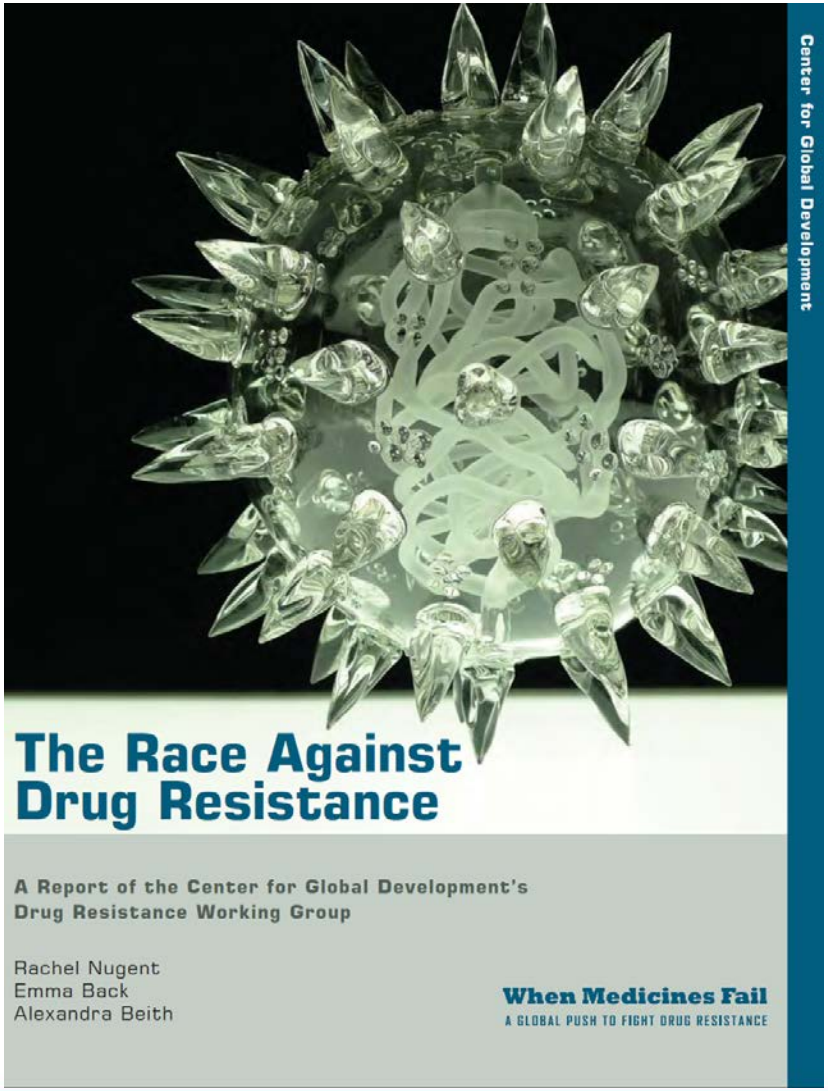
The ECDC point of view on the requests from the European Commission

Anna-Pelagia Magiorakos, MD, FIDSA, Senior Expert AMR and HAI for ARHAI Disease Programme
European Centre for Disease Prevention and Control

EMA, London, United Kingdom, 28 February, 2014

A Global concern of antimicrobial resistance



***Emergence and spread of new mechanisms of resistance**

*** Antimicrobial misuse**

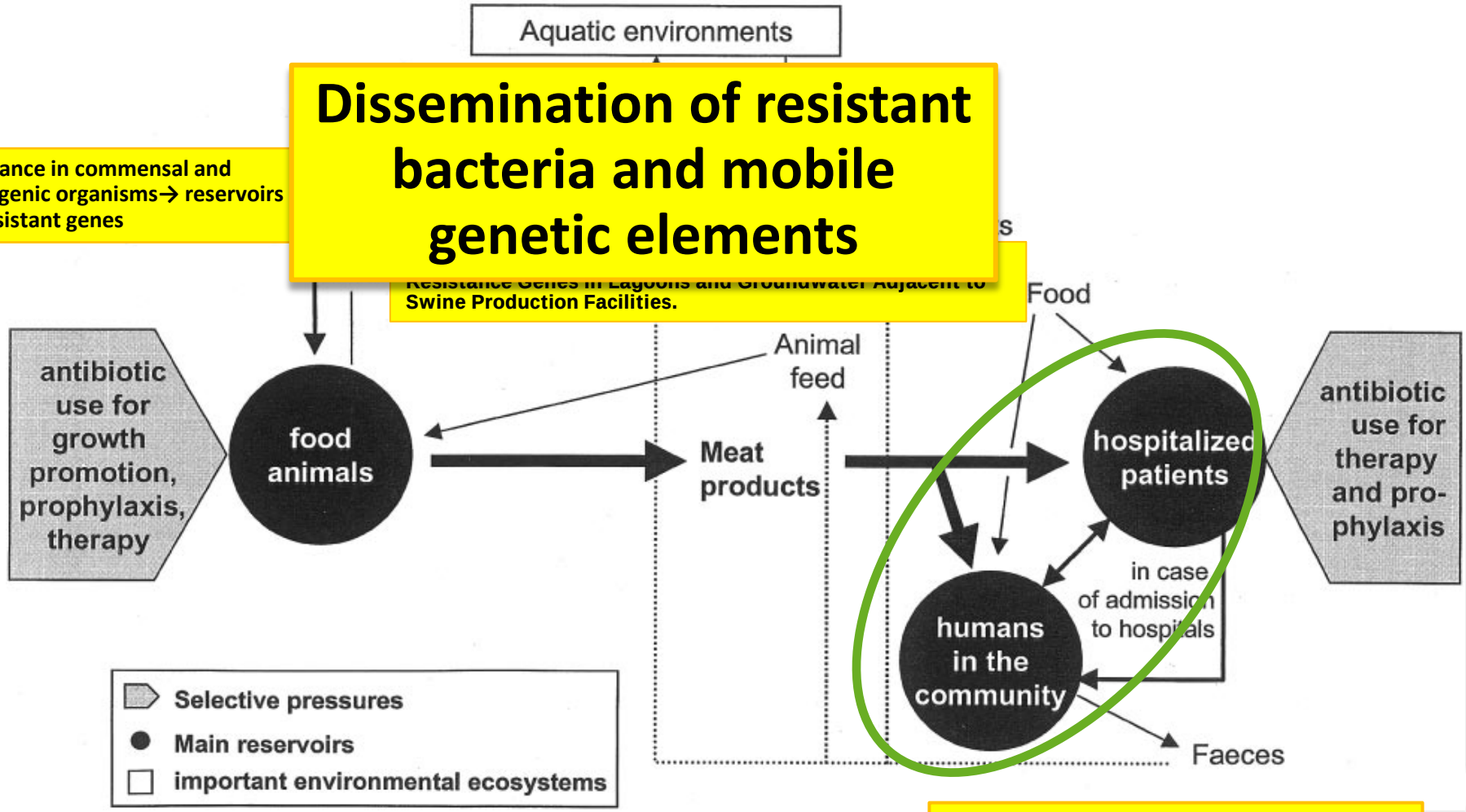
- Drug regulation
- Human and animal antimicrobial misuse

*** No new antimicrobials in the development pipeline**

*** Cycle: antimicrobial use → ↑ resistance → antimicrobial use ↑**

Source: Center for Global Development. 2010. The Race Against Drug Resistance
http://www.cgdev.org/files/1424207_file_CGD_DRWG_FINAL.pdf
Boucher *et al.* Clin Infect Dis. 2009 Jan 1;48(1):1-12

The ecological phenomenon of resistance



Horizontal transfer of mobile genetic elements to pathogenic bacteria in the animal and human gut

Adapted from: Witte W. Int J Antimicrob Agents; 2000;14(4):321-5
Koike et al. Applied and Environmental Microbiology, 73 (15):4813-4823 (2007).

Burden and outcomes of infections with multidrug-resistant (MDR) bacteria in the EU, Iceland and Norway

Human burden

Infections (6 most frequent MDR bacteria, 4 main types of infection)

	approx.	400,000	/ year
Attributable deaths	approx.	25,000	/ year
Extra hospital days	approx.	2.5 million	/ year

Economic burden

Extra in-hospital costs	approx.	€ 900 million	/ year
Productivity losses	approx.	€ 600 million	/ year

Limitation: these are underestimates.

Source: ECDC, 2009.
In: http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

Carbapenemases: main types of enzymes

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

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

ECDC/EMEA. http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=444
Boucher *et al*. Clin Infect Dis. 2009 Jan 1;48(1):1-12

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

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carmeli[3], M. E. Falagas[4,5], C. G. Giske[6], S. Harbarth[7], J. F. Hindler[8], G. Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. B. Rice[12], J. Stelling[13], M. J. Struelens[1], A. Vatopoulos[14], J. T. Weber[2] and D. L. Monnet[1]

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	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
***Enterococcus* spp.**	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.	
Enterobacteriaceae	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.	
Pseudomonas aeruginosa	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.	
***Acinetobacter* spp.**	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.	

Inappropriate, delayed or inadequate therapy

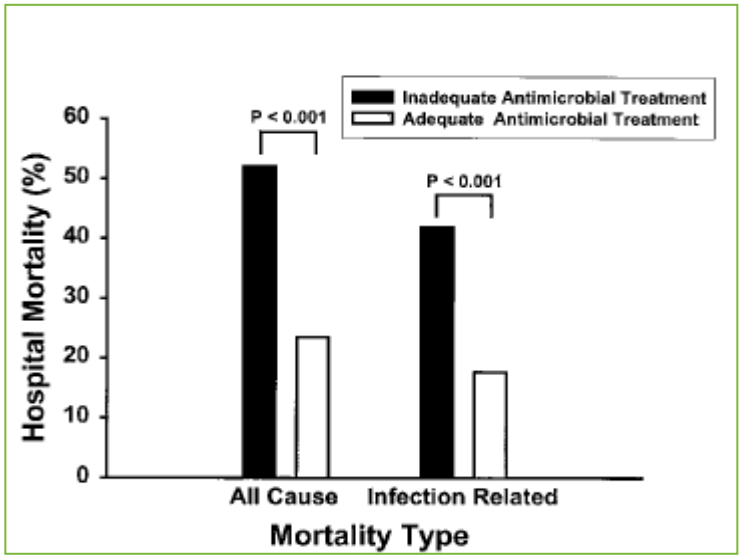
CHEST

Original Research

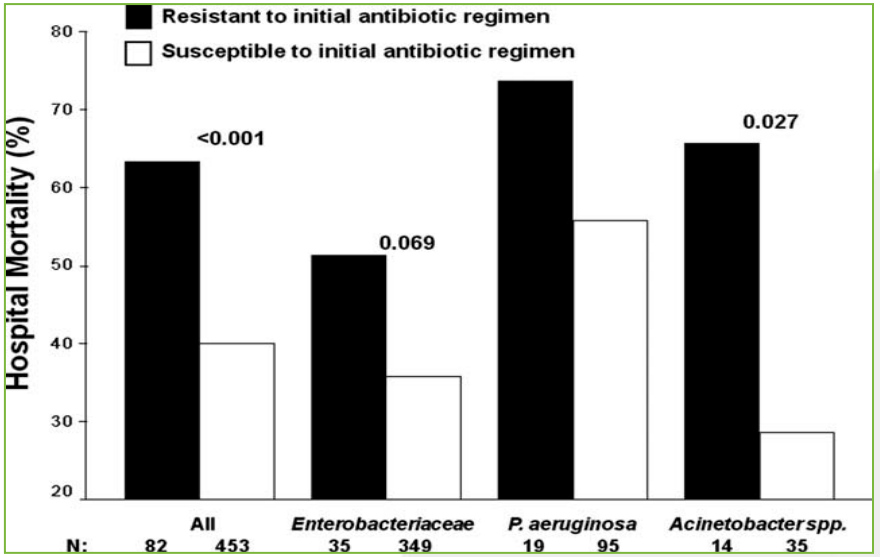
CRITICAL CARE MEDICINE

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

*Anand Kumar, MD; Paul Ellis, MD; Yaseen Arabi, MD, FCCP; Dan Roberts, MD; Bruce Light, MD; Joseph E. Parrillo, MD, FCCP; Peter Dodek, MD; Gordon Wood, MD; Aseem Kumar, PhD; David Simon, MD; Cheryl Peters, RN; Muhammad Ahsan, MD; Dan Chateau, PhD; and the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group**



Adapted from: Kollef *et a*l.1999



Adapted from: Micek *et a*l.2011

Kumar et al. Chest. 2009
Kollef et al. Chest. 1999

Micek *et a*l. J Hosp Med. 2011

Critically important antimicrobials for human medicine

1) Antimicrobial agent is used as sole therapy or one of few alternatives to treat serious human disease.

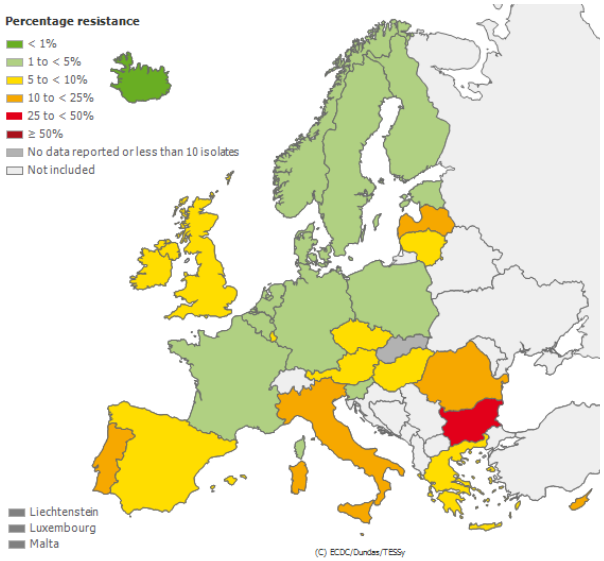
2) Antimicrobial agent is used to treat diseases caused by either: (1) organisms that may be transmitted via non-human sources or (2) diseases causes by organisms that may acquire resistance genes from non-human sources.

- "Serious disease: one that if left untreated are likely to result in irreversible morbidity or mortality"
- "Evidence for link of transmission is highest for *Enterococcus*, *E. coli*, *S. aureus*, *Salmonella* spp., Campylobacter spp." (and environmental sources)
- "Organisms that cause disease need not be resistant at present; however, the potential for transmission shows the path for acquisition now or in the future"

Critically important antimicrobials for human medicine

- Prioritizing strategies… to preserve their effectiveness in human medicine.
- Ensuring that critically important antimicrobials are included in antimicrobial susceptibility monitoring programmes.
- Refining and prioritizing risk profile and hazard analysis activities for interventions by species or by region.
- Developing risk management options such as restricted use, labelling, limiting or prohibiting extra-label use, and making antimicrobial agents available by prescription only.
- For the development of prudent use and treatment guidelines in humans and animals.
- To direct special research projects to address prevalence data gaps on existing or potential future CIAs.

Escherichia coli: percentage of invasive isolates resistant to third-generation cephalosporins; EU/EEA, 2008–2012



2008

2012

< 1%
1% to < 5%
5% to < 10%
10% to < 25%
25% to < 50%
≥ 50%
No data reported or less than 10 isolates
Not included

Non-visible countries
Liechtenstein
Luxembourg
Malta

Source: EARS-Net, 2013

The symbols ↑ and ↓ indicate a significant increasing or decreasing trend for the period 2008-2011, respectively. These trends were calculated on laboratories that consistently reported during 2008-2011.

Paolo
(Italy)

http://antibiotic.ecdc.europa.eu

Eur J Clin Microbiol Infect Dis (2010) 29:1501–1506
DOI 10.1007/s10096-010-1031-y

ARTICLE

Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers

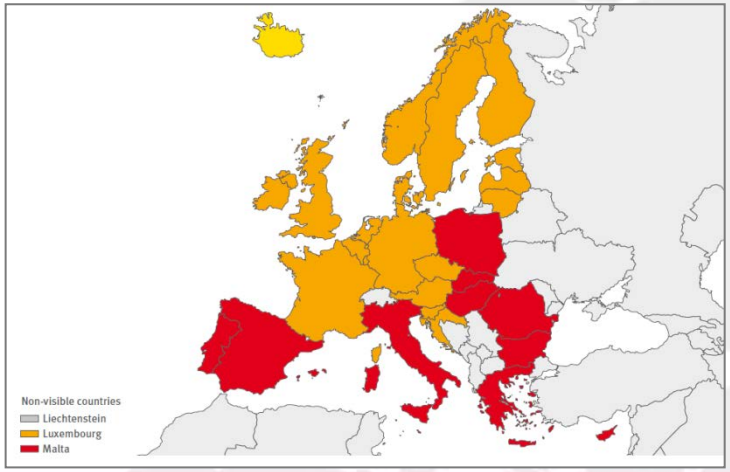
K. Kennedy · P. Collignon

Resistant to gentamicin, cipro, 3rd gen ceph
Pre-travel colonisation 7.8%, post- travel 49%

Clinical Impact of Fluoroquinolone-Resistant *Escherichia coli* in the Fecal Flora of Hematological Patients with Neutropenia and Levofloxacin Prophylaxis

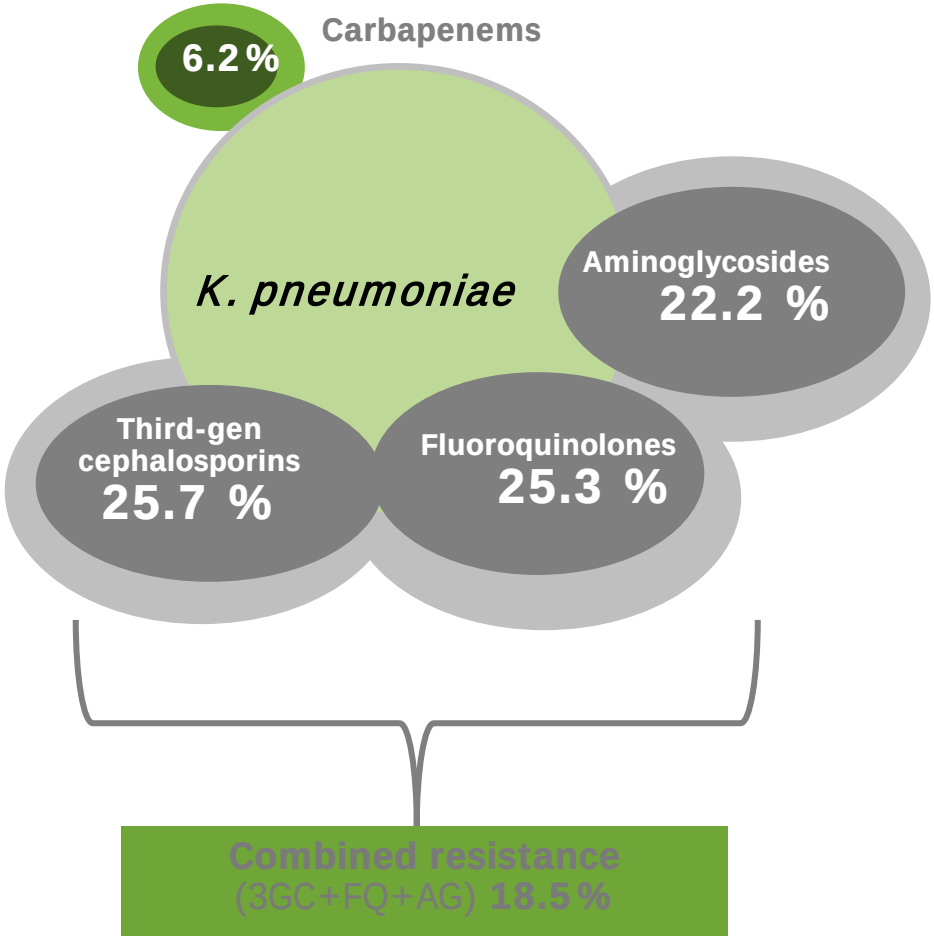
Yong Chong[1]*, Shinji Shimoda[1], Hiroko Yakushiji[2], Yoshikiyo Ito[3], Takatoshi Aoki[3], Toshihiro Miyamoto[1], Tomohiko Kamimura[3], Nobuyuki Shimono[4], Koichi Akashi[1]

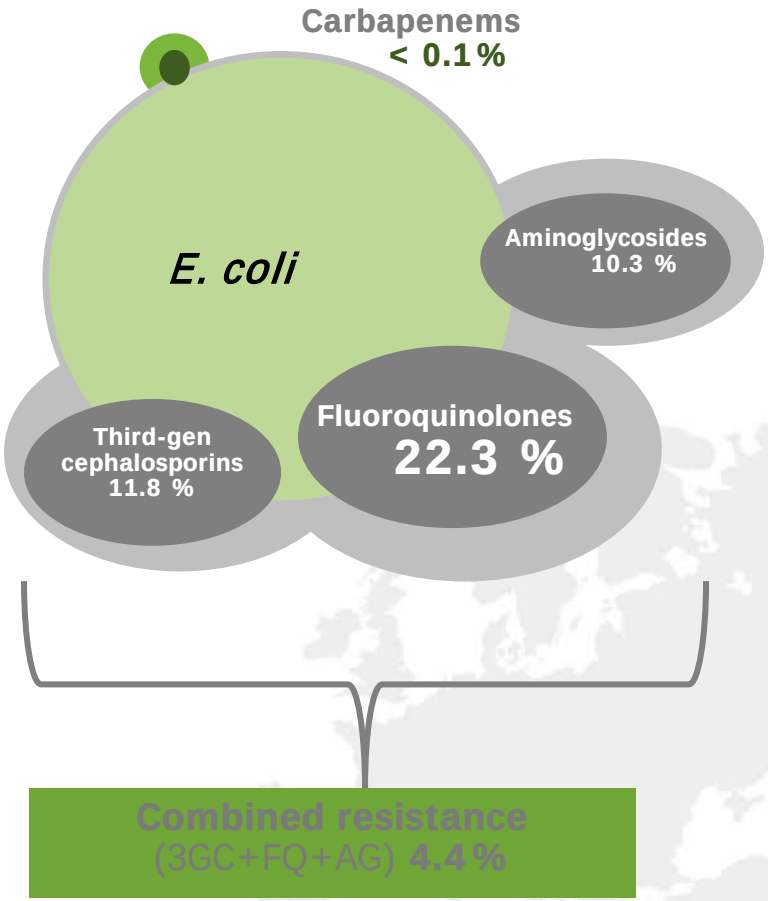
E. coli: **percentage of invasive isolates resistant to fluoroquinolones EU/EEA, 2012**



Kennedy K, Collignon P. Eur J Clin Microbiol Inf Dis, 2010
Chong Y et al. PLoS ONE, 2014
EARS-Net, 2013

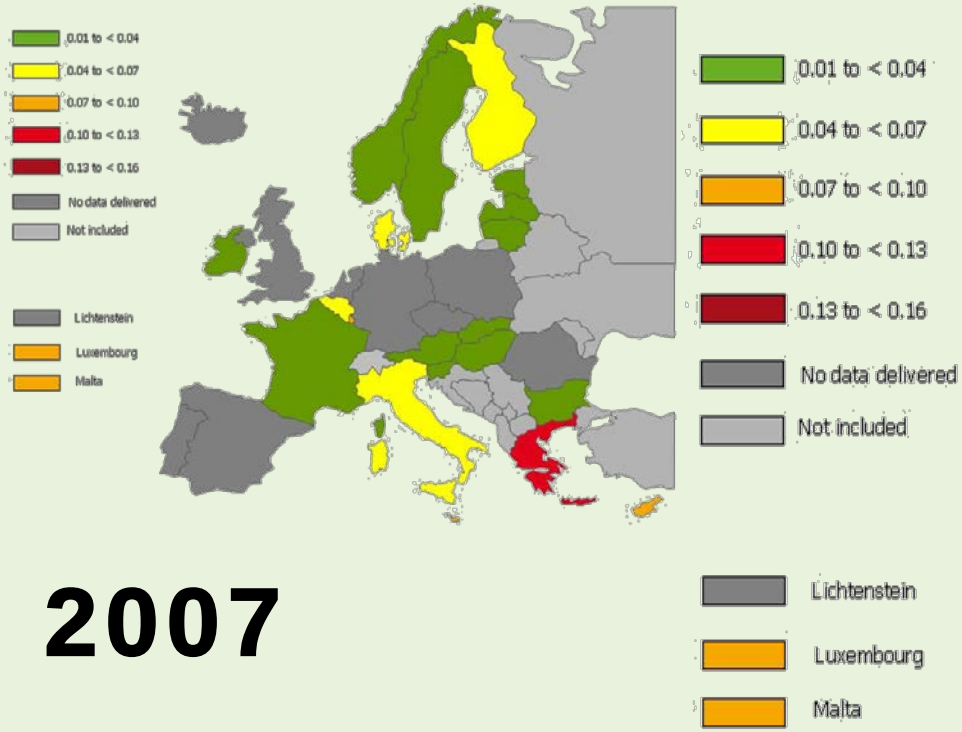
EU/EEA mean resistance percentage 2012 (population-weighted*)



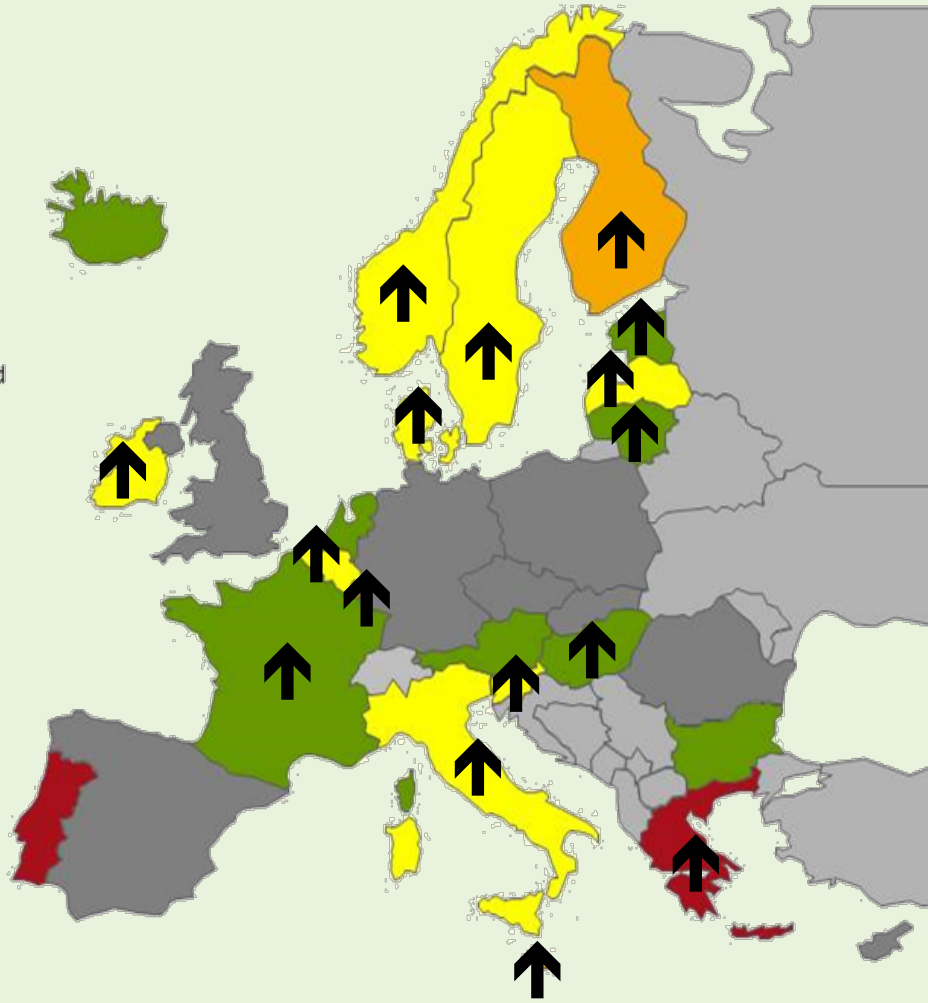


*) Population-based weights applied to each national estimate before calculating arithmetic mean for EU/EEA

Carbapenem consumption* (for the large majority in hospitals); EU/EEA, 2007–2010



2007



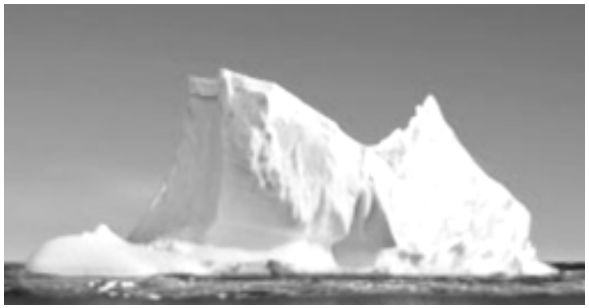
2010

*in Defined Daily Doses per 1000 inhabitants and per day

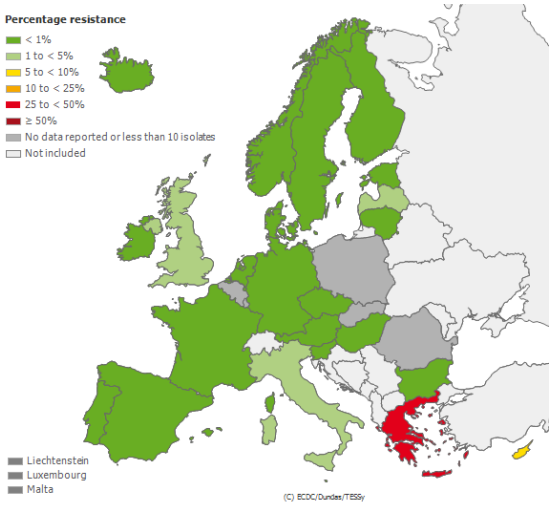
Source: ESAC-Net, 2012

The symbols ↑ and ↓ indicate a significant increase or decrease between 2007 and 2010, respectively. These trends are indicated only for countries that reported relevant data for both 2007 and 2010.

Klebsiella pneumoniae: percentage of invasive isolates resistant to carbapenems; EU/EEA, 2008–2012

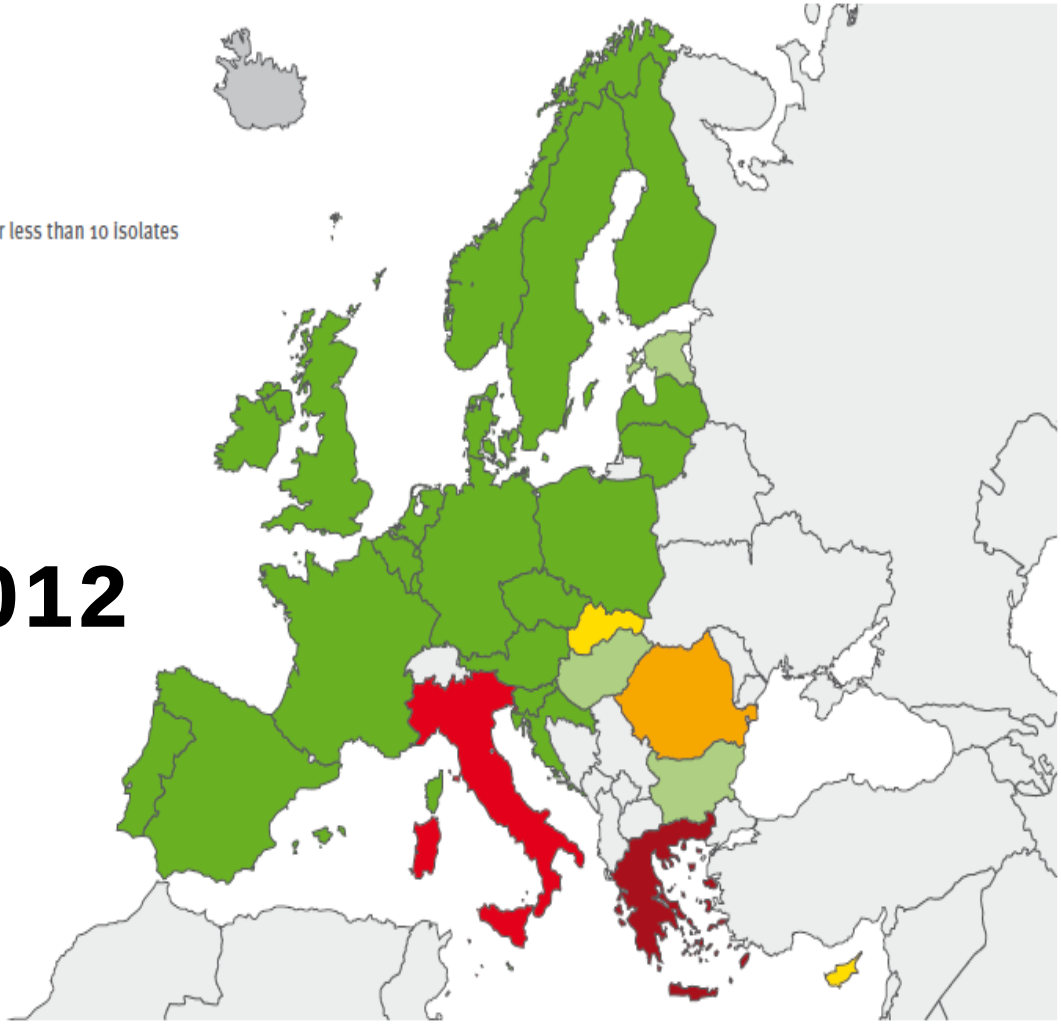


< 1%
1% to < 5%
5% to < 10%
10% to < 25%
25% to < 50%
≥ 50%
No data reported or less than 10 isolates
Not included



2008

2012

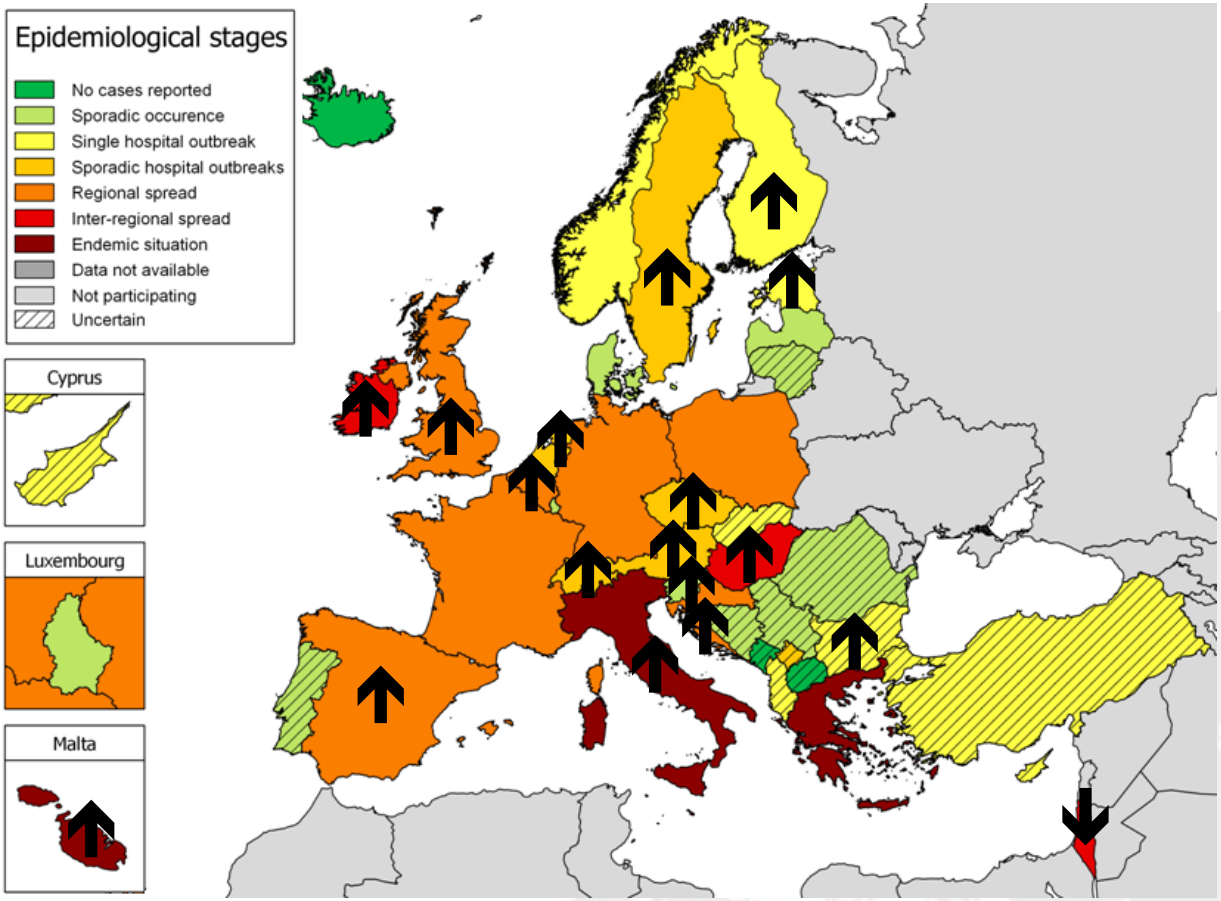


Source: EARS-Net, 2013

The symbols ↑ and ↓ indicate a significant increasing or decreasing trend for the period 2008-2011, respectively. These trends were calculated on laboratories that consistently reported during 2008-2011.


Mohammed
(United Kingdom)
http://antibiotic.ecdc.europa.eu

Country self-assessment of stages for spread of carbapenemase-producing *Enterobacteriaceae* (all isolates), 2010 and 2013



Source: Grundmann et al. Eurosurveill 2010, and EuSCAPE project, Glasner et al., Eurosurveill 2013.

The symbols ↑ and ↓ indicate a positive or negative change in stage between 2010 and 2013. This change could only be indicated for countries that reported for both years.

First report of IMI-1-producing colistin-resistant *Enterobacter* clinical isolate in Ireland, March 2013

T W Boo (teck.boo@hse.ie)[1,2], N O'Connell[3], L Power[3], M O'Connor[4], J King[1], E McGrath[1], R Hill[5], K L Hopkins[5], N Woodford[5]

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

A. Capone[1], M. Giannella[1], D. Fortini[2], A. Giordano[3], M. Meledandri[4], M. Ballardini[4], M. Venditti[5], E. Bordi[6], D. Capozzi[7], M. P. Balice[8], A. Tarasi[9], G. Parisi[10], A. Lappa[10], A. Carattoli[2], N. Petrosillo[1] and on behalf of the SEERBIO-GRAB network[†]

Antimicrobial Agents and Chemotherapy

Bactericidal Activity of Multiple Combinations of Tigecycline and Colistin against NDM-1-Producing Enterobacteriaceae

Mahableshwar Albur, Alan Noel, Karen Bowker and Alasdair MacGowan

Antimicrob. Agents Chemother. 2012, 56(6):3441. DOI:

Journal of Antimicrobial Chemotherapy (2008) **61**, 417–420
doi:10.1093/jac/dkm509
Advance Access publication 3 January 2008

JAC

Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections

Boo TW et al. Eurosurveillance, 2013; Mahableshwar A. AAC. 2012
Capone et al. CMI, 2013

Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from animals and the environment: an emerging public health risk of our own making?

Neil Woodford[1,2]*, David W. Wareham[2], Beatriz Guerra[3] and Christopher Teale[4]

Identification In Proteus Mirabilis of a Salmonella Genomic Island Containing the blaNDM-1 Carbapenemase Gene Together with the ESBL-encoding Gene blaVEB-6

L. Dortet, L. Poirel, P. Nordmann;
Hosp. de Bicetre, Le Kremlin Bicetre, FRANCE.

Scientific Opinion on carbapenem resistance in food animal ecosystems. EFSA Panel on Biological Hazards on Biological Hazards (BIOHAZ). *EFSA Journal* 2013;11(12):3501

Perspectives

- Need for well-performed studies documenting transmission
- Need for good surveillance of AMR in animals
- Control options for misuse in animal husbandry
- "When a new class of drug comes on the market, it should be considered critically important...unless strong evidence suggests otherwise”
- "Existing drugs e.g. carbapenems, linezolid, and daptomycin, not currently used in food production, should not be used in the future in animals, plants, or in aquaculture.

Key points in creating a response to Question 2

1. Modified terminology: "limited therapy for"➔ “necessary for”

1. Broaden clinical indications in which antibiotics are used
2. Need for antibiotics in humans needs to be highlighted
3. Ensure that evidence-based data included for transmission
4. Highlight changes in epidemiology/new resistance mechanisms can be found in zoonotic bacteria (e.g. NDM in *Salmonella* spp.)
5. Need for good surveillance data for AMR in animals
6. Need for a gap analysis of alternatives before suggesting new antimicrobials

8. When a new class of drug comes on the market, it should be considered critically important...unless strong evidence suggests otherwise”

Acknowledgments

- ECDC Antimicrobial Resistance and Healthcare-Associated Infections (ARHAI) Disease Programme:
- Dominique Monnet
- Carl Suetens
- Klaus Weist
- Liselotte Diaz Högberg
- Barbara Albiger
- Marc Struelens
- Ole Heuer
- Diamantis Plachouras
- Pete Kinross
- Pierluigi Lopalco

Thank you

www.ecdc.europa.eu| info@ecdc.europa.eu