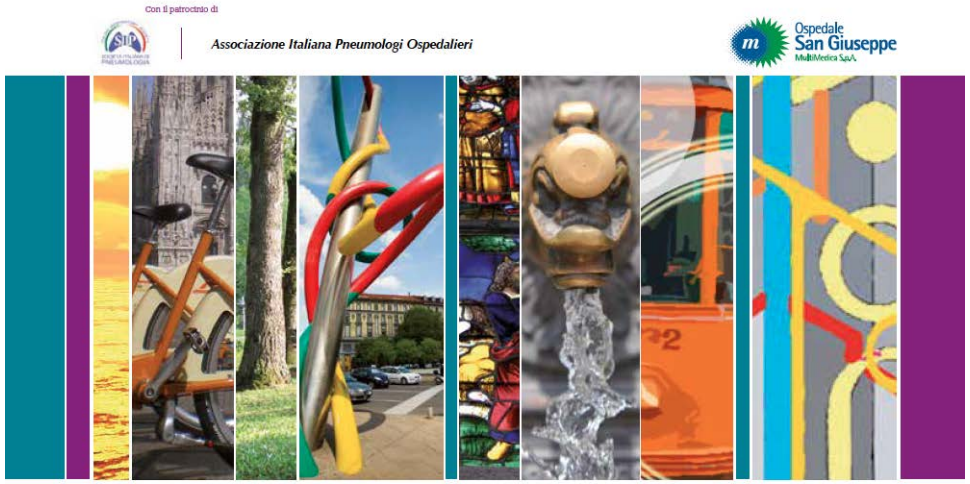
Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Massimo Puoti
SC Malattie Infettive
ASST GRANDE OSPEDALE
METROPOLITANO NIGUARDA
MILANO

I nuovi (e vecchi) batteri multi-resistenti: come difenderci



Disclosures

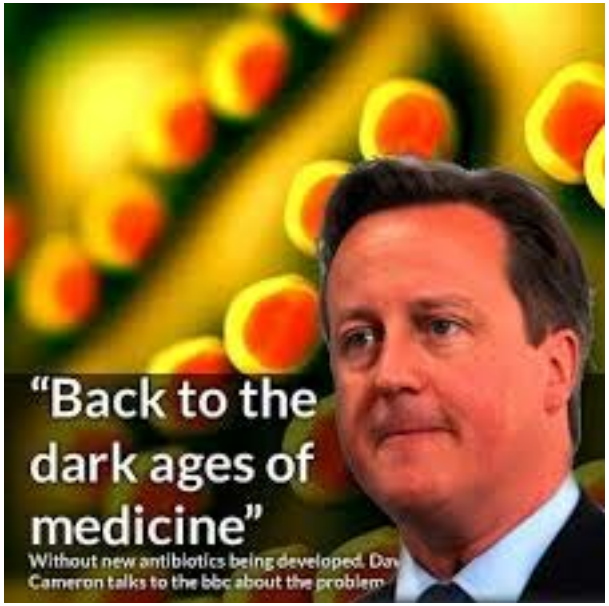
- Honoraria for consulting or speaking (past 5 years):

- AbbVie, Beckman, BMS, Janssen, Gilead Sciences, MSD, Roche, and ViiV

- Research grants:

- Gilead Sciences, ViiV, Roche, Pfizer Astellas and Novartis

The **White House** has authorized a 5-year National Action Plan to address antibiotic resistance and develop new antibiotics[4]



EUROPEAN ANTIBIOTIC AWARENESS DAY

Leaders' Declaration
G7 Summit
7-8 June 2015

G7 GERMANY
2015 | Schloss Elmau

Think Ahead. Act Together.
An morgen denken. Gemeinsam handeln.

Antimicrobial Resistances

Antimicrobials play a crucial role for the current and future success of human and veterinary medicine. We fully support the recently adopted WHO Global Action Plan on Antimicrobial Resistance. We will develop or review and effectively implement our national action plans and support other countries as they develop their own national action plans.

We are strongly committed to the One Health approach, encompassing all areas – human, and animal health as well as agriculture and the environment. We will foster the prudent use of antibiotics and will engage in stimulating basic research, research on epidemiology, infection prevention and control, and the development of new antibiotics, alternative therapies, vaccines and rapid point-of-care diagnostics. We commit to taking into account the annex (Joint Efforts to Combat Antimicrobial Resistance) as we develop or review and share our national action plans.

The first World Antibiotic Awareness Week – 16–22 November 2015

BE PART OF THE FIRST

WORLD ANTIBIOTIC AWARENESS WEEK

16-22 November 2015

HANDLE ANTIBIOTICS WITH CARE

Antibiotic resistance is one of the biggest threats to global health today. It is rising to dangerously high levels in all parts of the world. It is compromising our ability to treat infectious diseases and putting people everywhere at risk.

The World Health Organization is leading a global campaign 'Antibiotics: Handle with Care' calling on individuals, governments, health and agriculture professionals to take action to address this urgent problem.

Working together, we can ensure antibiotics are used only when necessary and as prescribed. Antibiotics are a precious resource that we cannot continue to take for granted—we need to handle them with care.

#AntibioticResistance

World Health Organization

World Health Organization
REGIONAL OFFICE FOR Europe

First World Antibiotic Awareness Week and awareness campaigns on prudent antibiotic use expanded throughout the WHO European Region

I nuovi (e vecchi) batteri multi-resistenti: come difenderci

- Definizione
- Rilevanza del problema in Italia
- Come difenderci:
  - political governance
  - clinical governance
- Nuove sfide nuove risposte

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

- **Applied to 5 groups of pathogens S. aureus, Enterococcus spp., Enterobacteriaceae (other than Salmonella and Shigella), P. aeruginosa and Acinetobacter spp.**
- **Non-susceptible to an antimicrobial agent: resistant, intermediate or non-susceptible → clinical breakpoints EUCAST, CLSI and FDA for acquired and not intrinsic antibiotic resistance**
- **MDR (MULTI DRUG RESISTANT non susceptible to at least 1 agent in > 3 antimicrobial categories specific for each bacterium**
- **XDR (EXTENSIVELY DRUG RESISTANT) non-susceptible to at least 1 agent in < 2 antimicrobial categories specific for each bacterium**
- **PDR (PAN DRUG RESISTANT) non susceptible to all agents in all antimicrobial categories**

Magiorakos A.-P. Clin Microbio Infect 2012 18: 268-81

Antimicrobial categories and agents used to define MDR, XDR PDR

Staphylococcus aureus

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
Ansamycins	Rifampin/rifampicin
Anti-MRSA cephalosporins	Ceftaroline
Anti-staphylococcal β-lactams (or cephamycins)	Oxacillin (or cefoxitin)*
Fluoroquinolones	Ciprofloxacin
	Moxifloxacin
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Fucidanes	Fusidic acid
Glycopeptides	Vancomycin
	Teicoplanin
	Telavancin
Glycylcyclines	Tigecycline
Lincosamides	Clindamycin
Lipopeptides	Daptomycin
Macrolides	Erythromycin
Oxazolidinones	Linezolid
Phenicols	Chloramphenicol
Phosphonic acids	Fosfomycin
Streptogramins	Quinupristin-dalfopristin
Tetracyclines	Tetracycline
	Doxycycline
	Minocycline

Enterococcus spp

Antimicrobial category	Antimicrobial agent
Aminoglycosides (except streptomycin)	Gentamicin (high level)
Streptomycin	Streptomycin (high level)
Carbapenems *	Imipenem Meropenem Doripenem
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin
Glycopeptides	Vancomycin Teicoplanin
Glycylcyclines	Tigecycline
Lipopeptides	Daptomycin
Oxazolidinones	Linezolid
Penicillins	Ampicillin
Streptogramins §	Quinupristin-dalfopristin
Tetracycline	Doxycycline Minocycline

- E. faecium intr. Res
- § E. faecalis intr res

Enterobacteriaceae

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)	Species with intrinsic resistance to antimicrobial agents or categories (51)*
Aminoglycosides	Gentamicin		*Providencia rettgeri (P. rettgeri), Providencia stuartii (P. stuartii)*
	Tobramycin		*P. rettgeri, P. stuartii*
	Amikacin		
	Netilmicin		*P. rettgeri, P. stuartii*
Anti-MRSA cephalosporins	Ceftaroline (approved only for *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca*)		
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid		*Escherichia hermannii (E. hermanii)*
	Piperacillin-tazobactam		*E. hermanii*
Carbapenems	Ertapenem		
	Imipenem		
	Meropenem		
	Doripenem		
Non-extended-spectrum cephalosporins: 1st and 2nd-generation cephalosporins	Cefazolin		*Citrobacter freundii (C. freundii), Enterobacter aerogenes (E. aerogenes), Enterobacter cloacae (E. cloacae), Hafnia alvei (H. alvei), Morganella morganii (M. morganii), Proteus penneri (P. penneri), Proteus vulgaris (P. vulgaris), P. rettgeri, P. stuartii, Serratia marcescens (S. marcescens)*
	Cefuroxime		*M. morganii, P. penneri, P. vulgaris, S. marcescens*
Extended-spectrum cephalosporins: 3rd and 4th generation cephalosporins	Cefotaxime or ceftriaxone		
	Ceftazidime		
	Cefepime		
Cephamycins	Cefoxitin		*C. freundii, E. aerogenes, E. cloacae, H. alvei*
	Cefotetan		*C. freundii, E. aerogenes, E. cloacae, H. alvei*
Fluoroquinolones	Ciprofloxacin		
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole		
Glycylcyclines	Tigecycline		*M. morganii, Proteus mirabilis (P. mirabilis), P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
Monobactams	Aztreonam		
Penicillins	Ampicillin		*Citrobacter koseri (C. koseri), C. freundii, E. aerogenes, E. cloacae, E. hermanii, H. alvei, Klebsiella spp., M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens*
Penicillins + β-lactamase inhibitors	Amoxicillin-clavulanic acid		*C. freundii, E. aerogenes, E. cloacae, H. alvei, M. morganii, P. rettgeri, P. stuartii, S. marcescens*
	Ampicillin-sulbactam		*C. freundii, C. koseri, E. aerogenes, E. cloacae, H. alvei, P. rettgeri, S. marcescens*
Phenicols	Chloramphenicol		
Phosphonic acids	Fosfomycin		
Polymyxins	Colistin		*M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens*
Tetracyclines	Tetracycline		*M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
	Doxycycline		*M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*
	Minocycline		*M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*

Pseudomonas aeruginosa

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Antipseudomonal carbapenems	Imipenem
	Meropenem
	Doripenem
Antipseudomonal cephalosporins	Ceftazidime
	Cefepime
Antipseudomonal fluoroquinolones	Ciprofloxacin
	Levofloxacin
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid
	Piperacillin-tazobactam
Monobactams	Aztreonam
Phosphonic acids	Fosfomycin
Polymyxins	Colistin
	Polymyxin B

Acinetobacter spps

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Antipseudomonal carbapenems	Imipenem
	Meropenem
	Doripenem
Antipseudomonal fluoroquinolones	Ciprofloxacin
	Levofloxacin
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
	Ticarcillin-clavulanic acid
Extended-spectrum cephalosporins	Cefotaxime
	Ceftriaxone
	Ceftazidime
	Cefepime
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam
Polymyxins	Colistin
	Polymyxin B
Tetracyclines	Tetracycline
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Magiorakos A.-P. Clin Microbio Infect 2012 18: 268-81

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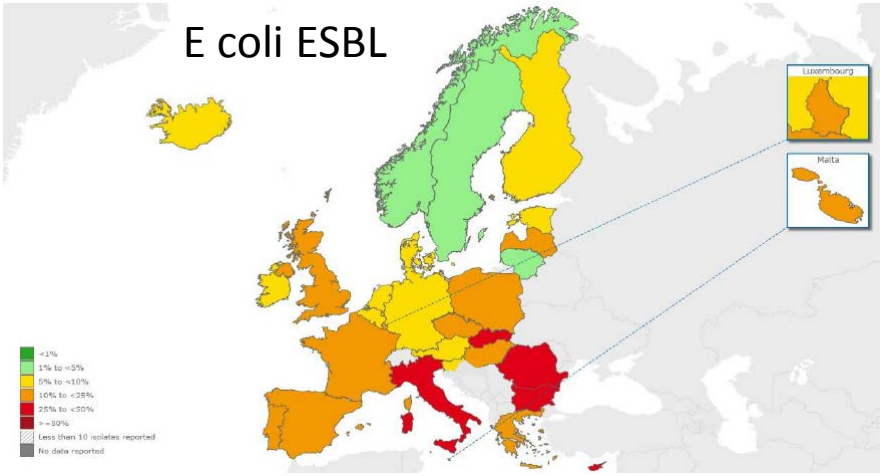
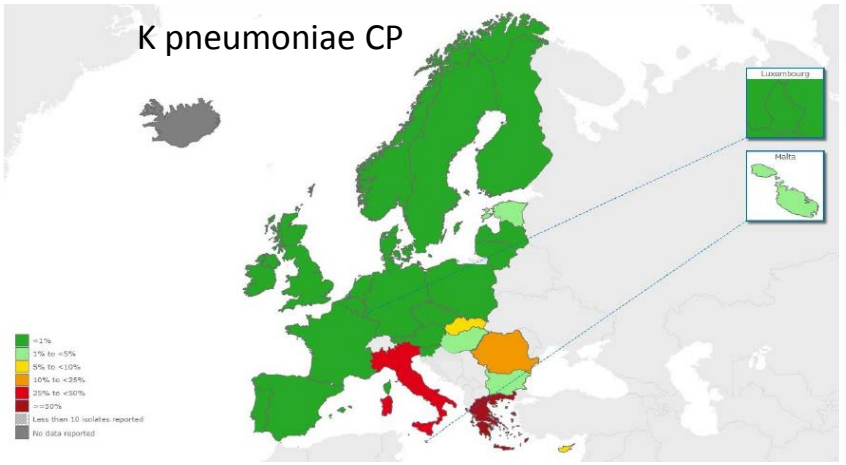
Epidemiology of MDR in Europe 2012
% of invasive (blood and cerebrospinal fluids) isolates

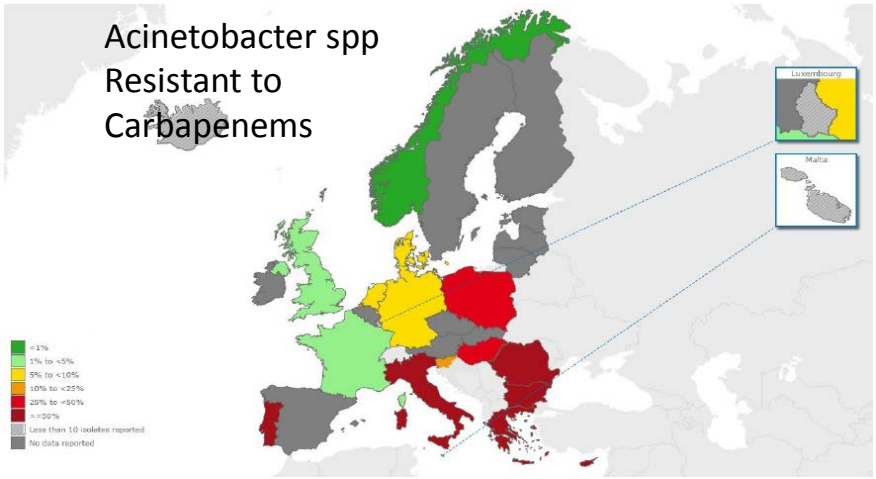
E coli ESBL



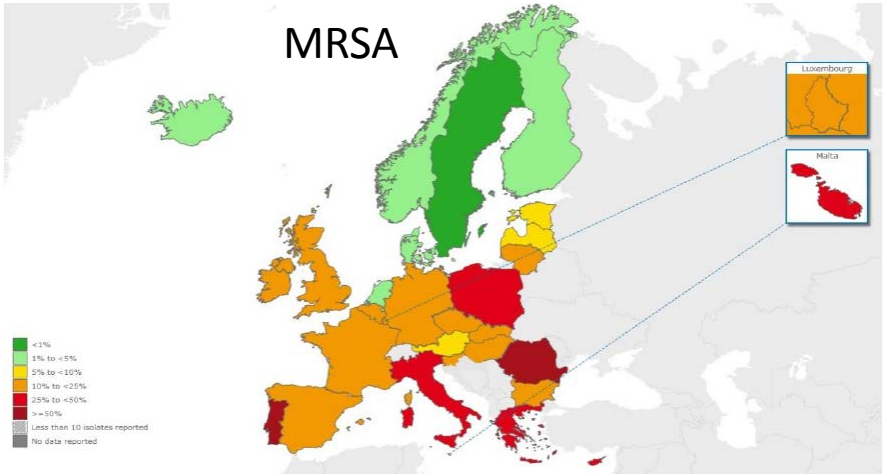
K pneumoniae CP



Acinetobacter spp
Resistant to
Carbapenems



MRSA

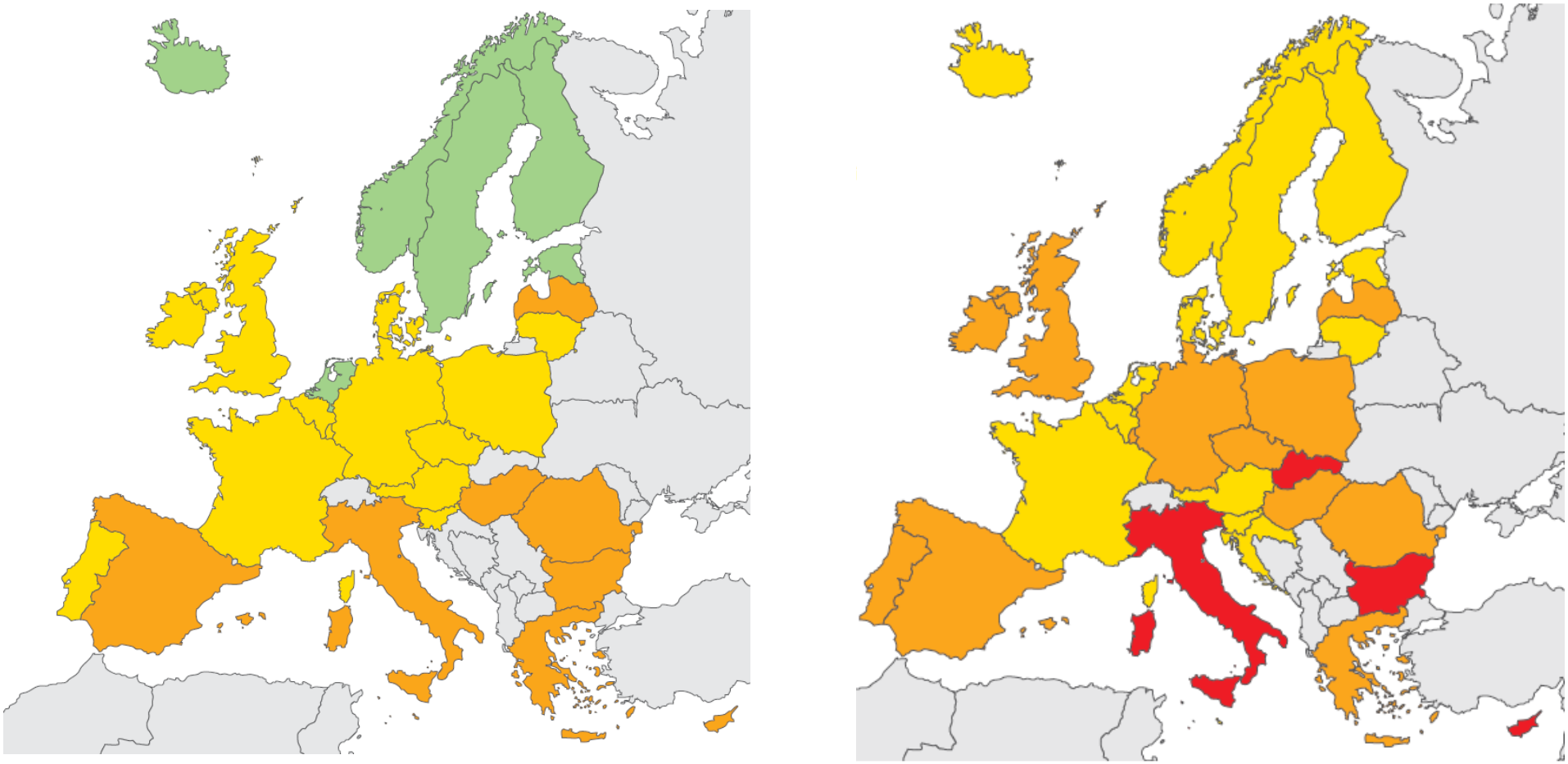


Italiani e Greci .. Una faccia una razza…

E. Monteleone G Salvatores. Mediterraneo 1991

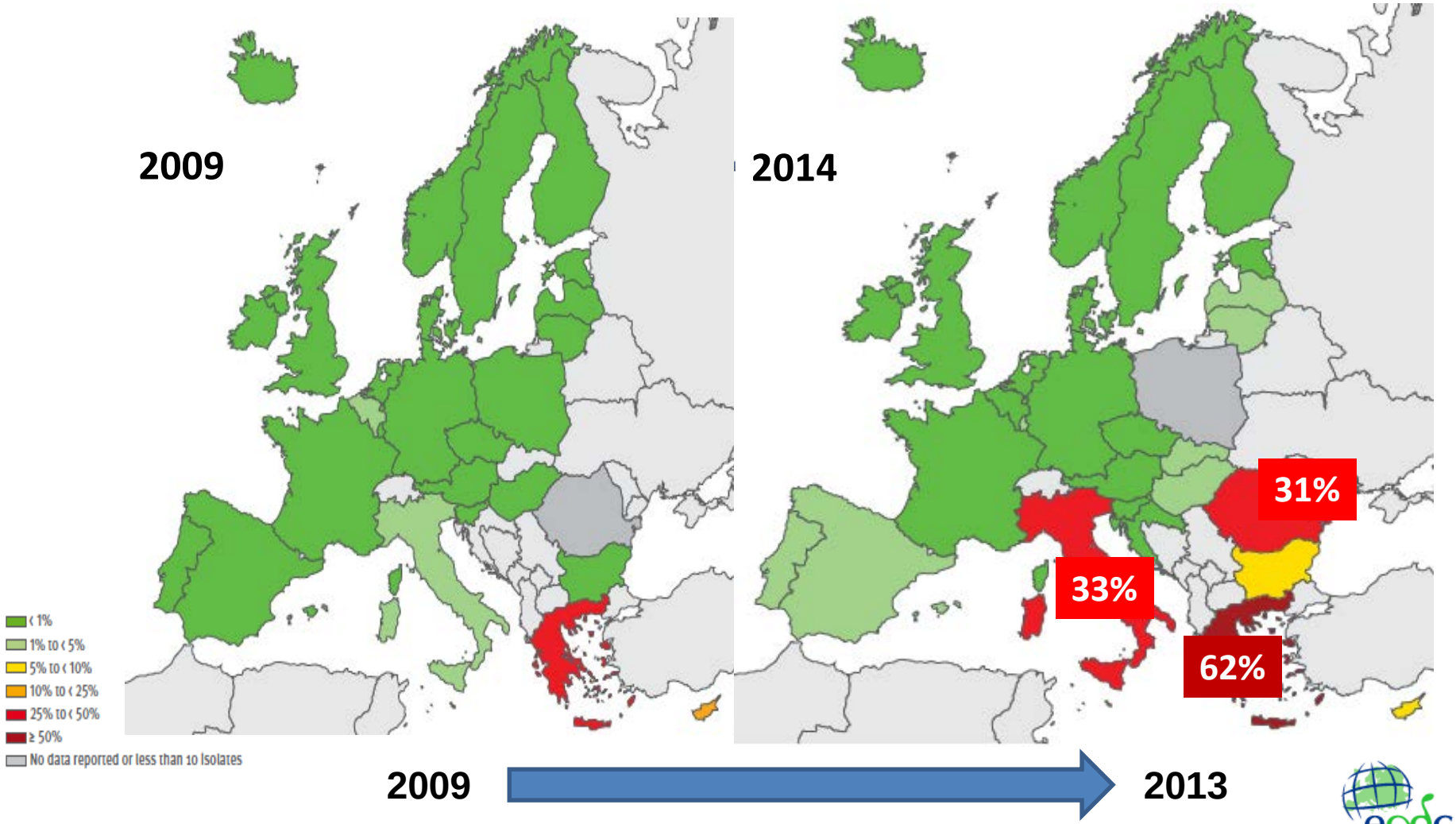
www.cdc.europa.eu

Escherichia coli: percentage of invasive isolates with resistance to third-generation cephalosporins



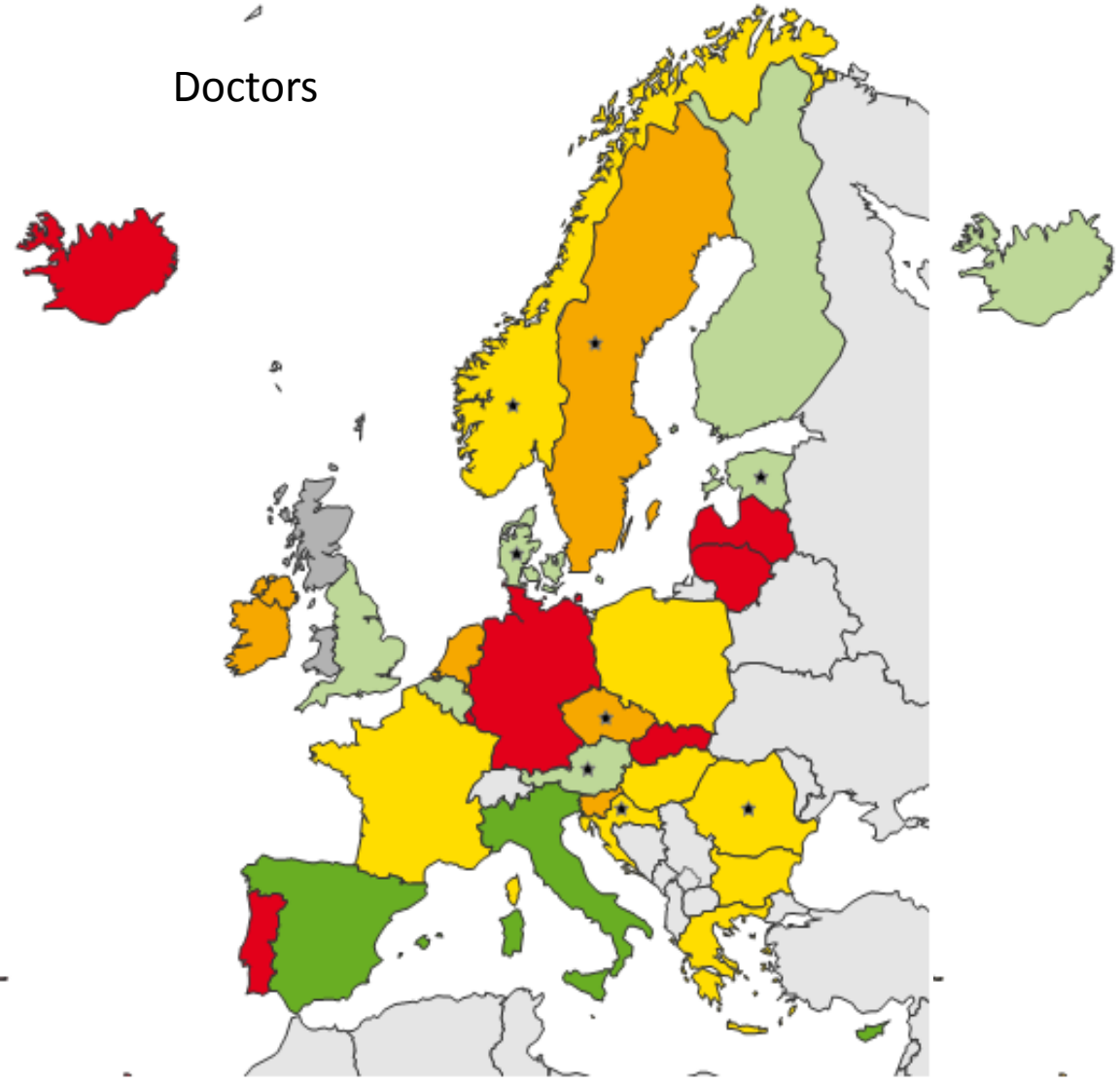
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

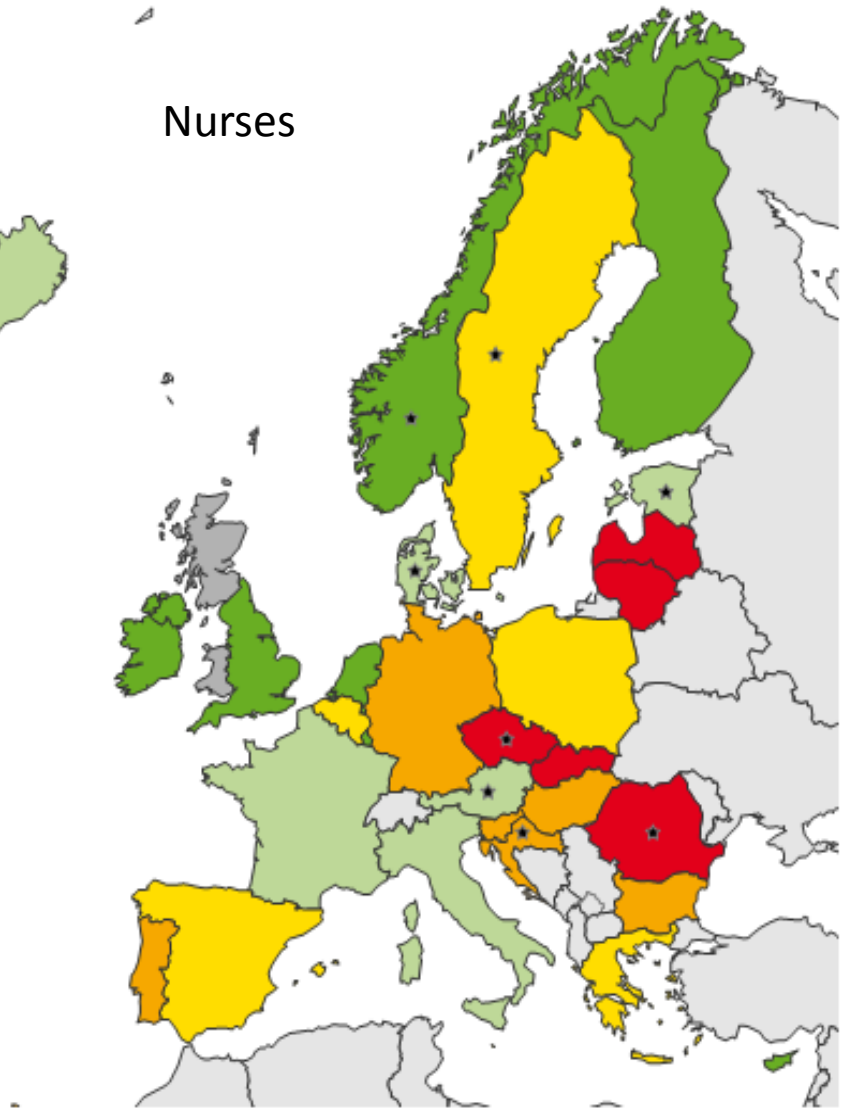
Carbapenem-resistant *Klebsiella pneumoniae*



EARS-NET

Infection control services in Europe: human resources





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How does antibiotic resistance spread?

Antibiotic resistance is the ability of bacteria to combat the action of one or more antibiotics. Humans and animals do not become resistant to antibiotic treatments, but bacteria carried by humans and animals can.

1 Animals may be treated with antibiotics and they can therefore carry antibiotic-resistant bacteria. **2 Vegetables** may be contaminated with antibiotic-resistant bacteria from animal manure used as fertilizer. **3 Antibiotic-resistant bacteria** can spread to humans through **food** and direct contact with animals.

In animal farming

4 Humans sometimes receive antibiotics prescribed to treat **infections**. However, bacteria develop resistance to antibiotics as a **natural, adaptive reaction**. Antibiotic-resistant bacteria can then **spread** from the treated patient to other persons.

In the community

5 Humans may receive antibiotics in **hospitals** and then carry antibiotic-resistant bacteria. These can spread to other patients via **unclean hands** or **contaminated objects**. **6** Patients who may be carrying antibiotic-resistant bacteria will ultimately be sent **home**, and can spread these resistant bacteria to **other persons**.

In healthcare facilities

7 Travellers requiring hospital care while visiting a country with a high prevalence of antibiotic resistance may **return** with antibiotic-resistant bacteria.
8 Even if not in contact with healthcare, travellers may **carry and import** resistant bacteria acquired from food or the environment during travel.

Through travel

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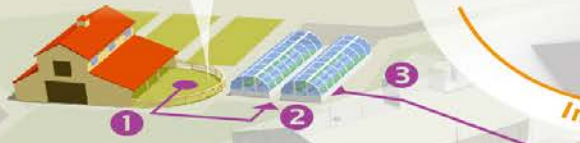
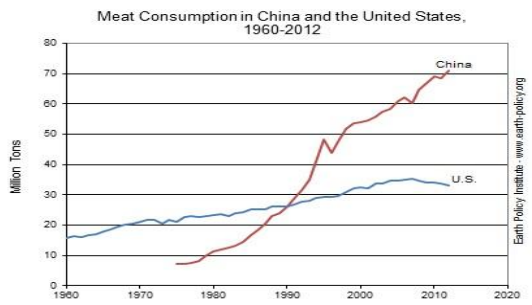
8 Even if not in contact with healthcare, travellers may **carry and import** resistant bacteria acquired from food or the environment during travel.

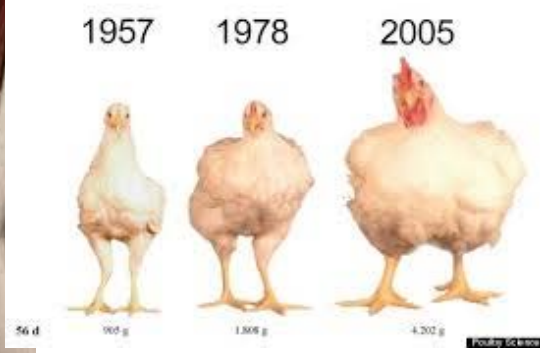
Through travel

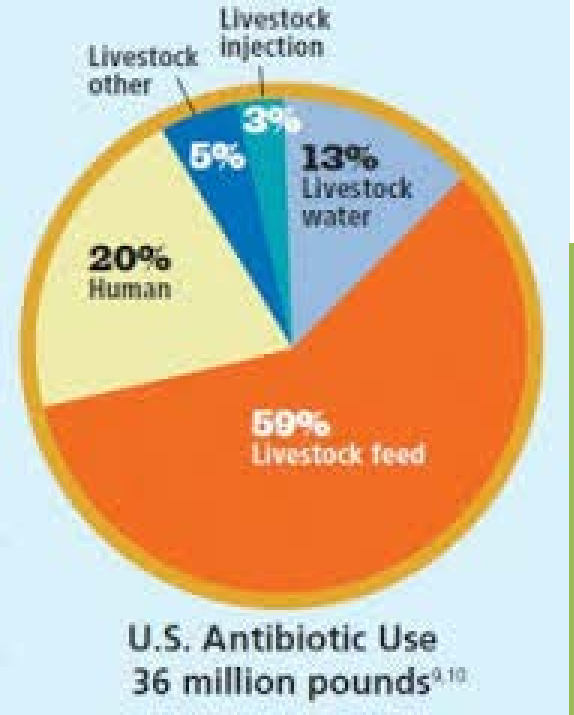


❶ **Animals** may be treated with antibiotics and they can therefore carry antibiotic-resistant bacteria. ❷ **Vegetables** may be contaminated with antibiotic-resistant bacteria from animal manure used as fertilizer. ❸ **Antibiotic-resistant bacteria** can spread to humans through **food** and direct contact with animals.

In animal farming







COPS
Colonizing
Opportunistic Pathogens
S. aureus → Livestock associated MRSA ST 398
C. difficile
E. Coli → ExPEC ST 131 Food borne UTI
K. pneumoniae

I nuovi (e vecchi) batteri resistenti come difenderci

- Regolamentazione dell'uso di antibiotici (e fungicidi) nell'allevamento nell'ambiente marino ed in agricoltura → in Italia e su scala globale

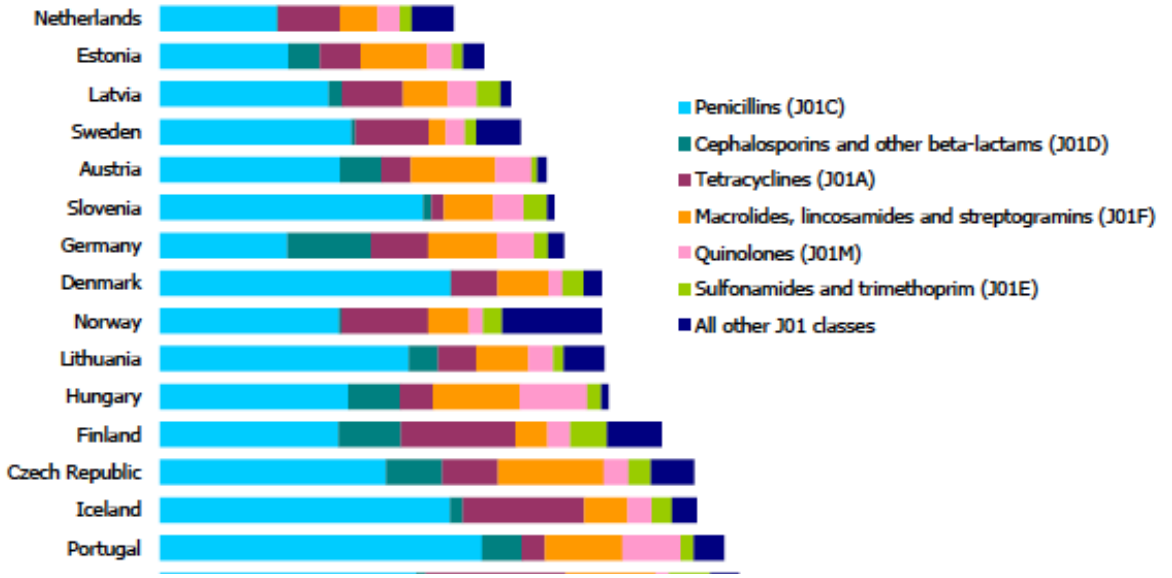
Combating Antimicrobial Resistance: Policy Recommendations to Save Lives

- **I. Adoption of Economic Incentives and Support for Other Collaborative Mechanisms to Address the Market Failure of Antibiotics**
- **II. New Regulatory Approaches to Facilitate Antimicrobial Development and Approval**
- **III. Greater Coordination of Relevant Federal Agencies' Efforts**
- **IV. Enhancement of Antimicrobial Resistance Surveillance Systems**
- **V. Strengthening Activities to Prevent and Control Antimicrobial Resistance**
- **VI. Significant Investments in Antimicrobial-Focused Research**
- **VII. Greater Investment in Rapid Diagnostics R&D and Integration into Clinical Practice**
- **VIII. Eliminating Non-Judicious Antibiotic Use in Animals, Plants, and Marine Environments**

Infectious Diseases Society of America 2012

4 **Humans** sometimes receive ant
prescribed to treat **infections**. How
bacteria develop resistance to anti
as a **natural, adaptive reaction**. An
resistant bacteria can then **spread**
treated patient to other persons.

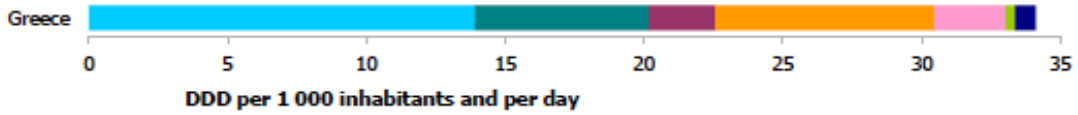
Figure 1. Consumption of antibiotics for systemic use in the community by antibiotic group in 30 EU/EEA countries, 2014 (expressed in DDD per 1 000 inhabitants and per day)



Emerging respiratory tract infections 4

Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections—needs, advances, and future prospects

Alimuddin Zumla, Jaffar A Al-Tawfiq, Virvel Enne, Mike Kidd, Christian Drosten, Judy Breuer, Marcel A Muller, David Hui, Markus Maeurer, Matthew Bates, Peter Mwaba, Rafaat Al-Hakeem, Gregory Gray, Philippe Gautret, Abdullah A Al-Rabeeah, Ziad A Memish, Vanya Gant



PLOS ONE

RESEARCH ARTICLE

A Novel Host-Proteome Signature for Distinguishing between Acute Bacterial and Viral Infections

Kfir Oved[1]*, Asi Cohen[1], Olga Boico[1], Roy Navon[1], Tom Friedman[1,2], Liat Etshtein[1,3], Or Kriger[1¤a], Ellen Bamberger[1,2,5], Yura Fonar[1¤b], Renata Yacobov[4], Ron Wolchinsky[6], Galit Denkberg[7], Yaniv Dotan[3,8], Amit Hochberg[4], Yoram Reiter[6], Moti Grupper[3,9], Isaac Srugo[3,5], Paul Feigin[10], Malka Gorfine[10], Irina Chistyakov[3,5], Ron Dagan[11], Adi Klein[4], Israel Potasman[3,9], Eran Eden[1]*

1 MeMed Diagnostics, Tirat Carmel, Israel, 2 Rambam Medical Center, Haifa, Israel, 3 Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, 4 Department of Pediatrics, Hillel Yaffe Medical Center, Hadera, Israel, 5 Department of Pediatrics, Bnai-Zion Medical Center, Haifa, Israel, 6 Faculty of Biology, Technion-Israel Institute of Technology, Haifa, Israel, 7 Applied Immune Technologies, Haifa, Israel, 8 Department of Internal Medicine, Bnai-Zion Medical Center, Haifa, Israel, 9 Infectious Diseases Unit, Bnai-Zion Medical Center, Haifa, Israel, 10 Faculty of Industrial Engineering and Management, Technion-Israel Institute of Technology, Haifa, Israel, 11 Pediatric Infectious Disease Unit and Clinical Microbiology Laboratory, Soroka Medical Center, Beer-Sheva, Israel

IS TRAIL THE HOLY GRAIL ?

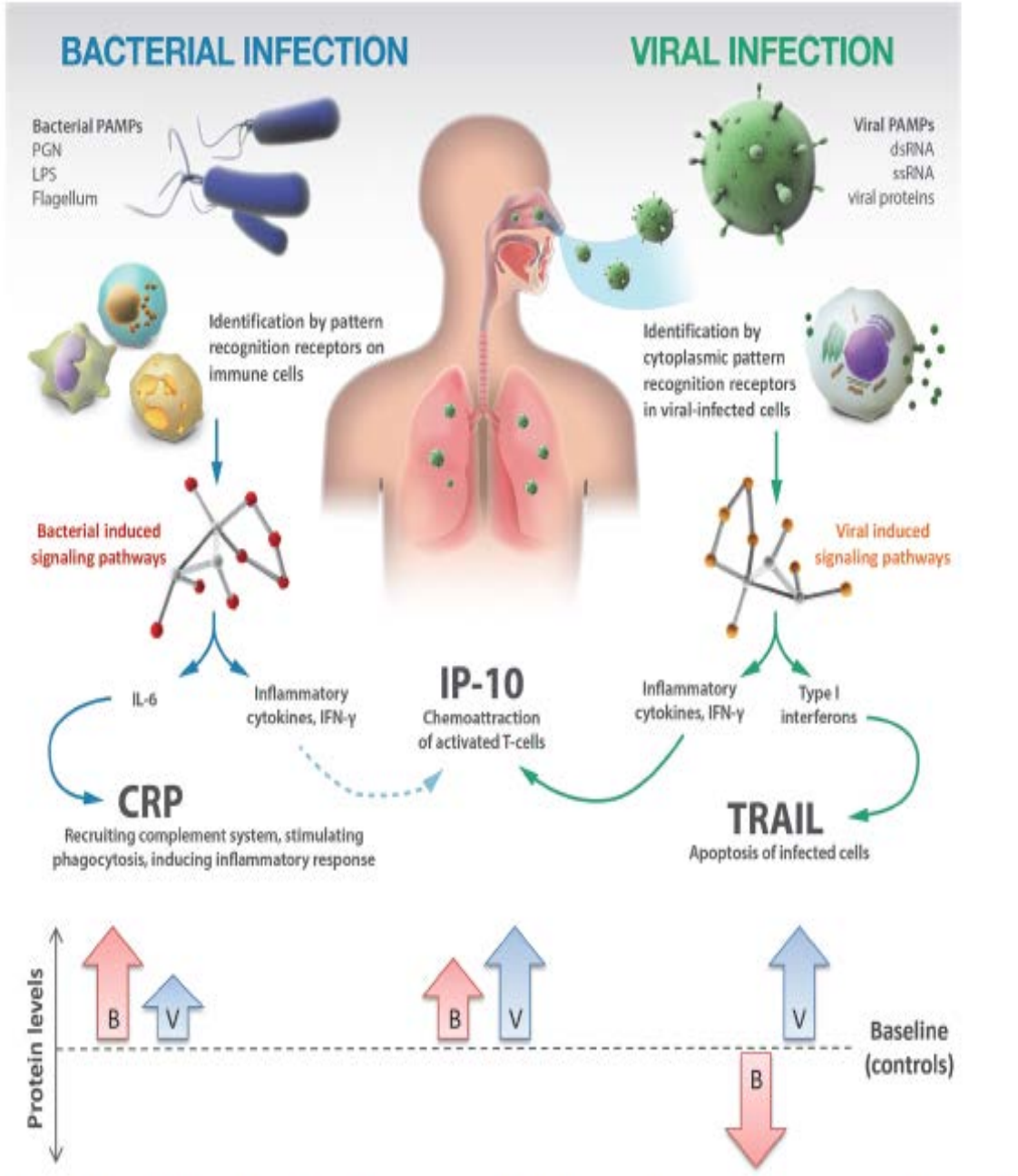


Fig 4. TRAIL, IP-10 and CRP participate in different signaling pathways and exhibit complementary dynamics in response to bacterial (B) and viral (V) infections. PAMPs—pathogen-associated molecular patterns; PGN—peptidoglycan; LPS—lipopolysaccharide.

doi:10.1371/journal.pone.0120012.g004

I nuovi (e vecchi) batteri resistenti come difenderci

- Regolamentazione dell'uso di antibiotici (e fungicidi) nell'allevamento nell'ambiente marino ed in agricoltura → in Italia e su scala globale
- Riduzione dell'impiego inappropriato di antibiotici nella medicina e pediatria generale
- Implementazione di tests rapidi "point of care" per la DD infezioni virali-batteriche per outpatients ed inpatients

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5 **Humans** may receive antibiotics in **hospitals** and then carry antibiotic-resistant bacteria. These can spread to other patients via **unclean hands** or **contaminated objects**. 6 Patients who may be carrying antibiotic-resistant bacteria will ultimately be sent **home,** and can spread these resistant bacteria to **other persons**.

ESCMID PUBLICATIONS 10.1111/1469-0691.12427

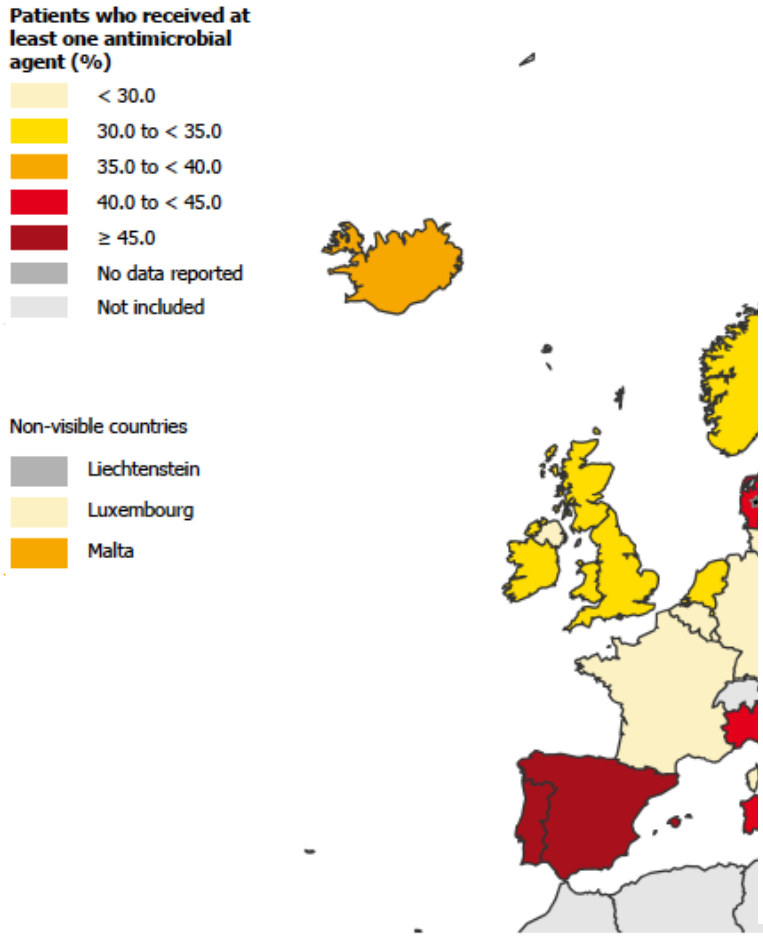
ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients

E. Tacconelli[1], M. A. Cataldo[2], S. J. Dancer[3], G. De Angelis[4], M. Falcone[5], U. Frank[6], G. Kahlmeter[7], A. Pan[8,9], N. Petrosillo[2], J. Rodríguez-Baño[10,11,12], N. Singh[13], M. Venditti[5], D. S. Yokoe[14] and B. Cookson[15]

	Situazione Endemica		Situazione epidemica	
	Evidenza	Raccomandazione	Evidenza	Raccomandazione
Igiene delle Mani	Moderata	Forte	Molto bassa	Forte
Screening attivo	Non considerato		Moderata	Forte
Precauzioni da contatto	Moderata	Forte	Moderata	Forte
Alert Code	Moderata	Condizionale	Moderata	Forte
Cohorting pz.	Non considerato		Moderata	Condizionale
Cohorting staff	Non considerato		Moderata	Forte
Stanza d'isolamento	Moderato	Forte	Moderata	Forte
Educazione personale	Moderata	Condizionale	Moderata	Condizionale
Pulizia ambientale	Moderata	Condizionale	Moderata	Condizionale
Screening ambientale	Non considerato		Basso	Condizionale
Antimicrobial Stewardship	Moderato	Condizionale	Molto Basso	Condizionale
Infratstruttura e programma	Non considerato		Moderato	Condizionale

Antimicrobial use in acute care hospitals in Europe

Prevalence of antimicrobial use in hospitals in acute Europe, ECDC PPS 2011-2012 in Europe



Percentage of antimicrobials for which the reason for use was documented in the patient's records in acute care hospitals in Europe, ECDC PPS 2011-2012 in Europe

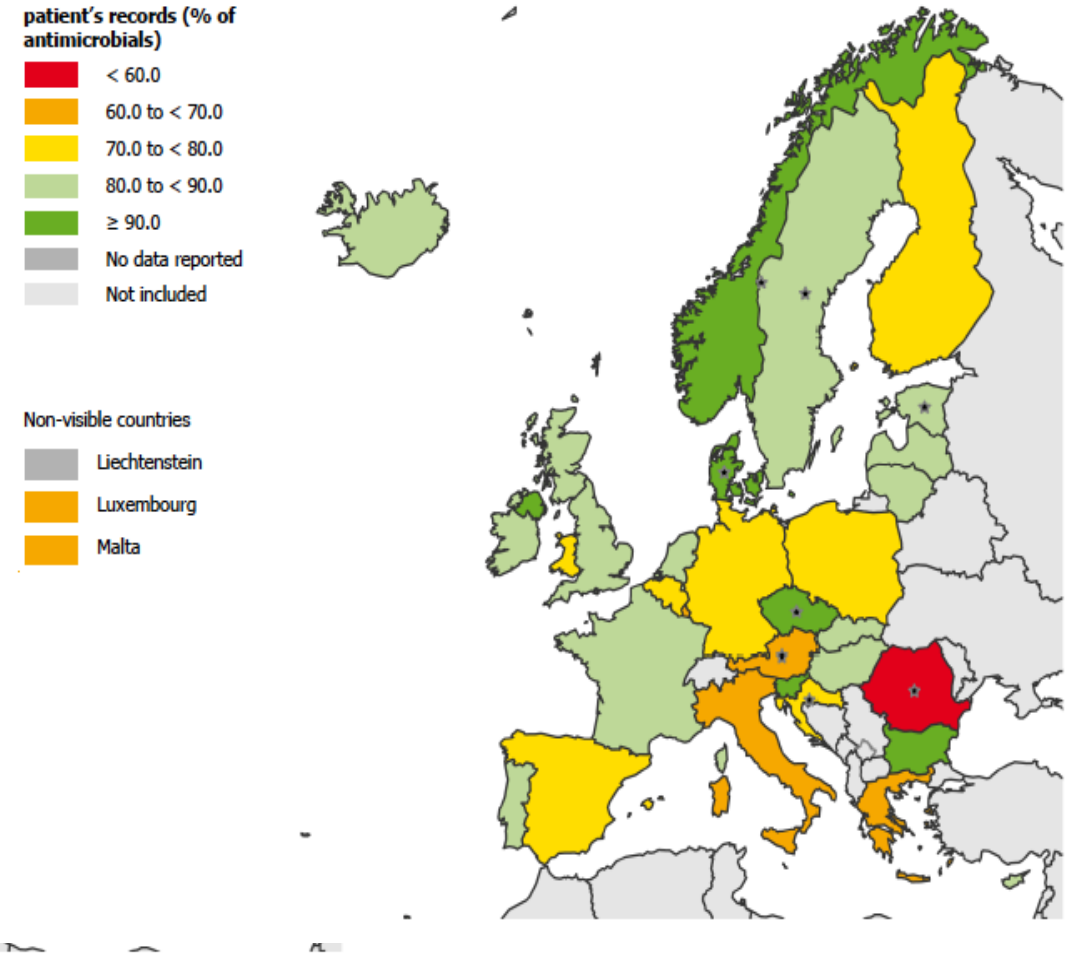
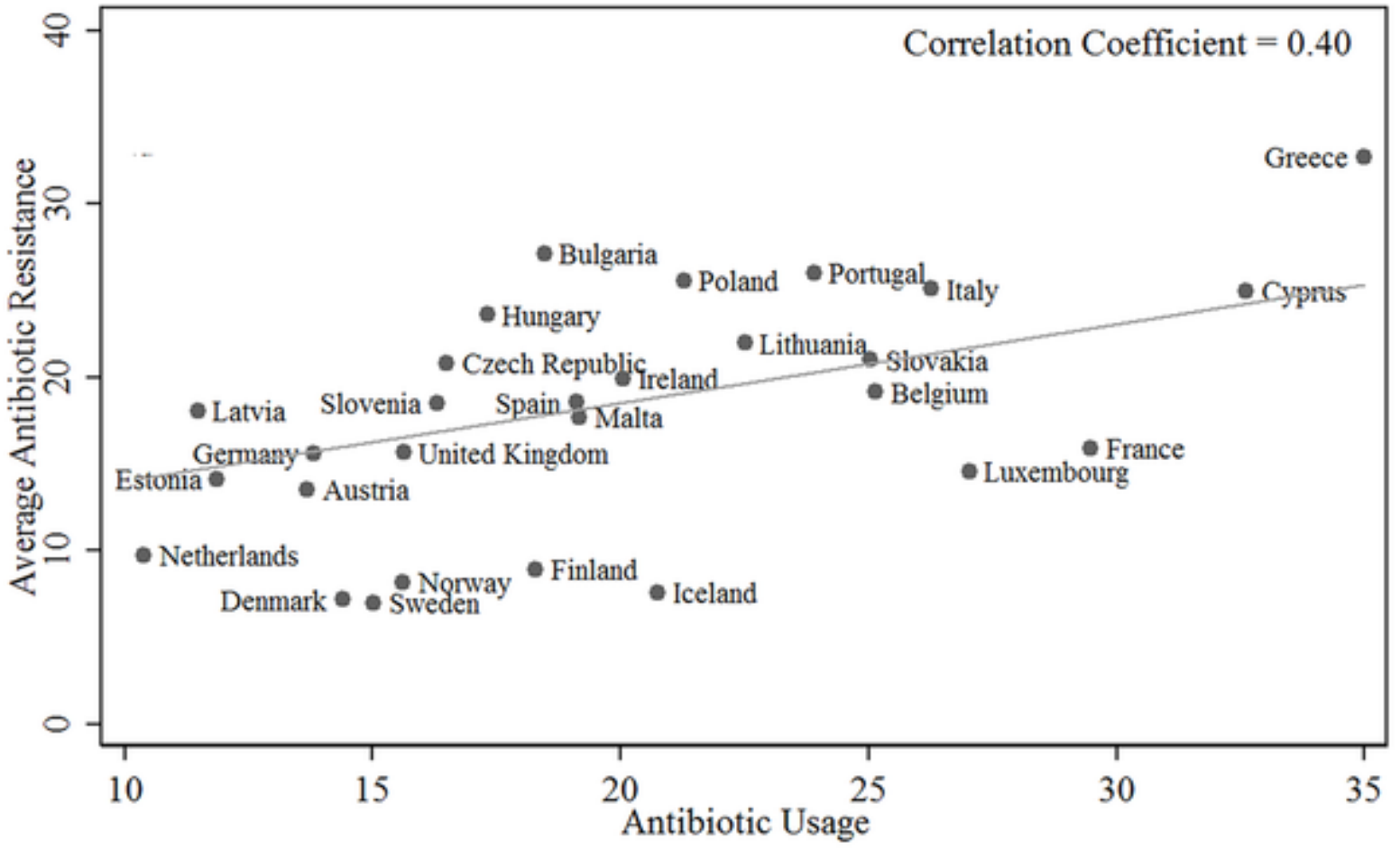


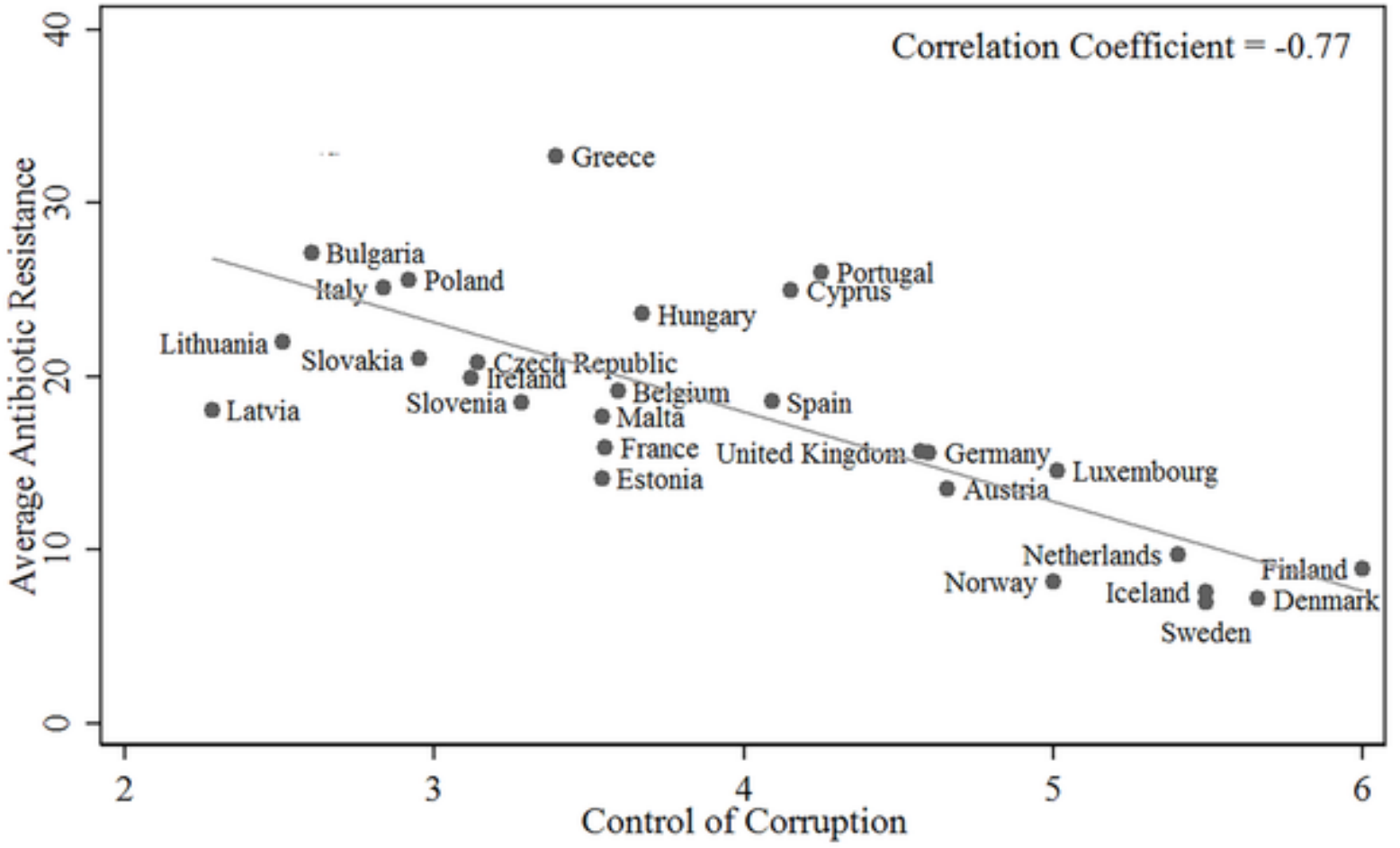
Fig 1. 'Average Microbial Resistance' against 'Antibiotic Use.'



Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
Antibiotic usage is from the European Surveillance of Antimicrobial Consumption (ESAC) Yearbook 2009

Collignon P, Athukorala Pc, Senanayake S, Khan F (2015) Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem. PLoS ONE 10(3): e0116746. doi:10.1371/journal.pone.0116746
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0116746

Fig 2. 'Average Microbial Resistance' against 'Control of Corruption.'



Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
The control of corruption indicator is from International Country Risk Guide

Collignon P, Athukorala Pc, Senanayake S, Khan F (2015) Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem. PLoS ONE 10(3): e0116746. doi:10.1371/journal.pone.0116746
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0116746

THE ROLE OF ANTIMICROBIAL STEWARDSHIP TO PREVENT THE SPREAD OF MDR GRAM NEGATIVES

Antimicrobial Stewardship Programs

ASPs are designed

- **to optimize antimicrobial therapy,**
- **to improve patients' outcomes,**
- **ensure cost-effective therapy and**
- **reduce adverse effects associated with antimicrobial use, including antimicrobial resistance**

MacDougall C et al. *Clin Microbiol Rev 2005; 18; 638–656*
Lesprit P et al. *Curr Opin Infect Dis 2008:21; 344–349*

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America 2016

- **Preauthorization and/or prospective audit and feedback for antibiotic prescription**
- Educational activities, ONLY to complement other stewardship activities.
- Develop and Implement Facility-Specic Clinical Practice Guidelines for Common Infectious Diseases Syndromes
- **Implement Interventions to Improve Antibiotic Use and Clinical Outcomes That Target Patients With Specic Infectious Diseases Syndromes (ie CDI)**
- Strategies (eg, antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing
- Clinical Decision Support Systems Integrated into the Electronic Health Record at the Time of Prescribing
- No antibiotic cycling
- **Implement PK monitoring and adjustment programs for aminoglycosides and vancomycin**
- Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum ß-Lactams and Vancomycin

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America 2016

- **Increase both appropriate use of oral antibiotics for initial therapy and the timely transition of patients from IV to oral antibiotics**
- For Patients With a Reported History of ß-Lactam Allergy Implement Allergy Assessments With the Goal of Improved Use of Frst-Line Antibiotics
- **Implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration**
- Stratified antibiograms (by location and age) selective and cascade reporting of antibiotics
- Rapid Viral Testing for Respiratory Pathogens to Reduce the Use of Inappropriate Antibiotics
- Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes
- ICUs with suspected infection, use of serial PCT measurements
- In patients with hematologic malignancy incorporating nonculture-based fungal markers
- Measure the impact of the program by monitoring antibiotic use as measured by days of therapy (DOTs) in preference to defined daily dose (DDD) **and measure antibiotic costs**

Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant *Staphylococcus aureus* infections across a region of Scotland: a non-linear time-series study

Timothy Lawes, José-María Lopez-Lozano, Cesar A Nebot, Gillian Macartney, Rashmi Subbarao-Sharma, Ceri RJ Dare, Karen D Wares, Ian M Gould

	Without intervention	With intervention	Marginal difference in MRSA prevalence density associated with successive interventions			MRSA cases prevented per year (95% CI)
			Absolute reduction (95% CI)	p value	Relative reduction† (95% CI)	
Hospitals						
Hand hygiene campaign (January, 2007)	1·890	1·500	0·390 (–0·527 to 1·307)	0·448	21% (–27 to 69)	246 (–316 to 822)
Universal screening (August, 2008)	1·417	1·129	0·288 (–0·725 to 1·53)	0·495	20% (–51 to 92)	180 (–444 to 796)
Hospital antibiotic stewardship (May, 2009)	1·091	0·499	0·592 (0·001 to 1·180)	0·049	54% (1 to 100)	355 (1 to 714)
Combined	1·890	0·947	0·943 (0·267 to 1·619)	0·006	50% (14 to 86)	592 (168 to 1017)
Community						
Indirect effects (hospital interventions)*	0·071	0·045	0·026 (0·008 to 0·038)	0·001	32% (11 to 54)	390 (128 to 652)
Primary care antibiotic stewardship (May, 2009)	0·045	0·028	0·017 (0·004 to 0·029)	0·012	37% (9 to 64)	281 (71 to 491)
Combined	0·071	0·038	0·033 (0·018 to 0·048)	<0·0001	47% (25 to 68)	567 (311 to 822)

Data are MRSA prevalance density in cases per 1000 OBDs (hospital) or cases per 10 000 IDs (community), unless indicated otherwise. Differences are calculated between observed (with intervention) and forecasted (without intervention) scenarios. MRSA=meticillin-resistant *Staphylococcus aureus*. OBDs=occupied bed days. IDs=inhabitants per day. *Effects of hospital-based interventions on community MRSA via reduction in hospital MRSA prevalence density (a predictor of rates in the community). †Described as (MRSA prevalence density without intervention — prevalence density with intervention)/MRSA prevalence density without intervention.

Table 2: **Potential effects of infection control measures and antibiotic stewardship**

7 **Travellers** requiring hospital care while visiting a country with a high prevalence of antibiotic resistance may **return** with antibiotic-resistant bacteria.

8 Even if not in contact with healthcare, travellers may **carry and import** resistant bacteria acquired from food or the environment during travel.

Through travel

Bloomberg Markets Tech Pursuits Politics Opinion Businessweek

A Scary New Superbug Gene Has Reached at Least 19 Countries

Bacteria that resist last-resort drugs were identified two months ago in China. Now scientists are finding them all over.

Graphic: NRDC, all-free-download.com, Source: The Lancet, Telegraph, Toronto Star, CIDRAP

I nuovi (e vecchi) batteri resistenti come difenderci

- Regolamentazione dell'uso di antibiotici (e fungicidi) nell'allevamento nell'ambiente marino ed in agricoltura → in Italia e su scala globale
- Riduzione dell'impiego inappropriato di antibiotici nella medicina e pediatria generale
- Implementazione di tests rapidi "point of care" per la DD infezioni virali-batteriche per outpatients ed inpatients
- Implementare programmi di antibiotic stewardship per ottimizzare l'uso degli antibiotici nella comunità ed in settings clinici
- Sorveglianza infezioni dei "malati viaggiatori"

I nuovi (e vecchi) batteri multi-resistenti: come difenderci

- Definizione
- Rilevanza del problema in Italia
- Come difenderci:
  - political governance
  - clinical governance
- Nuove sfide nuove risposte

How to escape from the ESKAPE gang

THE PERSISTENT CHALLENGE OF MDR *ENTEROCOCCUS SPP*

THE VANCO MIC CREEP OF *STAPHYLOCOCCUS AUREUS*

THE OMINOUS SPREAD OF KPC *KLEBISELLA PNEUMONIAE*

THE MDR/XDR *ACINETOBACTER* REBUS

THE INCREASING INCIDENCE of XDR/PDR *PSEUDOMONAS AERUGINOSA*

THE EXPLOSION OF ESBL *ENTEROBACTERIACEAE*

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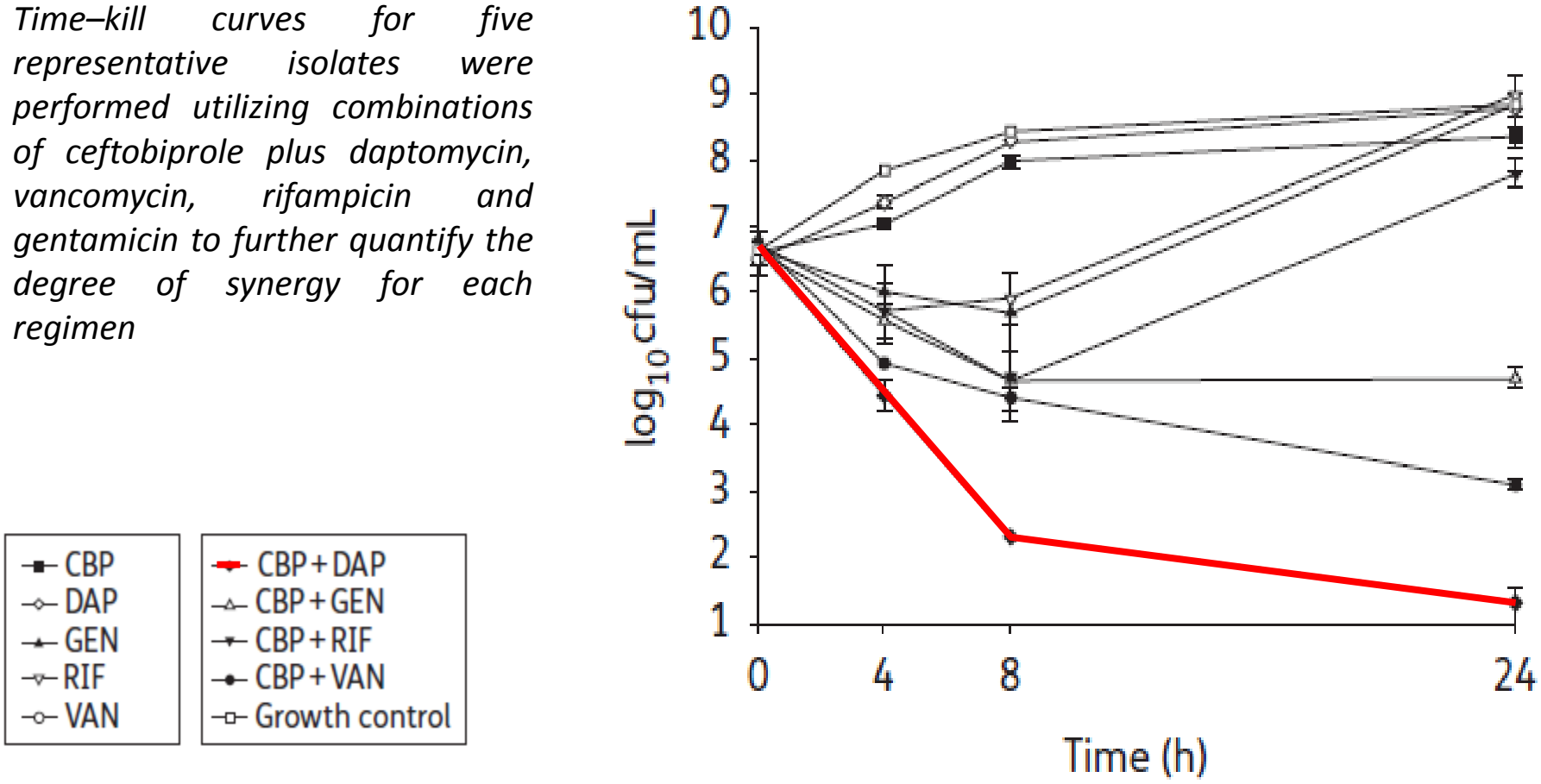
THE EXPLOSION OF ESBL *ENTEROBACTERIACEAE*

Potent synergy of ceftobiprole plus daptomycin against multiple strains of S. aureus with various resistance phenotypes. *Barber KE et al, J Antimicrob Chemother 2014; 69: 3006–10*

Broth microdilution MICs of ceftobiprole, daptomycin, vancomycin, rifampicin and gentamycin were evaluated for 20 MRSA isolates. Combination MICs were additionally evaluated in the presence of subinhibitory concentrations of ceftobiprole to assess synergism.

Time–kill curves for five representative isolates were performed utilizing combinations of ceftobiprole plus daptomycin, vancomycin, rifampicin and gentamicin to further quantify the degree of synergy for each regimen



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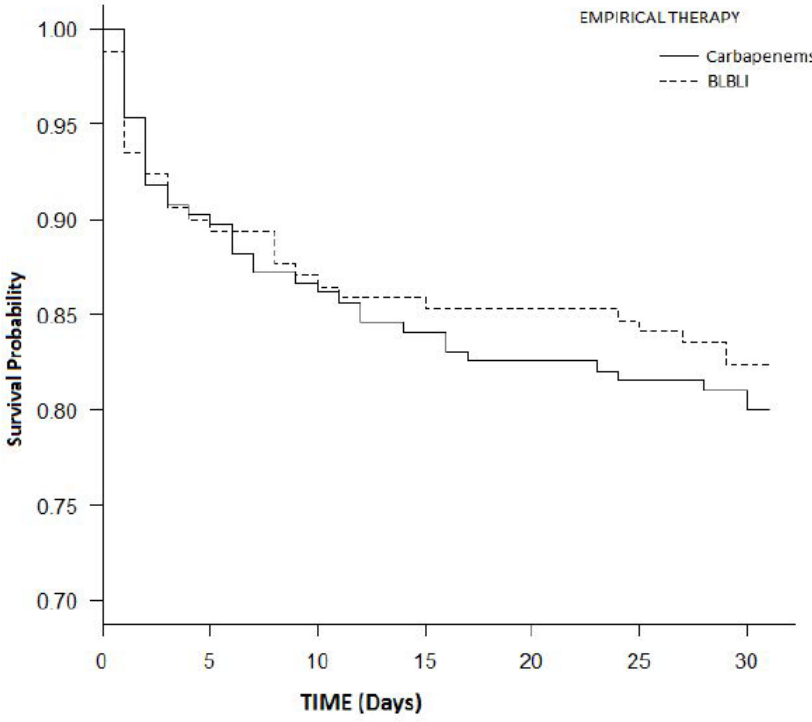
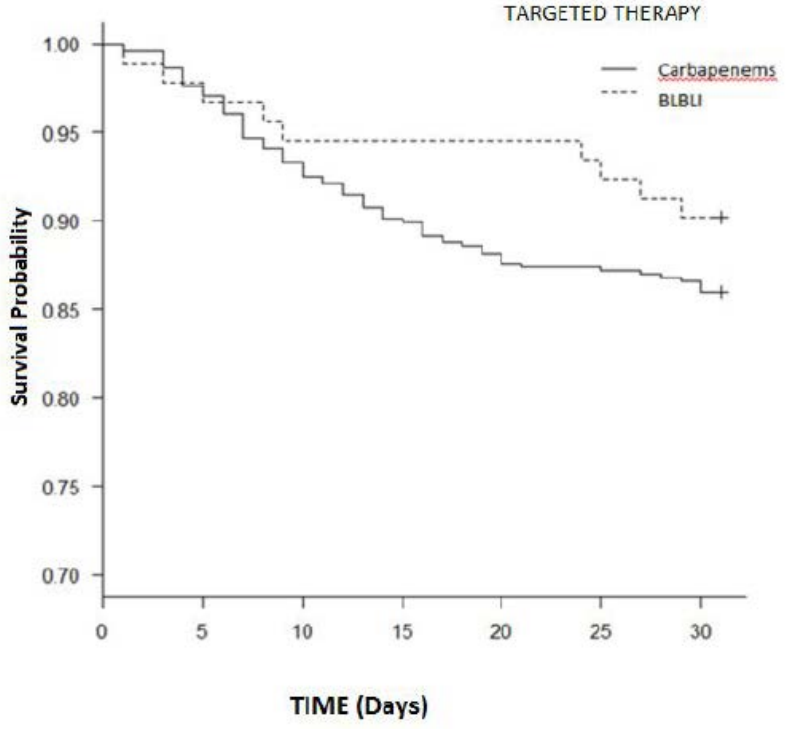
AAC Accepted Manuscript Posted Online 2 May 2016
Antimicrob. Agents Chemother. doi:10.1128/AAC.00365-16

β-Lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: a multinational, pre-registered cohort study.

Authors: Belén Gutiérrez-Gutiérrez,[1] Salvador Pérez-Galera,[1] Elena Salamanca,[1] Marina de Cueto,[1] Esther Calbo[2], Benito Almirante,[3] Pierluigi Viale,[4] Antonio Oliver,[5] Vicente Pintado,[6] Oriol Gasch,[7] Luis Martínez-Martínez,[8] Johann Pitout,[9] Murat

BLBLI, if active in vitro, appear as effective as carbapenems for ET and TT of BSI due to ESLB-E regardless of the source and specific species.
These data may help to avoid the overuse of carbapenems.





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International Journal of Antimicrobial Agents ■■ (2016) ■■–■■

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum β-lactamase urinary tract infections

Michael P. Veve [a,b], Jamie L. Wagner [a,b,1], Rachel M. Kenney [b], Jenny L. Grunwald [b], Susan L. Davis [a,b,*]

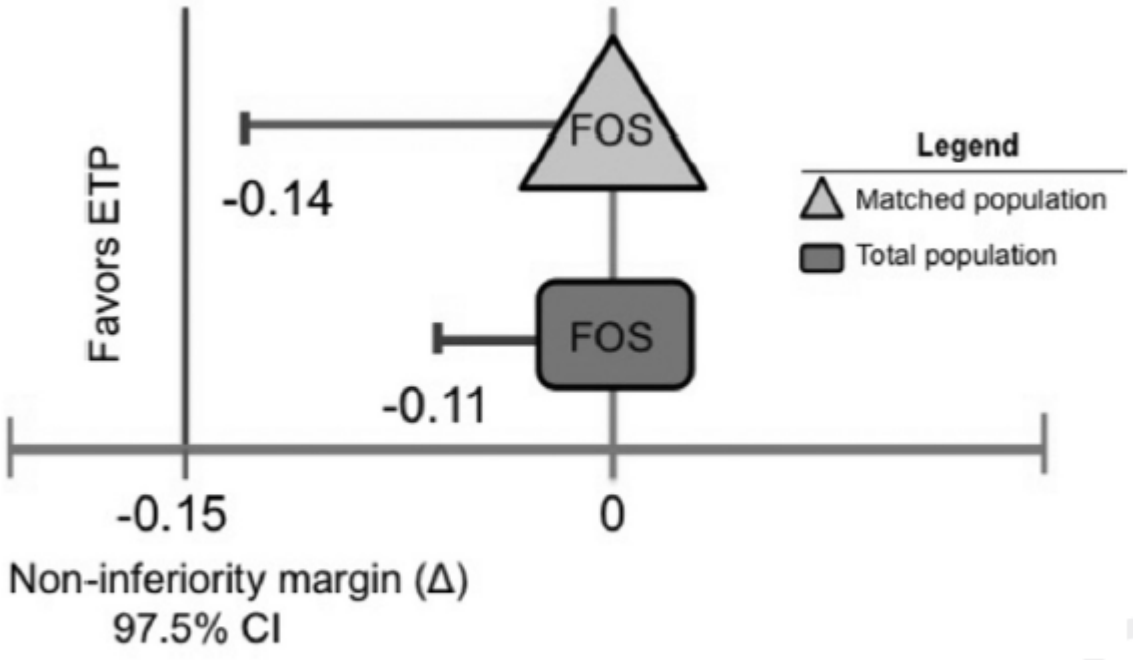

Fig. 1. Non-inferiority of fosfomycin (FOS) to ertapenem (ETP) for outpatient treatment of extended-spectrum β-lactamase urinary tract infections.

Fosfomycin was non-inferior to ertapenem for treating outpatient ESBL UTIs and should be considered as appropriate step-down therapy for these infections.

How to escape from the ESKAPE gang

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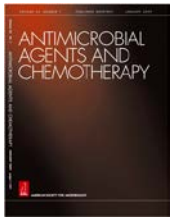
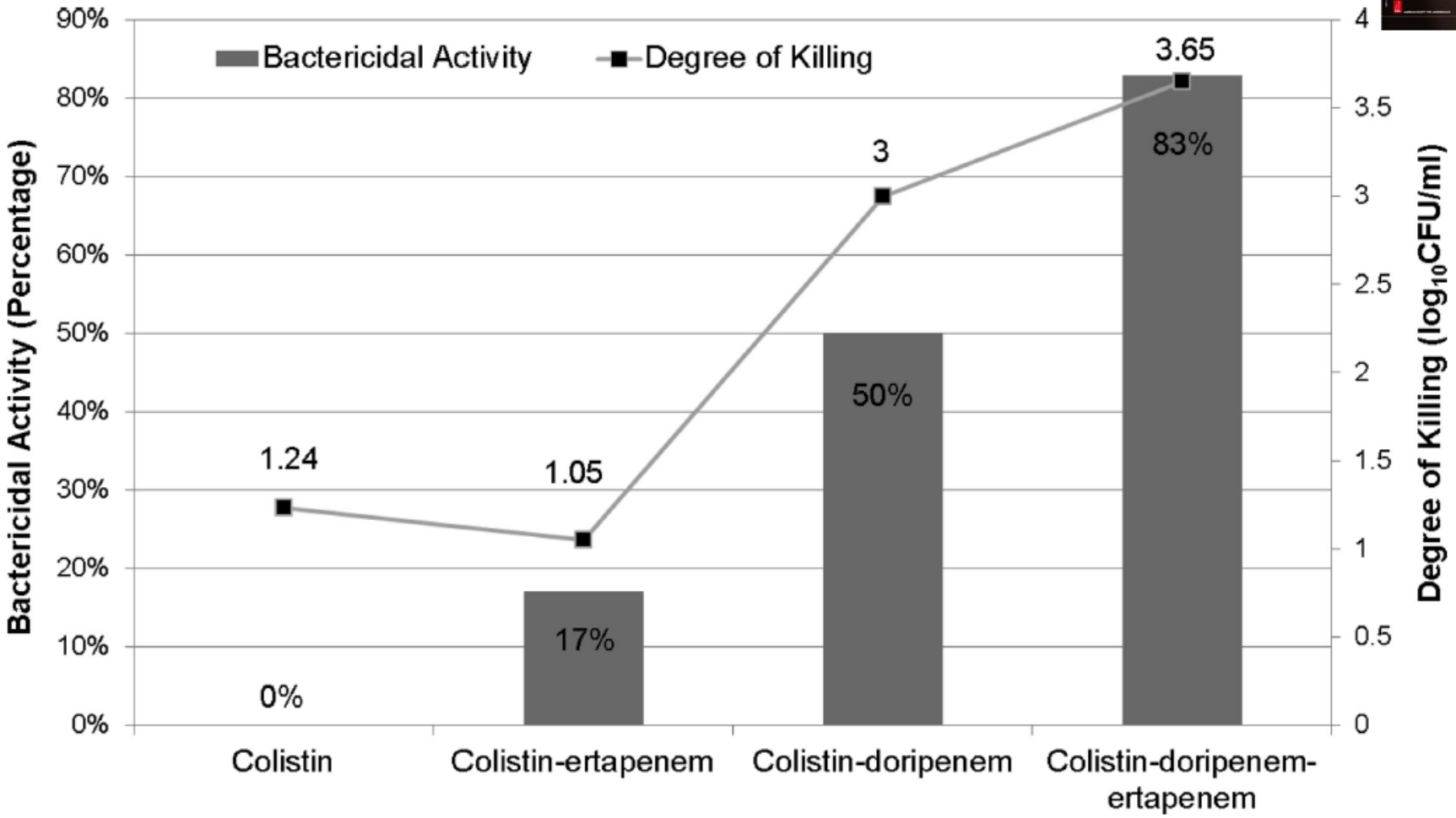
THE EXPLOSION OF ESBL *ENTEROBACTERIACEAE*

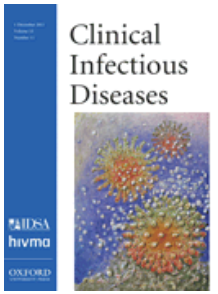
Bactericidal activity and degree of killing by single drugs and 2- and 3-drug combinations against KPC *K. pneumoniae* isolates



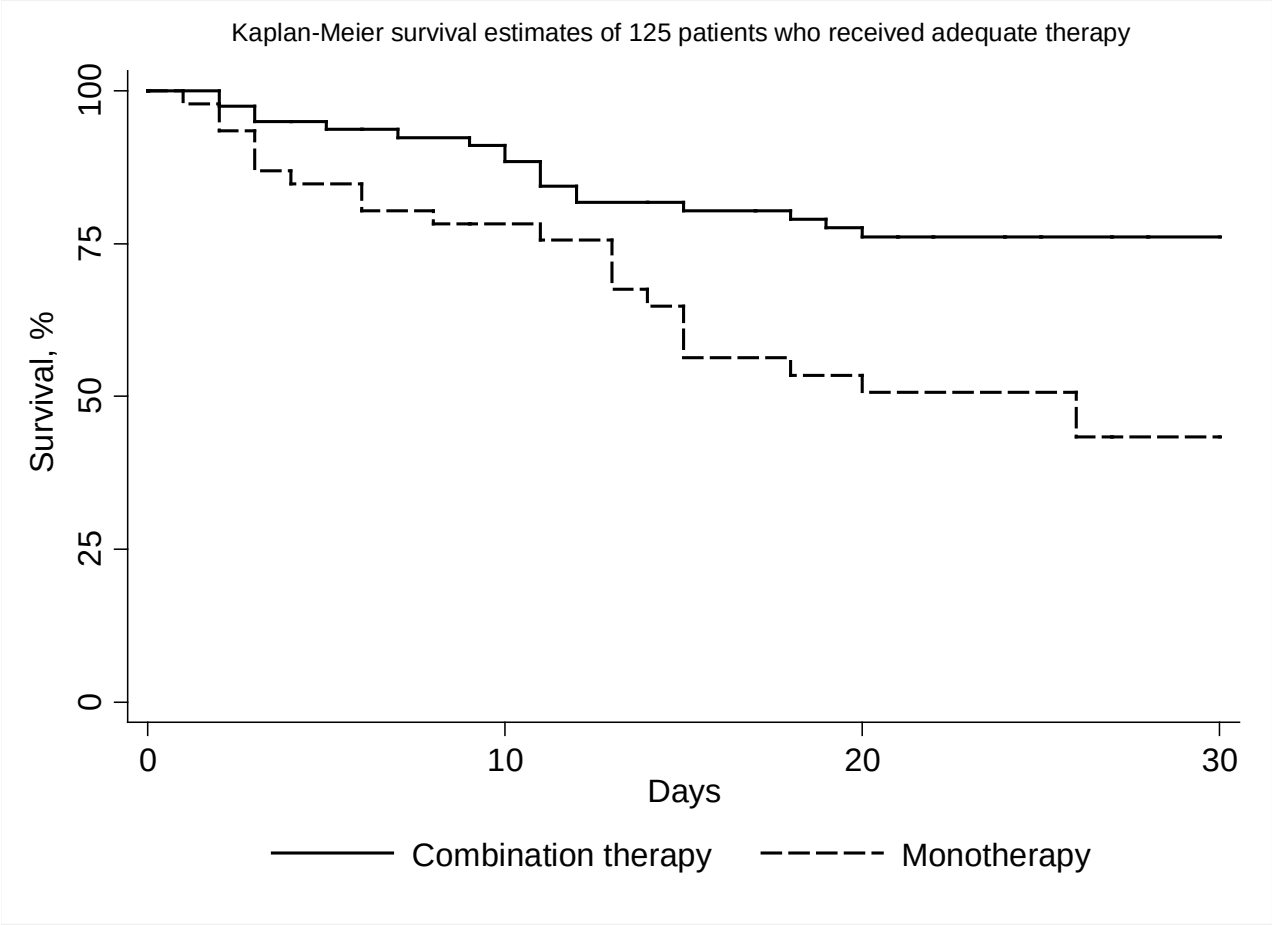


Hong AAC 2013

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy



Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]



Mortality:
25 of the 46 (54.3%) whose regimens were classified as monotherapy and 27 of the 79 (34.1%) who were on combination regimens (P = 0.02)

CID 2012:55 (1 October)

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+ MODEL
Journal of Microbiology, Immunology and Infection (2016) xx, 1–9
Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Colistin-sparing regimens against *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* isolates: Combination of tigecycline or doxycycline and gentamicin or amikacin

Hung-Jen Tang [a,b], Chih-Cheng Lai [c], Chi-Chung Chen [d,e], Chun-Cheng Zhang [a], Tzu-Chieh Weng [a], Yu-Hsin Chiu [f], Han-Siong Toh [a], Shyh-Ren Chiang [a], Wen-Liang Yu [d], Wen-Chien Ko [g,*], Yin-Ching Chuang [a,d,f,*]

Table 6 Summary of checkerboard assays of amikacin or gentamicin combined with doxycycline or tigecycline against 13 *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* isolates.

Combinations	Fractional inhibitory concentration index				Synergy (%)	Indifference (%)	Antagonism (%)
	Mean ± SD	Range	50%	90%			
AMK+TGC	0.63 ± 0.19	0.37–1	0.56	1	36.4	63.6	0.0
AMK+DOX	0.56 ± 0.16	0.31–1	0.51	0.75	48.5	51.5	0.0
GM+TGC	0.68 ± 0.19	0.37–1	0.62	1	28.6	71.4	0.0
GM+DOX	0.51 ± 0.20	0.25–1	0.5	0.75	67.6	32.4	0.0

AMK = amikacin; DOX = doxycycline; GM = gentamicin; SD = standard deviation; TGC = tigecycline.

- *Doxycycline alone or in combination with an aminoglycoside possesses potential antibacterial activity and can be considered an alternative for CRE infections..*

CEFTAZIDIME-AVIBACTAM

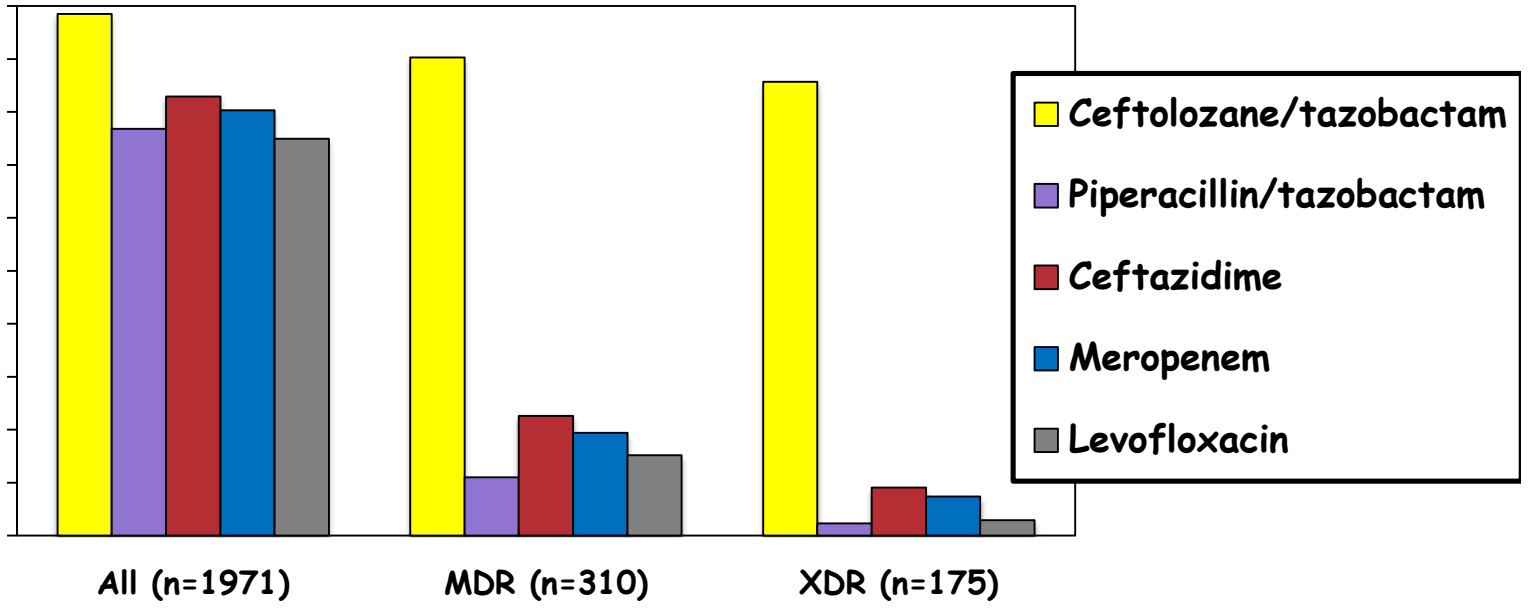
Avibactam is a non–b-lactam b-lactamase inhibitor, acting against the activities of Ambler class A and C and some Ambler class D enzymes

- Through the addition of avibactam, ceftazidime's activity is expanded to many ceftazidime-resistant and carbapenem-resistant Enterobacteriaceae and P. aeruginosa. This includes isolates producing a variety of Ambler class A and C b-lactamases including AmpC, ESBLs, and KPC, as well as select class D OXA enzymes.

- In contrast, ceftazidime-avibactam does not possess any appreciable activity against the Ambler class B metallo–b-lactamases.

- FDA approved as rescue option for CIAI and cUTI

In Vitro Activity of CEFTOLOZANE/TAZOBACTAM and Various Comparator Agents Against *P. aeruginosa* (US Hospitals 2011-2012)



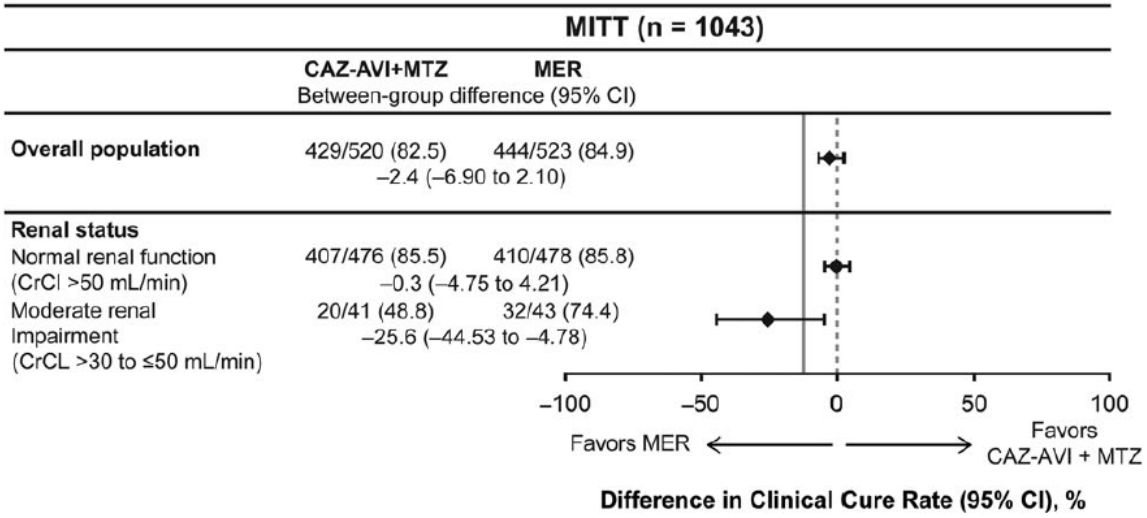
	Ceftolozane/ tazobactam		Piperacillin/ tazobactam		Ceftazidime		Meropenem		Levofloxacin	
	MIC_{50}/MIC_{90}	%S*[a]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]
All (1971)	0.5/2	98.5	8/>64	76.8	2/32	82.9	0.5/8	80.3	0.5/>4	74.9
MDR (310)	2/8	90.3	>64/>64	11	32/>32	22.6	8/>8	19.4	>4/>4	15.2
XDR (175)	4/16	85.7	>64/>64	2.3	32/>32	9.1	8/>8	7.4	>4/>4	2.9

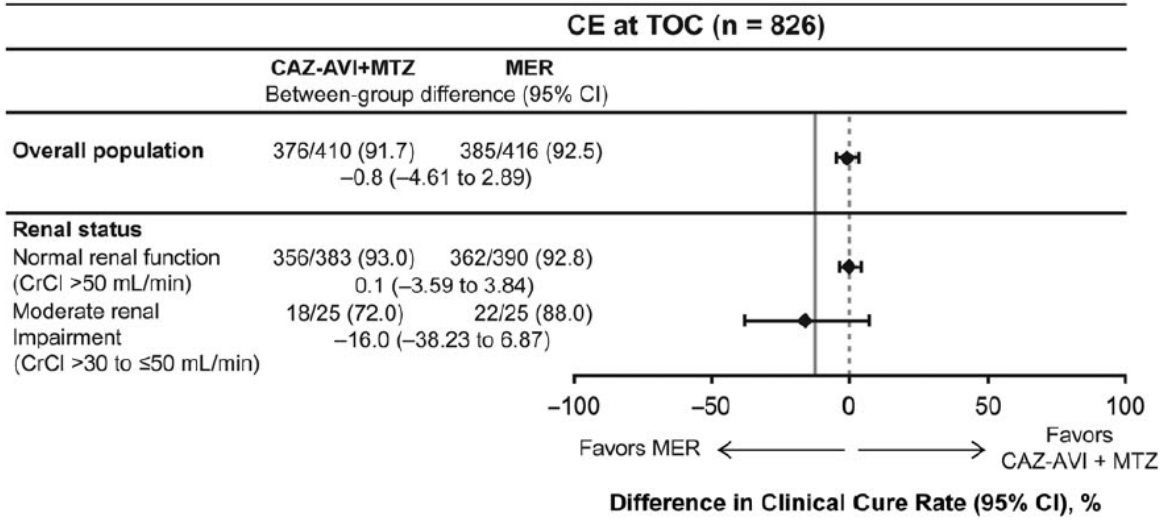
Farrell et al. Antimicrob Agents Chemother. 2013;57:6305-10.

Clinical Infectious Diseases
MAJOR ARTICLE

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,[3] Helen Broadhurst,[3] Greg G. Stone,[3] Douglas Rank,[4] Lily Llorens,[4] Paul Newell,[5] and Jan Pachl[6]





Clinical Infectious Diseases Advance Access published April 20, 2016

Ceftazidime/Avibactam and Ceftolozane/Tazobactam: "Second generation" beta-Lactam/beta-Lactamase Combinations

David van Duin[1] and Robert A. Bonomo[2,3,4,5]

- *Clinical trials showed non-inferiority to comparators of both agents when used in the treatment of complicated urinary tract infections and complicated intra-abdominal infections (when used with metronidazole).*
- *Results from pneumonia studies are not yet been reported.*

Clinical Infectious Diseases Advance Access published April 20, 2016

Ceftazidime/Avibactam and Ceftolozane/Tazobactam: "Second generation" beta-Lactam/beta-Lactamase Combinations

David van Duin[1] and Robert A. Bonomo[2,3,4,5]

The antimicrobial spectrum of activity of these antibiotics includes multi-drug resistant Gram-negative bacteria, including Pseudomonas aeruginosa. Ceftazidime/avibactam is also active against carbapenem resistant Enterobacteriaceae that produce KPC.

However, avibactam does not inactivate metallo-β-lactamases such as New Delhi metallo-β-lactamases.

NEW ANTIBIOTICS w/o RESISTANCE ?

- Teixobactin inhibition of cell wall synthesis (MRSA, VRE, MT)
- Pept-in (aggregating peptide CoNS)
- Antibody antibiotic coniugates (AAC) (MRSA)
- Aminomethylciclines (Paratek + Novartis)
- Multiple Antibiotic Resistance (MAR) locus small molecules inhibitors

Despite an immense sense of sadness this talk is dedicated to Giampietro Gesu
A Man A Doctor a Maestro and a Friend