Convegno

Antimicrobico-resistenza: cure e ambiente

Firenze, 6 giugno 2018

SALONE DELLE ROBBIANE - Villa la Quiete - FORMAS (*via di Boldrone 2)*

Il fenomeno della resistenza in Italia e Europa

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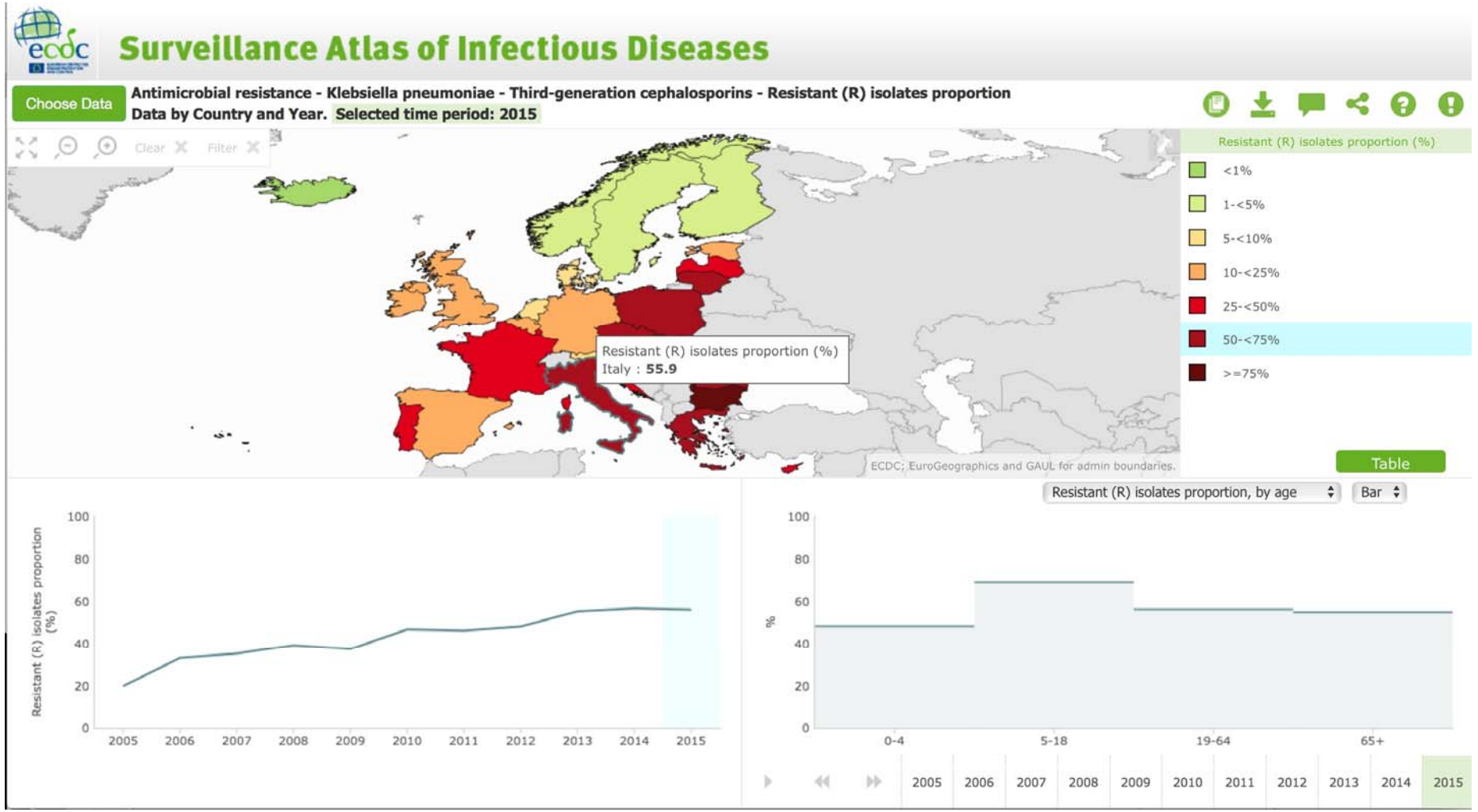
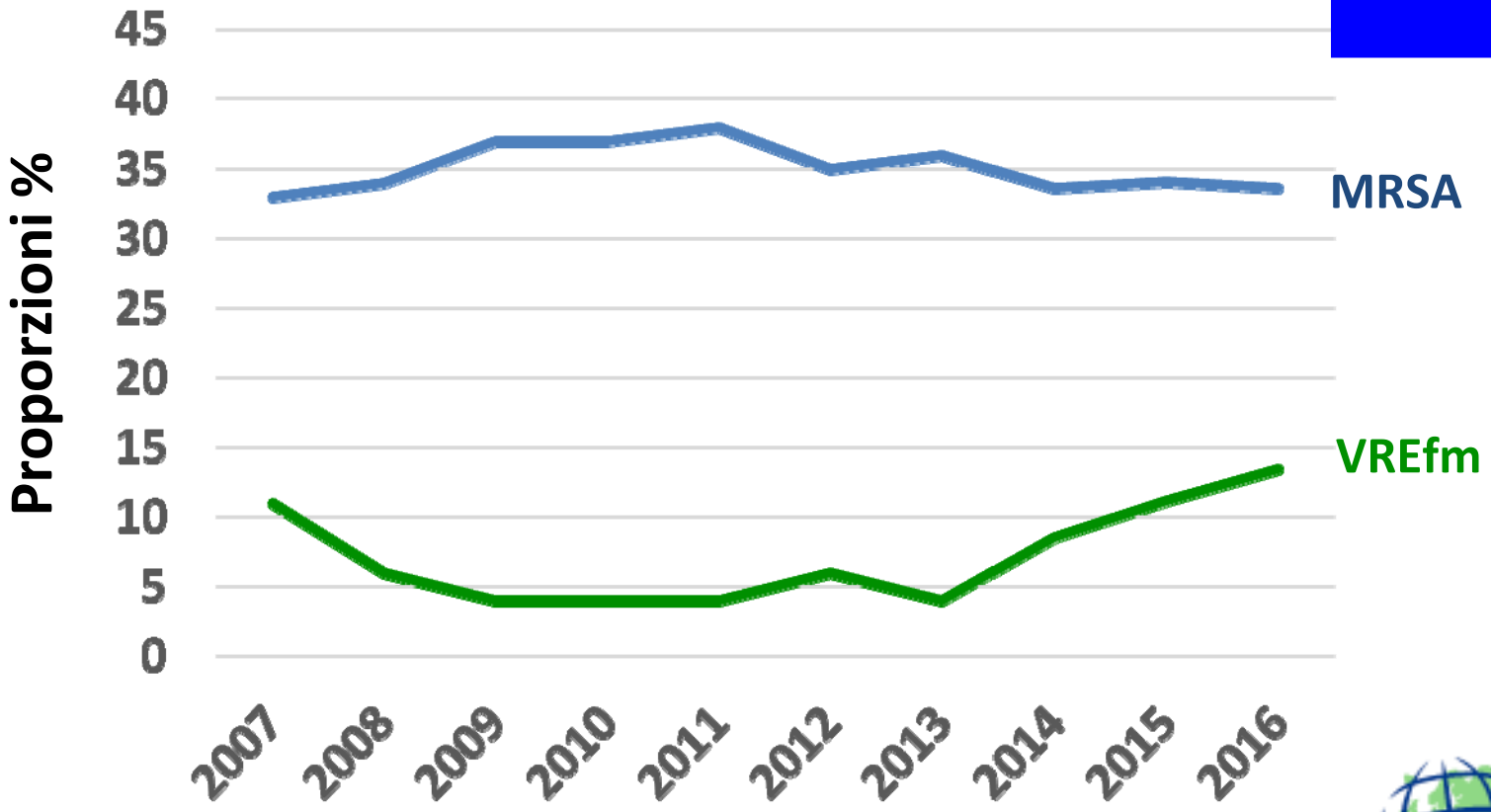
Resistenza agli antibiotici in Europa

http://atlas.ecdc.europa.eu/public/index.aspx



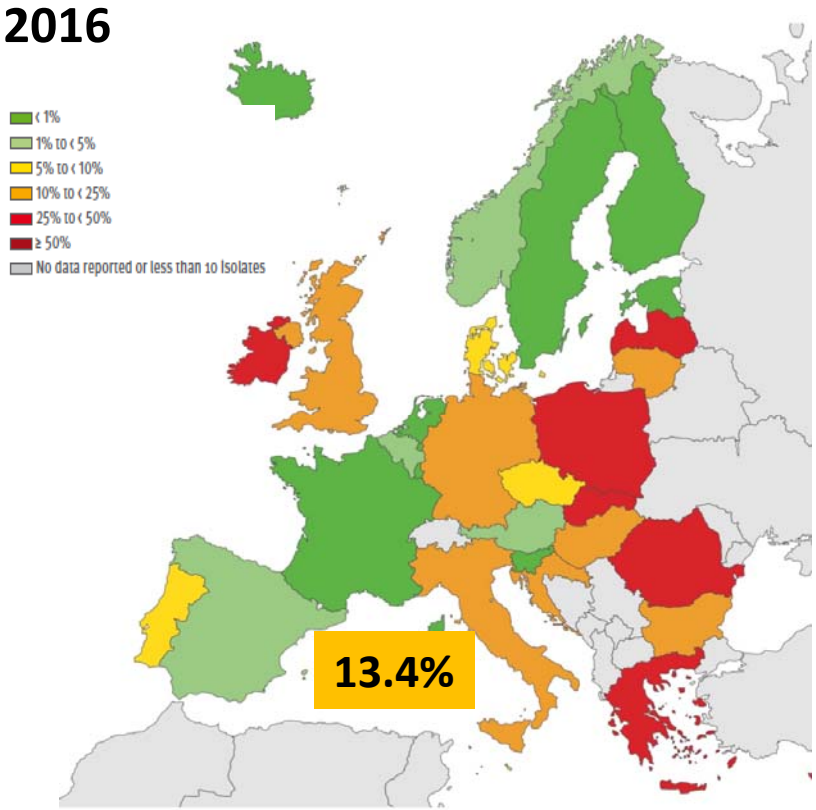
Trends per cocchi Gram-positivi- Infezioni invasive



EARS-NET

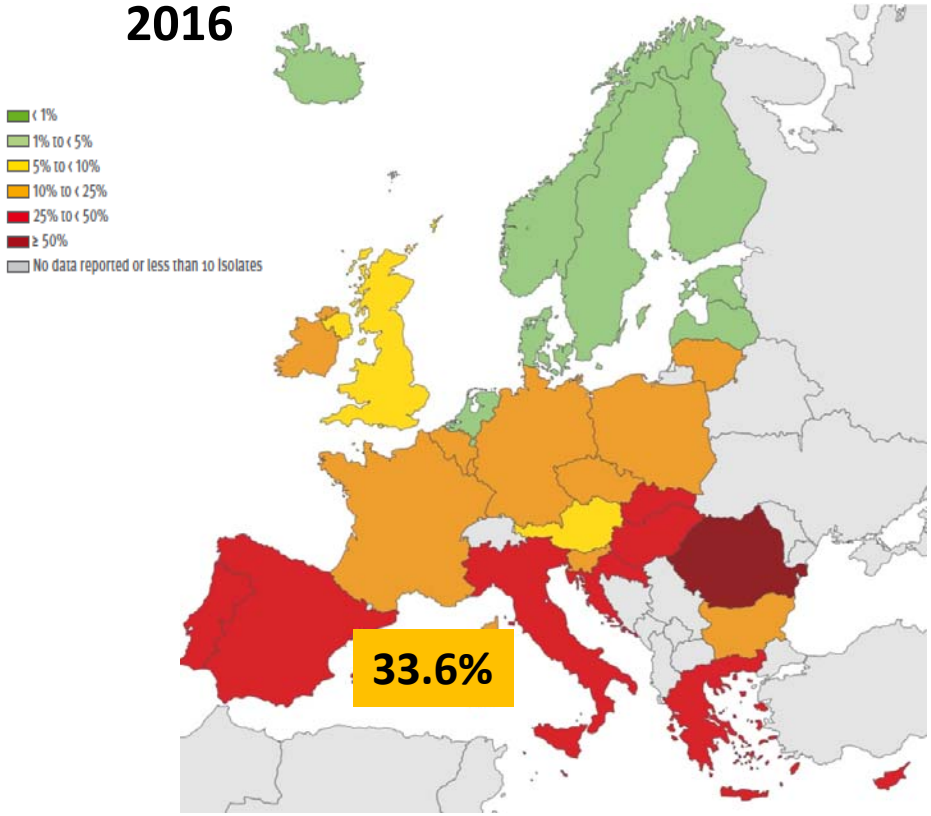
VR *Enterococcus faecium* (infezioni invasive)

2016



MR *Staphylococcus aureus* (infezioni invasive)

2016



ecdc

EARS-NET

EARS-NET Maps. Available at https://ecdc.europa.eu/sites/portal/files/documents/AMR%202016_Final-with-cover-for-web-2017.pdf. Accessed November 2017

Farmaci Anti-MRSA

Vecchi farmaci

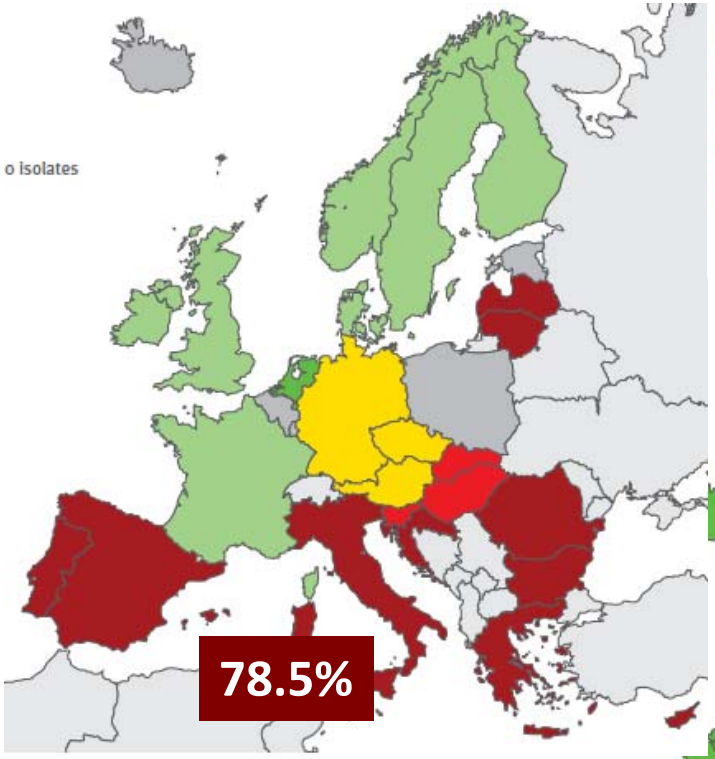
- Vancomycin
- Teicoplanin

Resistenza riportata ma raramente

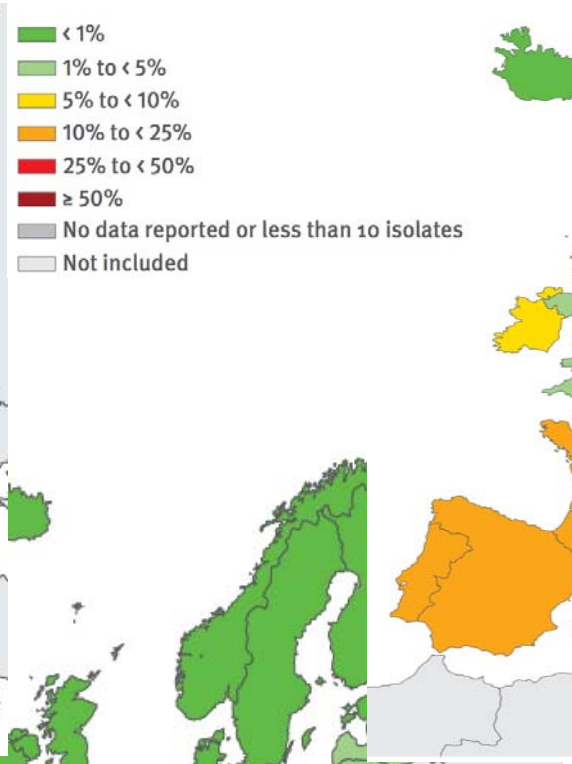
Nuovi farmaci

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

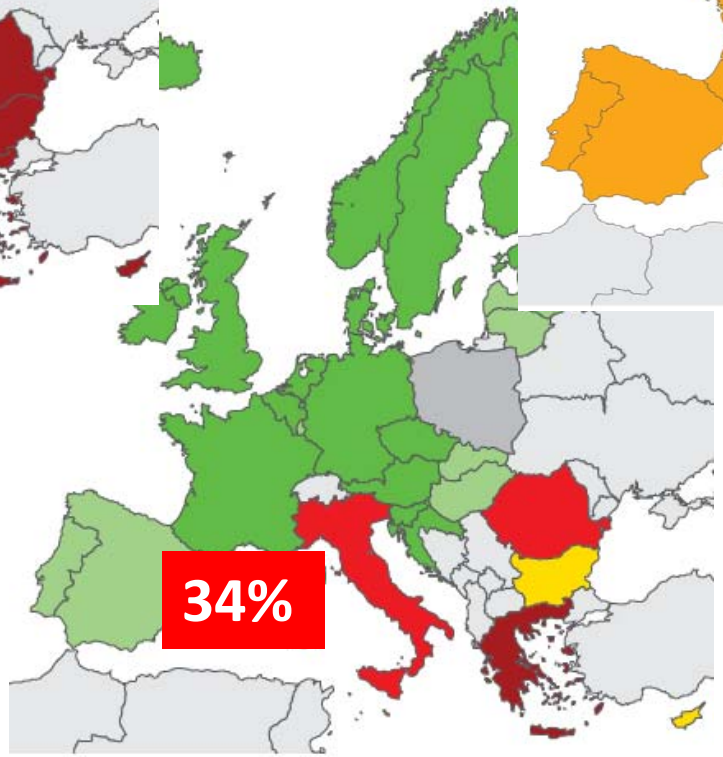
Patogeni Gram-negativi XDR incontrati con frequenza crescente nella pratica clinica



CRAb (carbapenem resistant *A. baumannii*)



XDR- *P. aeruginosa*



Carbapenem-R *K. pneumoniae*

EARS-NET

Principali patogeni causa di HAIs, Italia

"The levels of carbapenem-resistant Enterobacteriaceae (CRE) and *Acinetobacter baumannii* have now reached **hyper-endemic levels**"

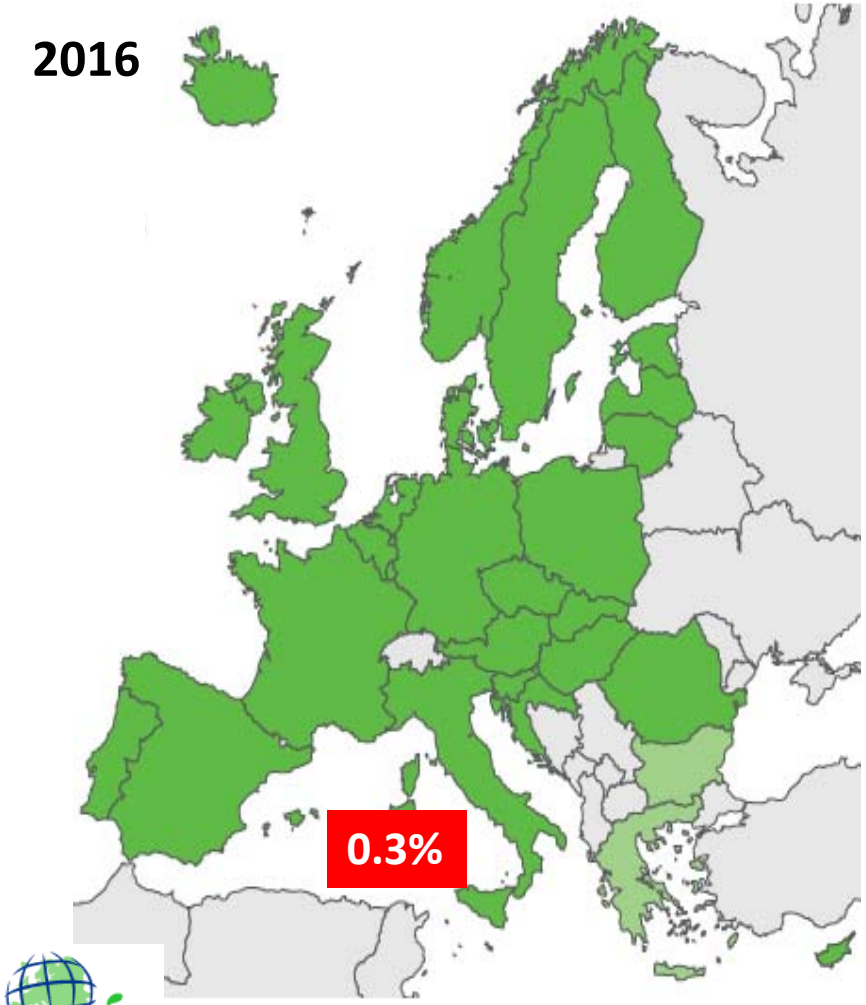
- If the current trends of carbapenem resistance and colistin resistance in gram-negative bacteria such as *Klebsiella pneumoniae* and *A. baumannii* are not reversed, **key medical interventions will be compromised in the near future.**

Come siamo messi rispetto agli altri paesi europei?

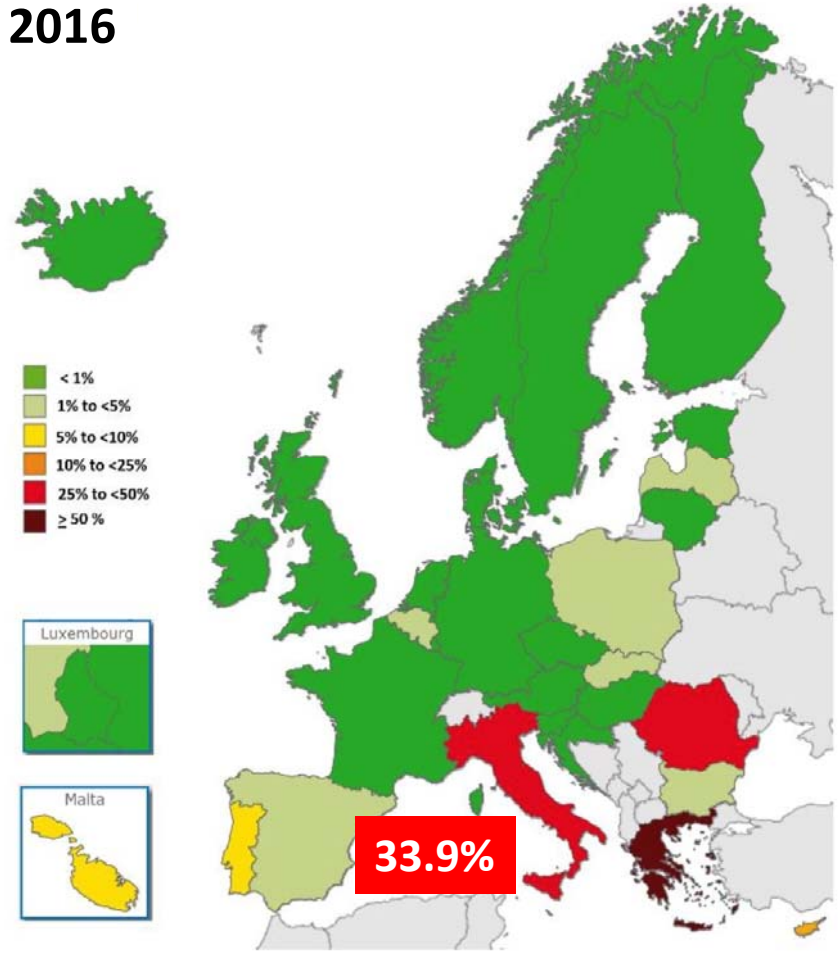
Patogeno resistente	Posizione in classifica su 30 paesi (% R)
E. coli FQ-R	2° (44%)
E. coli 3GC-R	2° (30%)
K. pneumoniae FQ-R	5° (54%)
K. pneumoniae 3GC-R	6° (56%)

EARS-NET – report 2015

CR *Escherichia coli* (isolati invasivi)



CR *Klebsiella pneumoniae* (isolati invasivi)



EARS-NET

EARS-NET Maps. Available at https://ecdc.europa.eu/sites/portal/files/documents/AMR%202016_Final-with-cover-for-web-2017.pdf. Accessed November 2017

CRE: diversi tipi di meccanismi di resistenza

Diminuzione di permeabilità (perdita di porine)

+

iperproduzione ESBL/AmpC

Produzione di carbapenemasi

Class A (serine) — **KPC**, **GES**

Class D (serine) — **OXA-48 (-181)**

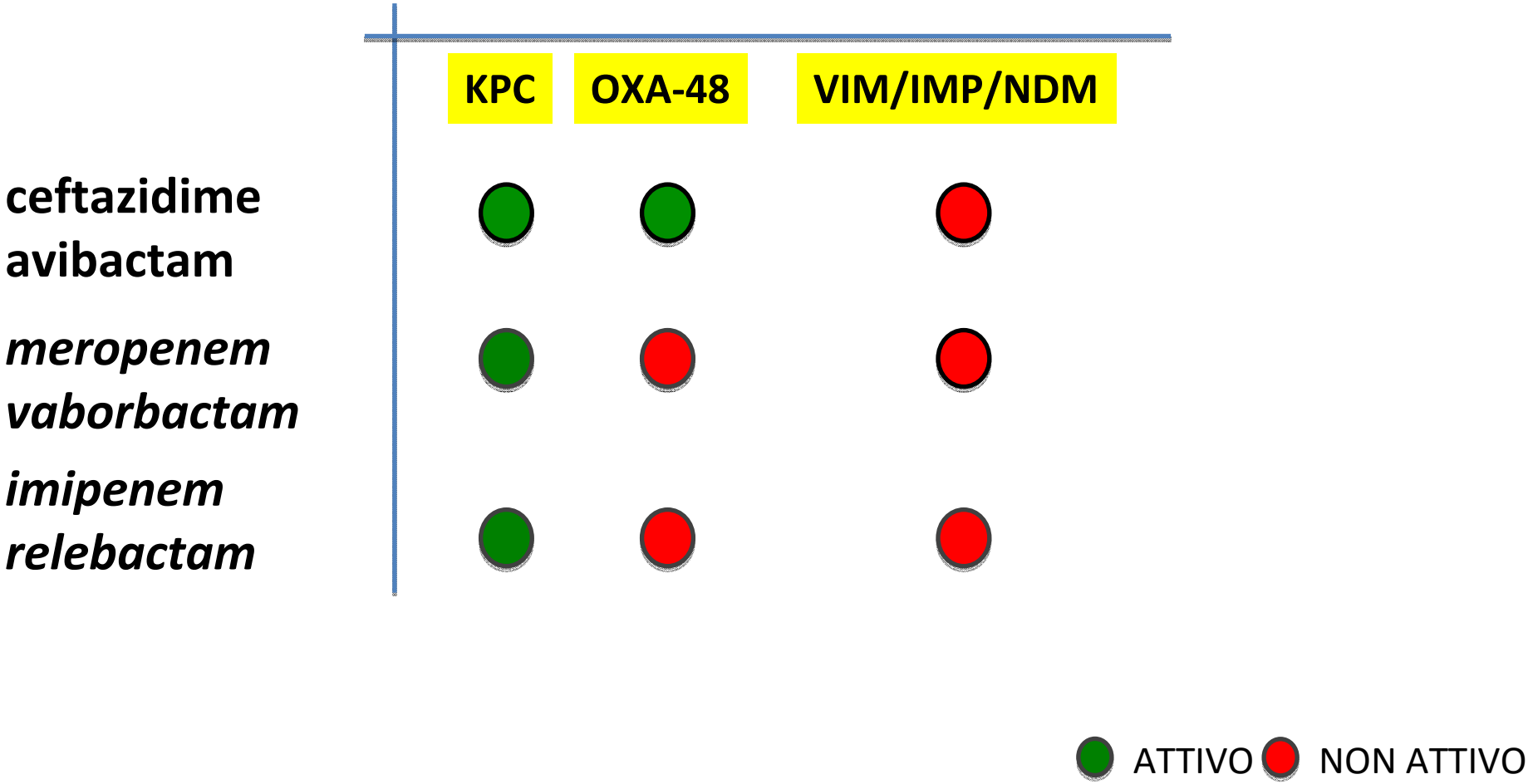
Class B (metallo) — **VIM**, **NDM**, **IMP**

Caratteristiche funzionali diverse delle carbapenemasi acquisite

	KPC-type	OXA-48-like	Metallo-enzymes (MBLs)
CARBAPEN. ACTIVITY	Strong	Weak	Strong
SPECTRUM	Extended (most β-lactams)	Narrow (penicilllins, NS cephems)	Extended (most β-lactams exc. monobactams)
INHIBITION	• Avibactam • Relebactam • Vaborbactam	• Avibactam	

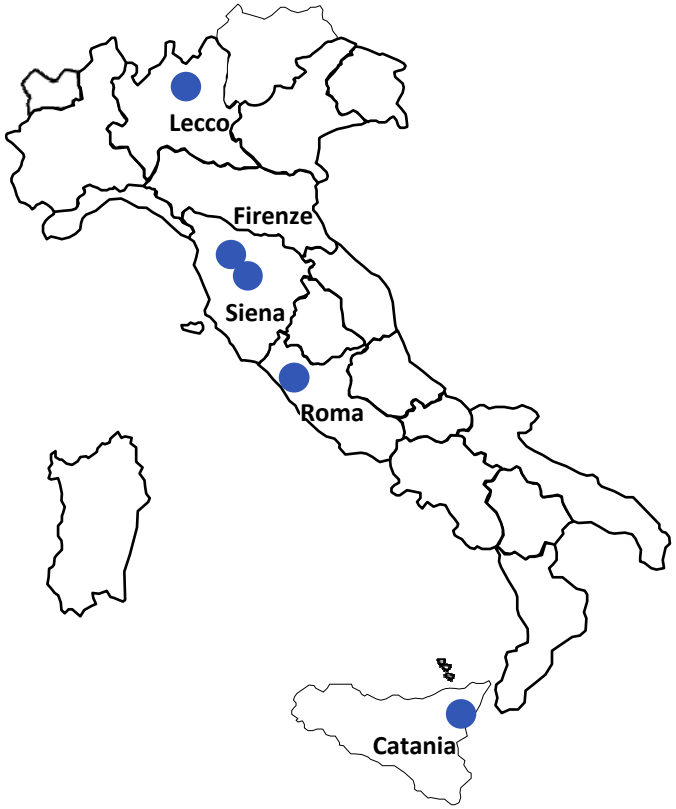
Adapted from: Naas T, et al. Current Drug Targets 2016;17:1006–1028. Drawz SM, et al. Antimicrob Agents Chemother 2014;58:1835–1846.
Adapted from: Oueslati S, et al. J Antimicrob Chemother 2015;70:1059–1063. Lahiri SD, et al. ACS Chem Biol 2015;10:591–600.
Adapted from: Bush K, Bradford PA. Cold Spring Harb Perspect Med 2016 ;6; pii: a025247.

Nuove opportunità antibiotiche anti-CRE

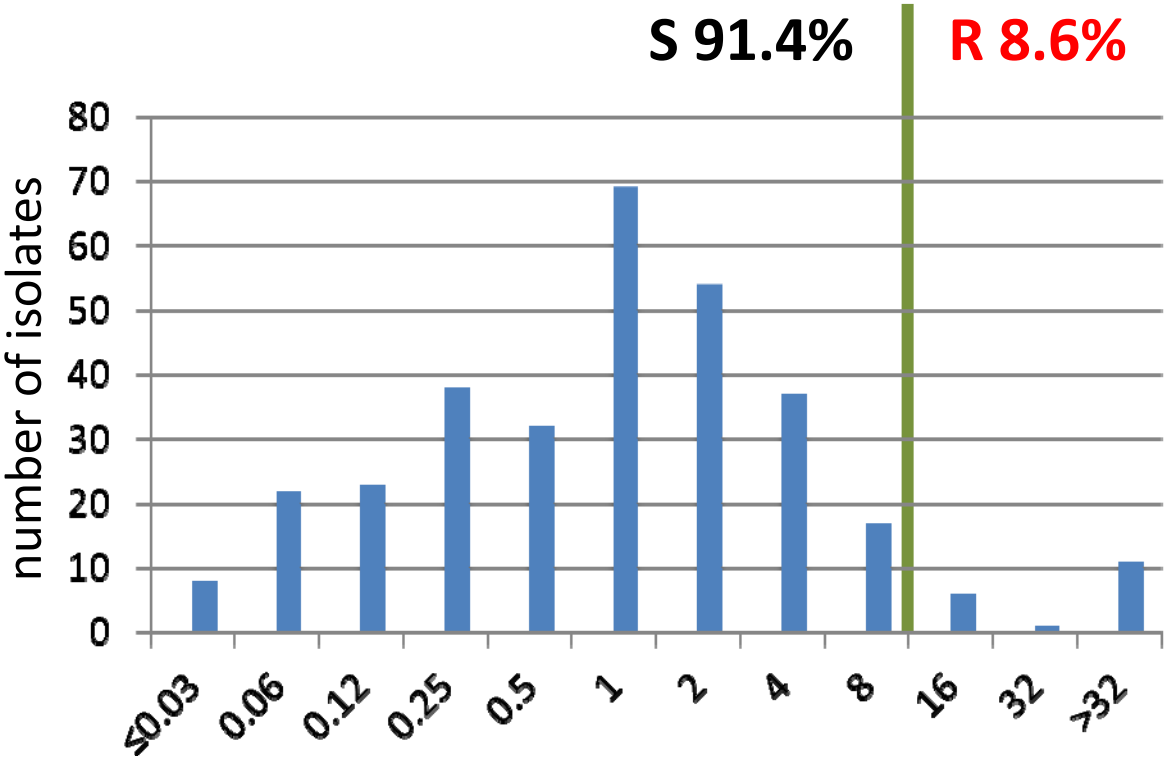


Utilità della rilevazione del meccanismo di resistenza

Sorveglianza CPE da urine (studio i-CREST)-2016



209 enterobatteri produttori di carbapenemasi



Rossolini, unpublished results

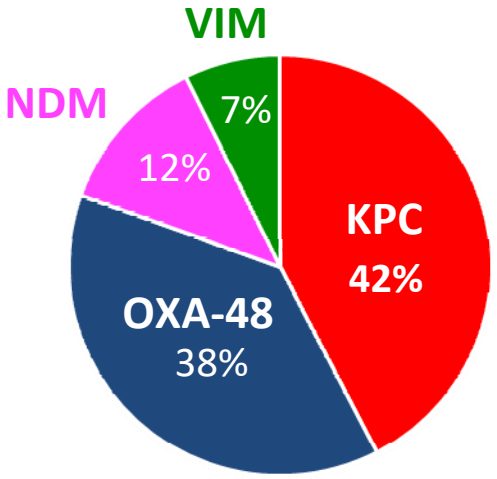
Sorveglianza CPE da urine (studio i-CREST)

Meccanismi di resistenza e sensibilità a CAZ-AVI (n=209)

CARBAPENEMASE	CAZ-AVI-S (%)	CAZ-AVI-R (%)
KPC	185 (96.3)	7 (3.7)
VIM	-	3 (100)
NDM	-	3 (100)
OXA-48	6 (100)	-
KPC+VIM	-	1 (100)
NDM+OXA-48	-	4 (100)
TOTAL	191 (91.4)	18 (8.6)

Unpublished results

Diversità delle carbapenemsi tra i CPE in Europa (EuSCAPE survey)

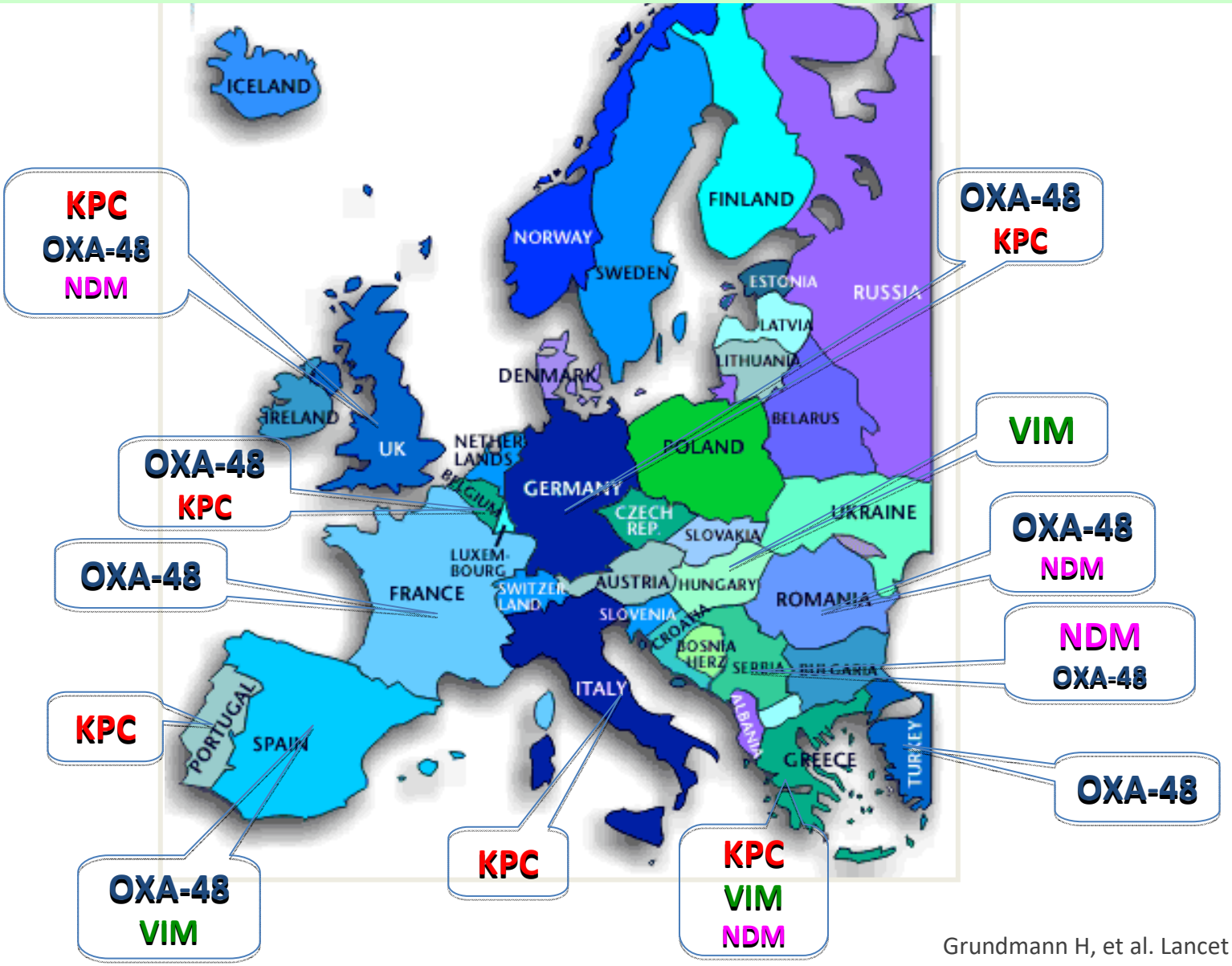


927 isolati CPE (850 *K. pneumoniae* e 77 *E. coli*) da 31 nazioni

- 455 laboratori da 36 nazioni
- Collezione isolati consecutivi non-replicati di CR *K. pneumoniae* / *E. coli* isolati clinici isolati in 6 mesi

Grundmann H, et al. Lancet Infect Dis 2017

Diversità delle carbapenemsi tra i CPE in Europa (EuSCAPE survey)

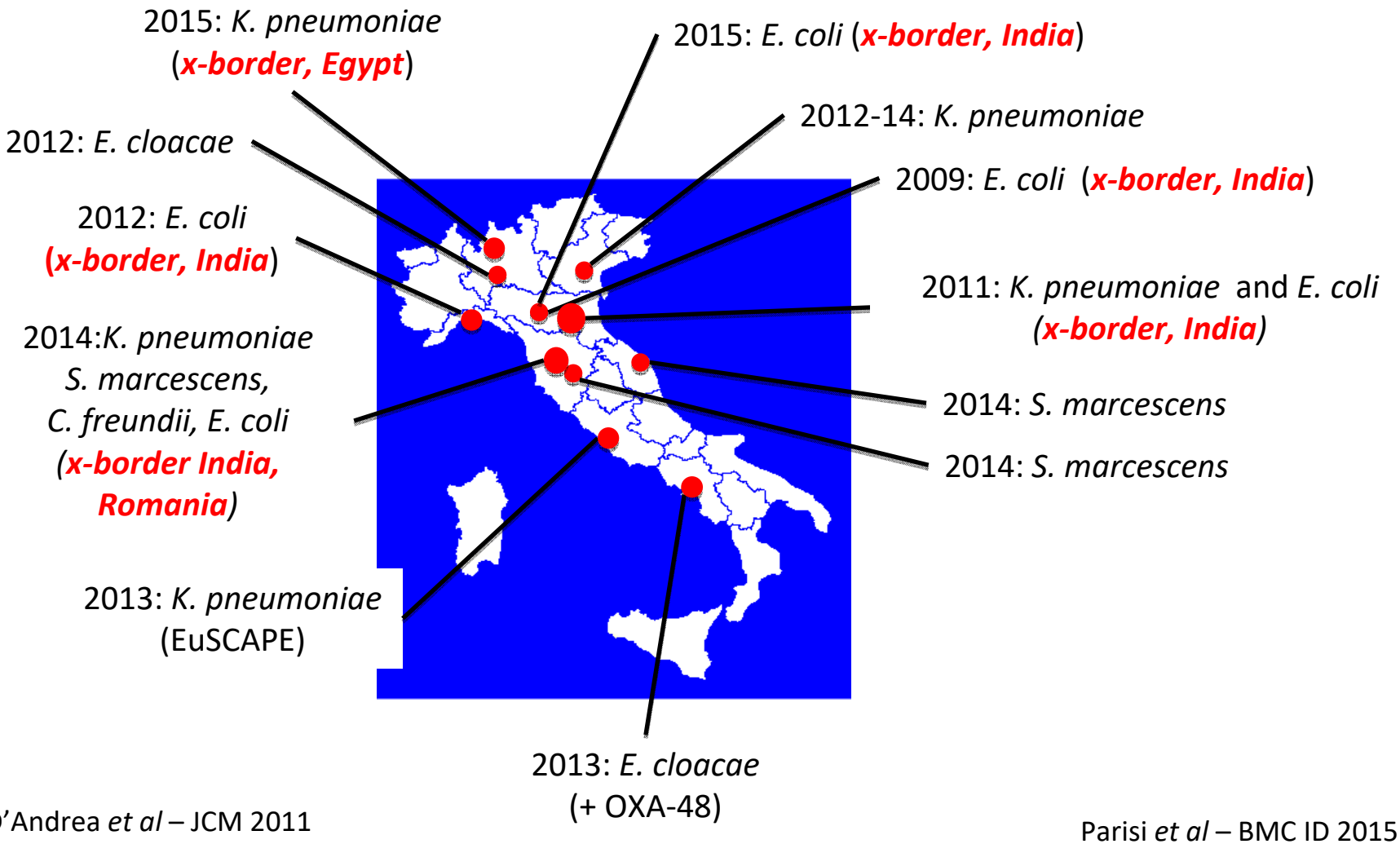


Grundmann H, et al. Lancet Infect Dis 2017

CR *K. pneumoniae,* Italia: meccanismi di R

Year (survey)	Isolates	Sources	REFs
2011 (AMCLI-CoSA) 21 centers	**234**	any clinical specimen	Giani *et al.*, Eurosurv 2013
2011-12 (ARISS-CoSA) 21 centers	**104**	Invasive infections	Conte *et al.*, JAC 2016
2013 (ARISS-CoSA) 26 centers	**131**	Invasive infections	Conte *et al.*, JAC 2016
2013-14 (EuSCAPE) 21 centers	**188**	any clinical specimen	Monaco *et al.*, Euro Surv 2014
2013 (AMCLI-CoSA) 13 centers	**130**	any clinical specimen	Giani *et al.*, Eurosurv 2017

NDM-produttori: rilevati sporadicamente dal 2009



D'Andrea *et al* – JCM 2011

Gaibani *et al* – Eurosurv 2011

Coppo *et al* – BMC Microbiol 2014

Parisi *et al* – BMC ID 2015

Principe *et al* – submitted

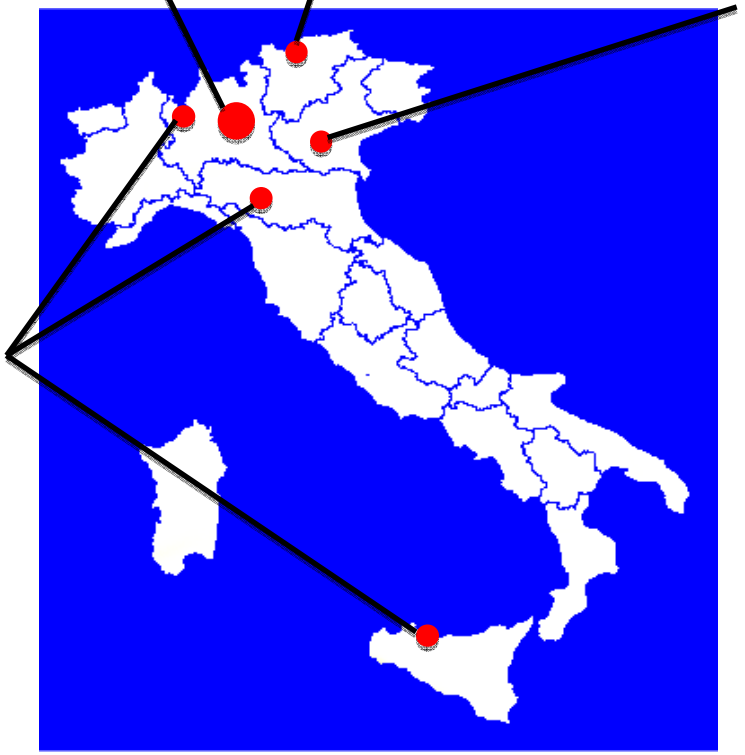
Giani *et al* - unpublished

OXA-48-produttori: "latecomers", lenta emergenza

2012:
K. pneumoniae
K. oxytoca
E. coli

2011: *E. coli* (***x-border, Egypt***)

2011: *K. pneumoniae*
(***x-border, Lybia***)

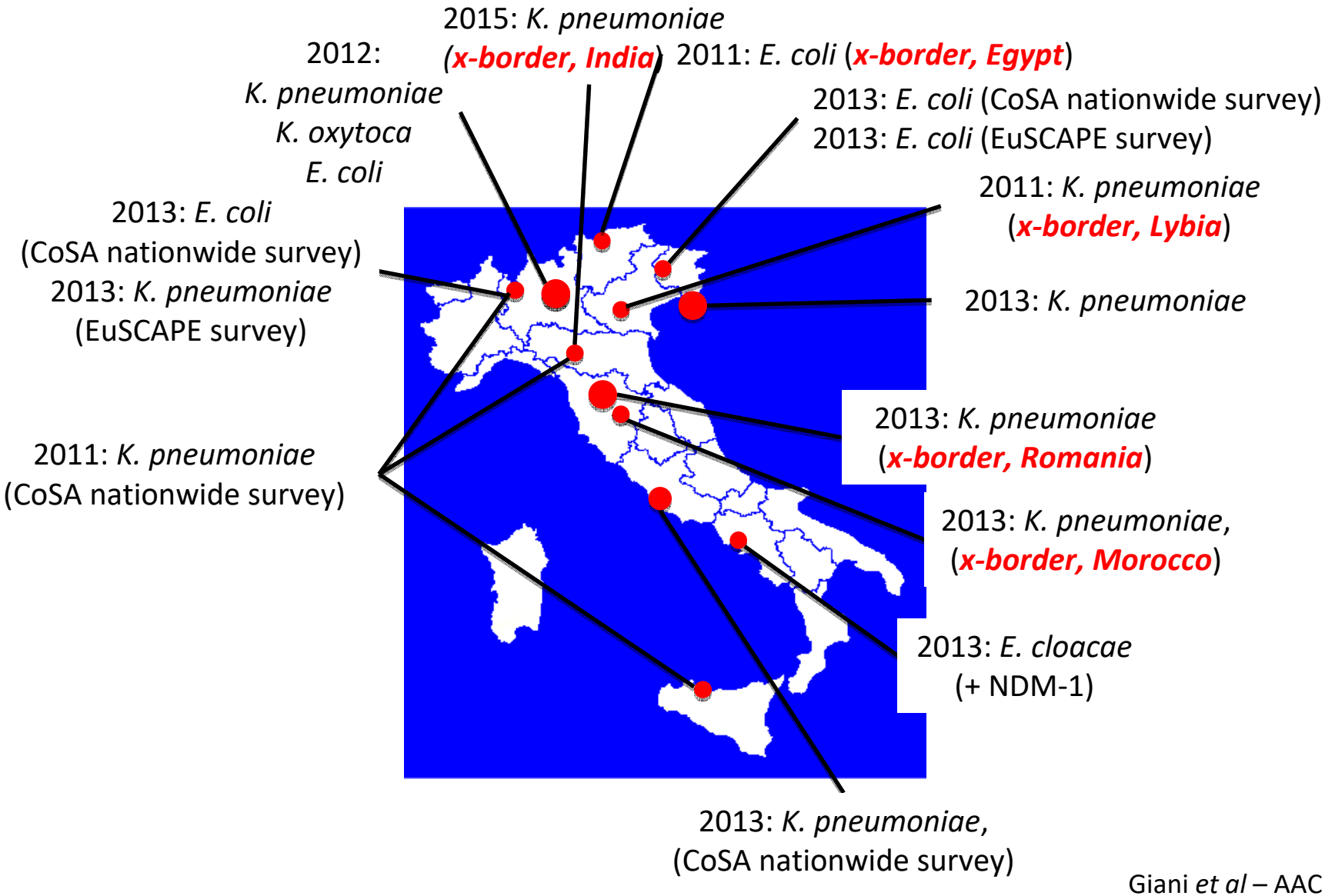


2011: *K. pneumoniae*
(CoSA nationwide survey)

Giani *et al* – Eurosurv 2013

Giani *et al* – AAC 2012
Kocsis *et al* – CMI 2013

OXA-48-produttori: "latecomers", lenta emergenza



Giani *et al* – Eurosurv 2013

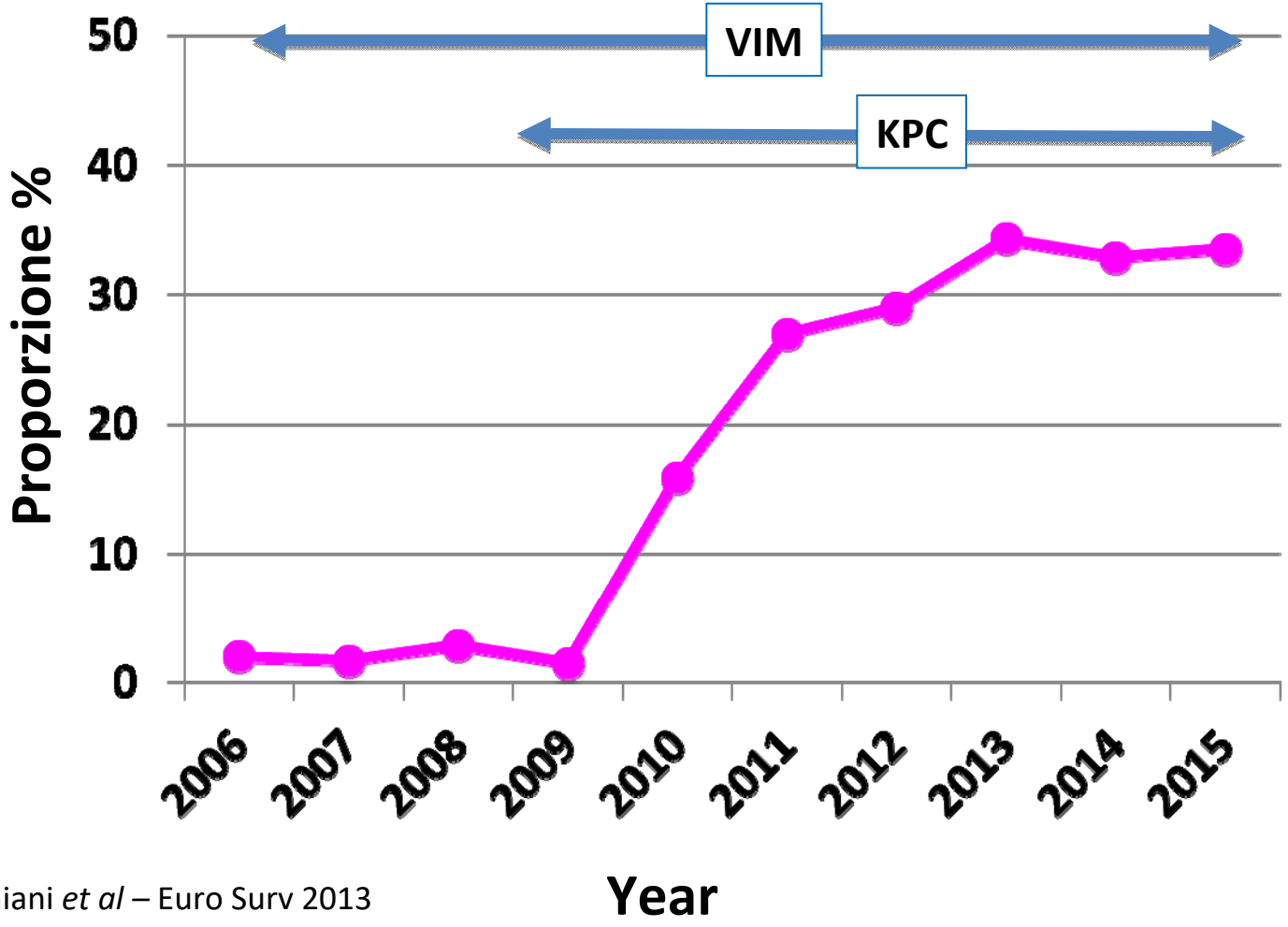
Giani *et al* – AAC 2012

Kocsis *et al* – CMI 2013

CR *K. pneumoniae*, Italia

Tipi di carbapenemasi:

	Impatto epidemiologico
NDM	+/-
OXA-48	+/-
VIM	+
KPC	+++



Giani *et al* – Euro Surv 2013
Conte *et al* – JAC 2016
Giani *et al* – Euro Surv 2017

EARS-NET

Criticità con le *K. pneumoniae* carbaR

- **Infezioni invasive associate ad una mortalità elevata (30-50% nelle BSIs)**

… che può essere più elevata per alcune categorie di pazienti

Bone Marrow Transplantation (2014), 1–7

www.nature.com/bmt

ORIGINAL ARTICLE

Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy

C Girmenia[1], GM Rossolini[2,3,4], A Piciocchi[5], A Bertaina[6], G Pisapia[7], D Pastore[8], S Sica[9], A Severino[10], L Cudillo[11], F Ciceri[12], R Scimè[13], L Lombardini[14], C Viscoli[15], A Rambaldi[16] and the Gruppo Italiano Trapianto Midollo Osseo (GITMO)[17]

Mortalità in riceventi trapianto allogenico SCT: 70.1%

Borer *et al* – ICHE 2009
Nguyen *et al* – DMID 2010
Ben-David *et al* – CMI 2011
Zarkotou *et al* – CMI 2011
Qureshi *et al* – AAC 2012
Tumbarello *et al* – CID 2012
Navarro *et al* – CMI 2012
Gutierrez-Gutierrez *et al* – Lancet 2017

Opzioni terapeutiche limitate con *carbapenemase-producing Enterobacteriaceae* (CPE)

K. pneumoniae KPC+

Antibiotic	MIC mg/L (S/I/R)
Amp/Sulb	>32 R
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Amikacin	>64 R
Gentamicin	2 S
Ciprofloxacin	>4 R
Tigecycline	1 S
Colistin	0.25 S

K. pneumoniae OXA-48+

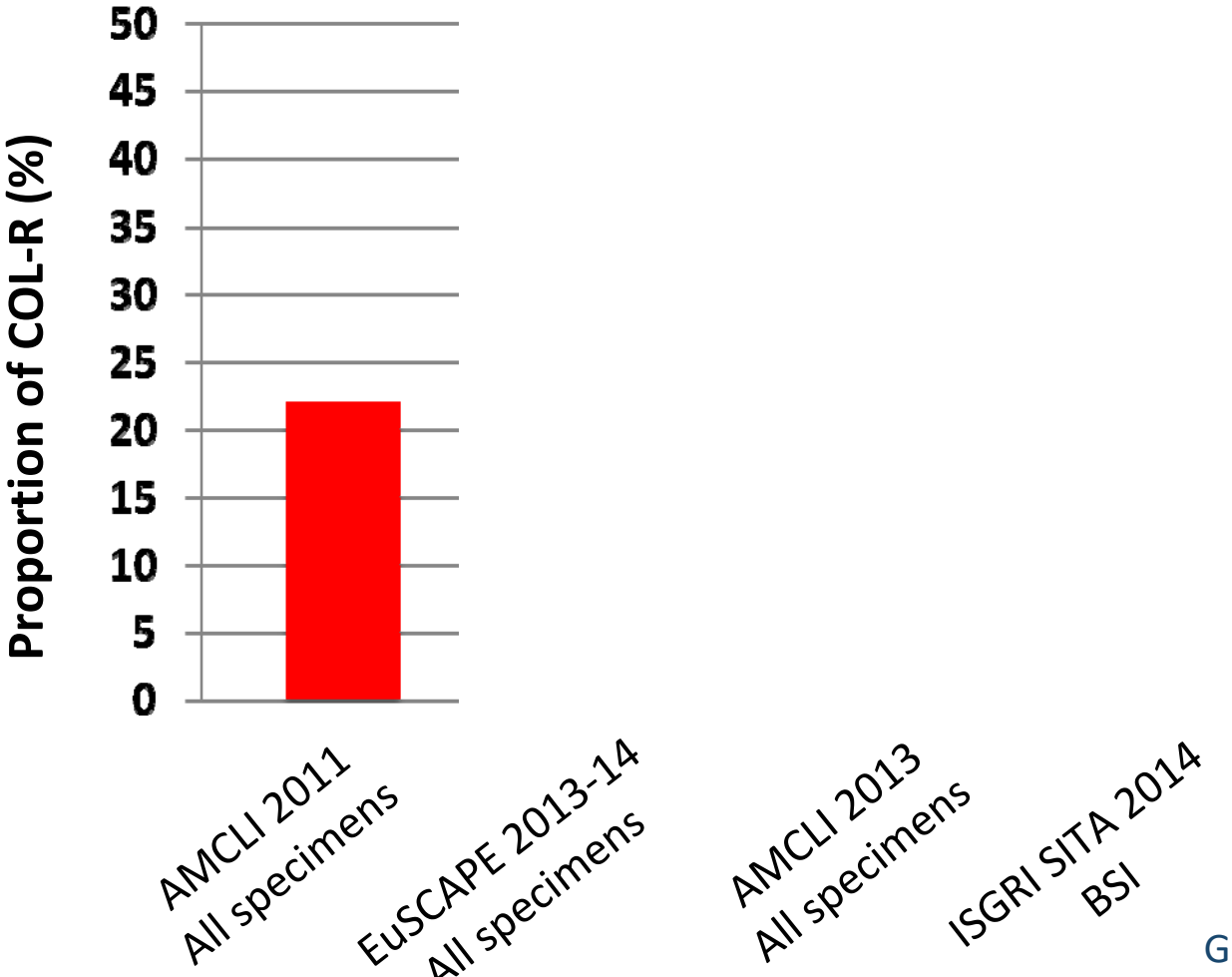
Antibiotic	MIC mg/L (S/I/R)
Amp/Sulb	>256 R
Pip/Tazo	>128 R
Cefotaxime	>64 R
Ceftazidime	64 R
Cefepime	16 R
Ertapenem	32 R
Imipenem	2 S
Meropenem	4 I
Amikacin	4 I
Gentamicin	1 S
Ciprofloxacin	>32 R
Tigecycline	1 S
Colistin	0.5 S

E. coli NDM+

Antibiotic	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>128 R
Cefotaxime	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	8 I
Meropenem	16 R
Amikacin	>64 R
Gentamicin	>16 R
Levofloxacin	>8 R
Tigecycline	0.5 S
Colistin	0.5 S

Giani T, et al. J Clin Microbiol 2009;47:3793–3794.
Giani T, et al. J Clin Microbiol 2014;52:2702–2705.
D'Andrea MM, et al. J Clin Microbiol 2011;49:2755–2758.

Resistenza alla colistina tra Carbapenem-R *Klebsiella*



Giani *et al* – Euro Surv 2013
Monaco *et al* – Euro Surv 2014
Giani *et al* – Euro Surv 2017
Giacobbe *et al* – CMI 2015

Colistina e carbapenemi-R *Klebsiella pneumoniae*: opzioni terapeutiche

Antibiotic	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Amikacin	>64 R
Gentamicin	1 S
Ciprofloxacin	>4 R
Tigecycline	1 S
Colistin	>8 R

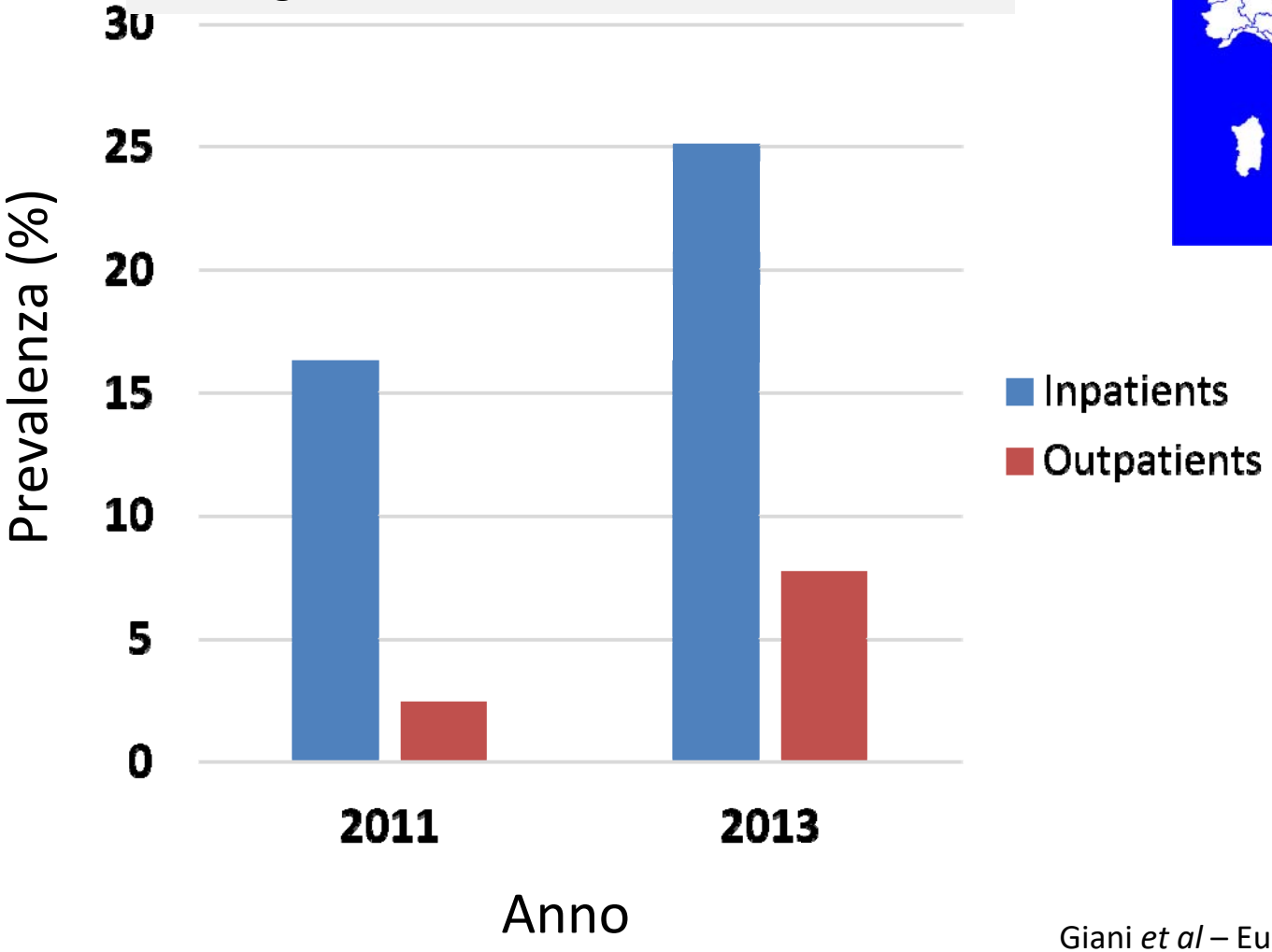
Colistin-R KPC-producer

Antibiotic	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Amikacin	>64 R
Gentamicin	>8 R
Ciprofloxacin	>4 R
Tigecycline	4 R
Colistin	>8 R
Fosfomycin	>64 R
Chloramphenicol	>16 R

Pandrug-R KPC-producer

K. pneumoniae resistente ai carbapenemi: in aumento anche fuori dell'ospedale

sorveglianze nazionali italiane AMCLI-CoSA



Giani *et al* – Euro Surv 2013
Giani *et al* – Euro Surv 2017

Conclusioni

- **Infezioni invasive da MDR** sono sempre più frequenti
- Problemi di **resistenza crescenti** soprattutto in enterobatteri (resistenza a carbapenemi e colistina)
- ***K. pneumoniae* KPC+**: prima soprattutto in infezioni acquisite in ambiente ospedaliero, ora anche in comunità
- **Nuovi farmaci in arrivo**: utili ma non copriranno tutte le esigenze
- **Prevenire la selezione e la diffusione** dei ceppi MDR/ XDR resta impegno prioritario (*infection control*, *antimicrobial stewardship*)
- Variabilità spazio-temporale: importanza di **dati aggiornati e contestualizzati**

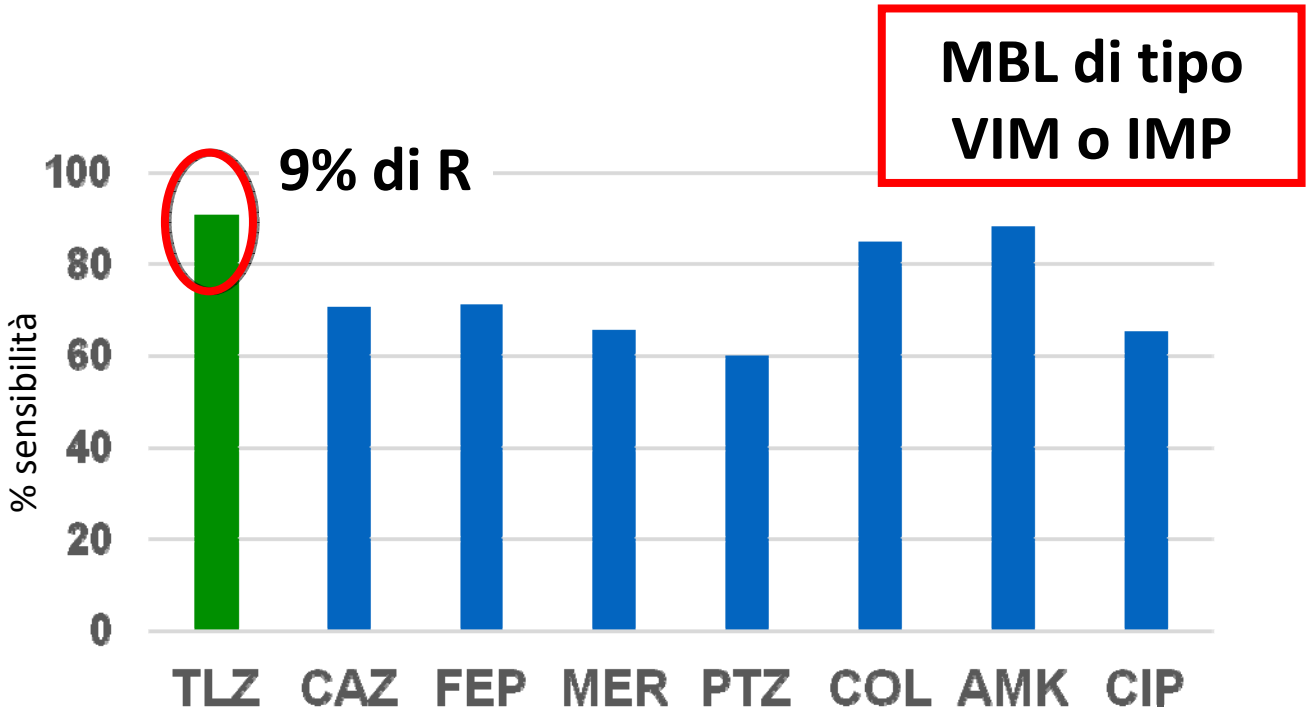
GRAZIE

per

l’ ATTENZIONE

tommaso.giani@unifi.it

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



Giani *et al* – JAC 2017