



Carbapenemase-producing bacteria in Europe- update from ECDC and future directions

Anna-Pelagia Magiorakos, MD, FIDSA
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Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

A.-P. Magiorakos¹, A. Srinivasan², R. B. Carey², Y. Carmeli³, M. E. Falagas^{4,5}, C. G. Giske⁶, S. Harbarth⁷, J. F. Hindler⁸, G. Kahlmeter⁹, B. Olsson-Liljequist¹⁰, D. L. Paterson¹¹, L. B. Rice¹², J. Stelling¹³, M. J. Struelens¹, A. Vatopoulos¹⁴, J. T. Weber² and D. L. Monnet¹

Bacterium	MDR	XDR	PDR
<i>Staphylococcus aureus</i>	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1a*	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1a.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1a-1e
<i>Enterococcus spp.</i>	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1b	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1b.	
<i>Enterobacteriaceae</i>	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1c	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1c.	
<i>Pseudomonas aeruginosa</i>	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1d	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1d.	
<i>Acinetobacter spp.</i>	The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories listed in Table 1e	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1e.	

Mortality rates of infections with carbapenem resistant *Enterobacteriaceae*

Type of infections studied	Outcomes
Patel et al. 2008 Infections with carbapenem-resistant <i>K. pneumoniae</i> BSI	↑ Risk factor for mortality in invasive infections with <i>K. pneumoniae</i> OR=4.69 (95% CI 1.9-11.58); P=0.001
Marchaim et al. 2008 Infections with imipenem-resistant <i>Enterobacter</i> spp.	↑ in-hospital mortality OR=8.3 (95% CI, 1.07-64); P=0.043
Gasink et al. 2009 Infections with KPC-producing <i>K. pneumoniae</i> infections	↑ in-hospital mortality AOR, 3.60 (95% CI, 1.87–6.91)
Borer et al. 2009 Infections in patients with <i>K. pneumoniae</i> BSI vs non BSI	↑ mortality; risk ratio 3.3 (95% CI, 2.9–28.5)
Ben-David et al. 2011 Infections in patients with BSI with carbapenem resistant <i>K. pneumoniae</i> BSI vs ESBL vs sensitive	<ul style="list-style-type: none"> • ↑ infection- related mortality CRKP • Differences in appropriate empirical antimicrobial therapy (79%, 39%, 12%; P <0.001)

Carbapenemases: main types of enzymes

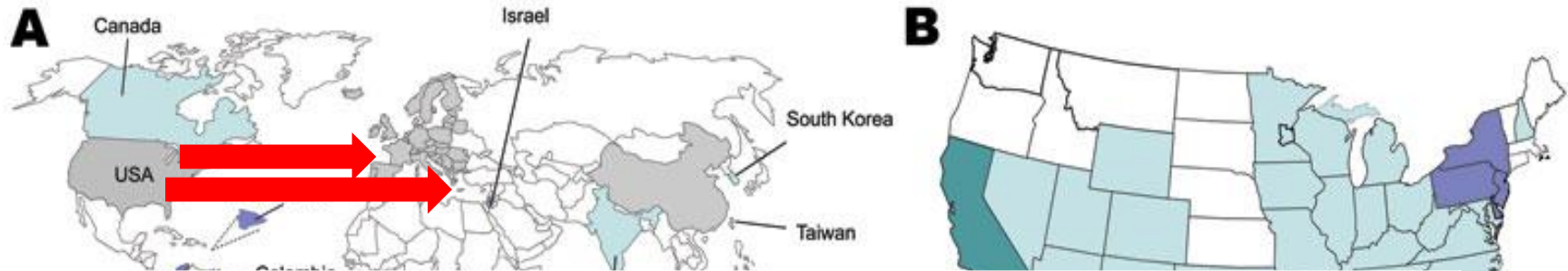
Acronym	Name or type	First isolated
KPC	<i>Klebsiella pneumoniae</i> carbapenemase	1996
VIM	Verona integron-encoded metallo-beta-lactamase	1997
OXA-48	OXA-type carbapenemase	2001
NDM-1	New Delhi metallo-beta-lactamase	2008

- Mobile genetic elements- propensity to spread

Limited treatment options

- Resistance profile can vary according to carbapenemase
- Other mechanisms of resistance
- Resistant to all beta-lactams, carbapenems
- Aminoglycosides, fluoroquinolones
- Tigecycline, colistin
- Fosfomycin

Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC) producers.



France (Naas et al. 2005)

KPC-2

Colombia (Villegas et al. 2006)

KPC-2

Israel (Leavitt et al. 2007)

KPC-2, KPC-3

Greece (Tsakris et al. 2008)

KPC-2

United Kingdom (Woodford et al. 2008)

KPC-3

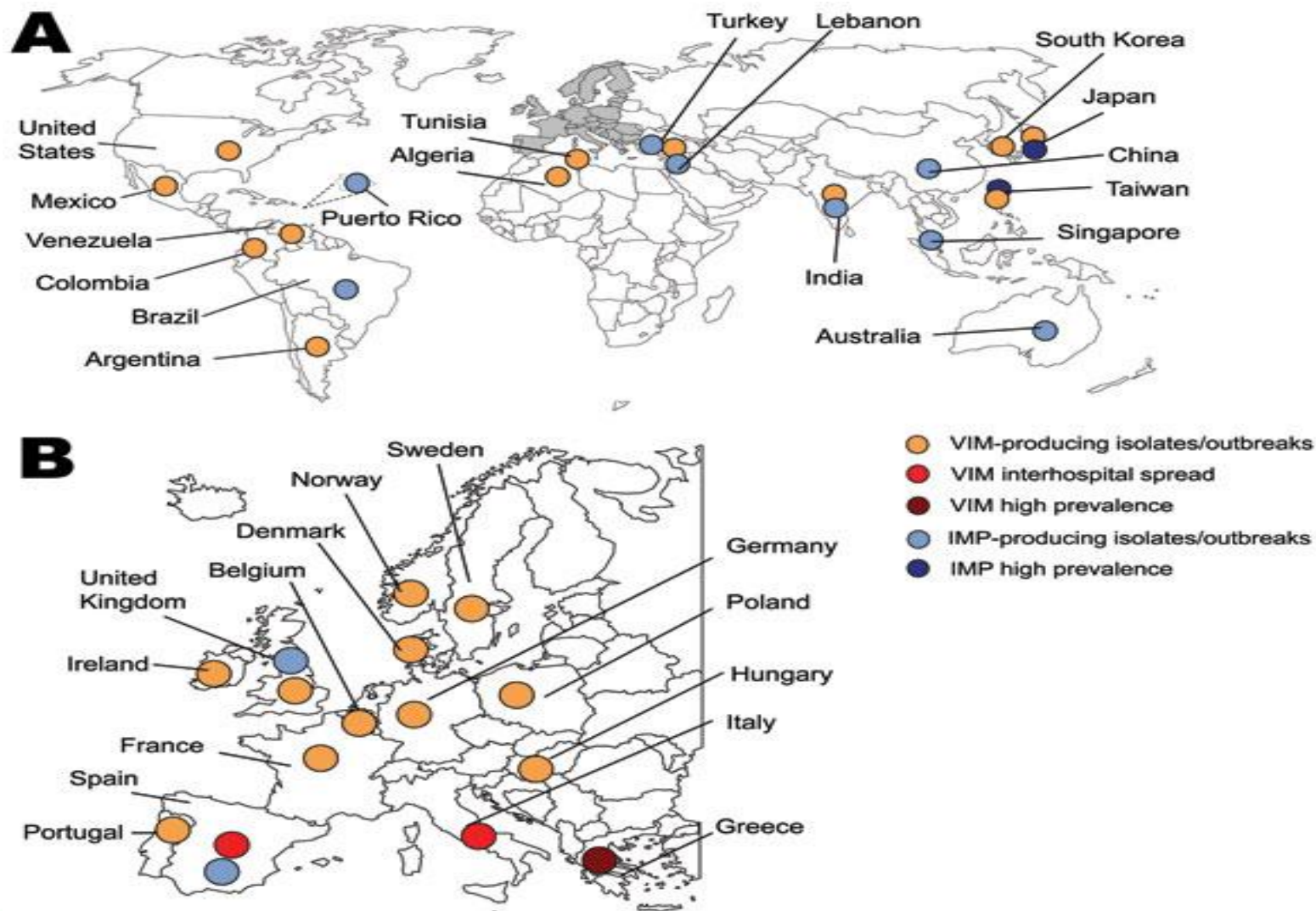
Ireland (Roche et al. 2009)

KPC-2

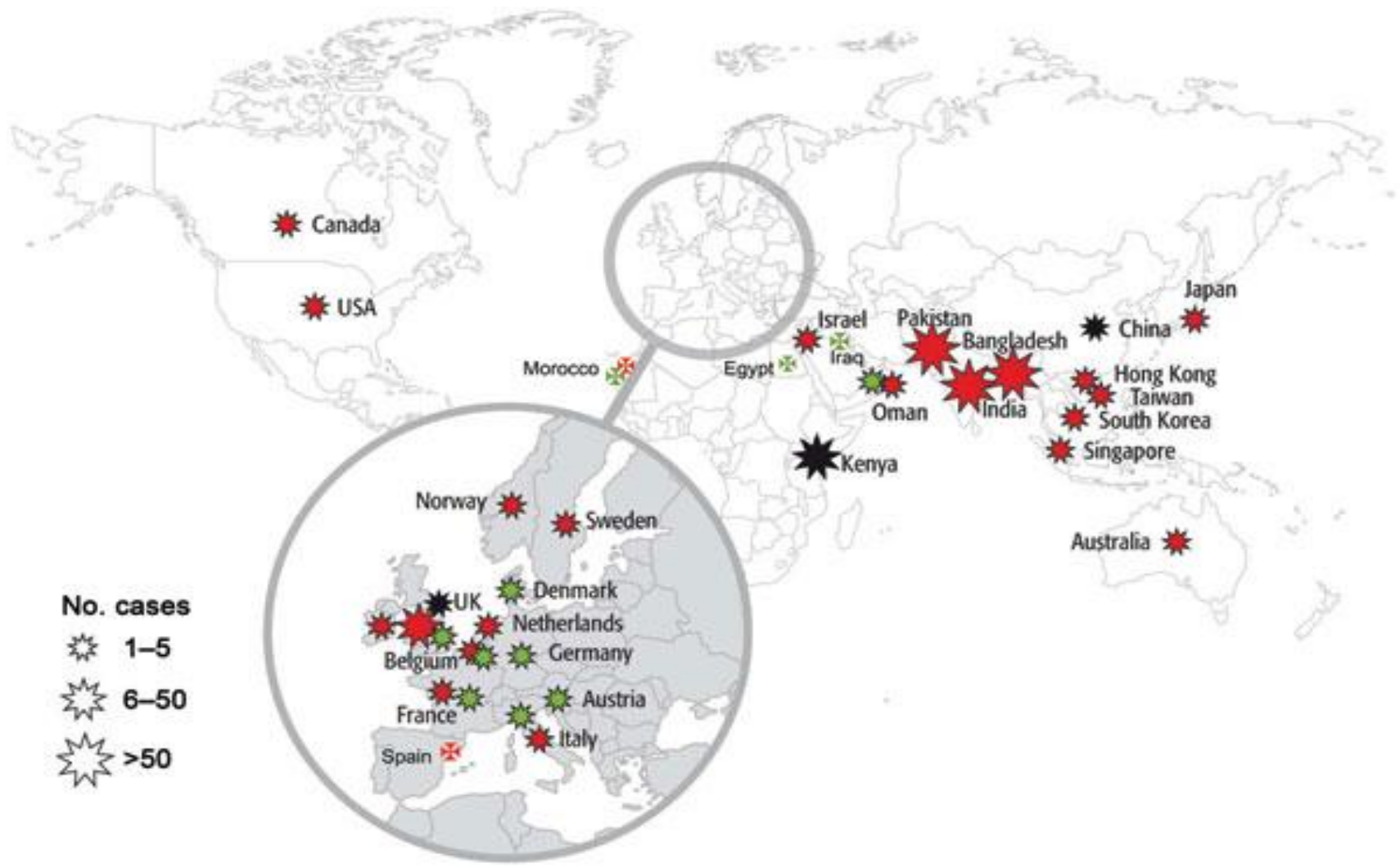
- Single KPC
- Several KPC
- Endemic



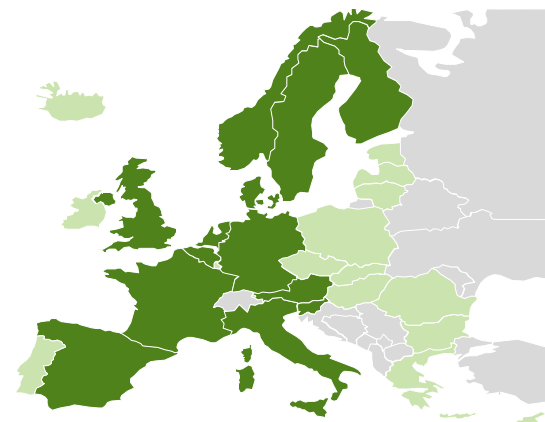
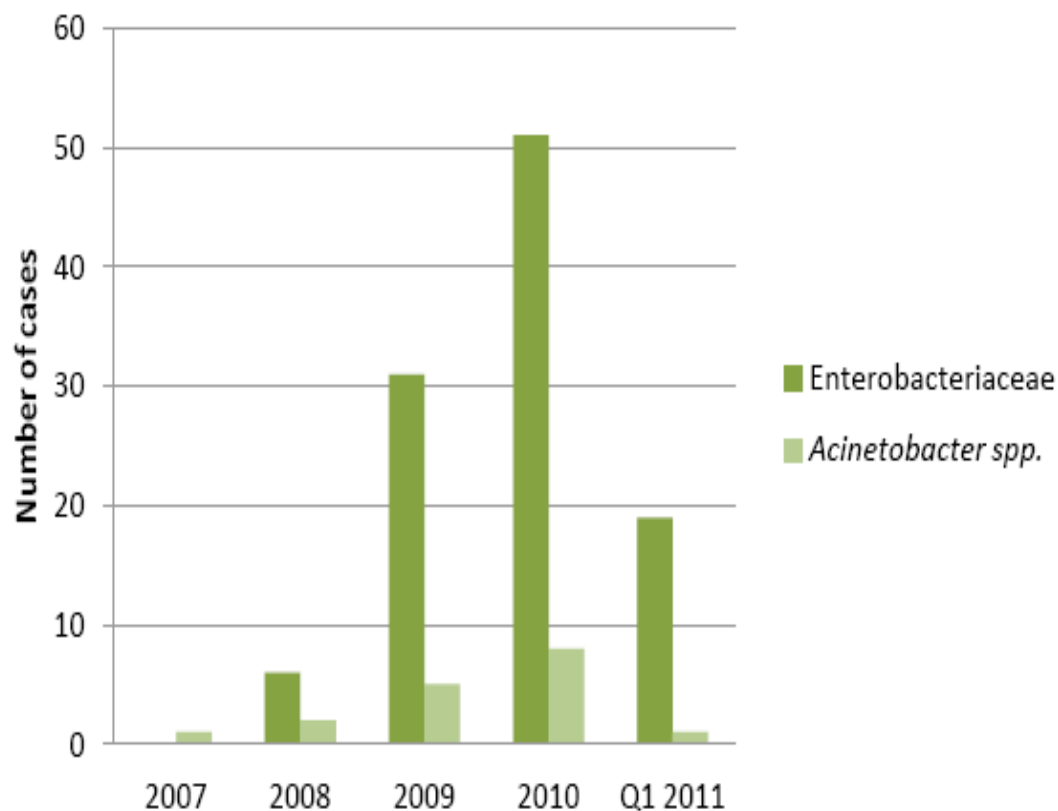
Worldwide geographic distribution of Verona integron–encoded metallo- β -lactamase (VIM) and IMP producers



Geographic distribution of New Delhi metallo-β-lactamase-1 producers; July 15, 2011



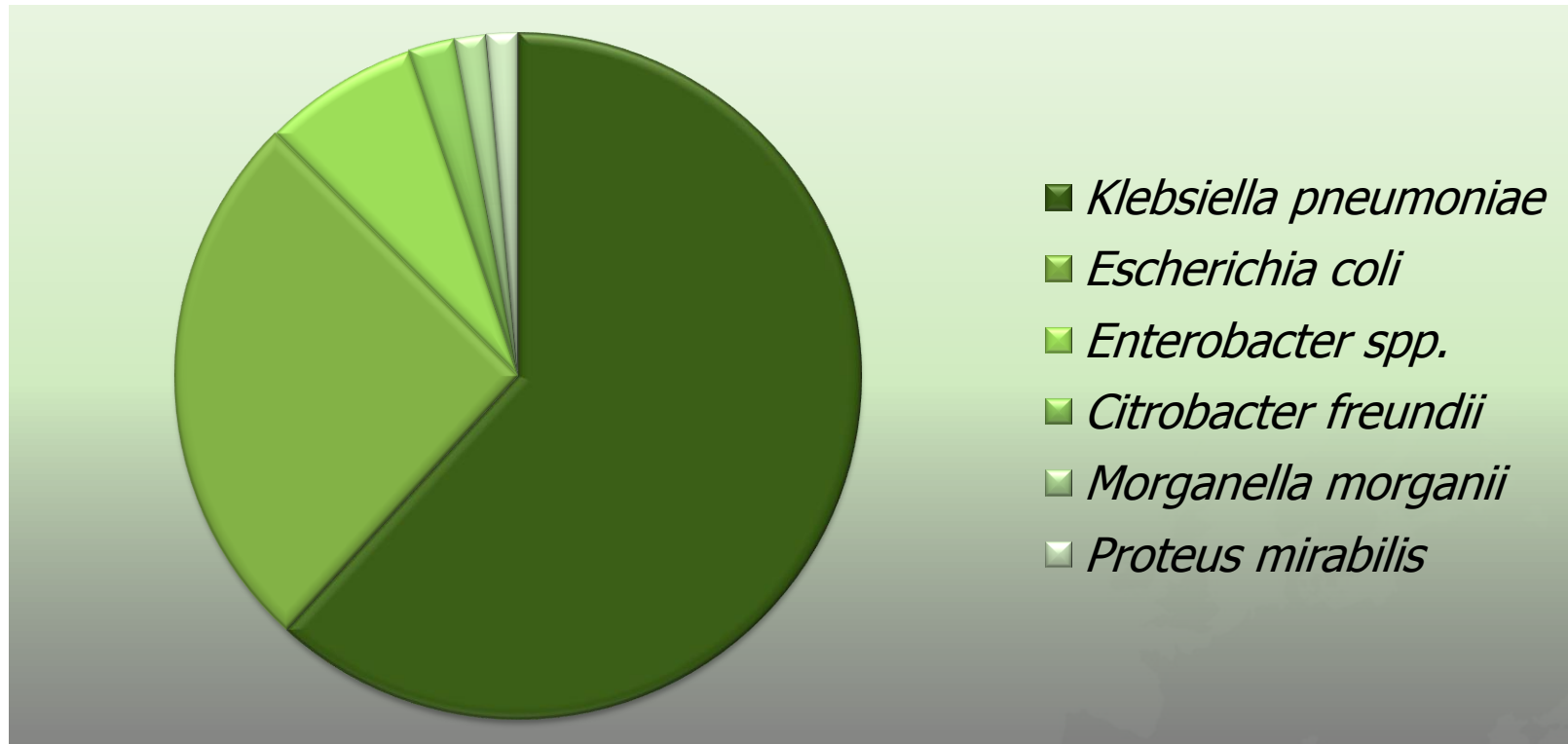
Trends in the number of cases annually of New Delhi metallo- β -lactamase (NDM)-producing *Enterobacteriaceae* and *Acinetobacter* spp. in EU/EEA countries, 2007-Q1 2011



- 106 cases in 13 countries
- Among 55 travel history available
- 31 cases received healthcare or travelled to India or Pakistan
- 5 cases had received healthcare in the Balkans
- 13 cases of presumed secondary transmission in Europe

Only Germany and UK reported data on NDM-producing *Acinetobacter* spp.

Species distribution of NDM- producing *Enterobacteriaceae* EU, Iceland and Norway; N= 135 isolates (106 cases)



Geographic distribution of OXA-48 producers

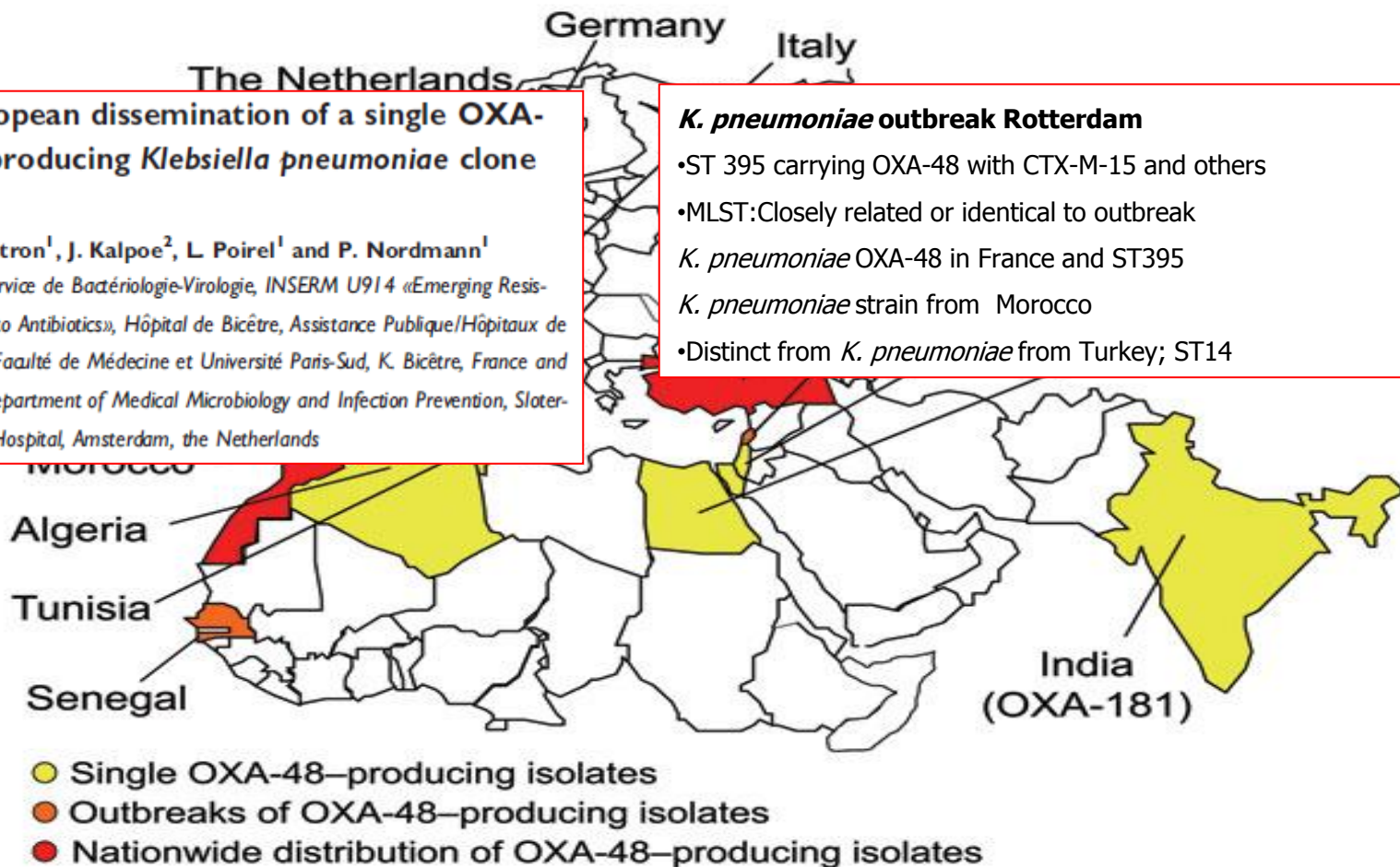
European dissemination of a single OXA-48-producing *Klebsiella pneumoniae* clone

A. Potron¹, J. Kalpoe², L. Poirel¹ and P. Nordmann¹

1) Service de Bactériologie-Virologie, INSERM U914 «Emerging Resistance to Antibiotics», Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, K. Bicêtre, France and
2) Department of Medical Microbiology and Infection Prevention, Slotervaart Hospital, Amsterdam, the Netherlands

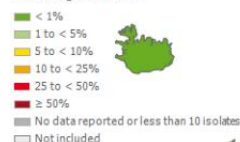
K. pneumoniae outbreak Rotterdam

- ST 395 carrying OXA-48 with CTX-M-15 and others
- MLST: Closely related or identical to outbreak *K. pneumoniae* OXA-48 in France and ST395
- K. pneumoniae* strain from Morocco
- Distinct from *K. pneumoniae* from Turkey; ST14



Klebsiella pneumoniae: proportion of invasive isolates resistant to carbapenems; EU/EEA, 2009–2010

Percentage resistance

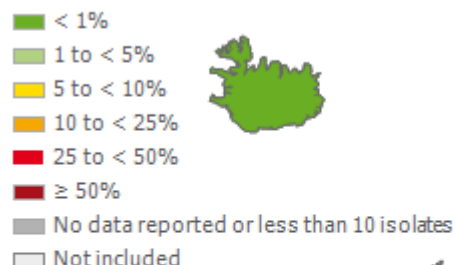


■ Liechtenstein
■ Luxembourg
■ Malta

(C) ECDC/Dundas/TESSy

2009

Percentage resistance



■ Liechtenstein
■ Luxembourg
■ Malta

(C) ECDC/Dundas/TESSy

2010

Increase from 22 to 28 countries reporting for *K. pneumoniae* (2005-2010)

- 18 countries reported continuously

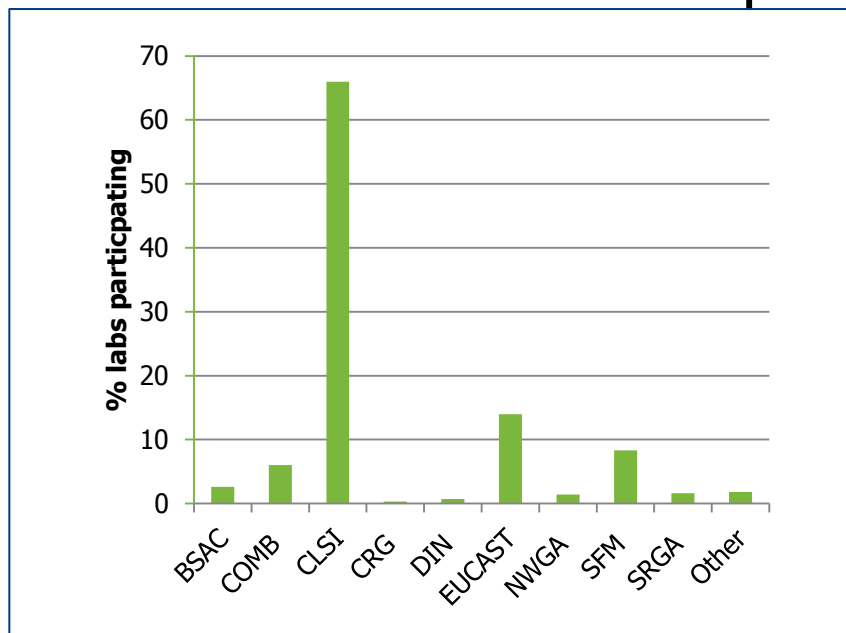
Increase of 56% (366 to 570) laboratories 2005→2010 for *K. pneumoniae*

- 140 laboratories reported continuously



Surveillance in Europe EARS-Net

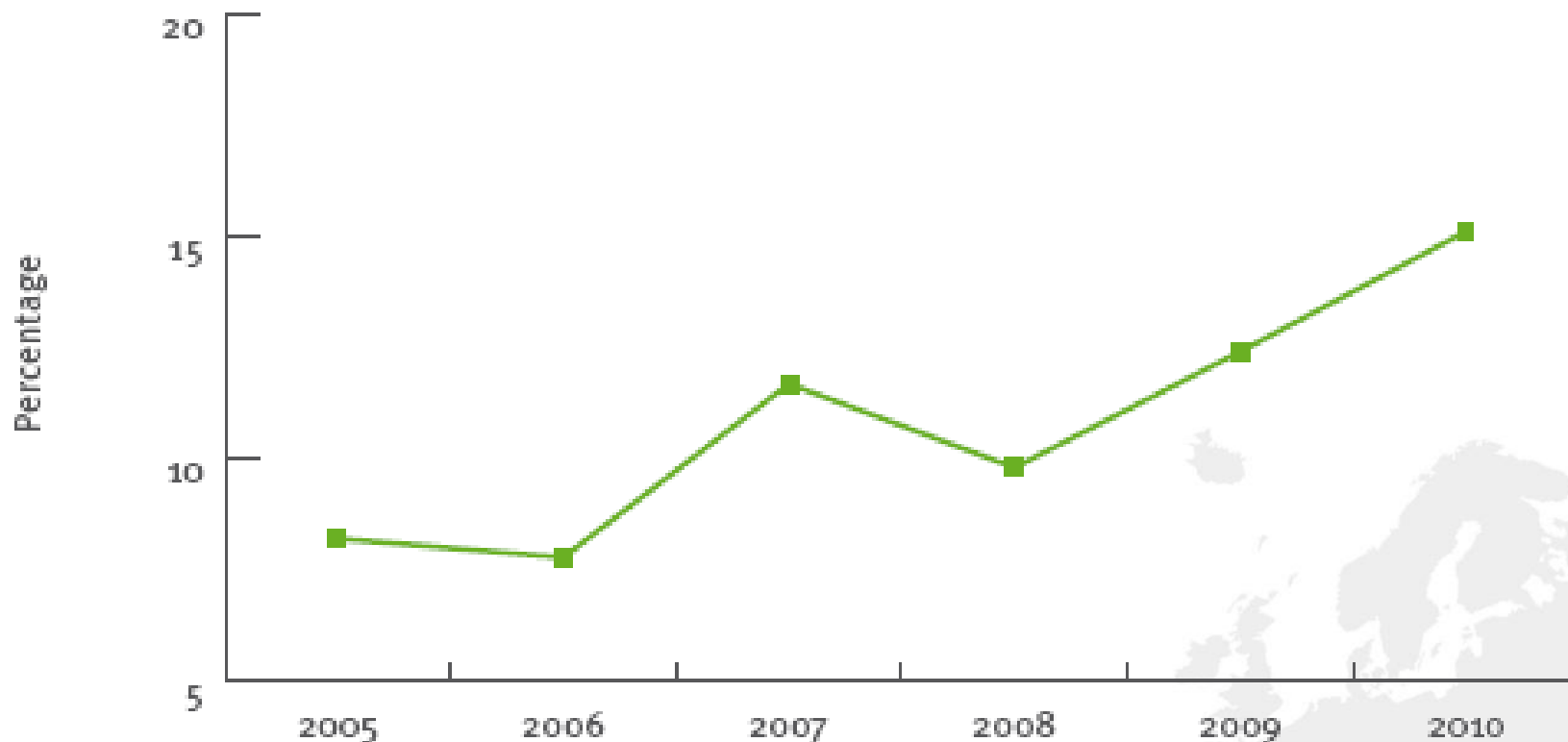
- Carbapenem resistance in invasive *K. pneumoniae* since 2005
- Continuously reporting laboratories in Europe 140
- Report resistance- no resistance mechanisms
- No confirmation of carbapenemases



- British Society of Antimicrobial Chemotherapy (BSAC),
- Combination (COMB)
- Clinical Laboratory Standards Institute
- Commissie Richtlijnen Gevoeligheidsbepalingen (CRG)
- Deutsches Institut für Normung (DIN)
- European Committee for Antimicrobial Susceptibility Testing (EUCAST)
- Norwegian Working Group on Antibiotics (NWGA)
- Société Française de Microbiologie (SFM)

Percentage of laboratories using interpretive criteria for antimicrobial susceptibility testing in 2010.

***Klebsiella pneumoniae*: percentage carbapenem-resistant invasive isolates reported to EARSS/EARS-Net by year, 2005–2010**



Only laboratories that continuously reported susceptibility results for carbapenems during the period 2005–2010 are included in the analysis.

Food for thought

- Susceptibility of *K. pneumoniae* to carbapenems is decreasing
- Detection and publication bias of current reports or CPE
- Is carbapenem resistance a good indicator of CPE in EARS-Net?
- What about confirmatory testing and reporting of this?
- Issues surrounding heterogeneity of breakpoints that laboratories are using
- Expansion of antimicrobials reported to EARS-Net in the era of pandrug resistance?



Reservoirs and concerns

- **Evidence for carbapenemases in the environment**

- Puddles from Marrakech and Plateau du Kik, Morocco: *S. marcescens* with OXA-48; isolates most likely identical; PFGE showed isolates clonally related
- Samples from seepage and tap water from New Delhi: *Enterobacteriaceae* and non-fermenters carrying NDM-1

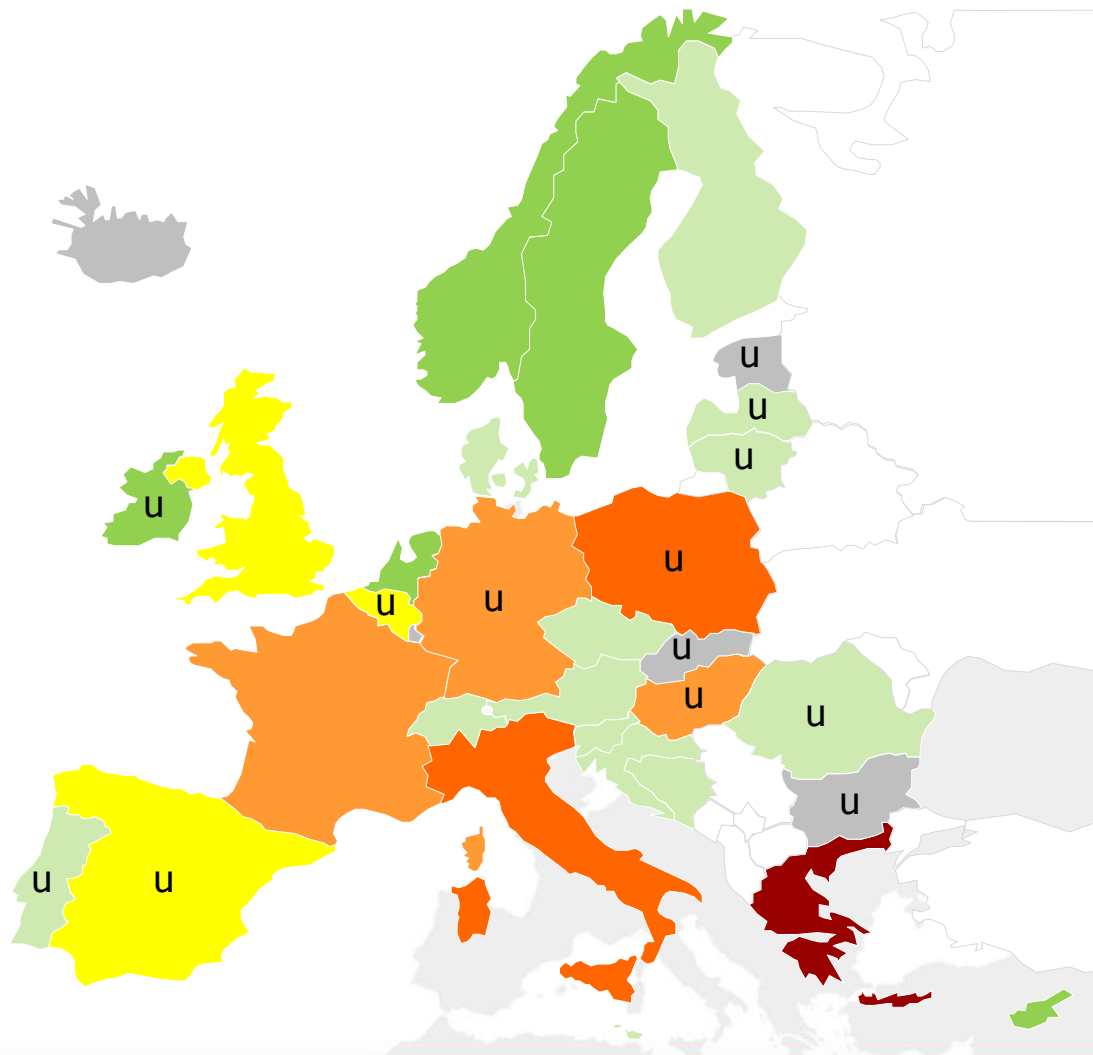
- **Increased reporting of autochthonous cases in Europe**

- **Unknown reservoir**

Carbapenemase-producing Enterobacteriaceae : extent of spread in Europe, as of July 2010

- Not reported
- Sporadic occurrence
- Single hospital outbreak
- Independent hospital outbreaks
- Regional spread
- Inter-regional spread
- Endemic
- u Other countries

Likely underdetection and/or underreporting of cases



Epidemiological scale and stages of nationwide expansion of healthcare-associated carbapenem-non-susceptible *Enterobacteriaceae*

Epidemiological scale	Description	Stage
No cases reported	No cases reported	0
Sporadic occurrence	Single cases, epidemiologically unrelated	1
Single hospital outbreak	Outbreak defined as more than two epidemiologically related cases in a single institution	2a
Sporadic hospital outbreaks	Unrelated hospital outbreaks with independent, i.e. epidemiologically unrelated introduction or different strains, no autochthonous inter-institutional transmission reported	2b
Regional spread	More than one epidemiologically related outbreak confined to hospitals that are part of a regional referral network, suggestive of regional autochthonous inter-institutional transmission	3
Inter-regional spread	Multiple epidemiologically related outbreaks occurring in different health districts, suggesting inter-regional autochthonous inter-institutional transmission	4
Endemic situation	Most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources	5

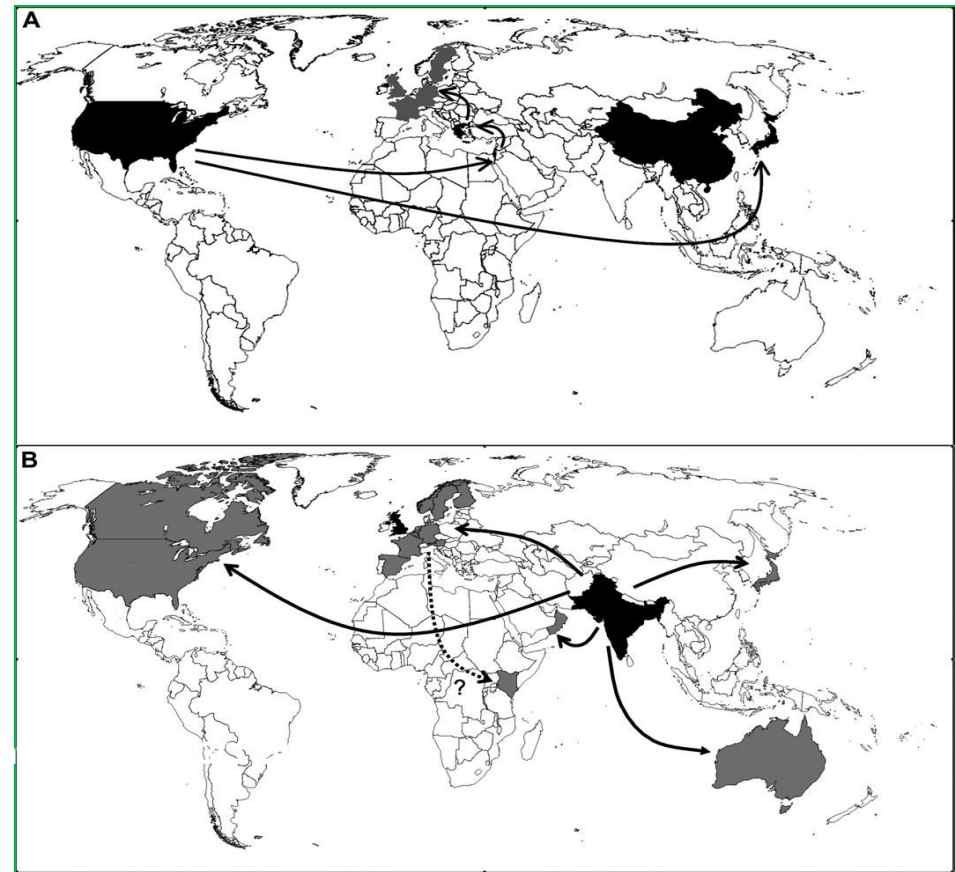
ECDC Risk Assessment on CPE

Patient mobility and transfer

Cross-border transfer of patients

Strong evidence that it is associated with risk for transmission when:

- Patients are transferred from countries with high rates of CPE to healthcare facilities in other countries
- Patients had received medical care abroad in areas with high rates of CPE



Adapted from Rogers *et al.* 2011

Risk factors for colonisation or infection with CPE

Prior use of antimicrobials

- Any antimicrobial
- **Carbapenems** (associated with a high risk estimate)
- Other antimicrobials (fluoroquinolones, cephalosporins, anti-pseudomonal penicillins)

Other

- **ICU admission**
- **Longer length of stay**
- **Mechanical ventilation**
- Hospital stay within the last 12 months
- Immunosuppression and recent transplantation
- Severity of illness
- Invasive procedures
- **Transfer of patients within units of same hospital**

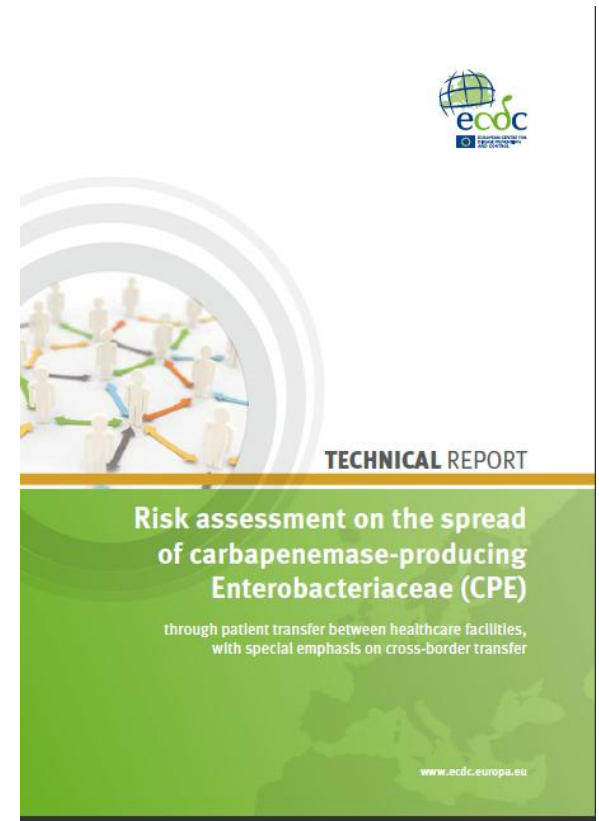
Risk assessment on the spread of carbapenemase-producing *Enterobacteriaceae*

Infection control during outbreaks

- Active surveillance by rectal screening
- Cohort nursing for carrier patients
- Additional contact precautions for carrier patients

Additionally

- Prudent use of antibiotics
- Control of ESBL
- Notification of public health authorities
- Surveillance



Why should we be concerned?

- ☐ Carbapenem resistance is on the rise in Europe
- ☐ Transmissibility
- ☐ Cross-border transfer of patients poses a risk
- ☐ Not only in hospitals
- ☐ Evidence of community/environmental reservoirs
- ☐ Autochthonous spread
- ☐ Pandrug resistance
- ☐ Penetration of *E.coli* carrying carbapenemases in environment
- ☐ Higher mortality of patients with CRE
- ☐ Infection control issues

How to contain inter-facility spread of CPE



Enhanced detection, surveillance & preparedness at national and EU level

Epidemic intelligence at European level

- Sharing of information between public health authorities, European Commission and ECDC:
 - Early warning and response system (EWRS): authorities
 - Information exchange systems (EPIS): experts
 - Epidemiological bulletins (*Eurosurveillance*): public



Why and how to turn the tide?

- ☐ National guidance documents
- ☐ Need for vigilance and active screening high risk patients
- ☐ Culture data communicated to healthcare facilities when transferring patients
- ☐ Rapid notification of clinicians and public health authorities
- ☐ Strict hand hygiene and infection control measures
- ☐ Antibiotic stewardship-prudent use of antimicrobials
- ☐ Standardisation of antimicrobial resistance breakpoints and MDR/XDR/PDR definitions
- ☐ Need for further research on molecular epidemiology and reservoirs of CPE