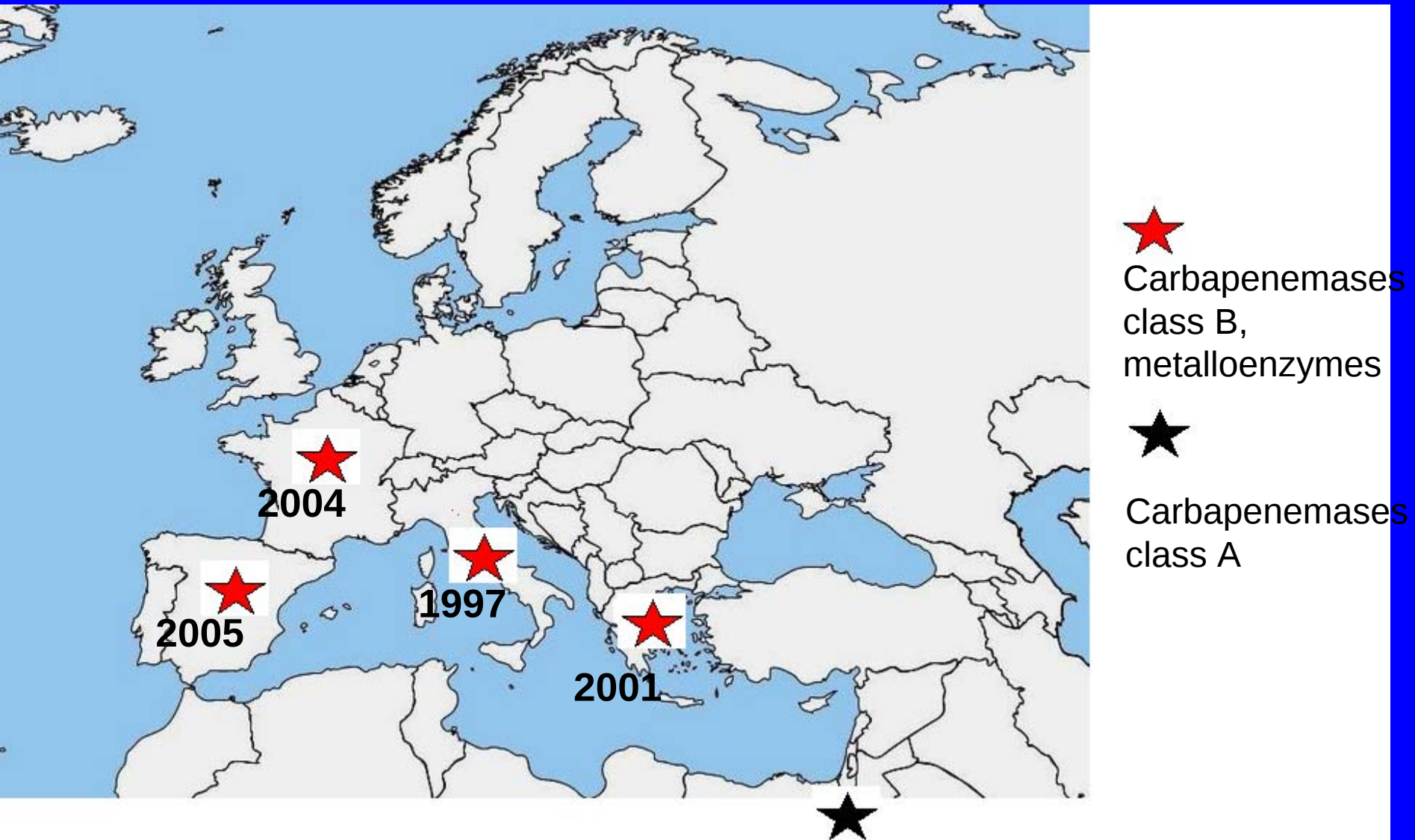


**Carbapenem-resistance in
Enterobacteriaceae :
bacteriology and infection control
view points
(in a country of low prevalence)**

**Vincent Jarlier
Bacteriology-Hygiene
Pitié-Salpêtrière Hospital, Paris**

**Central Infection control team
Assistance Publique – Hôpitaux de Paris**

1st detection of CARBAPENEMASES in EUROPE



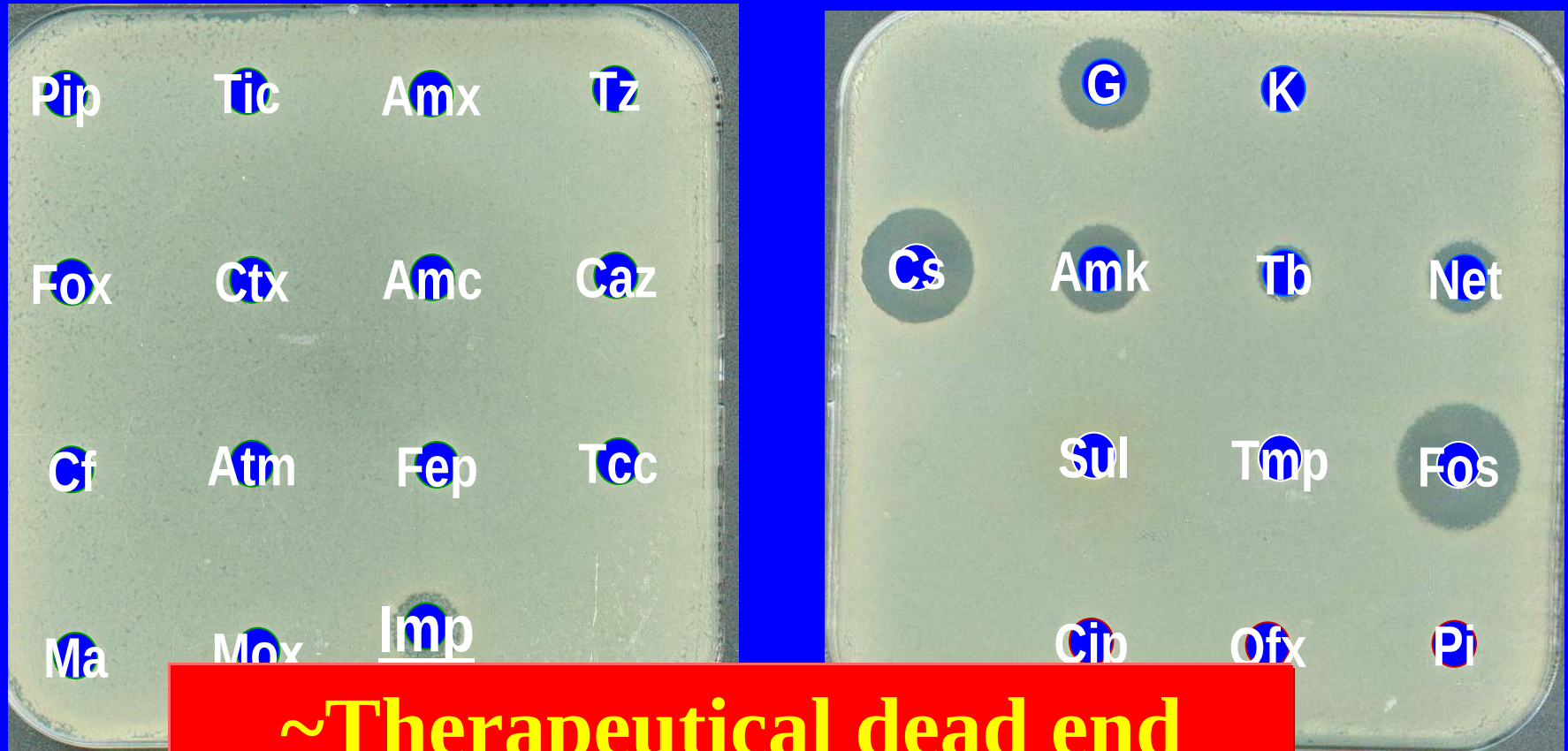
G.Arlet, ann biol clin, 2006

1st outbreak in France :
winter 2003-summer 2004

Paul Brousse hospital (Paris) 2004

Klebsiella pneumoniae VIM-1 + SHV-5

(index case : transfer from Athens)



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

Initial control measures

From December 2003 to June 2004

- IR-Kp carriers isolation in 1 bed rooms
- Promotion of alcohol-based-hand rubbing
- daily staff training
- Screening ICU patients at admission and 1/week (rectal swabs, 4 mg/l imipenem containing agar)

Extended control measures in June 2004 (1)

- **ICU divided in 3 separate sections**
 - 1 for cohorting IR-Kp carriers (“**IR-Kp ICU**”)
 - 2 for the IR-Kp-free patients (“**IR-Kp free ICU**”)
 - for expected duration $\gg$ 2days and “heavy” ICU (“**long**”)
 - for expected duration $\leq$ 2days and “ligh” ICU (“**short**”)
- **Acute care divided in two sections :**
 - 1 for IR-Kp-free patients but transferred from ICU or patients previously hospitalized in the ward (at risk to be carrier : “**contact patients**”)
 - 1 for new patients (not at risk : “**IR-KP**”)

Kassis-Chikani
Eurosurveillance
2010 in press

Paul Brousse hospital (Paris) 2004 *Klebsiella pneumoniae* VIM-1 + SHV-5 : splitting the ward in distinct sectors

TABLE 2

Organisation of distinct sections in intensive care unit and acute care facility during Period 2 of the control measures, abdominal surgery care centre, France, 2 June to 21 October 2004

	Separation with plastic wall ↓	
First floor intensive care unit	IR-Kp patients section	IR-Kp-free – long stay intensive care unit section
	IR-Kp patients who stayed in intensive care until discharge Number of beds ^a : 3	Patients requiring intensive care for an expected duration of more than 48 hours Number of beds ^a : 12
Third floor acute care facility	IR-Kp free patients non-intensive care unit section	IR-Kp-free – short stay intensive care unit section
	Patients directly admitted to the acute care facility Number of beds ^a : 25	Patients having major surgery but requiring monitoring for less than 48 hours Number of beds ^a : 5
Fourth floor acute care facility	Contact acute care section	
	Patients hospitalised on the same floor and at the same time as an IR-Kp patient Number of beds ^a : 36	

IR-Kp: imipenem-resistant VIM-1-producing *Klebsiella pneumoniae*.

^a Only single bedrooms.

Kassis-Chikani
Eurosurveillance
2010 in press

Extended control measures in June 2004 (2)

- nurse staff exclusively dedicated to “IR-Kp ICU”
- nurse staff exclusively dedicated to “IR-Kp free ICU”

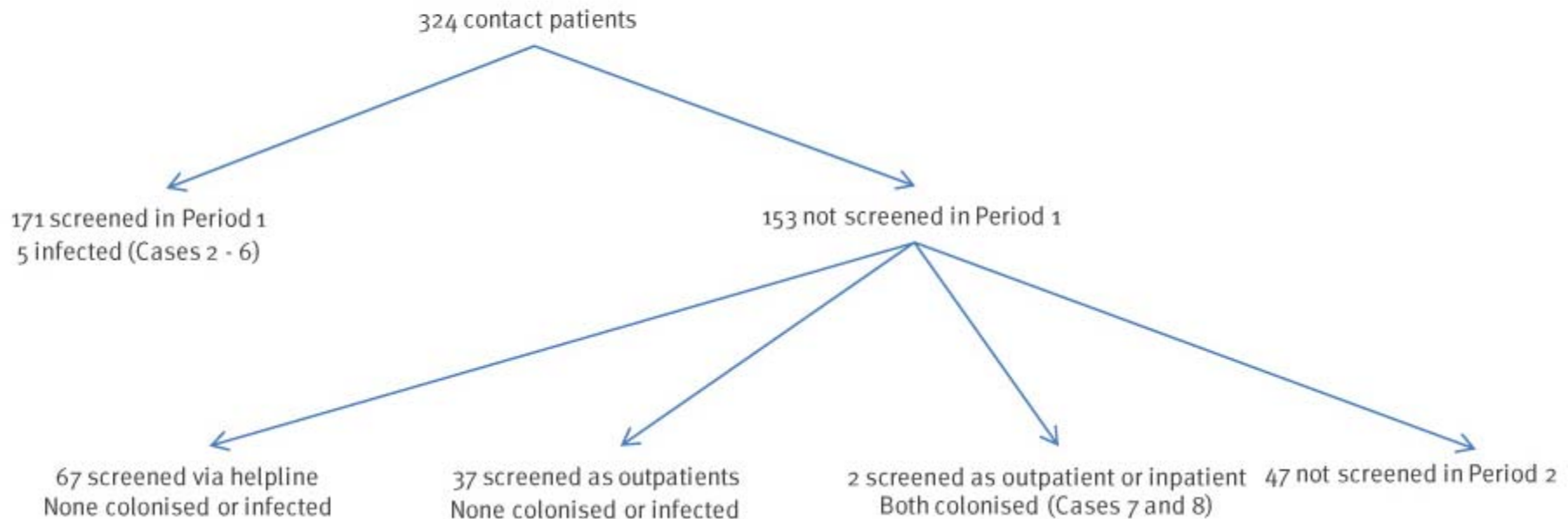
Extended control measures in June 2004 (3)

- Strict limitation of patient transfer to other wards or other care centers :
- Screening all contact patients till discharge and after and in case of readmission
- Limitation of broad spectrum antibiotics
- IR-Kp carriers informed on their status and received specific instructions at discharge

Paul Brousse hospital (Paris) 2004 *Klebsiella pneumoniae* VIM-1 + SHV-5 : screening : 277 patients (~1,000 swabs)

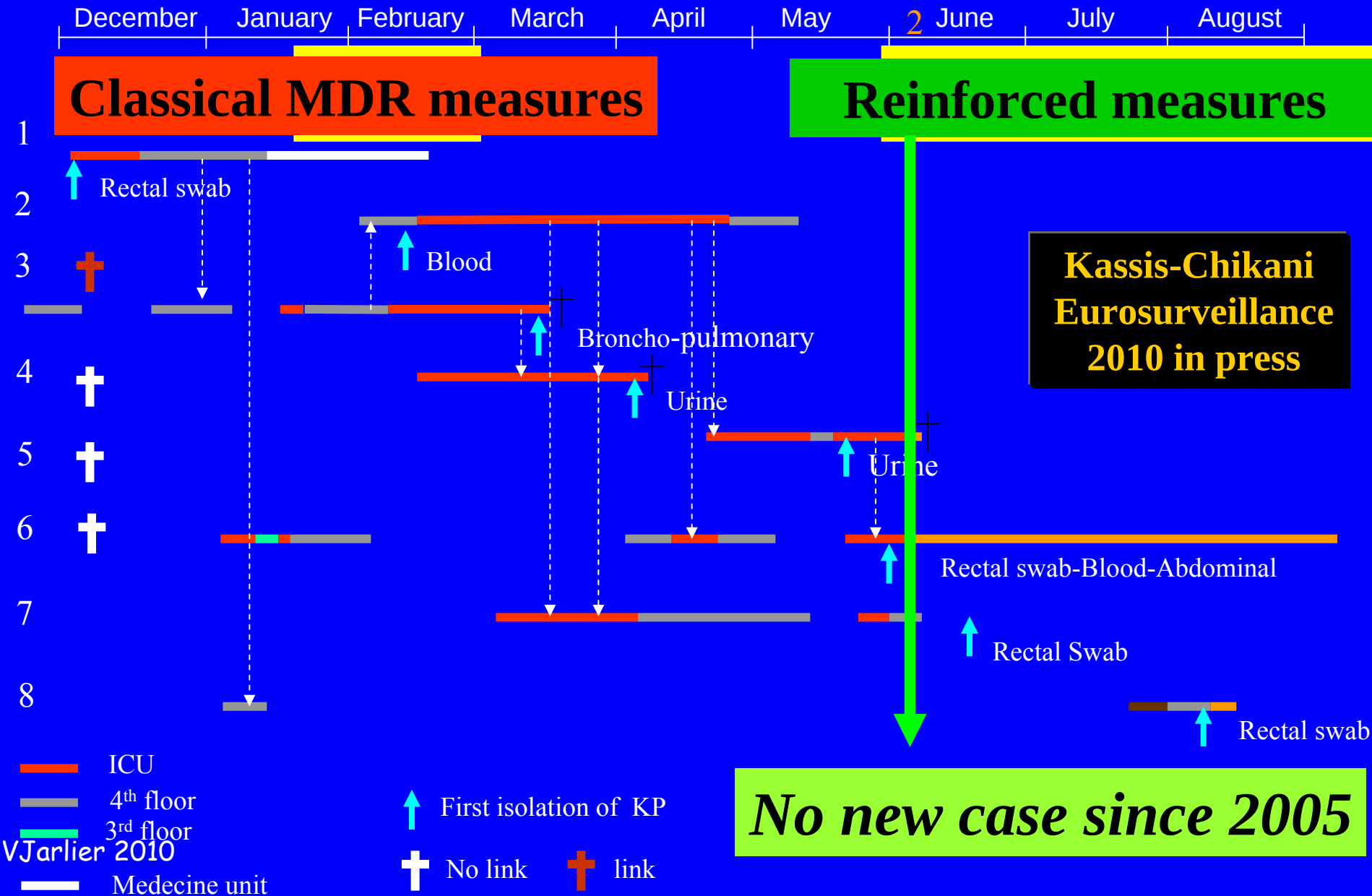
FIGURE 2

Patients screened in connection with an outbreak of imipenem-resistant *Klebsiella pneumoniae* in an abdominal surgery care centre, France, 2 December 2003 to 21 October 2004



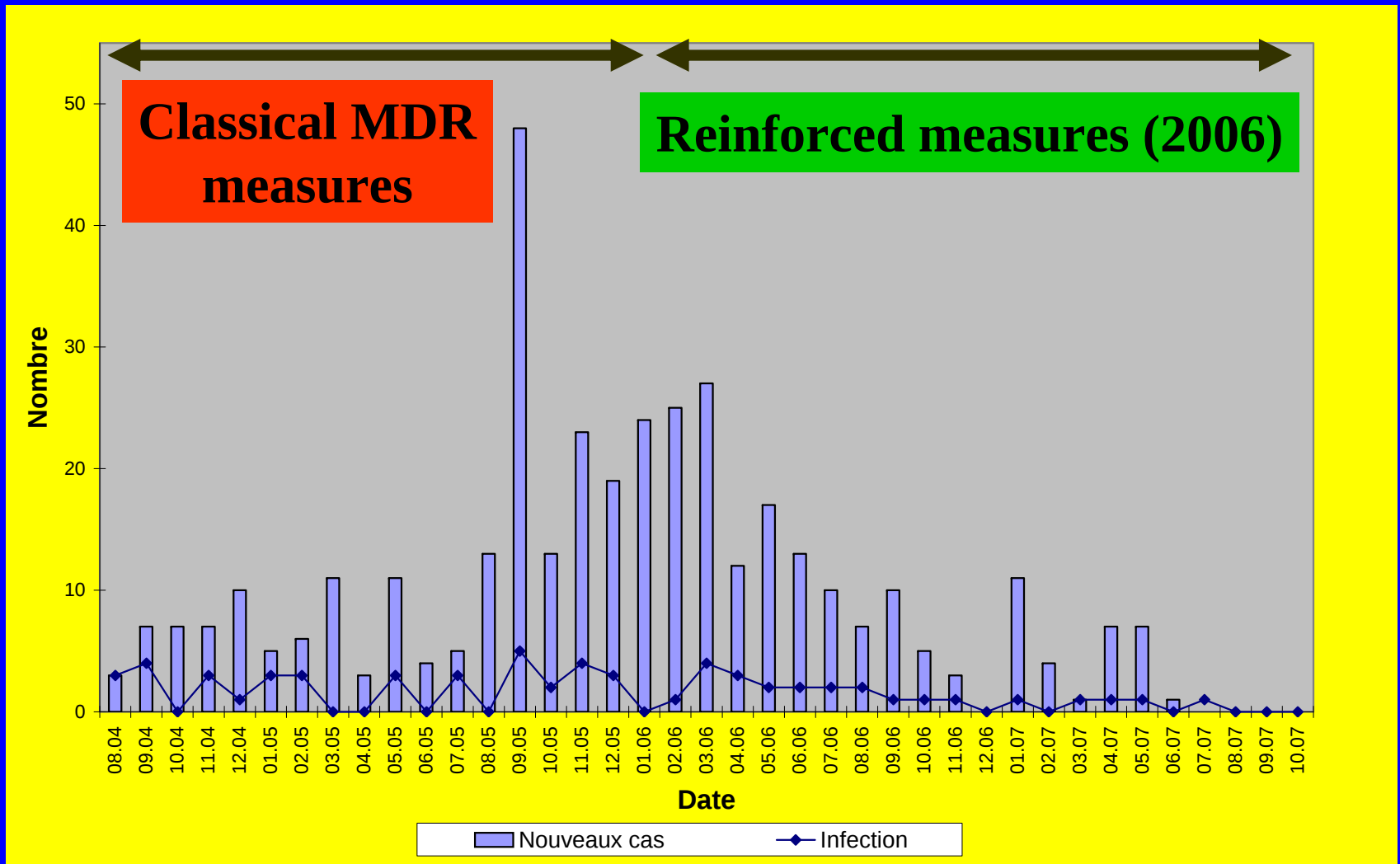
Kassis-Chikani
Eurosurveillance
2010 in press

Paul Brousse hospital 2004

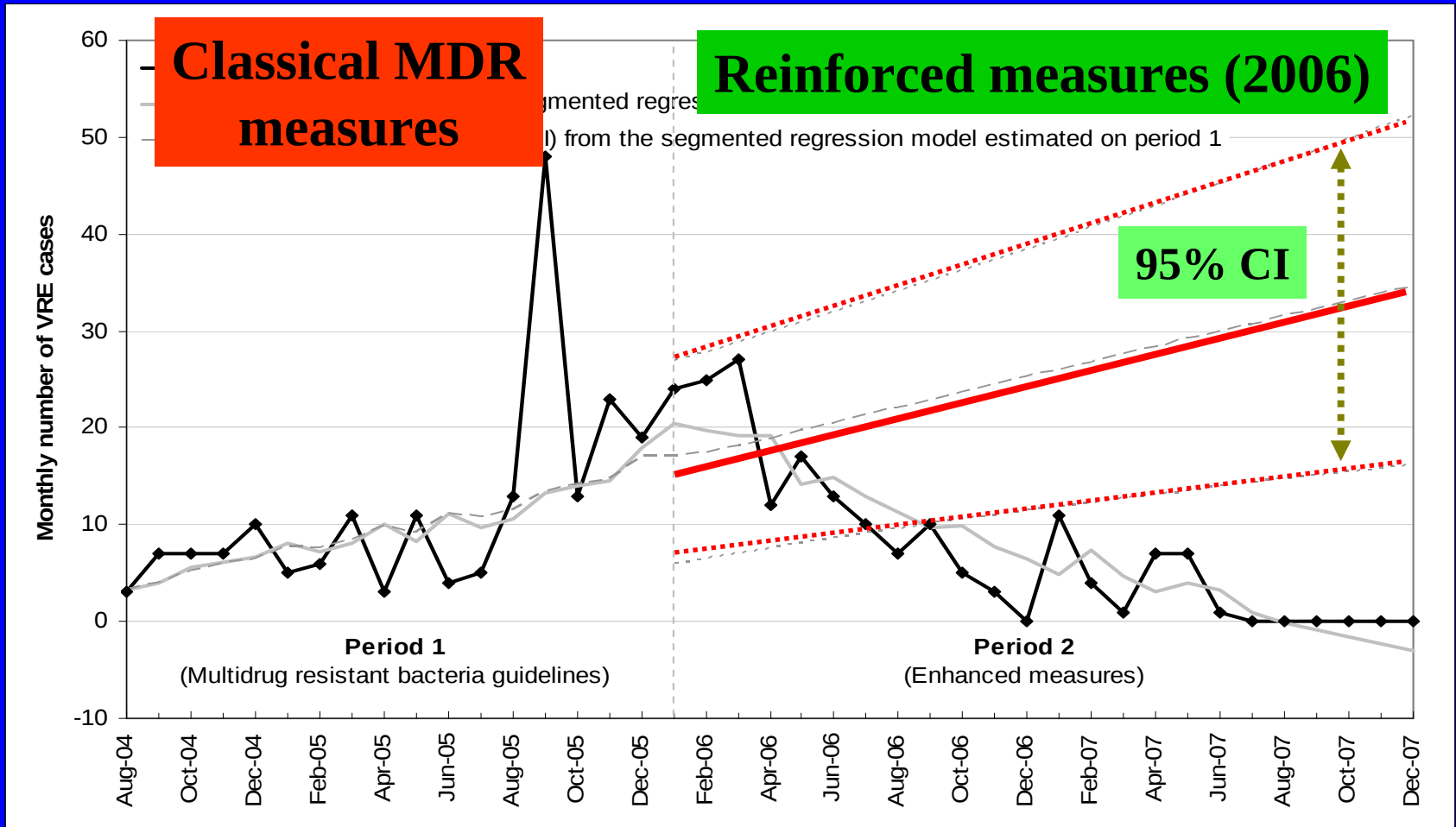


Practicing control of emerging MDROs in France : VRE Summer 2004-2007

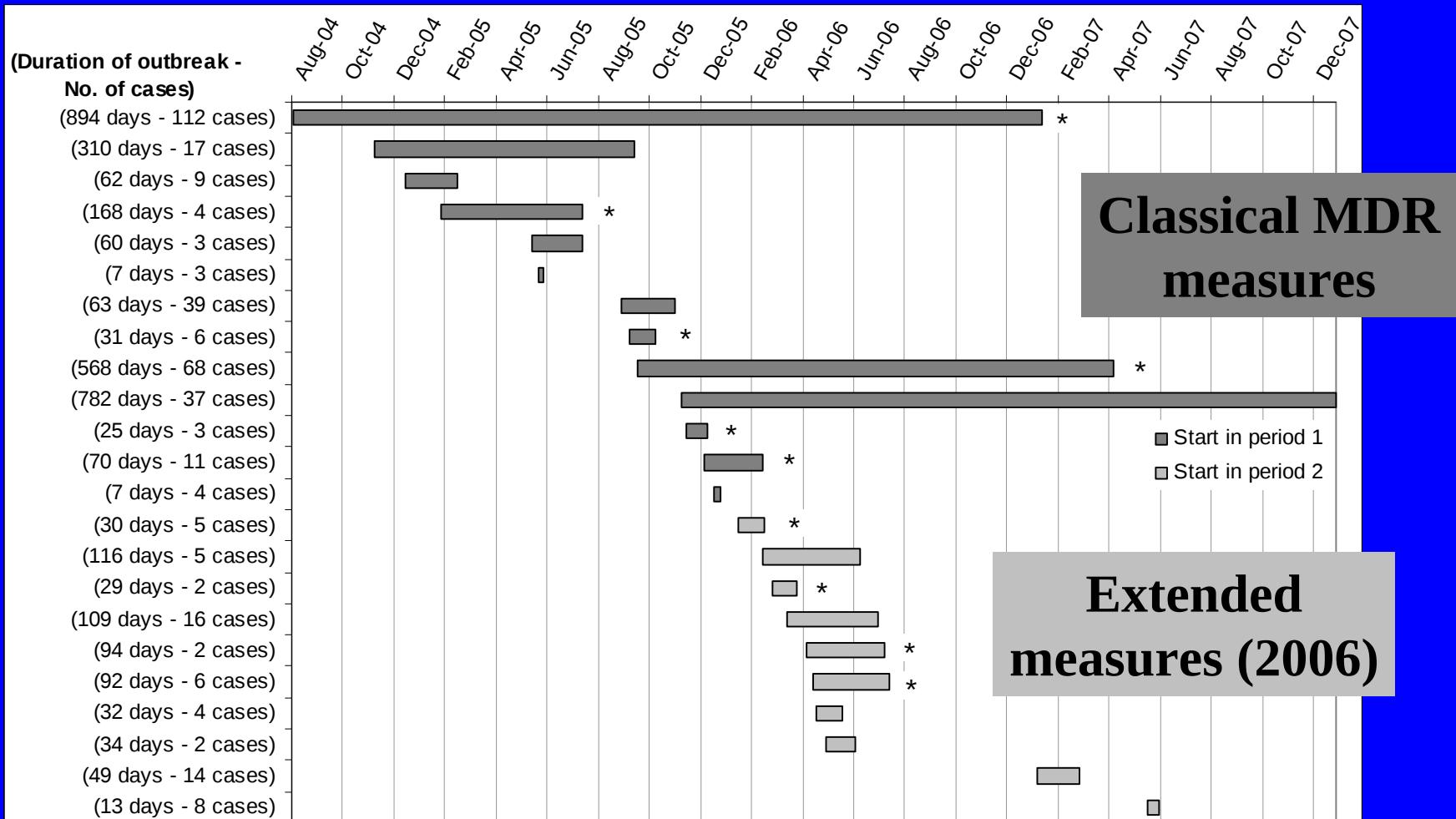
VRE cases per month 39 univ. hosp. Paris area (AP-HP) 2004-2007



VRE cases per month observed and predicted by time series analysis 39 univ. Hosp. Paris area (AP-HP) 2004-2007



The 23 VRE outbreaks in 39 univ. hosp. Paris area (AP-HP) 2004-2007



Releasing French national
guidelines for emerging
MDROs control (e.g. Carb-R
Enterobacteriaceae):
2006 (new edition 2010)

As soon as identification of the index case

- Isolate the patient in a single bedroom
- Alert hospital administrator and IC team
- Stop transfer to other units or hospitals of (a) the index case and (b) patients of the same unit (defined as contact patients)
- Limit admissions in the unit as much as possible
- Screen contact patients

The two days following the identification

- Identify other contact patients: including those already transferred to another unit of the hospital at time of detection of the index case.
- Screen them
- Re-enforce hand hygiene (alcohol base hand-rub solution)
- Clean daily patient environment with disinfectant
- Identify antibiotics that could be used in case of serious infection with the strain of the index case

During the entire period of the outbreak

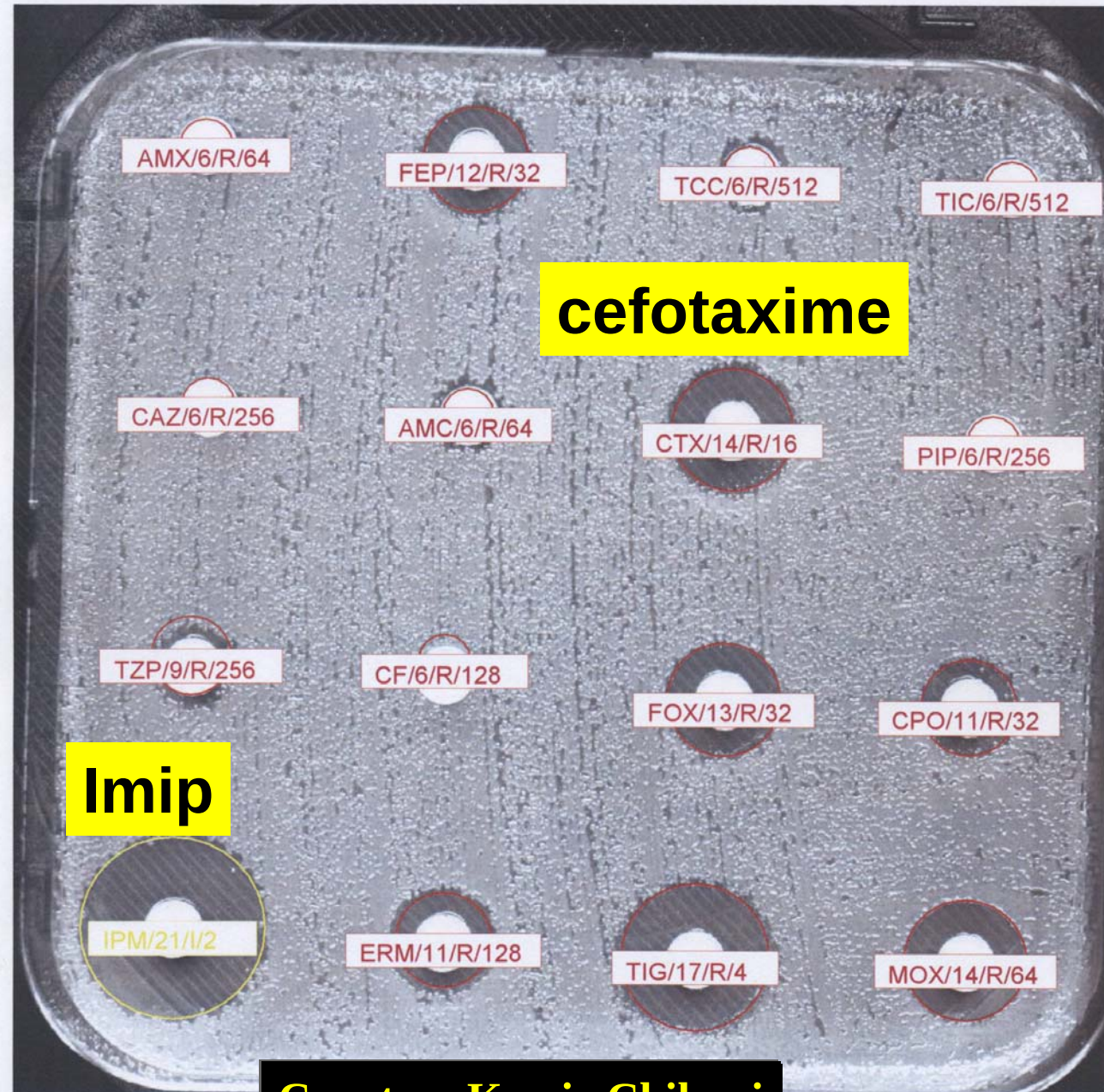
- . Cohort patients in distinct sections, each with dedicated nursing staff:
 - case patients (« case section »)
 - contact patients ("contact patient section ")
 - newly admitted patients ("free section ")
- . Screen once weekly all contact patients
- . After 3 neg screenings, contact patients can be transferred in other unit of hospital (continue to isolate and screen)
- . Resume screening in contact patients receiving antibiotic.
- . Restrict antibiotics use
- . Update the list of cases and contact discharged patients, set up an information system allowing to identify them in case of re-admission

Detecting carbapenemase-
producing
Enterobacteriaceae
at the bench

Detecting carbapenemase- producing *Enterobacteriaceae* :

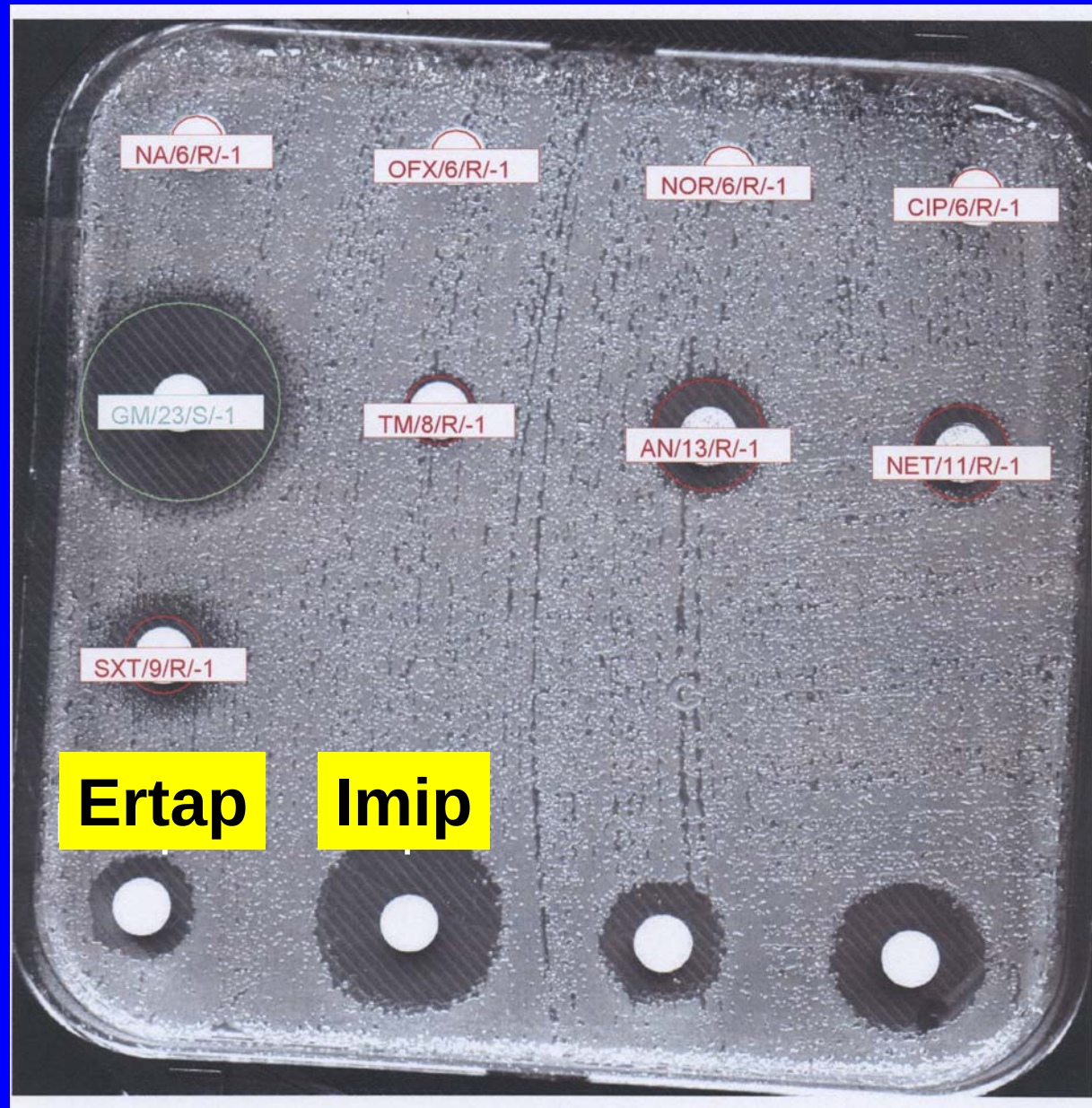
(1) warning

KPC-2
K.pneumoniae
Petri dish 1



Courtesy Kassis-Chikani

KPC-2
K.pneumoniae
Petri dish 2



Detecting carbapenemase-
producing
Enterobacteriaceae :

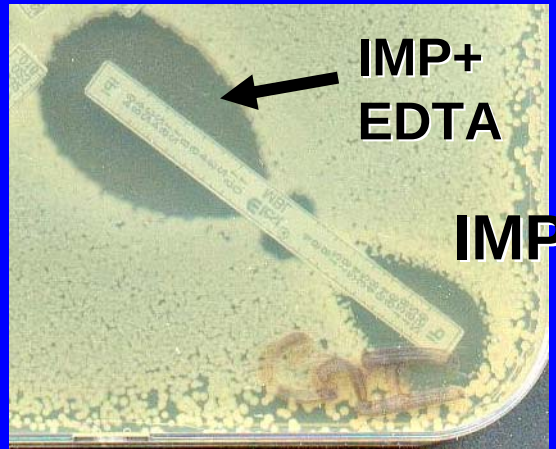
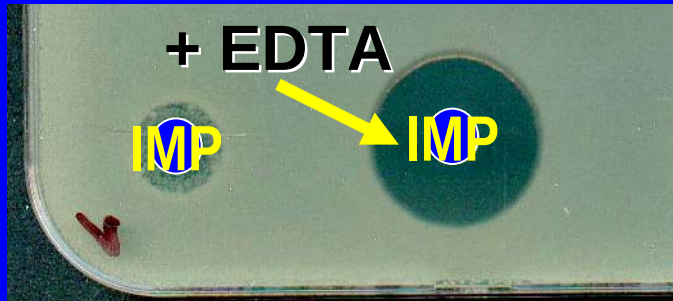
(2) phenotypic confirmation

Detecting carbapenemase-
producing
Enterobacteriaceae :

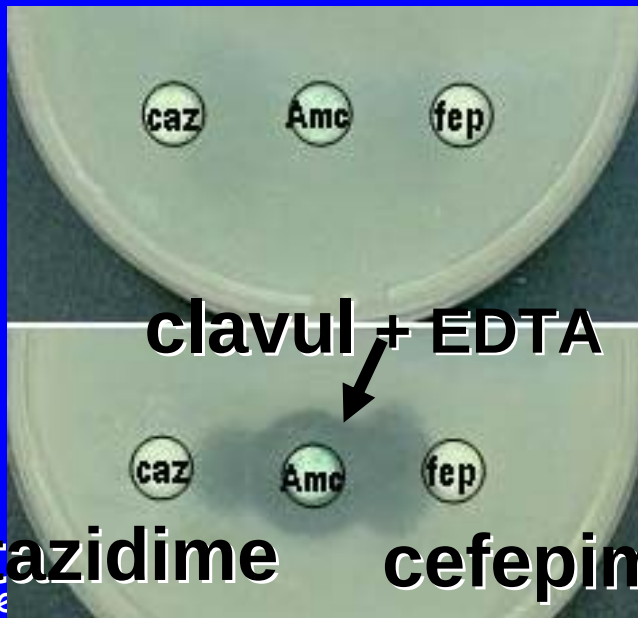
(2) phenotypic confirmation

Metalloenzymes

VIM



VIM-1 + SHV-5 :
Synergy tests for detecting
metallo-carbapemenases and
ESBL



Extended-spectrum
 β -lactamase (ESBL)
SHV-5

Kassis-Chikani
JAC 2006

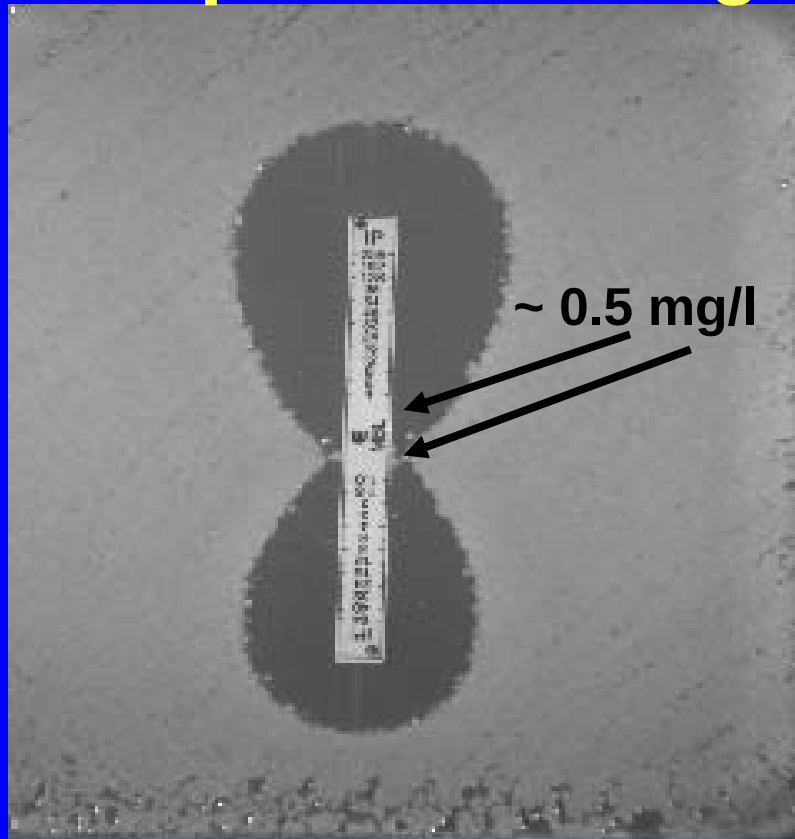
Detecting carbapenemase- producing *Enterobacteriaceae* :

(2) phenotypic confirmation

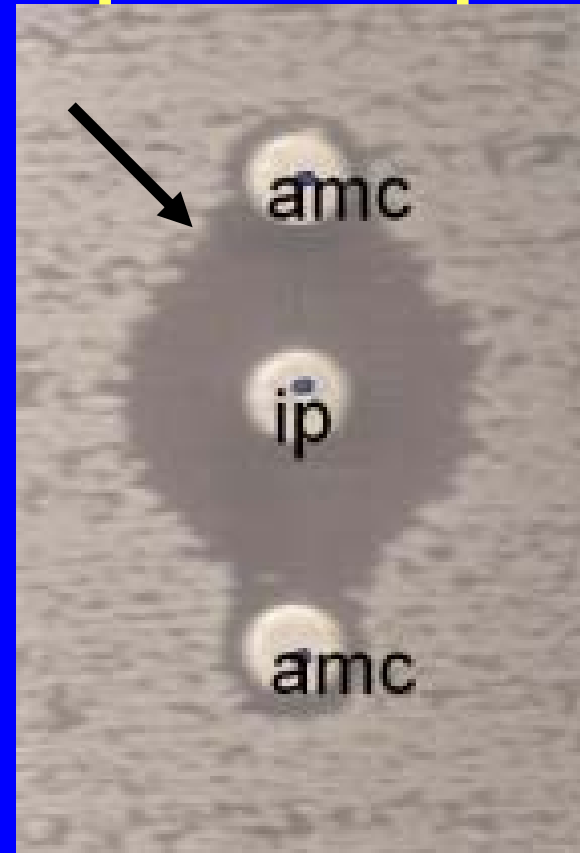
Class A enzymes

Synergy tests for mclasse A carbapemenases : Example of KPC-2

Imip-EDTA = neg



Imip-Clav = pos



KPC-2

K.pneumoniae

**Synergy C3G –
clavulanate**

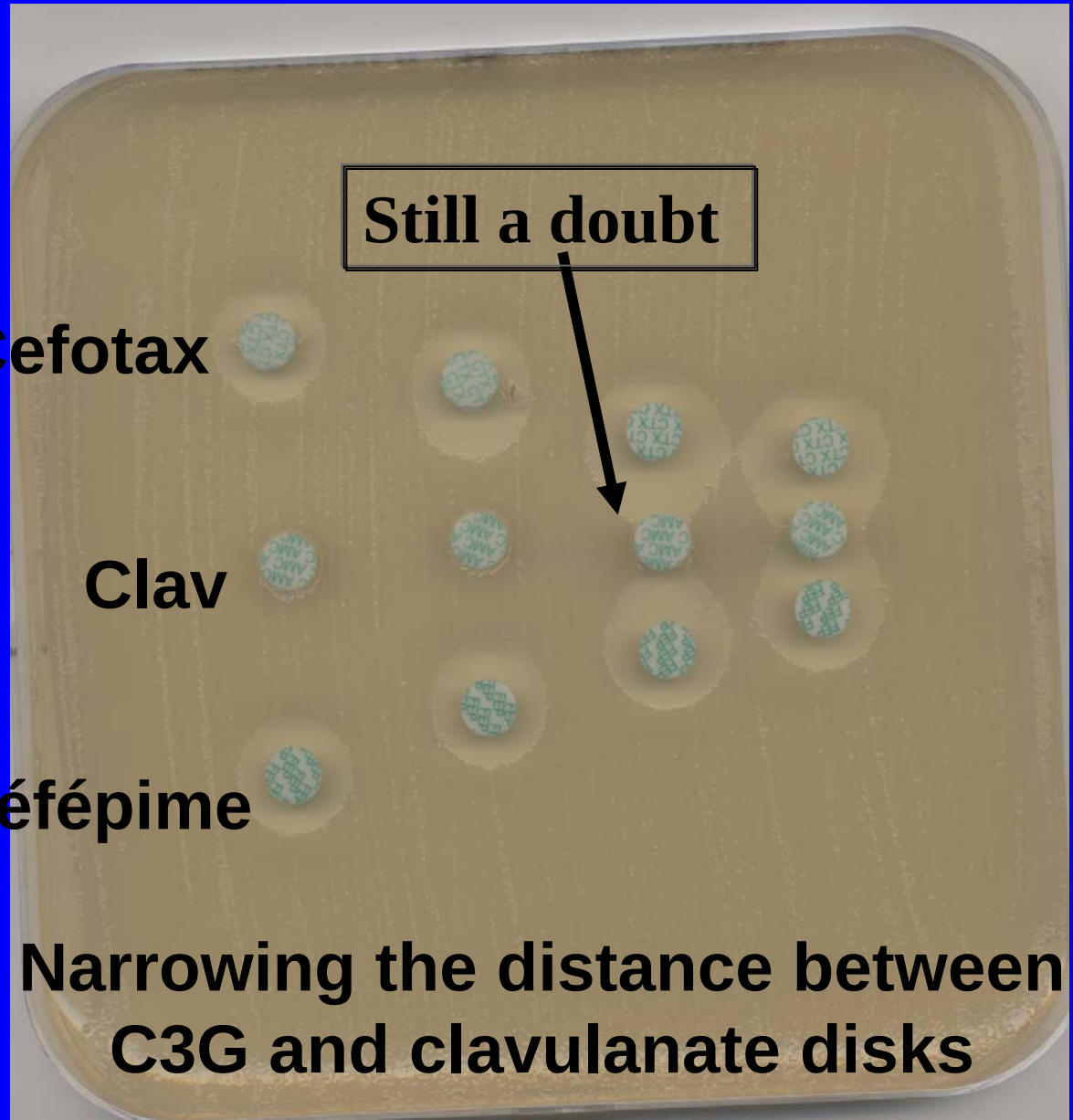
Cefotax

Clav

Céfépime

Still a doubt

**Narrowing the distance between
C3G and clavulanate disks**



KPC-2
K.pneumoniae

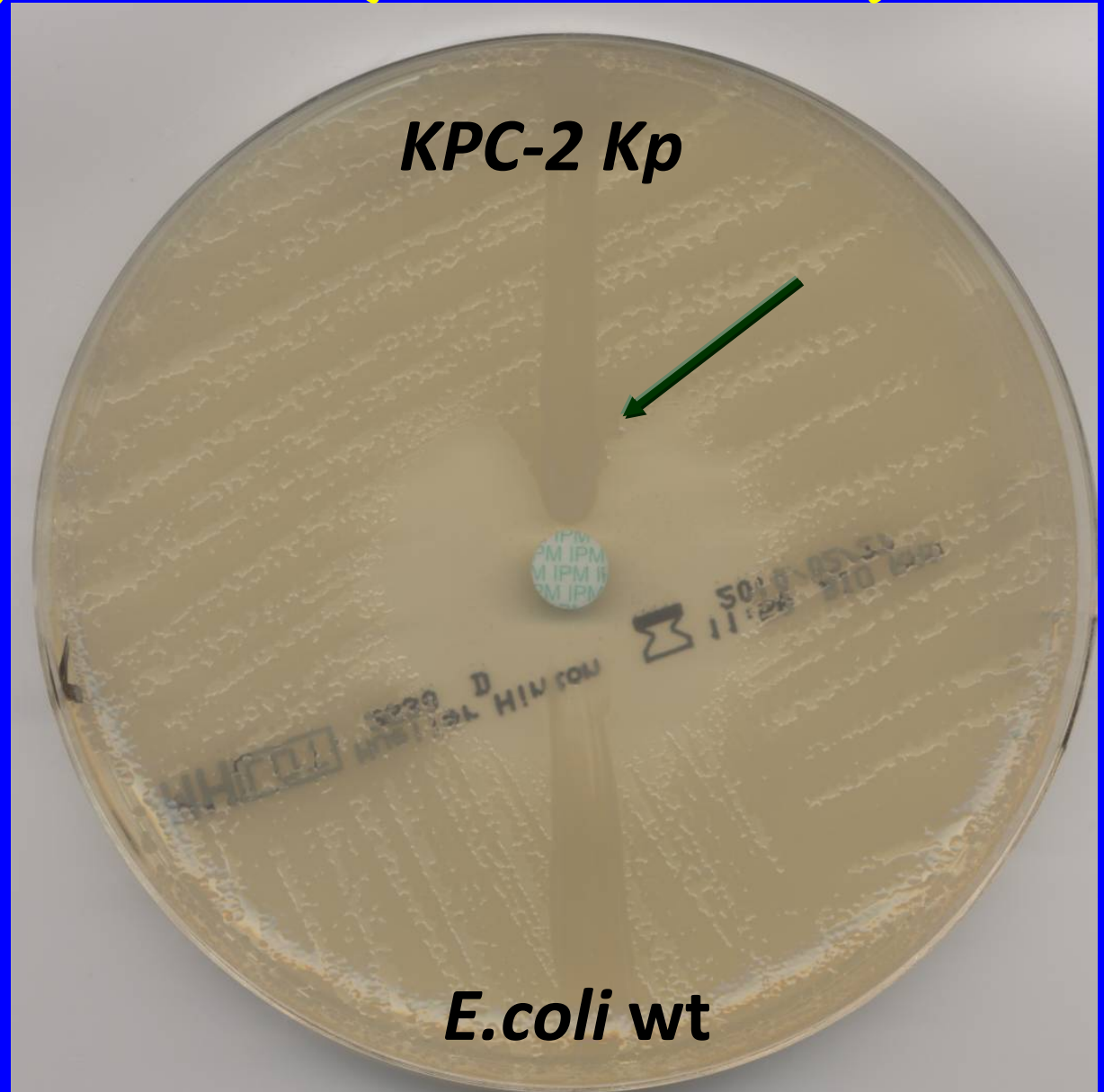
**Synergy C3G –
clavulanate**



Hodges test (~ Gots test)

KPC-2
K.pneumoniae

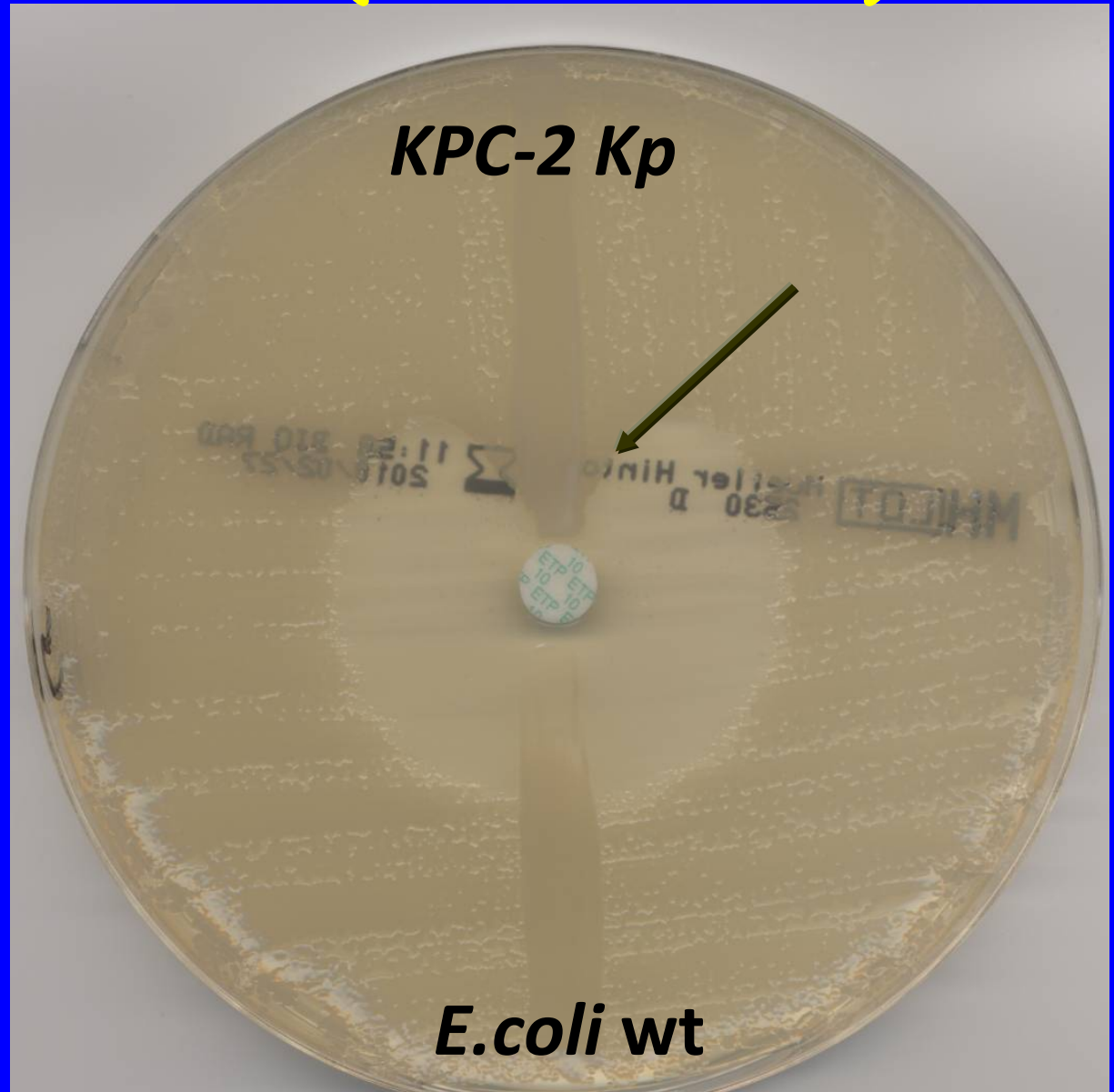
Hodges test
imipénème



Hodges test (~ Gots test)

KPC-2
K.pneumoniae

Hodges test
ertapénème



Detecting carbapenemase-
producing
Enterobacteriaceae :

(3) identification of
enzyme : molecular tests
required

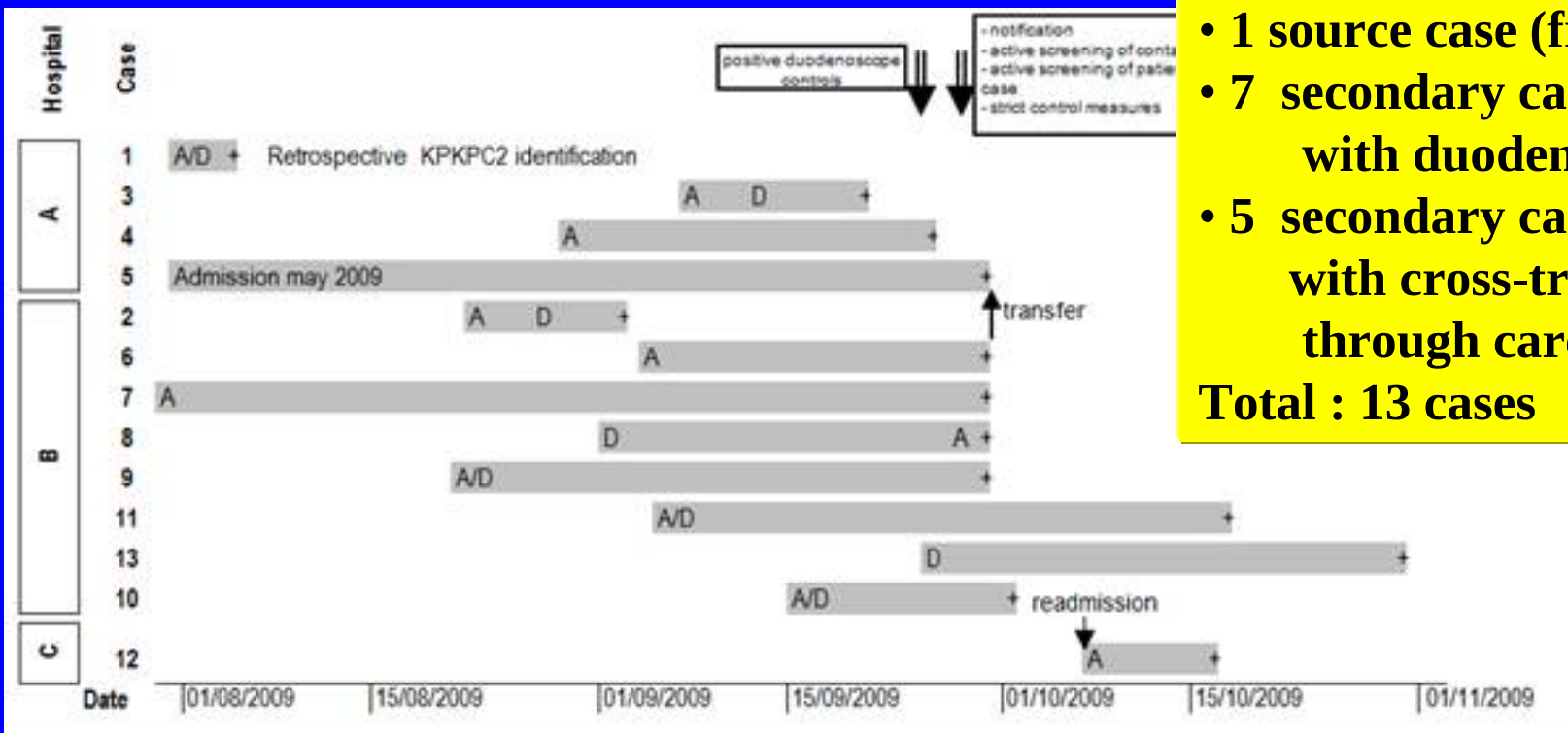
Controlling further
outbreaks of Carb-R
Enterobacteriaceae
in France :
applying the new
guidelines

Early warnings concerning
carbapenemase-R
Enterobacteriaceae in French
hospitals

(frame: French national system for
signaling abnormal nosocomial events)

- 24 events 2004-2010
- so far all controlled
(but wait and see!!!)

Investigations and control measures of a KP-KPC2 outbreak occurring in hospitals A,B and C Suburb South of Paris, September-December 2009

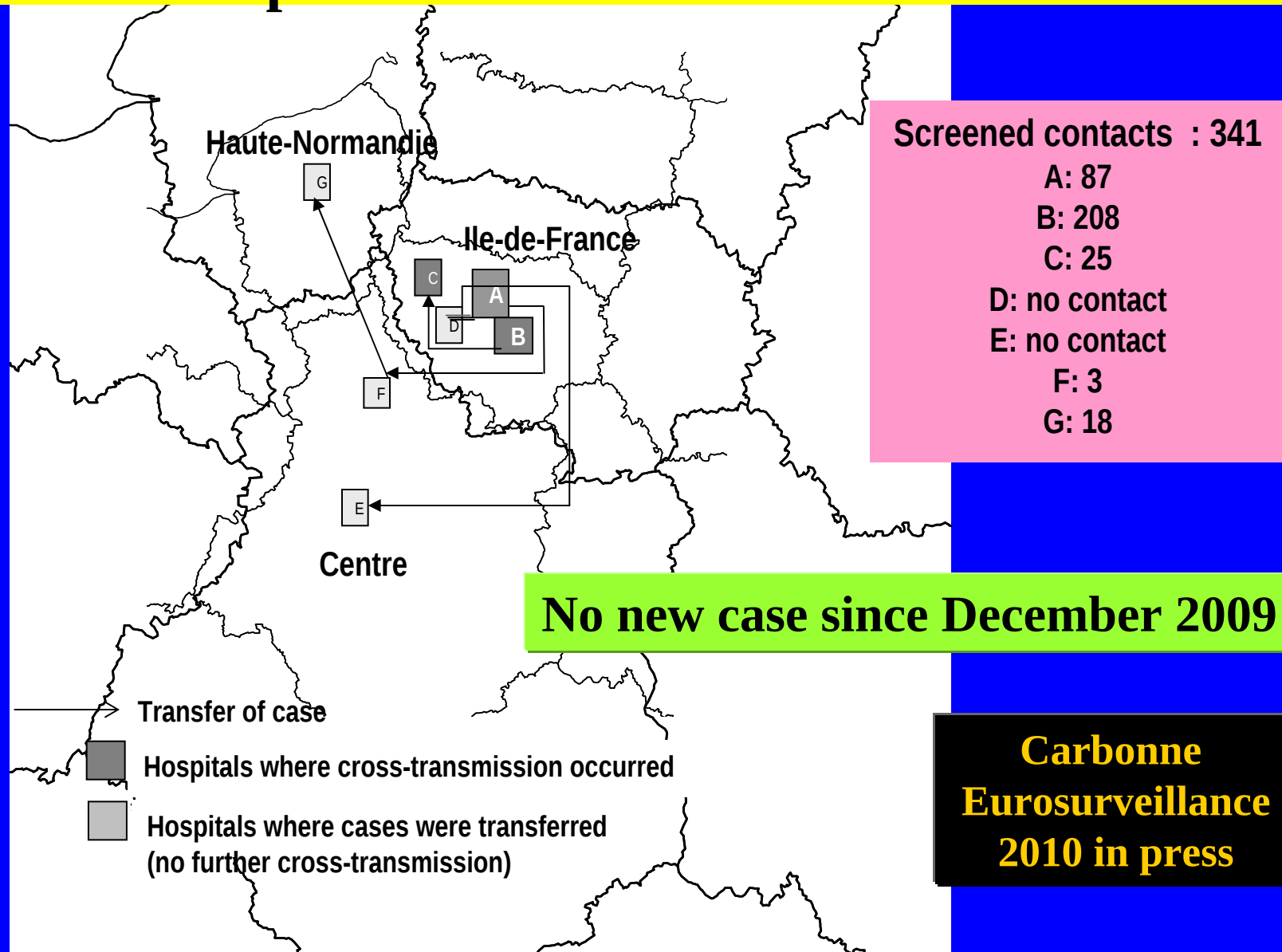


- 1 source case (from Greece)
 - 7 secondary cases linked with duodenoscopy
 - 5 secondary cases linked with cross-transmission through care
- Total : 13 cases**

A : date of admission
D : date of duodenoscopy
+ : date of 1st positive specimen

Carbonne
Eurosurveillance
2010 in press

Investigations and control measures of the KP-KPC2 outbreak in hospitals A,B,C and D,E,F,G September-December 2009



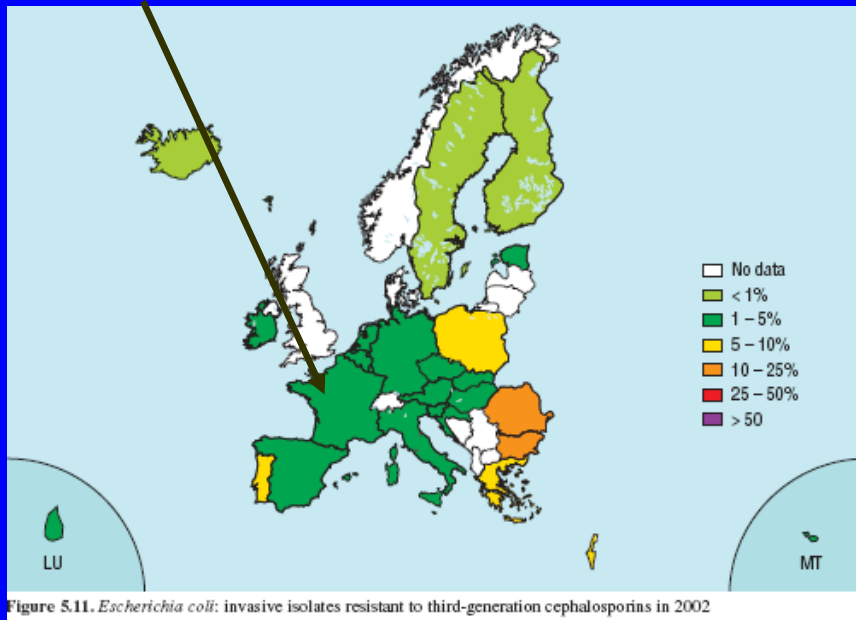
Carbonne
Eurosurveillance
2010 in press

ESBL and
Carbapenemases :
break « the infernal
circle »

ESBL *E.coli* in Europe

EARSS : *E.coli* resistant to 3rd gen. cephalosporins (%) in bacteremias

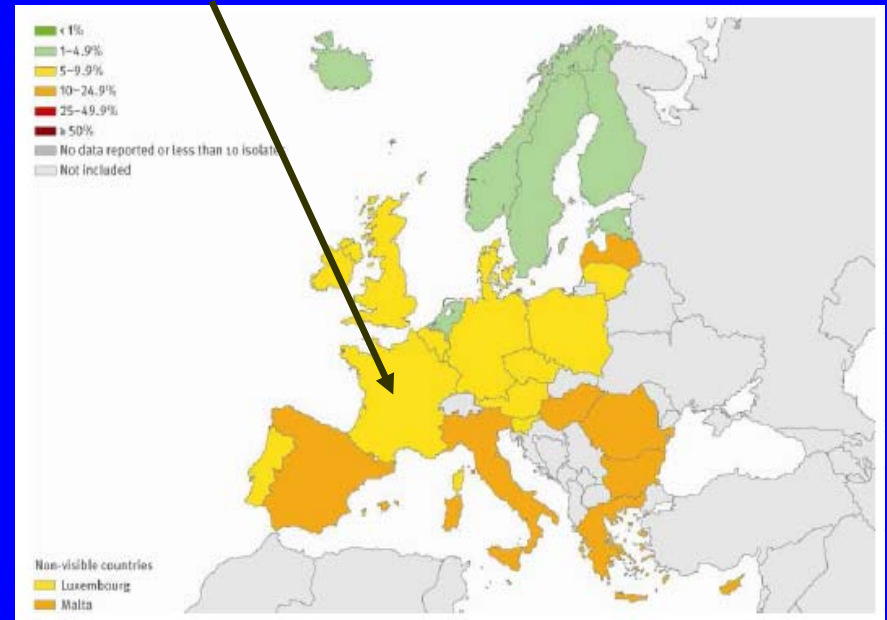
2%



2002

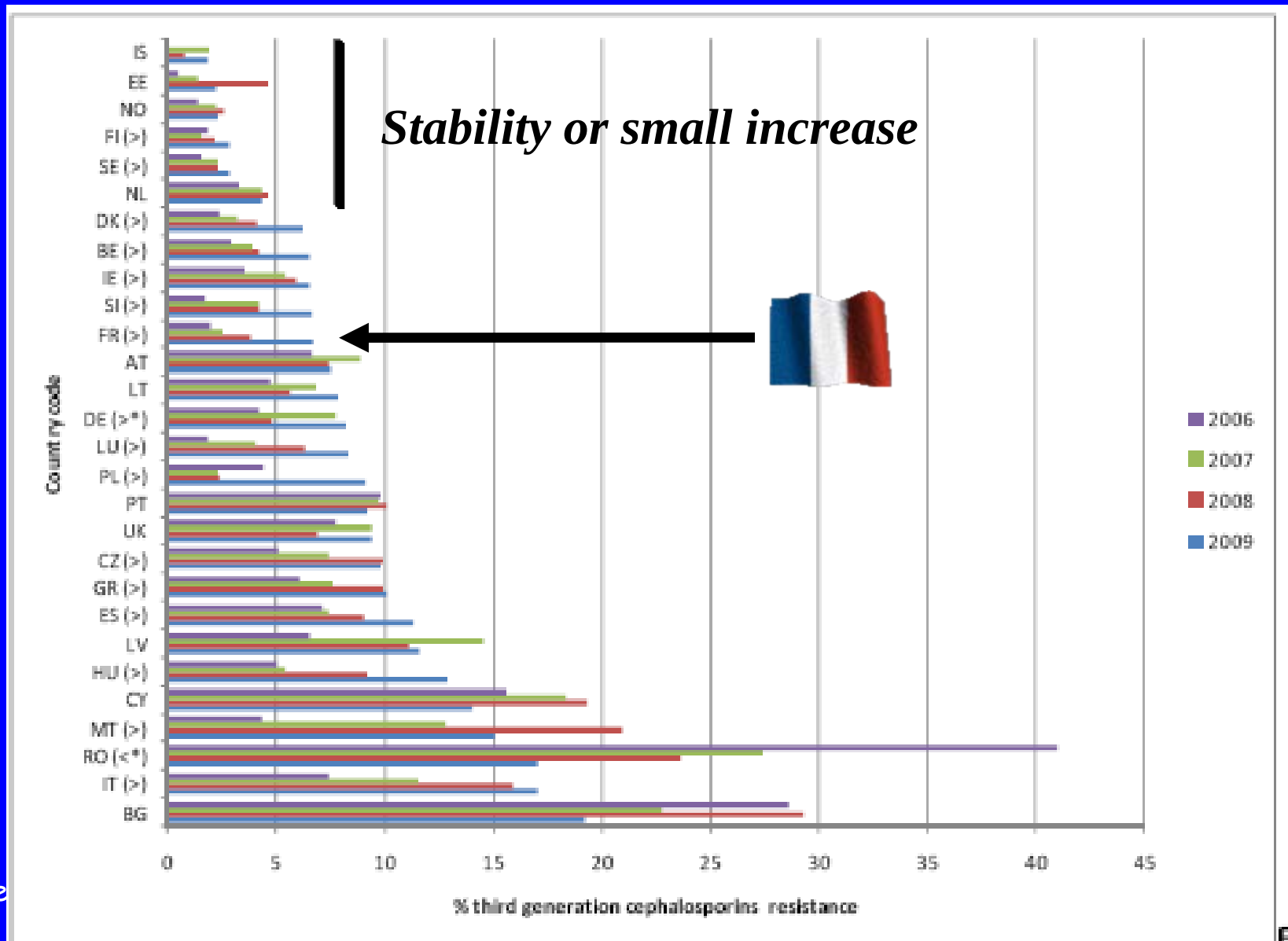
6.5%*

~5% ESBL



2009

% R 3rd gener. Cephalosporins in *E.coli* Bacteremias in Europe, EARSS 2006-09



ESBL *K.pneumoniae* in Europe

EARSS : *K.pneumoniae* resistant to 3rd generation cephalosporins in bacteremias

2%

19%

~15% ESBL

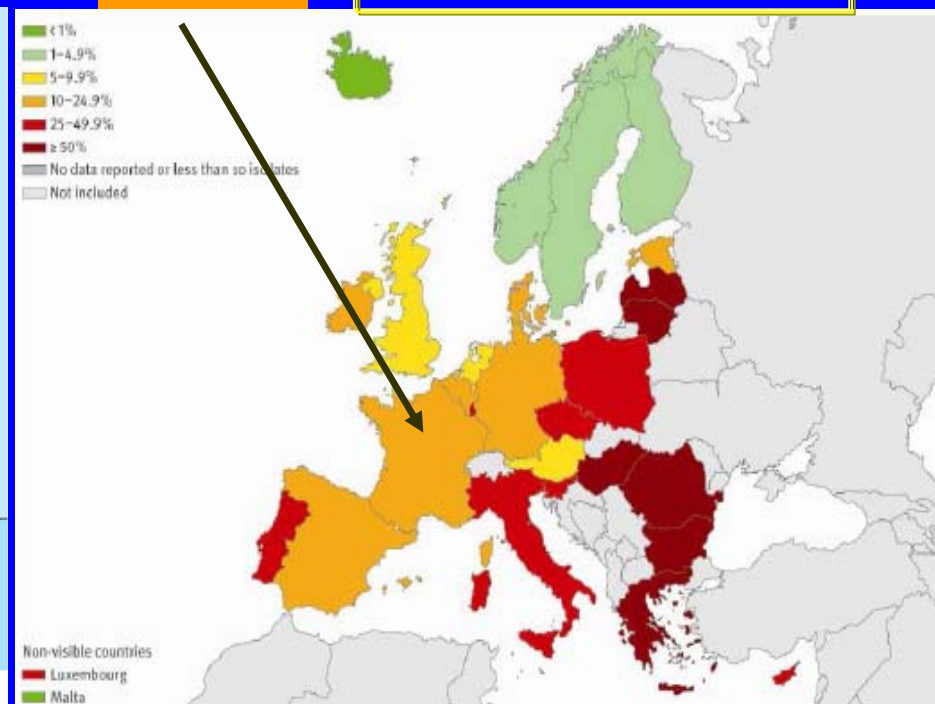
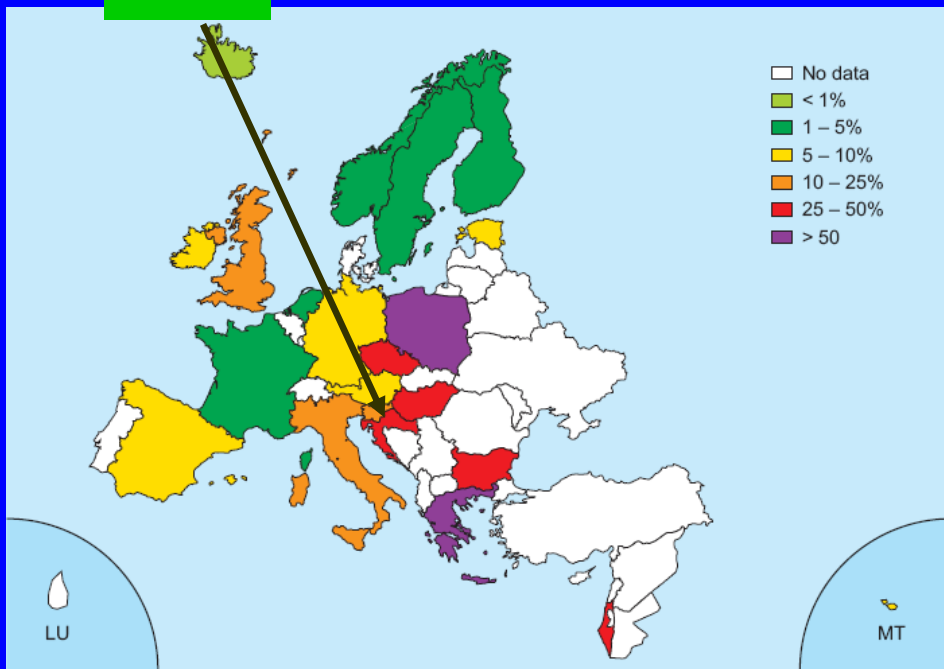
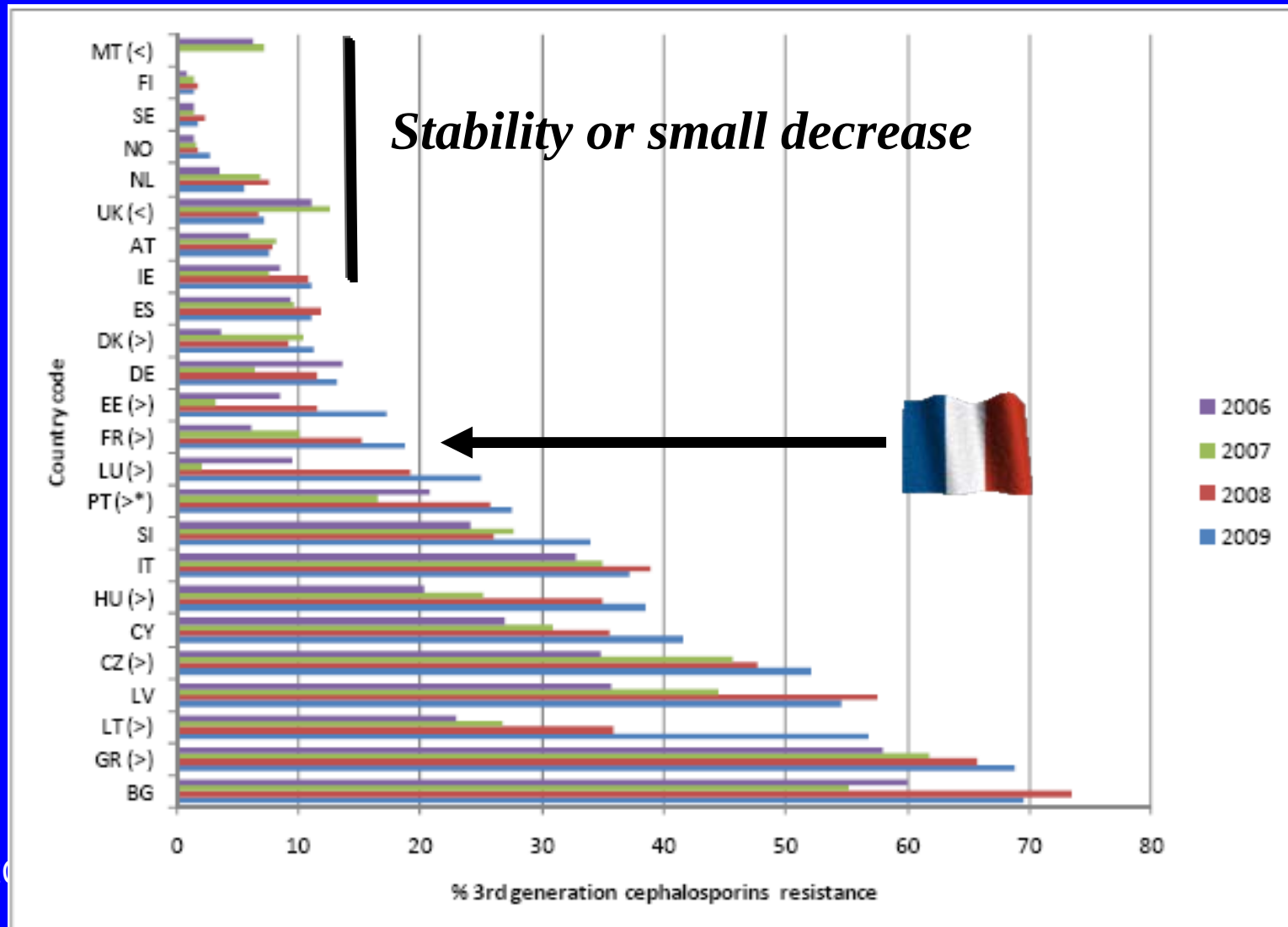


Figure 4.22. *Klebsiella pneumoniae*: proportion of invasive isolates resistant to third generation cephalosporins in 2005.

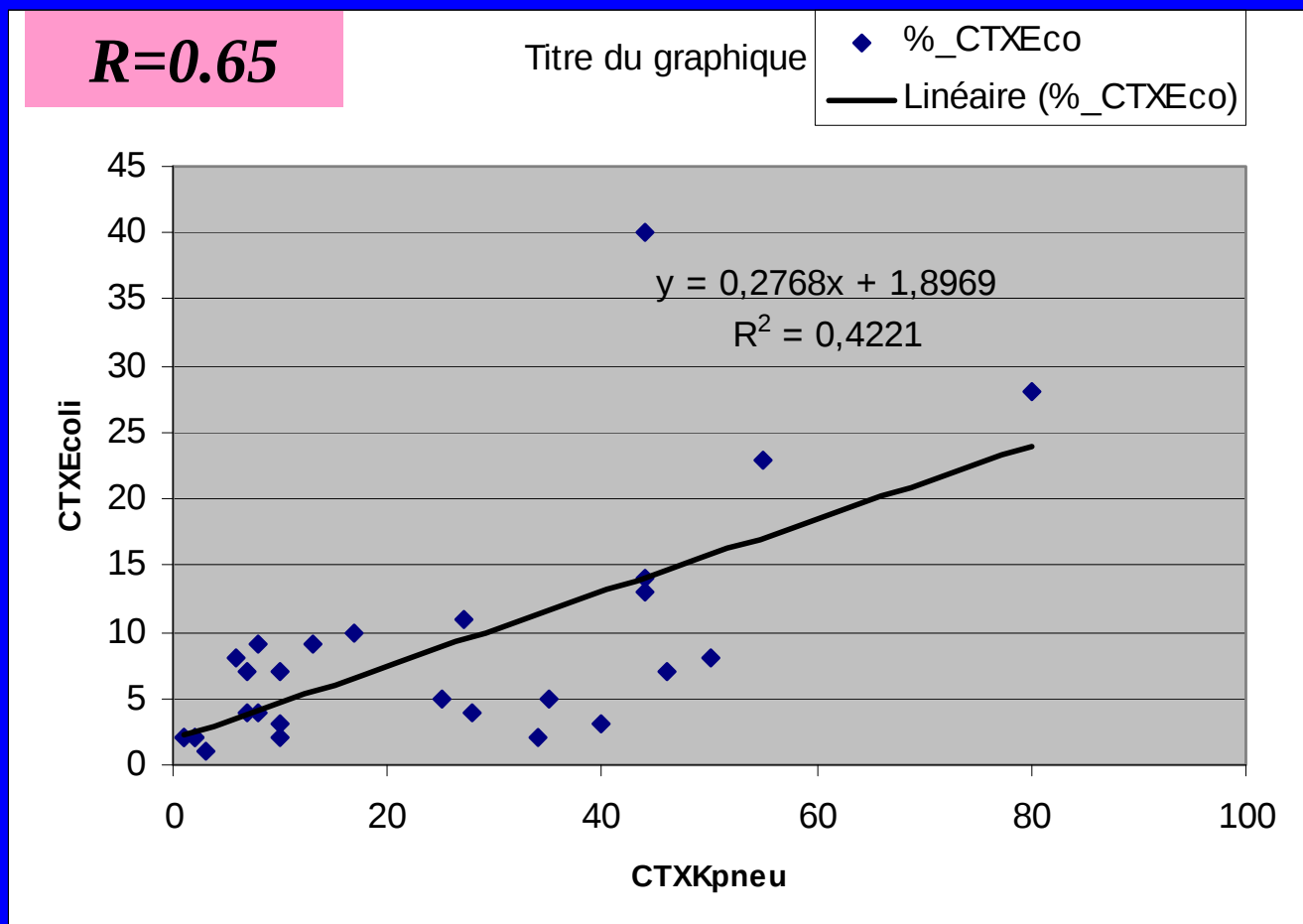
2002

2009

% R 3rd gener. Cephalosporins in *K.pneumoniae* Bacteremias in Europe, EARSS 2006-09

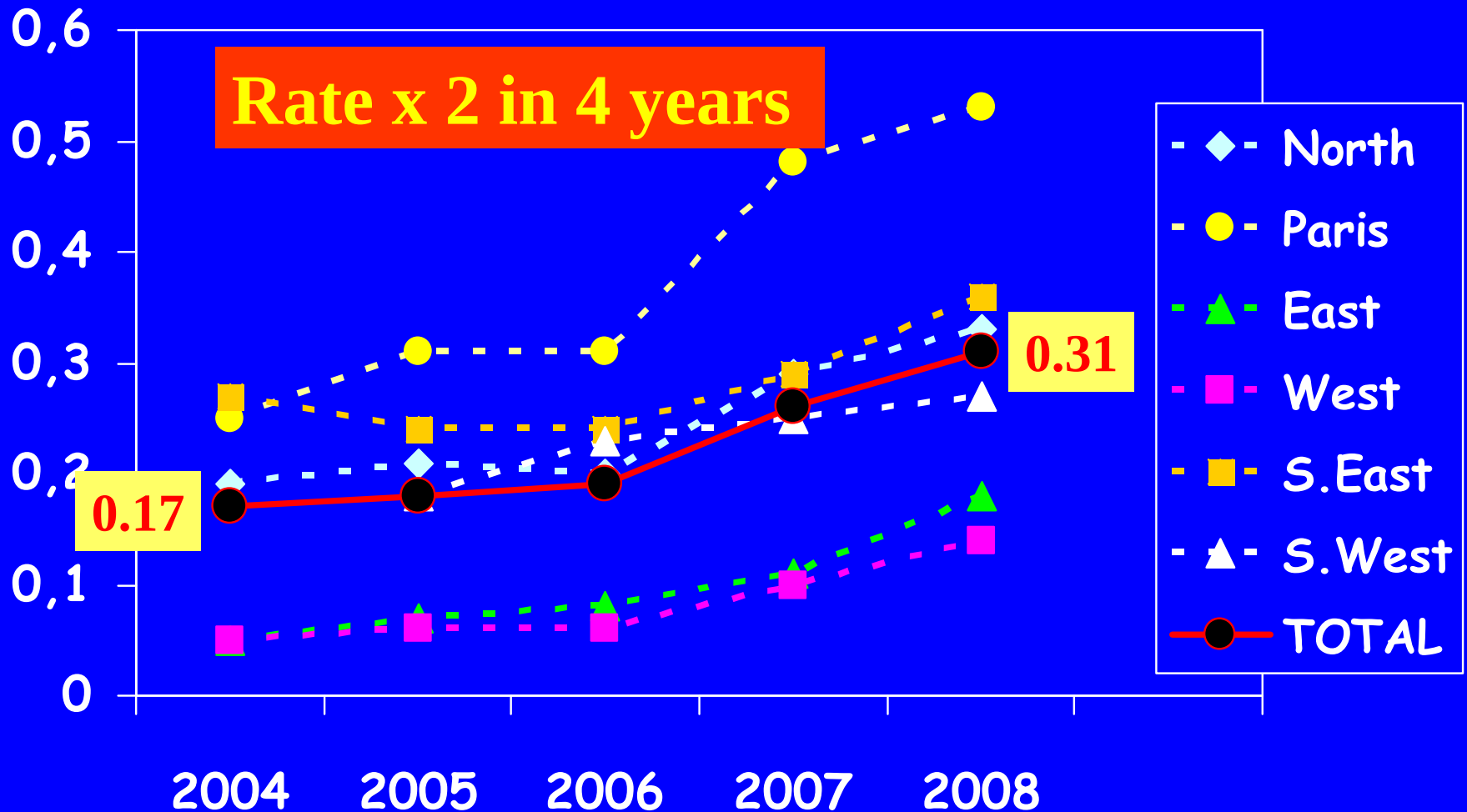


Relation 3rd Gen Cephalosporin-Resistance E.coli vs. K.pneumoniae EARSS 2007 : 26 countries

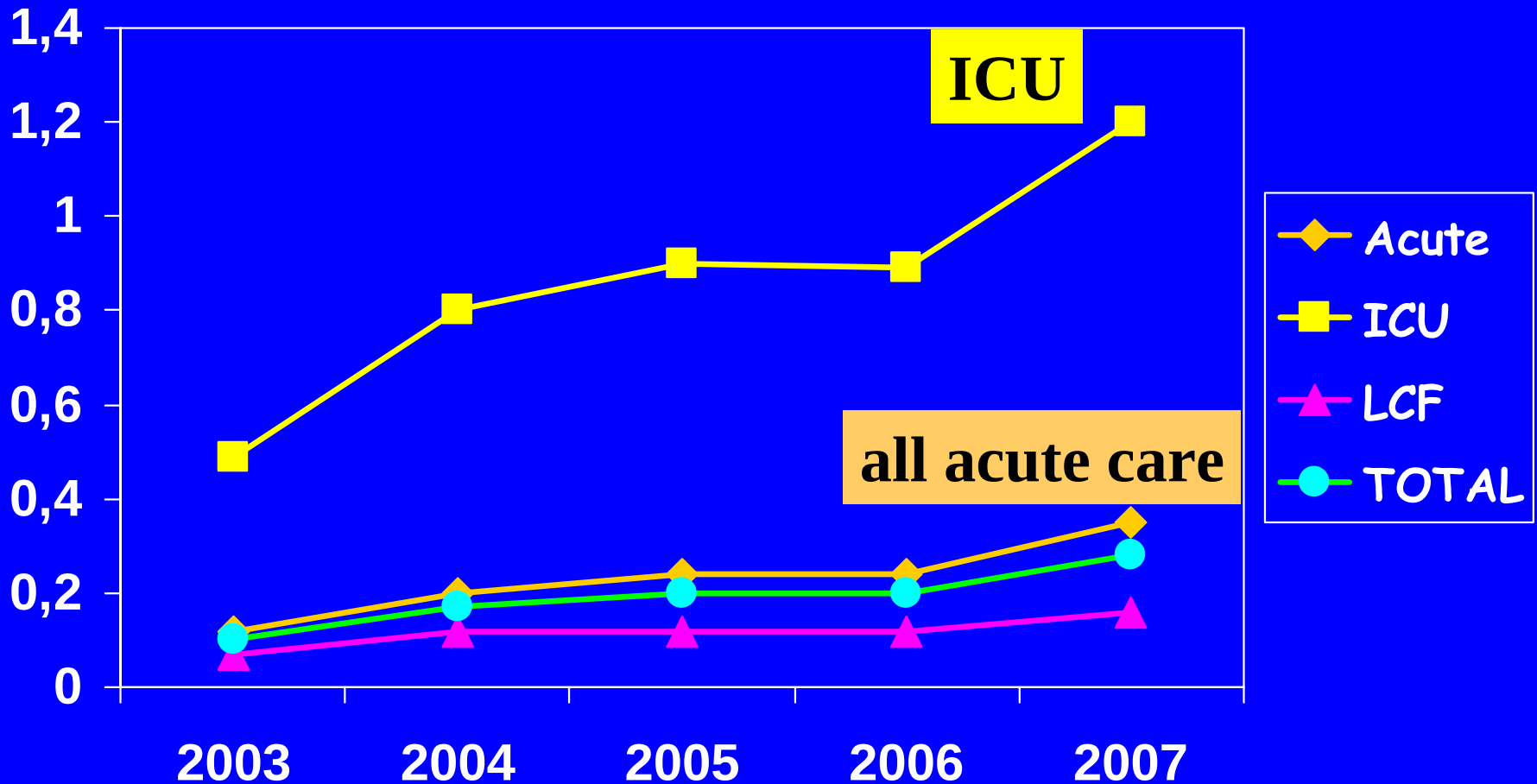


ESBL at national level

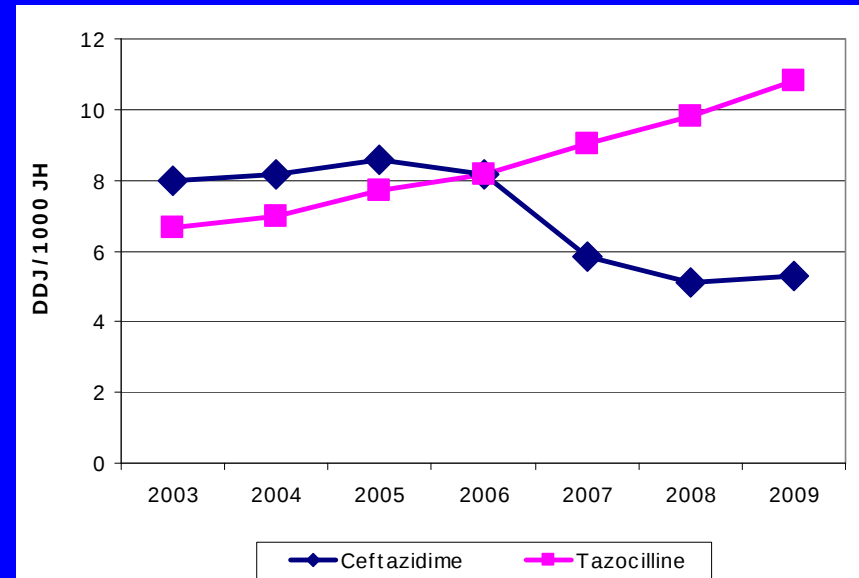
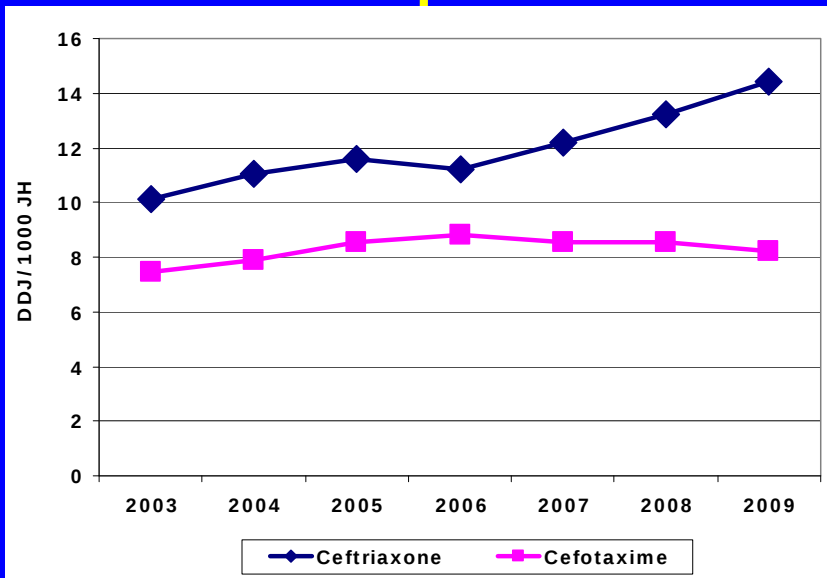
ESBL National survey (« RAISIN »)
Incidence rate / 1,000 DHs per area
2004-2008 (227 hospitals 3 months/year)



ESBL national survey (« RAISIN »)
Incidence rates / 1,000 DHs per activity
227 French hospitals (3 months/year)
2003-2007

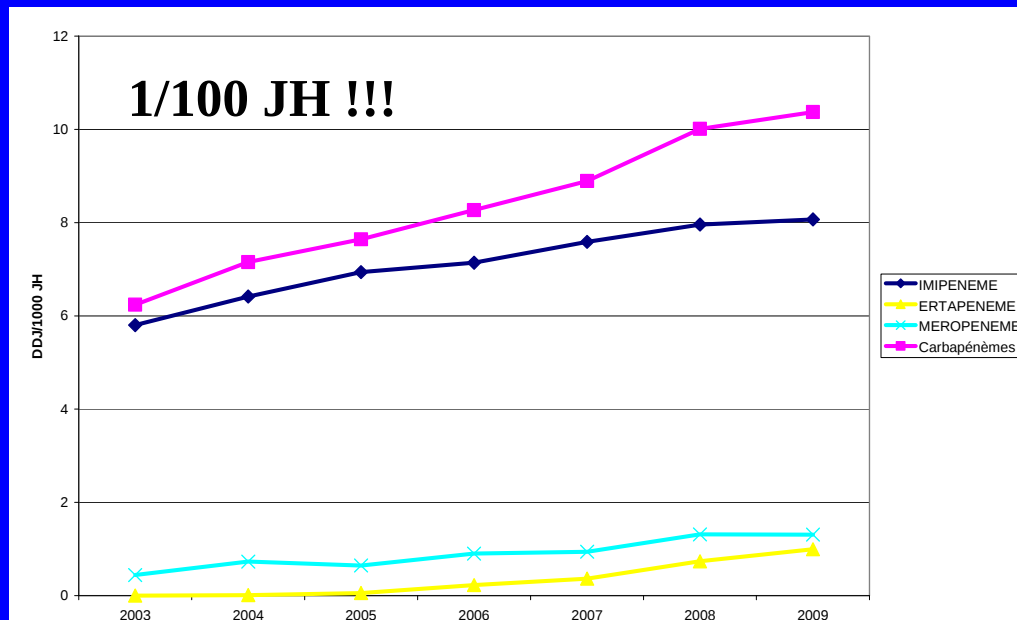


Consommation des Bactamines à large spectre à l'AP-HP 2003-09



**Cefotaxime
Ceftriaxone**

PIP-TAZ



Ratio

Carbapénèmes

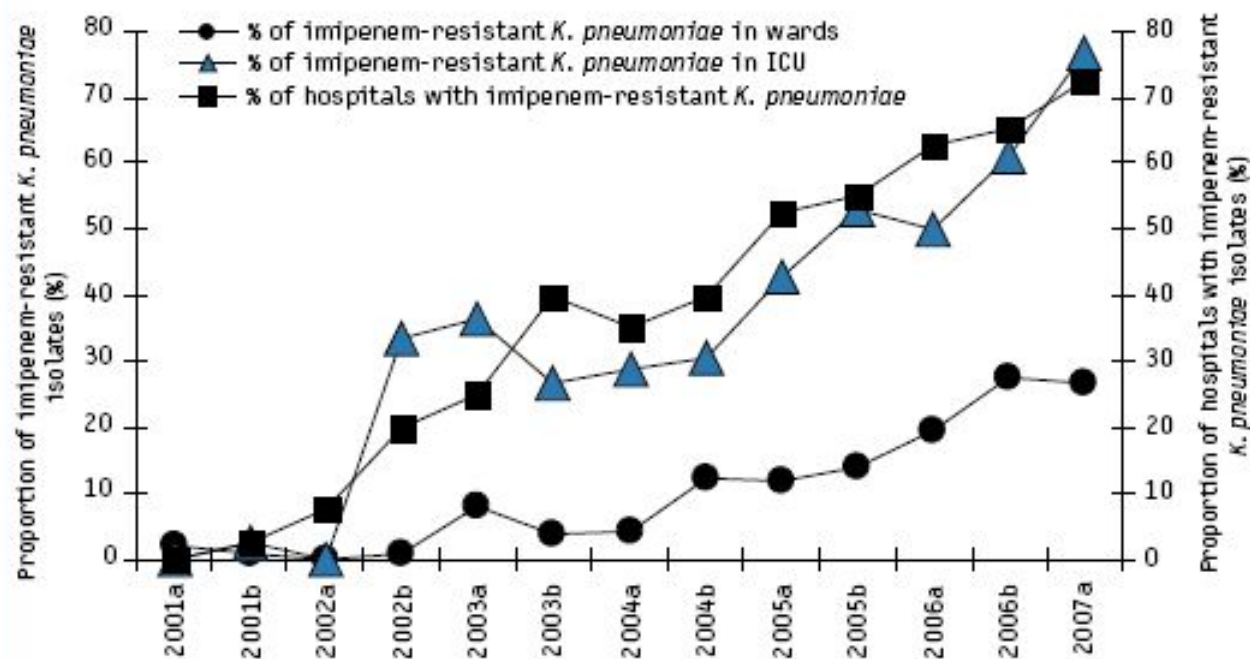
2 - 1 - 1

Carb-R *Enterobacteriaceae*

K.pneumoniae IMP-R en GRECE

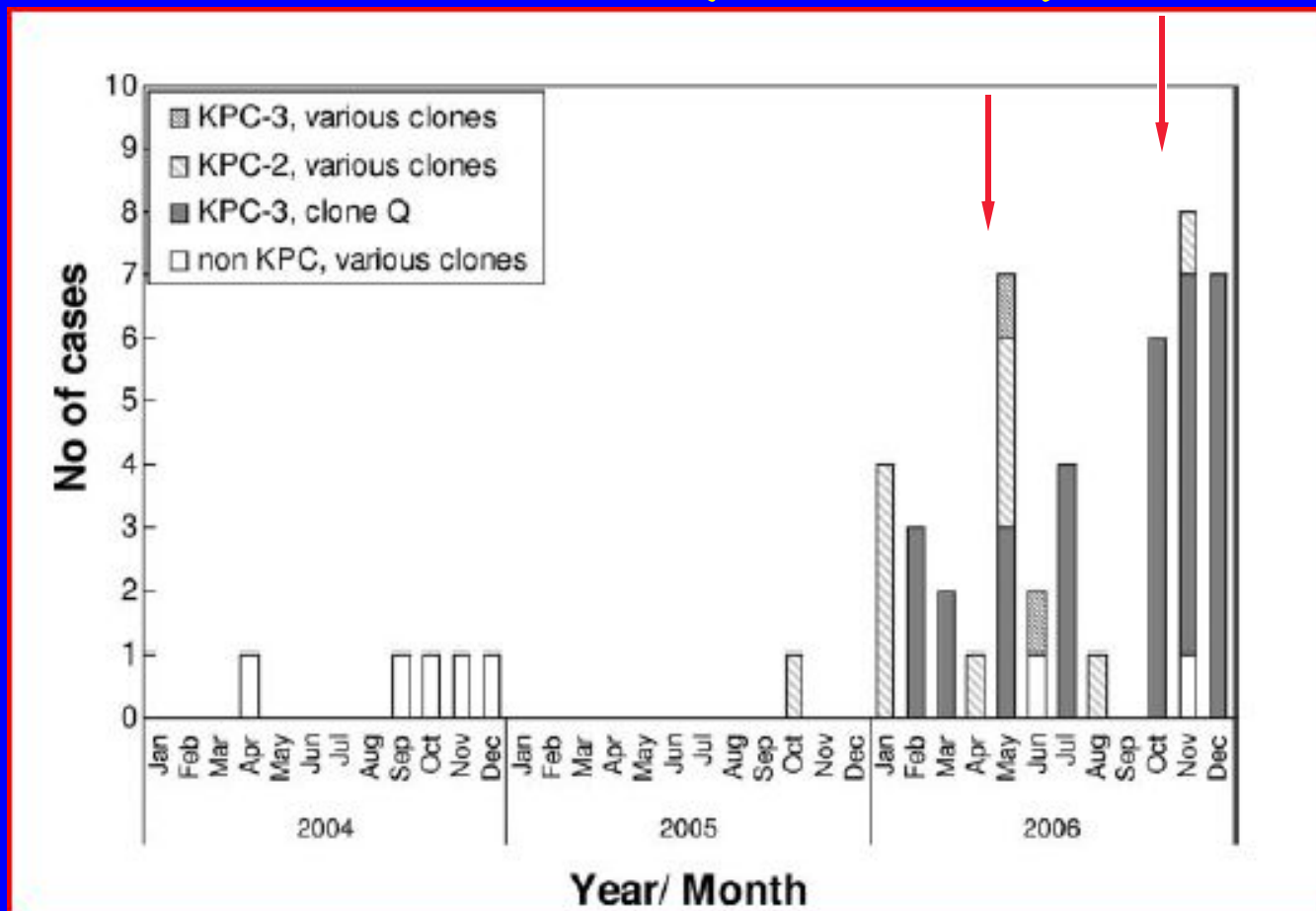
FIGURE 2

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>)

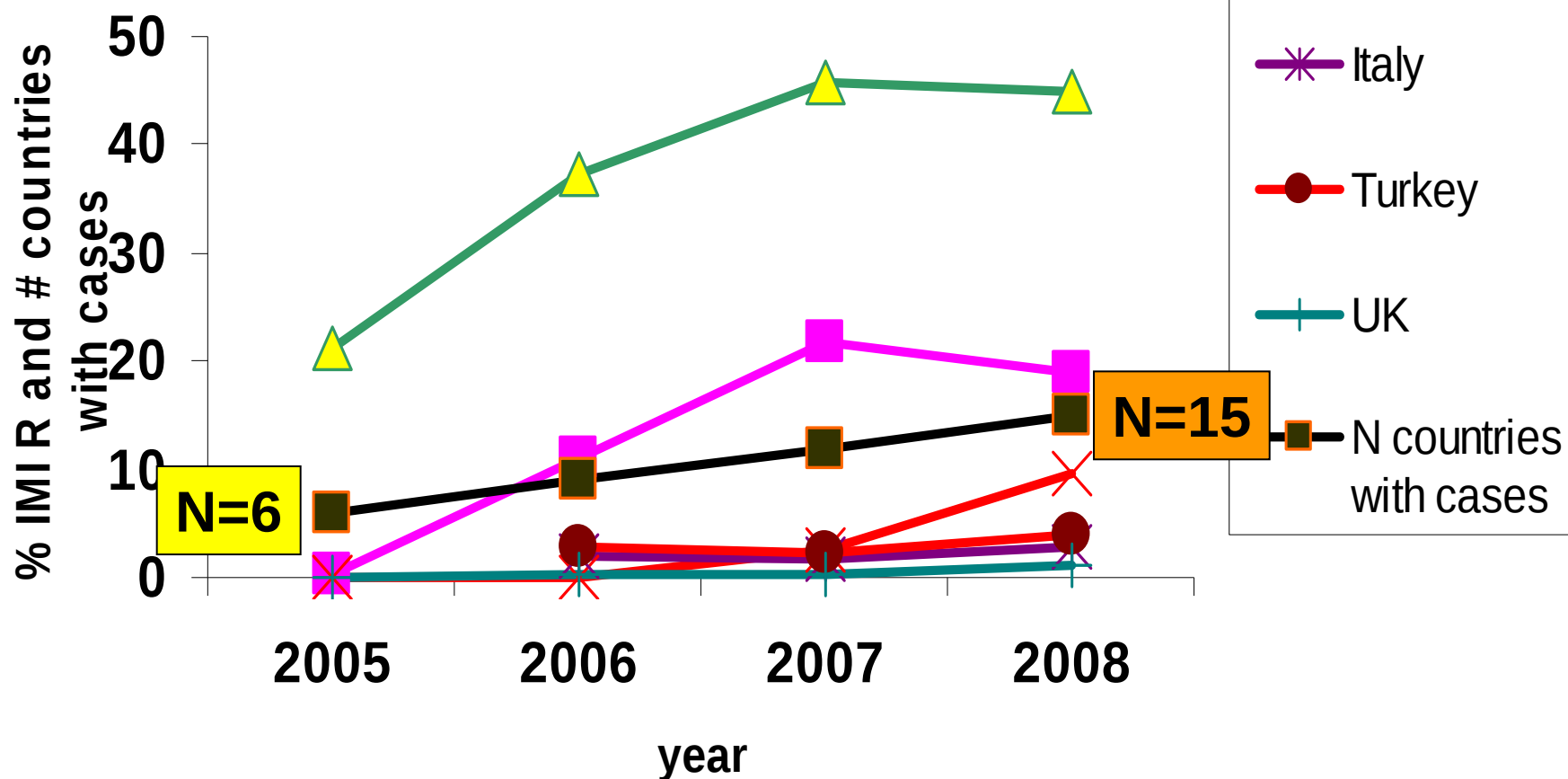
K.pneumoniae IMP-R en ISRAEL (Tel Aviv)



Epidémie de souches *K. pneumoniae* résistantes aux carbapénèmes possédant KPC-2 et KPC-3 dans un hôpital à Tel Aviv de 2004 à 2006.

12 clones différents et un clone majeur Q avec des **profils de sensibilité différents**

% R Imipenem in *K.pneumoniae* Bacteremias, EARSS 2005-08



The MDROs control programmes in France : starting 1993

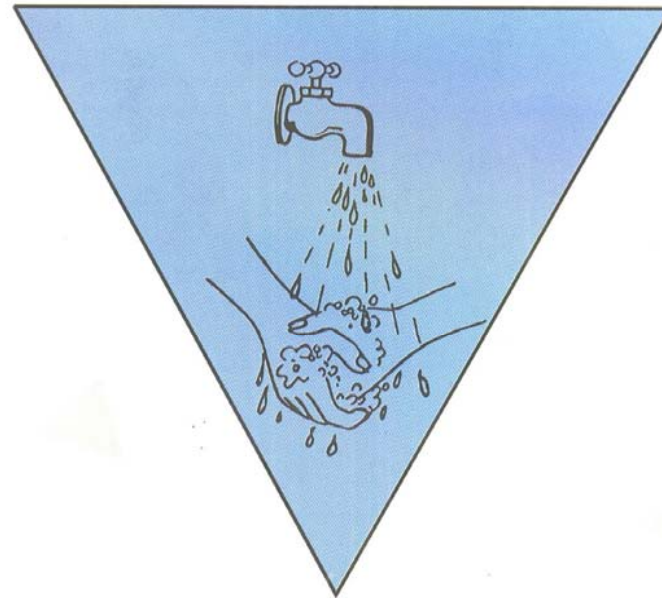
MDR program

**Regional
Univ. hospitals
Paris area
(AP-HP)**

1993

ASSISTANCE
PUBLIQUE  HÔPITAUX
DE PARIS

**MAITRISE DE LA DIFFUSION
DES GERMES HOSPITALIERS
MULTI-RÉSISTANTS**



MDR program

National

1999

The cover of the 1999 MDR program report features a green background with a photograph of hands being washed in a sink. The title is written in large, bold, yellow letters. The year '1999' is in white, and the subtitle is in white. The logo of the Ministry of Employment and Solidarity is at the bottom.

**Maîtrise de
la diffusion
des bactéries
multirésistantes
aux antibiotiques**

1999

**Recommandations pour
les établissements de santé**



MINISTÈRE DE L'EMPLOI
ET DE LA SOLIDARITÉ

Alcool based hand rub solution campaigns

2001-02



Le lavage des mains
C'est bien ! Mais...

...vous lavez-vous
toujours les mains
avant et après
chaque contact ?

**La Friction Hydro-Alcoolique
des mains c'est simple !**

C'est pratique, on peut l'utiliser partout.

La Friction Hydro-Alcoolique
Le contrôle des germes à portée de mains.

ASSISTANCE
PUBLIQUE

HÔPITAUX
DE PARIS

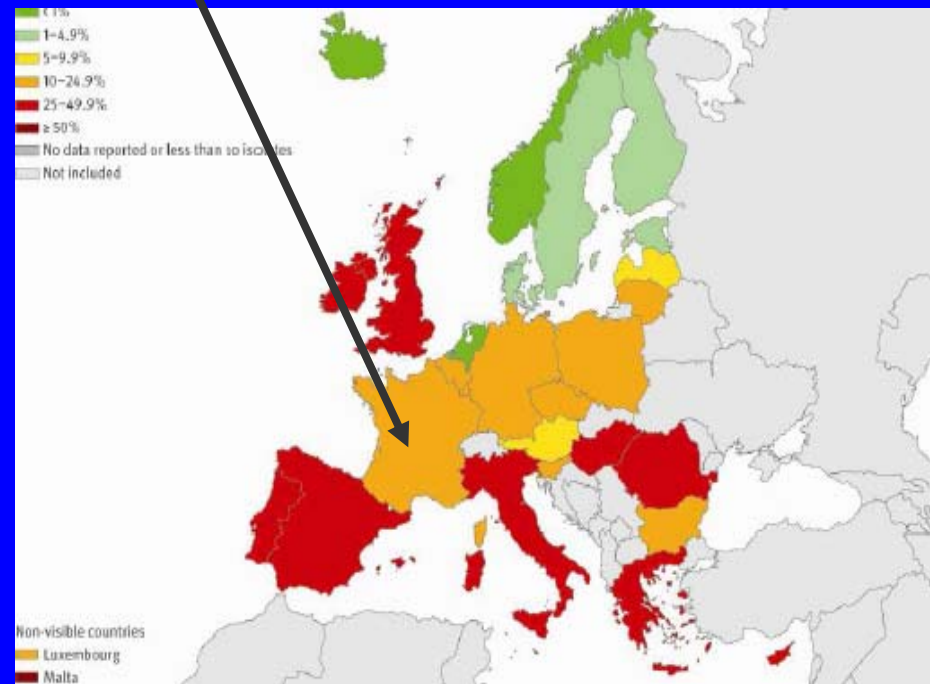
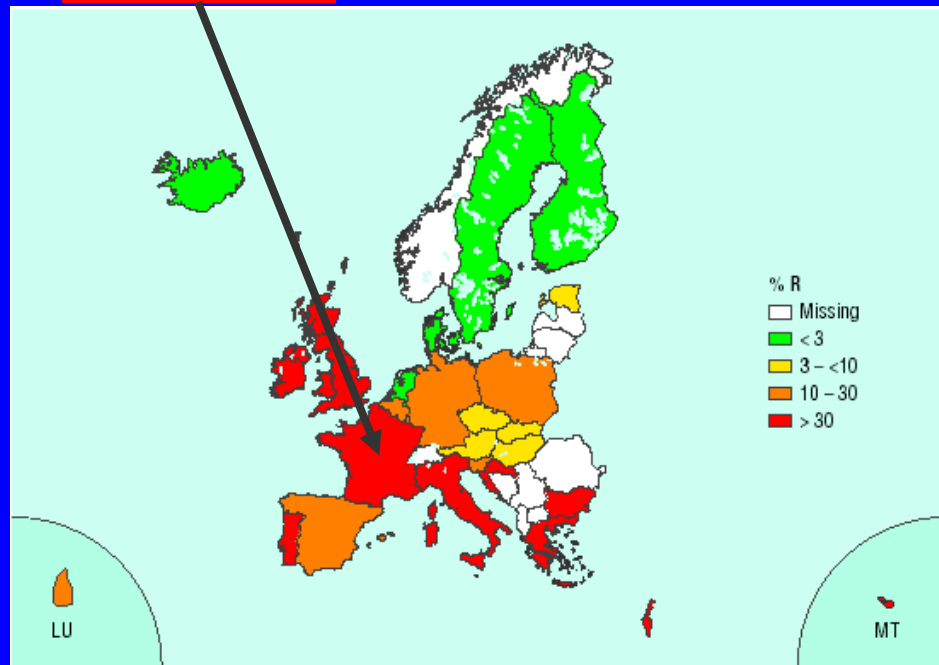
Donc la lutte contre les infections nosocomiales, l'AP-HP s'engage.

MRSA in Europe (% in *S.aureus*) EARSS 2001-2009

33.2%

23%

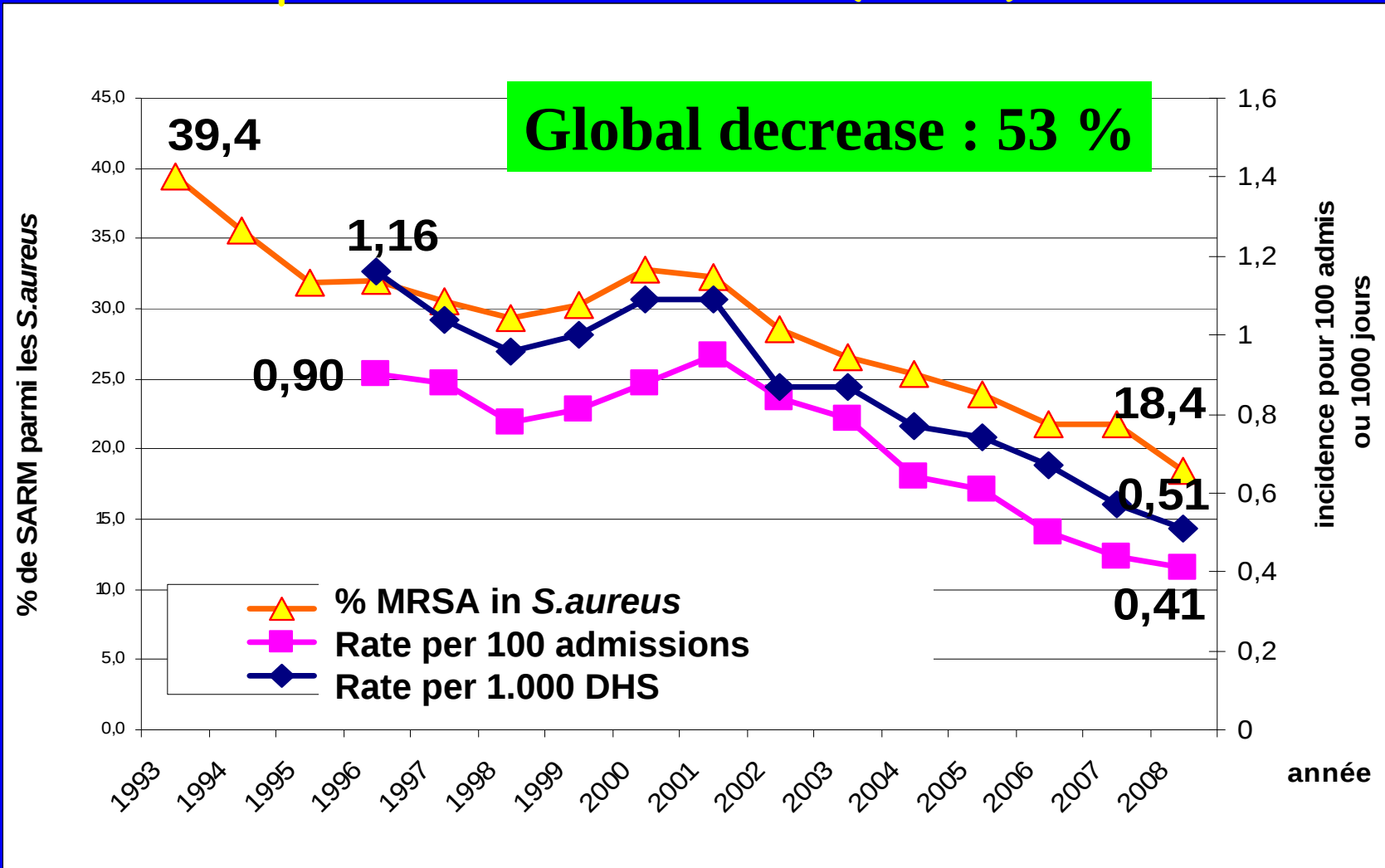
24% in 2008



2001

2009

% MRSA in *S.aureus* and MRSA incidence in acute care Univ. hospitals of Paris area (n=39) 1993-2007



Classical contact precautions used to control MRSA will not be enough for controlling emerging “digestive tract driven” MDROs such as ESBL and Carb-R *Enterobacteriaceae*

- Mobile resistance elements
 - spread of strains...
 - ...but also spread of mobile elements
- **Bacterial (and mobile elements) excretion**
 - $\sim 10^{10}$ per carrier and per day (feces)
 - $\sim 10^9$ per day and per UTI
- Wastes = feces and urines $\rightarrow$ environment

— risk of “back trough food chain”
VJarlier 2010

ESBL in hospital wastewater (1) 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 (2) 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

Antibiotic consumption in Europe - Community - ESAC 2002

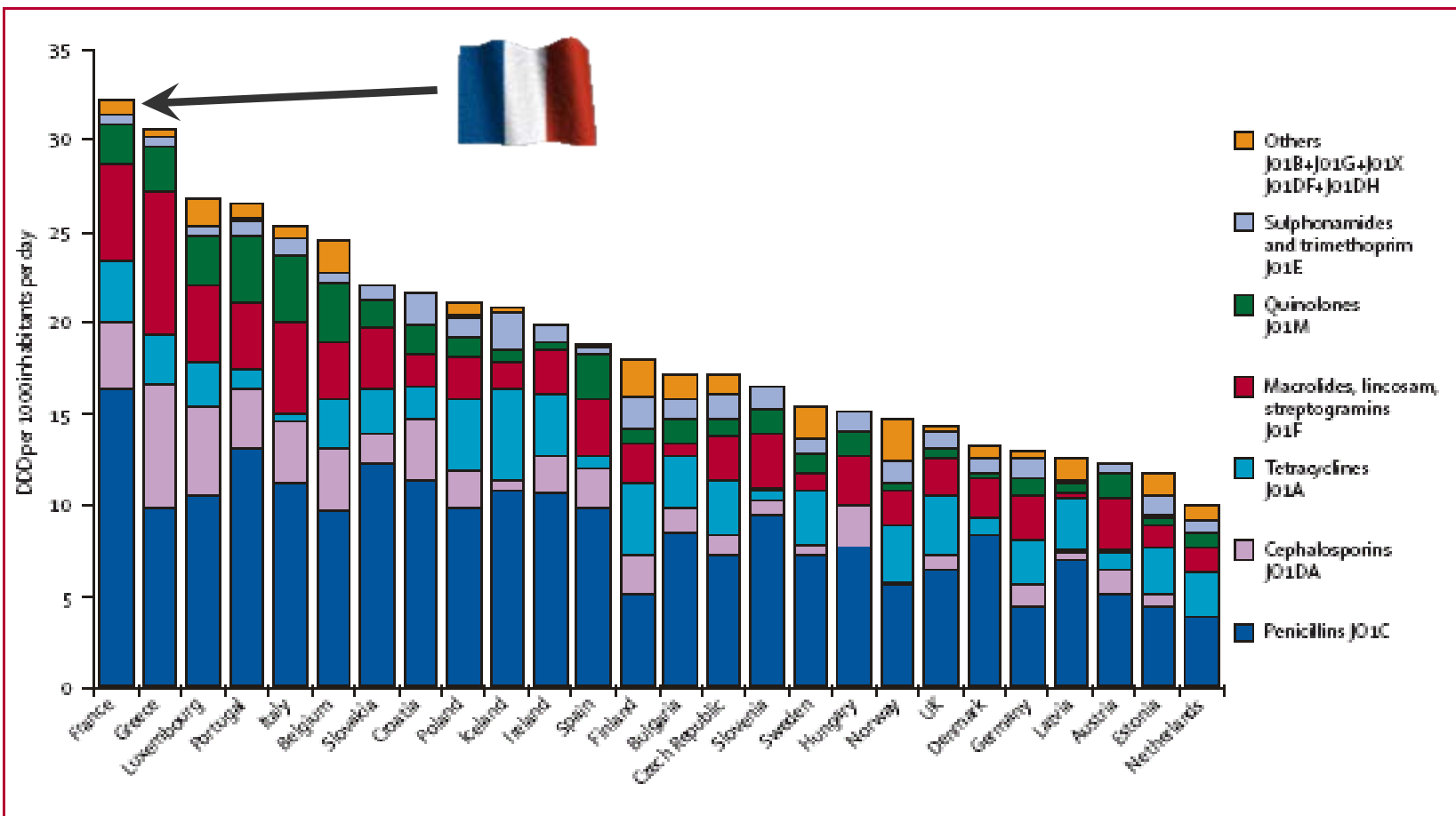
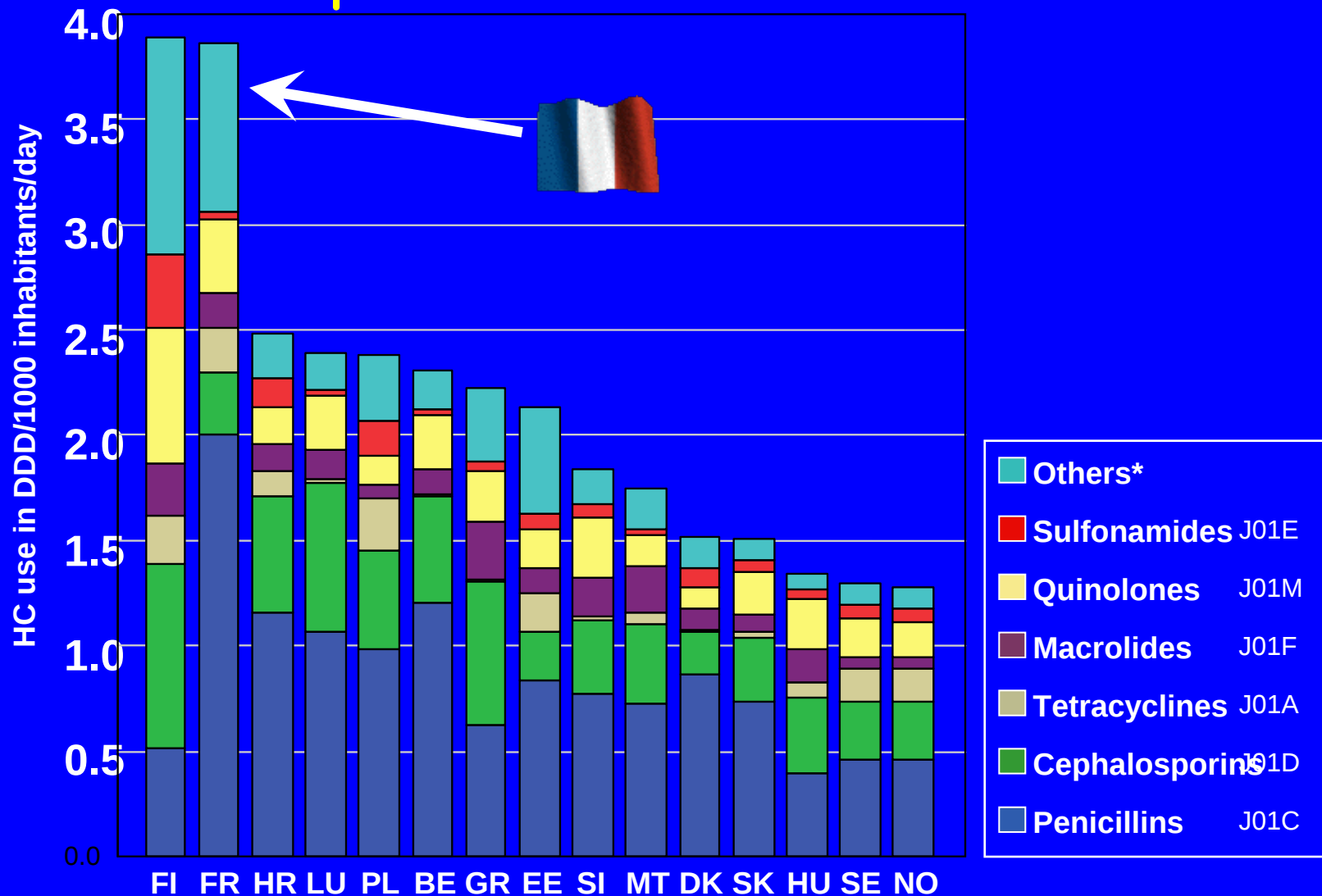


Figure 1: Total outpatient antibiotic use in 26 European countries in 2002

Antibiotic consumption in Europe - Hospital - ESAC 2002



**Antibiotic policy
campaigns
in hospitals
of Paris area
(AP-HP)
2006-10**

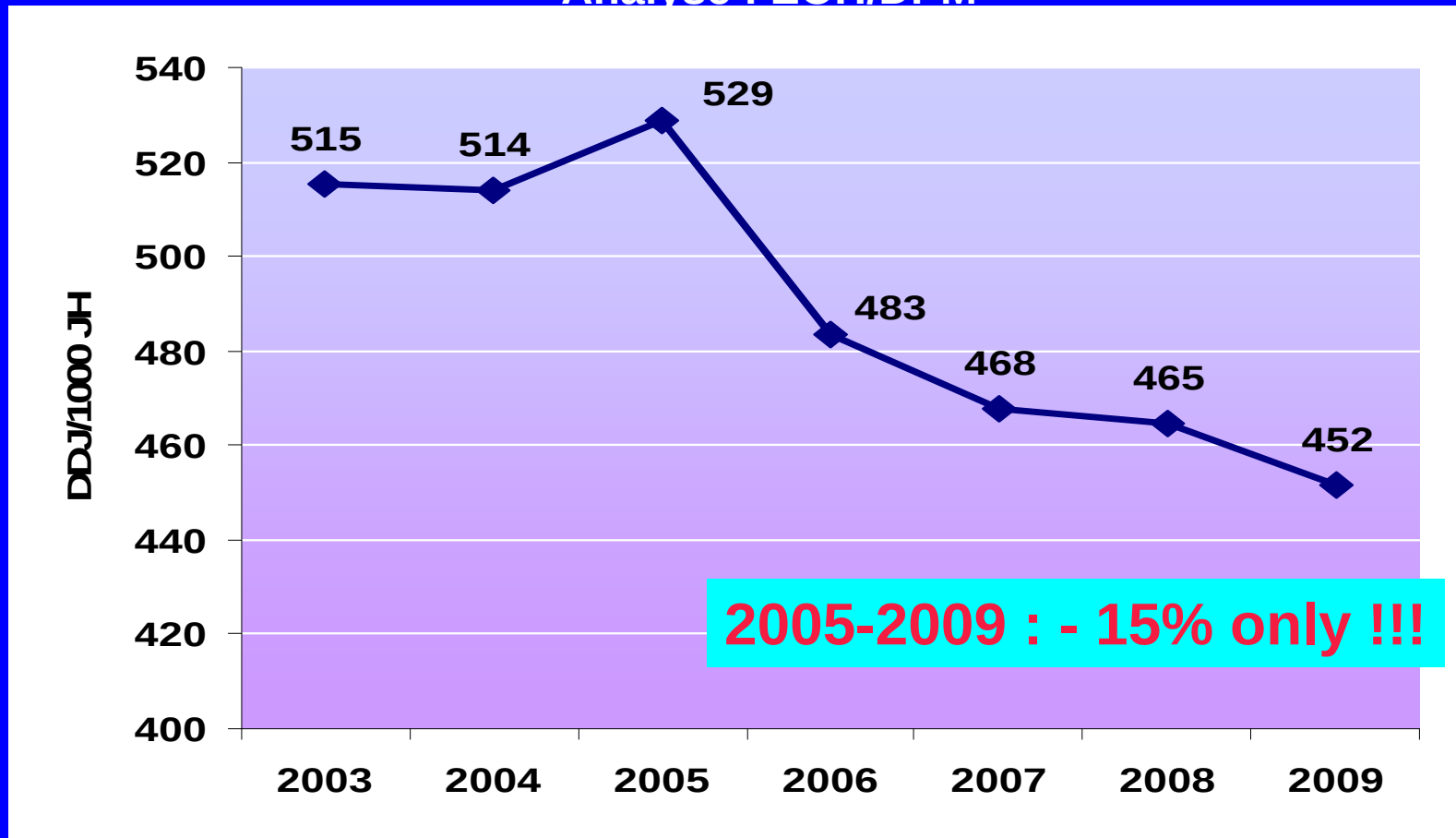


**Mieux utiliser les antibiotiques
pour préserver leur efficacité.**

Antibiotic consumption in the 39 hospitals of Assistance Publique - Hôpitaux de Paris 2003-09

Source : AGEPS-Direction des finances

Analyse : EOH/DPM



Absolute needs today in France

- Apply specific extended measures (quick and strong intervention as soon as 1st case) for controlling emerging MDRs (**Carb-R** *Enterobacteriaceae*, VRE...)
- Set up a global approach to limit (slow down) the spread of ESBL including *E.coli* (combine community, hospital, farming, environment) : take profit of a still low incidence !!!
- Drastic restriction of antibiotic use in the community, hospital, animal

Antibiotic stewardship and ESBL-carbapenemase problem

- → Decrease drastically global ATB consumption (e.g. in France by a factor of 2-3 !)
- → Promote all possible alternatives to 3rd gen. cephalosp., fluoroquinolones and **carbapenems**
e.g. : betalactams- inhibitors, cephamycins, nitrofuranes, fosfomycine...
- → revisit in depth national recommendations
(**UTIs**, abdominal surgery...)

Environment, water supply, food chain

*ATB policy + prevent X transm.
(school, family, elderly homes..)*

*Wastewater
treatment*

*Farming, Food
& water*

ESBL spread in community (x trans + ATB)

*Identify
carriers at
discharge*

*Identify risk
factors for
carriage at entry*

Admission

Discharge

**X
transmission
in HCFs**

**Patients entering
HCFs with ESBL
(low con^{tration})**

*Prevent
X trans-
mission*

ATB

*Decrease
antibiotic
pressure*

**Colonization
(high con^{tration})**

- Controlling MDROs = saving a precious collective treasure : antibiotics
- concern comparable to saving clean water and forests or preventing planet global warming
- 1st irruption of sustainable development in medicine

Stabilize (at least slow down) ESBL rates and prevent carbapenemases spread

- Hospital
- Community
- Environment
- Cross transmission
- ATB policy
- Food-water supply

→ **Global and integrated approach**