Clinica di Malattie Infettive e Tropicali
Università degli Studi dell'Insubria –
ASST Sette Laghi, Varese

Infezioni da MDR
Clinica ed epidemiologia

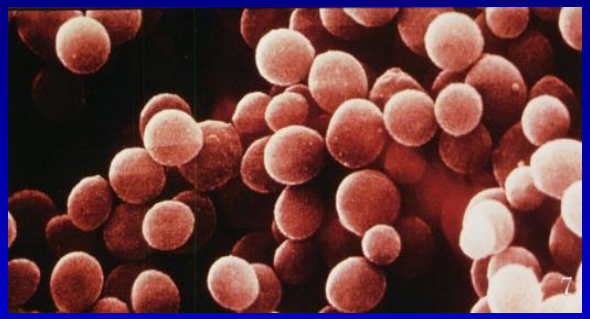
Daniela Dalla Gasperina

Definizione di Batteri Multiresistenti: MDR, XDR e PR

- MDR (Multidrug-resistant): mancanza di sensibilità ad uno o più agenti in tre o più categorie di antimicrobici attivi contro i batteri isolati
  - Nel caso di *Staphylococcus aureus*, la resistenza alla meticillina (MRSA) definisce il ceppo MDR, indipendentemente dalla resistenza ad altri antimicrobici.

van Duin D. & van Delden C. AJT 2013; 13: 31–41

Staphylococcus aureus meticillino-resistente (MRSA)



Antibiotico	Sensibilità (S/I/R)
Ampicillina	R
Clindamicina	R
Ciprofloxacina	R
Daptomicina	S
Eritromicina	R
Acido fusidico	R
Gentamicina	R
Linezolid	S
Tobramicina	R
Oxacillina	R
Penicillina	R
Cotrimoxazolo	S
Teicoplanina	S
Vancomicina	S
Fosfomicina	R

Definizione di Batteri Multiresistenti: MDR, XDR e PR

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  - Nel caso di *Staphylococcus aureus*, la resistenza alla meticillina (MRSA) definisce il ceppo MDR, indipendentemente dalla resistenza ad altri antimicrobici.

- XDR (Extensively-drug resistant): battere suscettibile a non più di due classi di categorie di antimicrobici attivi

- PR (Pan-resistant): battere non suscettibile a nessuno degli antimicrobici attivi, disponibili in commercio

van Duin D. & van Delden C. AJT 2013; 13: 31–41

Pseudomonas aeruginosa

XDR	
Co-trimoxazolo	R
Pip./Tazo.	R
Cefepime	R
Ceftazidime	R
Cefotaxime	R
Imipenem	R
Meropenem	R
Amikacina	S
Gentamicina	R
Ciprofloxacina	R
Levofloxacina	R
Colistina	S

PR	
Co-trimoxazolo	R
Pip./Tazo.	R
Cefepime	R
Ceftazidime	R
Cefotaxime	R
Imipenem	R
Meropenem	R
Amikacina	R
Gentamicina	R
Ciprofloxacina	R
Levofloxacina	R
Colistina	R

NO TIME TO WAIT:
SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS

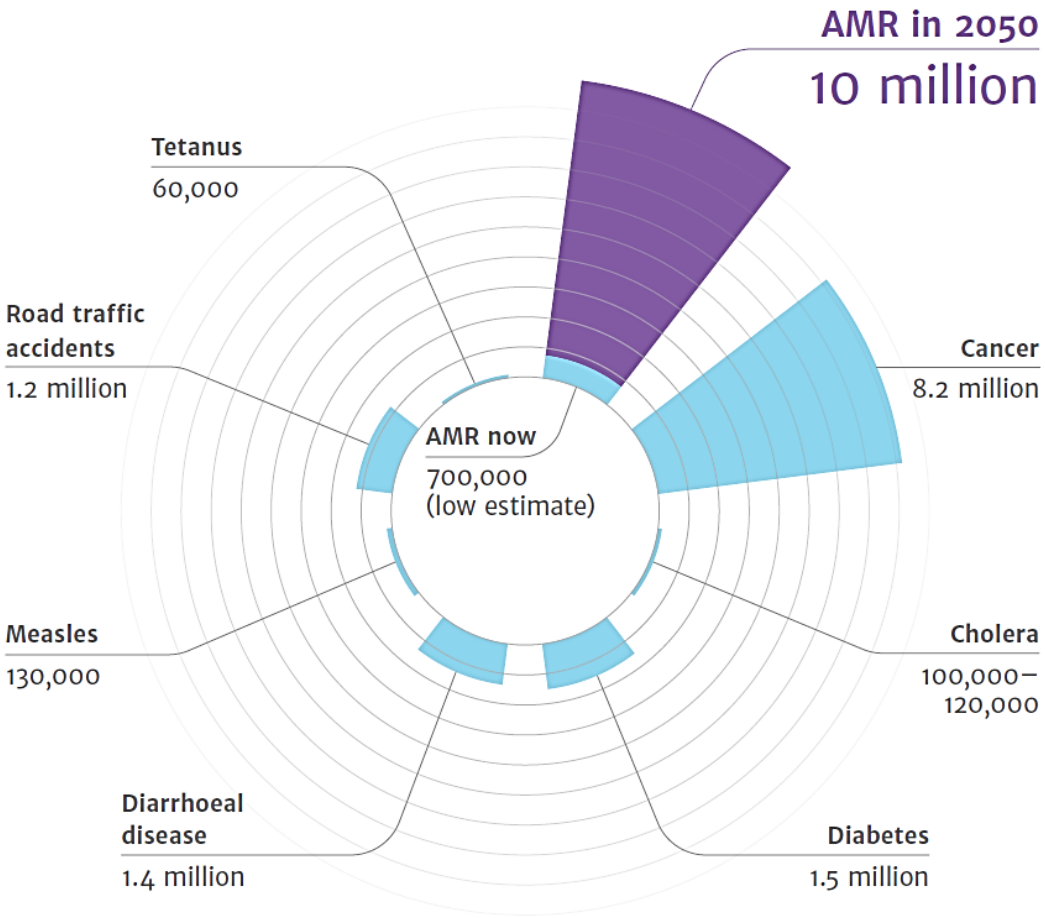
REPORT TO THE SECRETARY-GENERAL OF THE UNITED NATIONS

APRIL 2019

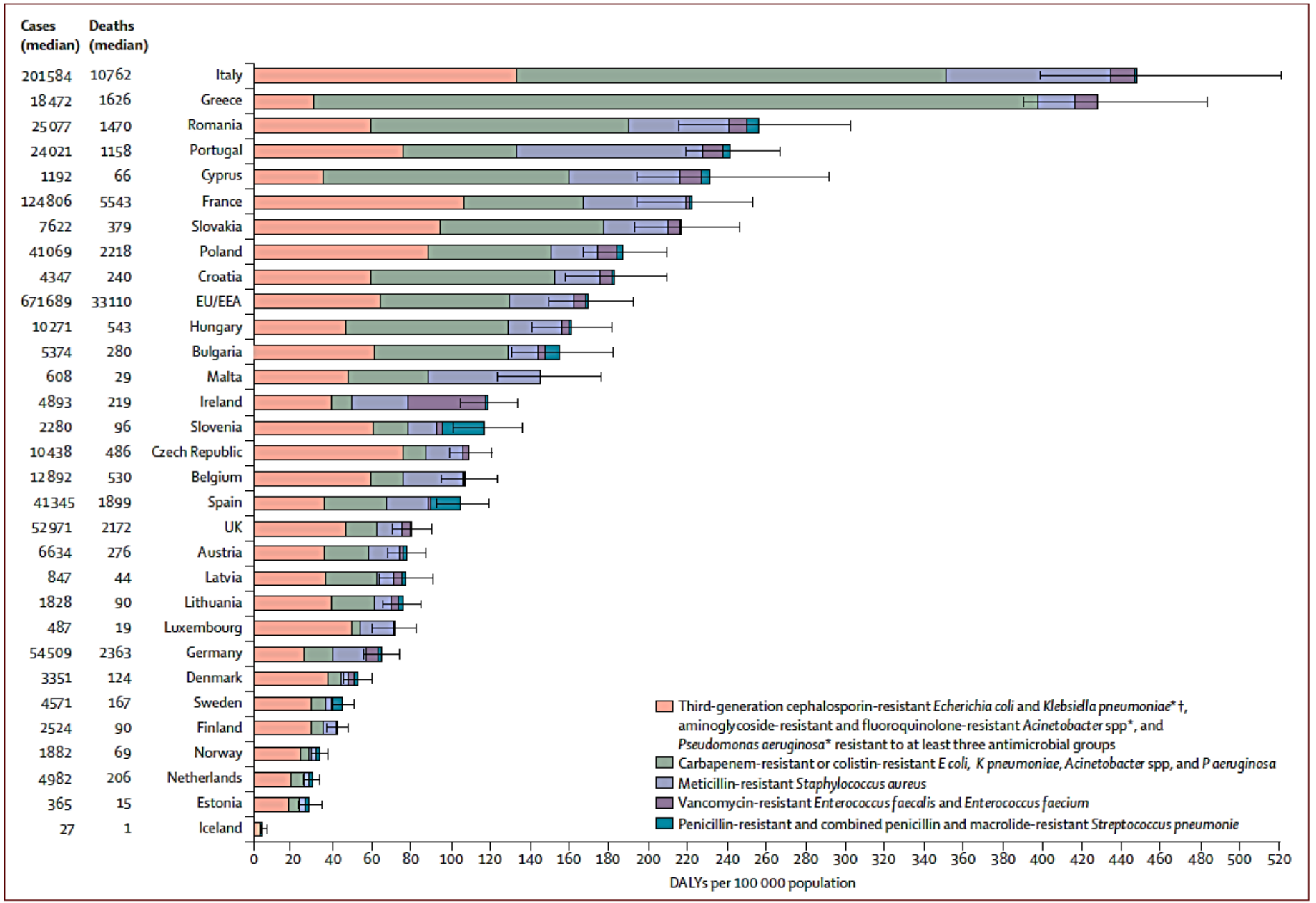
IACG | Interagency Coordination Group on Antimicrobial Resistance

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally



Attributable deaths and disability-adjusted life-years caused



Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and

Lancet Infect Dis 20
19: 56-

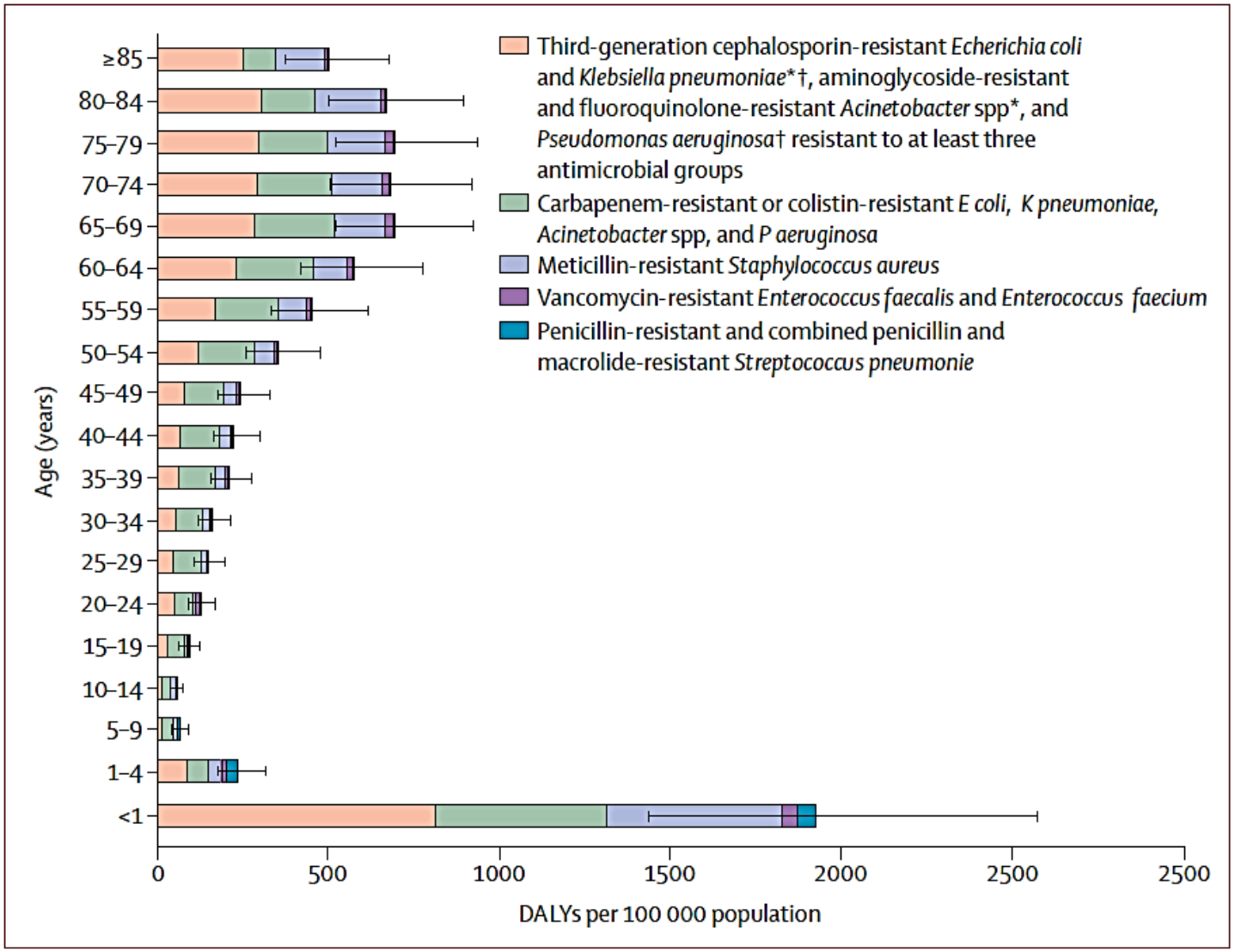
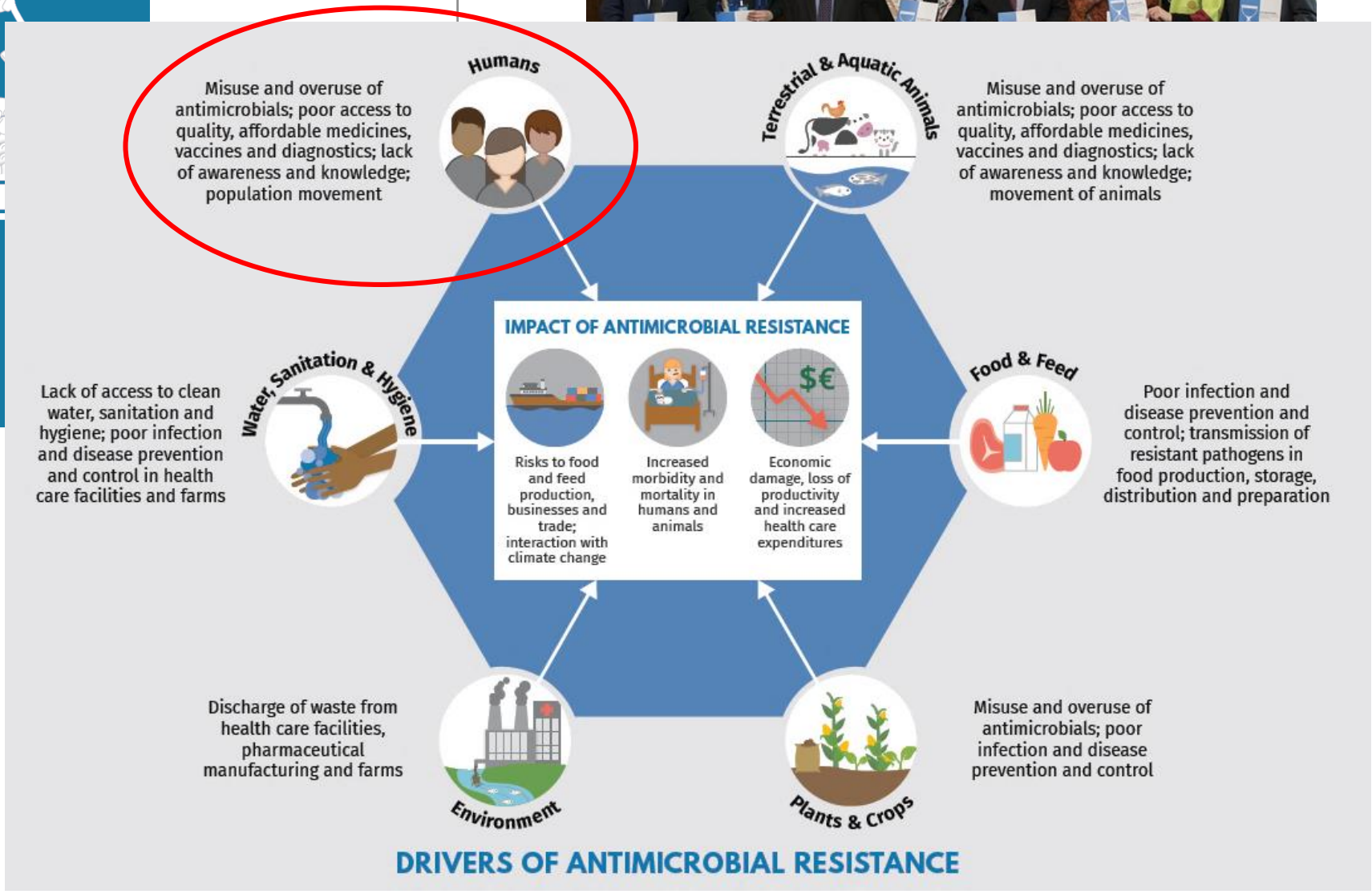


Figure 2: Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015

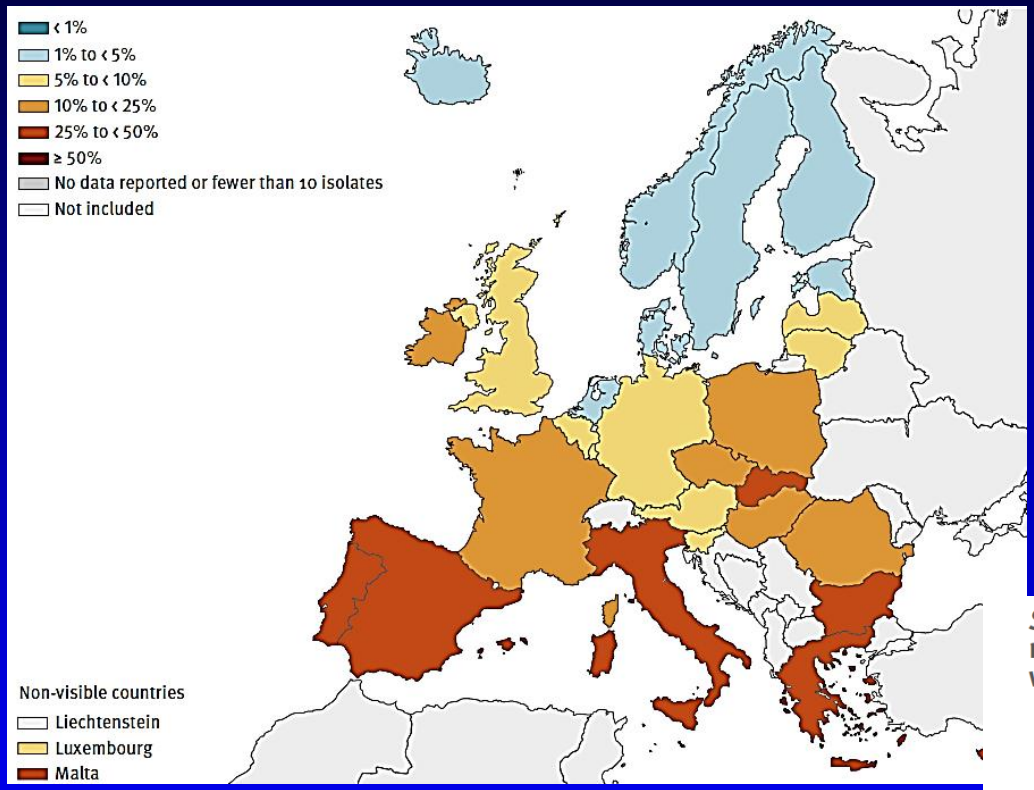
Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

	Median number of infections		Median number of attributable deaths		Factor increase in attributable deaths between 2007 and 2015
	2007	2015	2007	2015	
Third-generation cephalosporin-resistant *Escherichia coli**†	70 276 (63 113–77 778)	285 758 (246 318–328 828)	2139 (1901–2420)	8750 (7505–10 262)	4·12 (3·29–5·13)
Meticillin-resistant *Staphylococcus aureus*	112 782 (103 186–122 006)	143 947 (127 592–161 158)	5340 (4952–5723)	6810 (6096–7559)	1·28 (1·11–1·47)
Carbapenem-resistant *Pseudomonas aeruginosa*	17 972 (15 685–20 170)	59 529 (51 237–68 238)	1216 (1000–1469)	4008 (3235–4898)	3·29 (2·41–4·46)
Third-generation cephalosporin–resistant *Klebsiella pneumoniae** †	16 474 (15 097–17 825)	64 980 (58 360–72 048)	891 (830–950)	3508 (3197–3824)	3·95 (3·51–4·43)
Carbapenem-resistant *K pneumoniae*	2535 (2125–2952)	15 910 (13 352–18 377)	341 (288–404)	2094 (1779–2460)	6·16 (4·78–8·04)
Vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*	8277 (6699–9950)	15 917 (12 900–19 092)	538 (452–652)	1065 (874–1283)	1·95 (1·47–2·58)
Multidrug-resistant *P aeruginosa*‡	5603 (4796–6430)	8749 (7470–10 044)	357 (281–439)	556 (447–681)	1·55 (1·11–2·17)
Penicillin-resistant *Streptococcus pneumoniae*§	2183 (2033–2355)	2817 (2552–3104)	134 (126–143)	171 (159–184)	1·28 (1·15–1·42)
Penicillin-resistant and macrolide-resistant *S pneumoniae*¶	1916 (1782–2075)	2386 (2173–2648)	118 (110–126)	145 (135–158)	1·25 (1·12–1·40)
Carbapenem-resistant *E coli*	543 (442–647)	2616 (2283–2960)	29·2 (22·2–37·6)	141 (118–163)	4·76 (3·51–6·90)
Overall	239 238 (215 544–262 951)	602 609 (524 237–686 497)	11 144 (9999–12 407)	27 249 (23 544–31 471)	2·46 (1·01–3·00)

NO TIME TO WAIT:
SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS



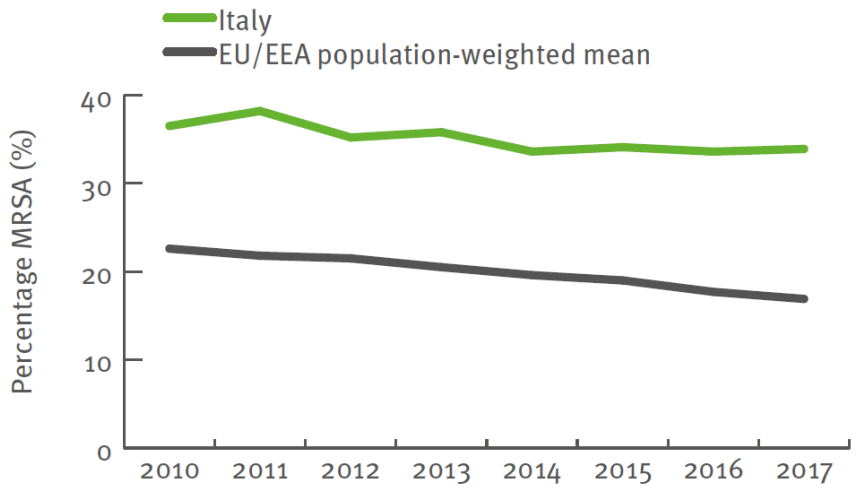
Staphylococcus aureus
Resistenza a Oxacillina/Meticillina (MRSA)



Italy

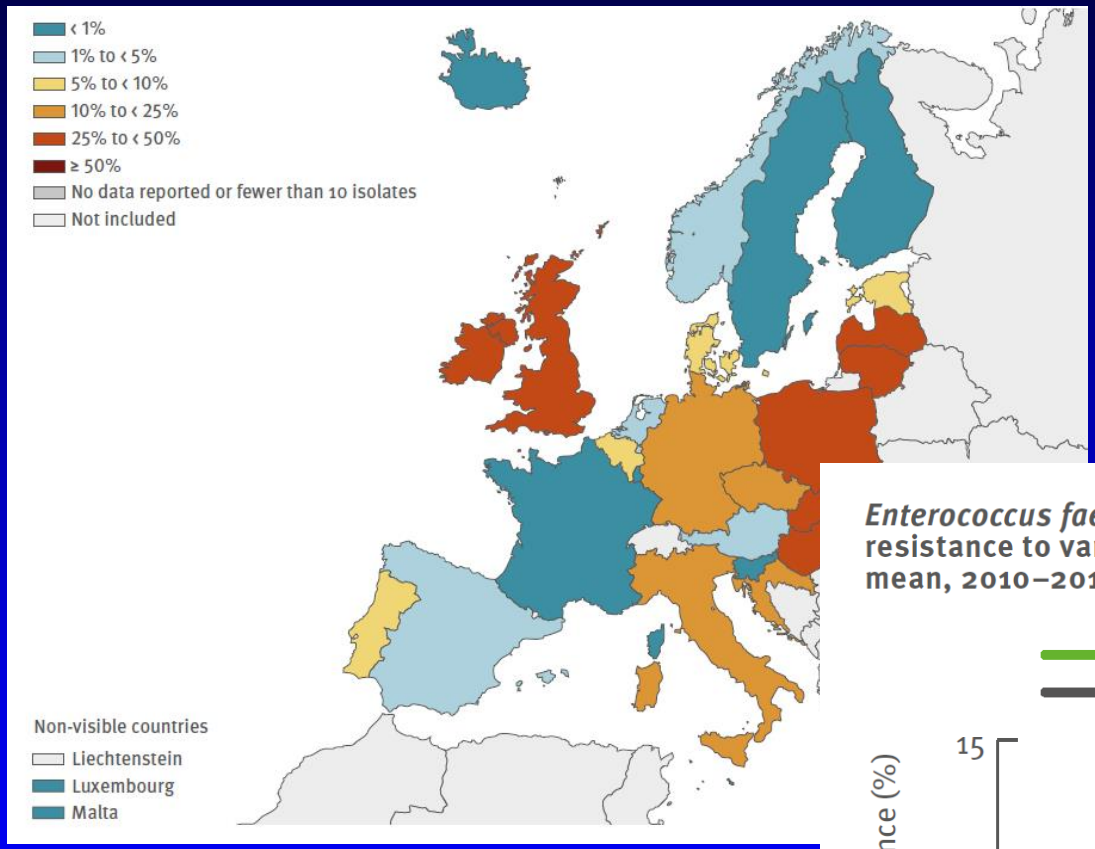
- 2011: 38.2%
- 2012: 35.2%
- 2013: 35.8%
- 2014: 33.6%
- 2015: 34.1%
- 2016: 33.6%
- 2017: 33.9%

***Staphylococcus aureus*. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), Italy and EU/EEA population-weighted mean, 2010–2017**



EARSS 2017

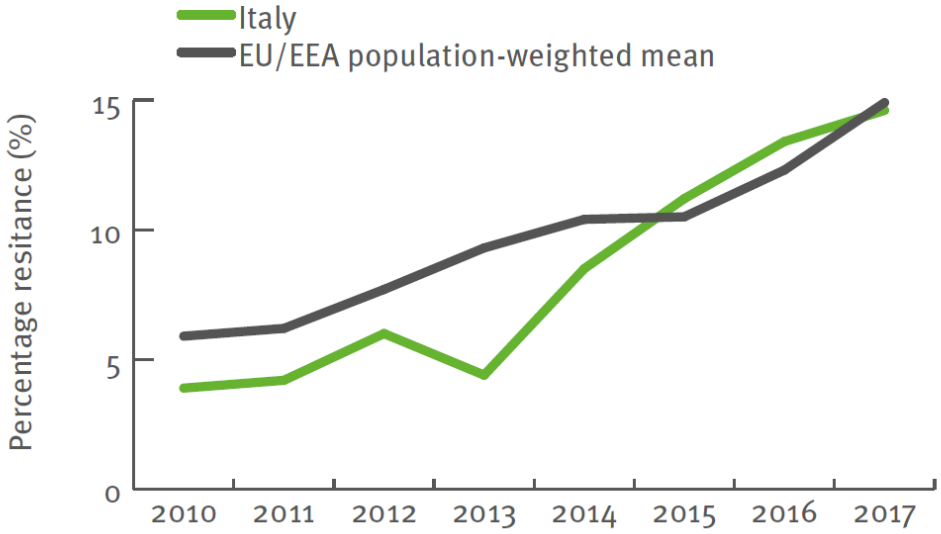
Enterococcus faecium
Invasive isolates with resistance to vancomycin



Italy

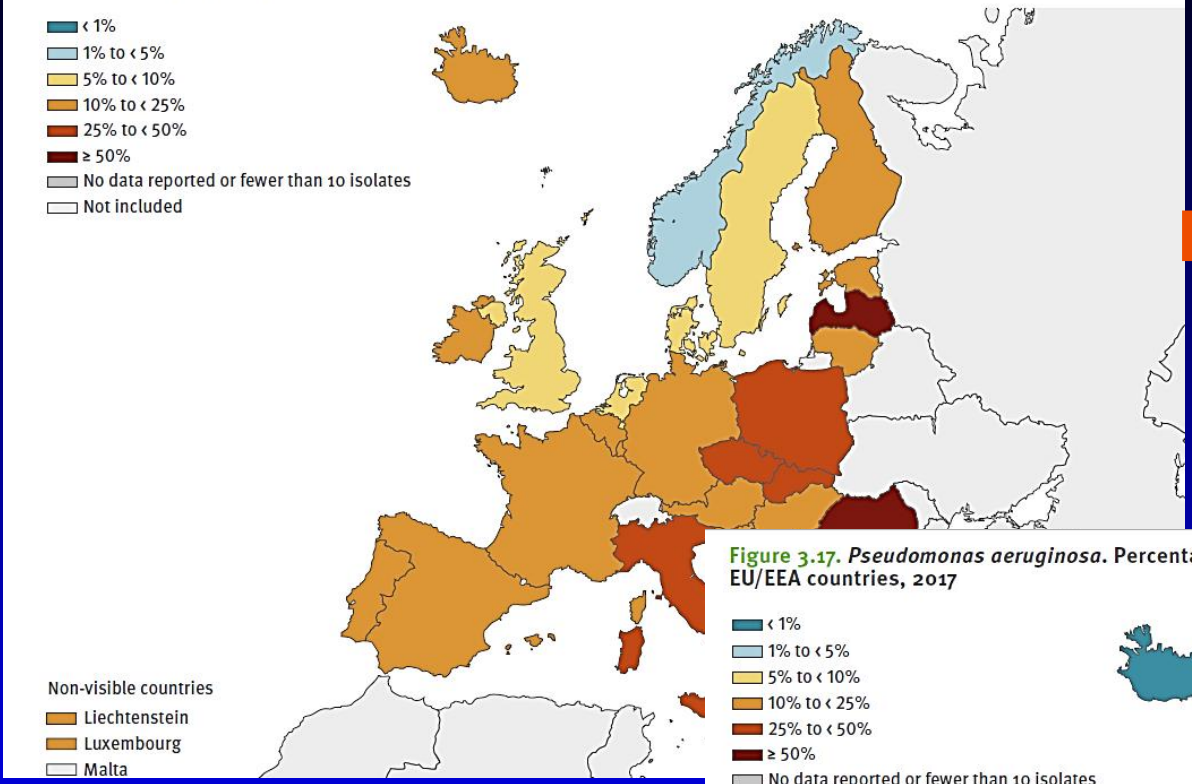
- 2013: 4.4%
- 2014: 8.5%
- 2015: 11.2%
- 2016: 13.4%

***Enterococcus faecium*. Percentage (%) of invasive isolates with resistance to vancomycin, Italy and EU/EEA population-weighted mean, 2010–2017**



EARSS 2017

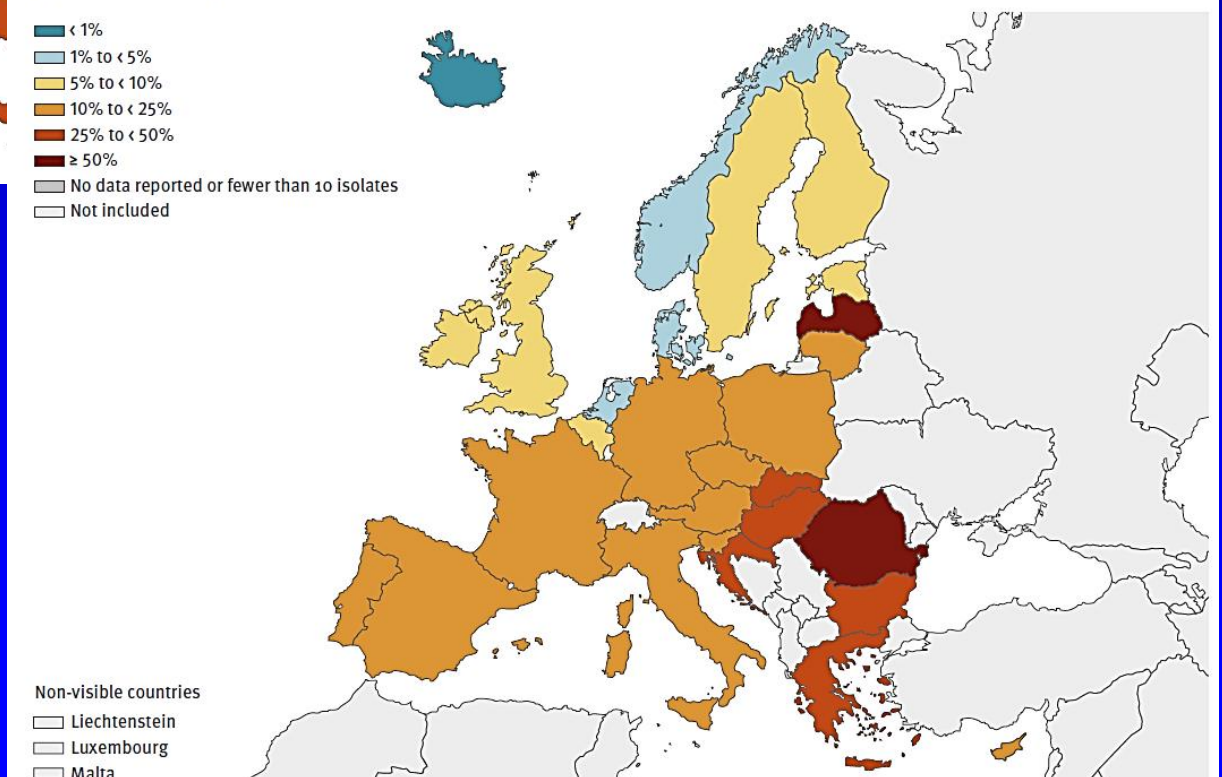
Figure 3.14. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2017



Pseudomonas aeruginosa

- 2017: 25.1%

Figure 3.17. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2017

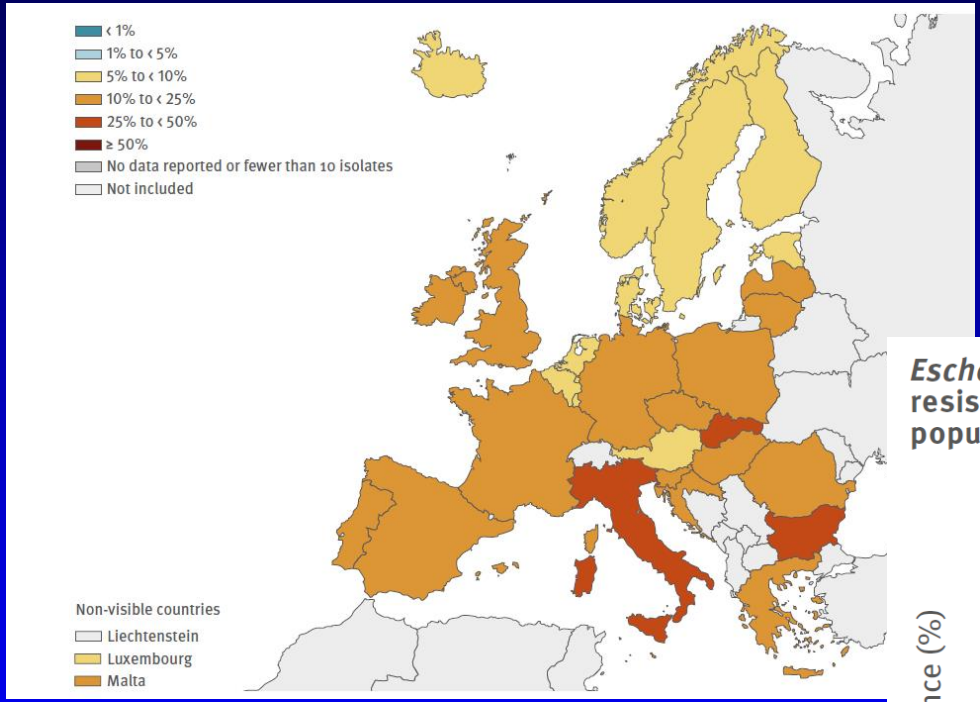


Italy

- 2013: 24.7%
- 2014: 23.2%
- 2015: 17.2%
- 2016: 19.1 %
- 2017: 18.0%

EARSS 2017

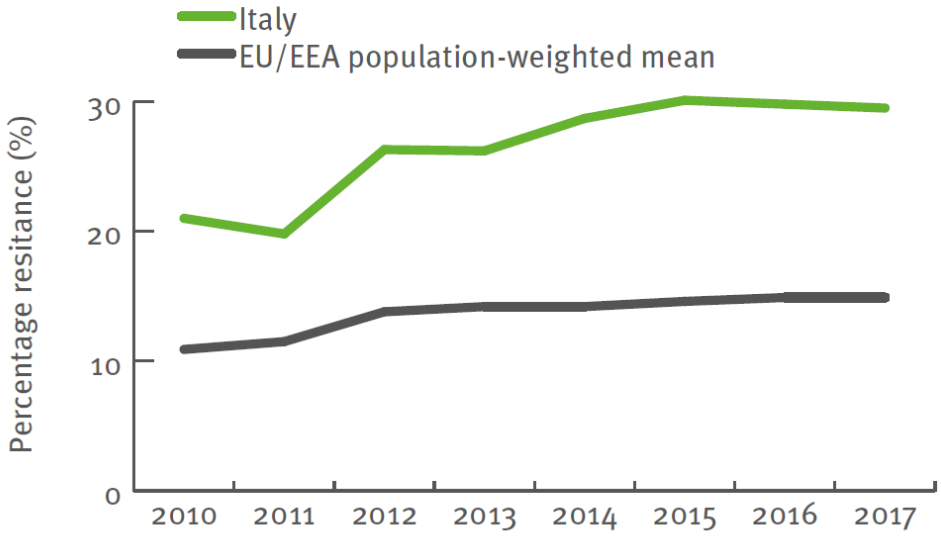
Escherichia coli
Invasive isolates with resistance to third-generation cephalosporins



Italy

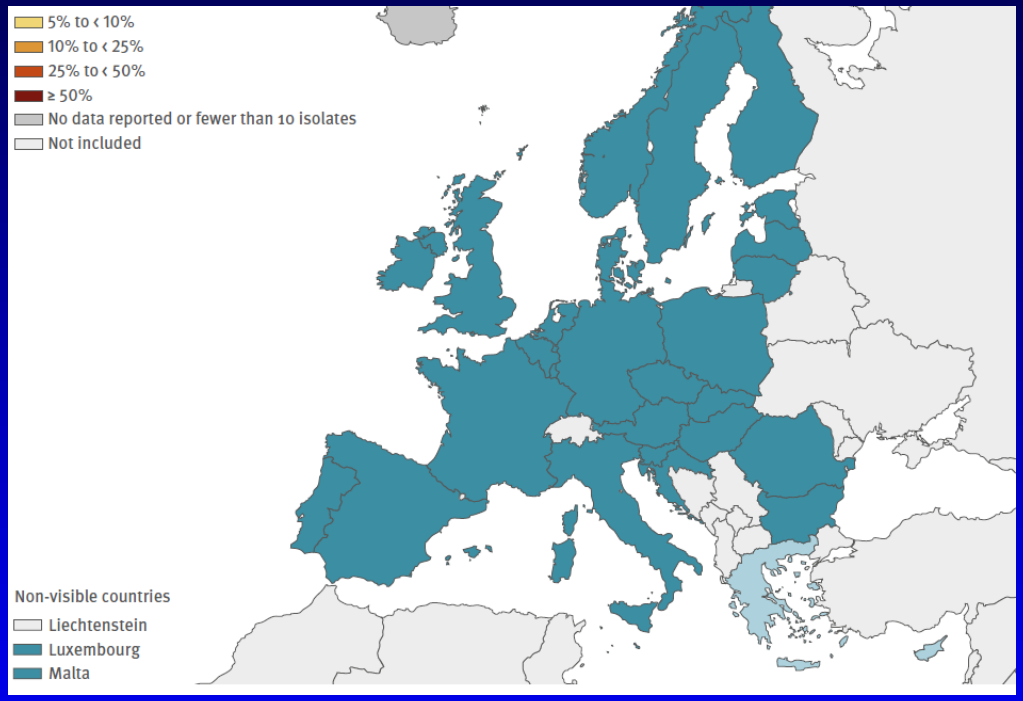
- 2014: 28.7%
- 2015: 30.1%

***Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, Italy and EU/EEA population-weighted mean, 2010–2017**



EARSS 2017

Escherichia coli
Invasive isolates with resistance to carbapenem



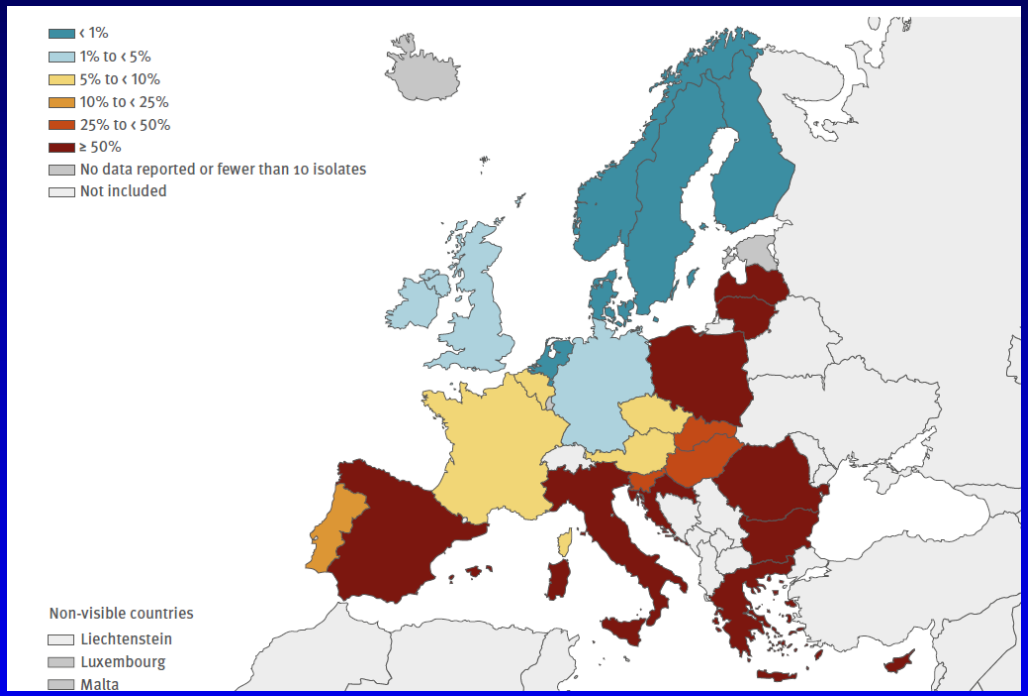
Italy

- 2014: 0.2%
- 2015: 0.2%
- 2016: 0.3%
- 2017: 0.3%

EARSS 2017

Acinetobacter spp.

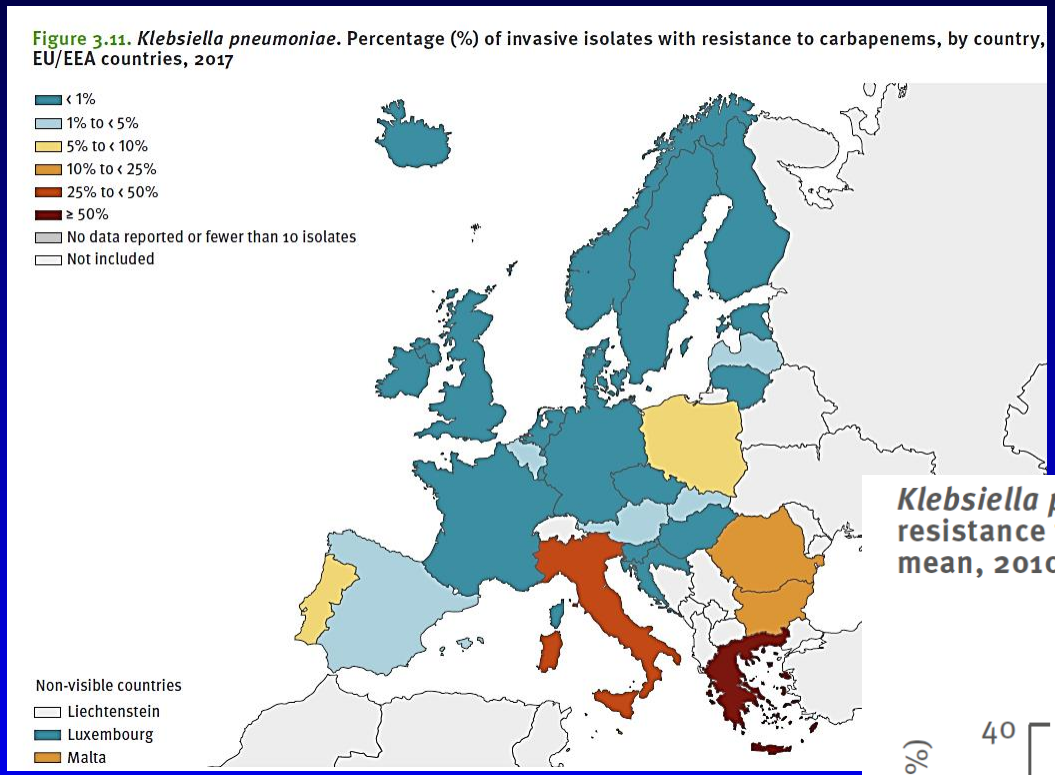
Invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems



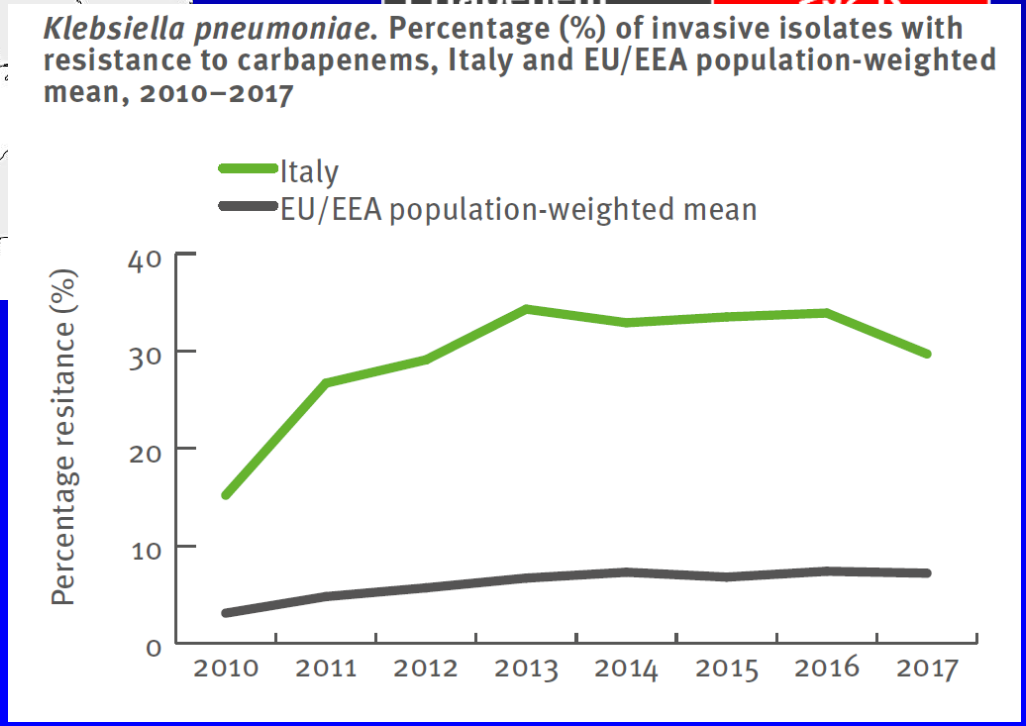
Antibiotico	
Ampicillina/sulbactam	I
Piperacillina/tazobactam	R
Cefepime	R
Cefotaxime	R
Ceftazidime	R
Imipenem	R
Meropenem	R
Amikacina	R
Gentamicina	R
Tetraciclina	R
Ciprofloxacina	R
Colistina	S

EARSS 2017

Klebsiella pneumoniae
Invasive isolates with resistance to carbapenems



Antibiotic	MIC mg/L
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R



EARSS 2017

Questi dati rispecchiano la realtà italiana ?

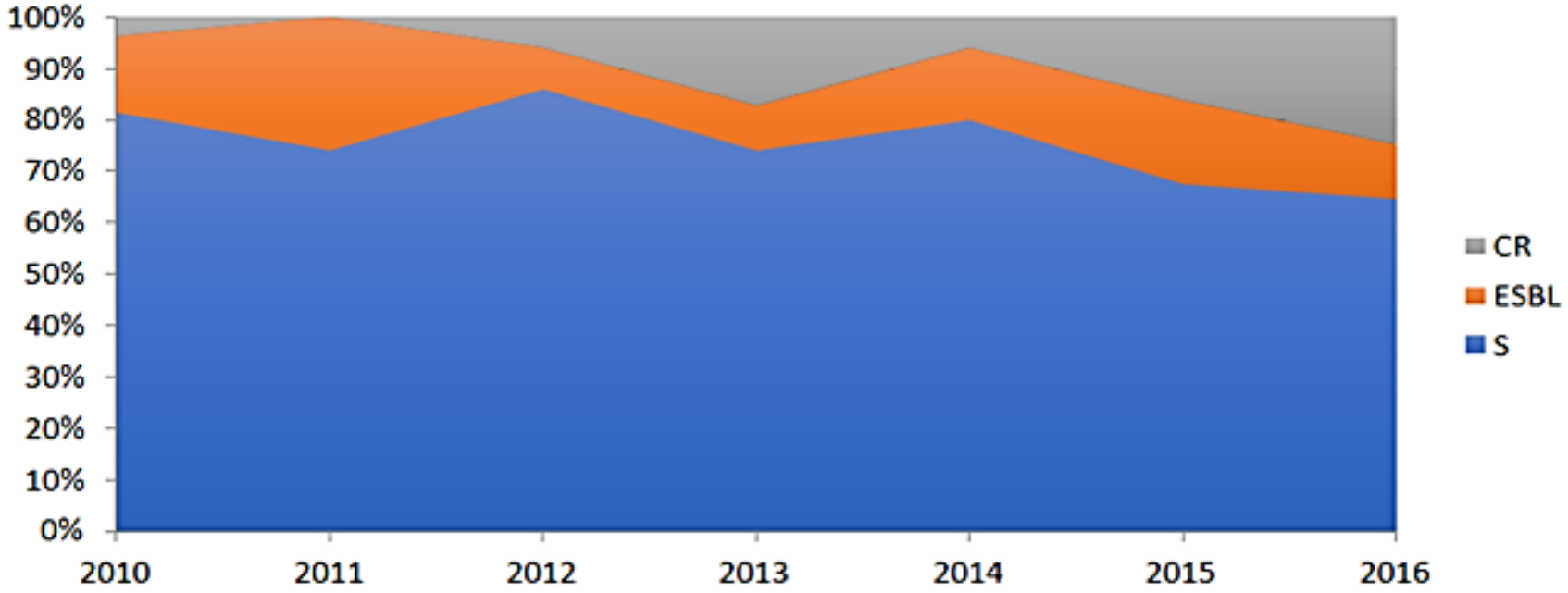
Coverage and representativeness of population, hospitals and isolates included in EARS-Net, Italy, 2014–2017

	2014	2015	2016	2017
Estimated national population coverage (%)	16	15	17	21
Population sample representativeness	Unknown	Unknown	Unknown	Medium
Hospital sample representativeness	Unknown	Unknown	Unknown	Unknown
Blood culture sets/1000 patient-days	31.6	Unknown	Unknown	Unknown
Isolate sample representativeness	Unknown	Unknown	Unknown	Unknown

AR-ISS - Sistema nazionale di sorveglianza sentinella dell'antibiotico-resistenza

- Differenze tra Regioni e tra Ospedali nella stessa regione
- Valori di percentuale di resistenza più alti al centro-nord per MRSA e per VR-*E.faecium,* al sud per *K. pneumoniae* resistente ai carbapenemi e multiresistenza per *E. coli* e *P. aeruginosa* al centro-sud

Klebsiella pneumoniae



Numero pazienti: 259
Numero batteriemie: 389

SPiNCAR -Supporto al Piano Nazionale di Contrasto Antibioticoresistenza

CS N°4/2019 – AL VIA SPiNCAR IL SISTEMA ITALIANO PER CONTRASTARE L'ANTIBIOTICORESISTENZA NELLE AZIENDE SANITARIE E NELLE COMUNITÀ: ISTITUTO, UNIVERSITÀ, ISTITUZIONI SANITARIE E REGIONI INSIEME NEL PIANO D'AZIONE

21 Marzo 2019 Comunicati Stampa

ISS, 21 marzo 2019

- Raccogliere dati per definire la situazione attuale nelle diverse realtà, tramite una piattaforma informatica, coordinata dall'Istituto Superiore di Sanità

- Identificare standard minimi e percorsi per incentivare miglioramenti continui, anche grazie alla collaborazione di esperti di vari enti, tra cui EMA e OCSE.

Cosa fare ?

In arrivo qualche nuovo antibiotico, ma soprattutto miglioramento della gestione della terapia antibiotica

Duval RE et al. Molecules 2019; 24, 3152

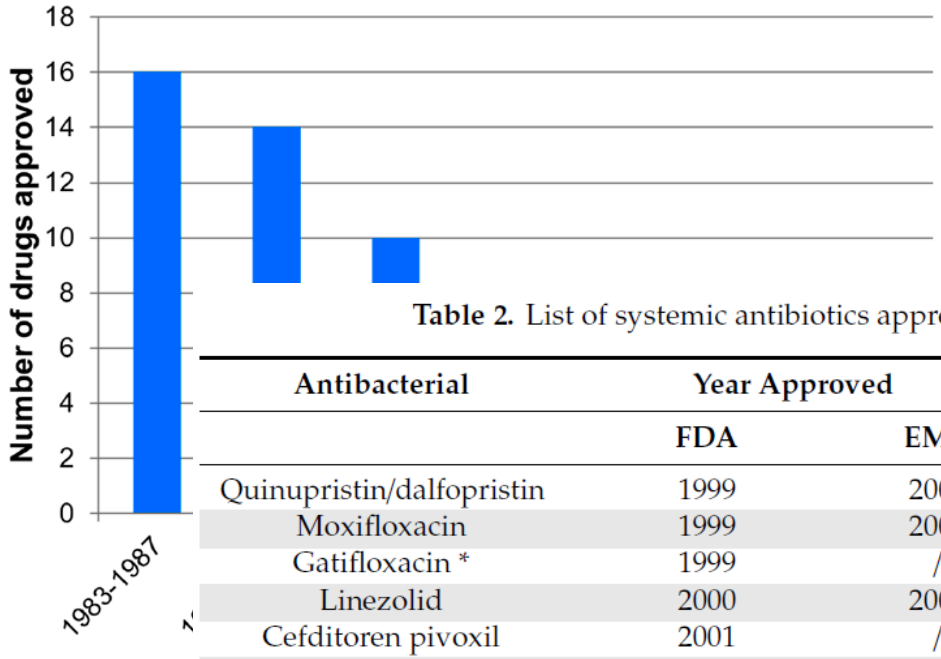


Figure 2. Evolution of the FD
completed with References [1

Table 2. List of systemic antibiotics approved by the FDA and EMA since 1999.

Antibacterial	Year Approved		Novel Mechanism?	Spectra
	FDA	EMA		
Quinupristin/dalfopristin	1999	2000	No	GPB
Moxifloxacin	1999	2001	No	GPB-GNB
Gatifloxacin *	1999	/	No	GPB-GNB
Linezolid	2000	2001	Yes	GPB
Cefditoren pivoxil	2001	/	No	GPB-GNB
Ertapenem	2001	2002	No	GNB-GPB
Gemifloxacin *	2003	/	No	GPB-GNB
Daptomycin	2003	2006	Yes	GPB
Telithromycin *	2004	2001	No	GPB
Tigecycline	2005	2006	Yes	GPB-GNB
Doripenem *	2007	2008	No	GNB-GPB
Telavancin	2009	2011	Yes	GPB
Ceftarolin fosamil	2010	2012	No	GPB-GNB
Ceftolozane-tazobactam	2014	2015	No	GNB-GPB
Tedizolid	2014	2015	No	GPB
Oritavancin	2014	2015	No	GPB
Dalbavancin	2014	2015	No	GPB
Ceftazidime-avibactam	2015	2016	No	GNB
Meropenem-vaborbactam	2017	2018	No	GPB-GNB
Delafloxacin	2017	/	No	GPB-GNB
Omadacycline	2018	/	No	GPB-GNB

Modified from [10] and completed with [11,12]. FDA: Food and Drug Administration; EMA: European Medicines Agency; *: withdraw from the market; /: not approved, so far, by EMA; GPB: Gram-positive bacteria; GNB: Gram-negative bacteria.

Summary of Systemic Novel Antibiotics against Gram-positive bacteria approved by FDA and/or EMA during last decade

Drug	Antibiotic class	Spectrum		
		MRSA	Vanco I staph	VRE/vanco R staph
Ceftaroline (Zinforo®)	Cephalosporin	X		
Ceftobiprole (Mabelio®)	Cephalosporin	X		
Telavancin //	Lipoglycopeptide	X	X	
Dalbavancin (Xydalba®)	Lipoglycopeptide	X		
Oritavancin *(Orbactiv®)	Glycopeptide	X	X	X
Tedizolid (Sivextro®)	Oxazolidinone	X	X	X
Delafloxacin (FDA)	Fluoroquinolone	X		
Omadacycline (FDA)	Tetracycline	X		?

// Withdrawn; *Not available in Italy

From multiple studies

Summary of Novel Antibiotics for the Treatment of Carbapenem-Resistant Gram-negative Bacilli

Antibiotic class	Drug	CRE			MDR *Pseudomonas*		MDR *Acinetobacter*
		KPC	Oxa48	MBL	MDR	MBL	
Ceph + BLI	Ceftolozane tazobactam (Zerbaxa®)				X		
	Ceftazidime- avibactam (Zavicefta®)	X	X		X		
	Ceftaroline-Avibactam (phase I)	X	X		?		
Carbapenem + BLI	Imipenem- relebactam (FDA)	X					
	Meropenem-vaborbactam (FDA, EMA)	X					
Monobactams + BLI	Aztreonam-avibactam (phase III)	X	X	X	X	X	
Aminoglycosides	Plazomicin (FDA)	X	X	X	X	X	?
Tetracyclines	Eravacycline (FDA)	X	X	X			X
	Omadacycline (FDA)	X	X	X			X
Cephalosporins	Cefiderocol (FDA, EMA)	X	X	X	X	X	X

From multiple studies

RAPID RISK ASSESSMENT

Regional outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacteriaceae, Italy, 2018–2019

4 June 2019

- Italy reported an outbreak of NDM-producing CRE affecting 7 hospitals in the northwestern area of Tuscany, with 350 cases reported between November 2018-May 2019.
- Among these cases, there were 50 with bloodstream infection, 43 with isolation in the urine, 15 with isolation in respiratory tract samples and 242 with gastrointestinal tract carriage.

- The change in the type of carbapenemase further reduces treatment options because NDM-producing CRE are not susceptible to some of the new beta-lactam/beta-lactamase inhibitor combinations such as ceftazidime-avibactam and meropenem-vaborbactam.
- The isolates are resistant to aminoglycosides but retain susceptibility to fosfomycin and colistin

Raccomandazioni per le strategie terapeutiche per le infezioni da batteri resistenti ai carbapenemi

- Combinazione di più molecole:
  - Vecchie molecole come aminoglicosidi, COLISTINA, tigeciclina, FOSFOMICINA, Minociclina
  - Nuove molecole
- Ottimizzazione della durata del trattamento per fare in modo che duri il meno possibile ma con dosi corrette
- Migliorare la capacità diagnostica

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

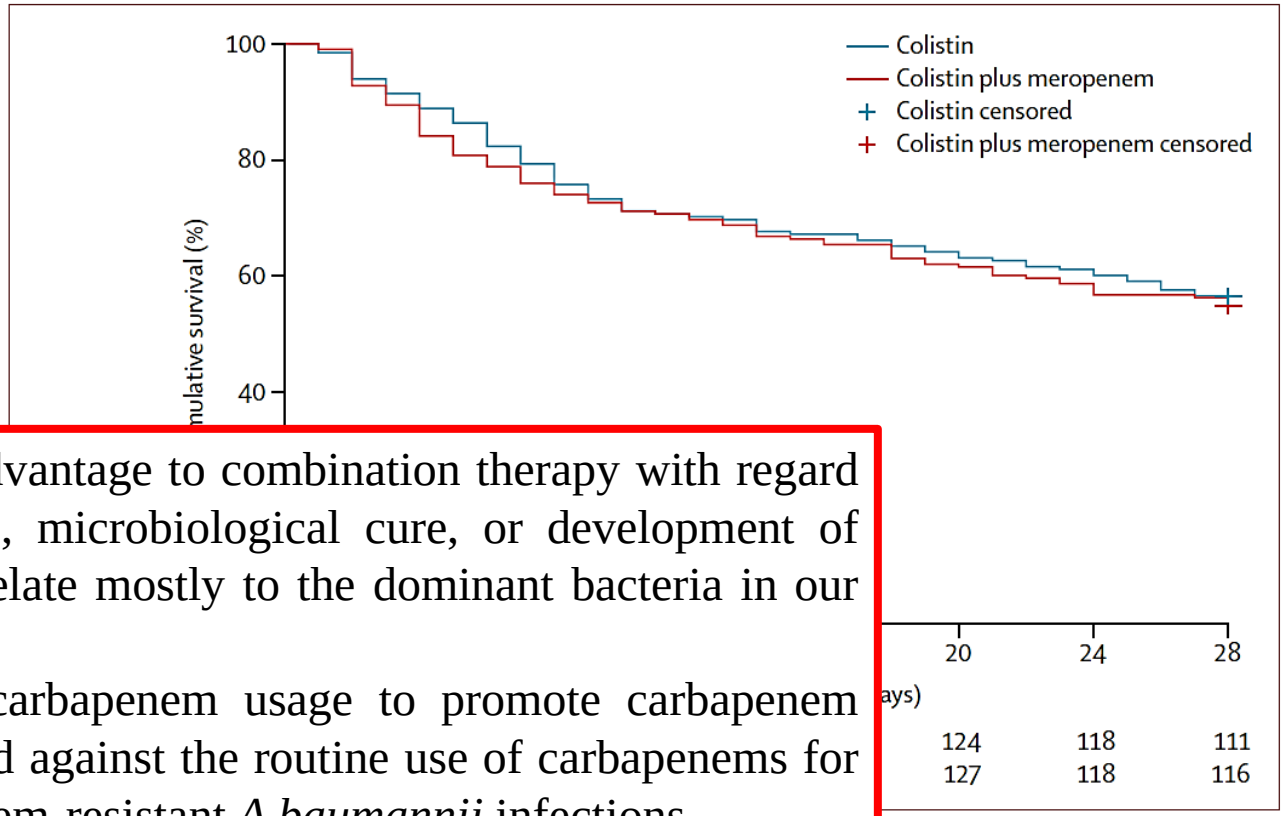
Summary

Background Colistin–carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria.

Methods A randomised controlled superiority trial was done in six

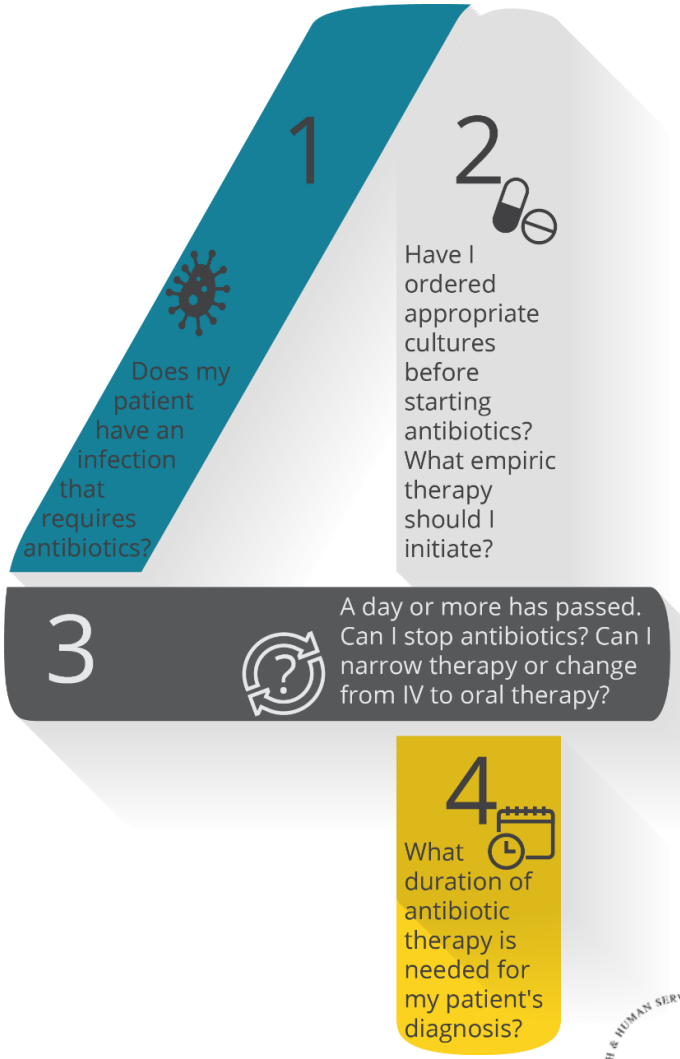
Lancet Infect Dis 2018; 18: 391–400

Published Online February 15, 2018



- We did not observe an advantage to combination therapy with regard to survival, clinical cure, microbiological cure, or development of resistance. Our results relate mostly to the dominant bacteria in our cohort, *A baumannii*.
- Given the potential of carbapenem usage to promote carbapenem resistance, we recommend against the routine use of carbapenems for the treatment of carbapenem-resistant *A baumannii* infections..

The Four Moments of Antibiotic Decision-Making



1. Does my patient have an infection that requires antibiotics?

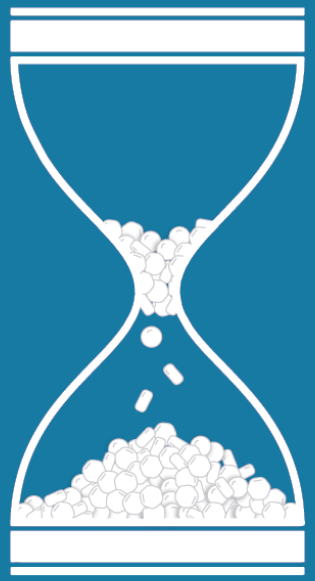
2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?

3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?

4. What duration of antibiotic therapy is needed for my patient's diagnosis?

AHRQ Agency for Healthcare Research and Quality

JOHNS HOPKINS MEDICINE



NO TIME TO WAIT:
SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS

ONE HEALTH RESPONSE TO ANTIMICROBIAL RESISTANCE

Humans

Food & Feed

Plants & Crops

Environment

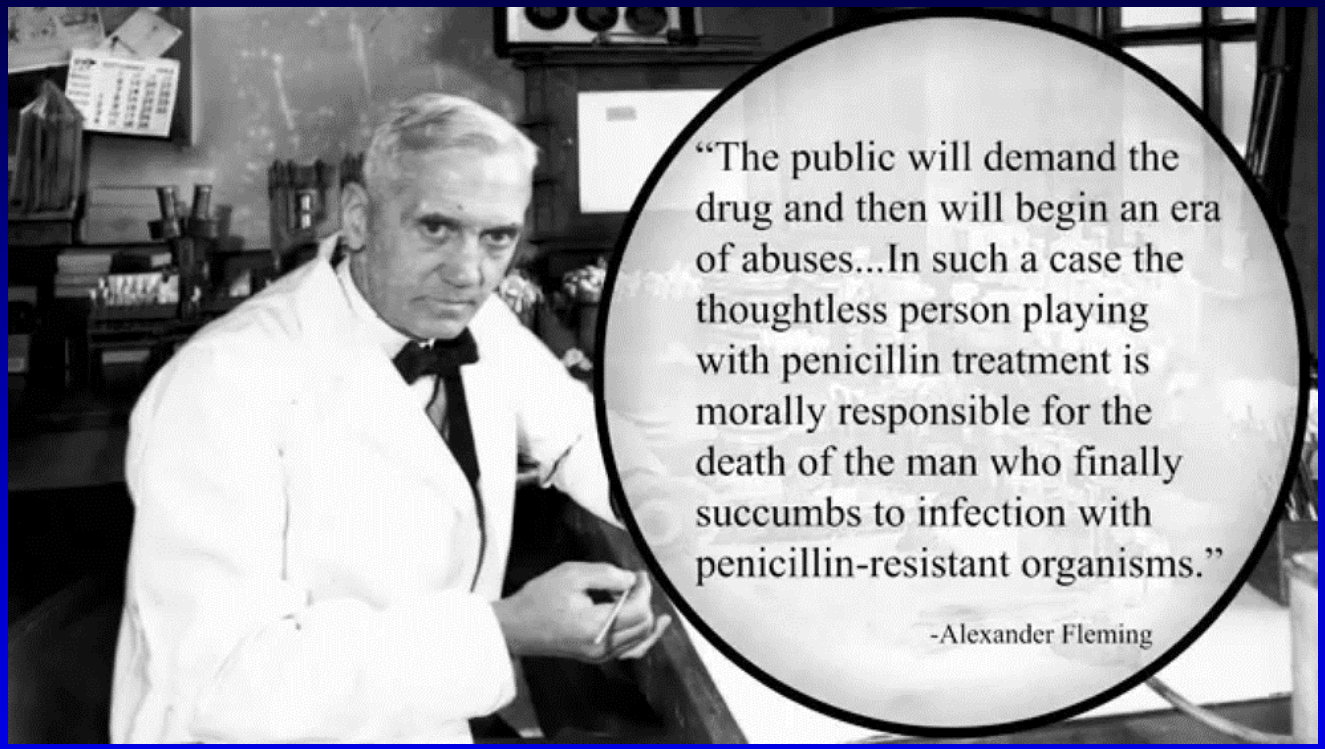
Terrestrial & Aquatic Animals

Antimicrobial resistance is a global crisis. There is no time to wait.
A sustained One Health response with a shared vision and goals is essential to tackle antimicrobial resistance and achieve the Sustainable Development Goals.

Interagency Coordination Group on Antimicrobial Resistance Recommendations

- ACCELERATE PROGRESS IN COUNTRIES
- INNOVATE TO SECURE THE FUTURE
- COLLABORATE FOR MORE EFFECTIVE ACTION
- INVEST FOR A SUSTAINABLE RESPONSE
- STRENGTHEN ACCOUNTABILITY AND GLOBAL GOVERNANCE

SUSTAINABLE DEVELOPMENT GOALS



Grazie

d.dallagasperina@uninubria.it