I nuovi antibiotici per il trattamento delle infezioni da multiresistenti

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World Health Organization

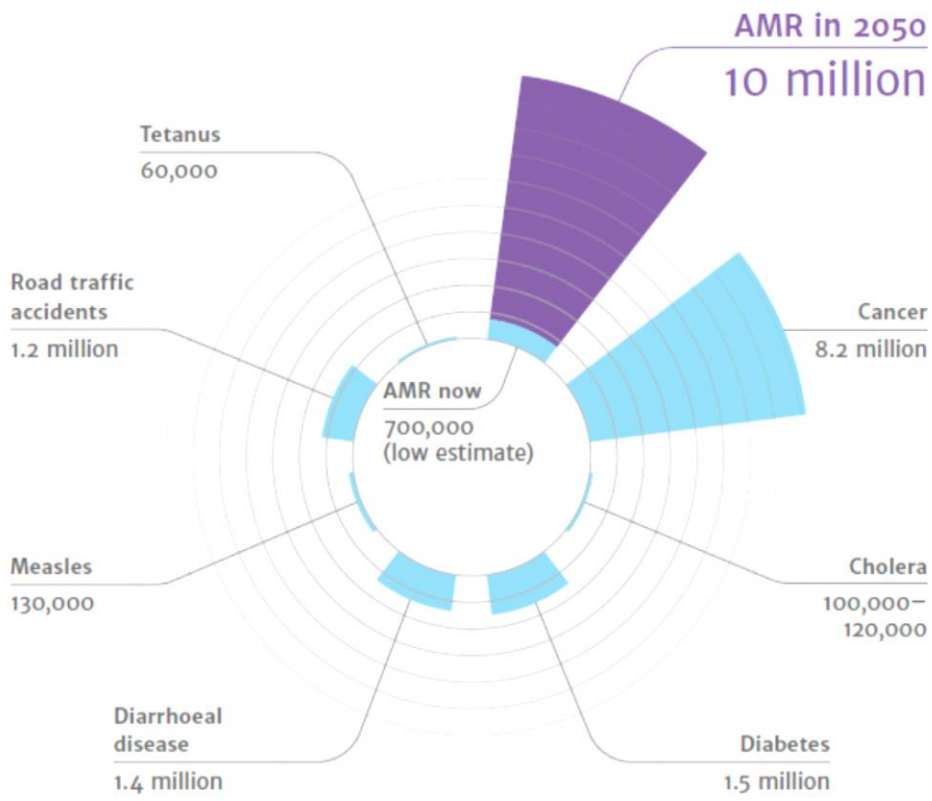
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS

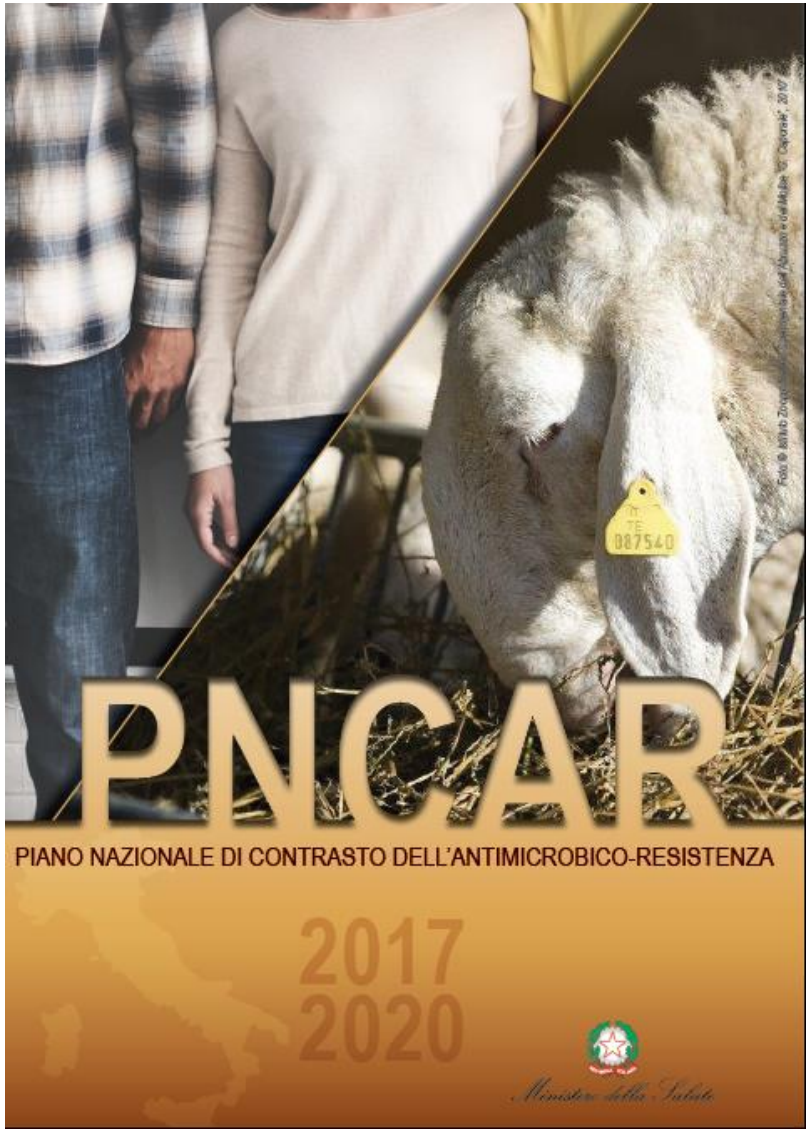
THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2016

DEATHS ATTRIBUTABLE TO AMR EVERY YEAR




PNCAR
PIANO NAZIONALE DI CONTRASTO DELL'ANTIMICROBICO-RESISTENZA
2017
2020
Ministero della Salute

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

Lancet Infect Dis 2018

Published Online
November 5, 2018

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

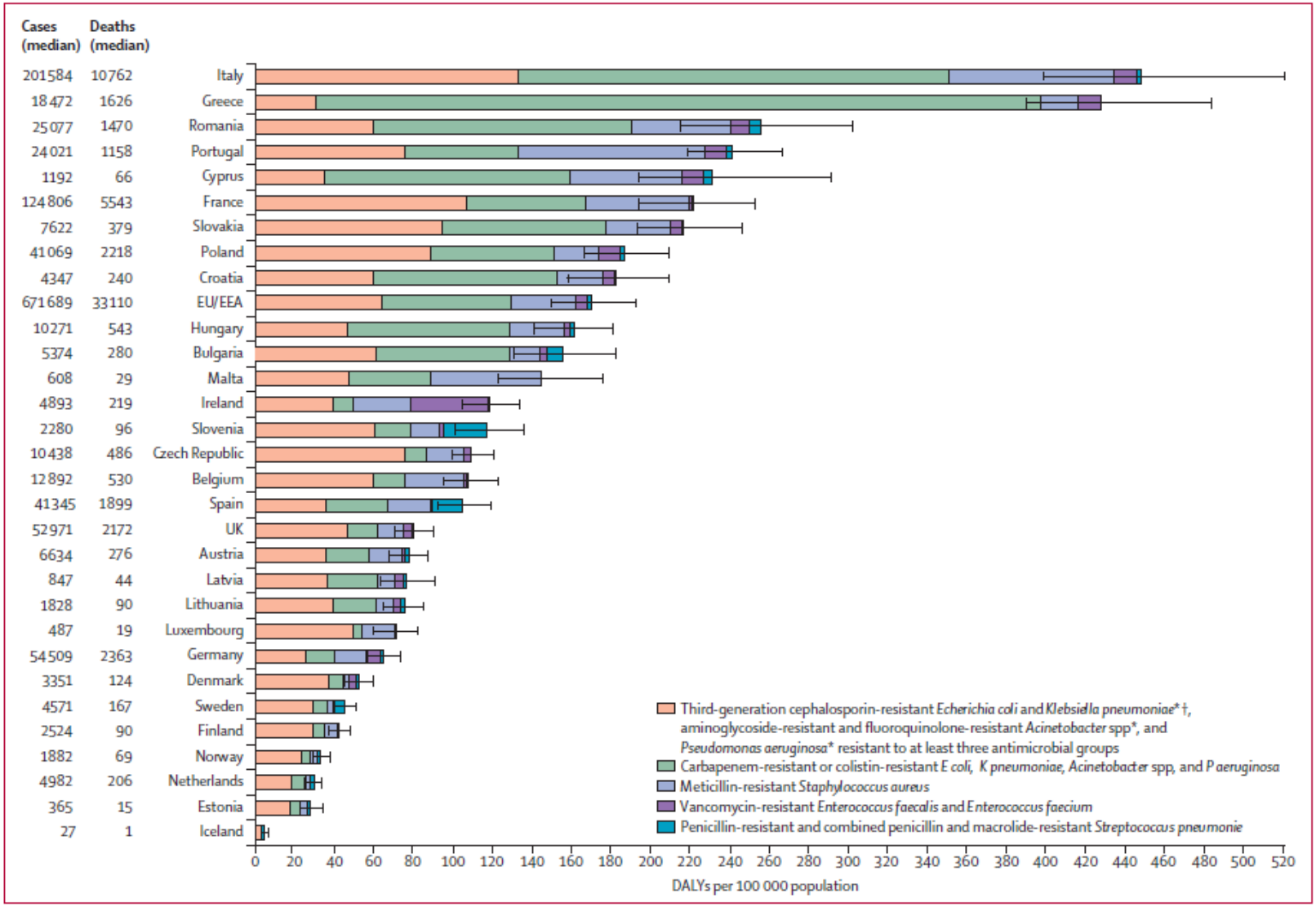
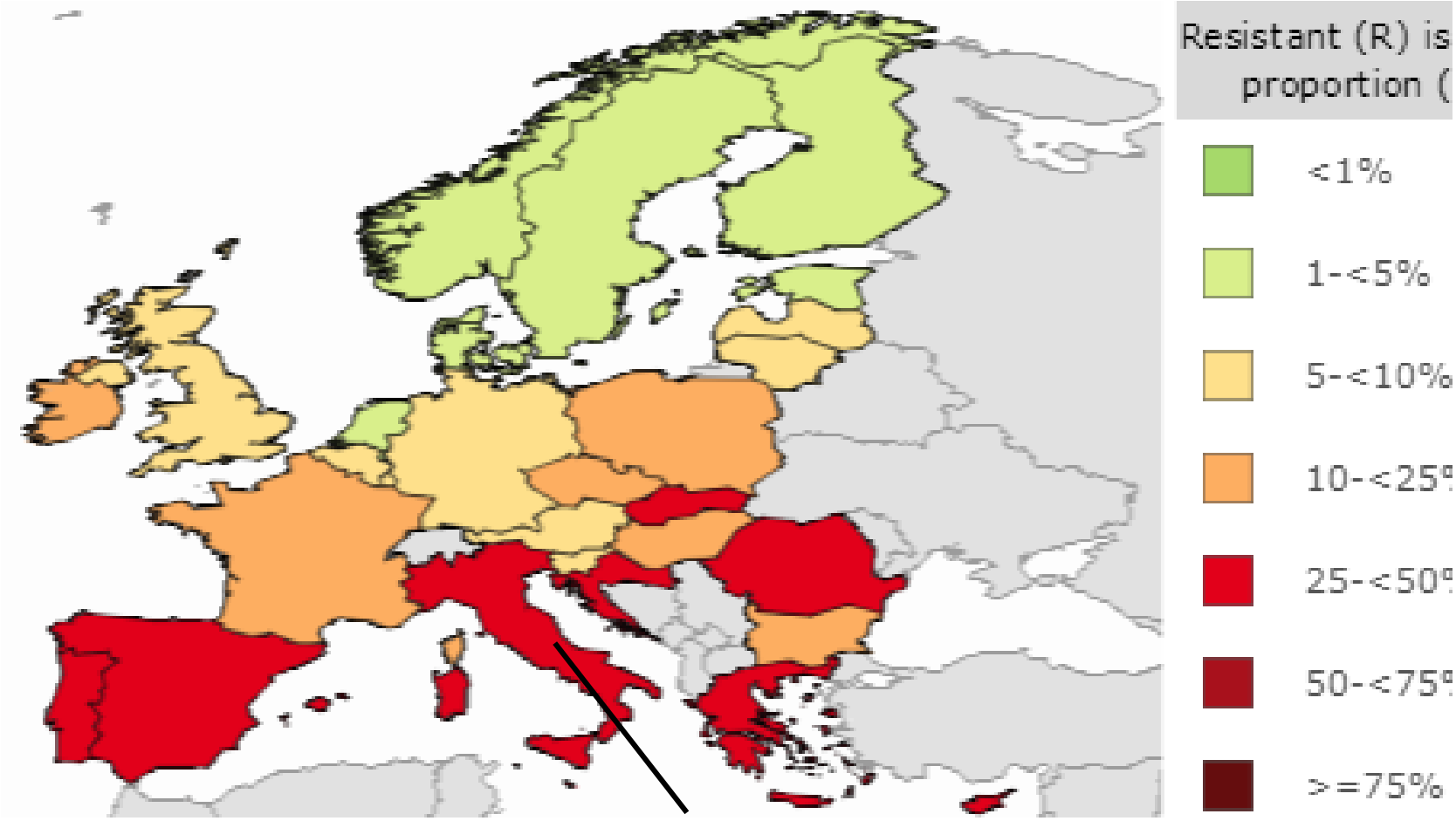


Figure 3: **Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015**

Error bars are 95% uncertainty intervals. Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALY rates are age-standardised to limit the effect of demographic differences across countries; numbers of cases and deaths are not age-standardised. DALYs=disability-adjusted life-years. *Excludes those re colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance produced an extended-spectrum β-lactamase.[9]

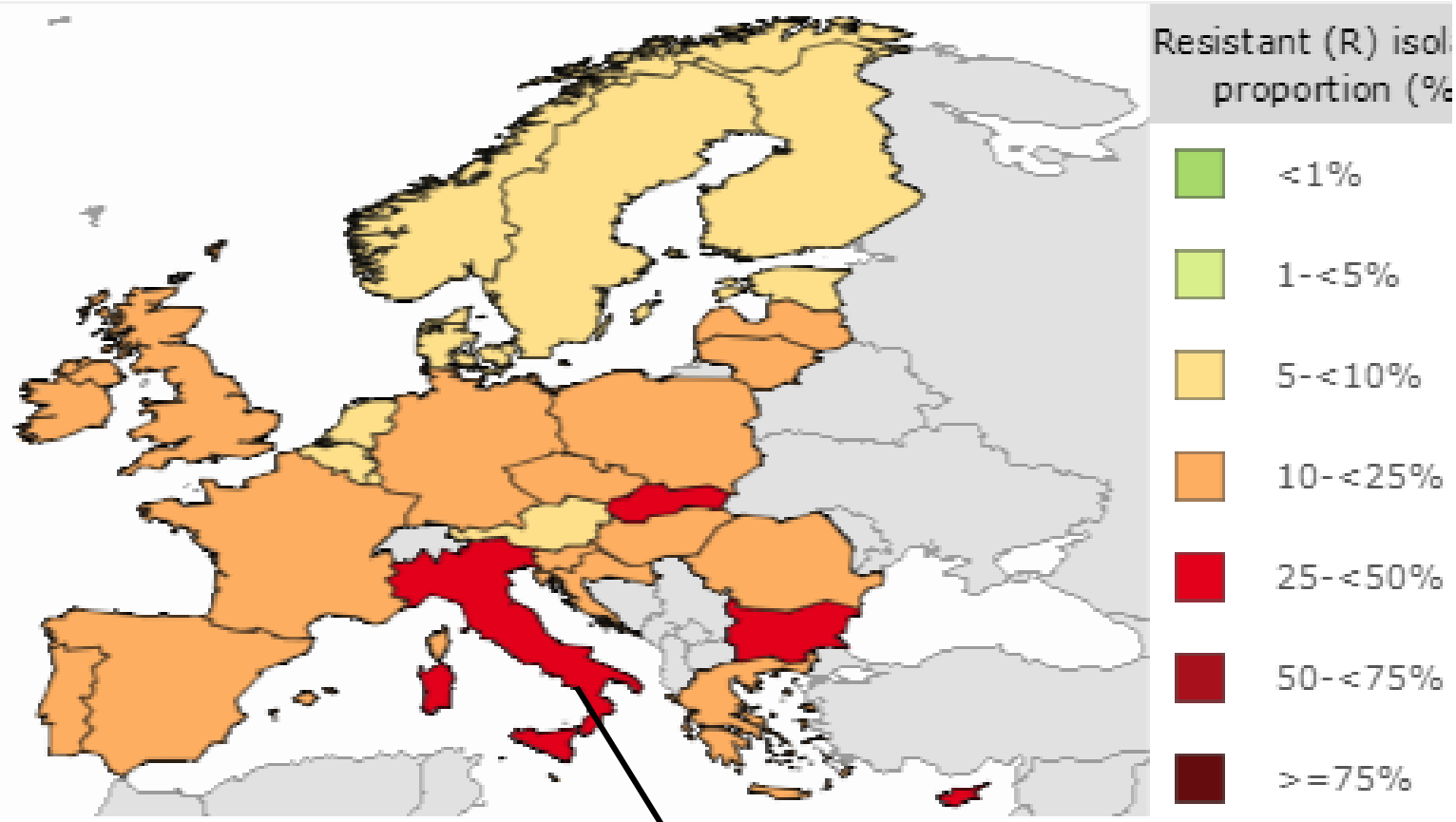
Lancet Infect Dis 2018

Published Online November 5, 2018



MRSA 33,9%

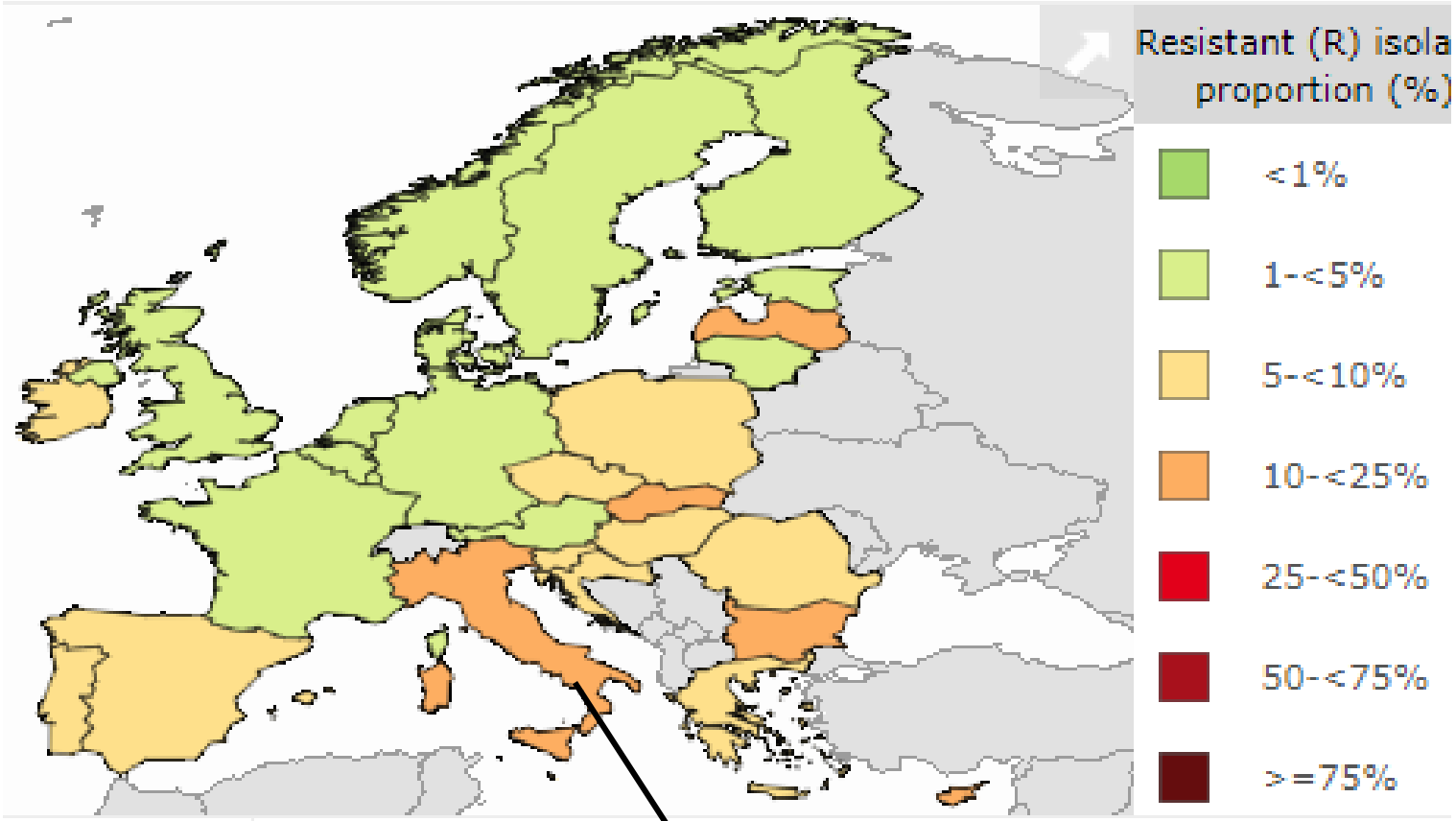
Data from the ECDC Surveillance Atlas - Antimicrobial resistance 2017



E.coli 3G cephalo

29.5%

Data from the ECDC Surveillance Atlas - Antimicrobial resistance 2017

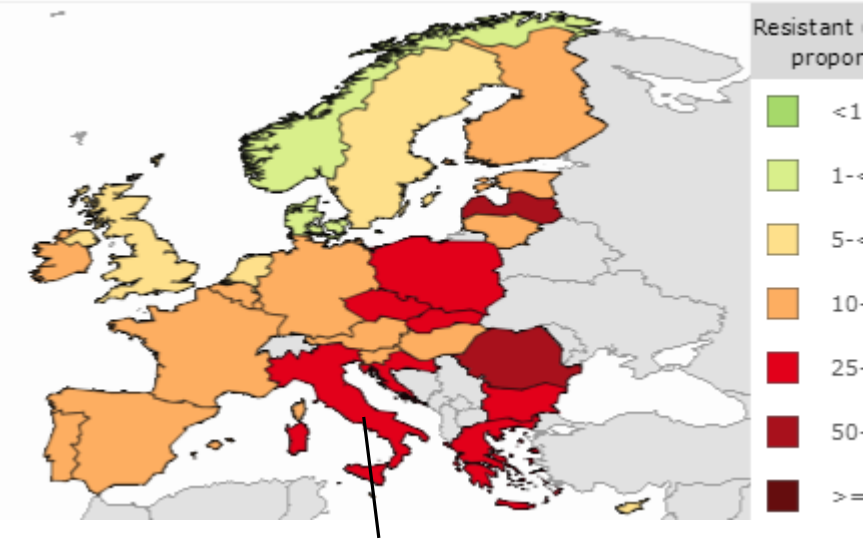


E.coli 3GC+FQ+AG

13.7%

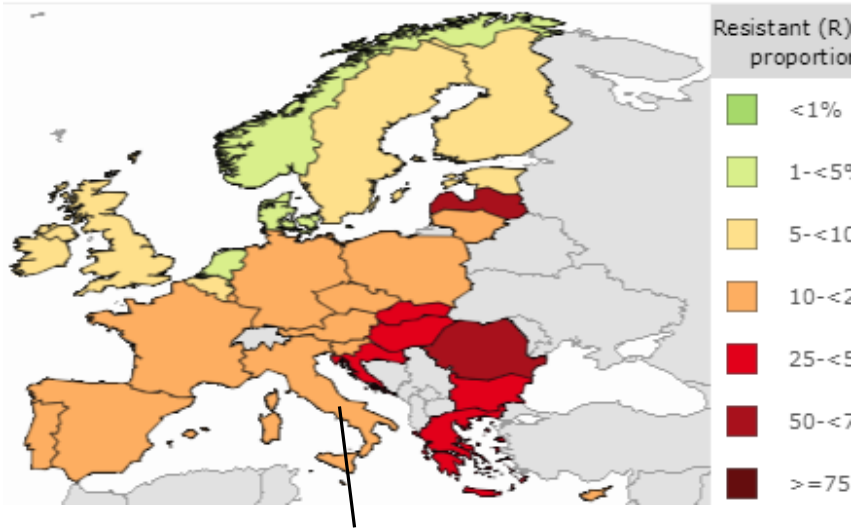
13.7%

Data from the ECDC Surveillance Atlas - Antimicrobial resistance 2017



25.1%

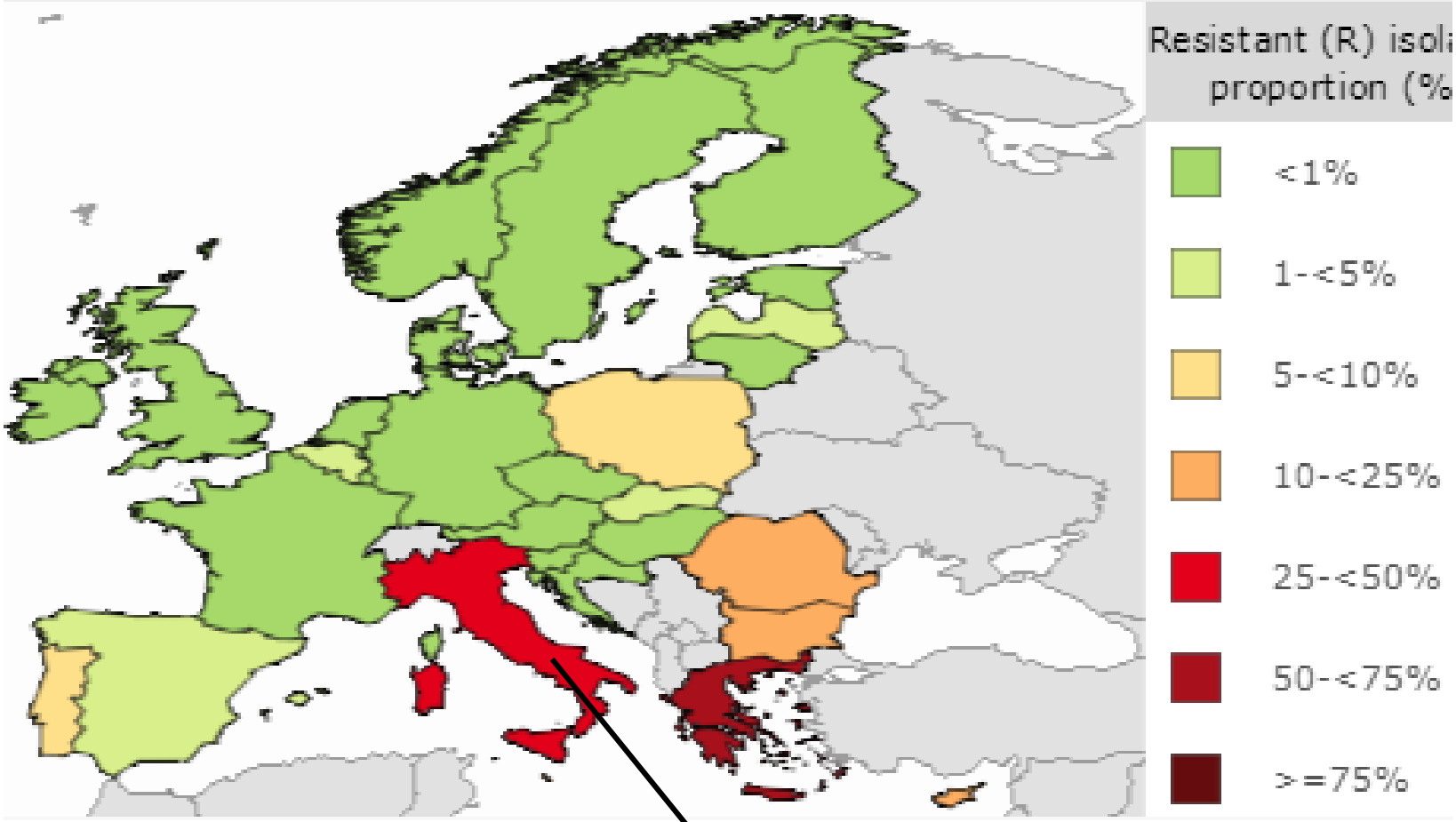
Pseudomonas aeruginosa FQ



19.9%

Pseudomonas aeruginosa Carba

Data from the ECDC Surveillance Atlas - Antimicrobial resistance 2017



Klebsiella pneumoniae CR

29.7%

Data from the ECDC Surveillance Atlas - Antimicrobial resistance 2017

VIRULENCE
2016, VOL. 7, NO. 3, 341–352
http://dx.doi.org/10.1080/21505594.2015.1132142

Taylor & Francis
Taylor & Francis Group

REVIEW

Bloodstream infections in older patients

Dafna Yahav[a,b], Noa Eliakim-Raz[a,b], Leonard Leibovici[b,c], and Mical Paul[b,d]

- Più del 50% dei casi di infezione nosocomiale del torrente ematico (BSI) in pazienti > 65 anni
- in questa popolazione la prognosi è più severa, con una mortalità a 30 giorni fino al 50%

LE INFEZIONI NOSOCOMIALI DEL TORRENTE EMATICO NEL GIOVANE ADULTO, NELL'ANZIANO E NEL GRANDE ANZIANO: DIFFERENZE EPIDEMIOLOGICHE, GESTIONALI E DI MORTALITÀ.

F Giovannenze, R Murri, M Camici, C Palazzolo, F Taccari, G Scoppettuolo, R Cauda, M Fantoni

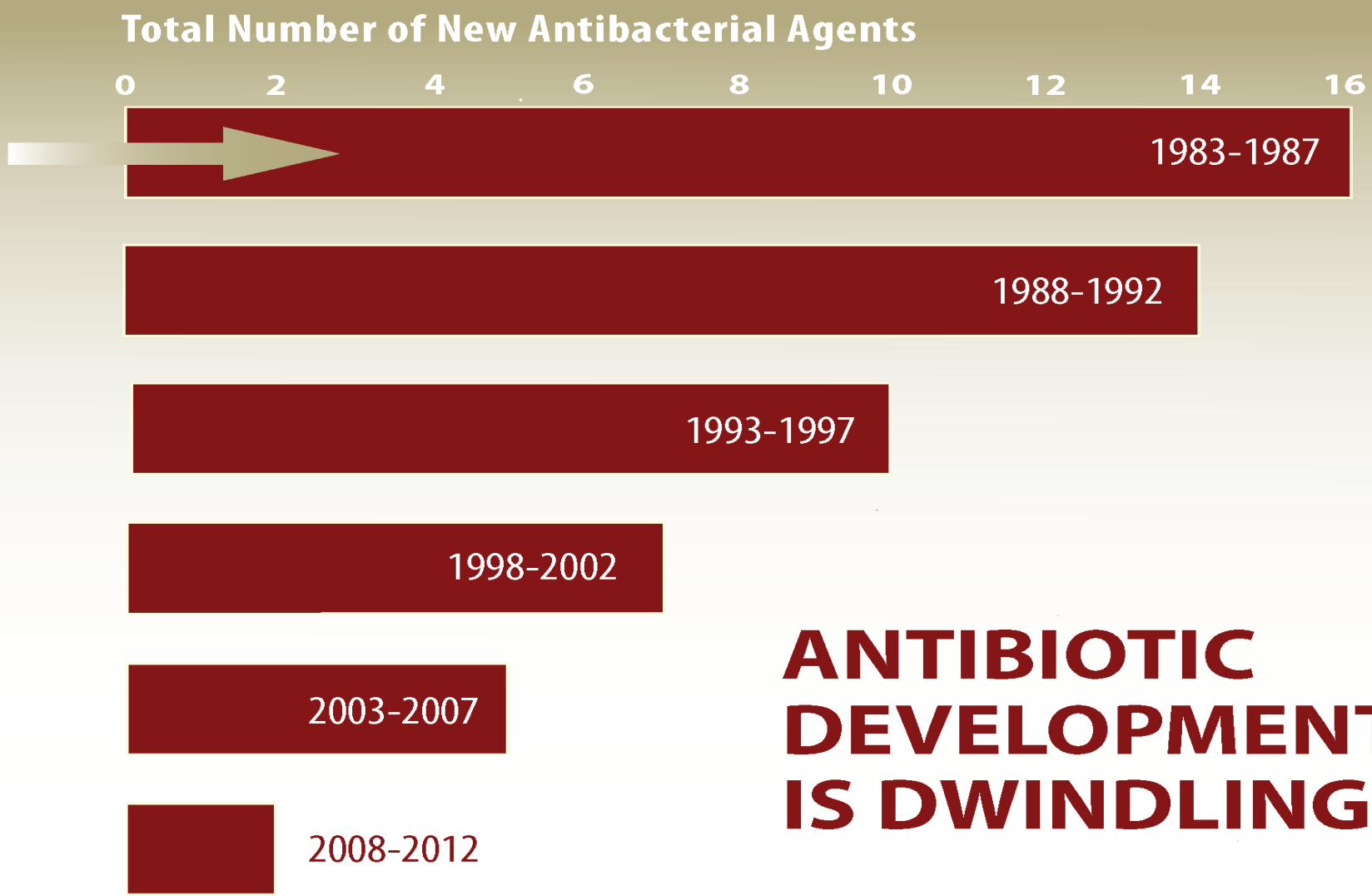
1034 pazienti con BSI

Variables	Total N = 688	Older adults (65-74 yo) N= 277	Elderly (>=75 yo) N= 411
MDR BSI (%)	182 (26.5)	73 (26.4)	109 (26.5)
Candida BSI (%)	146 (21.2)	56 (20.2)	90 (21.9)
Staph aureus BSI (%)	110 (16)	41 (14.8)	69 (16.8)
MRSA BSI (%)	44 (6.4)	15 (5.4)	29 (7.1)
Enterococcus spp BSI (%)	82 (11.9)	28 (10.1)	54 (13.1)
Enterobacteriaceae CRE BSI (%)	38 (5.5)	18 (6.5)	20 (4.9)
Enterobacteriaceae ESBL BSI (%)	60 (8.7)	26 (9.4)	34 (8.3)
Non-fermenting Gram-negative MDR or XDR BSI (%)	42 (6.1)	18 (6.5)	24 (5.8)

LE INFEZIONI NOSOCOMIALI DEL TORRENTE EMATICO NEL GIOVANE ADULTO, NELL'ANZIANO E NEL GRANDE ANZIANO: DIFFERENZE EPIDEMIOLOGICHE, GESTIONALI E DI MORTALITÀ.

F Giovannenze, R Murri, M Camici, C Palazzolo, F Taccari, G Scoppettuolo, R Cauda, M Fantoni

- I germi MDR ed i miceti sono gli unici patogeni associati ad un aumento di mortalità (HR 1.53 e 2.65, p=0.03 e <0.01)



ANTIBIOTIC DEVELOPMENT IS DWINDLING

Source: *The Epidemic of Antibiotic-Resistant Infections*, CID 2008:46 (15 January)
Clin Infect Dis. (2011) May 52 (suppl 5): S397-S428. doi: 10.1093/cid/cir153

TEDIZOLID

DALBAVANCINA

CEFTOLOZANO/TAZOBACTAM

DELAFLOXACINA

CEFTAZIDIME/AVIBACTAM

CEFTAROLINA

MEROPENEM/VABORBACTAM

PLAZOMICINA

FOSFOMICINA

TEDIZOLID

DALBAVANCINA

CEFTOLOZANO/TAZOBACTAM

DELAFLOXACINA

CEFTAZIDIME/AVIBACTAM

CEFTAROLINA

MEROPENEM/VABORBACTAM

PLAZOMICINA

FOSFOMICINA

TEDIZOLID

DALBAVANCINA

CEFTOLOZANO/TAZOBACTAM

DELAFLOXACINA

CEFTAZIDIME/AVIBACTAM

CEFTAROLINA

MEROPENEM/VABORBACTAM

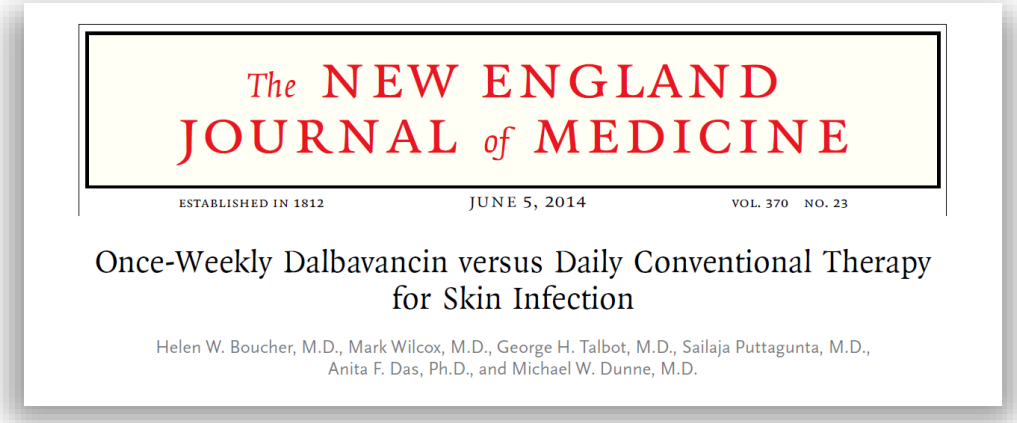
PLAZOMICINA

FOSFOMICINA

DALBAVANCINA

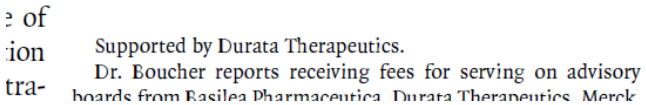
- Dalbavancina è un glicopeptide semisintetico (lipoglicopeptide)
- Attivo solo sui GRAM+
- Strutturalmente correlato a teicoplanina
- Ha azione battericida

**Streit, et al. DMID 2004, p137*


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

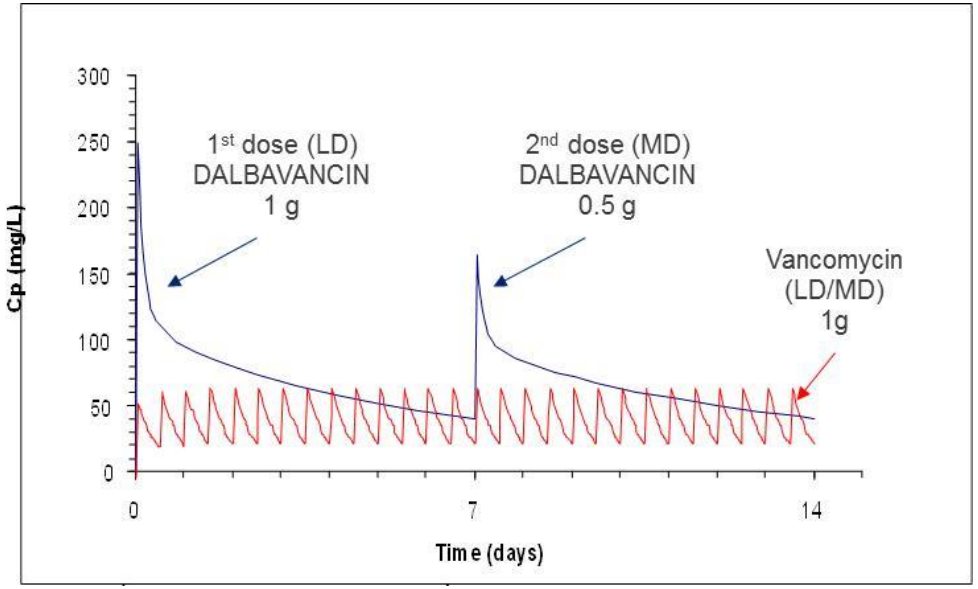
Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.


Supported by Durata Therapeutics.
Dr. Boucher reports receiving fees for serving on advisory

- DISCOVER 1 e 2 , studio randomizzato di non inferiorità (margine del 10%)
- Diagnosi: cellulite di almeno 75 cm^2 di eritema o ascesso maggiore o ferita infetta e almeno 1 segno sistemico di infezione. Piede diabetico escluso
- **Dalbavancina** 1000 mg al giorno 0 + 500 mg al giorno 8 vs **vancomicina** 1 g ogni 12 ore per 3 giorni e poi eventuale switcha **linezolide** orale

Profilo PK unico

Dalbavancin dosed with 1,000 mg IV on Day 1 and 500 mg IV on Day 8



Dalbavancin's pharmacokinetic profile enables:

- Broad tissue distribution
- Continuous cidality
- Once weekly dosing
- Maintenance of high plasma concentration

Dorr, JAC 2005;55 Supp S2:ii25; data on file

- Emivita 372 ore (da 333 a 405)

- la concentrazione plasmatica a 14 gg dalla somministrazione di 1000 mg (>1mg/l) eccede di almeno 16 volte la MIC_{90} di molti stafilococchi e streptococchi, inclusi multiresistenti

- Buona penetrazione tissutale in cute, osso, liquido sinoviale, vescicole. Dati sulle concentrazioni encefaliche e liquorali sono scarsi

- Non sono state evidenziate differenze significative fra 1 somministrazione 1500 mg oppure 1000 mg + 500 al 7° giorno

- Non aggiustamenti posologici in pz in emodialisi o con insufficienza epatica (per Child–Pugh B e C scarsi dati di letteratura)

- Non richiede un CVC per l'infusione

Dalbavancina

Indicazioni registrate	trattamento delle infezioni batteriche acute della cute e della struttura cutanea (ABSSSI) negli adulti. Occorre prendere in considerazione le linee guida ufficiali sull'uso appropriato degli agenti antibatterici.
Posologia	Dose raccomandata e durata del trattamento per gli adulti: Nei pazienti adulti affetti da ABSSSI, la dose raccomandata per la dalbavancina è *1.500 mg somministrati come singola infusione da 1.500 mg (non ancora rimborsata SSN vedi G.U.134 del 10/06/2016)* oppure 1.000 mg seguiti, una settimana dopo, da 500 mg .
ATC	J01XA04
Classe di rimborsabilità e regime di fornitura	H OSP. Scheda AIFA cartacea per la prescrizione. La prescrizione è riservata allo specialista infettivologo o, in sua assenza, ad altro specialista con competenza infettivologica identificato dal Comitato Infezioni Ospedaliere (CIO) istituito per legge presso tutti i presidi ospedalieri (Circolare Ministero della Sanità n. 52/1985).
Registrazione	Procedura Centralizzata EMA
Confezioni disponibili e prezzo	1 flacone 500 mg polvere per concentrato per soluzione per infusione Prezzo ex factory: 773,48 euro.

International Journal of Antimicrobial Agents 51 (2018) 571–577

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

Emilio Bouza [a,b,c,d], Maricela Valerio [a,*], Alex Soriano [e], Laura Morata [e], Enrique García Carus [e], Carmen Rodríguez-González [b,f], Ma Carmen Hidalgo-Tenorio [g], Antonio Plata [h], Patricia Muñoz [a,b,c,d,*], Antonio Vena [a,b,d] on behalf of the DALBUSE Study Group (Dalbavancina: Estudio de su uso clinico en España)

[a] Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Doctor Esquerdo 46, 28007 Madrid, Spain

Table 2
Type of primary infection and causative micro-organisms

Infection type	Overall [N (%)]
Prosthetic joint infection	20 (29.0)
ABSSSI [b]	15 (21.7)
Osteomyelitis [c]	12 (17.4)
Catheter-related bacteraemia [d]	8 (11.6)
Endocarditis	7 (10.1)
Intra-abdominal infection	3 (4.3)
Other endovascular infections	2 (2.9)
Septic arthritis	1 (1.4)
Sinusitis	1 (1.4)
Overall	69 (100)

In this study, >35% of patients received combined treatment. Surprisingly, the clinical course was worst in this population, probably because they were more ill and physicians are more prone to prescribe combination therapy. In our opinion, the role of combination therapy with dalbavancin needs to be evaluated further. Favourable results of 'in vitro' studies have been reported and reveal a synergistic effect with dalbavancin/daptomycin and dalbavancin/linezolid against MRSA strains [44].

Clinical Infectious Diseases

BRIEF REPORT

Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna

Selma Tobudic,[1] Christina Forstner,[1,2] Heinz Burgmann,[1] Heimo Lagler,[1] Michael Ramharter,[1,3] Christoph Steininger,[1] Matthias (G) Vossen,[1] Stefan Winkler,[1] and Florian Thalhammer[1]

[1]Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Austria; and [2]Institute for Infectious Diseases and Infection Control, Jena University Hospital, and [3]Bernhard Nocht Hospital for Tropical Diseases, Bernhard Nocht

CID 2018:67 (1 September)

In this retrospective study clinical outcomes and safety of dalbavancin as primary and sequential treatment of Gram-positive bacteremia with infective endocarditis were evaluated. Clinical success under dalbavancin was high (92.6%) but in the majority of patients (24/27) dalbavancin was only used after clearance of bacteria from bloodstream.

QUALE POSIZIONAMENTO

- Pazienti con scarsa compliance o difficoltà OPAT
- Pazienti con difficoltà a terapia orale (es disfagia) Necessità/opportunità di dimissione/trasferimento in tempi brevi

IN ATTESA DI CONFERME

- Infezioni ortopediche
- Endocarditi e mediastiniti, infezione di devices cardiaci
- CLABSI
- Attività anti-Enterococco (no *Ent faecium*)
- Catether lock solution (in combinazione con eparina)
- Uso in combinazione con altri agenti
- Infezione del biofilm

CEFTAZIDIME/AVIBACTAM

Studi registrativi

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program

Florian M. Wagenlehner,[1] Jack D. Sobel,[2] Paul Newell,[3] Jon Armstrong,[3] Xiangning Huang,[4] Gregory G. Stone,[5] Katrina Yat

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program

John E. Mazuski,[1] Leanne B. Gasink,[2] Jon Armstrong,[5] Helen Broadhurst,[5] Greg G. Stone,[3] Douglas Rank,[4] Lily Llorens,[4] Paul Newell,[5] and Jan Pachl[6]

Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

Yehuda Carmeli, Jon Armstrong, Peter J Laud, Paul Newell, Greg Stone, Angela Wardman, Leanne B Gasink

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

Lancet Infect Dis 2018; 18: 285–95

Indicazioni terapeutiche

EMA AIFA

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options

E riguardo le CRE...?

Clinical Infectious Diseases

MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

Clinical Infectious Diseases

BRIEF REPORT

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,3,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[5] Ellen G. Press,[1] Barry N. Kreiswirth,[5] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,3,4]

Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients

Juan J. Castón[a], Isabel Lacort-Peralta[b], Pilar Martín-Dávila[c], Belén Loeches[d], Salvador Tabares[e], Liz Temkin[f], Julián Torre-Cisneros[a,*], José R. Paño-Pardo[d,g]

Clinical Infectious Diseases

MAJOR ARTICLE

Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae*

Mario Tumbarello,[1,a] Enrico Maria Trecarichi,[1,a] Alberto Corona,[2] Francesco Giuseppe De Rosa,[3] Matteo Bassetti,[4] Cristina Mussini,[5] Francesco Menichetti,[6] Claudio Viscoli,[7] Caterina Campoli,[8] Mario Venditti,[9] Andrea De Gasperi,[10] Alessandra Mularoni,[11] Carlo Tascini,[12] Giustino Parruti,[13] Carlo Pallotto,[14] Simona Sica,[15] Ercole Concia,[16] Rosario Cultrera,[17] Gennaro De Pascale,[18] Alessandro Capone,[19] Spinello Antinori,[20] Silvia Corcione,[3] Elda Righi,[4] Angela Raffaella Losito,[1] Margherita Digaetano,[5] Francesco Amadori,[6] Daniele Roberto Giacobbe,[7] Giancarlo Ceccarelli,[9] Ernestina Mazza,[10] Francesca Raffaelli,[1] Teresa Spanu,[21] Roberto Cauda,[1] and Pierluigi Viale[8]

Tumbarello et Al. Clin Infect Dis. June 09, 2018.

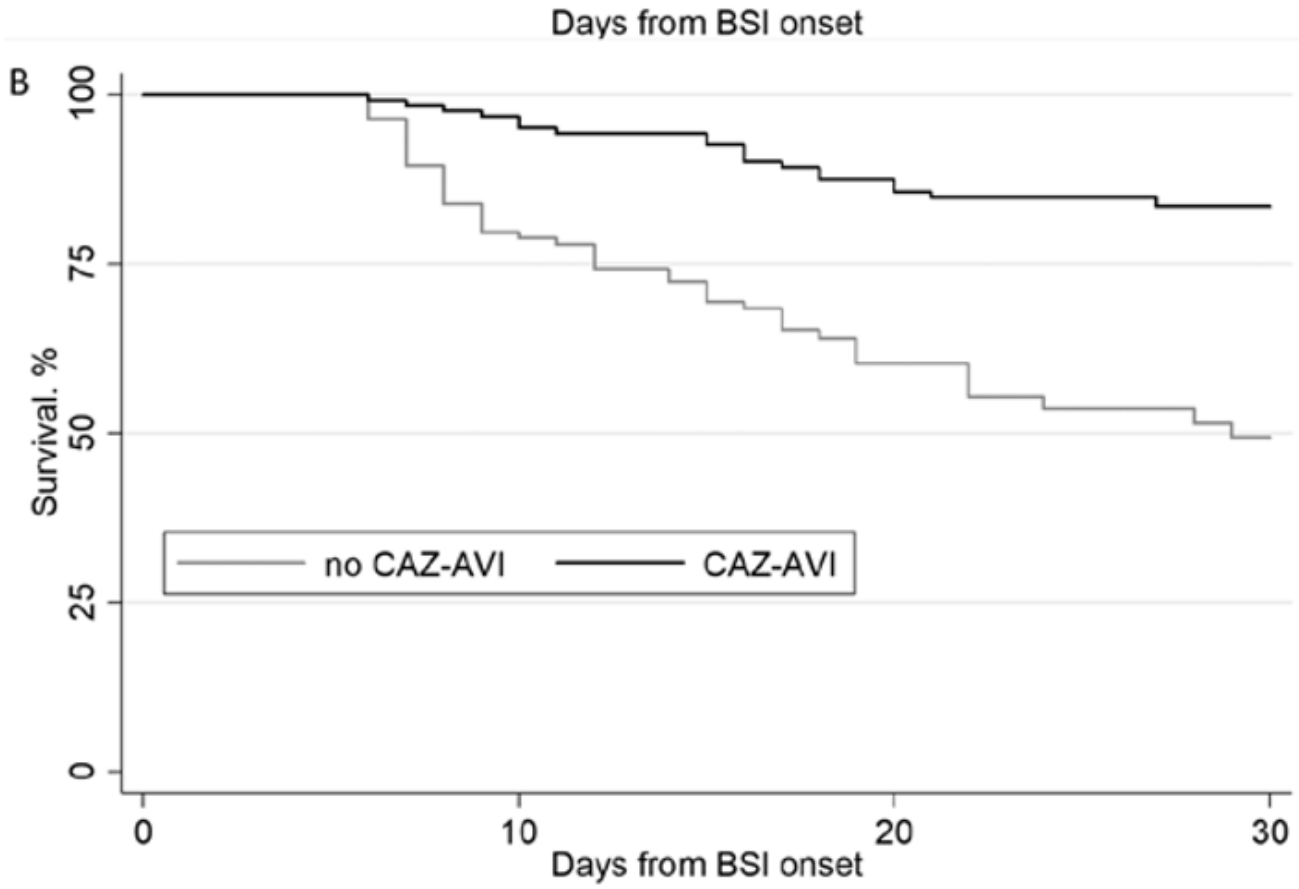
Methods. We retrospectively reviewed 138 cases of infections caused by KPC-producing *K. pneumoniae* (KPC-Kp) in adults who received CAZ-AVI in compassionate use programs in Italy. Case features and outcomes were analyzed, and survival was then specifically explored in the large subcohort whose infections were bacteremic.

Results. The 138 patients started CAZ-AVI salvage therapy after a first-line treatment (median, 7 days) with other antimicrobials. CAZ-AVI was administered with at least 1 other active antibiotic in 109 (78.9%) cases. Thirty days after infection onset, 47 (34.1%) of the 138 patients had died. Thirty-day mortality among the 104 patients with bacteremic KPC-Kp infections was significantly lower than that of a matched cohort whose KPC-Kp bacteremia had been treated with drugs other than CAZ-AVI (36.5% vs 55.8%, $P = .005$). Multivariate analysis of the 208 cases of KPC-Kp bacteremia identified septic shock, neutropenia, Charlson comorbidity index ≥3, and recent mechanical ventilation as independent predictors of mortality, whereas receipt of CAZ-AVI was the sole independent predictor of survival.

Conclusions. CAZ-AVI appears to be a promising drug for treatment of severe KPC-Kp infections, especially those involving bacteremia.

Tumbarello et Al. Clin Infect Dis. June 09, 2018.

Kaplan-Meier survival analyses in the cohorts with *Klebsiella pneumoniae* carbapenemase–producing *K.pneumoniae* bloodstream infections (BSIs)



Tumbarello et Al. Clin Infect Dis. June 09, 2018.

J Antimicrob Chemother 2017; **72**: 2483–2488
doi:10.1093/jac/dkx179 Advance Access publication 16 June 2017

Journal of Antimicrobial Chemotherapy

Emergence of ceftazidime/avibactam non-susceptibility in an MDR *Klebsiella pneumoniae* isolate

Anna Both[1], Henning Büttner[1], Jiabin Huang[1], Markus Perbandt[1,2], Cristina Belmar Campos[1], Martin Christner[1], Florian P. Maurer[1], Stefan Kluge[3], Christina König[2], Martin Aepfelbacher[1], Dominic Wichmann[3]† and Holger Rohde[1]*†

Clinical Infectious Diseases

BRIEF REPORT

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

Lancet Infect Dis 2018; 18: 285–95

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,3,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[6] Ellen G. Press,[1] Barry N. Kreiswirth,[6] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,3,4]

CRE- spunti di riflessione

- Gli **studi registrativi non sono utili**, per come sono stati disegnati e condotti, a fornire un valido supporto circa l'**utilizzo in infezioni da CRE**

- La **letteratura** sull'utilizzo di **ceftazidime-avibactam nelle infezioni da CRE** è ancora **modesta** e si tratta sempre di esperienze di pochi casi, per cui manca la significatività statistica

- In vitro le potenzialità sono molte e in vivo si vedono risultati buoni, ma sarà solo usandolo che si capirà davvero l'utilità del farmaco (**regimi carbapenem-sparing vs terapie di salvataggio**) e la sua validità (**ha senso usare un farmaco per risparmiare carbapenemici se induce forse più resistenze di questi ultimi?**)

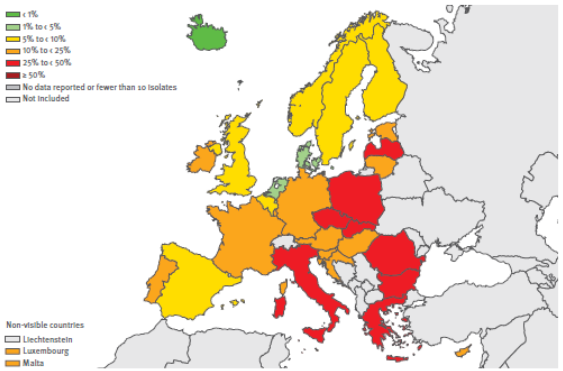
- Vista l'insorgenza di alcune **resistenze** già in corso di trattamento, **valutare bene la monoterapia vs associazioni** (tuteliamo il farmaco, ma soprattutto i pazienti!)

- A breve saranno disponibili nuovi farmaci disegnati ad hoc

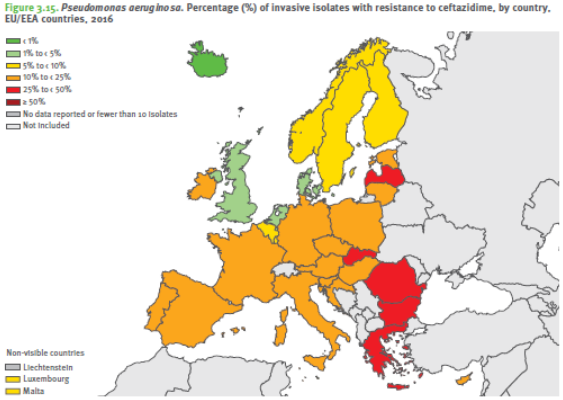
CEFTOLOZANO/TAZOBACTAM

Pseudomonas aeruginosa - percentage of invasive isolate with resistance to…

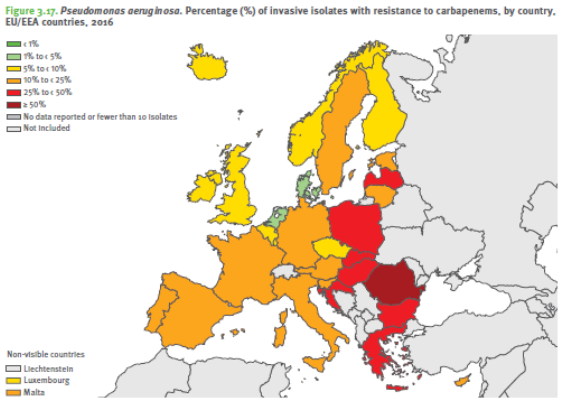
piperacillin/tazobactam

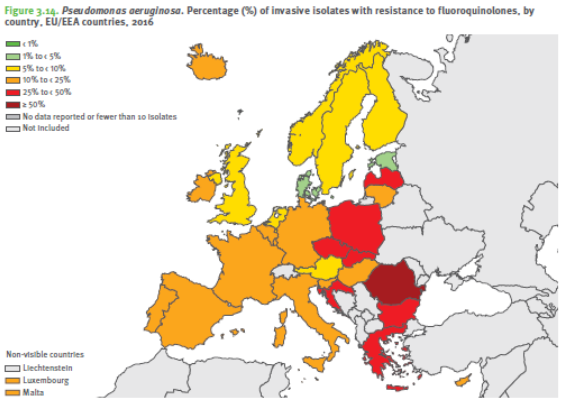


ceftazidime

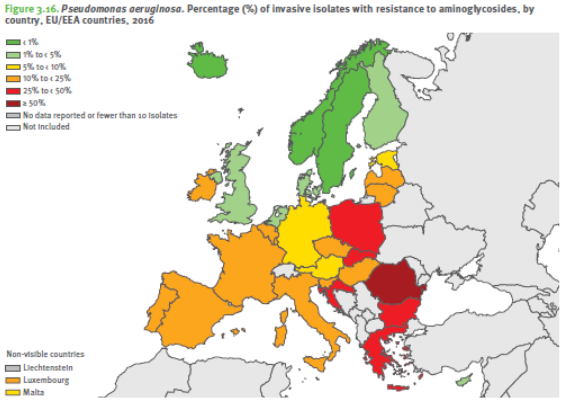


carbapenem

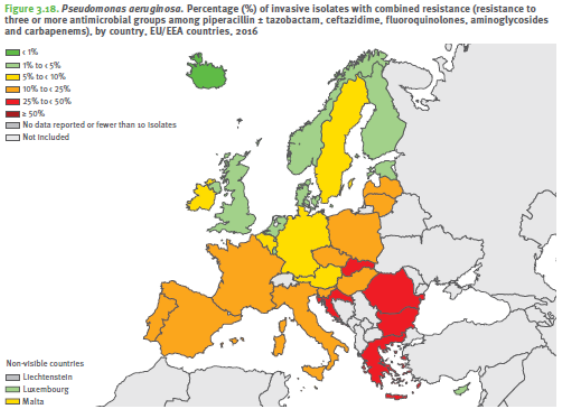




fluoroquinolones



aminoglycosides



combined resistance

Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net), 2016

Spettro di attività

- ***Enterobacteriaceae***
- ***P. aeruginosa*** **compresi ceppi resistenti**
- Attività in vitro contro Haemophilus, and Moraxella, altri Gram-negative fermentanti
- streptococchiβ-emolitici (*Streptococcus pyogenes e Streptococcus agalactiae),* una certa attività contro pneumococchi

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

993 patients enrolled → Randomization 1:1

- Meropenem 1 g IV q8
- Ceftolozane/tazobactam 1.5 g IV q8 + metronidazole 500 mg q8

Treatment duration: 4-10 days , and up to 14 days in case of multiple abscesses, non–appendix-related peritonitis, failure of prior antimicrobial therapy, or hospital-acquired infection.

- Study design: multicenter, prospective, double-blind, randomized trial
- Objectives: to demonstrate statistical noninferiority of C/T+metronidazole vs meropenem in clinical cure rates at the TOC visit in the MITT-microbiological intent to- treat (primary) and ME-microbiologically evaluable (secondary) populations using a noninferiority margin of 10%.
- MITT population: all randomized patients with at least 1 baseline pathogen identified in abscess or peritonitis fluid, regardless of susceptibility to study drug.
- ME population: The subset of clinically evaluable patients who had at least 1 baseline infecting pathogen identified that was susceptible to study drug
- The primary outcome measure was clinical cure, defined as complete resolution of infection or enough improvement requiring no further interventions

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

1083 patients enrolled → Randomization 1:1 → Levofloxacin 750 mg IV q24 / Ceftolozane/tazobactam 1.5 g IV q8

Treatment duration: 7 days.

- Study design: multicenter, randomised, double-blind, double-dummy, non-inferiority trial
- The primary endpoint was a composite of microbiological eradication and clinical cure 5–9 days after treatment in the microbiological modified intention-to-treat (MITT) population, with a non-inferiority margin of 10%
- The modified intention-to-treat (MITT) and safety populations comprised all patients who received at least one dose of study drug
- The microbiological MITT (mMITT) population included all patients in the MITT population with growth of one or two uropathogens of at least 10^5 CFU/mL in urine culture
- Per protocol population: all mMITT patients who adhered to the treatment protocol and had a clinical assessment and interpretable urine culture at the test of cure

Wagenlehner, et al. Lancet 2015; 385:1949-56

J Antimicrob Chemother 2017; **72**: 1386–1395
doi:10.1093/jac/dkx009 Advance Access publication 6 February 2017

Journal of Antimicrobial Chemotherapy

Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012–15)

Michael A. Pfaller[1,2], Matteo Bassetti[3], Leonard R. Duncan[1] and Mariana Castanheira[1]*

- A total of 6553 Gram-negative organisms (603 P. aeruginosa and 5950 Enterobacteriaceae) were consecutively collected from 41 hospitals located in 17 European countries plus Israel and Turkey.
- Conclusions: Ceftolozane/tazobactam was the most active β-lactam agent tested against P. aeruginosa and demonstrated higher in vitro activity than currently available cephalosporins and piperacillin/tazobactam when tested against Enterobacteriaceae.

J Antimicrob Chemother 2018; **73**: 664–671
doi:10.1093/jac/dkx453 Advance Access publication 5 December 2017

Journal of Antimicrobial Chemotherapy

Italian nationwide survey on *Pseudomonas aeruginosa* from invasive infections: activity of ceftolozane/tazobactam and comparators, and molecular epidemiology of carbapenemase producers

Tommaso Giani[1,2], Fabio Arena[1], Simona Pollini[1,2], Vincenzo Di Pilato[3], Marco Maria D'Andrea[1,2], Lucia Henrici De Angelis[1], Matteo Bassetti[4] and Gian Maria Rossolini[2,5]* on behalf of the *Pseudomonas aeruginosa* Working Group†

- Ceftolozane/tazobactam was the most active molecule, retaining activity against 90.9% of P. aeruginosa isolates, followed by amikacin and colistin.
- Overall, 48 isolates (5.1%) were positive for carbapenemase genes, while the remaining ceftolozane/tazobactam-resistant isolates tested negative for carbapenemase production.
- **Ceftolozane/tazobactam exhibited potent in vitro activity against P. aeruginosa causing invasive infections in Italy. Carbapenemase production was the most common mechanism of resistance to ceftolozane/ tazobactam.**

Future MICROBIOLOGY

EDITORIAL

Antibiotic stewardship from toolkit to local implementation: the *'gutta cavat lapidem'* strategy

Massimo Fantoni[1], Rita Murri*[,1] & Roberto Cauda[1]

Antibiotic Stewardship

Gemelli

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