

Infezioni multi-resistenti: nuove opportunità terapeutiche

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Dichiarazione su potenziali conflitti di interesse

Consulenze, partecipazione *advisory boards*, *speaker's bureau*, contratti/contributi di ricerca e di eventi studio: Accelerate Diagnostics, Alifax, Angelini ACRAF, Astellas, Biomerieux, Cepheid, NordicPharma

Microbiologi mancati



Consulenze microbiologiche in TI come intervento di Stewardship

American Journal of Infection Control 43 (2015) 1018–21

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American Journal of Infection Control

journal homepage: www.ajicjournal.org



Brief report

Impact of a clinical microbiology–intensive care consulting program in a cardiothoracic intensive care unit

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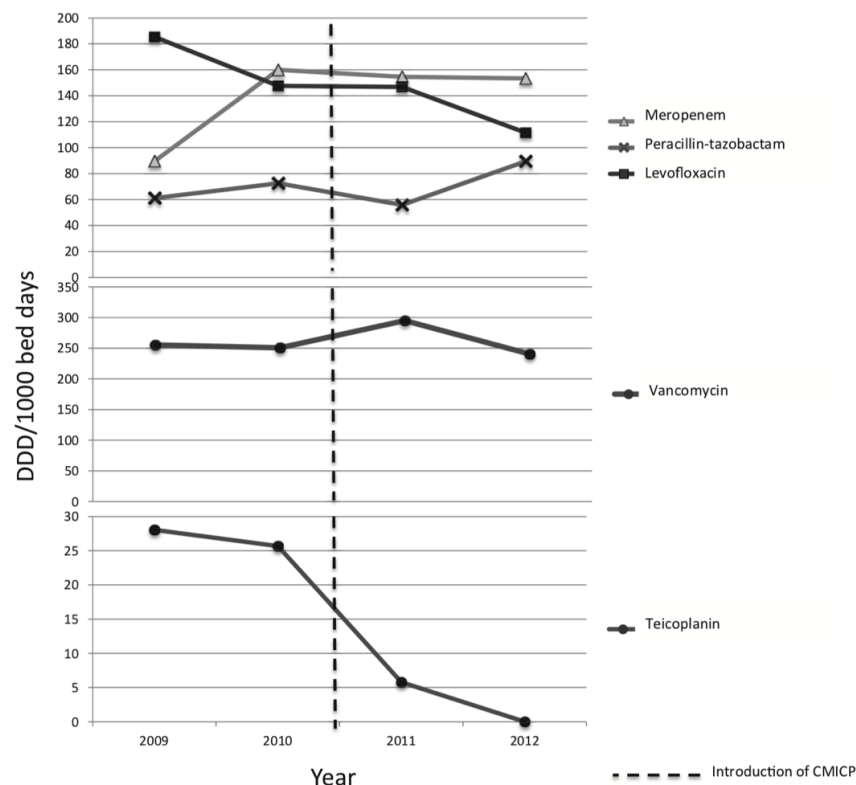
^a Department of Medical Biotechnologies, University of Siena, Siena, Italy

^b Cardiothoracic Anesthesia and Intensive Care Unit, Siena University Hospital, Siena, Italy

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^e Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy



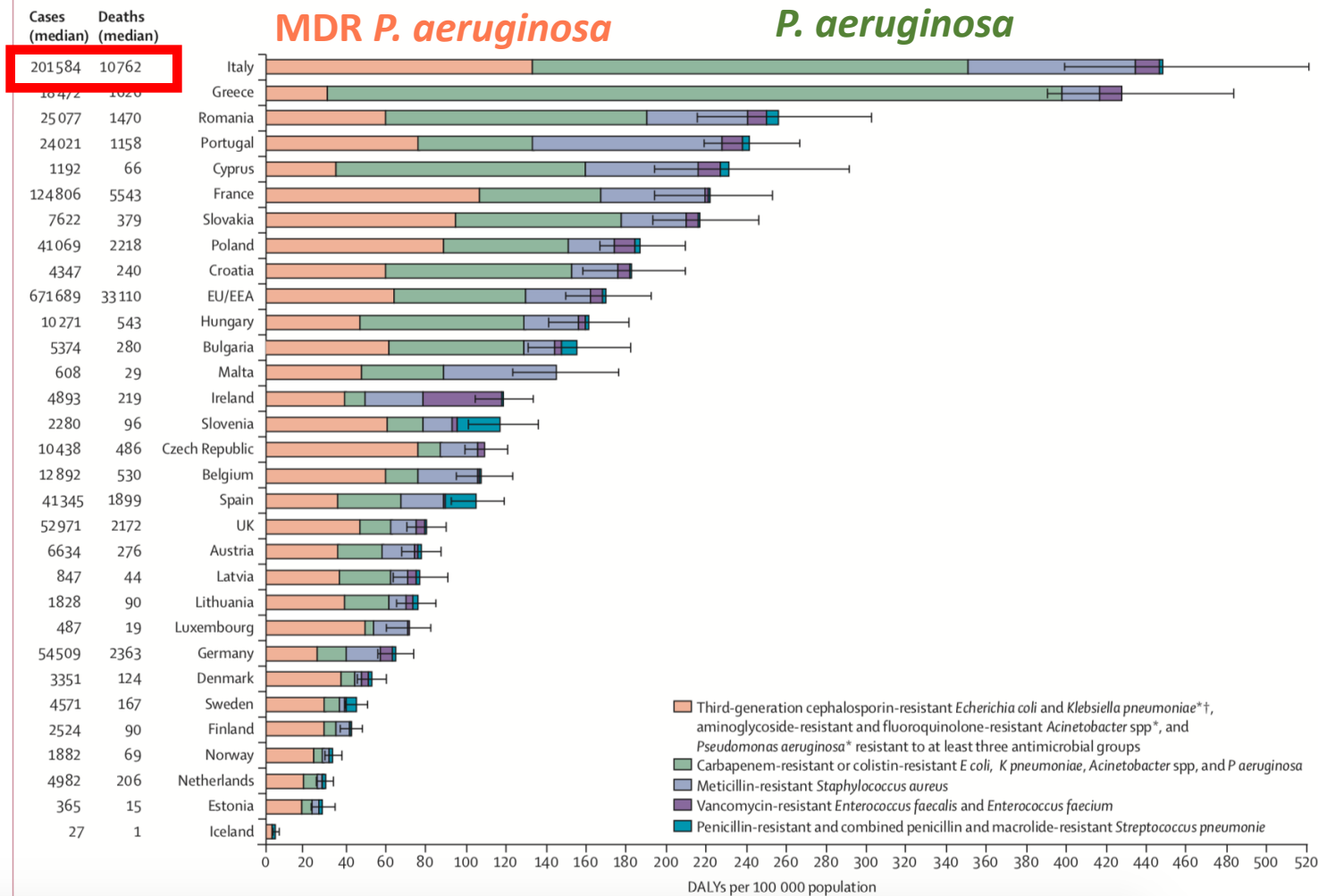
Impatto stimato infezioni da germi MDR

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



CARBA-R or COL-R *K. pneumoniae*,
Acinetobacter spp.,
P. aeruginosa

3GCR *Enterobacterales*
MDR *P. aeruginosa*



Antibiotici anti-MRSA

Older antibiotics

Vancomycin

Teicoplanin

**Resistance reported
but remains overall
uncommon**

Mutational in most cases

Transferable resistance:
- glycopeptides (exceptional)
- oxazolidinones (very rare)

Recent/new antibiotics

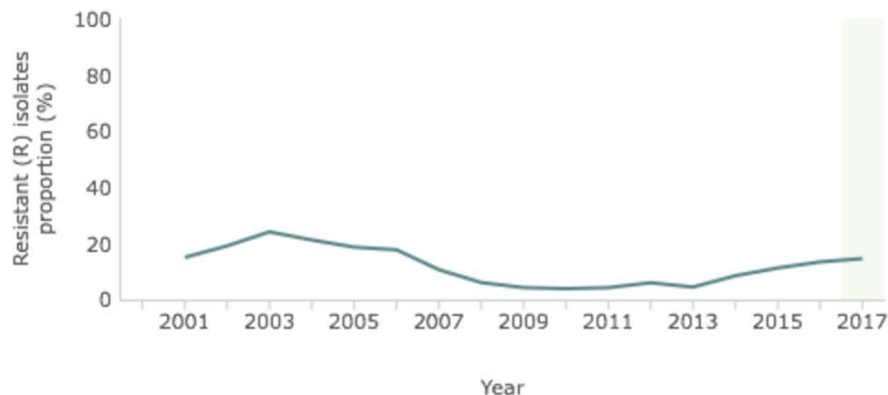
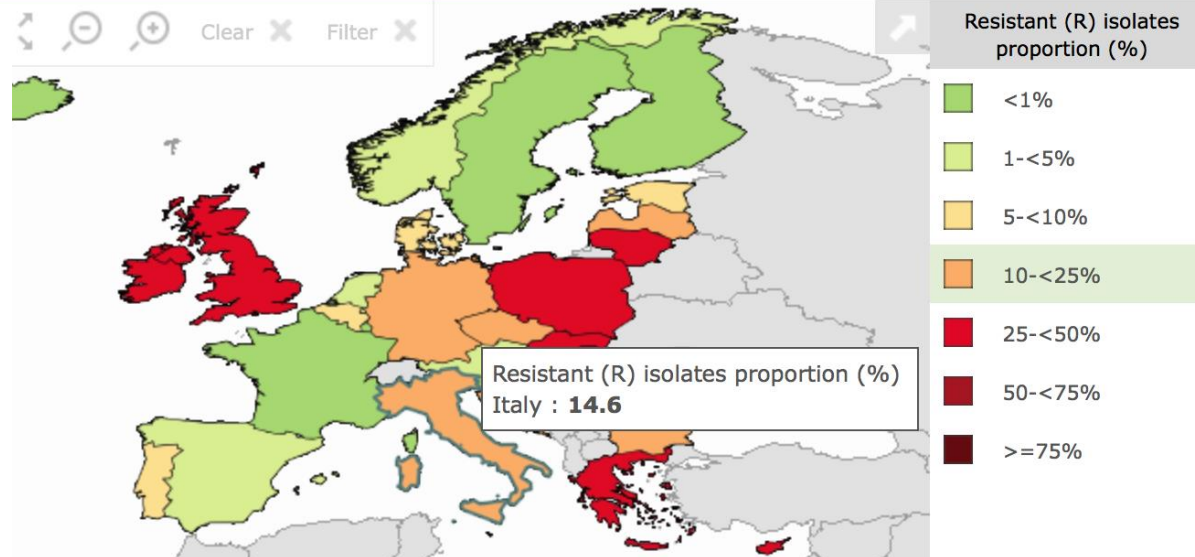
- **Daptomycin**
- Tigecycline
- Linezolid
- Tedizolid
- **Telavancin**
- **Dalbavancin**
- **Oritavancin**
- Ceftaroline
- Ceftobiprole

Resistenza ai Glicopeptidi in *Enterococcus faecium* (VRE)



Surveillance Atlas of Infectious Diseases

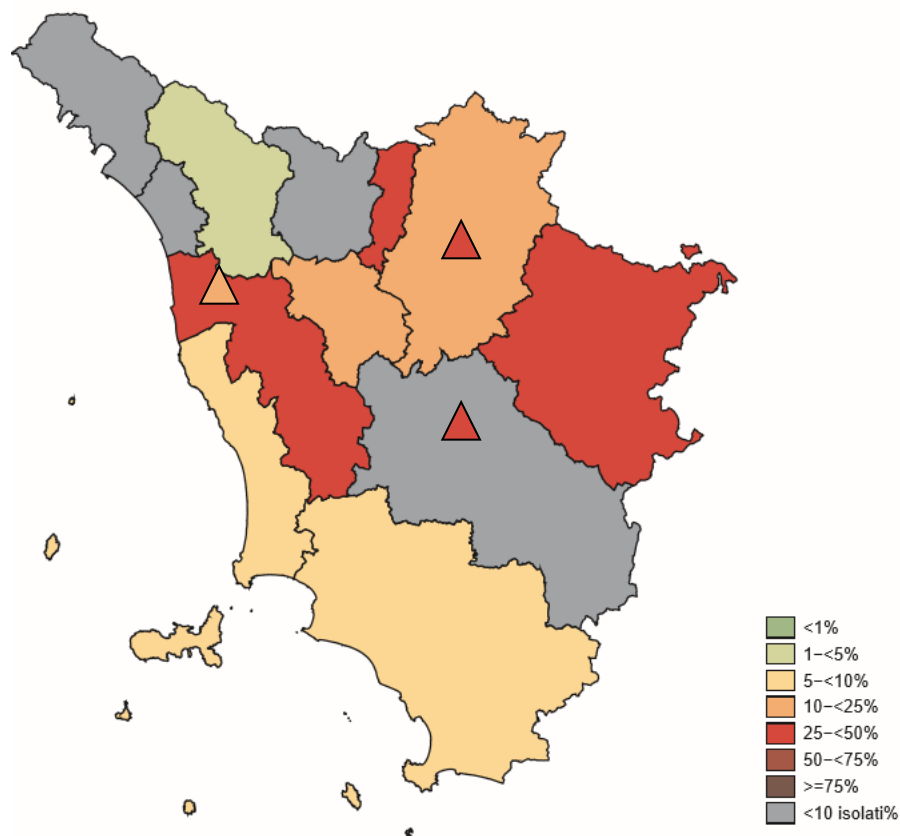
Antimicrobial resistance ▼ Enterococcus faecium ▼ Vancomycin ▼
Resistant (R) isolates proportion ▼ ▶ ◀◀ 2017 ▼ ▶▶



Resistenza ai Glicopeptidi in *Enterococcus faecium* (VRE), BSI Toscana 2018

Isolamento e profili di antibiotico sensibilità per *Enterococcus faecium*, batteriemie, Toscana 2018, Fonte ARS-SMART, ECDC

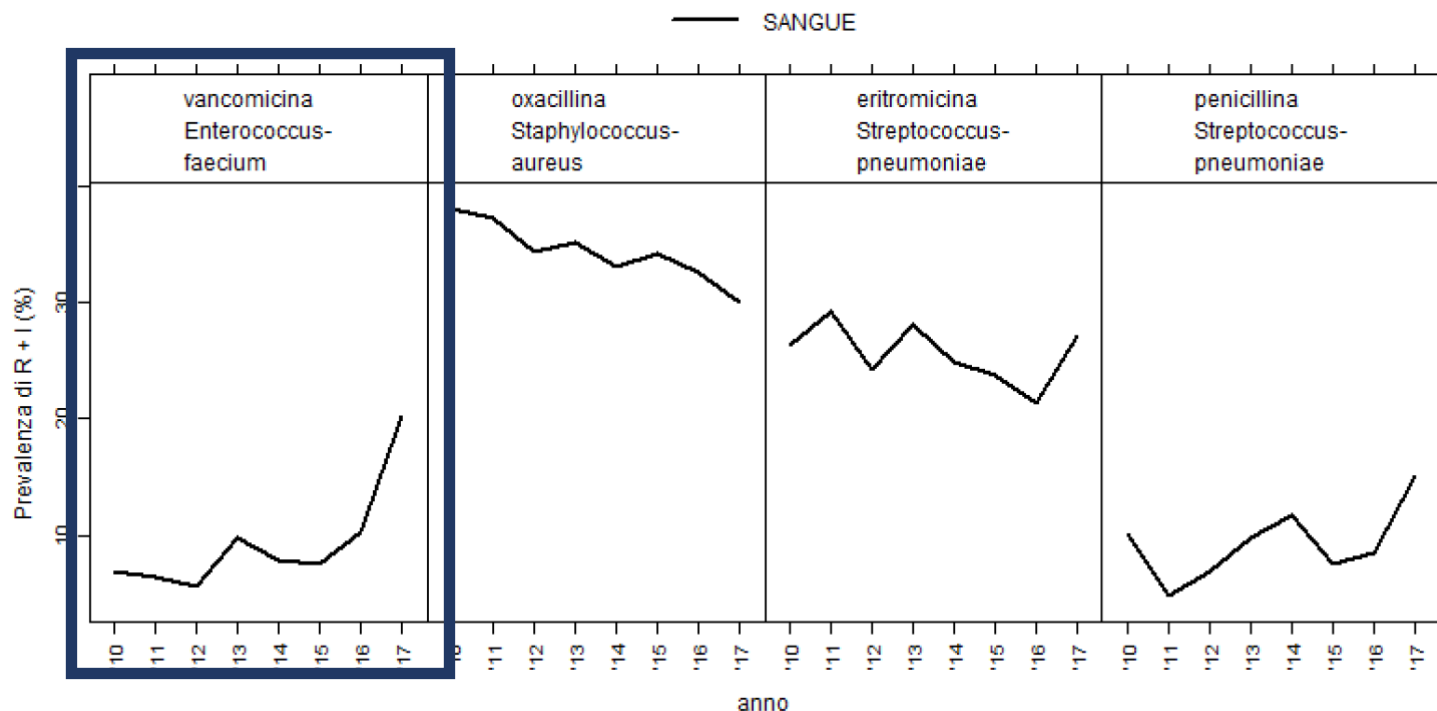
C) *E. faecium* resistente alla Vancomicina (VRE) Toscana 2018



TOSCANA 2018	TOSCANA 2017	ITALIA 2017	ITALIA 2016	EU 2016
23,1	24,5	14,6	13,4	11,8

6.1. *Staphylococcus aureus*, *Streptococcus pneumoniae* ed *Enterococcus faecium*

Figura 7. Resistenze nelle infezioni invasive da *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecium*



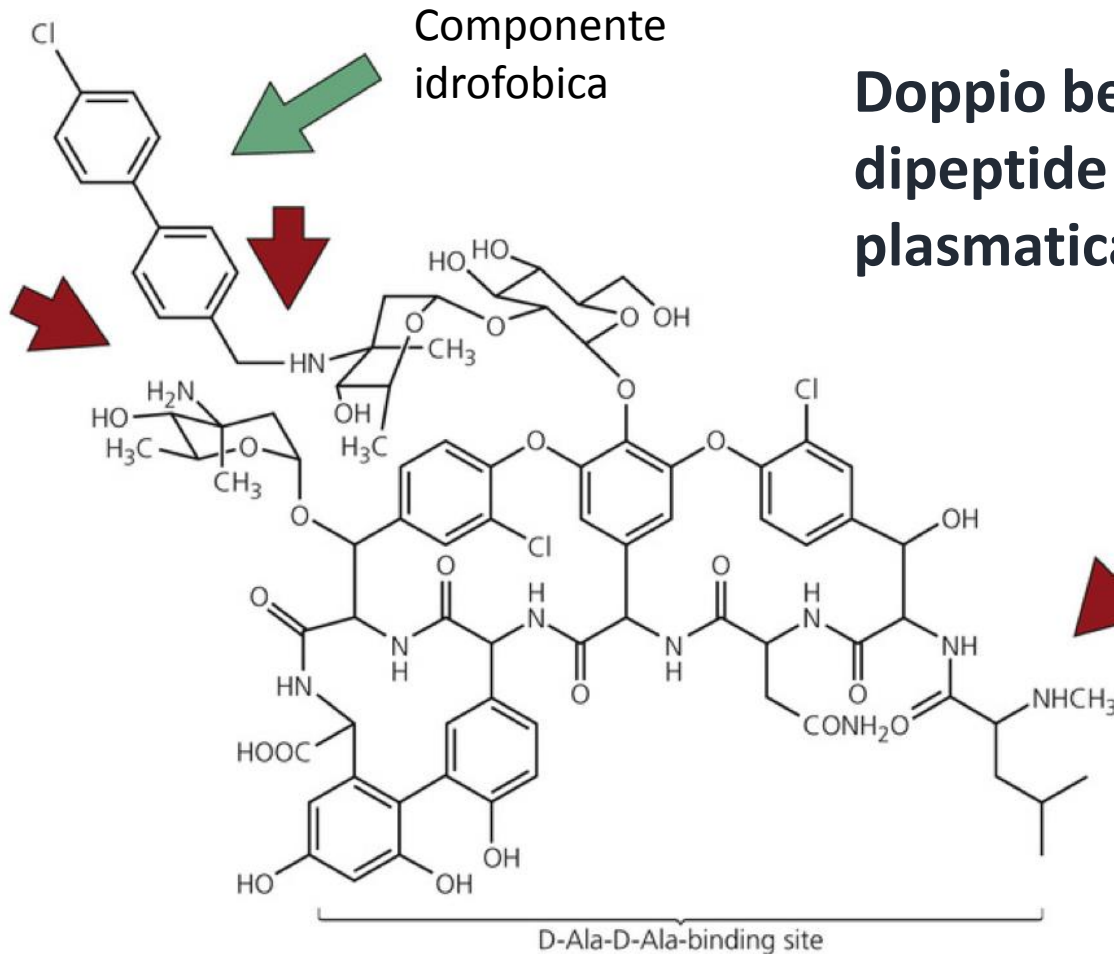
Recent significant increase

Fenotipi di resistenza *Enterococcus faecium/faecalis*.

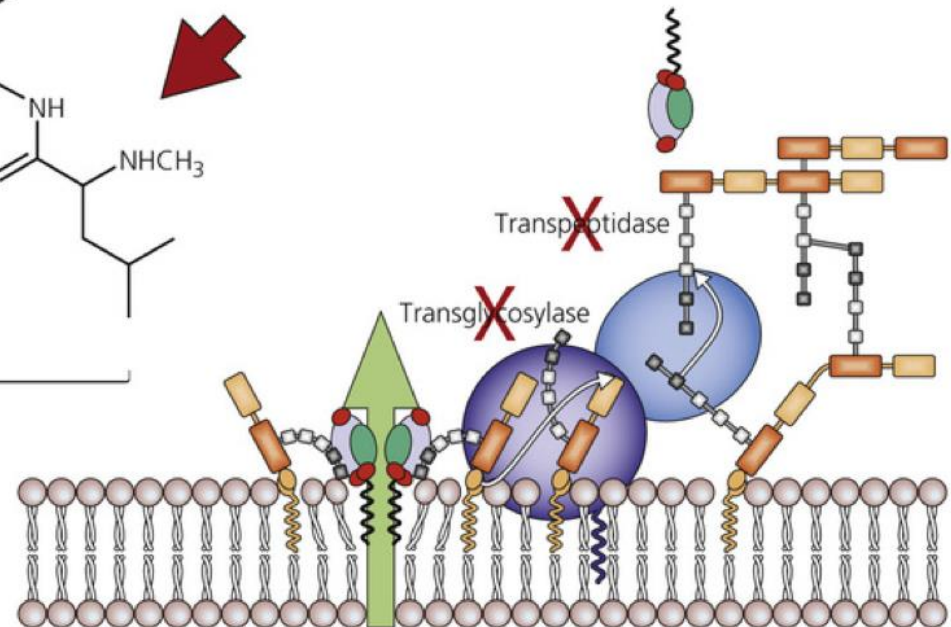
Enterococcus spp.

Antibiotics	Ampicillin-R <i>Enterococcus</i>	VRE (VanA)	VRE (VanB)
Oxacillin	●	●	●
Ampicillin	●	●	●
Vancomycin	●	●	●
Teicoplanin	●	●	●
Dalbavancin	●	●	●
Telavancin	●	●	●
Oritavancin	●	●	●

Oritavancina: meccanismo di azione



Doppio bersaglio molecolare:
dipeptide D-Ala-D-Ala e membrana plasmatica



Pseudomonas aeruginosa MDR, Europa 2017



Surveillance Atlas of Infectious Diseases

Antimicrobial resistance ▼

Pseudomonas aeruginosa ▼

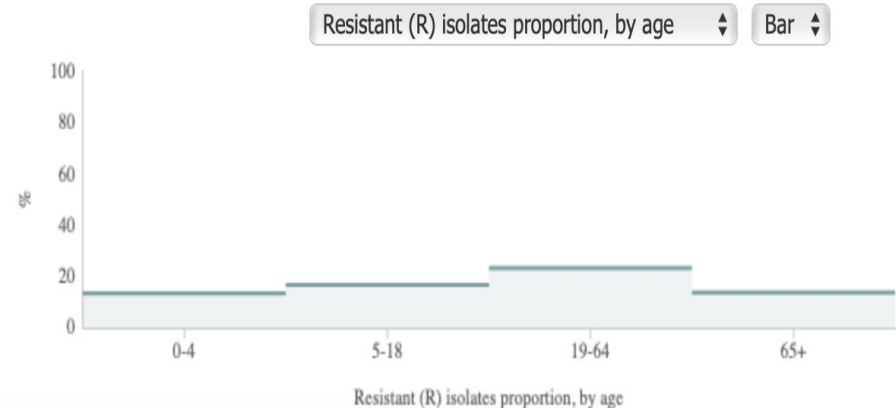
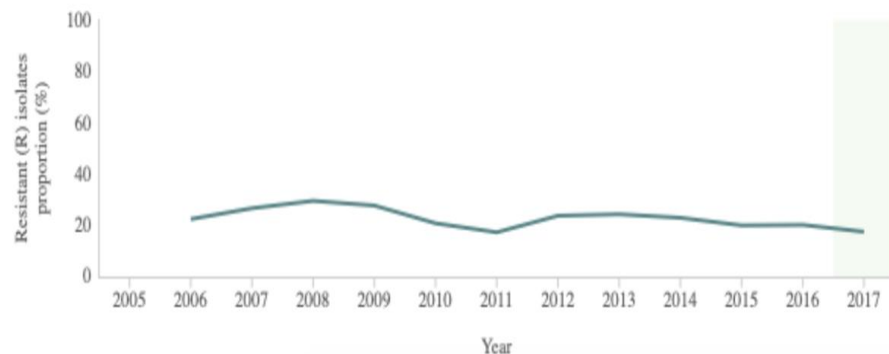
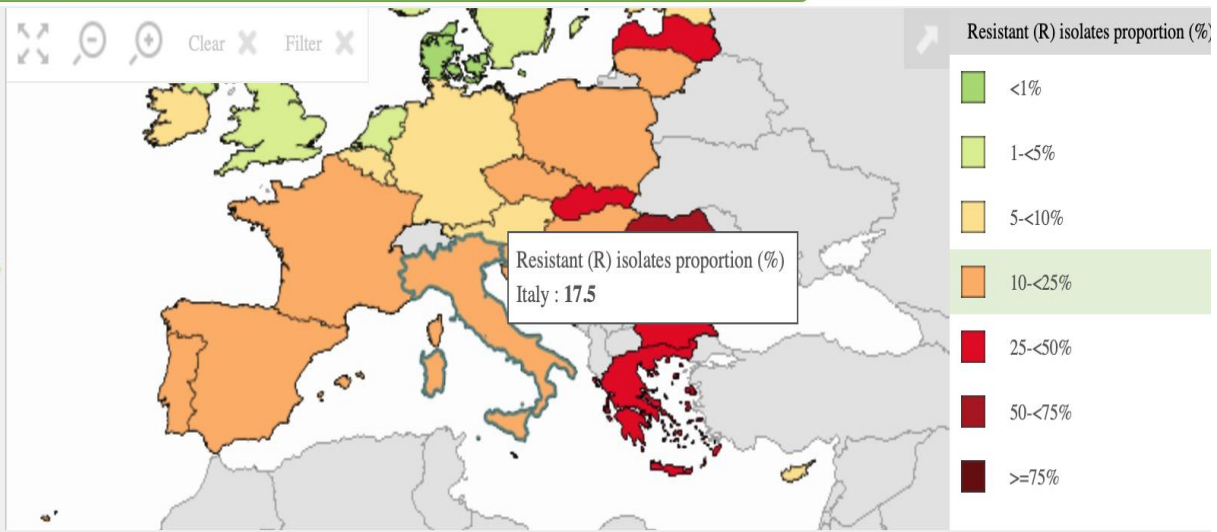
Combined resistance (at least three of piperac. and tazob., fluoroq., ceftaz., aminogl. and carbapenems) ▼

Resistant (R) isolates proportion ▼ | ▶ ◀◀ 2017 ▶▶

⋮



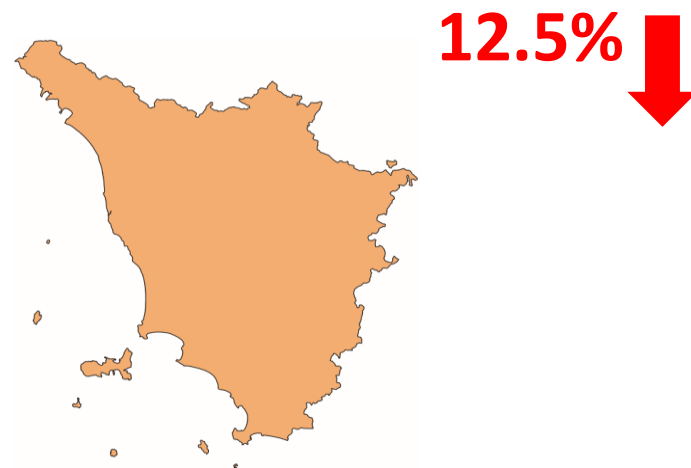
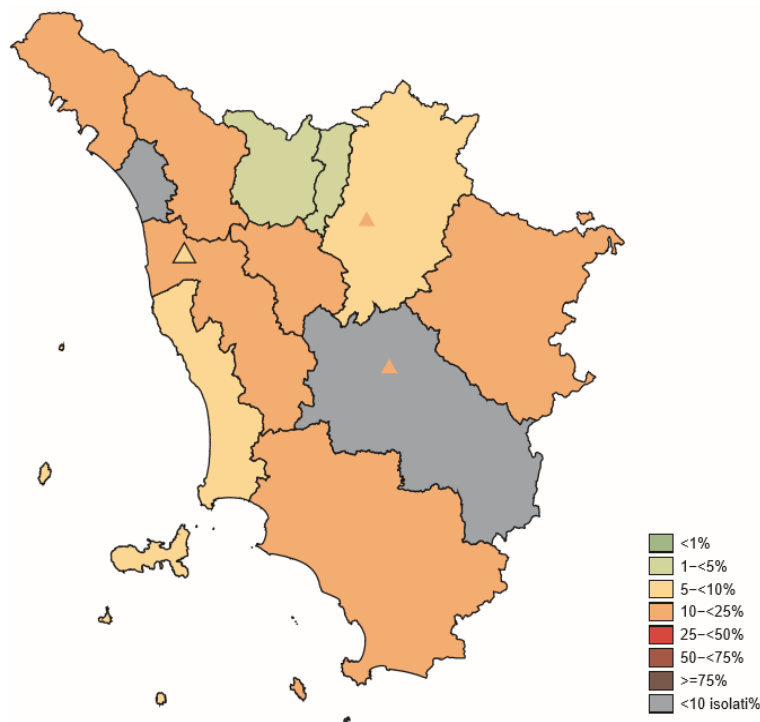
Region ▼	Resistant (R) isolates proportion (%)
France	10.6
Germany	7.2
Greece	32.4
Hungary	18.1
Iceland	0.0
Ireland	7.6
Italy	17.5
Latvia	42.9
Lithuania	16.9
Luxembourg	5.4



Pseudomonas aeruginosa MDR, Toscana 2018

Isolamento e profili di antibiotico sensibilità per *Pseudomonas aeruginosa*, batteriemie, Toscana 2018, Fonte ARS-SMART, ECDC

D) *P. aeruginosa* multiresistente (resistenza contemporanea ad almeno 3 classi antibiotiche tra piperacillina/ tazobactam, ceftazidime, fluorochinoloni, aminoglicosidi e carbapenemi) ,Toscana 2018

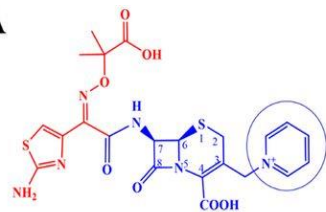


TOSCANA 2018	TOSCANA 2017	ITALIA 2017	ITALIA 2016	EU 2016
12,5	17,5	17,5	20,1	10,3

Ceftolozane-tazobactam

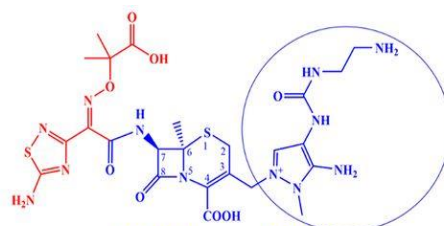
1st

A



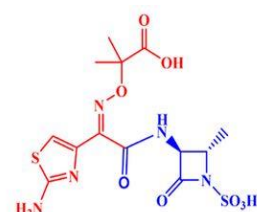
Ceftazidime (CAZ)

MICs
PDC-3 2 mg/L
E221K 64 mg/L



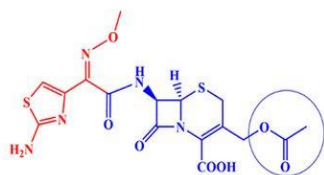
Ceftolozane (TOL)

MICs
PDC-3 0.5 mg/L
E221K 64 mg/L



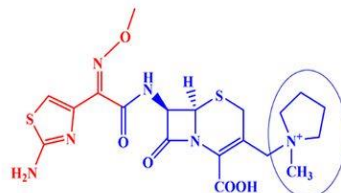
Aztreonam (AZT)

MICs
PDC-3 1 mg/L
E221K 8 mg/L



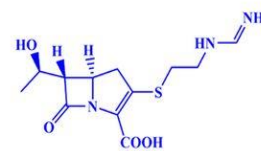
Cefotaxime (TAX)

MICs
PDC-3 8 mg/L
E221K 4 mg/L



Cefepime (FEP)

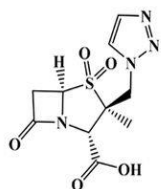
MICs
PDC-3 ≤0.06 mg/L
E221K 0.25 mg/L



Imipenem (IMI)

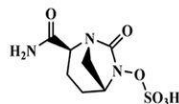
MICs
PDC-3 0.25 mg/L
E221K 0.5 mg/L

B



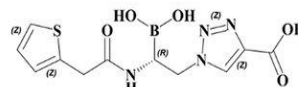
Tazobactam
(Classic inhibitor)

TOL-TAZO MICs
PDC-3 0.5 mg/L
E221K 8 mg/L



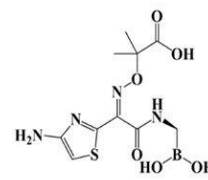
Avibactam
(DBO)

CAZ-AVI MICs
PDC-3 0.25 mg/L
E221K 0.5 mg/L



S02030
(BATSI)

CAZ-S02030 MICs
PDC-3 0.25 mg/L
E221K 16 mg/L



LP06
(BATSI)

CAZ-LP06 MICs
PDC-3 0.25 mg/L
E221K 8 mg/L

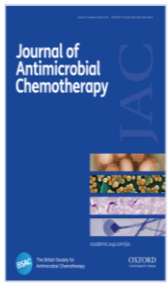
Anti-Pseudomonas activity:

- resistant to endogenous AmpC-type β -lactamase
- unaffected by MexAB and MexXY efflux systems

2nd

β -lactamase inhibitor
tazobactam extends
ceftolozane's spectrum of
activity against many
Enterobacterales ESBs

Melissa D. Barnes et al. mBio 2018; doi:10.1128/mBio.02085-18



Volume 73, Issue 3

March 2018

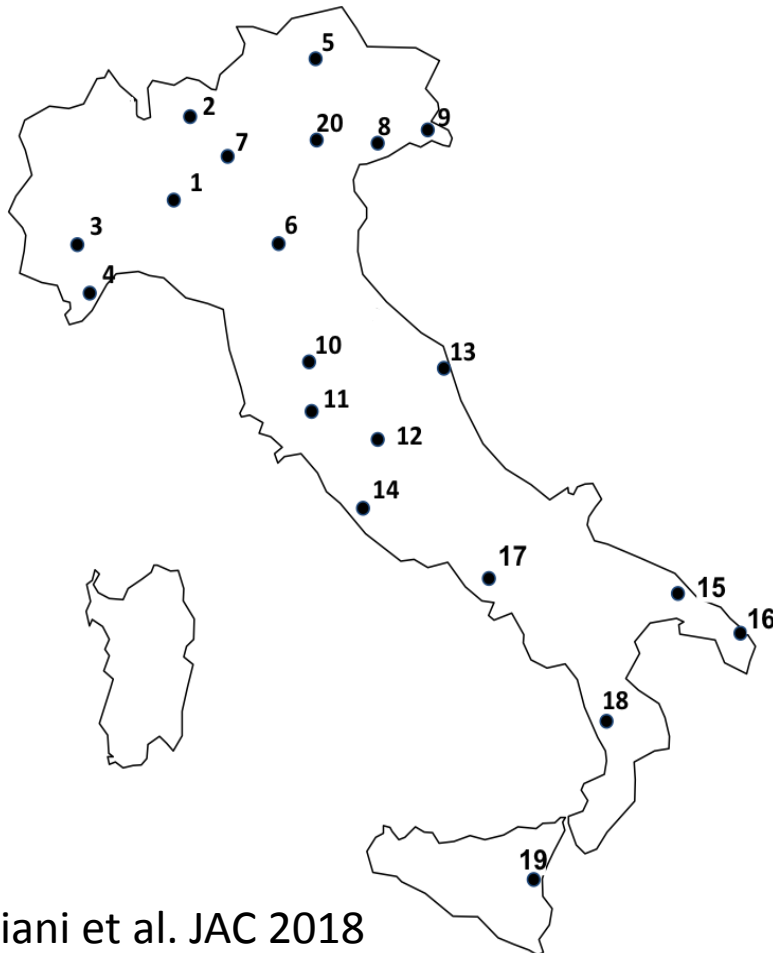
EDITOR'S CHOICE

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

Tommaso Giani, Fabio Arena, Simona Pollini, Vincenzo Di Pilato, Marco Maria D'Andrea, Lucia Henrici De Angelis, Matteo Bassetti, Gian Maria Rossolini ✉, *Pseudomonas aeruginosa* Working Group [Author Notes](#)

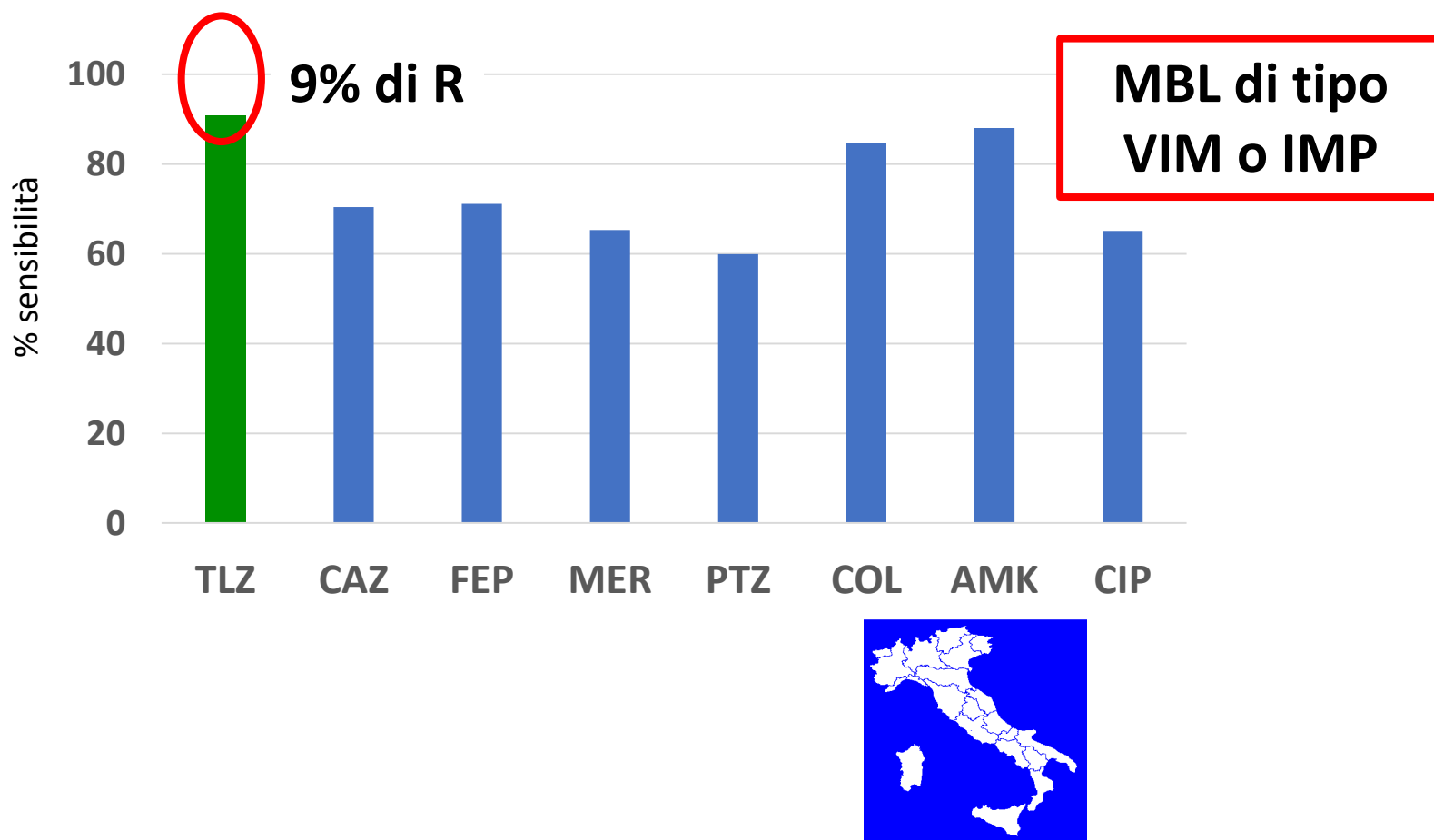
Journal of Antimicrobial Chemotherapy, Volume 73, Issue 3, March 2018, Pages 664–671,

<https://doi.org/10.1093/jac/dkx453>



- 935 non-replicate *P. aeruginosa* clinical isolates (382 from BSI and 553 from HAP/VAP)
- 37.2% exhibited an MDR phenotype (i.e. resistant to at least one tested antibiotic in three or more antimicrobial classes)
- Ceftolozane/tazobactam was the most active agent; 90.9% susceptibility
- Ceftolozane/tazobactam was also active against 9/15 isolates that were non-susceptible to all other tested agents

Sensibilità ai farmaci *Pseudomonas aeruginosa*
(N= 935 isolates from BSI and HAP/VAP)



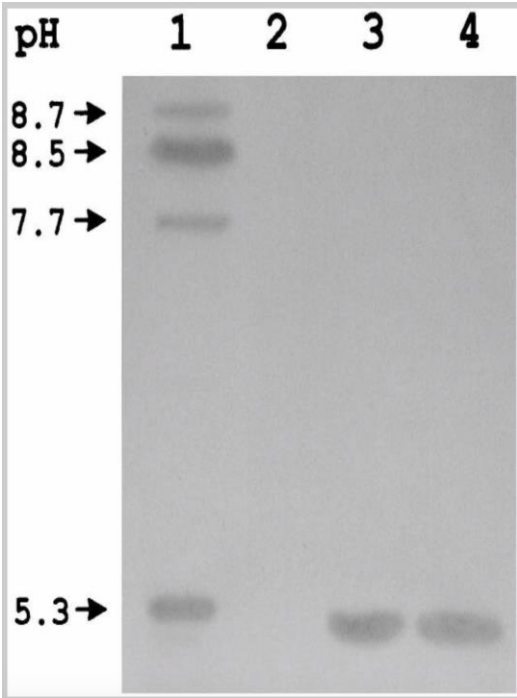
Cloning and characterization of blaVIM, a new integron-borne metallo-beta-lactamase gene from a *Pseudomonas aeruginosa* clinical isolate.

Lauretti L¹, Riccio ML, Mazzariol A, Cornaglia G, Amicosante G, Fontana R, Rossolini GM.

[+ Author information](#)



Save items



February 1997 from an Italian patient admitted at the Intensive Care Unit Department of the Verona University Hospital (northern Italy)
***P. aeruginosa* Carbapenem-resistant infection**

Verona imipenamse: VIM-1

Klebsiella pneumoniae resistente ai carbapenemi, Europa 2017



Surveillance Atlas of Infectious Diseases

Antimicrobial resistance ▼

Klebsiella pneumoniae ▼

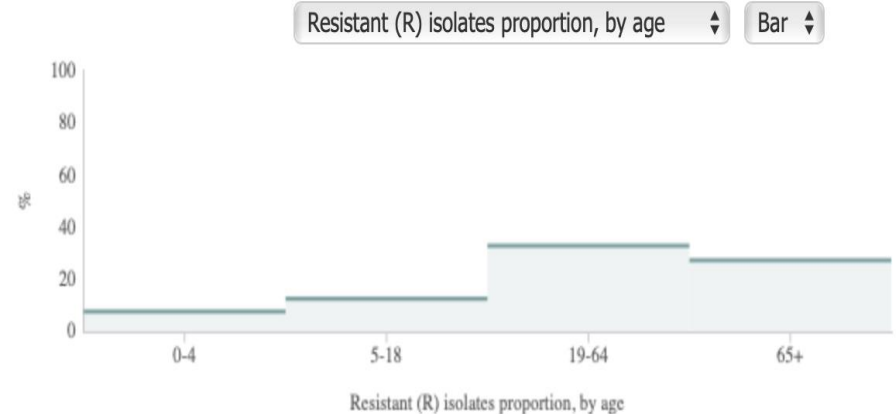
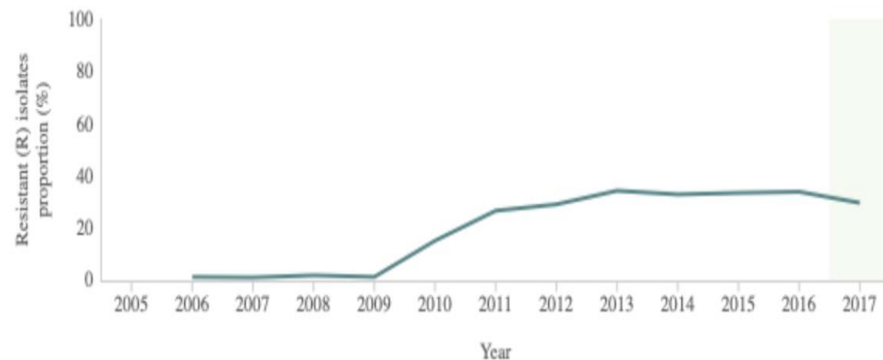
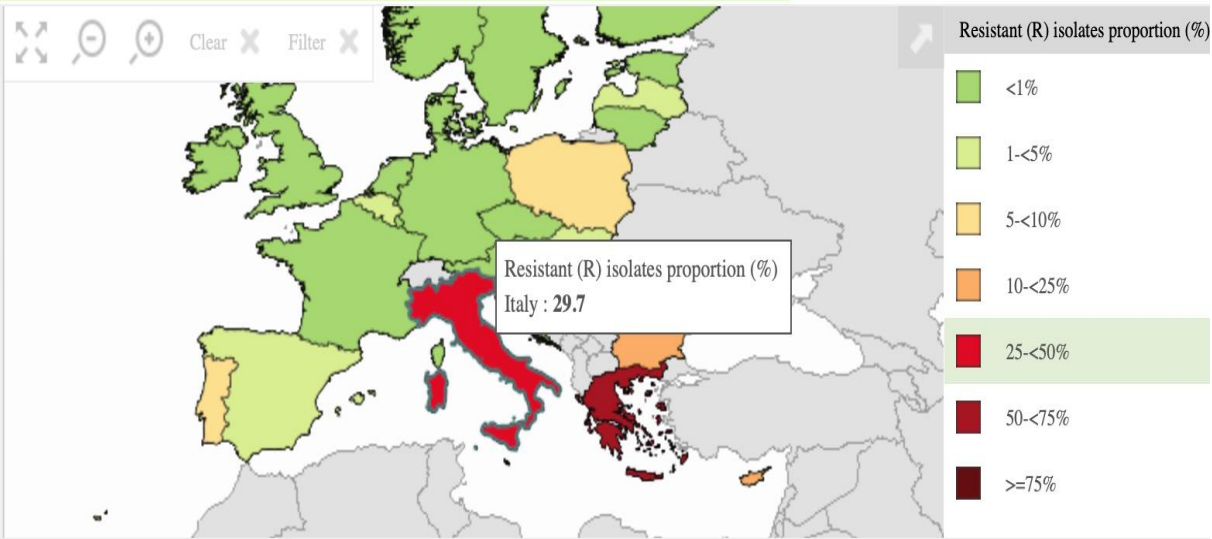
Carbapenems ▼

Resistant (R) isolates proportion ▼

2017 ▼



Region	Resistant (R) isolates proportion (%)
France	0.7
Germany	0.5
Greece	64.7
Hungary	0.3
Iceland	-
Ireland	0.2
Italy	29.7
Latvia	1.7
Lithuania	0.6
Luxembourg	0.0

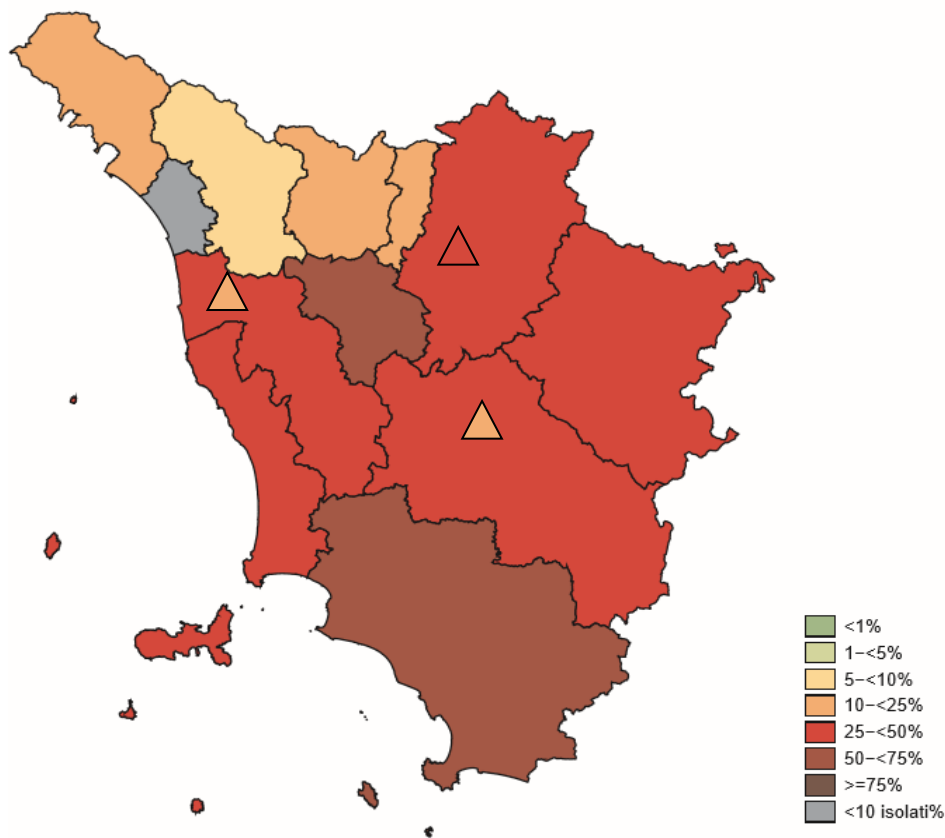


Klebsiella pneumoniae resistente ai carbapenemi, Toscana 2018

Isolamento e profili di antibiotico sensibilità per *Klebsiella pneumoniae*, batteriemie, Toscana 2018, Fonte ARS-SMART, ECDC

E) *K. pneumoniae* resistente ai carbapenemi, Toscana 2018

29.1% ↓



TOSCANA 2018	TOSCANA 2017	ITALIA 2017	ITALIA 2016	EU 2016
29,1	35,5	29,7	33,9	6,1

Carbapenem-resistant *Klebsiella pneumoniae*

Outer membrane
impermeability
(porin loss/modification)
+
ESBL/AmpC β -lactamase
production



- Not transferable
- Sporadic cases or small outbreaks

Carbapenemase production (CPE):
KPC, OXA-48-like, VIM, NDM



- Transferable
- Association with bacterial clones capable of efficient dissemination (HIGH-RISK CLONES) (CG258)



Large outbreaks
Epidemic diffusion

Klebsiella pneumoniae KPC, cloni a alto rischio

K. pneumoniae KPC (CG101)

Antibiotic	(S/I/R)
Amp/Sulb	R
Pip/Tazo	R
CAZ-AVI	S
Ceftriaxone	R
Ceftazidime	R
Cefepime	R
Ertapenem	R
Imipenem	R
Meropenem	R
Amikacin	R
Gentamicin	R
Ciprofloxacin	R
Tigecycline	S
Colistin	S/R
TRI/SXT	S

*bla*_{KPC-2}
*bla*_{TEM-type}
*bla*_{OXA-9like}

armA

mut. *parC*, *gyrA*

mut. *mgrB*, *pmrAB*

Possibile attività di
Ceftazidime-
avibactam

Spettro di attività inibitori delle Beta-lattamasi

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Class B	e. g. IMP, VIM, NDM1	✗	✗	✗
Class C	Enterics chromos. AmpC	✗	✗	✓
	<i>Pseudomonas</i> chromos. AmpC	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Class D	Non carbapenemase e. g. OXA-1, -31, -10, -13	Variable	Variable	Variable
	Carbapenemase e. g. OXA-23, -40, -48, -58	Variable	Variable	Variable OXA-48



RAPID RISK ASSESSMENT

**Emergence of resistance to ceftazidime-avibactam
in carbapenem-resistant Enterobacteriaceae**

12 June 2018

Spettro di attività CAZ-AVI



Collezione di enterobatteri da urine
cresciuti su terreno CARBA-SMART

209 enterobatteri
produttori di
carbapenemasi

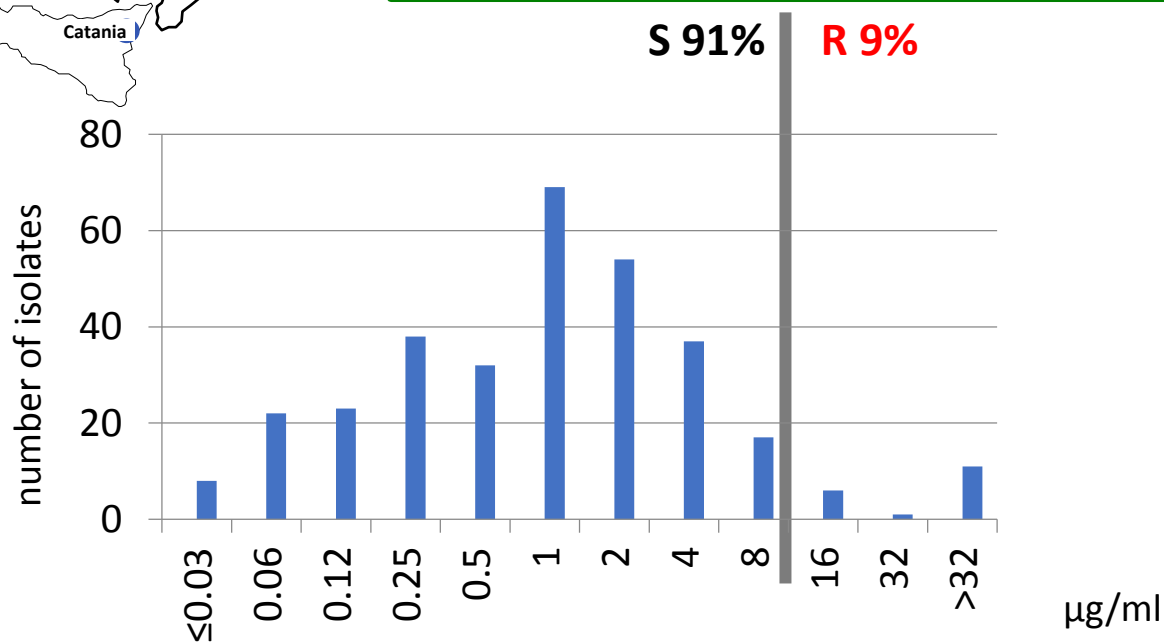
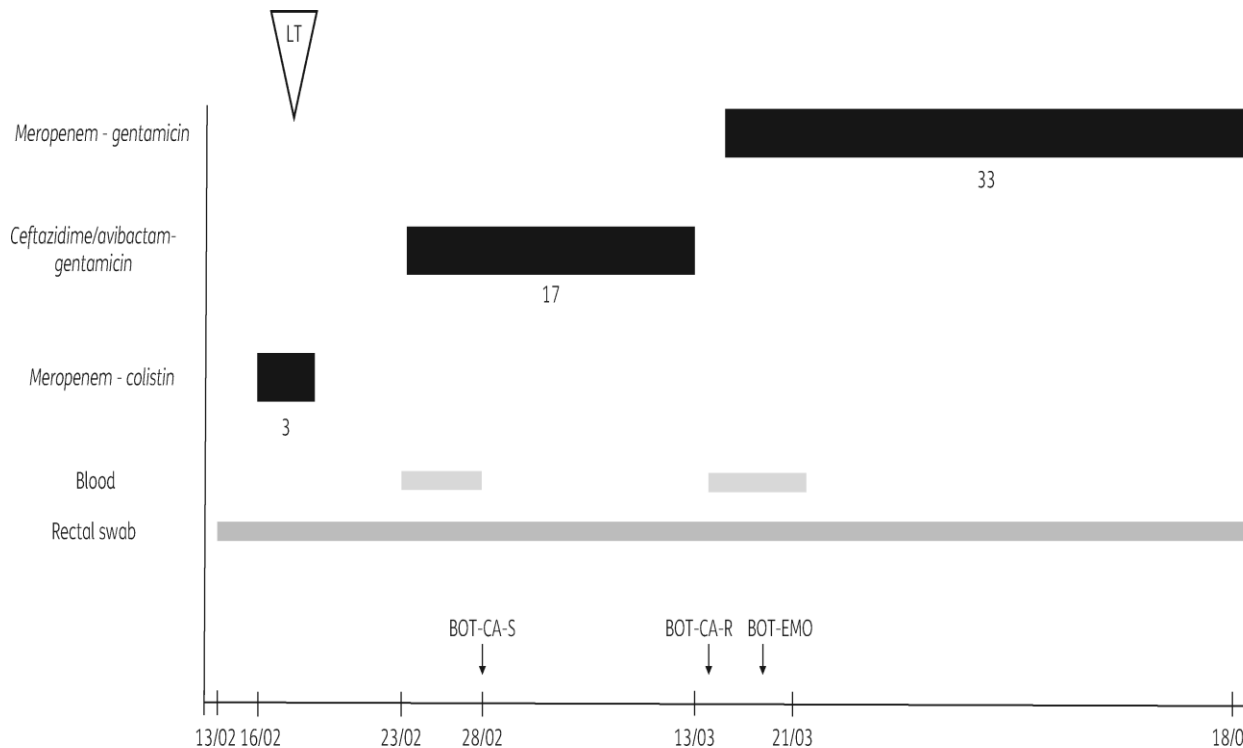


Figure 1. History of the isolation and antimicrobial treatments of a patient with KPC-Kp infections. Black bars ...



**CAZ-AVI resistant
ST1519 KPC-KP
Liver-transplant patient
Bologna (Italy)**

D179Y substitution in the *bla*_{KPC-3} gene

Spettro di attività inibitori delle Beta-lattamasi

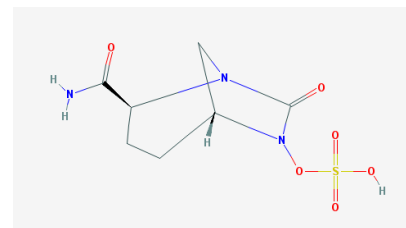
		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Class B	e. g. IMP, VIM, NDM	✗	✗	✗
Class C	Enterics chromos. AmpC	✗	✗	✓
	<i>Pseudomonas</i> chromos. AmpC	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Class D	Non carbapenemase e. g. OXA-1, -31, -10, -13	Variable	Variable	Variable
	Carbapenemase e. g. OXA-23, -40, -48, -58	Variable	Variable	Variable OXA-48

Partners di Avibactam

Avibactam partners:

❖ Ceftazidime/Avibactam

- EUCAST bp: ≤ 8 S, > 8 R
- Enterics, including ESBL, AmpC, CRE (**no MBL**)
- *Pseudomonas* (**no MBL**)
- No advantage with *Acinetobacter*



Activity on MBL producers



❖ *Aztreonam/Avibactam*

- Aztreonam not a substrate of MBLs
- Avibactam inhibits relevant enzymes active on Aztreonam



Regional outbreak of lactamase-producing Enterobacteriaceae, T

4 June 2019

Summary

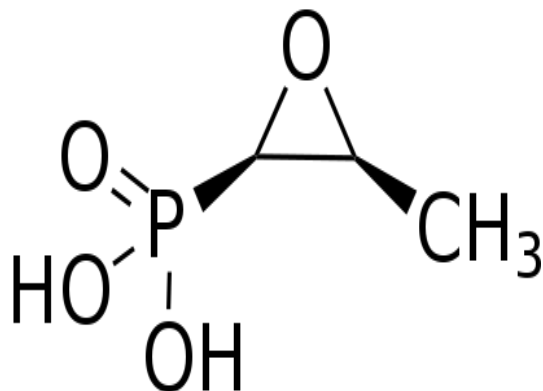
A large outbreak of New Delhi metallo-beta-lactamase (NDM)-producing carbapenem-resistant Enterobacteriaceae (CRE) has been reported from the Tuscany region in Italy. Between November 2018 and May 2019, seven Tuscan hospitals notified a total of 350 cases. Due to its size and the resulting change in the epidemiology of CRE, the reported outbreak is a significant event, despite previous endemicity of *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE in this geographic area. 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.

Numerous reported outbreaks and examples of cross-border transmission of NDM-producing CRE in the European Union/European Economic Area (EU/EEA) demonstrate the transmission potential of NDM-producing CRE in European healthcare systems. Outbreaks such as the one in Tuscany present a risk for cross-border transmission and further spread to other EU/EEA countries, especially since the affected area is a major tourist destination. Given the previous rapid establishment of KPC-producing CRE in Italy (which resulted in an endemic situation), the risk for further spread of NDM-producing CRE from the current outbreak is considered to be high for Italy and moderate for cross-border spread to other EU/EEA countries.

Sporadic cases of community acquisition of NDM-producing CRE have also been described for other European countries. However, the introduction and dissemination of these bacteria have mainly been associated with healthcare settings. Therefore, the risk of acquisition of NDM-producing CRE related to this outbreak is likely restricted to persons with recent healthcare contact.

Farmaci potenzialmente attivi contro MBL

- Tigeciclina
- Colistina



- **Fosfomicina**

- Antibiotico naturale prodotto da *Streptomyces*, descritto per la prima volta nel 1969

Stapley *et al* – Antimicrob Agents Chemother (Bethesda) 1969

Kahan *et al* – Ann NY Acad Sci 1974

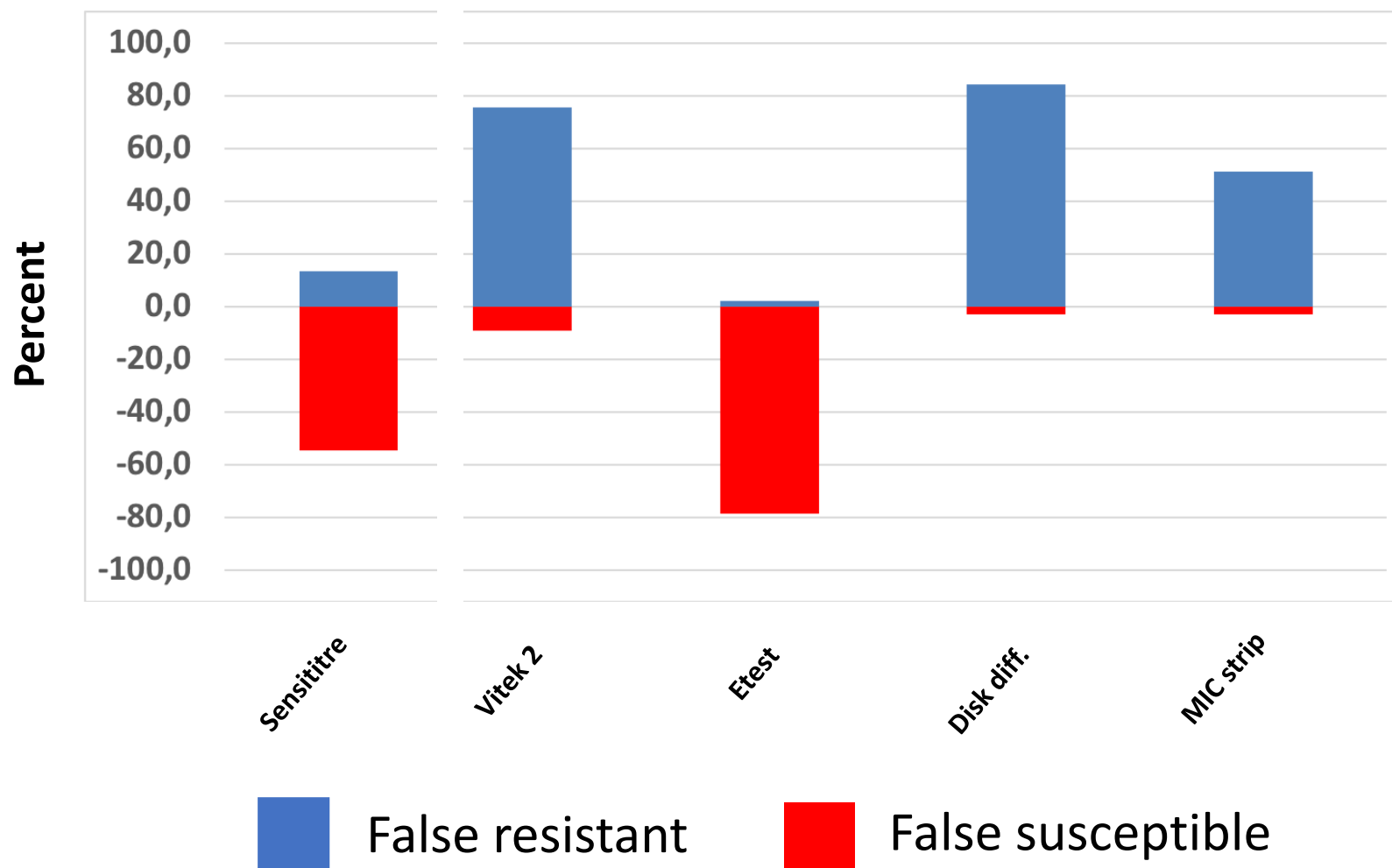
Brown *et al* – J Bacteriol 1995

Attività di fosfomicina vs *Enterobacterales* produttori di carbapenemasi

Referenza	Paese	Ceppi	MIC ₅₀	MIC ₉₀	% S
Endimiani, AAC 2010	USA	68 KPC-Kp	16	64	75
Livermore, IJAA 2011	UK	81 CPE	32	>128	61
Kaase, JCM 2014	Germania	107 CRE (80 CPE)	8	512	78
Rizek, JIC 2015	Brasile	50 KPC-Kp	16	32	NR
Rodriguez-Avial, IJAA 2015	Spagna	164 CPE	16	256	71
Vasoo, AAC 2015	USA Singapore	173 CPE	NR	NR	78
Antonelli, 2016 (unpub.)	Italia	225 CRE (218 CPE)	32	>128	62
Wang, CID 2018	Cina	1801 CRE (1544 CPE)	256	>256	40

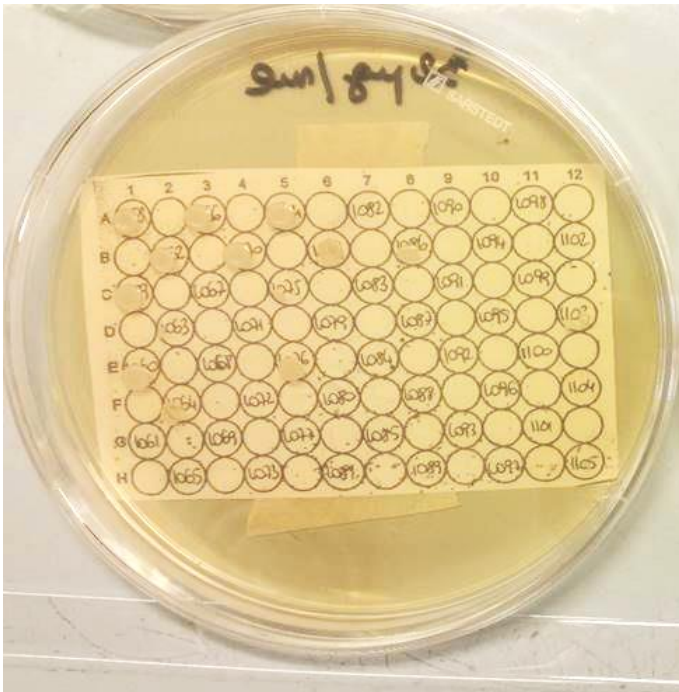
Fosfomicina: saggi di attività

N=78 KPC-producing *K. pneumoniae* (45 S, 33 R)



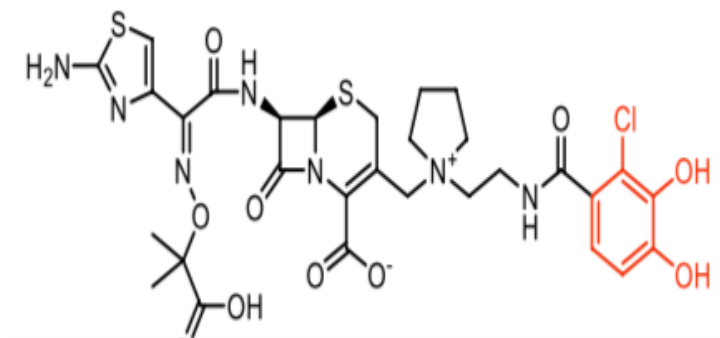
Fosfomicina test di sensibilità

- Metodo di riferimento è agar diluizione (secondo ISO_20776)



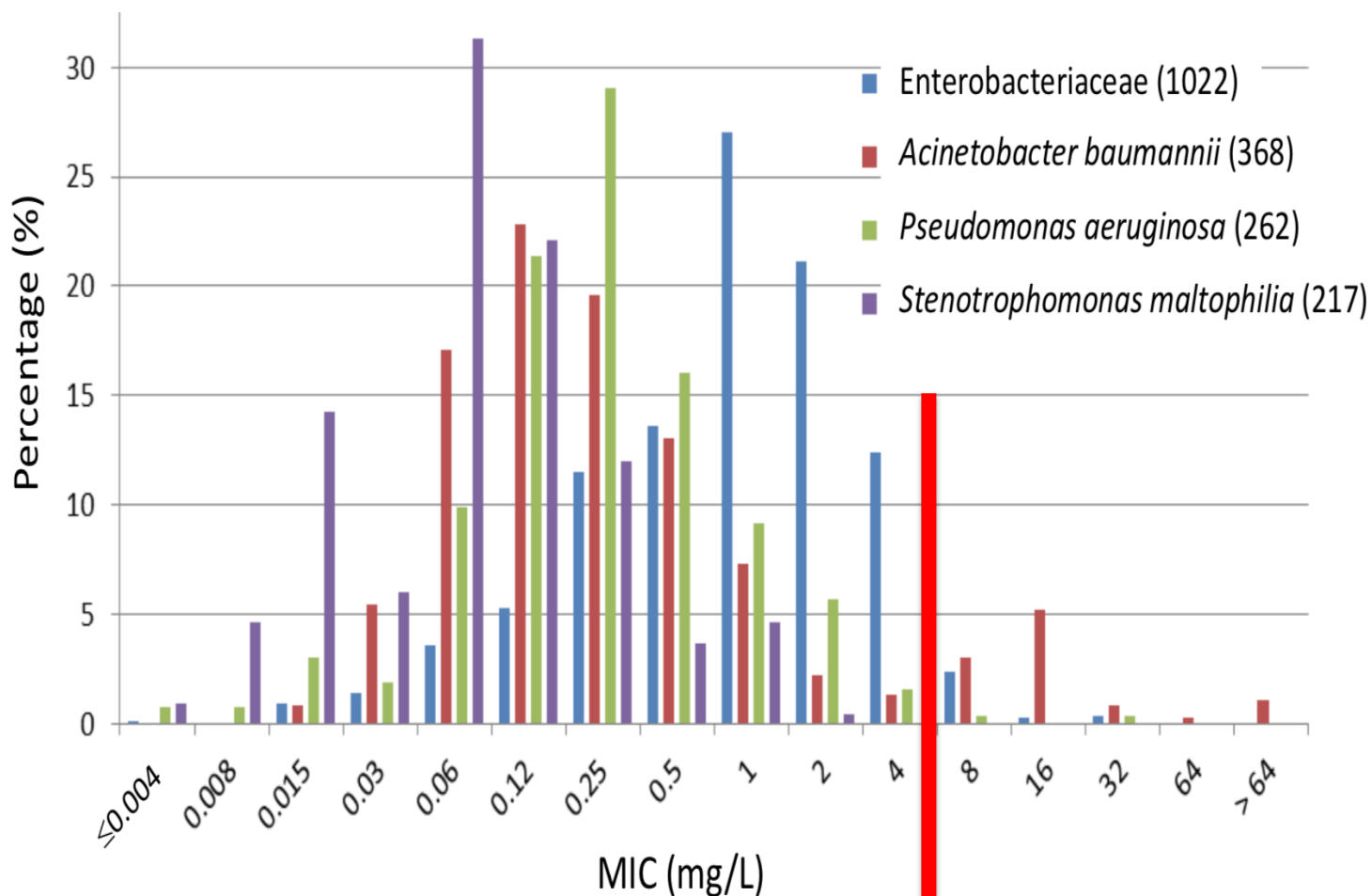
- Utilizzare terreno terreno addizionato con 25 µg/ml di glucosio 6-P

Cefiderocol



- ❖ La prima **cefalosporina-sideroforo**
- ❖ Ha una modifica che permette il **legame con il ferro**
- ❖ Il complesso **ferro+cefiderocol** viene attivamente trasportato dentro la cellula batterica attraverso i trasportatori del ferro
- ❖ Cefiderocol alta affinità per **PBP3** e **blocca la sintesi della parete**

Cefiderocol spettro di azione



JAC 2017

107 *A. baumannii*
82 *P. aeruginosa*

MIC₉₀ = 0.5 mg/L

Saggio sensibilità per cefiderocol

CLSI M100_S29, 2019

CEFIDEROCOL	MIC breakpoint mg/L	
Specie	S ≤	R >
<i>Enterobacterales</i>	4	8
<i>P. aeruginosa</i>	4	8
<i>A. baumannii</i>	4	8



Possibile uso compassionevole

- **Metodo di riferimento:**
microdiulizione in brodo
utilizzando **Iron-Depleted CAMHB (ID-CAMHB)**

Conclusioni

- **La resistenza agli antibiotici è un fenomeno complesso e di crescente interesse**
- **Nessun farmaco viene risparmiato dallo sviluppo di resistenze**
- **Ci sono alcune nuove molecole ma la loro attività va preservata al massimo attraverso un uso razionale (...e razionato)**
- **Vista la complessità dell'epidemiologia è importante disporre di Laboratori di Microbiologia di alto livello che siano in grado di fornire informazioni tempestive ed attendibili**

Grazie dell'attenzione

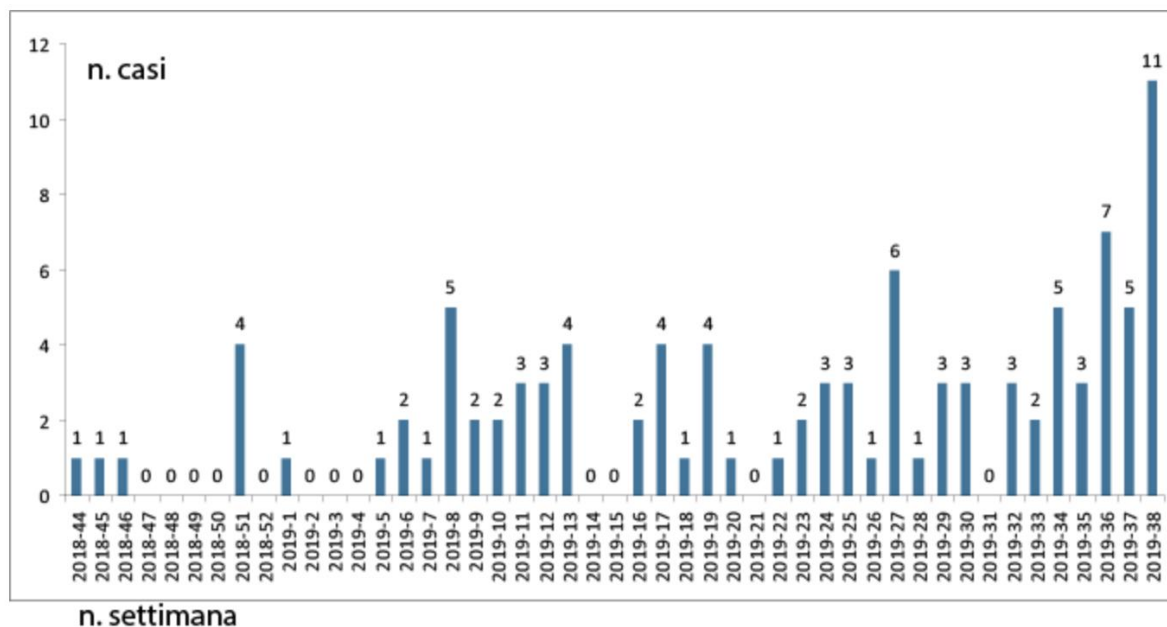
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Aggiornamento 25 settembre 2019

Tra novembre 2018 e il 22 settembre 2019 i batteri NDM sono stati isolati nel sangue di 102 pazienti.

Casi NDM in Toscana per settimana, novembre 2018-22 settembre 2019



Le settimane n. 36, n. 37 e n. 38 sono quelle relative al mese di settembre 2019

I **casi** sono risultati **letali nel 37% dei pazienti con sepsi**, percentuale paragonabile alla letalità per questa condizione causata da altri batteri resistenti agli antibiotici carbapenemici.

Outbreak of NDM-1-producing Enterobacteriaceae in northern Italy, July to August [REDACTED]

Like 0

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P Gaibani^{1,2}, S Ambretti^{1,2}, A Berlinger¹, M Cordovana¹, P Farruggia³, M Panico³, M P Landini¹, V Sambri¹[+ View Affiliations](#)[+ View Citation](#)[« Previous Article](#) | [Table of Contents](#) | [Next Article »](#)[Abstract](#)[Full-Text](#)[References](#)[Supplementary
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Between July [REDACTED] and August [REDACTED] the New Delhi metallo-beta-lactamase 1 (NDM-1) gene was detected in *Klebsiella pneumoniae* and *Escherichia coli* isolates obtained from six patients hospitalised in four healthcare facilities in northern Italy. The patient who had been hospitalised in New Delhi, India, from February to May [REDACTED] and subsequently in the Bologna area, Italy, from May to July [REDACTED] may have been the source of the outbreak. Our findings suggest ongoing spread of this carbapenem-resistance gene in Italy and highlight the need for intensive surveillance.

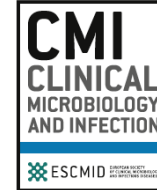
N.B...mai dichiarato chiuso...



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Research note

Genomics of *Klebsiella pneumoniae* ST16 producing NDM-1, CTX-M-15, and OXA-232

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Results

Characteristics of the outbreak strains

An outbreak involving 23 infected/colonized patients occurred from 24 February to 29 March 2017 in three different wards of the Treviso Hospital and two long-term care facilities (LTCFs) in the Treviso area. The outbreak clone was identified as ST16 by MLST and pulsed field gel electrophoresis. Retrospectively, nine ST16 carbapenem-resistant strains were isolated in these hospitals before the outbreak from September 2016 to January 2017 and included in the study (Table S1).

The 32 Italian ST16 showed different distribution of two major carbapenemase genes: 14 strains were positive for *bla*_{NDM-1}, two for *bla*_{OXA-232}, and 16 for both *bla*_{NDM-1} and *bla*_{OXA-232} (Table S1). Six carbapenem-resistant strains were also CTX-M-15 extended-spectrum β -lactamase (ESBL) producers.

KL8 (LTCF, March 2017), producing NDM-1, CTX-M-15, and OXA-232, and KL11 (Treviso hospital, March 2017), producing NDM-1 and CTX-M-15, were selected for WGS as prototypic strains of the outbreak clone. KL29 (LTCF, September 2016), producing CTX-M-15 and OXA-232 was also sequenced as prototypes of the strains collected before the outbreak (Table 1).

N.B...mai dichiarato chiuso...