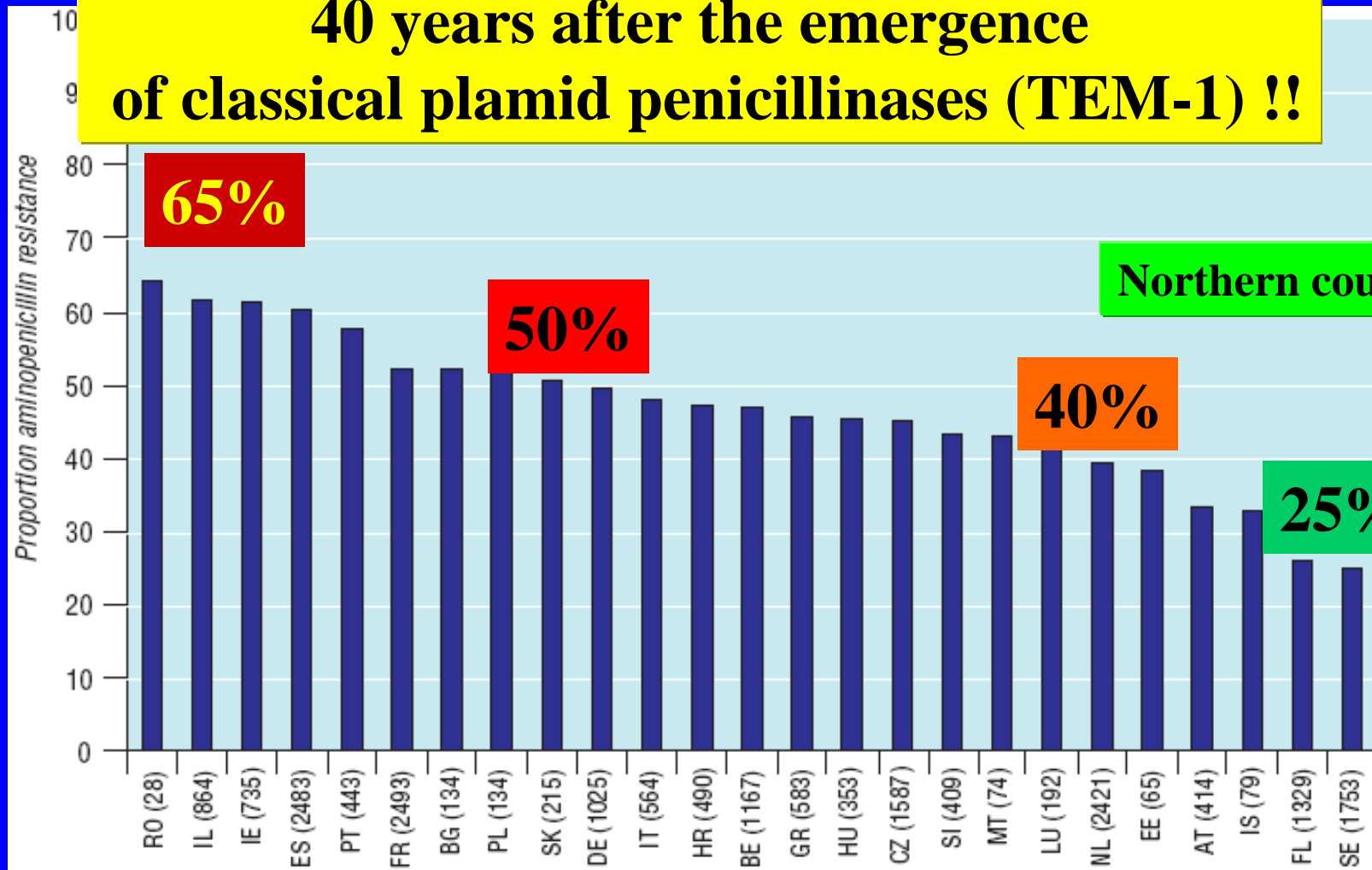
VJ

% R 3rd gener. Cephalosporins in *E.coli* bacteremias (ESBL~70-80%) in Europe, EARS-net 2008-11

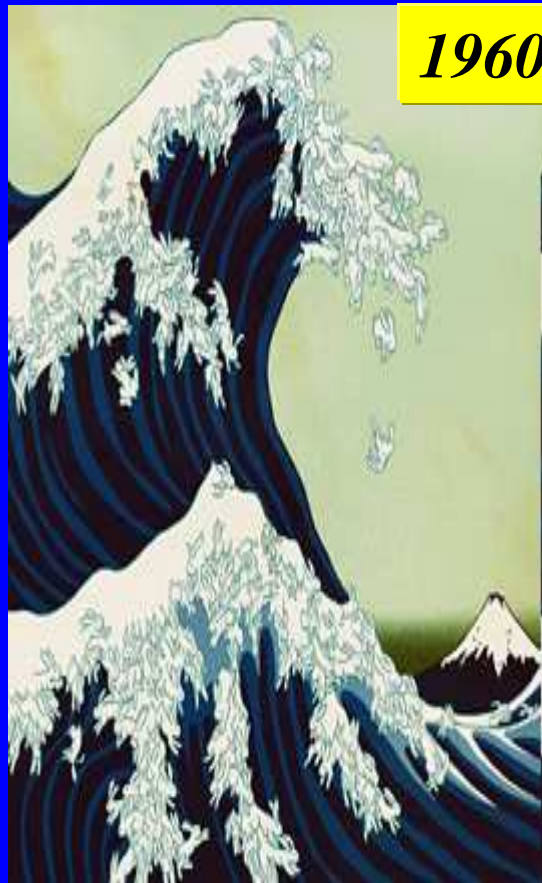


E. coli resistant to amoxicillin (%) in bacteremias, EARSS 2002

40 years after the emergence of classical plamid penicillinases (TEM-1) !!



The 3 waves of plasmid-born β -lactamase mediated resistance in enterobacteria (Hokusai's vision)

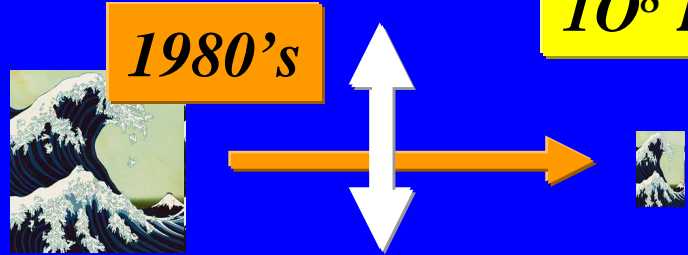


1960's

Same ways of spread:
strains (plasmids) between
humans, animals, environment:
digestive tracts \rightarrow wastes \rightarrow
agriculture \rightarrow food (& back)

“a new fecal threat”

10^8 E.coli/gr



1980's

2000's

Penicillinases (TEM-1...)
Amox-R

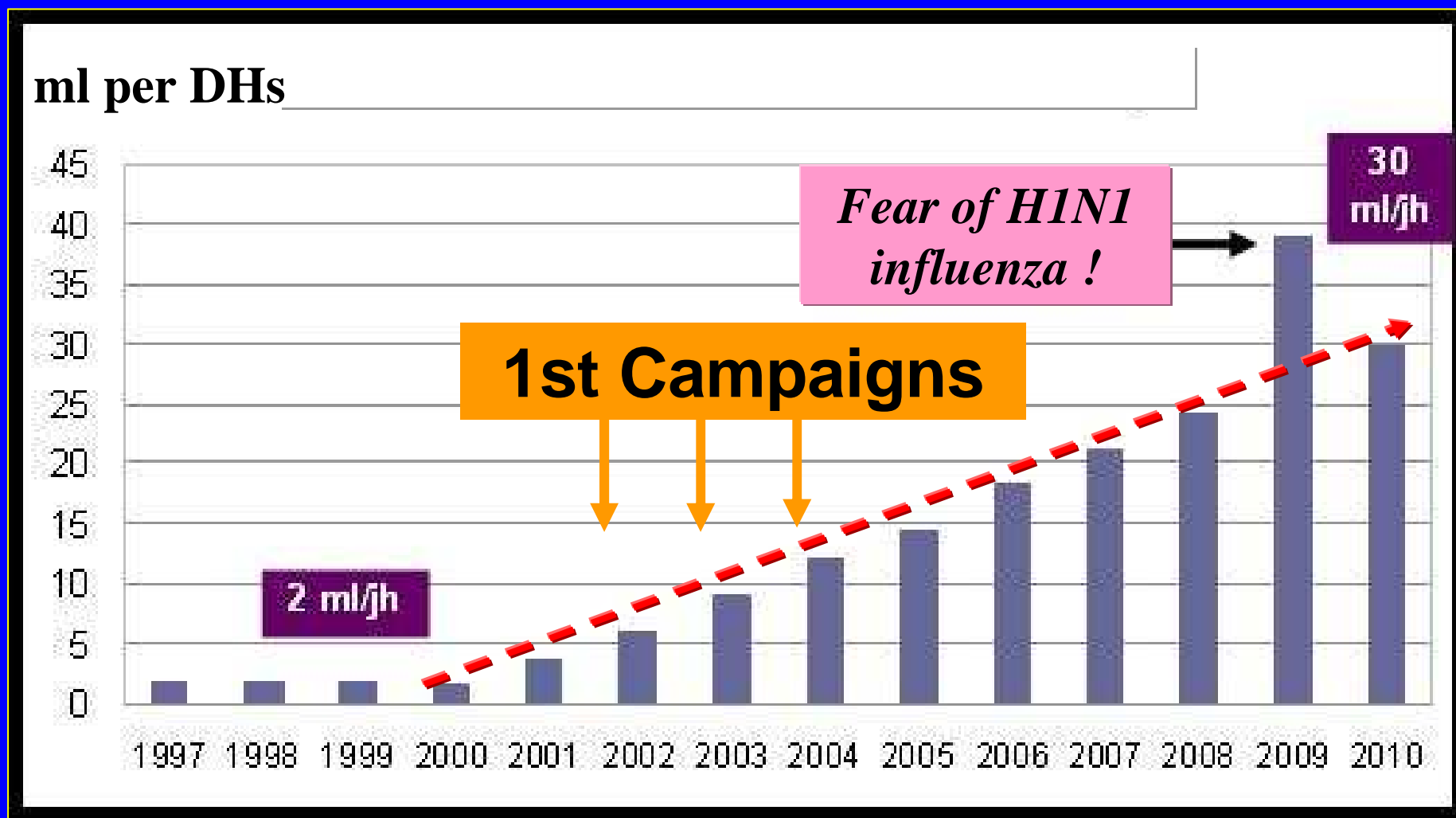
ESBLs
Amox-C3G-R

Carbapemenases
Amox-C3G-Carb-R

\rightarrow C3G use

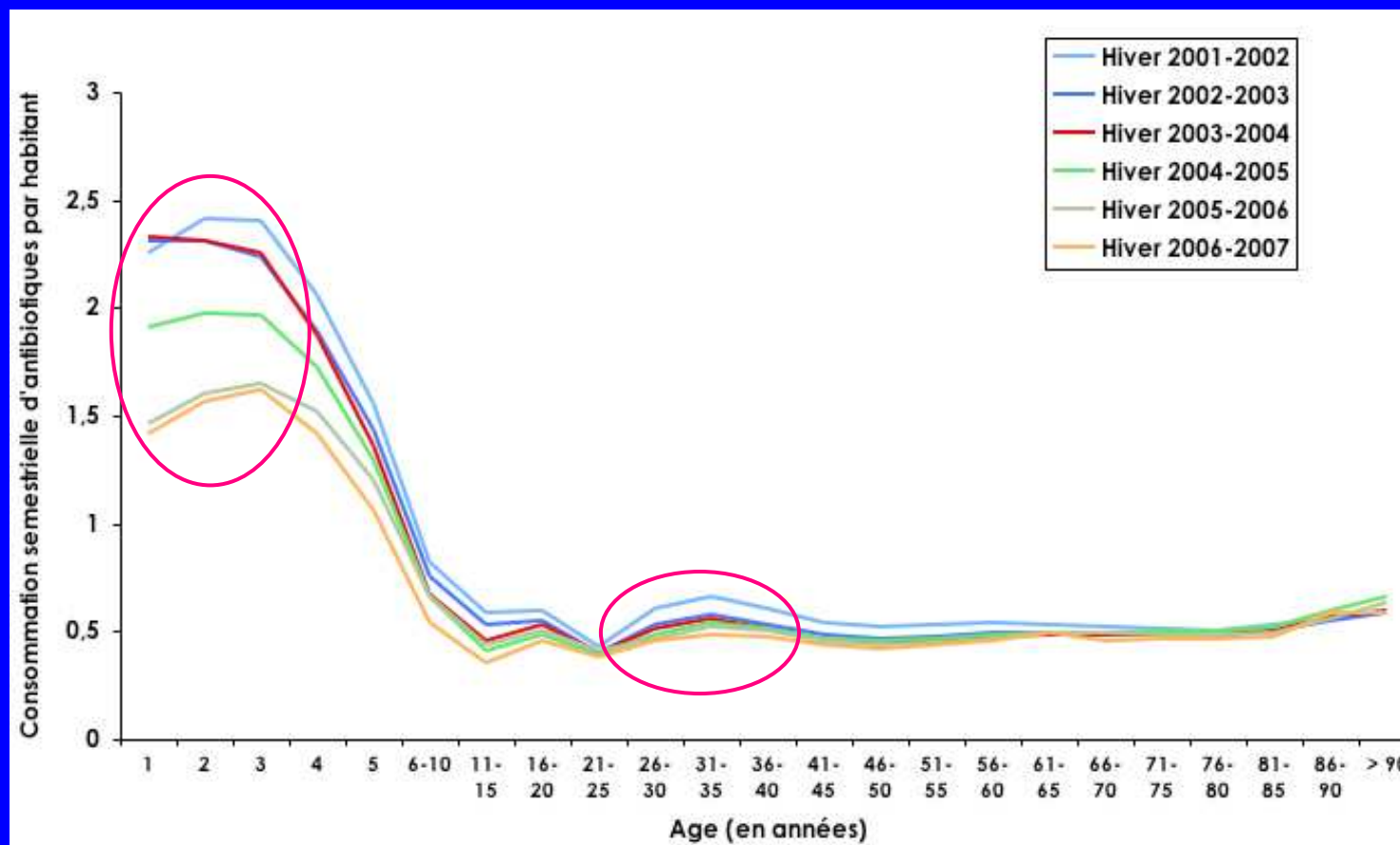
\rightarrow Carb use

ABHR solutions consumption AP-HP 1997 - 2010



Evolution de la consommation antibiotique par tranche d'âge (périodes octobre - mars)

Prescriptions d'antibiotiques en fonction de l'âge sur les périodes octobre – mars



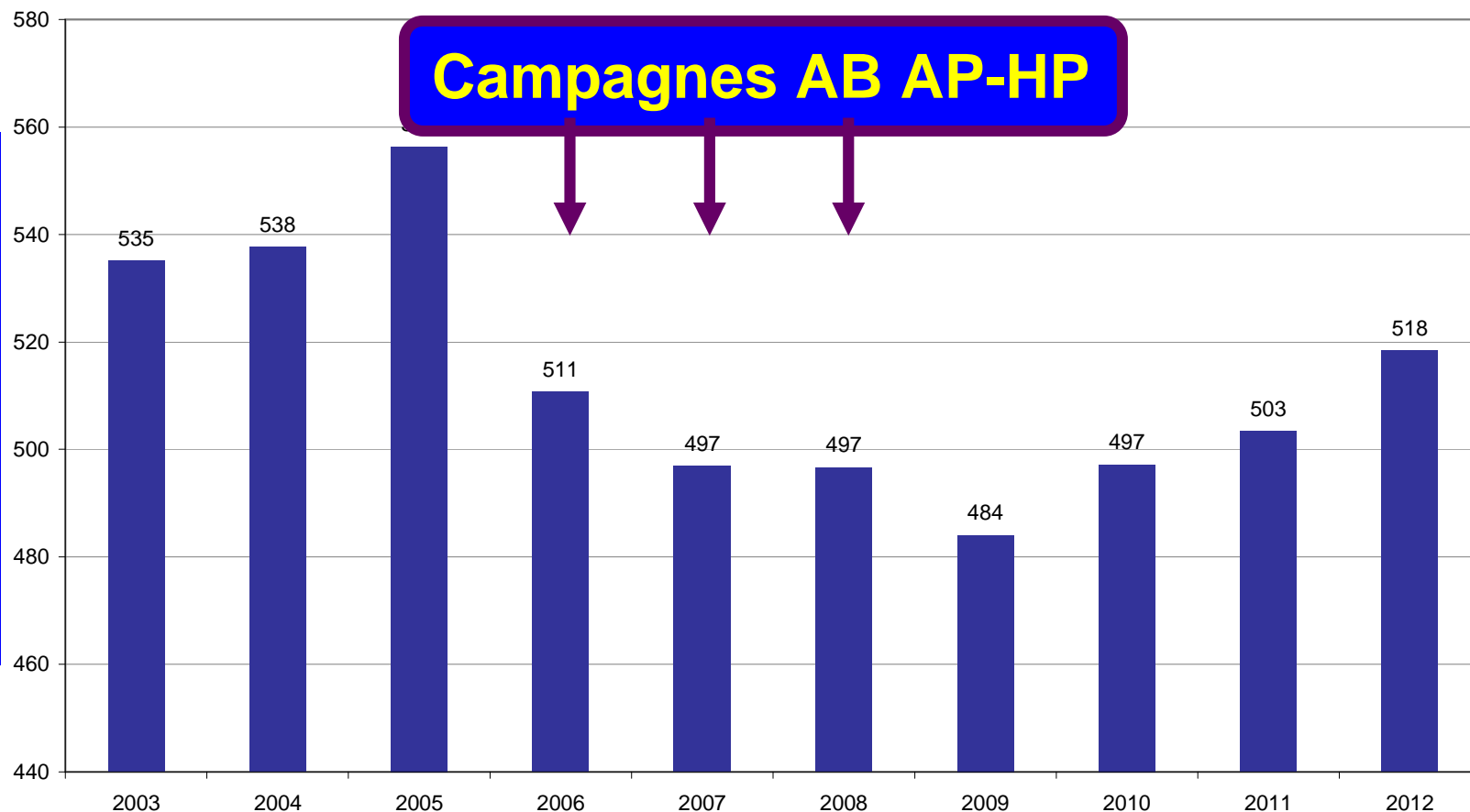
Jeunes actifs (26/35 ans) : baisse continue de la consommation d'antibiotiques (-5,7 % de 2002 à 2007)

Consommation des Antibiotiques AP-HP

Source AGEPS

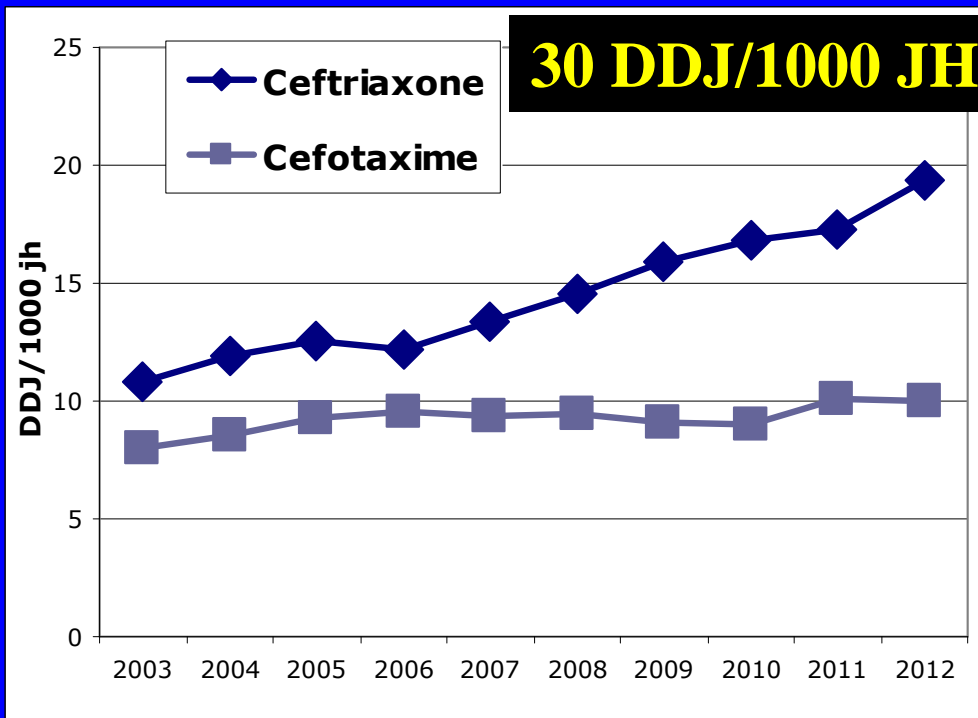
Consommation antibiotiques à l'AP-HP

DDJ/ 1000 JH

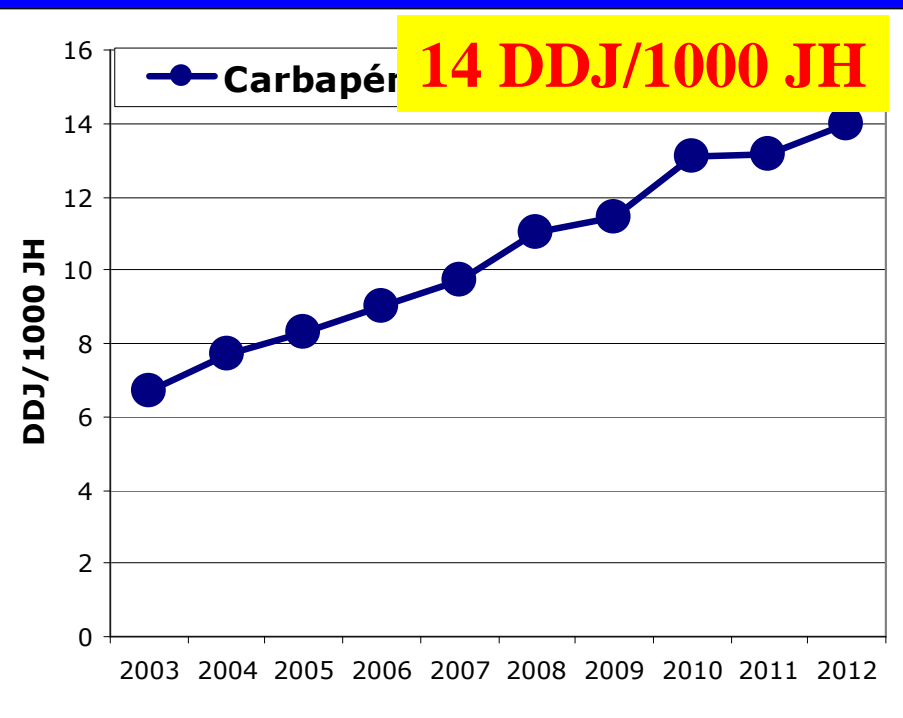


Evolution de la consommation des C3G et des pénèmes à l'AP-HP

Ceftriaxone - Cefotaxime



Carbapénèmes



Enquête excréta APHP 2011-12

13230 lits, 536 unités, 28 hôpitaux

- 61% des lits avec **WC partagés**
- 43% des WC équipés de **douchettes rince-bassin**
- 85 % des unités **n'utilisent pas de couvercle** pour le transport des bassins
- 62% des services : bassin dédié au patient pendant son séjour

Enquête excréta APHP 2011-12

13230 lits, 536 unités, 28 hôpitaux

- 68% des services équipés de lave-bassins
- 26 % des lave-bassins avec **maintenance préventive**
- 65 % des lave-bassins ont au ≥ 1 panne / an
- Risque de panne lié au manque de maintenance
- 52% des lave-bassins sont dans des **locaux sans SHA**
(20% ni SHA ni point d'eau pour l'hygiène des mains)

Enquête excréta APHP 2011-12

13230 lits, 536 unités, 28 hôpitaux

- . Rinçage dans la **chambre** : **62% des unités**
- . Directement dans lave-bassin : **19% des unités**
- . **Formation AS** sur les bonnes pratiques de gestion des excréta : **8% des unités**

Treatment of wastewater and inactivation of ESBL enterobacteria

- Mean concentration in *E.coli* in sludge:
 - before treatment : 10^3 - 10^4 /gr
 - after treatment 1 (“stabilization”) : 10^3 - 10^4 /gr
 - after heating : 10^3 /gr
 - after drying : 0
- Presence of ESBL *E.coli* in 0.1 gr : 44 / 72 samples

Table 4 – ESBL detection in sewage sludge samples.

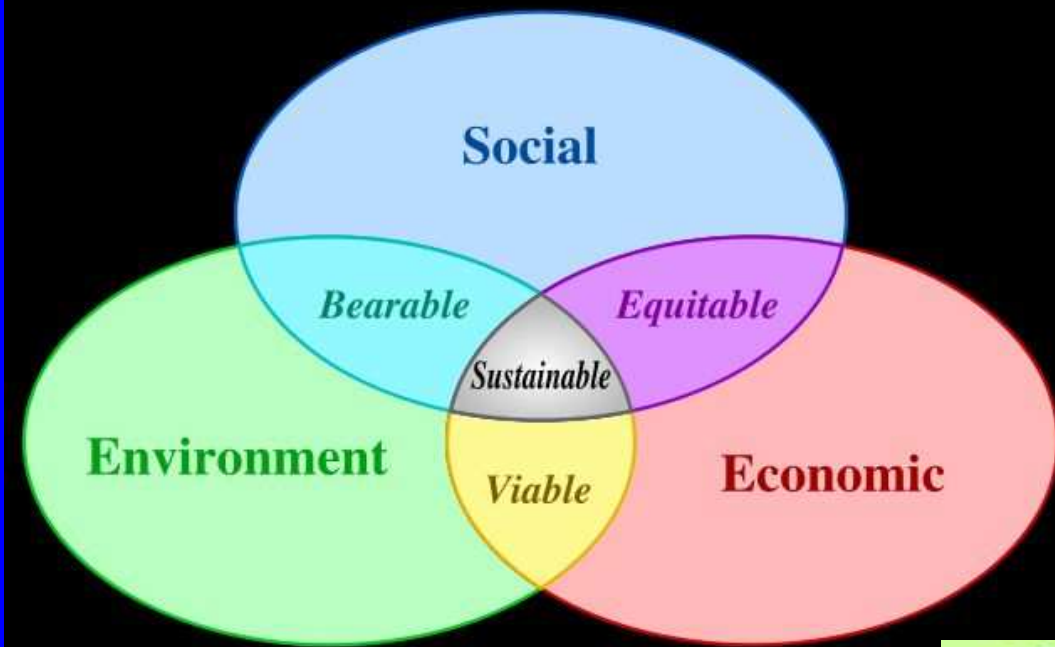
Sludge type	n = Number of samples investigated	n = ESBL-positive sludge samples (%)
Activation	27	20 (74.1)
Stabilized	12	8 (66.7)
Dehydrated	21	14 (66.7)
Dehydrated (lime)	0	0
Not dehydrated (lime)	6	2 (33.3)
Dried	6	0
Total	72	44 (61.1)

Antibiotic resistance : a "pollution"

- materialized by living bacteria and resistant genes (plasmids, transposons, integrons...)
- accumulates in all sectors of environment
- circulates between environment, animals, humans
- stable, no (or slow ?) spontaneous disintegration

- success primarily driven by antibiotic use
- amplified by cross transmission

Could be compared with radioactive wastes...



Sustainable development

- Water
- Forest
- Nuclear energy
- Antibiotic susceptibility

