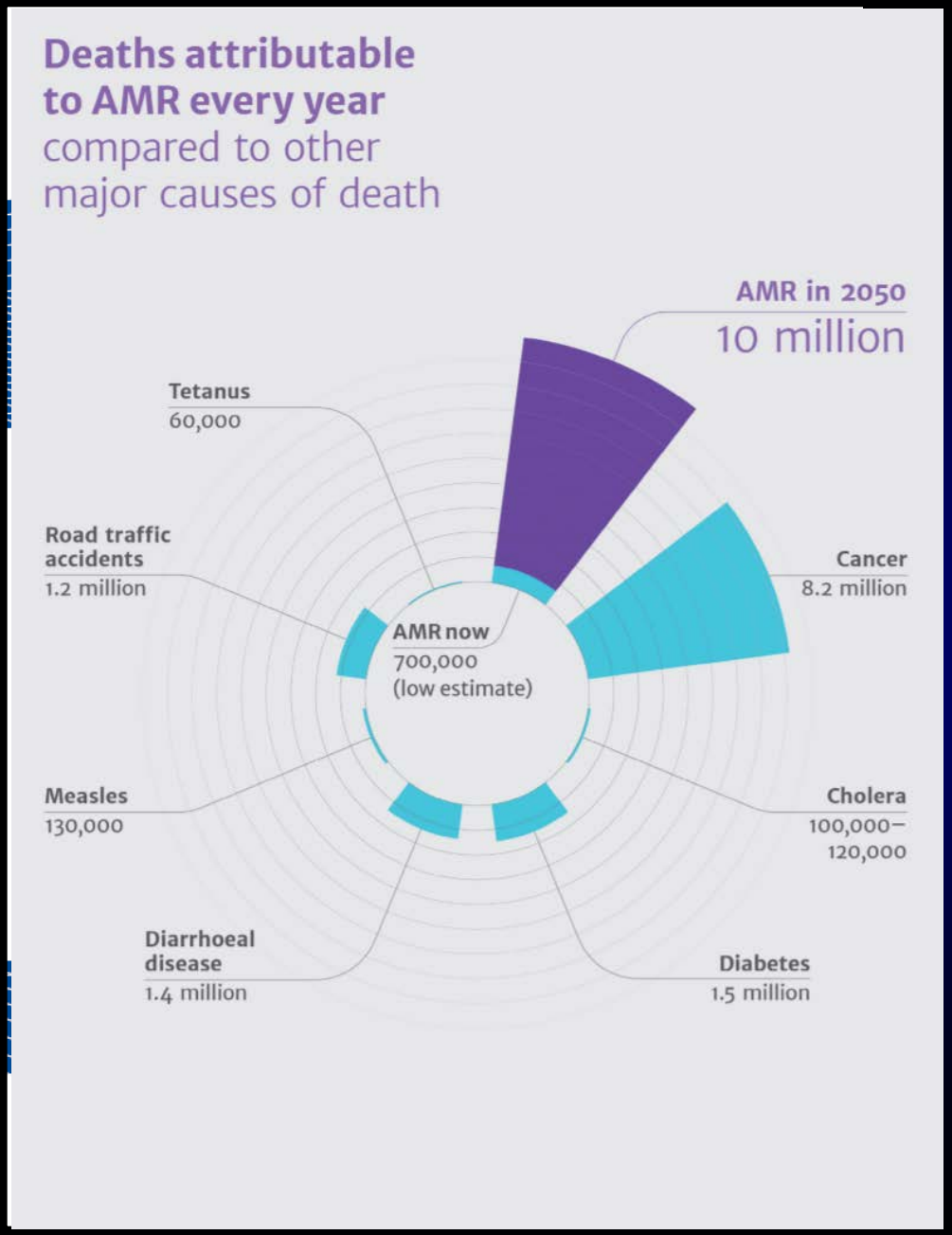
# L'antibiotico resistenza: un problema globale

## e soprattutto italiano

Massimo Galli
Clinica delle Malattie Infettive
*DIBIC L. Sacco UNIMI*



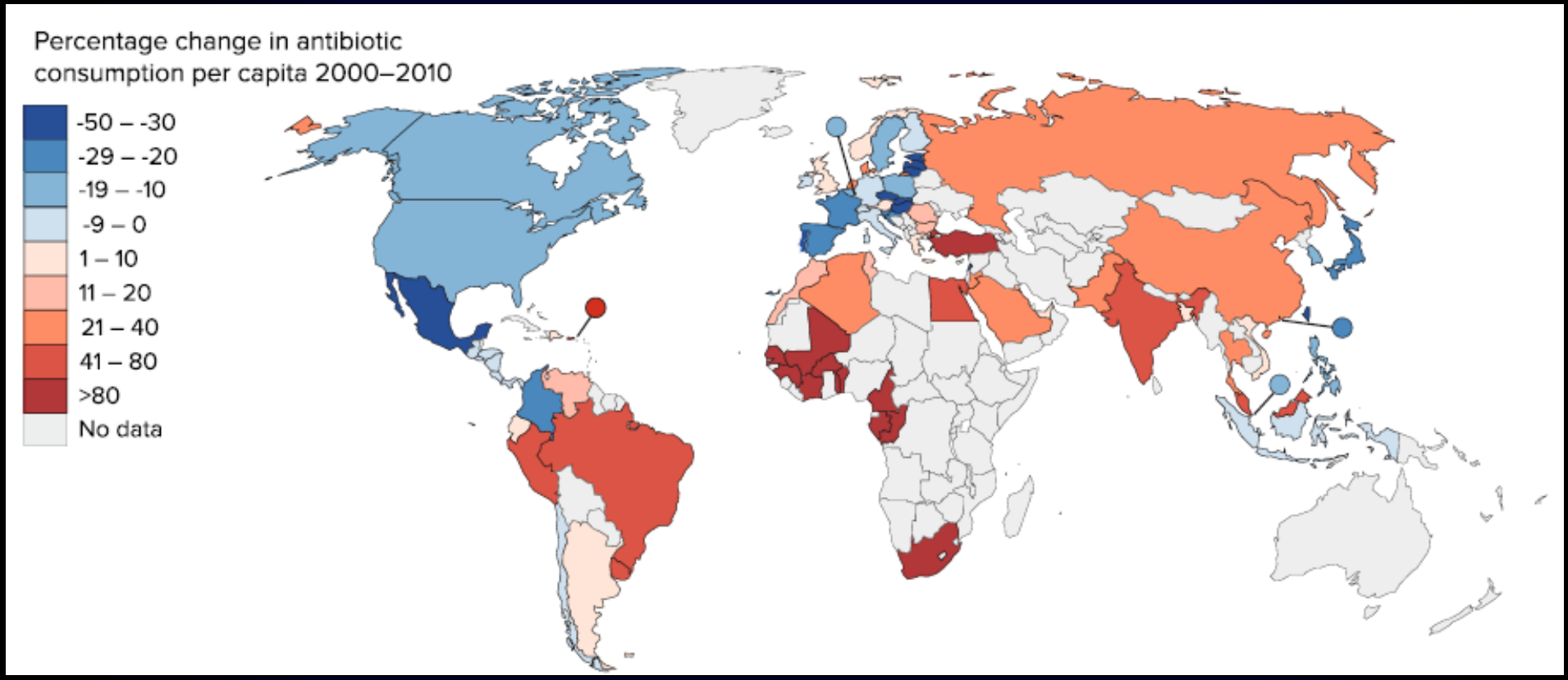

# The coming cost of superbugs by 2050

10 millions extra deaths per year by 2050

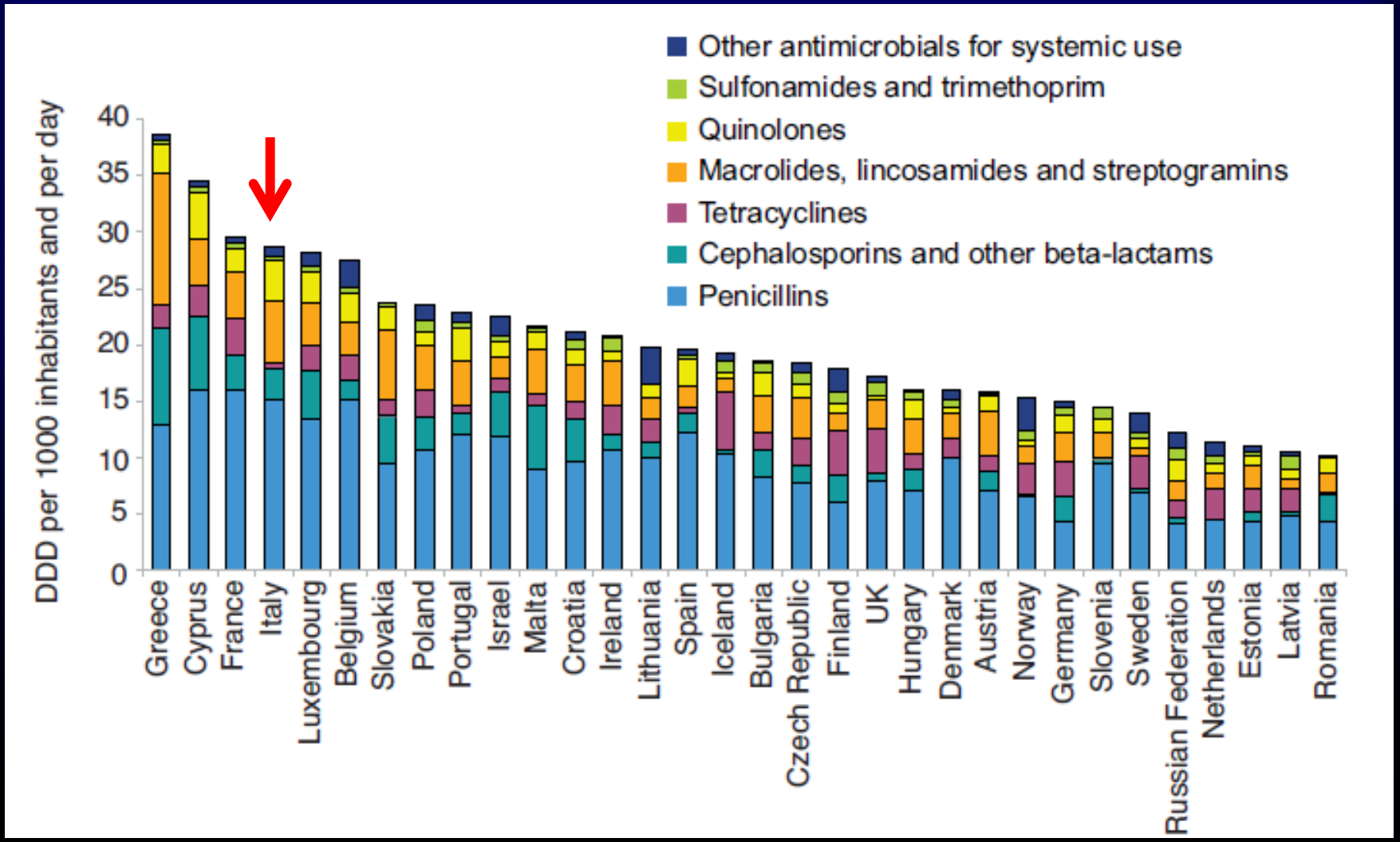
Macroeconomic loss

8 trillions $ less per year

100 trillions $ by 2050


Percentage change in antibiotic consumption per capita 2000–2010
-50 – -30
-29 – -20
-19 – -10
-9 – 0
1 – 10
11 – 20
21 – 40
41 – 80
>80
No data

# Outpatients use of selected antibiotics in 2009 in 32 Countries




DDD: defined daily dose

ESAC 2009

# AMR-Burden of disease in Europe
# (based on AMR data from 2007 for 5 MDR pathogens )

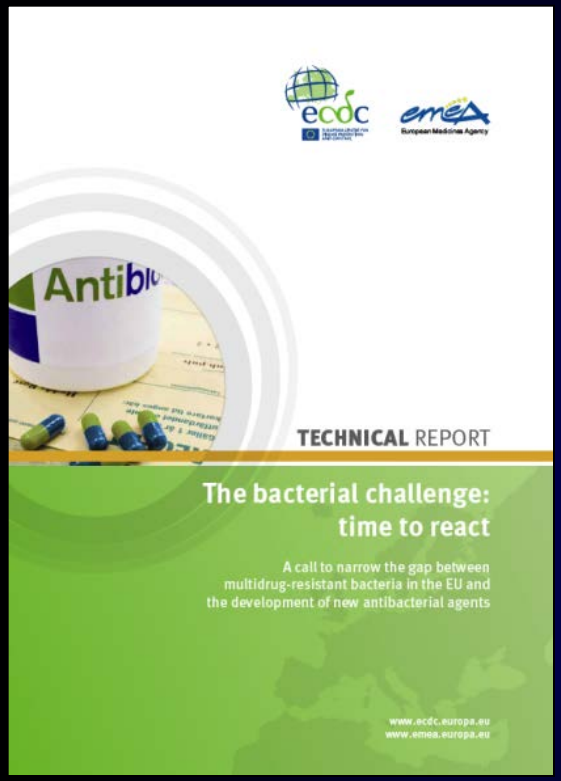
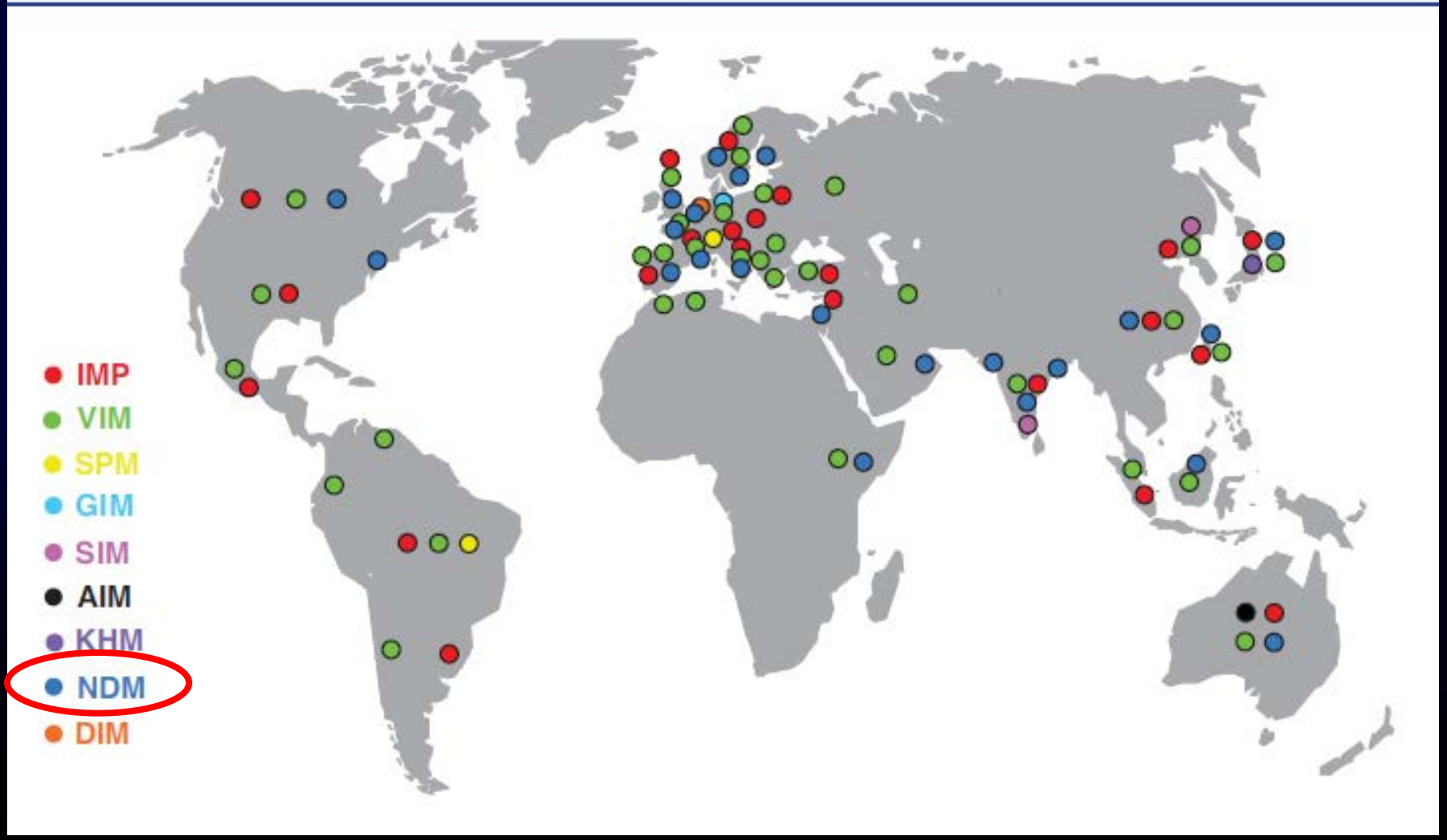



**Table 1.1 Estimated annual burden due to selected antibiotic-resistant bacteria in European Union Member States, Iceland and Norway, 2007**

| Antibiotic-resistant bacteria | No. cases of infection* | No. extra deaths | No. extra hospital days |
|---|---|---|---|
| **Antimicrobial resistant Gram-positive bacteria** | | | |
| Methicillin-resistant *Staphylococcus aureus* (MRSA) | 171 200 (12%) | 5400 (37%) | 1 050 000 (16%) |
| Vancomycin-resistant *Enterococcus faecium* | 18 100 (9%) | 1500 (28%) | 111 000 (22%) |
| **Antimicrobial resistant Gram-negative bacteria** | | | |
| 3rd generation cephalosporin-resistant *Escherichia coli* | 32 500 (27%) | 5100 (52%) | 358 000 (27%) |
| 3rd generation cephalosporin-resistant *Klebsiella pneumoniae* | 18 900 (27%) | 2900 (52%) | 208 000 (27%) |
| Carbapenem-resistant *Pseudomonas aeruginosa* | 141 900 (3%) | 10 200 (7%) | 809 000 (3%) |

- 25.000 extra deaths
- 2.5 milion extra hospital days
- 1.5 billion EURO for extra hospital costs and loss of productivity

# Worldwide distribution of different metallo-ß-lactamases




NDM: New Delhi metallo-ß-lactamase

WHO 2012

# The WHO priority list

| PRIORITY: CRITICAL | PRIORITY 2: HIGH | PRIORITY 3: MEDIUM |
|---|---|---|
| **Acinetobacter baumannii** carbapenem-resistant | **Enterococcus faecium** vancomycin-resistant | **Streptococcus pneumoniae** penicillin-non-susceptible |
| **Pseudomonas aeruginosa** carbapenem-resistant | **Staphylococcus aureus** methicillin-resistant vancomycin-intermediate and resistant | **Haemophilus influenzae** ampicillin-resistant |
| **Enterobacteriaceae** carbapenem-resistant, ESBL-producing | **Helicobacter pylori** clarithromycin-resistant | **Shigella spp.** fluoroquinolone-resistant |
| | **Campylobacter spp.** fluoroquinolone-resistant | |
| | **Salmonellae** fluoroquinolone-resistant | |
| | **Neisseria gonorrhoeae** cephalosporin-resistant fluoroquinolone-resistant | |

Source: WHO

«priorities in urgent need of new antibiotics»

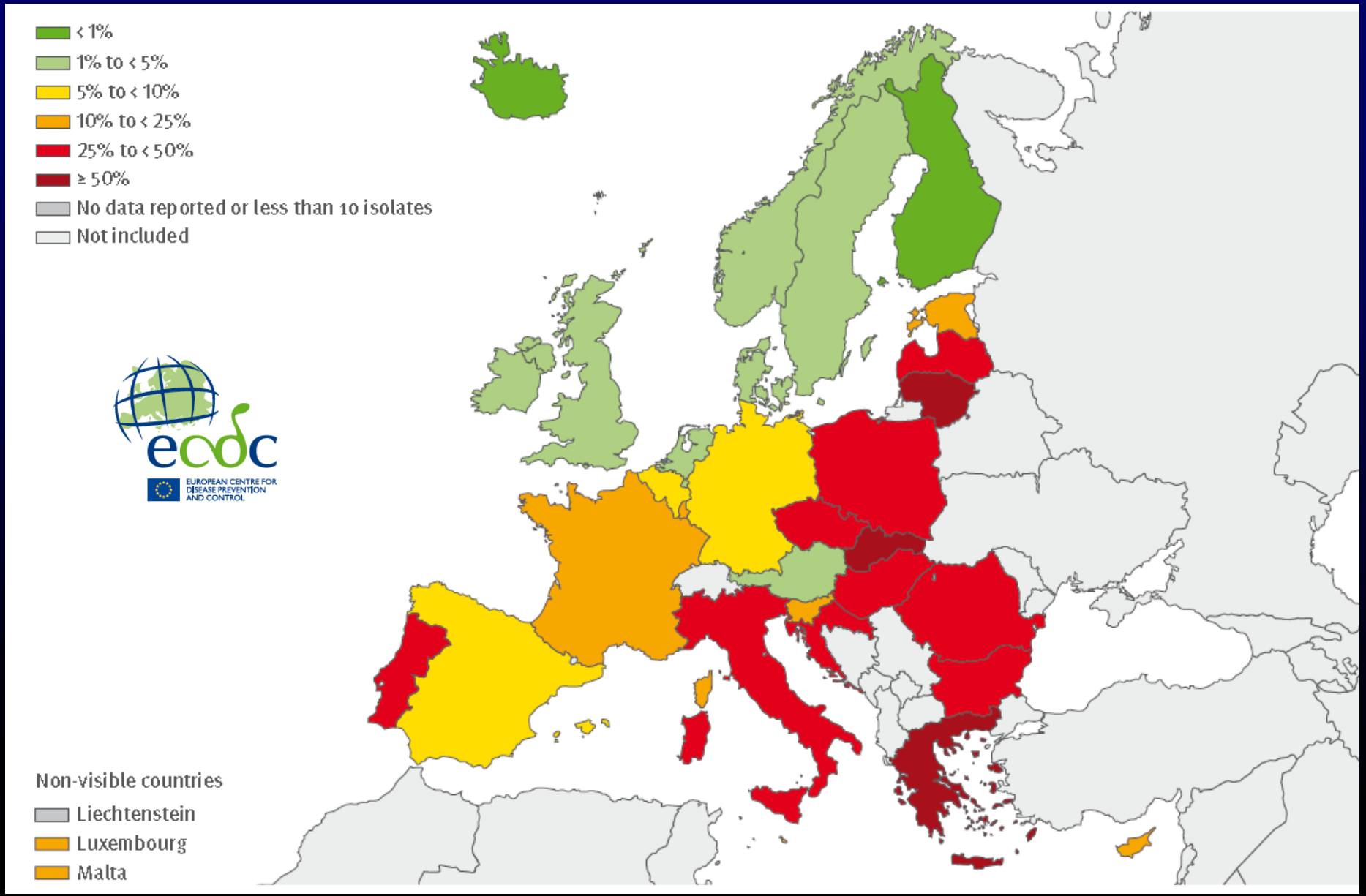
# Trends across OECD countries
## Antibiotic resistance is growing


**In Italia l'antibiotico-resistenza è raddoppiata tra il 2005 e il 2014**

# Antibiotic resistance in Italy in 2015: comparison with the European mean and 4-year trends

| | Italy 2015 %RES | EU/EAA 2015 (mean) | Trend 2012-2015 |
|---|---|---|---|
| *Klebsiella pneumoniae* | | | |
| 3rd gen cephalosporins | 55.9 | 30.3 | ↑ |
| aminoglycosides | 34.0 | 22.5 | |
| carbapenems | 33.5 | 18.6 | |
| *Escherichia coli* | | | |
| 3rd gen cephalosporin | 30.1 | 13.1 | ↑ |
| aminoglycosides | 20.2 | 10.4 | |
| fluoroquinolones | 44.4 | 22.8 | ↑ |
| *Pseudomonas aeruginosa* | | | |
| piperacillin-tazobactam | 29.5 | 18.1 | |
| ceftazidime | 21.7 | 13.3 | |
| aminoglycosides | 17.2 | 13.3 | ↓ |
| carbapenems | 23.0 | 17.8 | |
| *Acinetobacter spp.* | | | |
| carbapenems | 78.3 | NA | |
| *Staphylococcus aureus* | | | |
| oxacillin (MRSA) | 34.1 | 16.8 | |
| *Streptococcus pneumoniae* | | | |
| penicillin (NS) | 12.3 | | |
| macrolides | 24.5 | | ↓ |
| *Enterococcus faecium* | | | |
| vancomicin (VRE) | 11.2 | 8.3 | ↑ |

# *Klebsiella pneumoniae*. % of invasive isolates with combined resistance (resistance to 3rd-generation cephalosporins, fluoroquinolones and aminoglycosides), 2012



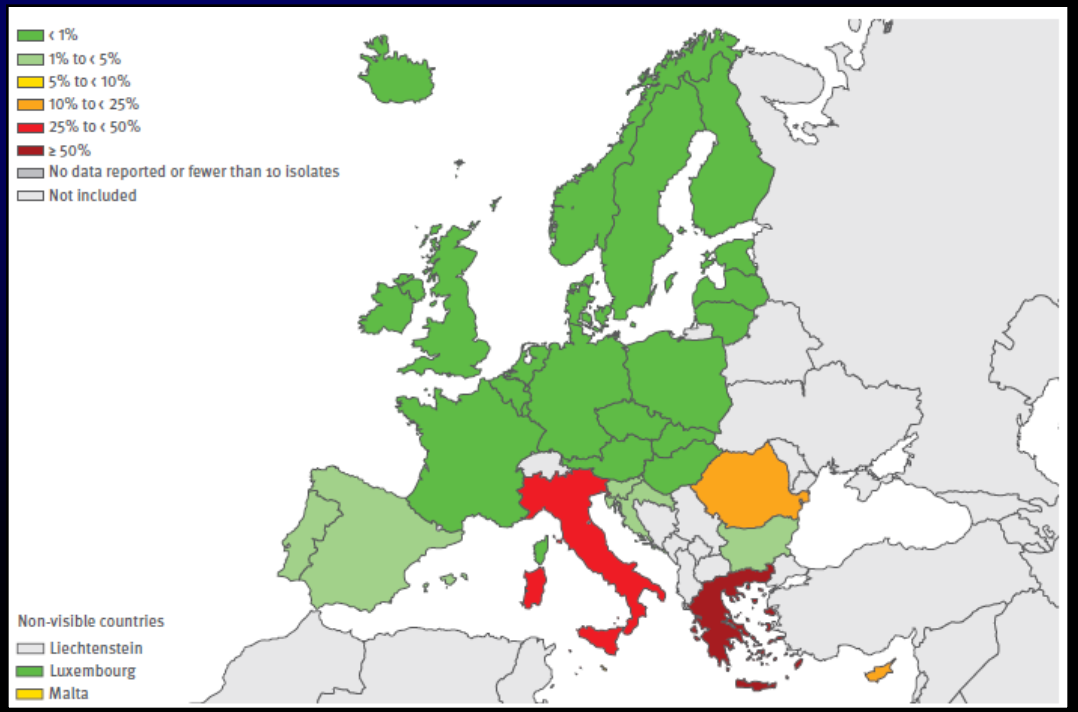
# *Klebsiella pneumoniae* resistent to carbapenems

2009


ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

*EARS-NET database*

2015



Journal of Infection and Public Health (2016) 9, 24–33

http://www.elsevier.com/locate/jiph

# Diffusion and transmission of carbapenem-resistant *Klebsiella pneumoniae* in the medical and surgical wards of a university hospital in Milan, Italy

Anna L. Ridolfo[a,b,*], Sara G. Rimoldi[c], Cristina Pagani[c], Andrea F. Marino[a], Anna Piol[a], Matteo Rimoldi[a], Pietro Olivieri[a], Massimo Galli[b], Lucia Dolcetti[a], Maria R. Gismondo[c]

**Our findings indicate that the spread of CRKP in Northern Italy hospitals may go far beyond high-risk settings (i.e., intensive care units) and that strict surveillance should be extended to general areas of care.**

*J Antimicrob Chemother* 2016; **71**: 3386–3391
doi:10.1093/jac/dkw337 Advance Access publication 1 September 2016

Journal of Antimicrobial Chemotherapy

# Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* from invasive infections in Italy: increasing diversity with predominance of the ST512 clade II sublineage

Viola Conte[1], Monica Monaco[2], Tommaso Giani[1], Fortunato D'Ancona[3], Maria Luisa Moro[4], Fabio Arena[1], Marco Maria D'Andrea[1], Gian Maria Rossolini[1,5–7]* and Annalisa Pantosti[2] on behalf of the AR-ISS Study Group on Carbapenemase-Producing *K. pneumoniae*†

**Although a trend to a polyclonal evolution of the Italian KPC-KP was noted, this study showed that the KPC-KP population remained largely oligoclonal with the wide diffusion of an ST512 lineage carrying cps-2capsular type and producing the KPC**

RAPID COMMUNICATIONS

# Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco[1,2], T Giani[2,3], M Raffone[1,4], F Arena[3], A Garcia-Fernandez[1], S Pollini[3], Network EuSCAPE-Italy[5], H Grundmann[6], A Pantosti (annalisa.pantosti@iss.it)[1], G M Rossolini[3,7,8]

| ANTIBIOTIC | S | | I | | R | |
|---|---|---|---|---|---|---|
| | n° | % | n° | % | n° | % |
| Ciprofloxacin | 1 | 0.6 | 0 | 0 | 178 | 99.4 |
| Amikacin | 19 | 11.3 | 14 | 8.3 | 135 | 80.3 |
| Ertapenem | 0 | 0 | 0 | 0 | 179 | 100 |
| Imipenem | 0 | 0 | 6 | 3.4 | 173 | 96.6 |
| Meropenem | 0 | 0 | 1 | 0.6 | 178 | 99.4 |
| Trimetho/Sulfa | 32 | 17.8 | 0 | 0 | 147 | 82.2 |
| Gentamicin | 149 | 83.2 | 6 | 3.4 | 24 | 16.7 |
| Colistin | 103 | 57.0 | 0 | 0 | 76 | 43.0 |
| Tigecycline | 168 | 94.0 | 10 | 5.5 | 1 | 0.5 |

J Antimicrob Chemother 2016
doi:10.1093/jac/dkw195
Advance Access publication 3 June 2016

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

# *mcr-1.2*, a New *mcr* Variant Carried on a Transferable Plasmid from a Colistin-Resistant KPC Carbapenemase-Producing *Klebsiella pneumoniae* Strain of Sequence Type 512

**Vincenzo Di Pilato,[a] Fabio Arena,[b] Carlo Tascini,[c] Antonio Cannatelli,[b] Lucia Henrici De Angelis,[b] Simona Fortunato,[c] Tommaso Giani,[b] Francesco Menichetti,[c] Gian Maria Rossolini[b,d,e,f]**

Department of Surgery and Translational Medicine, University of Florence, Florence, Italy[a]; Department of Medical Biotechnologies, University of Siena, Siena, Italy[b]; Infectious Disease Unit, Nuovo Santa Chiara Hospital, Pisa, Italy[c]; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy[d]; Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy[e]; Don Carlo Gnocchi Foundation, Florence, Italy[f]

*Department of Infectious, Parasitic and Immune-Mediated Diseases, Istituto Superiore di Sanità, Rome, Italy*

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

LETTER TO THE EDITOR

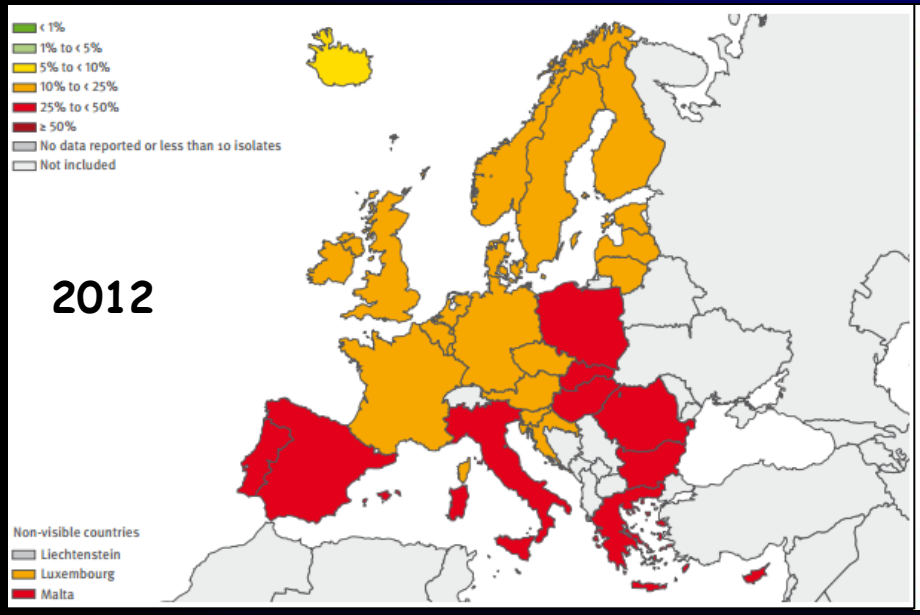
# First Detection of the *mcr-1* Colistin Resistance Gene in *Escherichia coli* in Italy

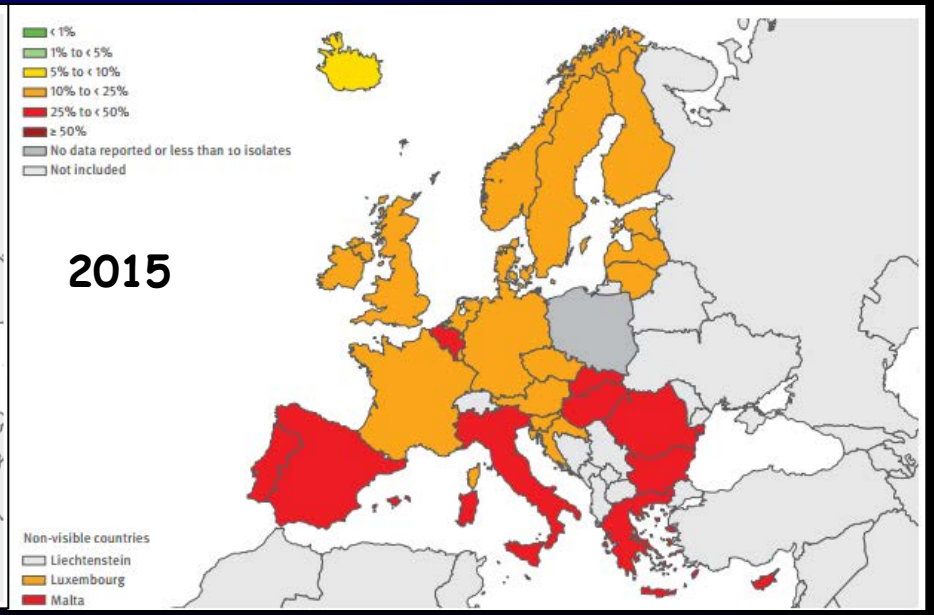
Antonio Cannatelli,[a] Tommaso Giani,[a] Alberto Antonelli,[a,b] Luigi Principe,[c] Francesco Luzzaro,[c] Gian Maria Rossolini[a,b,d,e]*

| Isolate | Isolation date | Source | Ward | ST | MIC mg/liter (S/I/R)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | AMC | CTX | CAZ | COL |
| LC-279/13[c] | June 2013 | Urine | Neurology | 354 | 8 (S) | 8 (R) | 2 (I) | 8 (R) |
| LC-705/14 | August 2014 | Urine | Medicine | 131 | 8 (S) | ≤1 (S) | ≤1 (S) | 8 (R) |
| LC-902/14[c] | October 2014 | Urine | Outpatient | 602 | 4 (S) | >64 (R) | ≤1 (S) | 8 (R) |
| LC-968/14 | November 2014 | Surgical wound | Intensive care unit | 10 | 16 (R) | ≤1 (S) | ≤1 (S) | 8 (R) |
| LC-17/15 | January 2015 | Urine | Neurosurgery | 95 | 4 (S) | ≤1 (S) | ≤1 (S) | 8 (R) |
| FI-4531 | November 2015 | Urine | Outpatient | 648 | 8 (S) | ≤1 (S) | ≤1 (S) | 8 (R) |
| FI-4592 | November 2015 | Urine | Orthopedics | 804 | 4 (S) | ≤1 (S) | ≤1 (S) | 8 (R) |
| FI-4451 | November 2015 | Urine | Medicine | 117 | ≤2 (S) | ≤1 (S) | ≤1 (S) | 8 (R) |

# *Escherichia coli* resistente ai fluorochinoloni

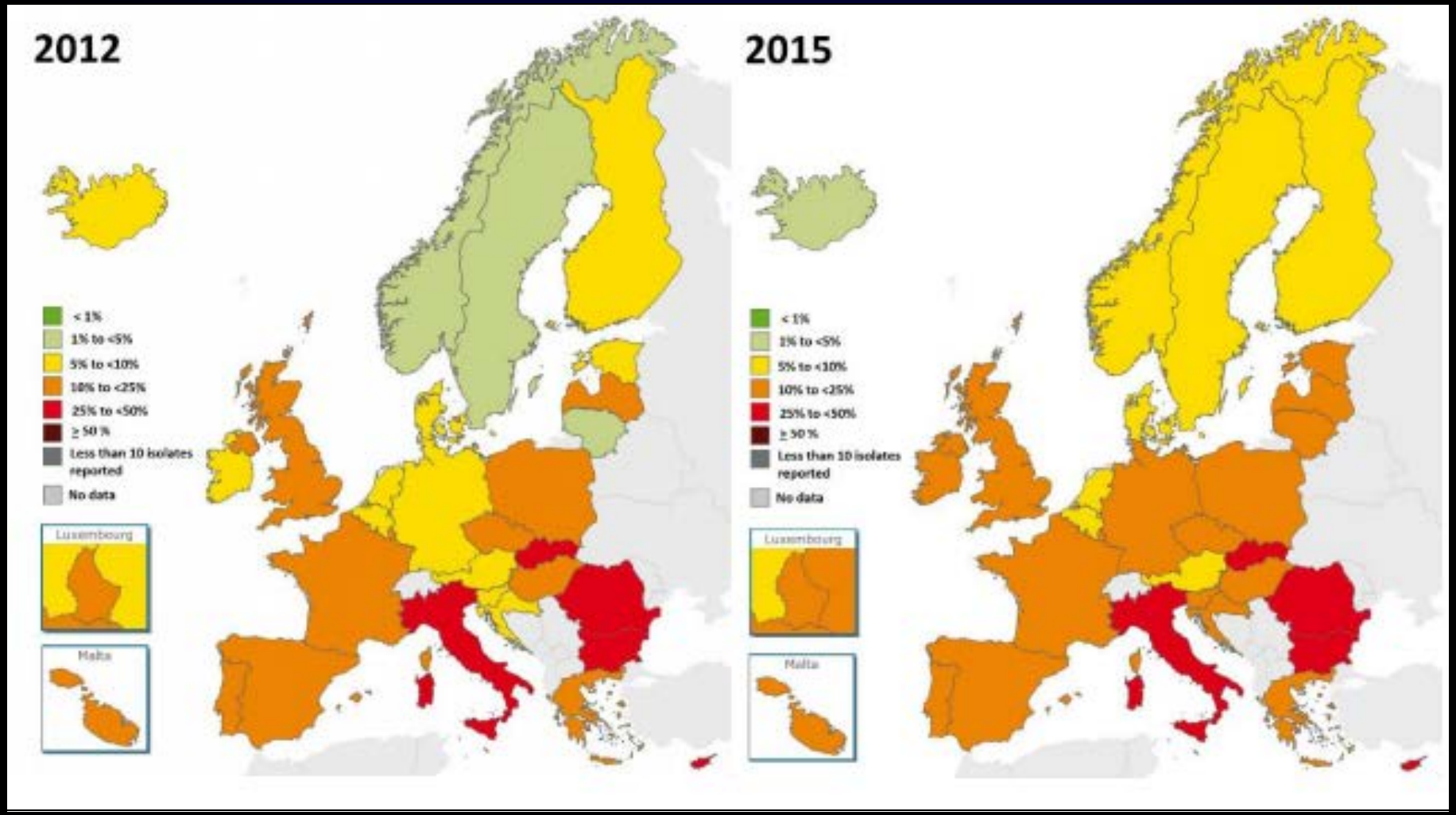
*EARS-NET database*



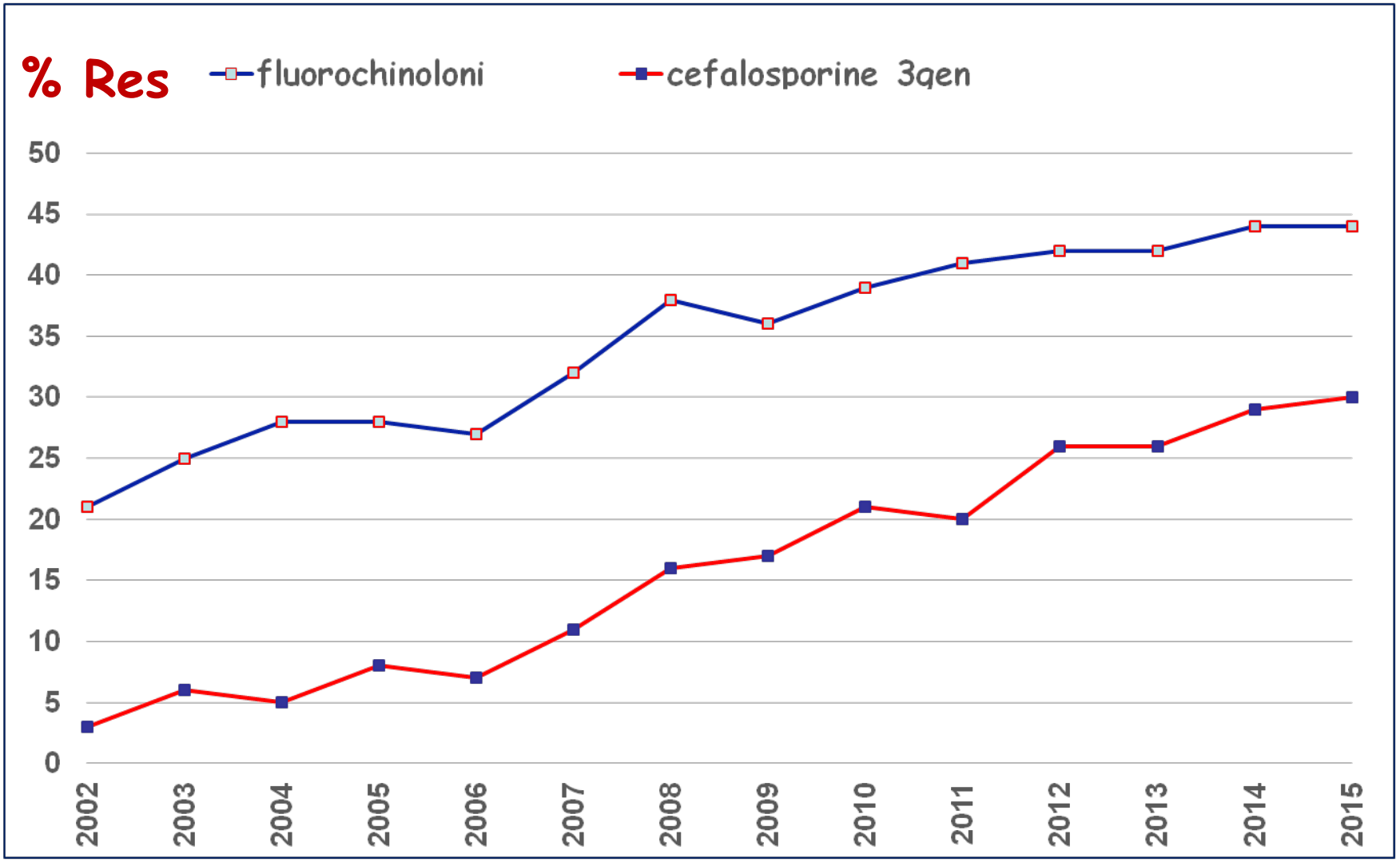
# *E.coli* resistente alle cefalosporine di terza generazione

EARS-NET database



# Resistenza in ceppi invasivi di *E.coli* in Italia

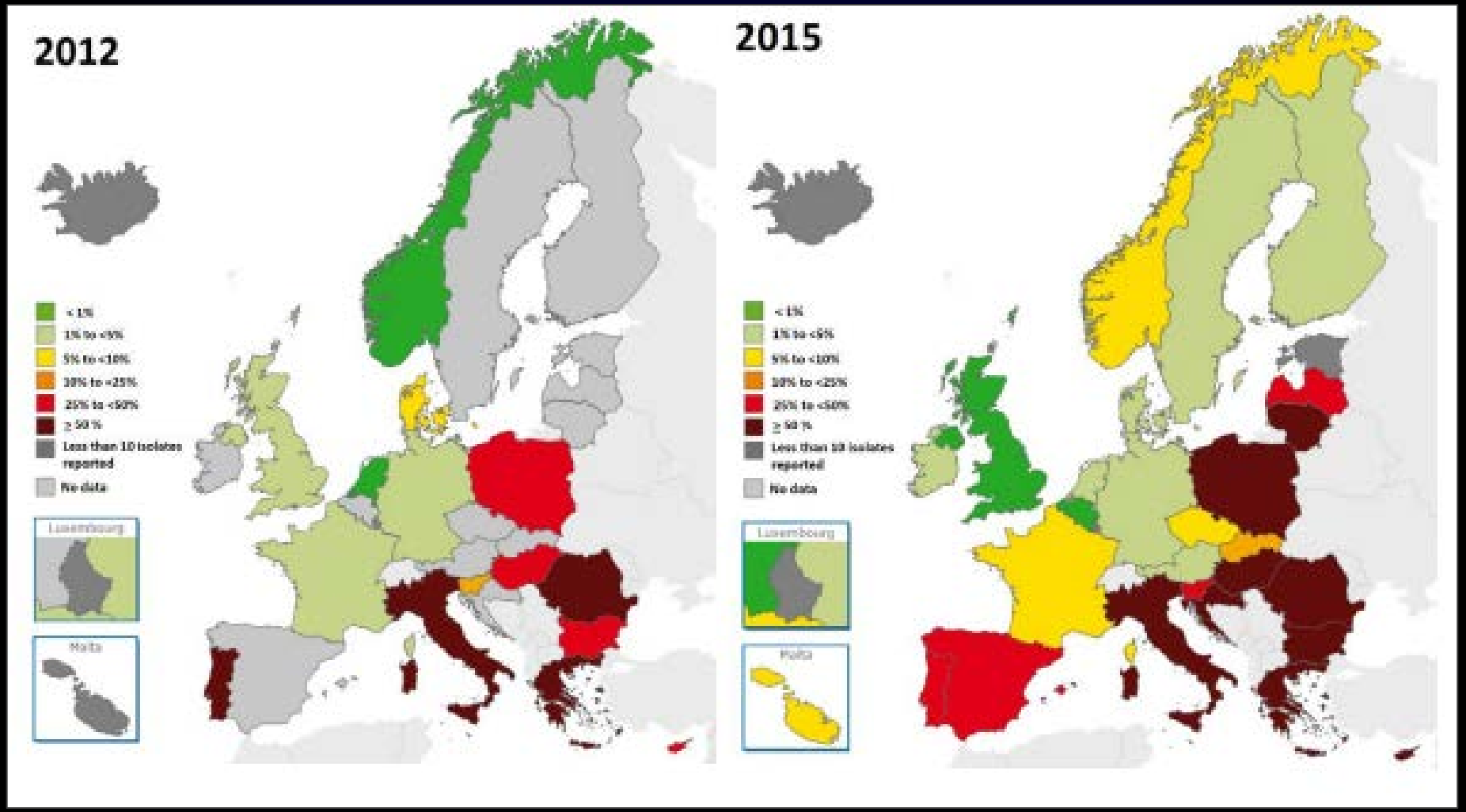
EARS-NET database



# *Acinetobacter spp:*

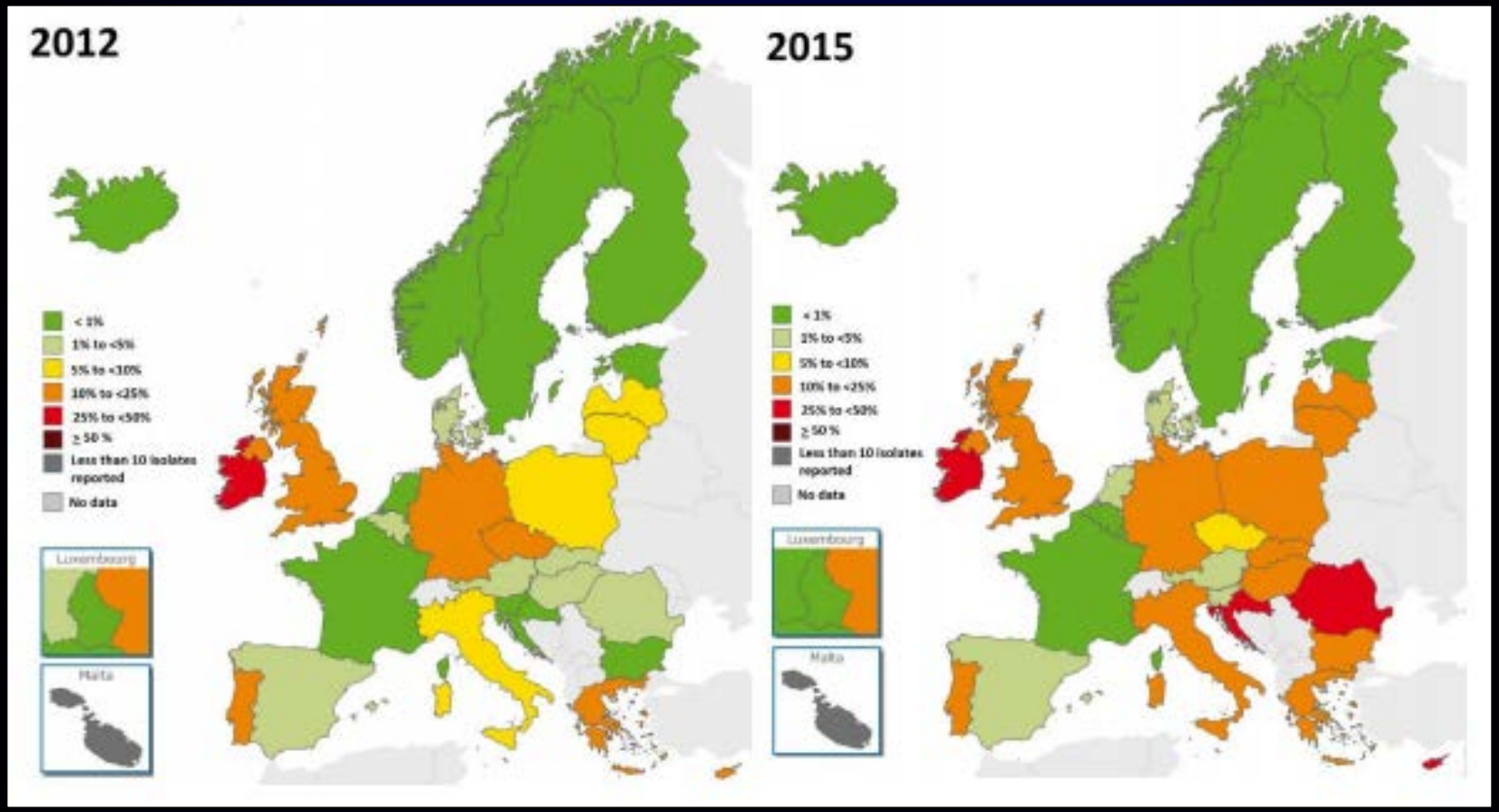
# isolati invasivi resistenti ai carbapenemi

*EARS-NET database*

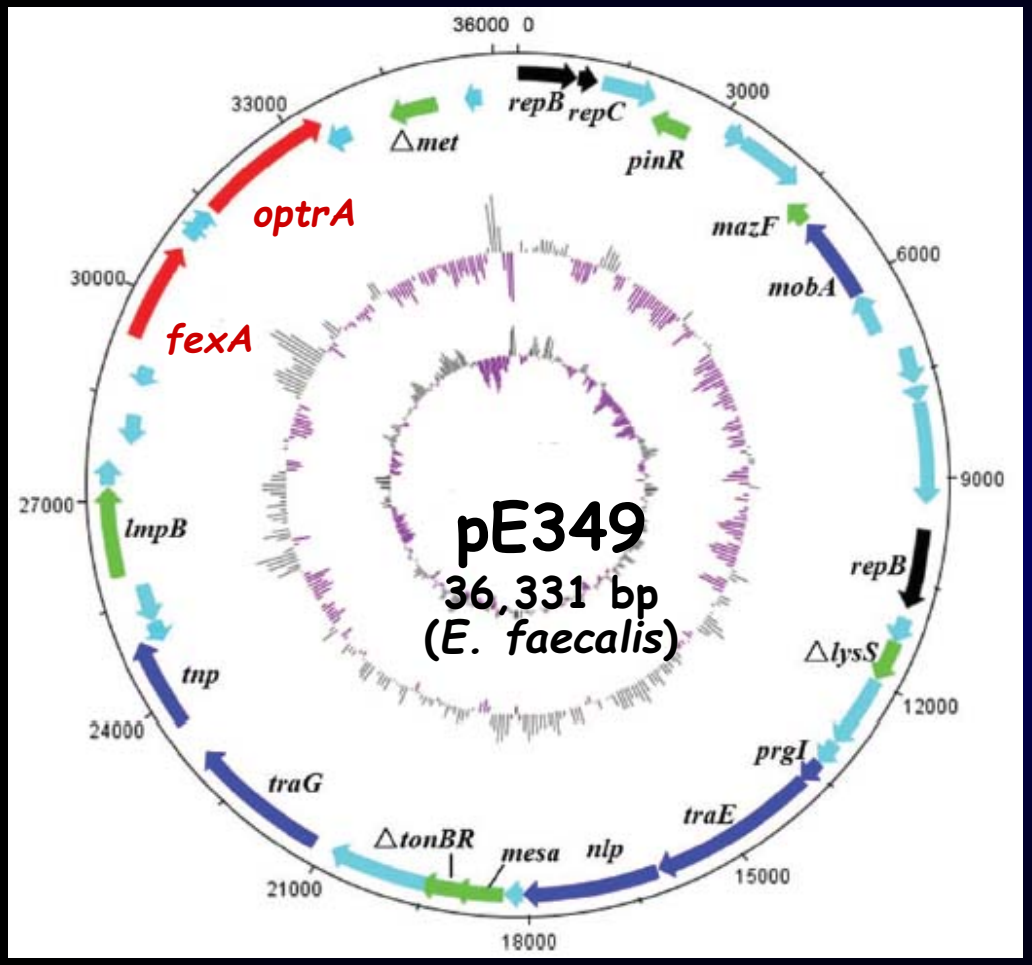


# *Enterococcus faecium* resistente alla vancomicina

*EARS-NET database*



# *optrA*-mediated linezolid resistance




- ***optrA*** confers transferable resistance to oxazolidinones (linezolid and tedizolid) and phenicols (chloramphenicol and florfenicol).
- First reported in China (2015) in enterococci (*E. faecalis* and *E. faecium*) of animal and human origin.

***optrA*** = oxazolidinone-phenicol transferable resistance

*Wang & al, JAC 2015*

*J Antimicrob Chemother* 2016; **71**: 1118–1129
doi:10.1093/jac/dkv438
Advance Access publication 24 December 2015

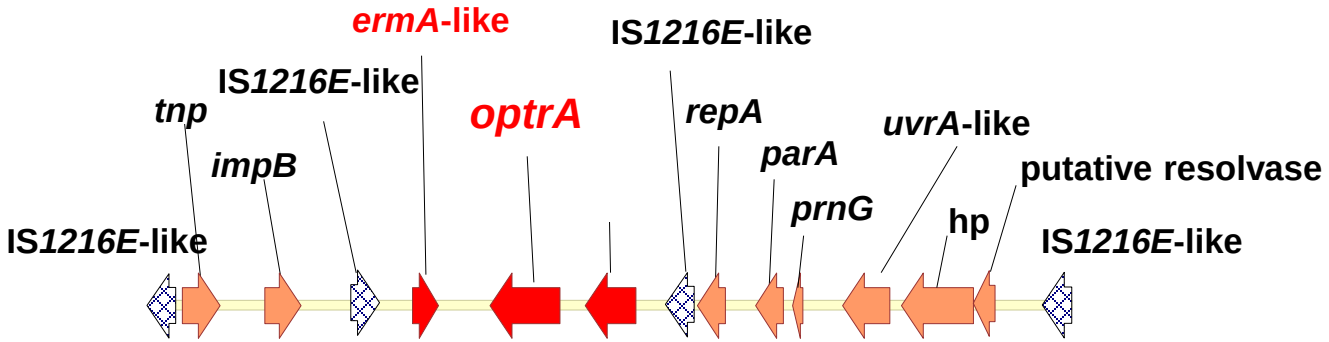
## Detection in Italy of two clinical *Enterococcus faecium* isolates carrying both the oxazolidinone and phenicol resistance gene *optrA* and a silent multiresistance gene *cfr*

Andrea Brenciani[1], Gianluca Morroni[1], Chiara Vincenzi[1,2], Esther Manso[2], Marina Mingoia[1], Eleonora Giovanetti[3] and Pietro E. Varaldo[1]*

**P 037**

## FIRST DETECTION OF LINEZOLID-RESISTANT OPTRA-POSITIVE CLINICAL ISOLATE OF *ENTEROCOCCUS FAECALIS* IN ITALY

Ilaria Baccani[1], Alberto Antonelli[1], Andrea Brenciani[2], Gianluca Morroni[2], Marco Maria D'Andrea[3], Lucia Henrici De Angelis[4], Angelo Galano[5], Eleonora Giovanetti[6], Pietro Emanuele Varaldo[6], Gian Maria Rossolini[7]




Genetic context of *optrA* gene in *Enterococcus faecalis* Ef-2353 (isolated in Florence University Hospital from a surgical wound) *optrA* gene was inserted in a plasmid of ~50 kb

***poxtA*** = **phenicol–oxazolidinone–tetracycline resistance gene**

*J Antimicrob Chemother*
doi:10.1093/jac/dky088

Journal of Antimicrobial Chemotherapy

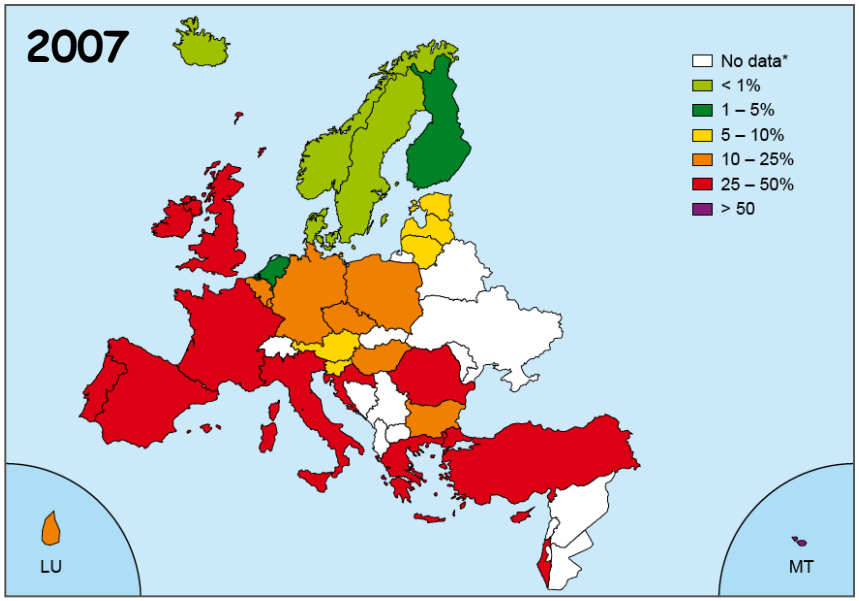
# Characterization of *poxtA*, a novel phenicol–oxazolidinone–tetracycline resistance gene from an MRSA of clinical origin

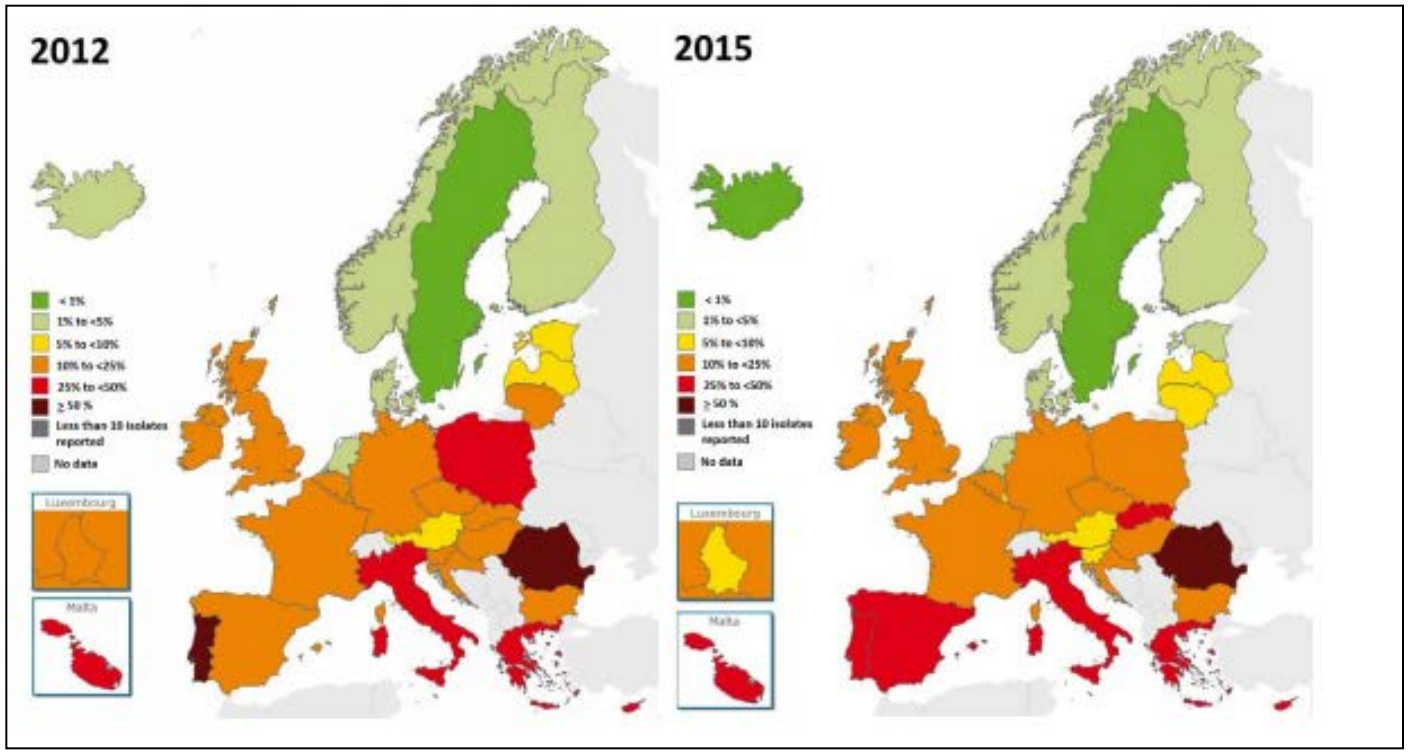
Alberto Antonelli[1], Marco Maria D'Andrea[2], Andrea Brenciani[3], Cesira L. Galeotti[1,4], Gianluca Morroni [5], Simona Pollini[1], Pietro Emanuele Varaldo[3] and Gian Maria Rossolini[1,6]*

- A novel acquired resistance gene, named poxtA, was found in a MRSA strain. The poxtA gene encodes a protein of the ARE ABC-F family, which is distantly related to OptrA and able to confer reduced susceptibility to phenicols, oxazolidinones and tetracyclines.
- The strain had been isolated from a cystic fibrosis patient after linezolid treatment and was found to carry at least two different linezolid resistance mechanisms,including a G152D substitution in the L3 ribosomal protein and the cfr gene, an acquired gene encoding a ribosomal rRNA methylase, which can mediate resistance to oxazolidinones and several other anti-ribosomal drugs

# MRSA in Europa

*EARS-NET database*



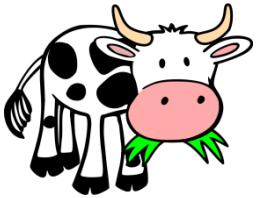



# Risk factors for previously unknown meticillin-resistant *Staphylococcus aureus* carriage on admission to 13 surgical wards in Europe.

- 111/2901 (3.8%) new MRSA carriers identified at admission.
- Independent risk factors for MRSA carriage
  - urinary catheterization (OR: 4.4; 95% CI 2.0-9.9),
  - nursing home residency (OR: 3.8; 95% CI 1.9-7.7),
  - chronic skin disease (OR: 2.9; 95% CI 1.5-5.8),
  - wounds/ulcers (OR: 2.4; 95% CI 1.5-4.0),
  - recent hospitalization (OR: 2.2; 95% CI 1.5-3.3),
  - diabetes (OR: 1.6; 95% CI 1.02-2.5),
  - age >70 years (OR: 1.5; 95% CI 1.03-2.3).
- Risk factors varied between centres. The c-statistic for the common prediction rule for all centres was 0.64, indicating limited predictive power.
- **Identifying local risk factors is important.**

*Pan et al J Hosp Infect. 2013;83:107-13*

# Study of MRSA in milk farms in North-East Italy
# Comparison of genotypes of MRSA from cow milk and MRSA from nasal carriage of farmers




| | | |
|---|---|---|
| A | t4208/ ST398 | t899/ ST398 |
| C | t032/ ST22 | t032/ ST22 |
| E | t899/ ST398 | t899/ ST398 |
| G | t127/ST1 | t127/ ST1 |
| I | t899/ ST398 | t899/ ST398 |
| S | t127/ ST1 | t127/ ST1 |
| T | t127/ ST1 | t852/ST22 |
| Z | t899/ ST398 | t899/ ST398 |

# Livestock-associated MRSA (LA-MRSA)

- ✓ Negli animali da compagnia infezioni da MRSA di cute e tessuti molli, prevalentemente post-chirurgiche (nei cani più che nei gatti, ma segnalazioni anche in conigli e cavalli).
  I ceppi implicati sono indistinguibili da quelli che causano infezione nell'uomo (ad esempio in UK lo ST22)

- ✓ Nel maiale implicato **ST398** (spa type t034,t108, t011, t899, t1254, tutti PVL negativi), riscontrato anche in bovini e polli

*Orfeo e gli animali.*
*Palermo, Museo Archeologico*

# Carriage di MRSA in allevatori di maiali e veterinari


- Alto tasso di MRSA *carriage* negli allevatori olandesi; il 39% dei maiali al macello risulta MRSA-positivo *(de Neeling et al, Vet Microb 2007)*
- A un congresso internazionale di suinicoltura nel 2006 il **12.6% dei veterinari** (provenienti da 9 paesi) sono risultati portatori di MRSA, che in 31/34 casi appartenevano a **ST 398** *(Wulf et al, CMI 2008)*

- Nel 2010 utilizzati nel mondo 63.000 tonnellate di antibiotici negli animali.
- Nel 2013 131.000 tonnellate (78.000 nella sola Cina), con un trend che porterebbe all'uso di più di 200.000 all'anno nel 2030.
- In Italia gli antibiotici usati a scopo auxologico sono stati il 71% del totale dei commercializzati, rispetto al 70% negli USA e all'84% in Cina.
- I polli da carne che ospitavano *E.coli* ESBL in Italia erano più dell'80%, quelli che ospitavano *E.coli* resistente a 5 o più classi di antibiotici il 64%. Più del16% risultava resistente a fluorochinolonici più colistina (ministero della Salute 2014).

frontiers in Microbiology

ORIGINAL RESEARCH
published: 10 November 2017
doi: 10.3389/fmicb.2017.02232

# Occurrence of Extended Spectrum β-Lactamases, KPC-Type, and MCR-1.2-Producing *Enterobacteriaceae* from Wells, River Water, and Wastewater Treatment Plants in Oltrepò Pavese Area, Northern Italy

OPEN ACCESS

**Edited by:**
*Manuela Caniça,*
*Istituto Nacional de Saúde, Portugal*

*Mariasofia Caltagirone*[1], *Elisabetta Nucleo*[1], *Melissa Spalla*[1], *Francesca Zara*[1], *Federica Novazzi*[1], *Vittoria M. Marchetti*[1], *Aurora Piazza*[1,2], *Ibrahim Bitar*[1,3], *Marica De Cicco*[1], *Stefania Paolucci*[4], *Giorgio Pilla*[5], *Roberta Migliavacca*[1*] and *Laura Pagani*[1]

During one-year study and taking in account the whole Gram-negative bacterial population, an average percentage of cefotaxime resistance of 69, 32, and 10.3% has been obtained for the wastewater treatment plants, streams, and wells, respectively. These results, of concern for public health, highlight the need to improve hygienic measures to reduce the load of discharged bacteria with emerging resistance mechanisms.

| site type | predicted exposure to antimicrobial-treated livestock | rodent species sampled[a] | prevalence (% samples containing resistant *E. coli*) of antibiotic resistance in faecal samples of different rodent and livestock populations | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | amp | apr | chl | tet | trm | nal |
| uninhabited island | none | water vole[b] | 10–85 | 0 | 2–65 | 5–75 | 5–85 | 0–35 |
| upland forest | upland sheep | field vole, bank vole and wood mouse | 0–5 | 0 | 0–5 | 0–5 | 0–5 | 0 |
| lowland woodland | reared gamebirds and cattle on adjacent dairy farms | bank vole and wood mouse | 12–22 | 0–1 | 4–6 | 12–18 | 11–18 | 0 |
| fields on dairy farms | cattle on fields | wood mouse | 0–27 | 0 | 0–27 | 0–30 | 0–42 | 0 |
| | | cattle | 5–75 | 0 | 0 | 8–92 | 5–92 | 0 |
| intensive poultry farms | poultry in buildings | house mouse[c] | 47–55 | 0 | 21–25 | 57–75 | 57–68 | 0–10 |
| | | bank vole and wood mouse | 0–5 | 0 | 0 | 0–9 | 0–12 | 0 |
| | | poultry | 5–8 | 0 | 0 | 15–45 | 3–6 | 0–18 |

[a]Rodent species: water vole, *Arvicola amphibious*; field vole, *Microtus agrestis*; bank vole, *Myodes glareolus*; wood mouse, *Apodemus sylvaticus*; house mouse, *Mus musculus*.

[b]Water voles on these islands are fossorial rather than riparian as on the mainland.

[c]Captured in and around the buildings housing poultry.

Arnold KE, Williams NJ,Bennett M. Biol. Lett. 2016; 12: 20160137.

# Avifauna dell'Asinara

| SPECIE | STANZIALE | MIGRATORIA | N CAMPIONI | CEPPI ISOLATI |
|---|---|---|---|---|
| Balia nera | | x | 2 | 0 |
| Beccafico | | x | 25 | 7 |
| Cannaiola | | x | 2 | 0 |
| Capinera | | x | 16 | 2 |
| Codirosso | | x | 26 | 6 |
| Culbianco | | x | 1 | 1 |
| Luì grosso | | x | 4 | 1 |
| Magnanina | x | | 2 | 1 |
| Magnanina Sarda | x | | 1 | 1 |
| Occhiocotto | x | | 46 | 14 |
| Passera sarda | x | | 3 | 2 |
| Pettirosso | | x | 22 | 5 |
| Pigliamosche | | x | 7 | 4 |
| Saltimpalo | x | | 2 | 0 |
| Scricciolo | x | | 1 | 1 |
| Sterpazzola | | x | 1 | 0 |
| Stiaccino | | x | 2 | 1 |
| Torcicollo | | x | 3 | 2 |
| Tordo bottaccio | | x | 1 | 0 |
| Tottavilla | x | | 1 | 0 |
| Zigolo Nero | x | | 2 | 1 |
| TOTALE | **8** | **13** | **170** | **49** |

RESEARCH ARTICLES

# Risk Factors for Infection with Pathogenic and Antimicrobial-Resistant Fecal Bacteria in Northern Elephant Seals in California

Stoddard RA, et al Public Health Rep. 2008;123:360-70.

*Mirounga angustirostris*

*Contributed Paper*

# Gastrointestinal Bacterial Transmission among Humans, Mountain Gorillas, and Livestock in Bwindi Impenetrable National Park, Uganda

INNOCENT B. RWEGO,*§ GILBERT ISABIRYE-BASUTA,* THOMAS R. GILLESPIE,†‡ AND TONY L. GOLDBERG*†‡

*Makerere University, Department of Zoology, P.O. Box 7062, Kampala, Uganda
†Department of Pathobiology, College of Veterinary Medicine, University of Illinois, 2001 South Lincoln Avenue, Urbana, IL 61802, U.S.A.
‡Department of Anthropology, University of Illinois, Urbana, IL 61801, U.S.A.

Rwego et al Conservation Biology 2008; 22: 1600–1607

*Gorilla gorilla beringei*

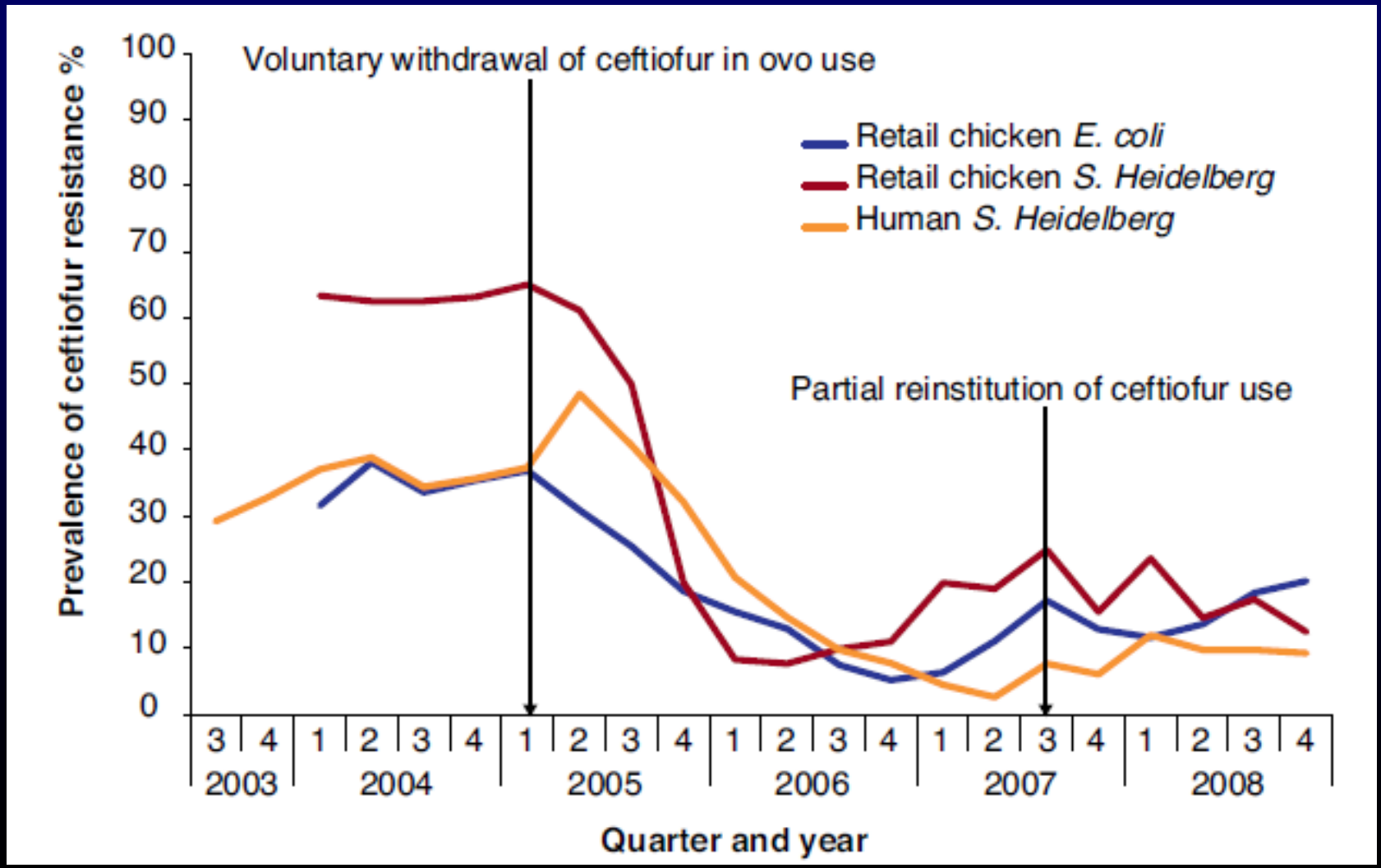
17% of *E.coli* isolates from gorillas were clinically resistant to at least one antibiotic used by local people, and the proportion of individual gorillas harboring resistant isolates declined in proportion to decreasing degrees of habitat overlap with humans.

# PNCAR

- Stewardship antibiotica 'diffusa'
- Ruolo dell'Infettivologo nella gestione della terapia antibiotica in Ospedale e Territorio.
- Rete consulenziale.
- Presenza e partecipazione nei ruoli fissati da PNCAR presso le regioni

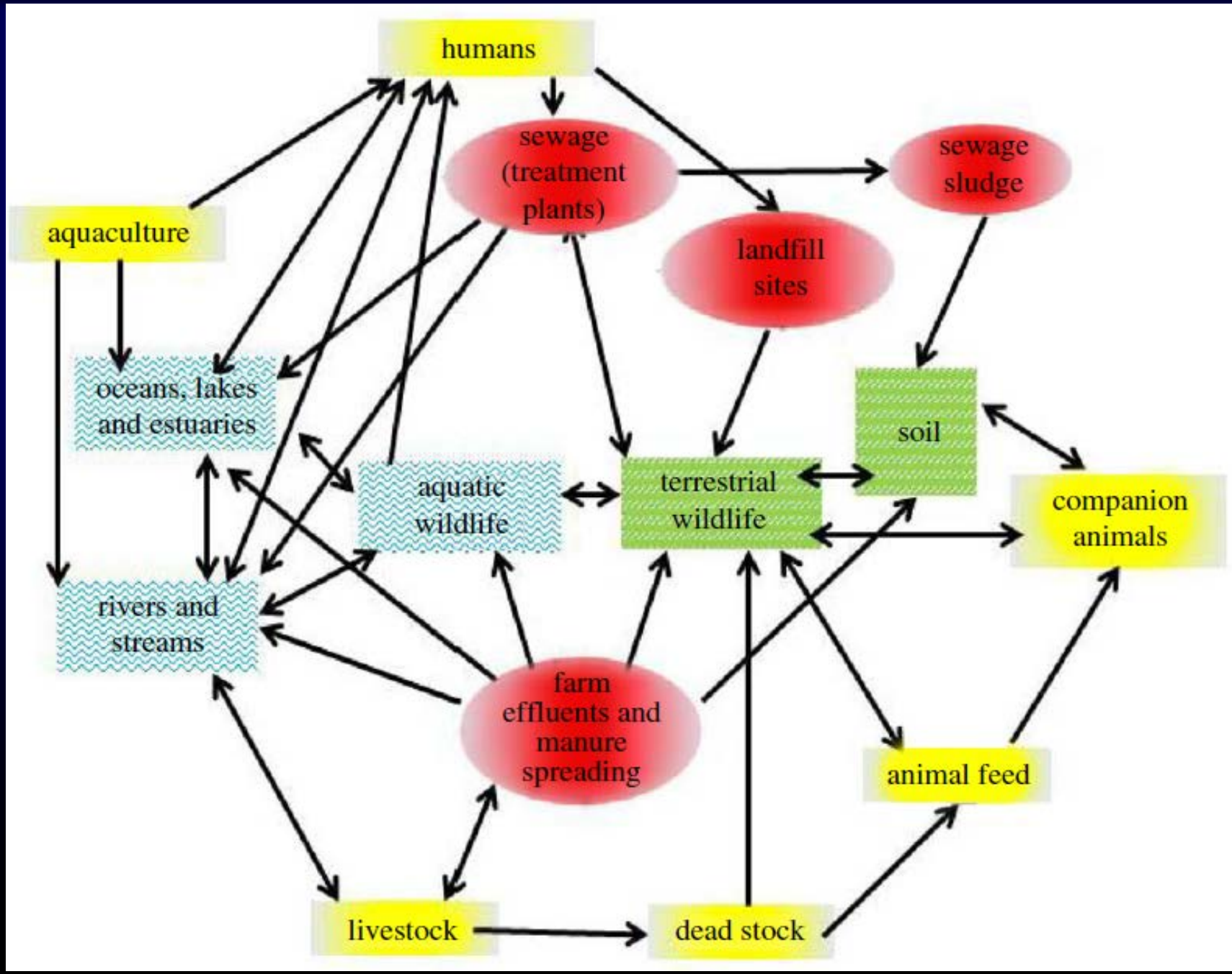
# Grazie per l'attenzione

# Cephalosporin resistance after stopping its use in poultry in Quebec, Canada




Dutil et al EID 2010; 16: 48-54

# *Escherichia coli* resistente ai carbapenemi, Europa 2015


humans
sewage (treatment plants)
sewage sludge
aquaculture
landfill sites
oceans, lakes and estuaries
soil
aquatic wildlife
terrestrial wildlife
companion animals
rivers and streams
farm effluents and manure spreading
animal feed
livestock
dead stock