

Situation épidémiologique et hypothèse d'évolution de la résistance aux antibiotiques

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Délégué aux infections nosocomiales

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2 modèles d'évolution et d'émergence de bactéries résistantes

- **Espèce pathogène stricte**
 - pas de portage dans les flores
 - **réservoir = malades**
 - résistance = **mutation** seulement

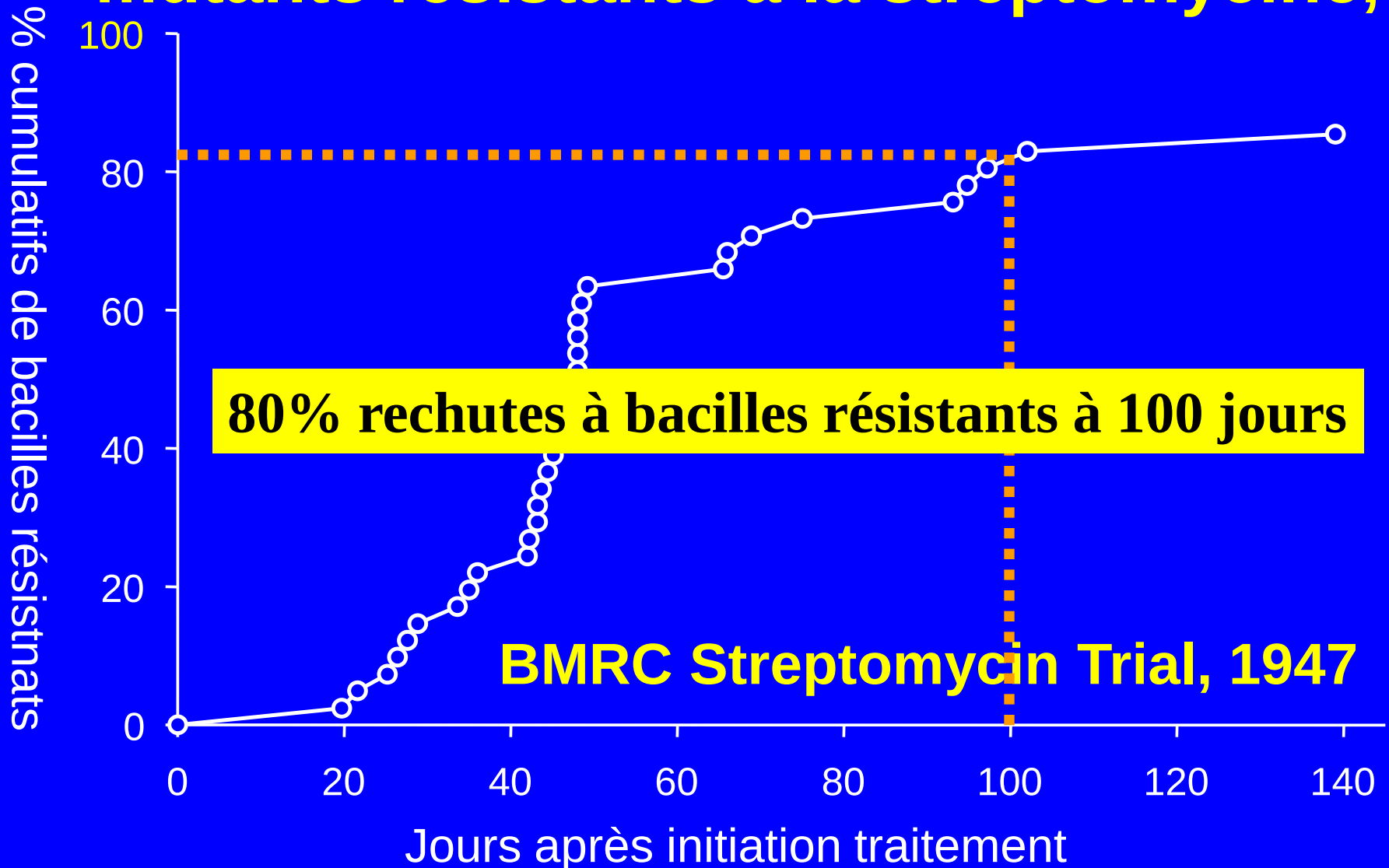
Bacille de la tuberculose

- **Espèces commensales**
 - réservoir intestinal ++ homme (ex. *E.coli* 10^8 /gr), animal
 - réservoir 2aire = malades
 - résistance = **acquisition de gènes (plasmides...) et mutations**

Entérobactéries (et entérocoques)

Bacille de la tuberculose

Sélection sous traitement de bacilles mutants résistants à la streptomycine,



Sélection de bacilles mutants résistants sous monothérapie

Année de publication*	Antibiotique (nombre de patients)	Pourcentage de rechutes à souches résistantes à (mois)					
		1	2	3	4	5	>6
1948	Streptomycine (41)	12	63	73	82	85	/
1960	Isoniazide (87)	10	/	36	/	/	52
1972	Rifampicine (85)	/	/	/	48	/	/
1985	Ofloxacine (19)	/	5	26	58	63	/

Bacille de la tuberculose : accumulation de résistances

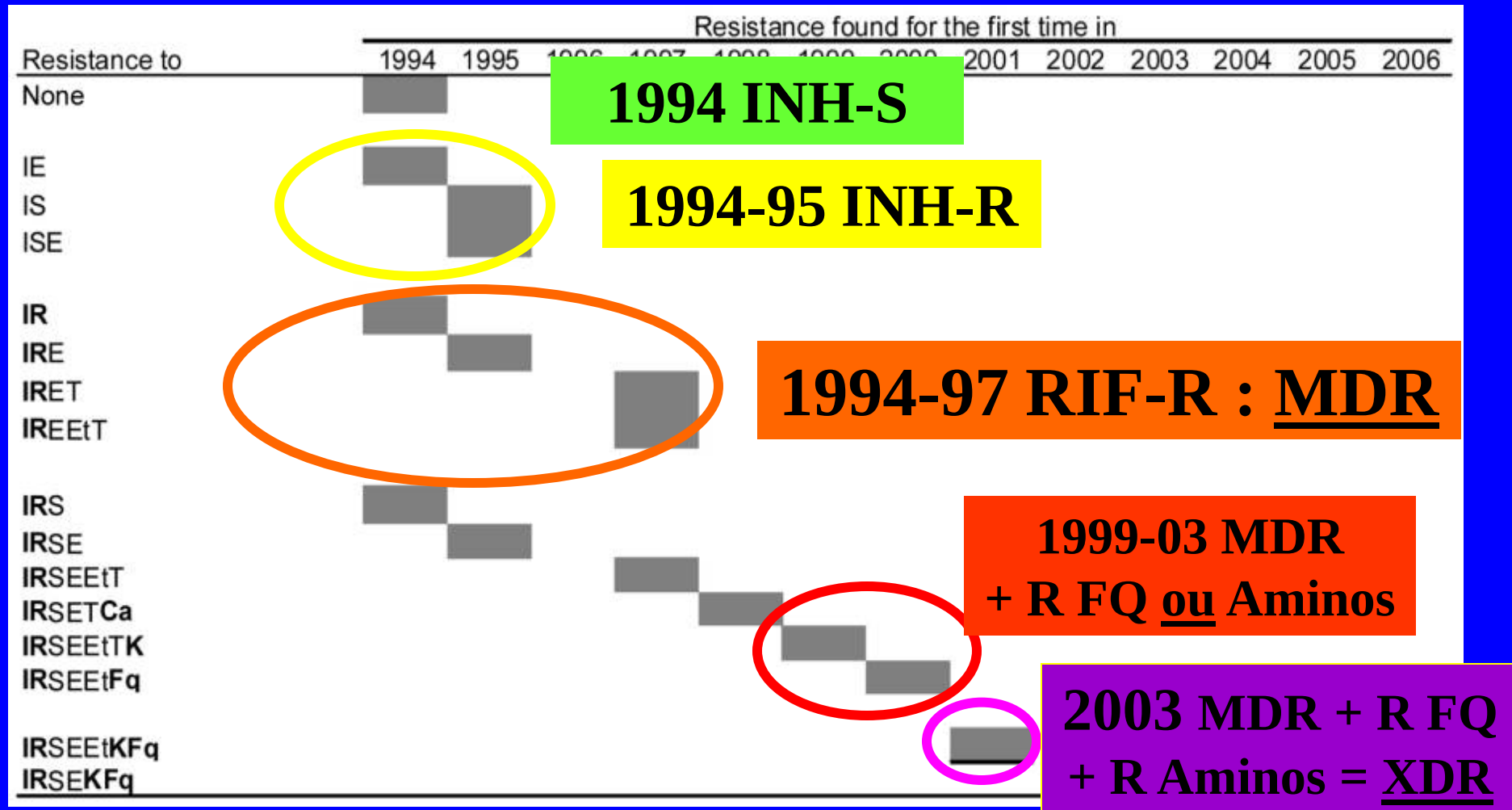
Sensible

→ R (INH ou RIF)

→ MDR (INH + RIF)

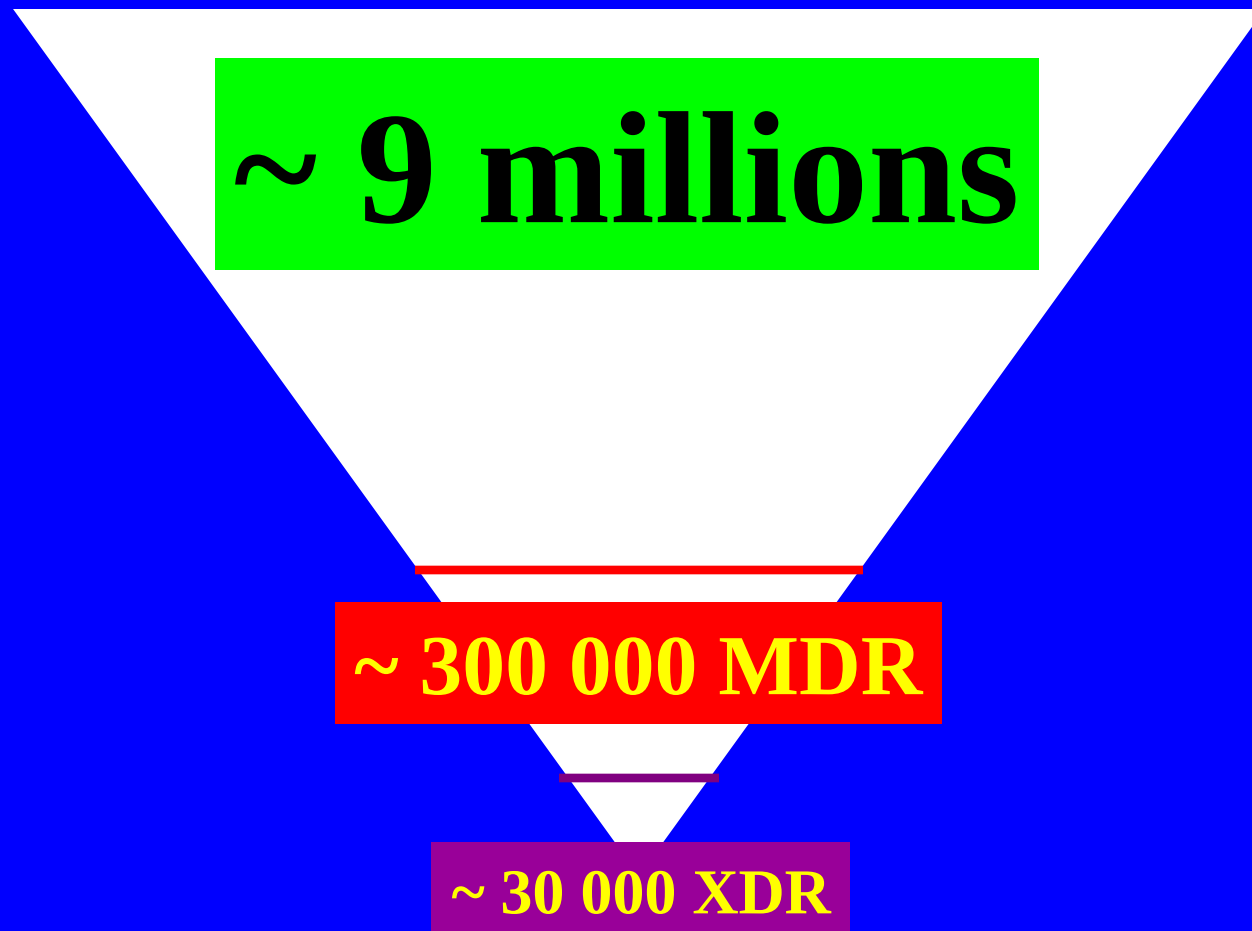
→ XDR (INH + RIF + FQ + AMI)

Sélection in vivo « par étapes » de mutants de + en + résistants à partir de la souche F15/LAM4/KZN (malades d'Afrique du sud)



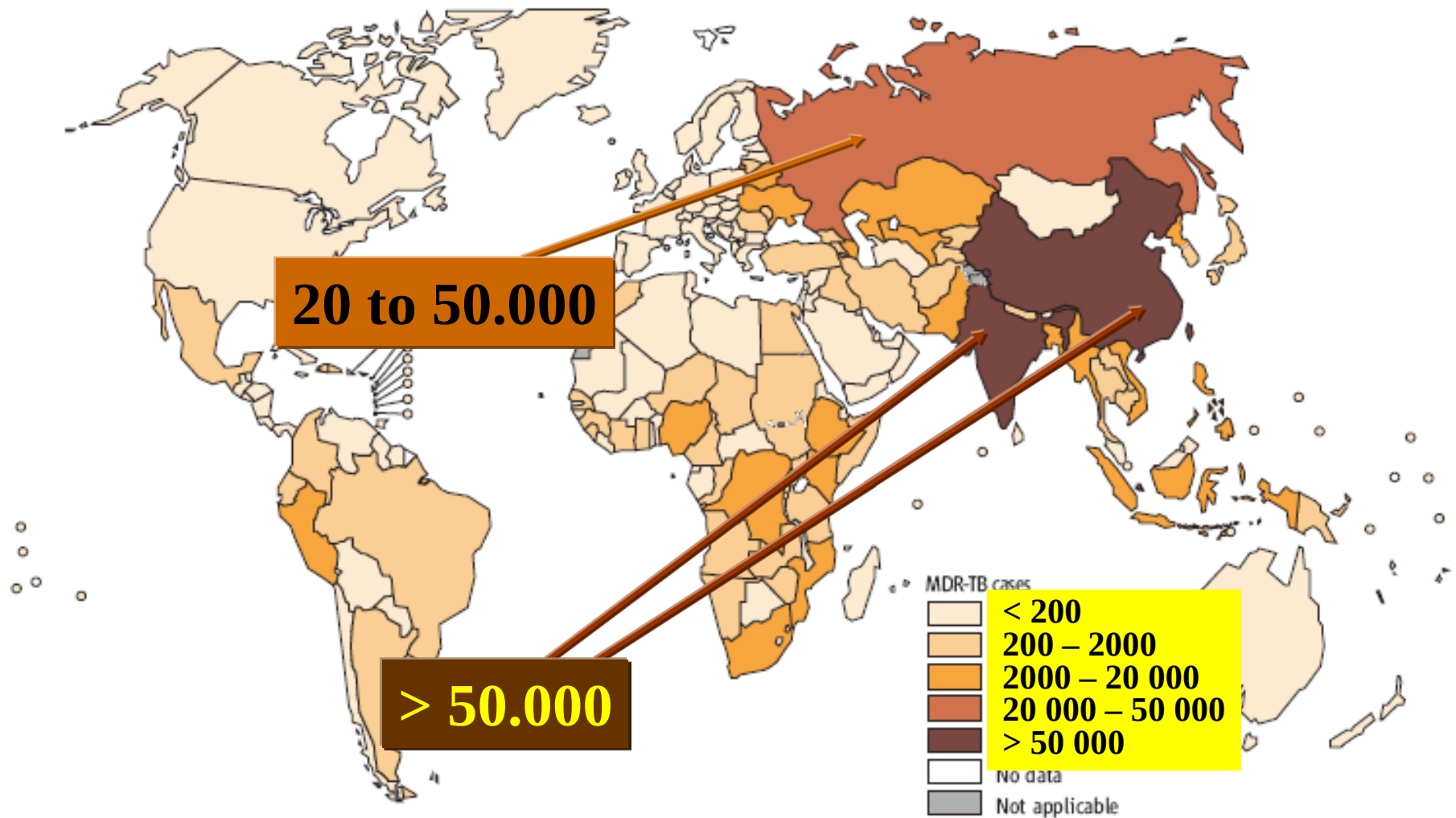
TB-MDR et XDR dans le monde

Estimated number of cases of susceptible, MDR and XDR TB in the world (OMS, 2010)



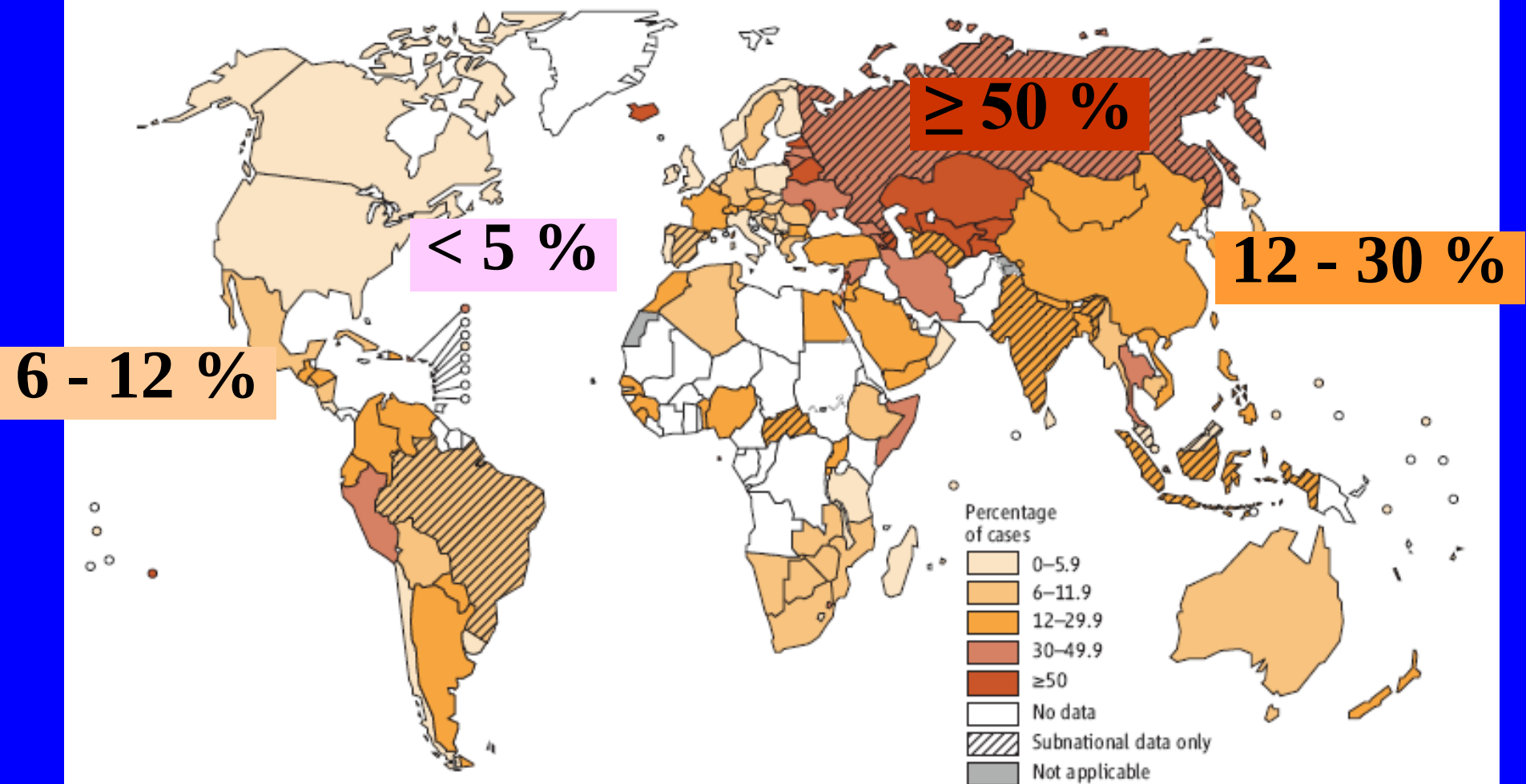
Estimated number of MDR-TB WHO report 2013

Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2012



Estimated MDR-TB in previously treated cases (%) WHO report 2013

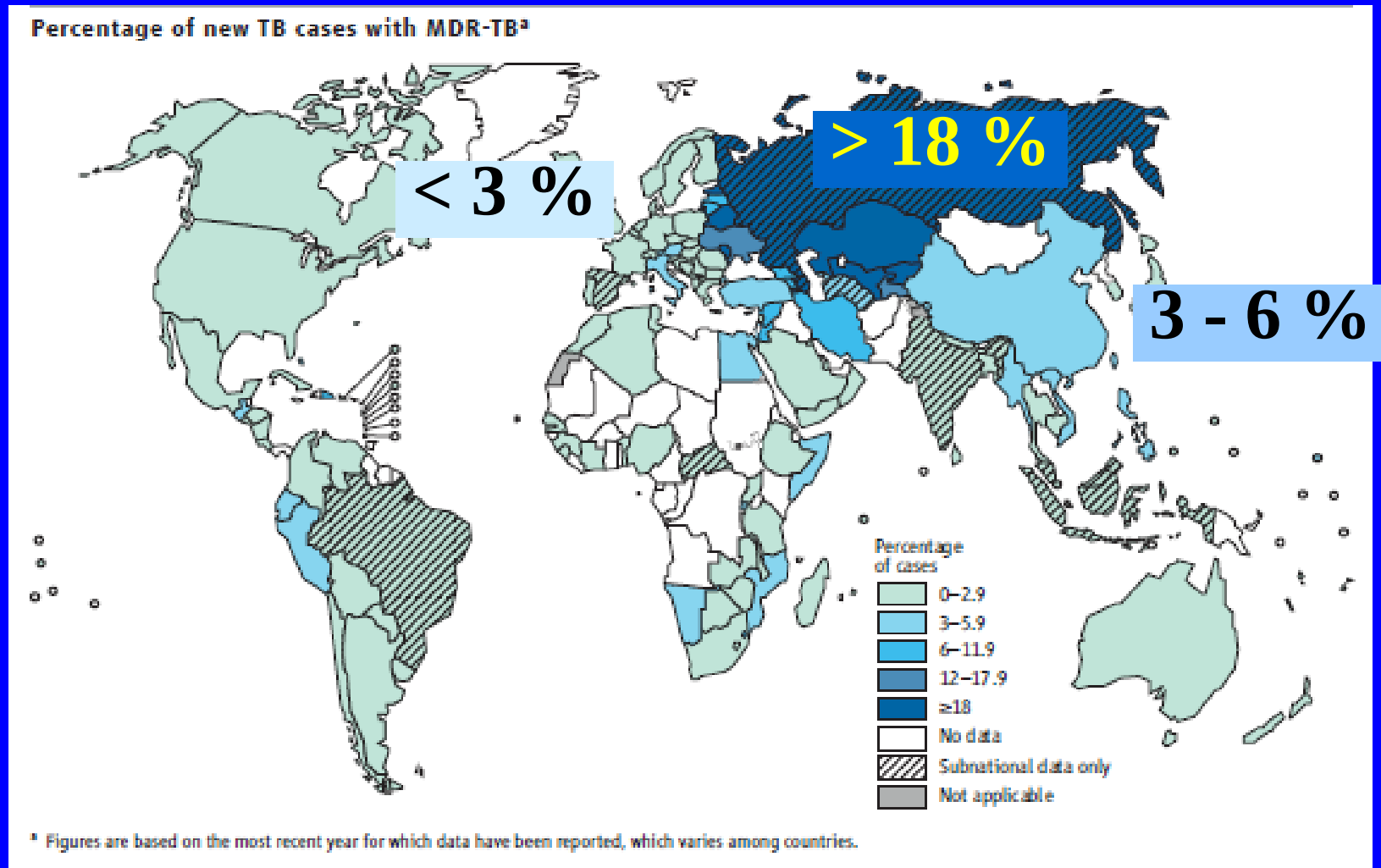
Percentage of previously treated TB cases with MDR-TB^a



^a Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (< 10).

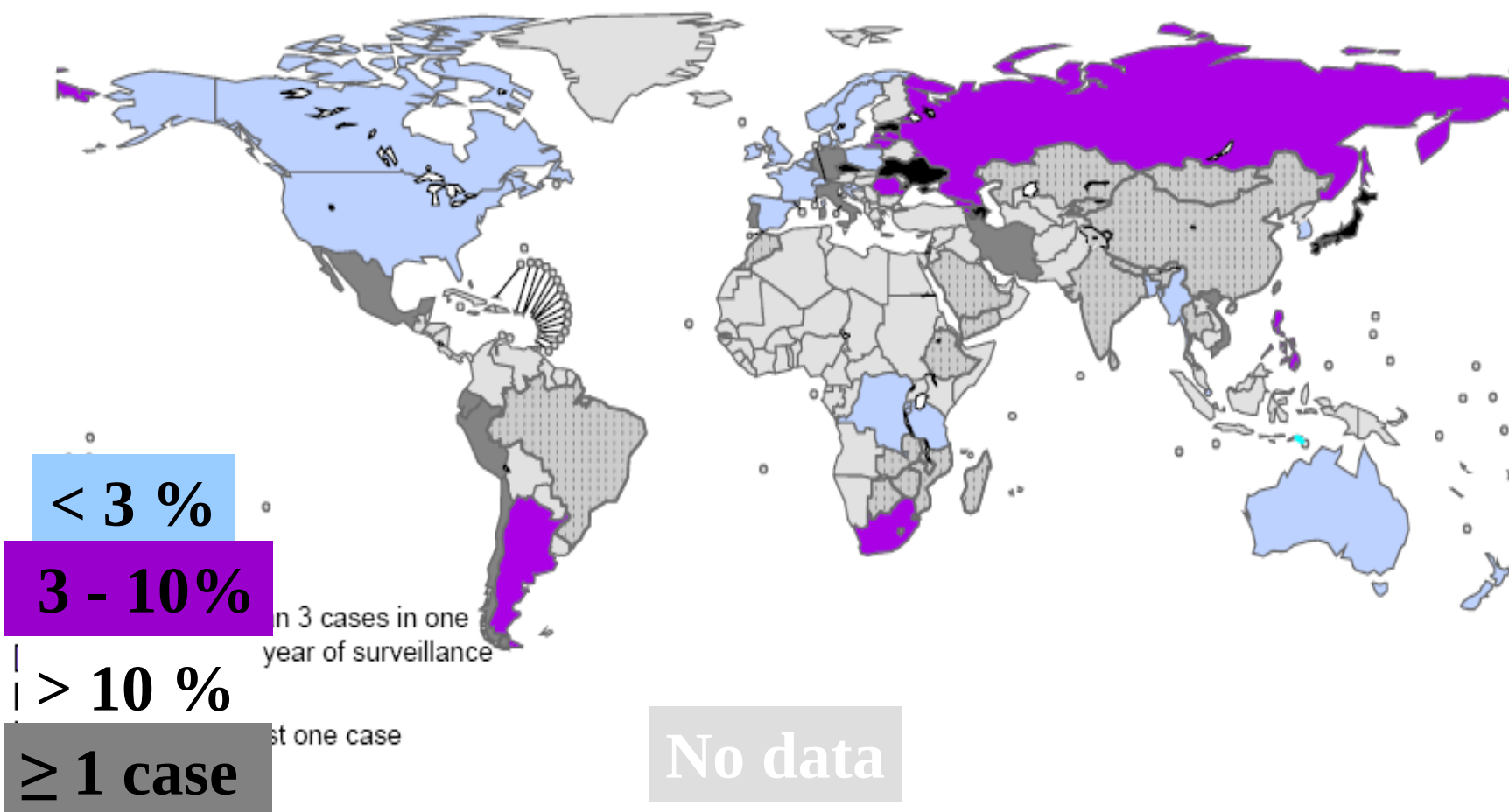
Estimated MDR-TB in new cases (%)

WHO 2013 report

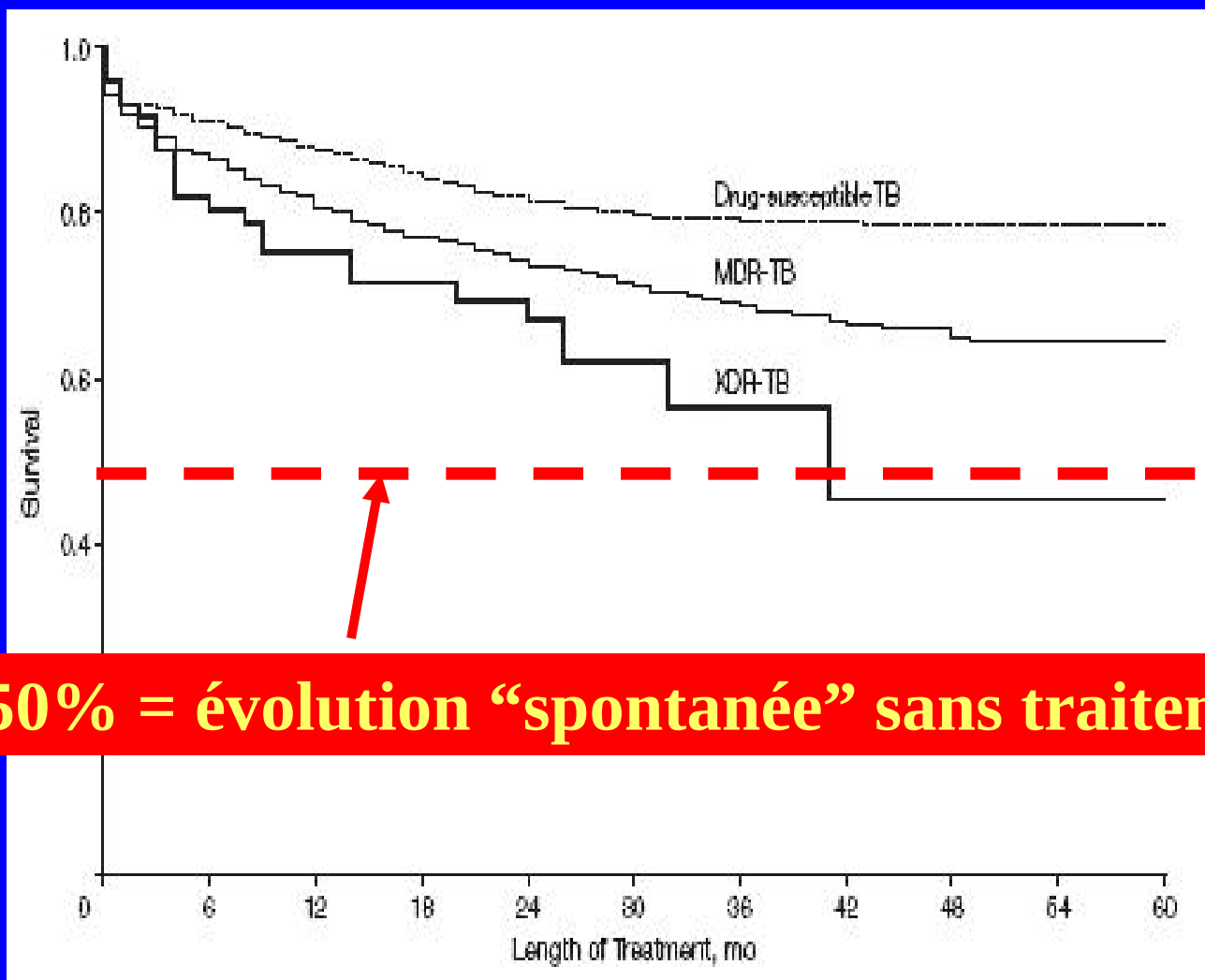


XDR-TB (in % of MDR cases)

* Sub-national averages applied to Russia



Issue fatale des TB-MDR et XDR



TB sensible

TB MDR

TB XDR

50% = évolution “spontanée” sans traitement

Transmission de souches MDR-XDR

South Africa XDR-TB outbreak 2006

- 53 cases
- all patients HIV +
- **nosocomial transmission** ~ 2/3 of cases
- **community transmission** ~ 1/3 of cases
- 52/53 patients died

TB-MDR et XDR en France

Répartition par pays de naissance des cas de TB-MDR recensés en France 2006-2014

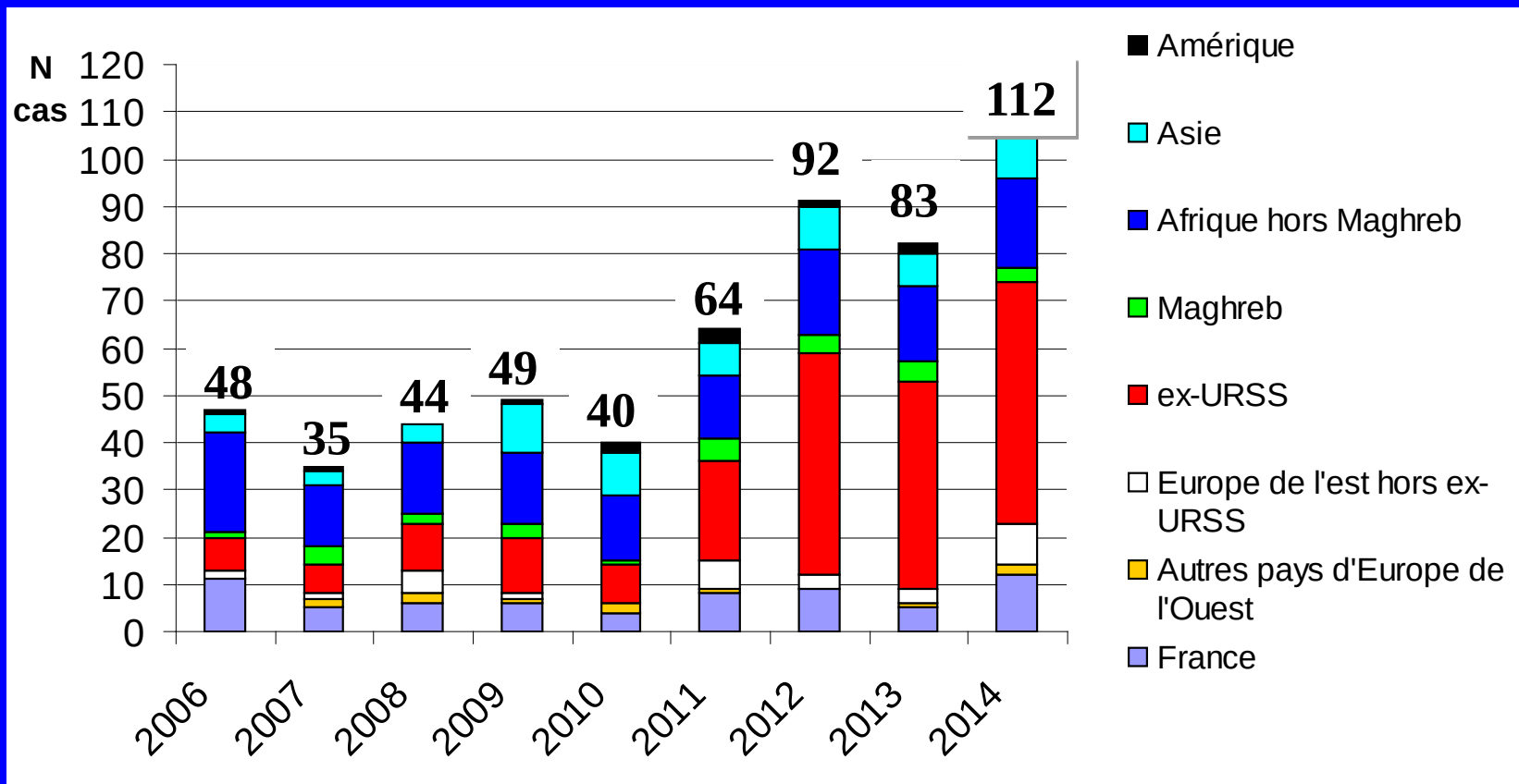
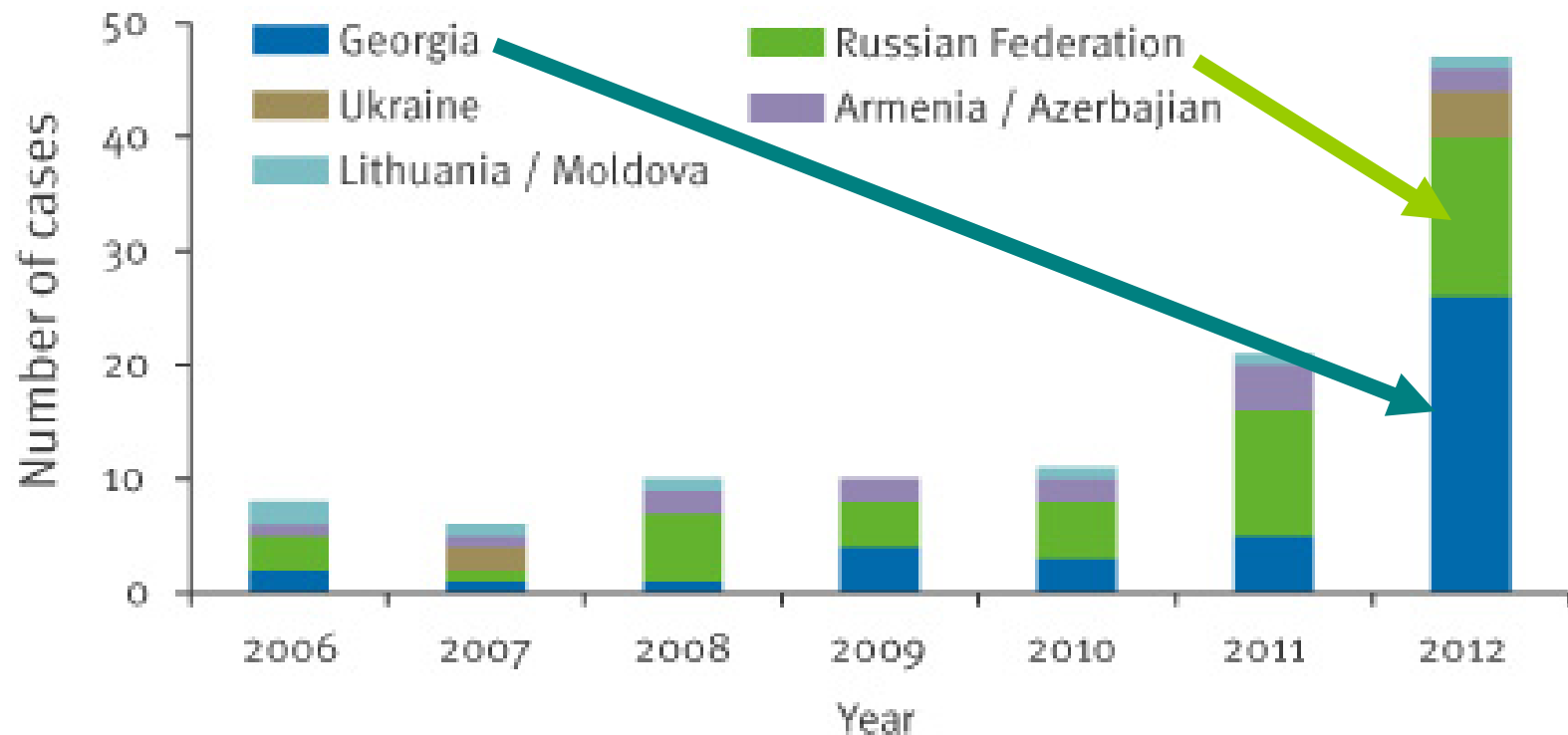
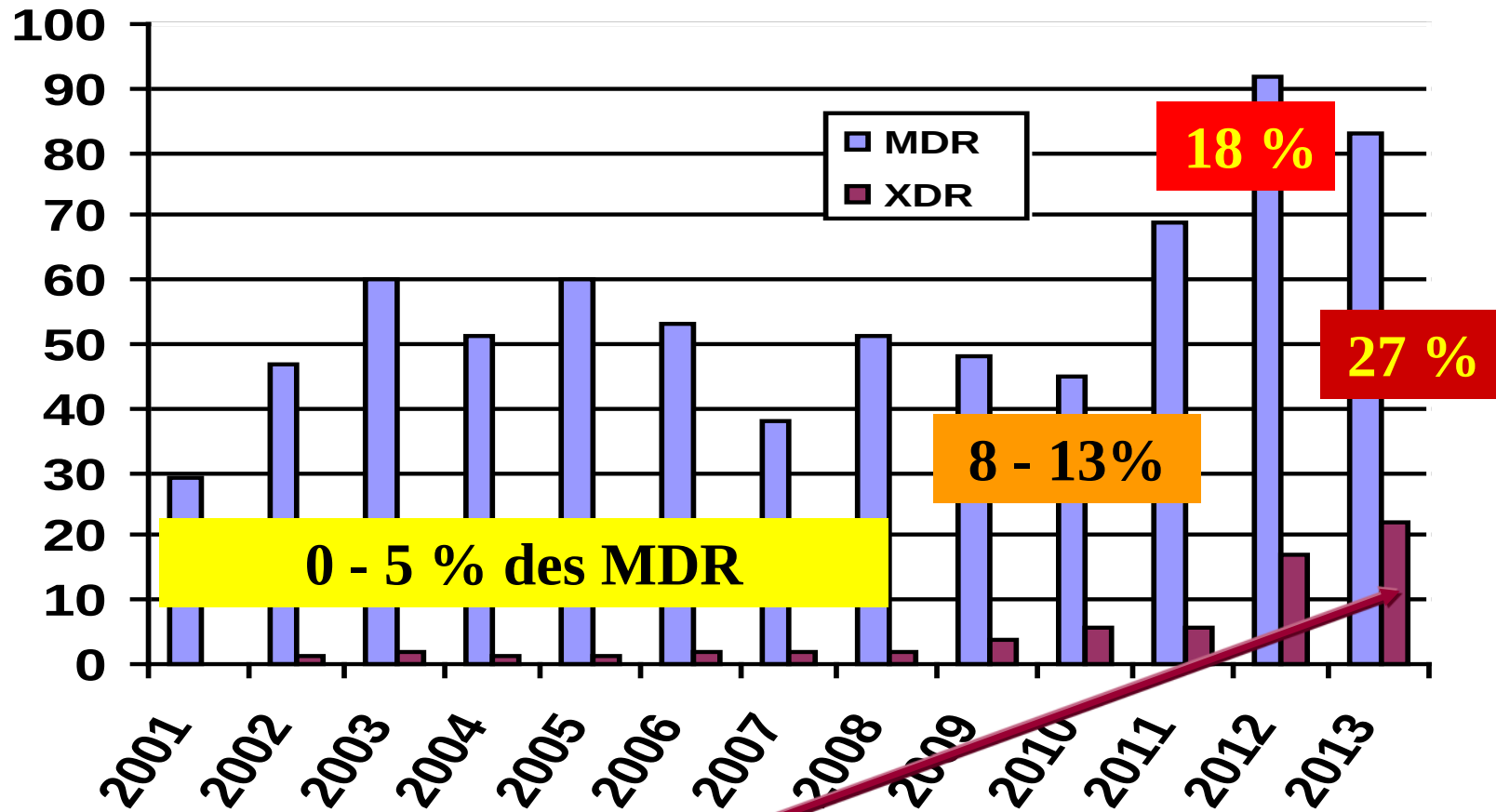


FIGURE 2

Distribution by country of birth of patients with multidrug-resistant tuberculosis born in the former Soviet Union, France, 2006–12 (n=113)



Cas de TB MDR-XDR recensés en France 2001-2013



19/22 XDR de 2013: géorgiens

<http://cnrmyctb.free.fr>

Tuberculose résistante : tendances évolutives

Traitement de 2^{ème} ligne des cas résistants :

- moins actifs que traitement de 1^{ère} ligne

 - durée de contagiosité allongée

 - risque de transmission croisée

- toxicité, intolérance

 - problèmes de compliance

 - risque de résistances additionnelles (→ XDR)

Tuberculose résistante : tendances évolutives

Cas résistants

+

**Antituberculeux 2^{ème} ligne disponibles
(fluoroquinolones, aminosides...)**

+

Organisation sanitaire inadéquate

=

Évolution vers XDR

Tuberculose résistante : tendances évolutives

Cas XDR

+

**nouveaux antituberculeux disponibles
(bédaquiline...)**

+

Organisation sanitaire inadéquate

=

Évolution vers “toto-résistance”

"Emerging" multiresistant bacteria

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

Enterobactéries résistantes aux carbapénèmes par carbapéménase

(R à ~toutes bêta-lactamines ±
aminosides et quinolones)

=

**résultat d'une évolution
de 40 ans**

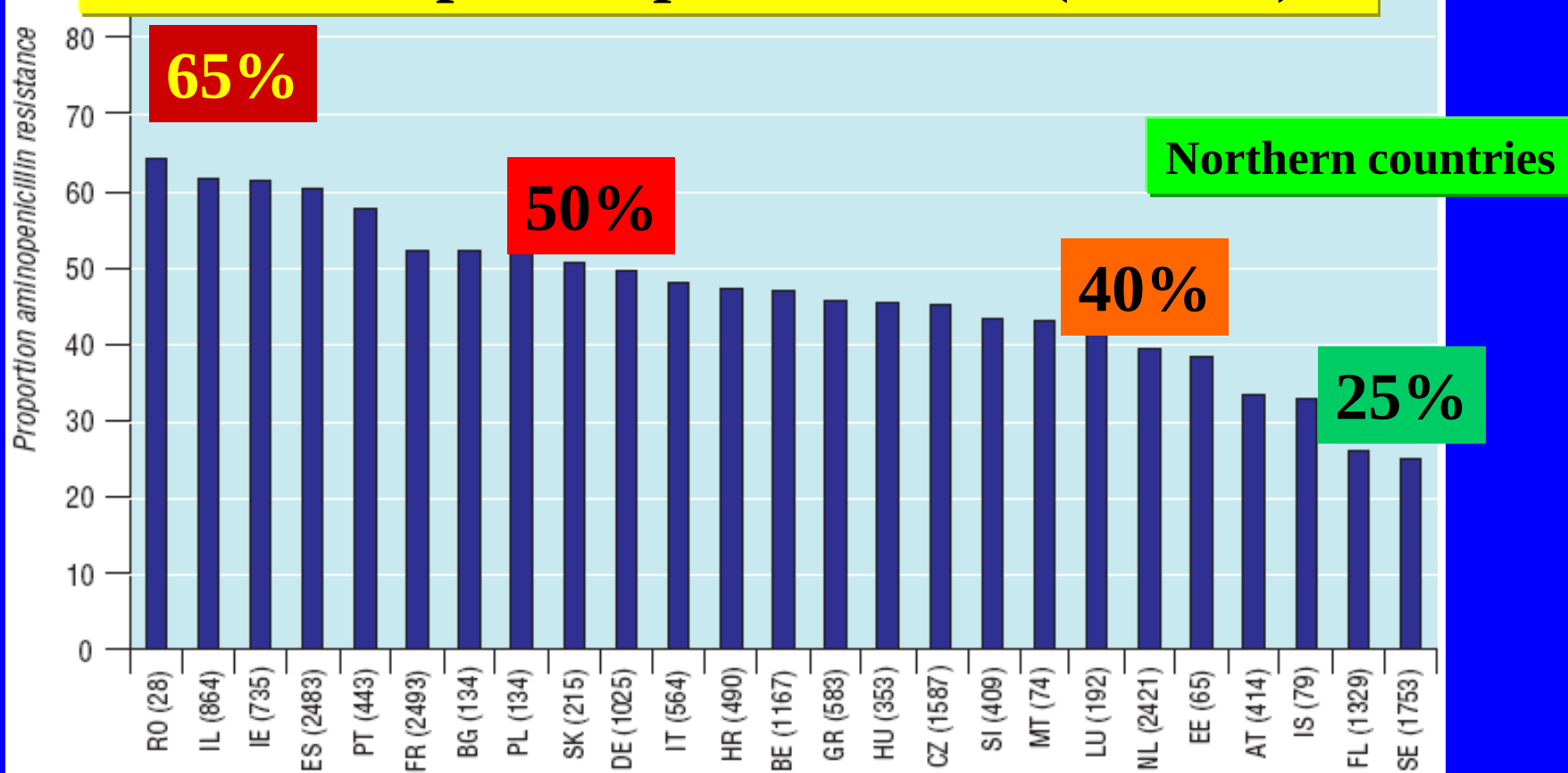
Les 3 vagues de résistance acquise par β -lactaminases plasmidiques chez les entérobactéries

- 1960's : pénicillines
ampicilline
amoxicilline
 - R ampicilline
 - pénicillinases (TEM, SHV) (*E.coli*, *Shigella*...)
- 1980's : C3G
céfotaxime
ceftriaxone
ceftazidime
 - R cephalosporines de 3^{ème} génération
 - β -lactamases à spectre étendu (BLSE) :
dérivés de TEM, SHV à partir 1984
puis nouvelles BLSE (CTX-M) à partir 2000
- 1990's : pénèmes
imipénème
méropénème
 - R carbapénèmes
 - carbapéménases (*Klebsiella*, *E.coli*, ...) à partir de la fin 1990's

Etape 1 : résistance à l'ampicilline

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

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



Etape 2 : résistance aux C3G (BLSE plasmidiques)

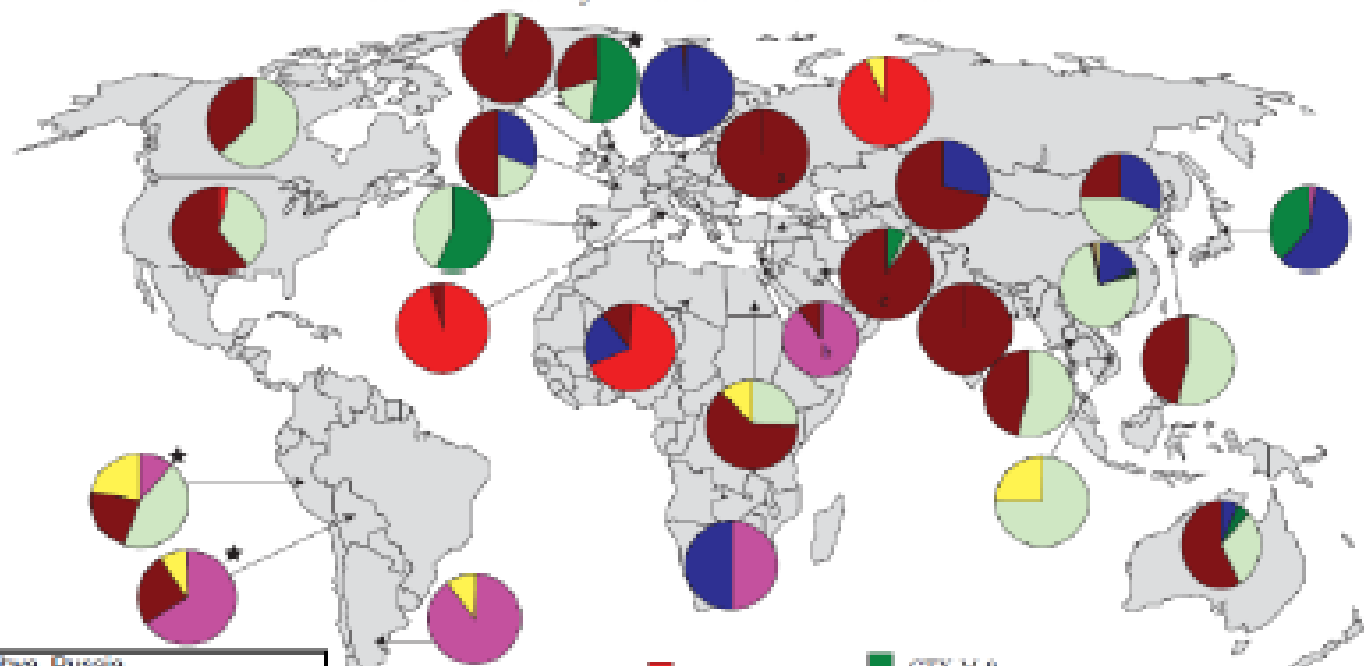
Extension des R aux céphalosporines 3^{ème} Gén. par BLSE CTX-M à partir des années 2000s

Epidemiology of CTX-M β -Lactamases

Journal of Antimicrobial Chemotherapy (2009) **64**, Suppl. 1, i13–i10
doi:10.1093/jac/dkp256

The changing epidemiology of resistance

Peter M. Hawkey^{1,2*} and Annie M. Jones³



CTX-M-1	Italy, Libya, Russia
CTX-M-2	Israel, South America, South Africa
CTX-M-3	Japan, Poland, South Africa
CTX-M-9	Spain, UK
CTX-M-14	Canada, South East Asia
CTX-M-15	India, Middle East, Europe, USA

CTX-M-1
CTX-M-2
CTX-M-3

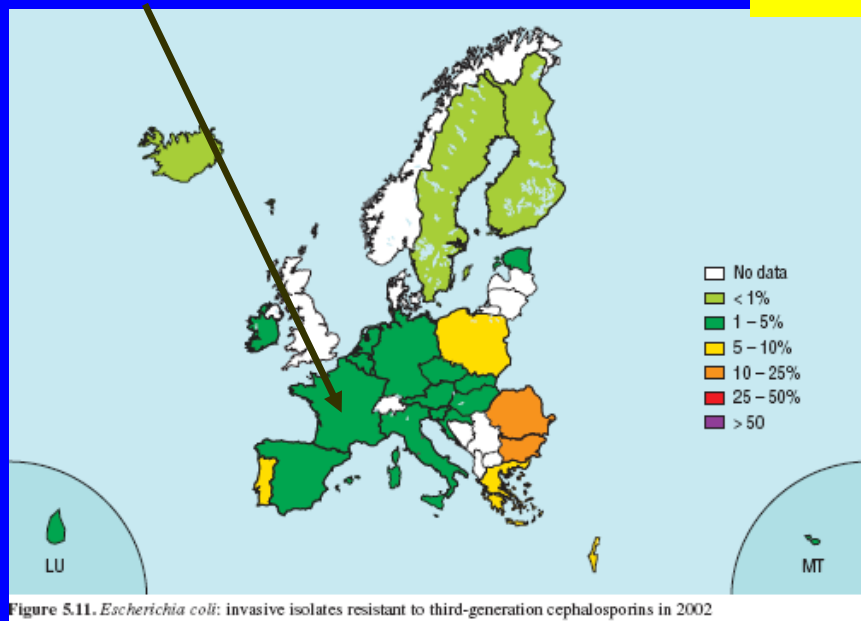
CTX-M-9
CTX-M-14
CTX-M-15
Others

★ Pseudomonas
a Lebanon, b Israel, c Kuwait

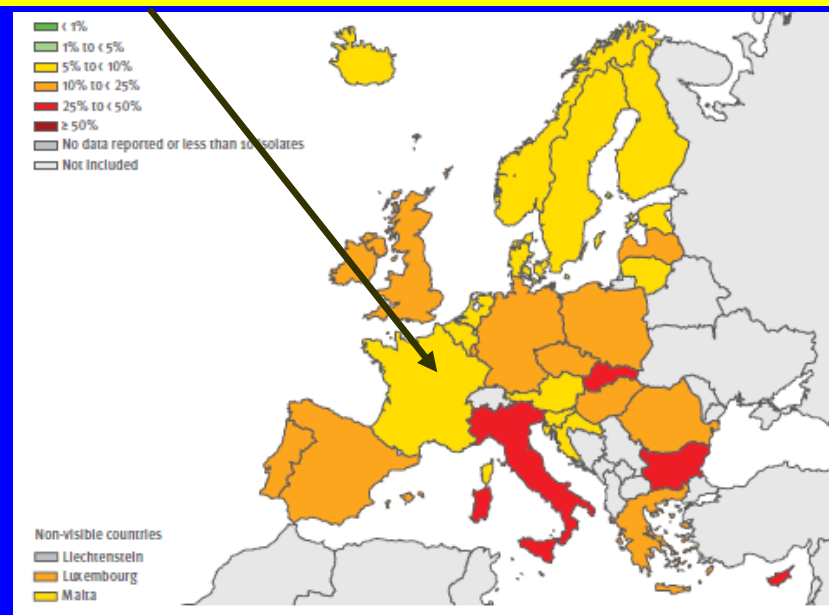
EARS-net : E. coli resistant to 3rd gen. cephalosporins (%) in bacteremias

8% in 2012, 8% in 2013
(6% ESBL)

1%



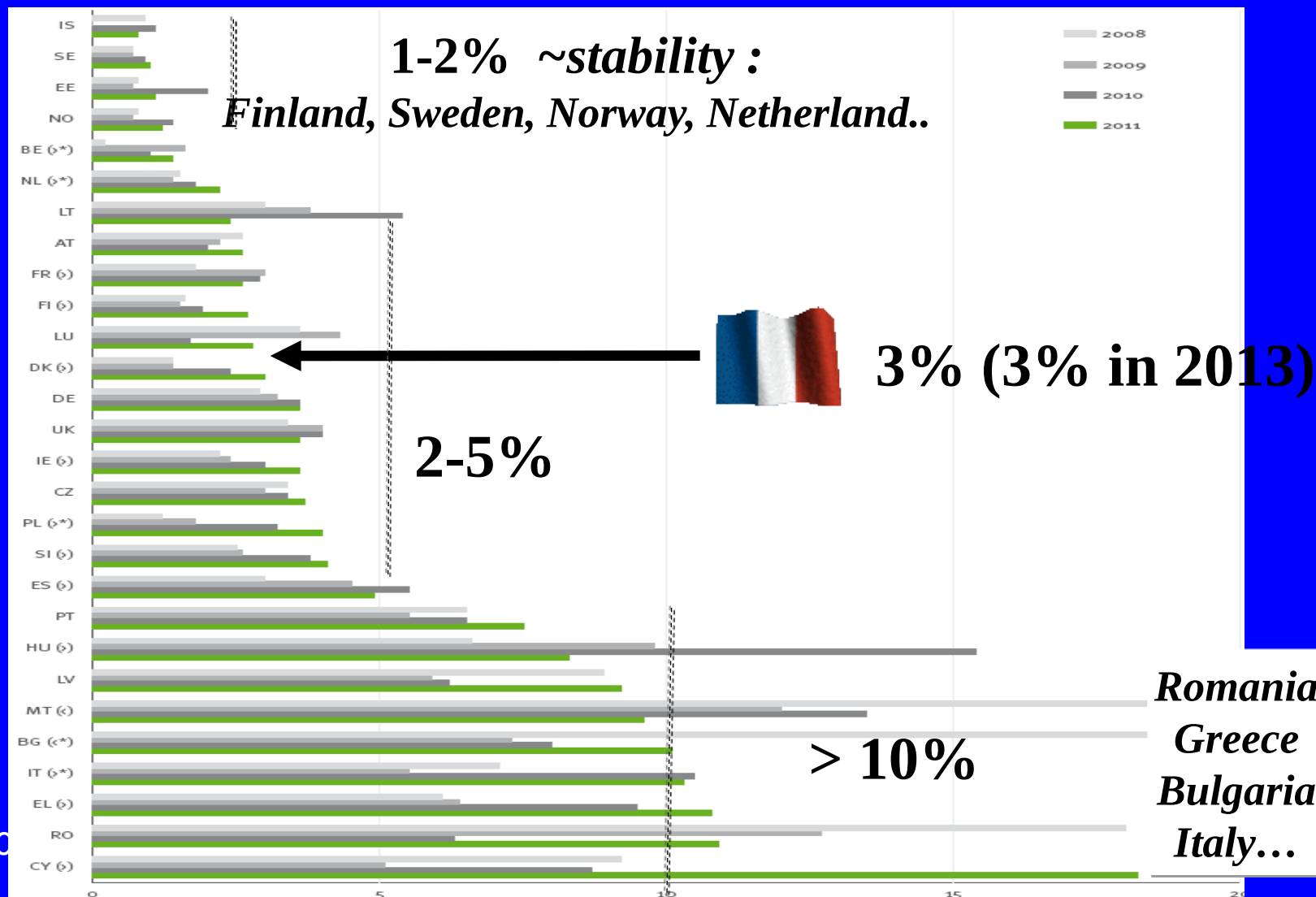
2002



2013

Extrapolation : ~3,000 ESBLcases /year in France in 2013

% 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

25% in 2011 ; 23% in 2012 ; 28% in 2013

4%

~21% ESBL

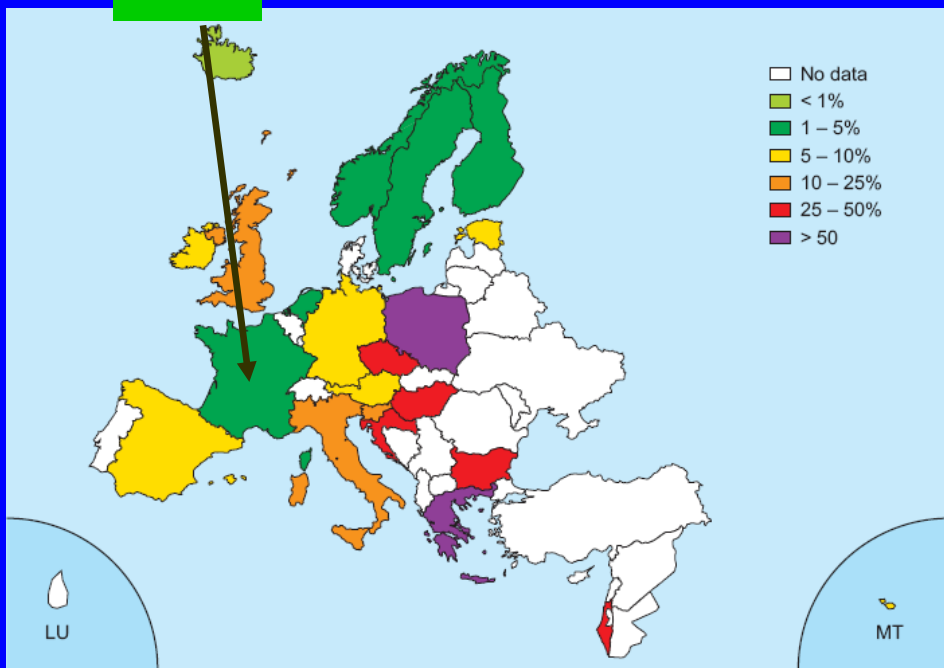
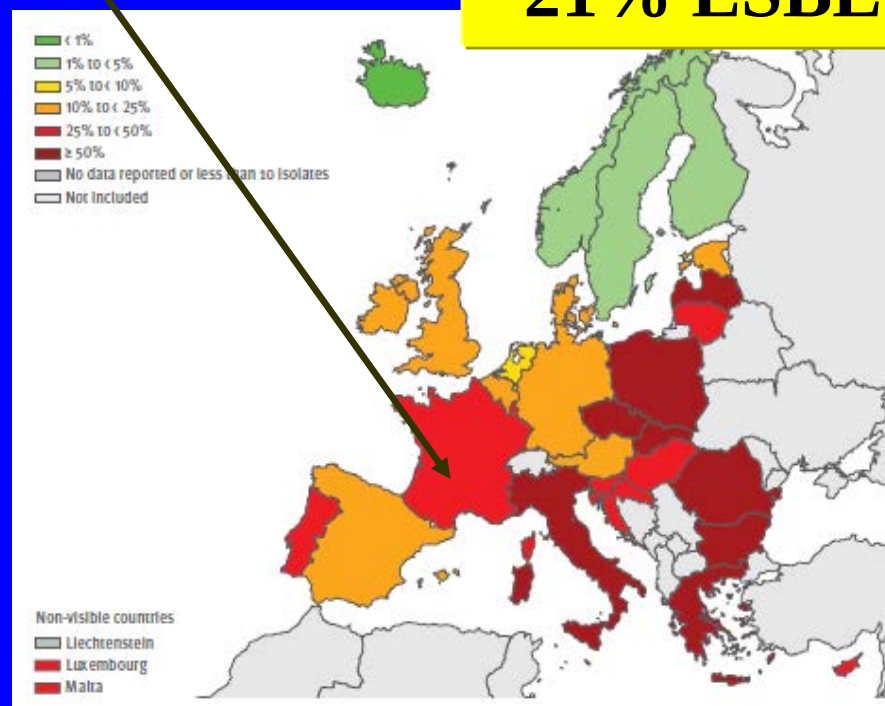


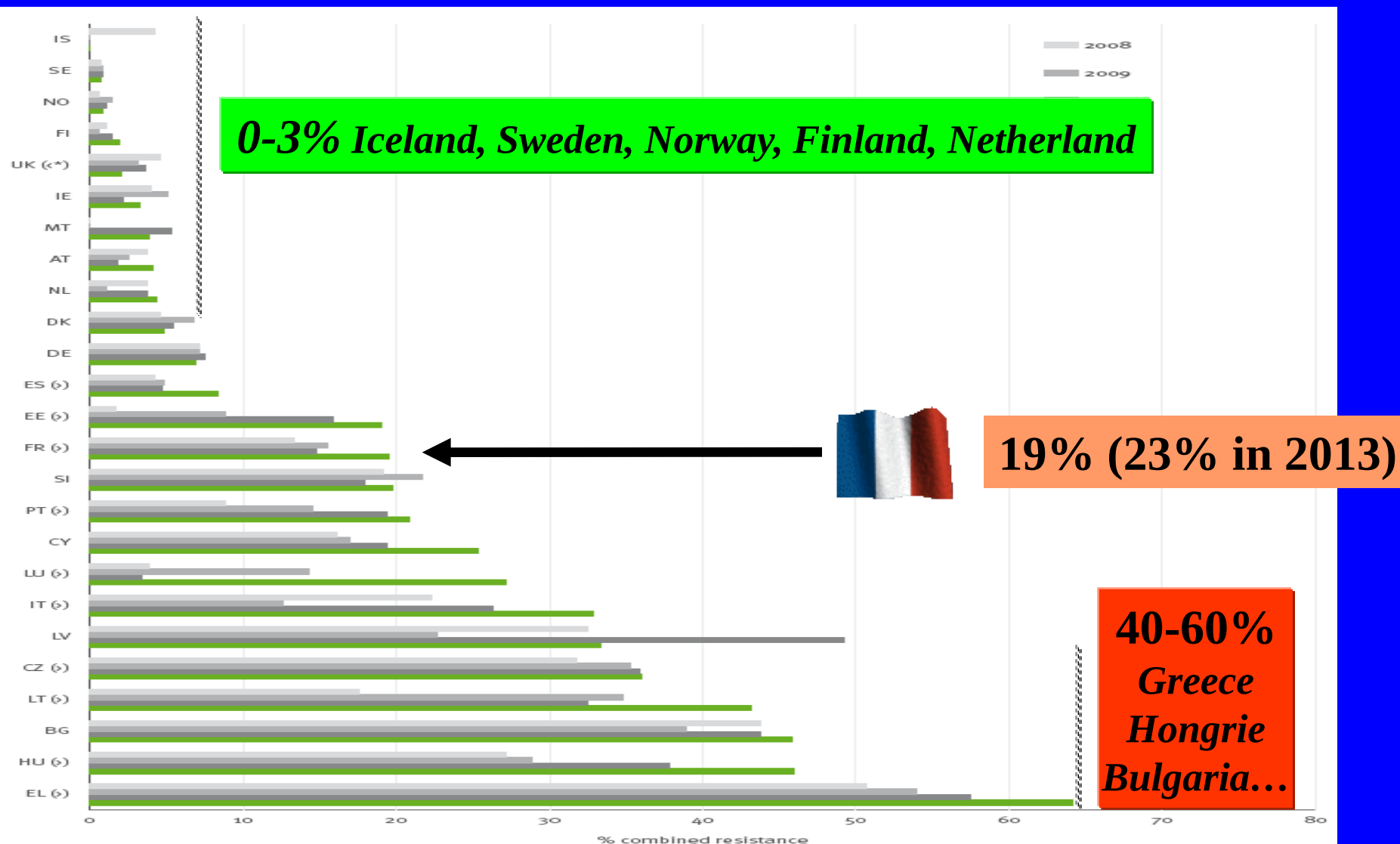
Figure 4.22. *Klebsiella pneumoniae*: proportion of invasive isolates resistant to third generation cephalosporins in 2005.



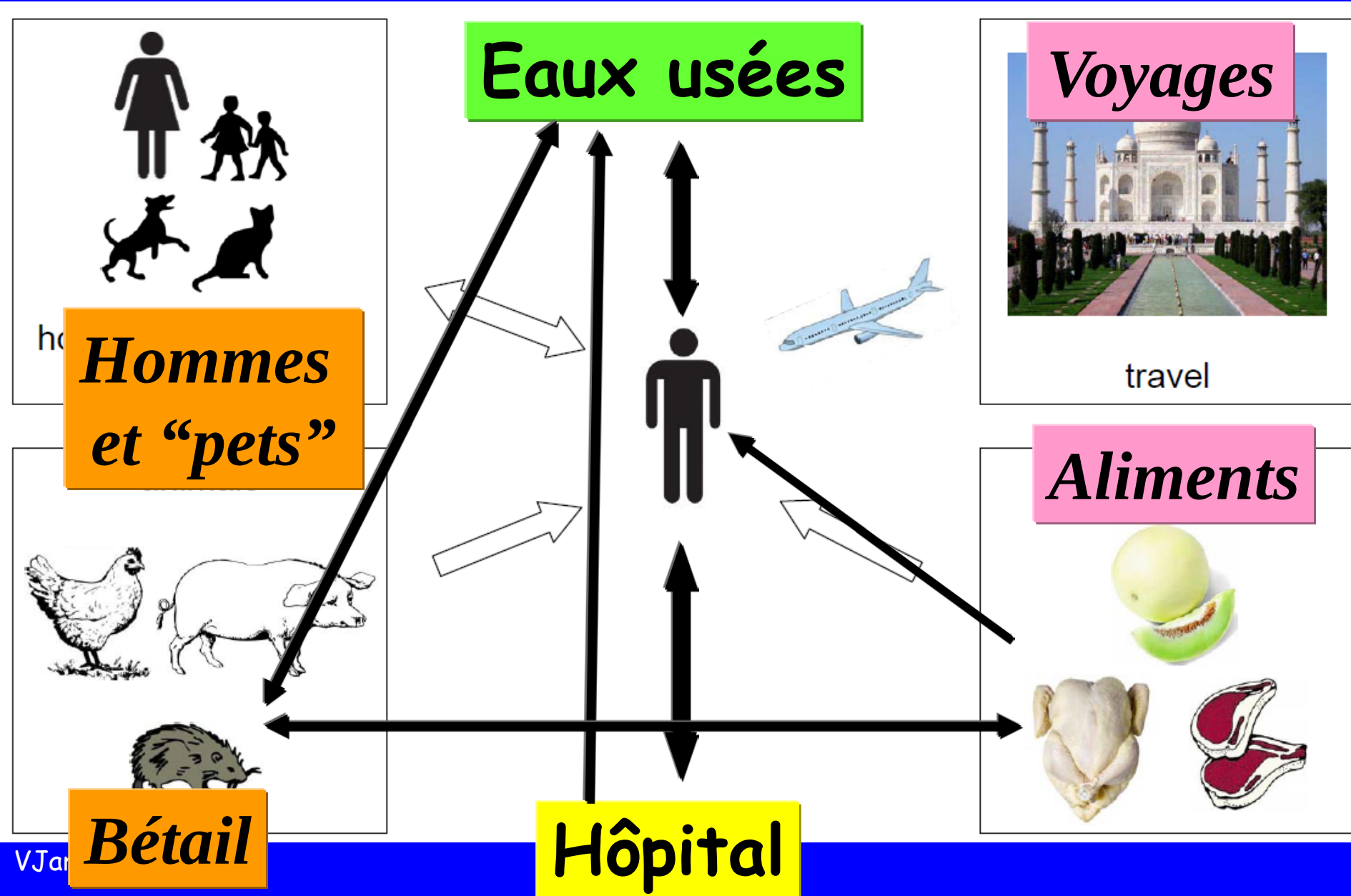
2005

2013

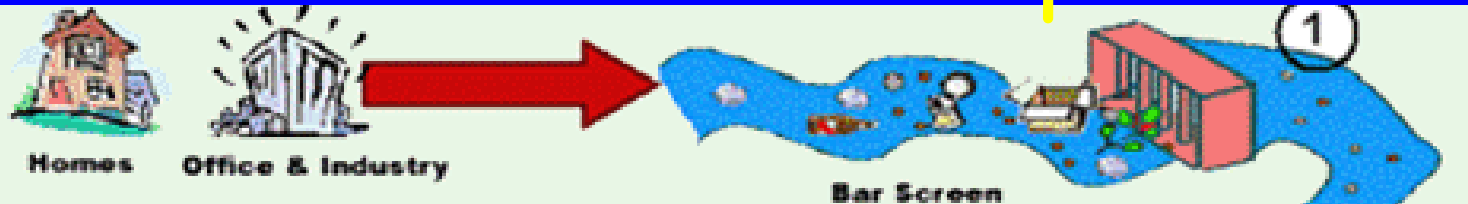
% R 3rd gener. Cephalosporins + FQ + aminoglycosides in *K. pneumoniae* bacteremias in Europe, EARSS 2008-11



Circulation des entérobactéries BLSE



Traitement de l'eau : devenir en aval des stations d'épuration



Eau pour agriculture ou vers rivières

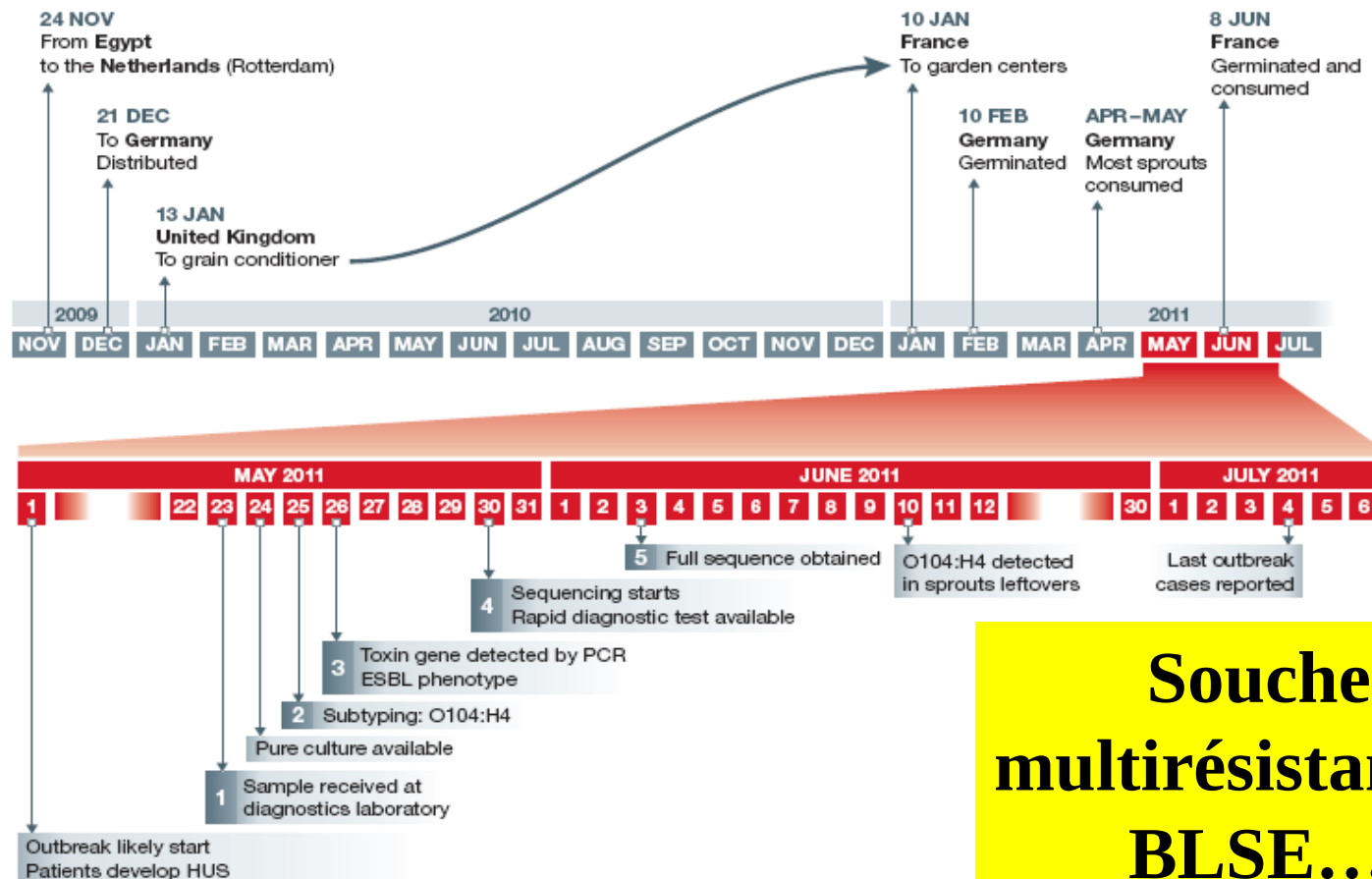


Engrais pour agriculture

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

Helge Karch¹, Erick Liorio-Huie²,
Eliora Z. Ron^{6†}, Tony

**~4000 cas gastro-entérite hémorragique
~900 SHU, 54 décès**



**Souche
multirésistante :
BLSE...**

Epidémie européenne de gastroentérites à EHEC O104:H4, 2011

Résistance de la souche

- BLSE (CTX-M)
- Céphamycines (hyperproduction céphalosporinase?)
- Quinolones
- Cyclines
- Cotrimoxazole

Marqueurs de pathogénicité

- *stx1*
- *aggR*

Etape 3 : résistance aux pénèmes (carbapéménases plasmidiques)

n.b. les plamides codant pour les
carbapéménases codent aussi pour
des BLSE et des pénicillinases
classiques !!!
(séquelles de l'évolution)

Entérobactéries « carbapéménase » KPC (début : fin années 1990's, USA)

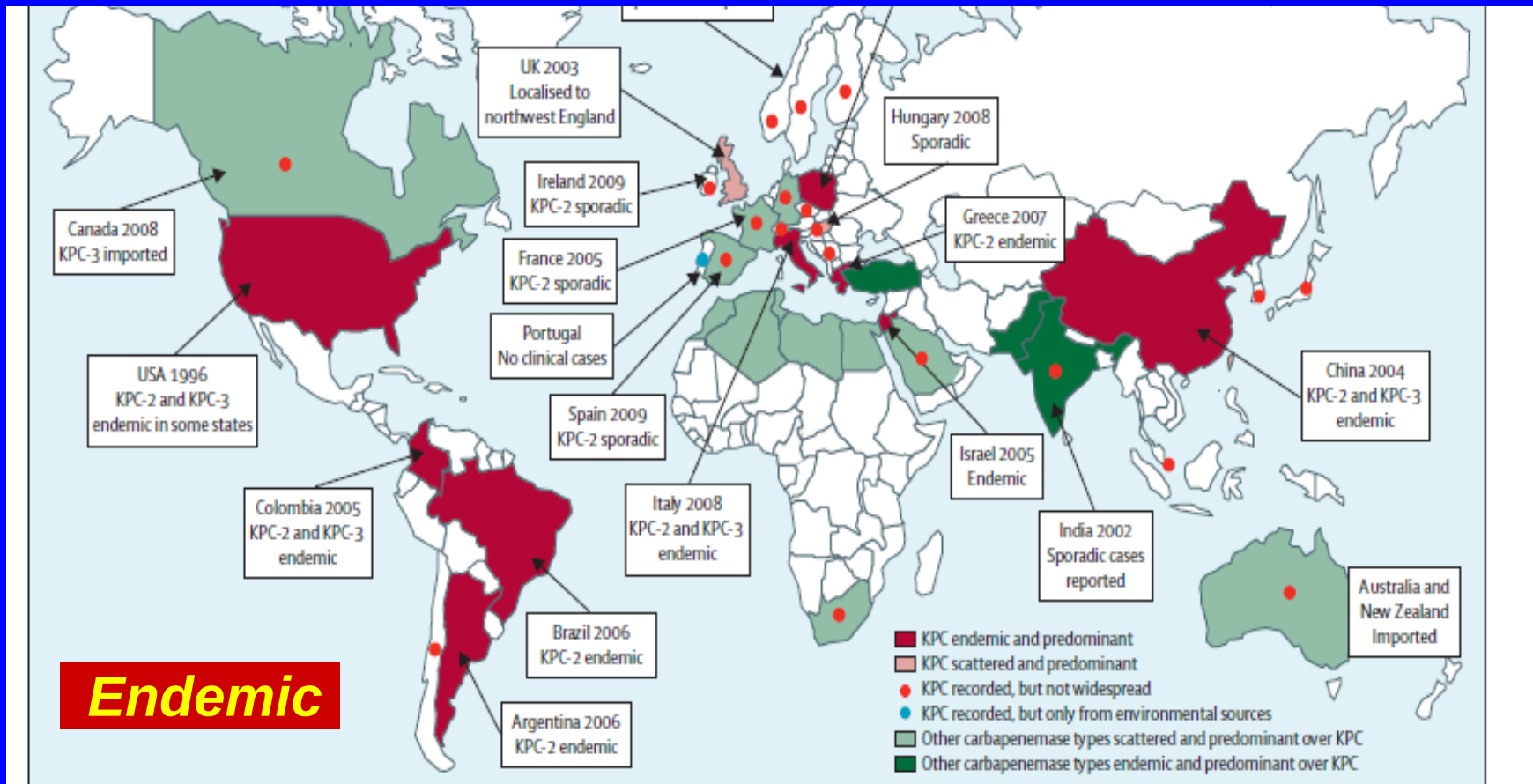
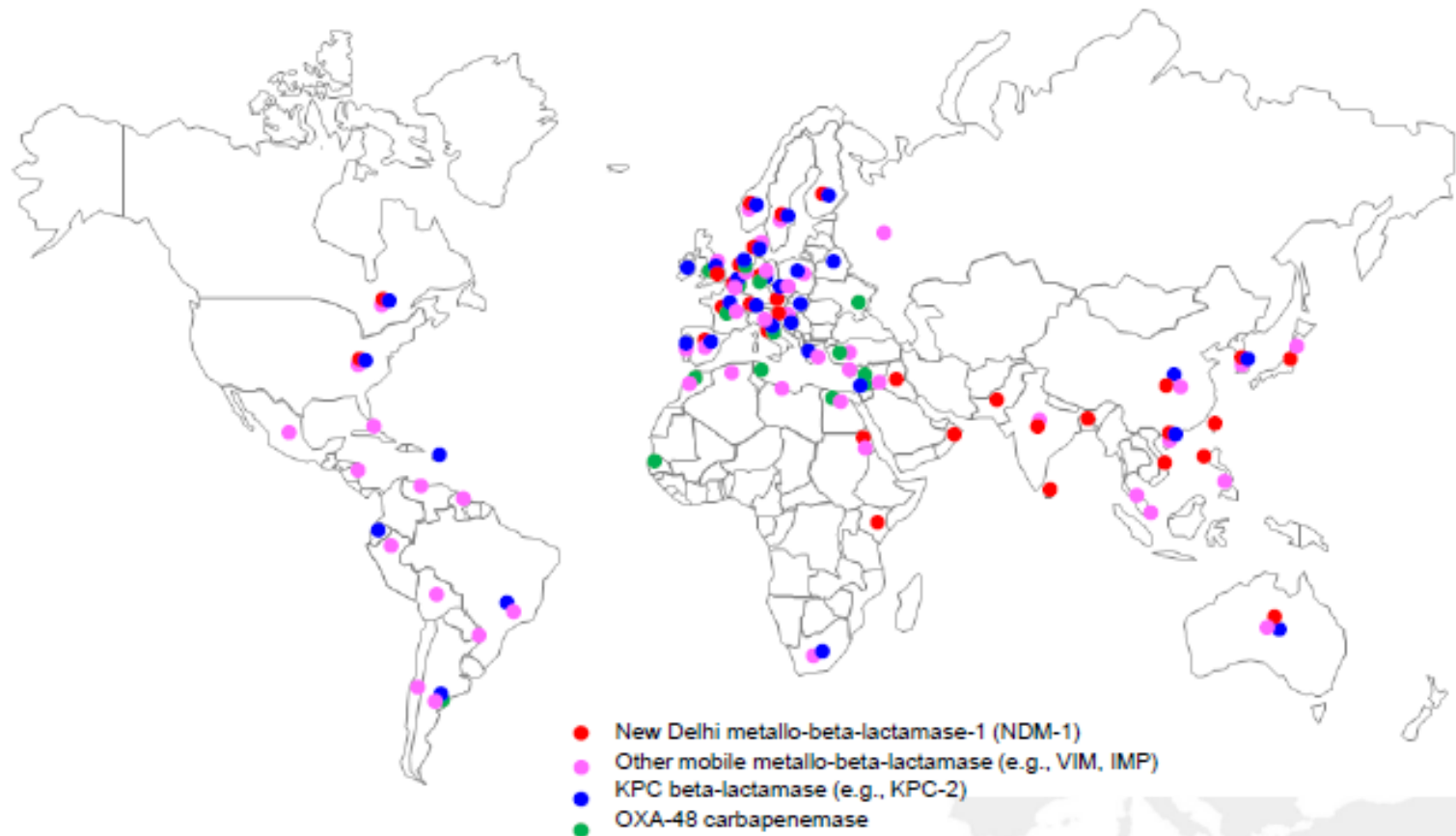


Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin
Other carbapenemase types include VIM, OXA-48, or NDM. KPC= *Klebsiella pneumoniae* carbapenemase.

Entérobactéries « carbapénémase »

NDM-1 (début : 2008, Indes)

Worldwide emergence and spread of carbapenemases (as of March 2011)

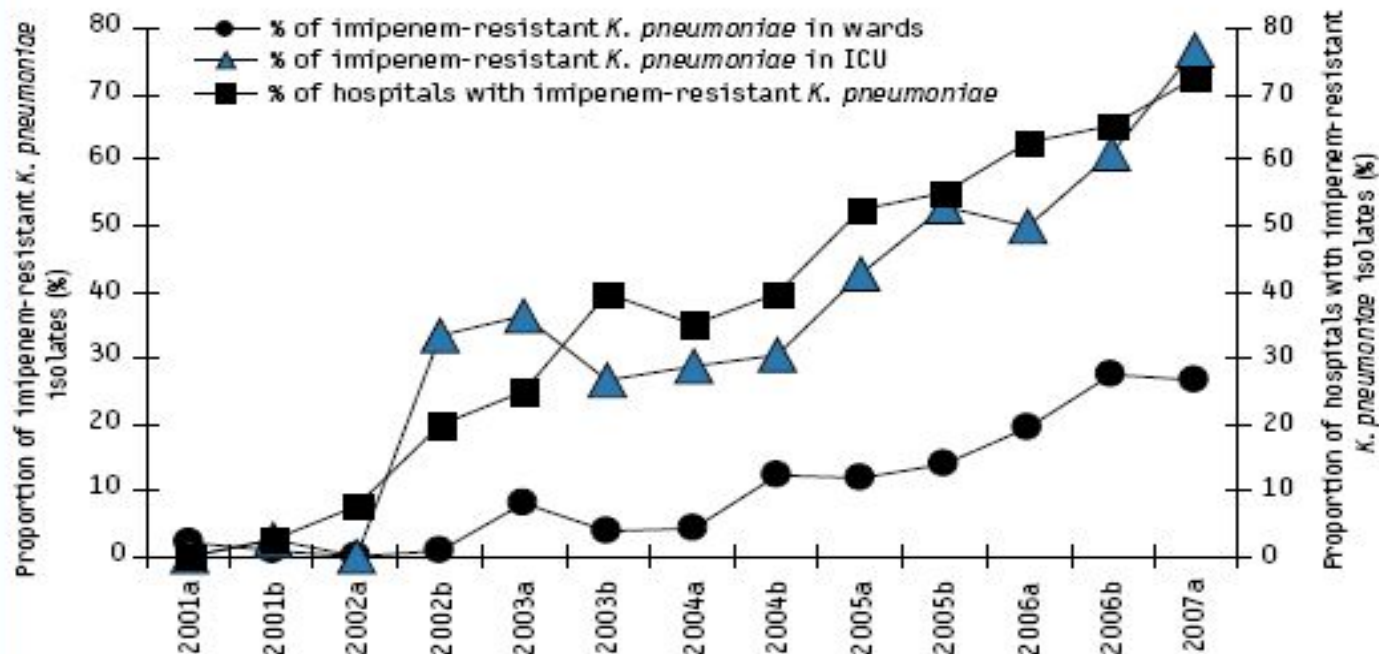


Adapted and updated from: Walsh T. Int J Antimicrob Agents 2010;36(Suppl 3): S8-S14.

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

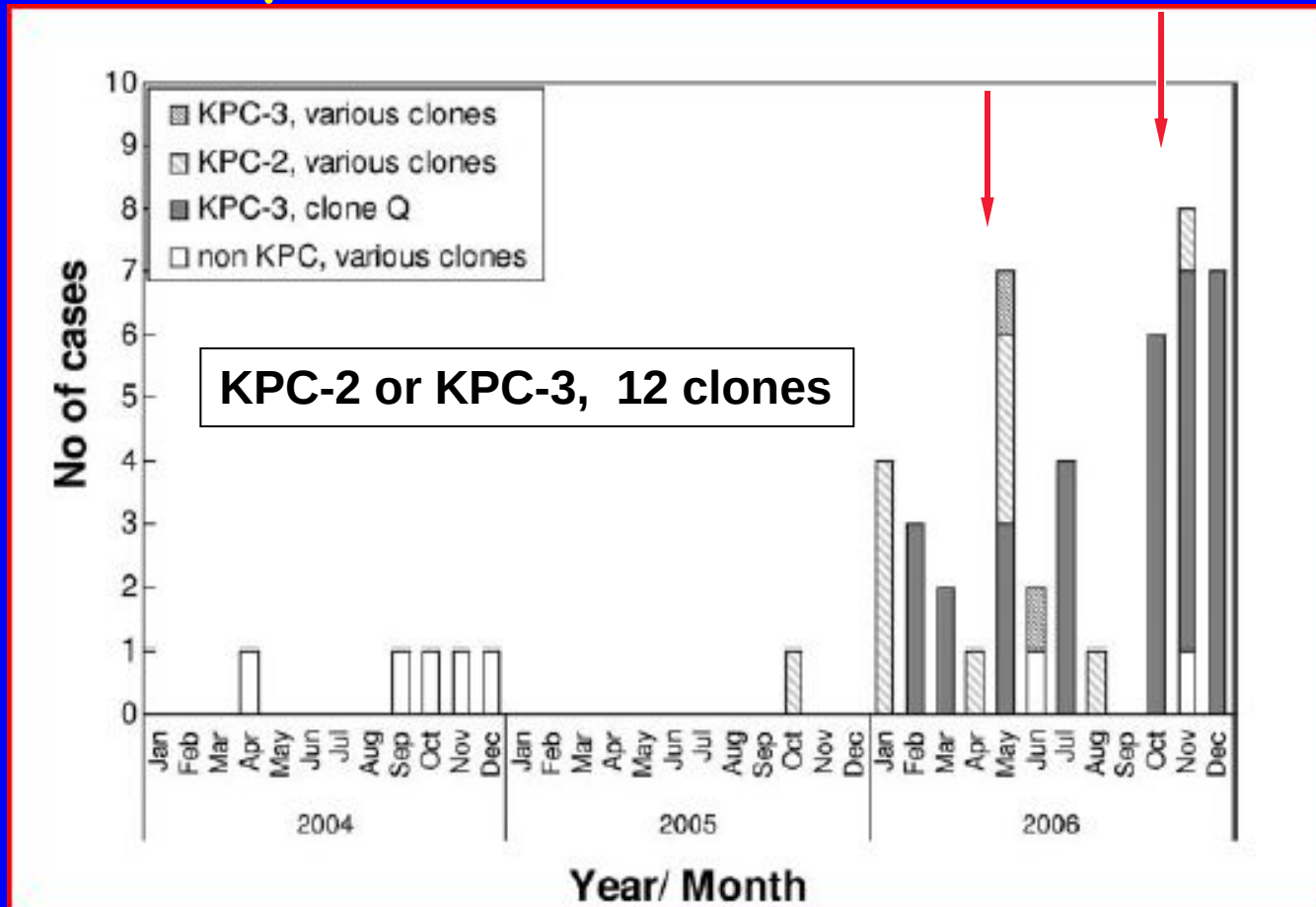
FIGURE 2

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

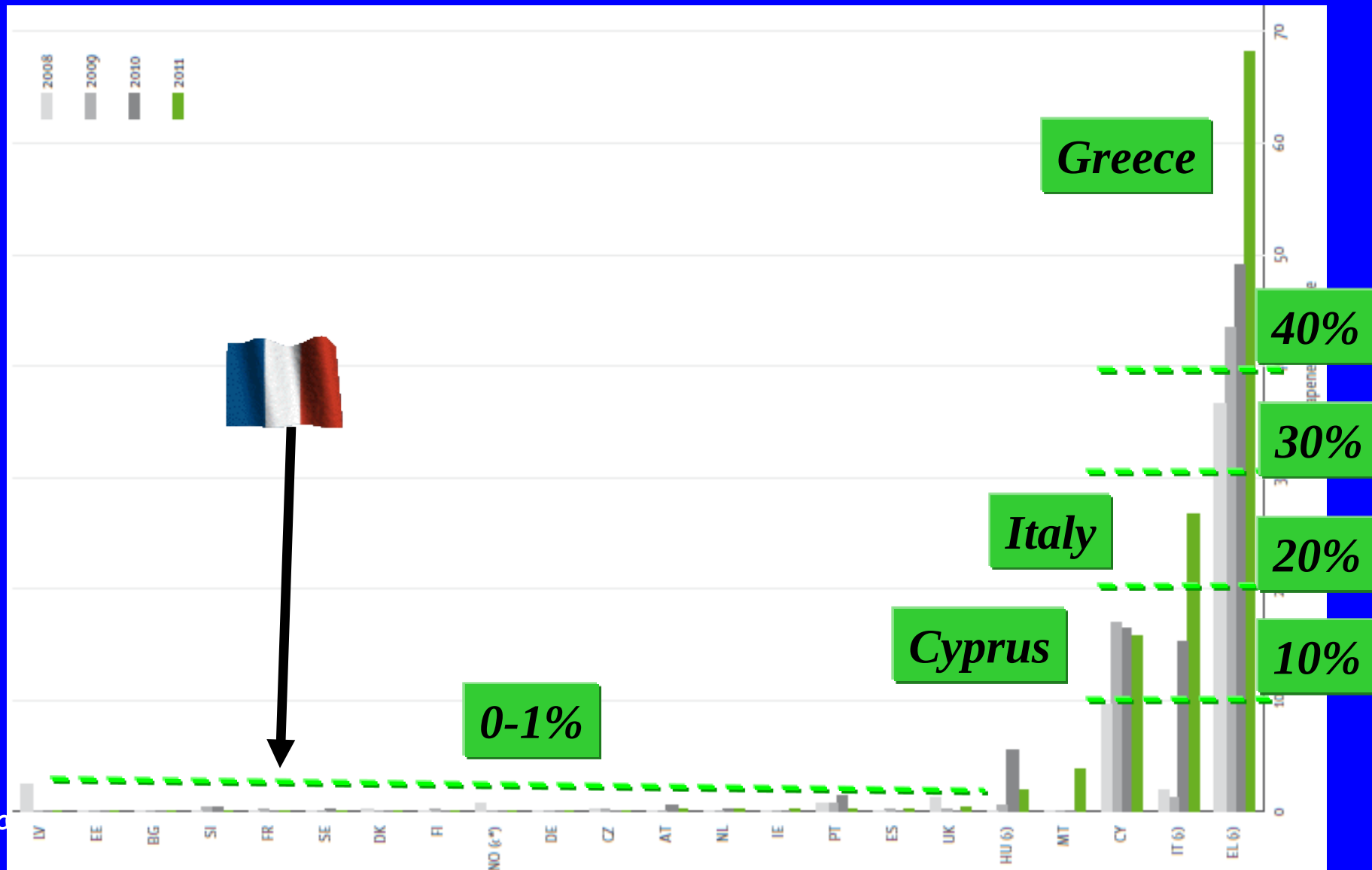


Data from the Greek System for the Surveillance of Antimicrobial Resistance (<http://www.mednet.gr/whonet>)

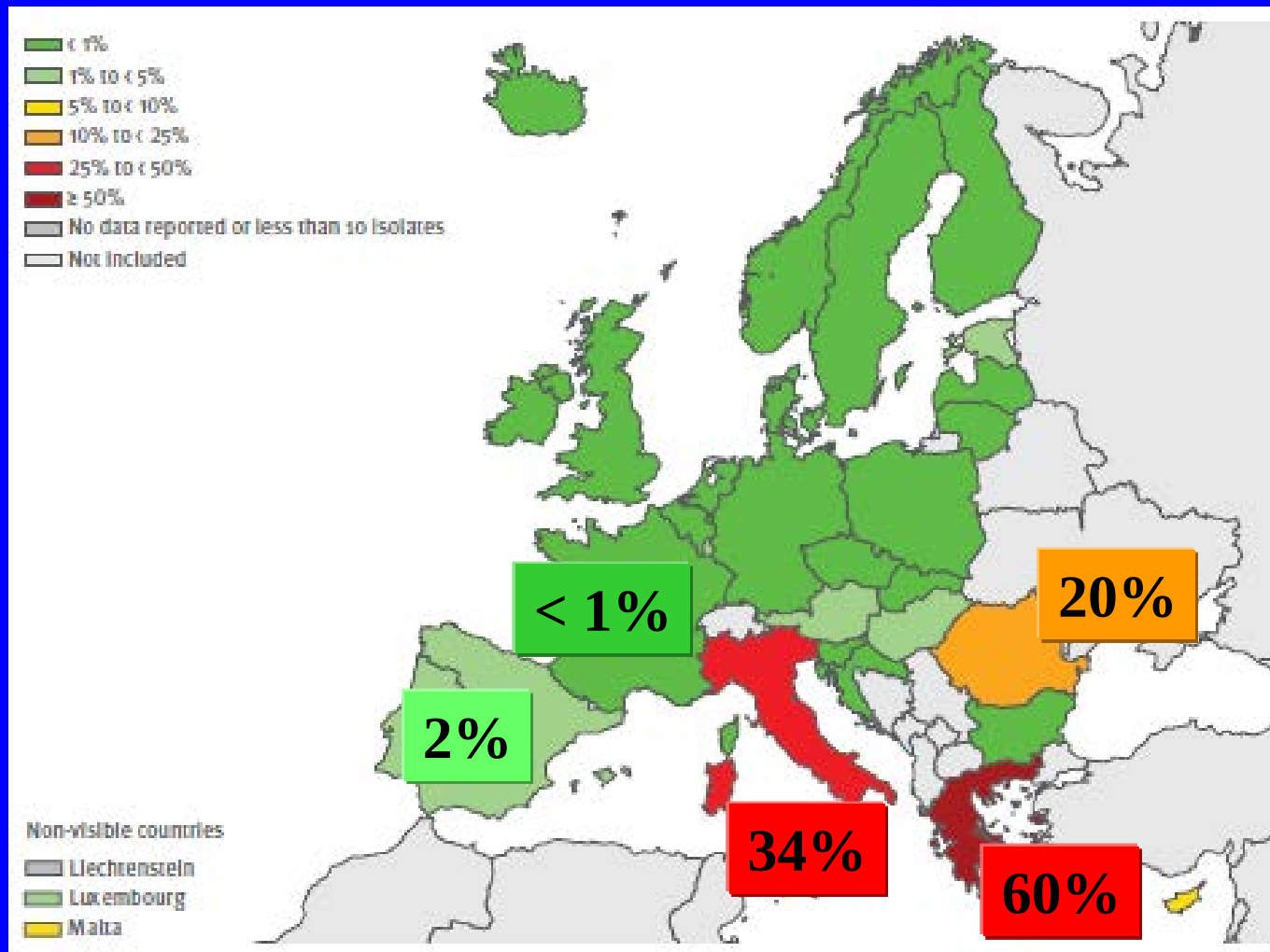
K.pneumoniae IMP-R in Tel Aviv hospitals (Israel) 2004-06



% carbapenem resistance in *Klebsiella pneumoniae* (bacteriemias) Europe 2008-2011



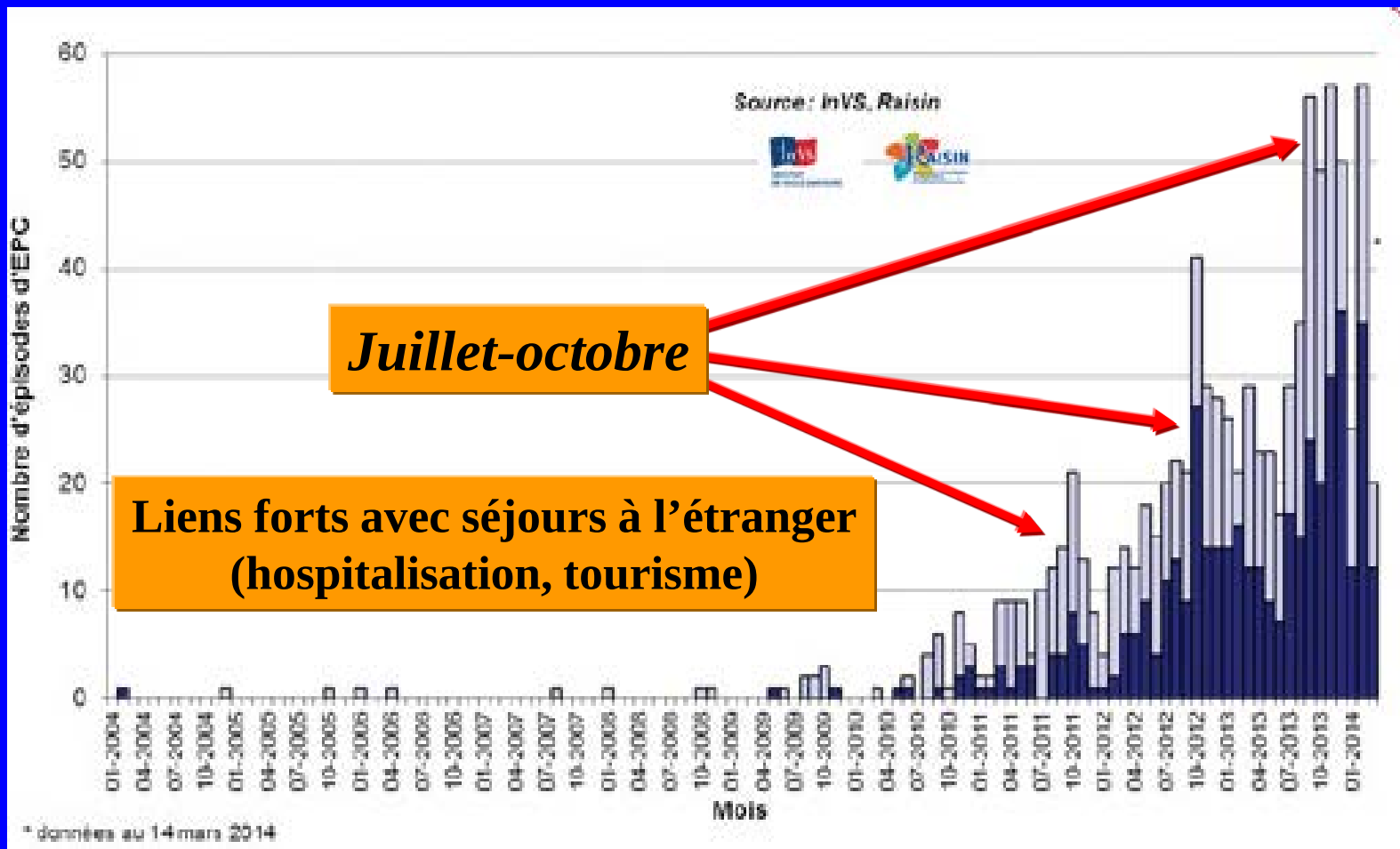
% carbapenem resistance in *Klebsiella pneumoniae* (bacteriemias) Europe 2013



CPE events

France 2004 - March 2014 (n=913)

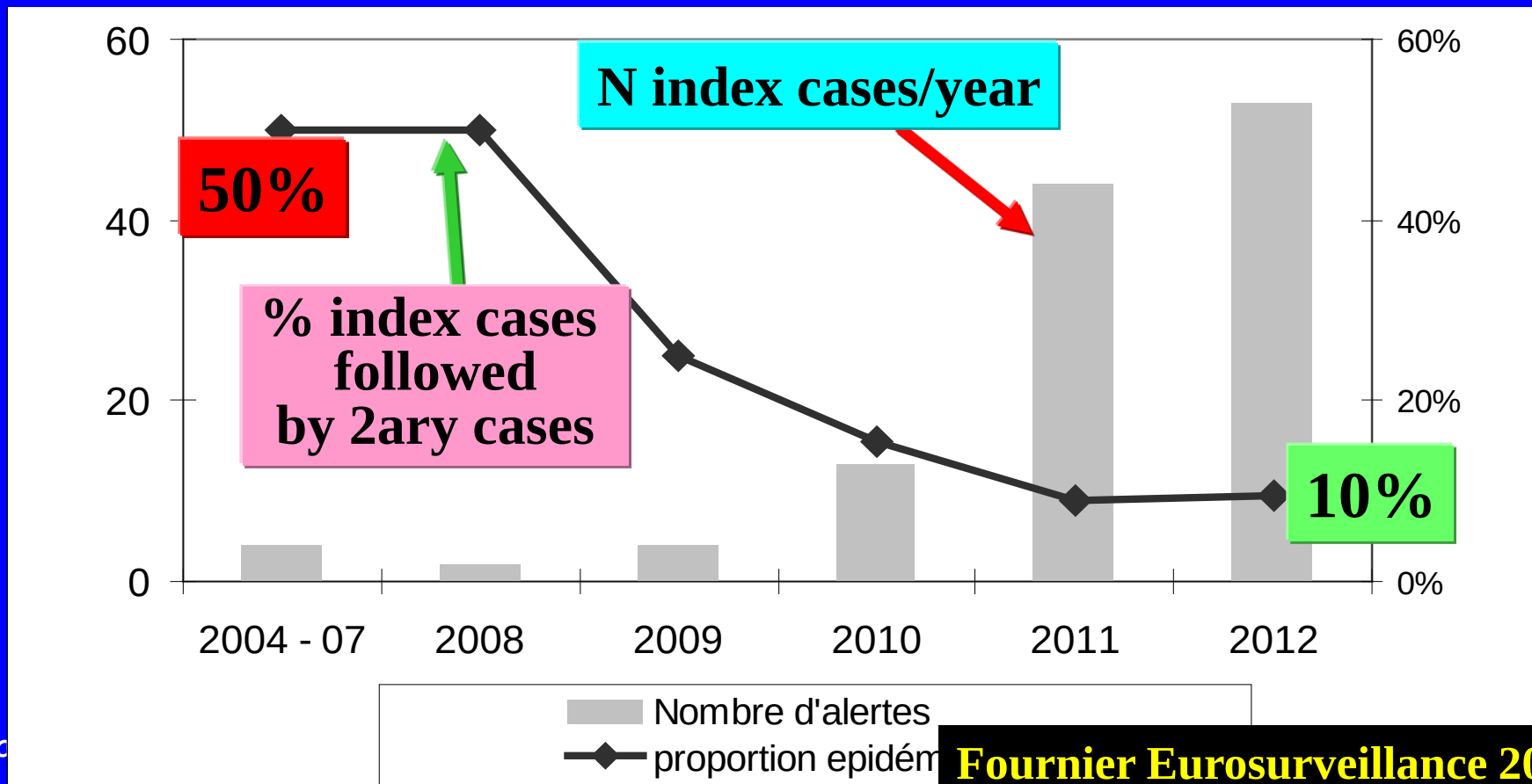
« Early warning system »



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

120 index cases

4/5 transfer from or previous stay in abroads hospitals



Tendances évolutives des
entérobactéries
multi-résistantes :

le cycle infernal
BLSE → carbapéménases

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

1960's

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

“the new fecal threat”

10^8 *E.coli*/gr

1980's

2000's

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

ESBLs
Amox-C3G-R

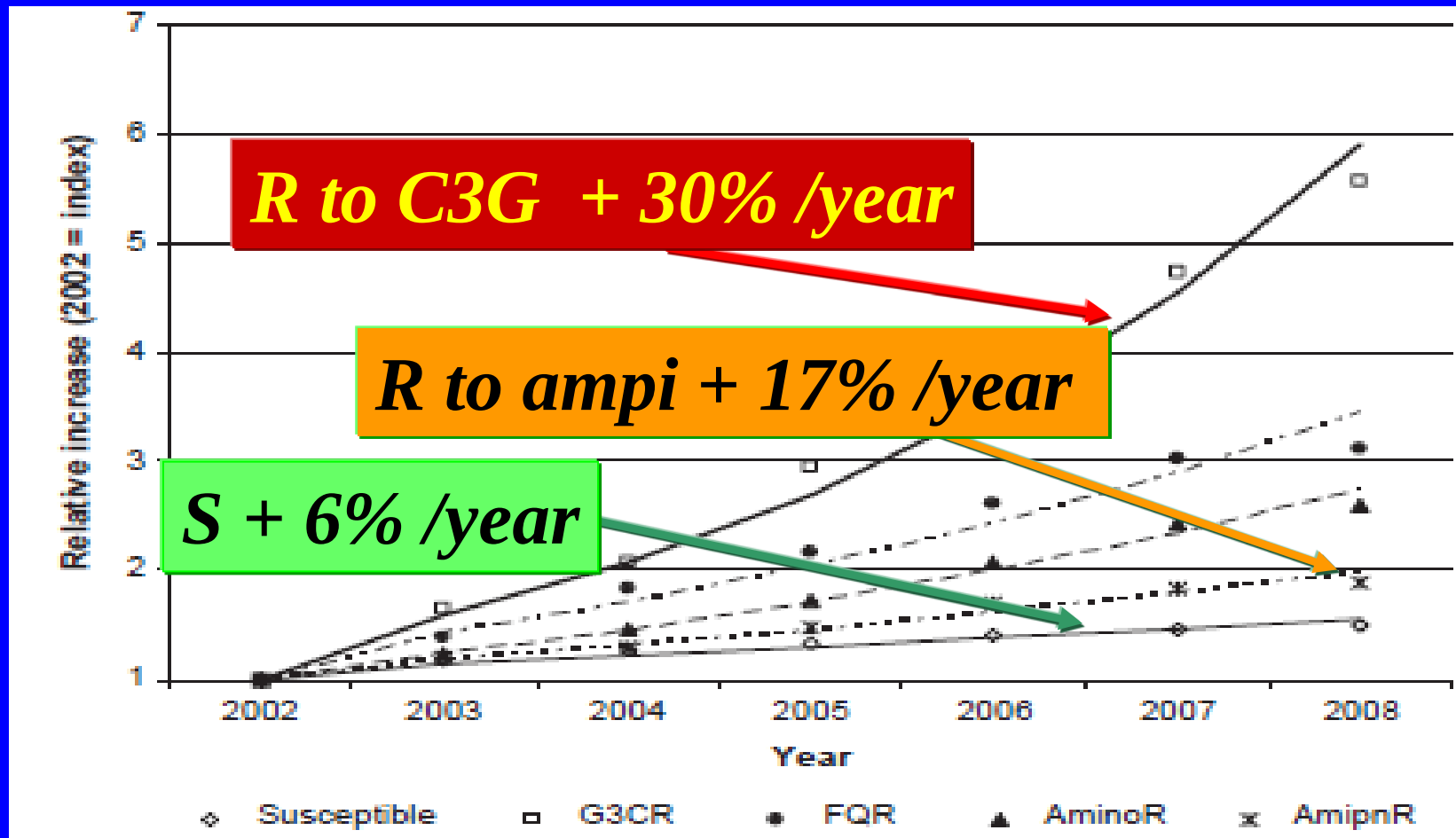
Carbapemenases

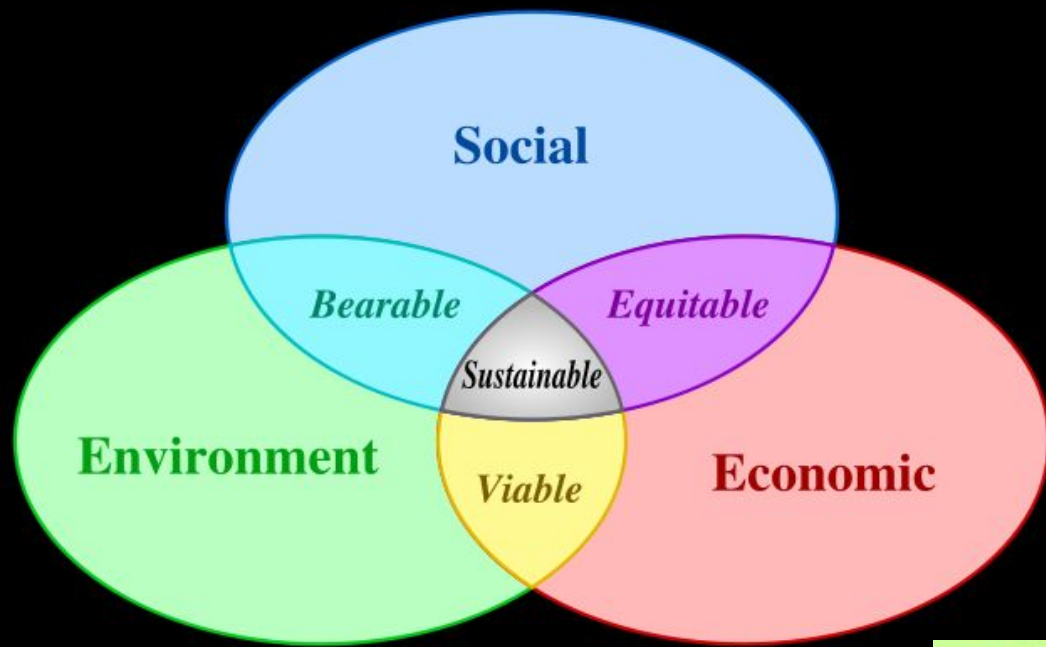
→ **C3G use**

→ *Carb use*

Impact de la résistance chez les entérobactéries et l'incidence des infections graves

Trends (relative increase)
of *E. coli* bacteraemias by pattern of resistance
in Europe (labs consistently reporting 2002-08)





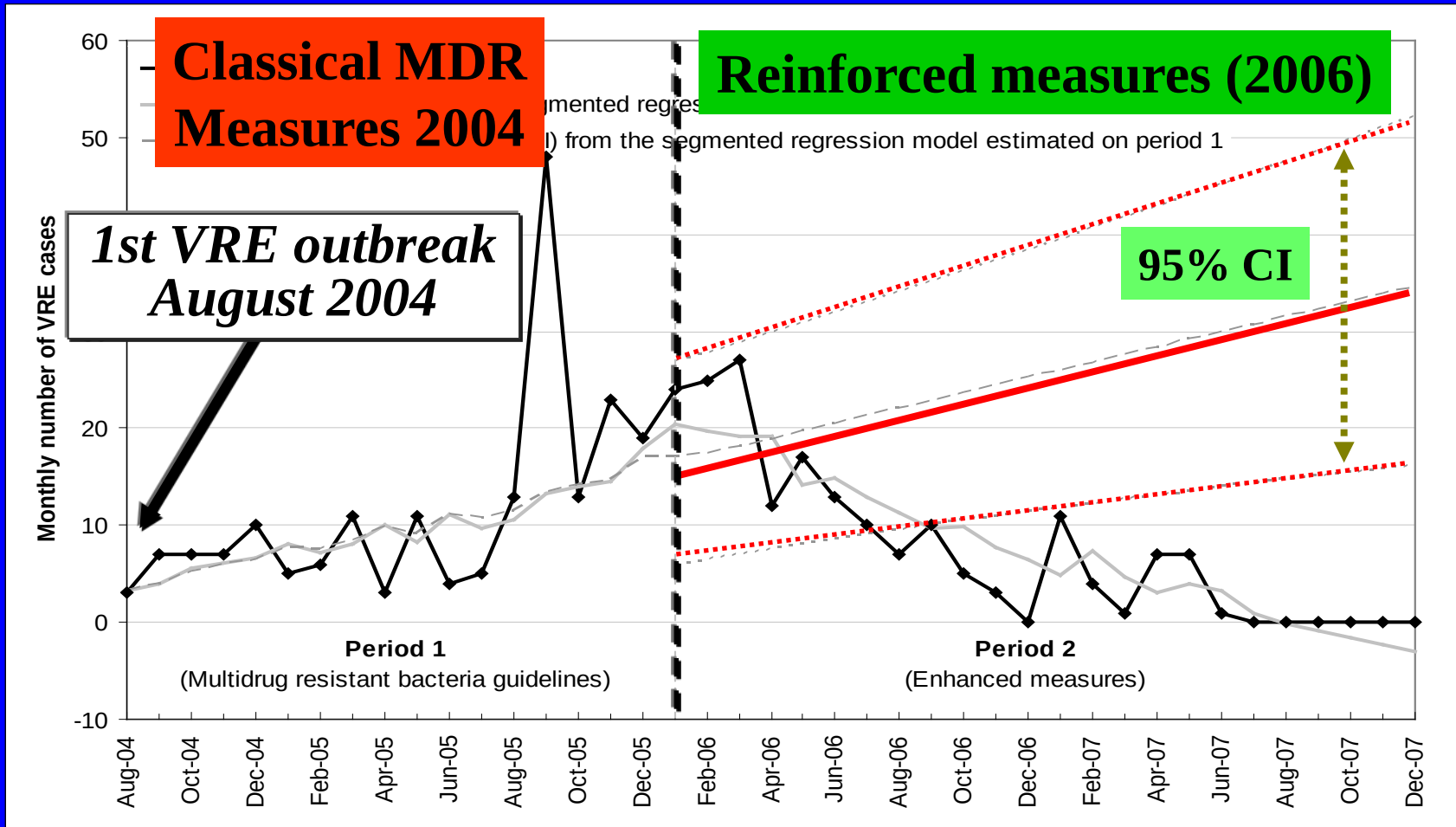
Sustainable development

- Global warming
- Antibiotic susceptibility



Enterocoques résistants aux glycopeptides (vancomycine)

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



VJarlier 2015

