# EPIDEMIOLOGIA DEI GRAM NEGATIVI E POTENZIALITA' DI CEFTAZIDIME-AVIBACTAM

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Università degli Studi di Verona

# Quali le problematiche, oggi emergenti in antibioticoterapia?

- Aumento delle resistenze batteriche (MDR-PDR-XDR)
- Riduzione marcata della ricerca e sviluppo di nuovi antibiotici

World Health Organization

# GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

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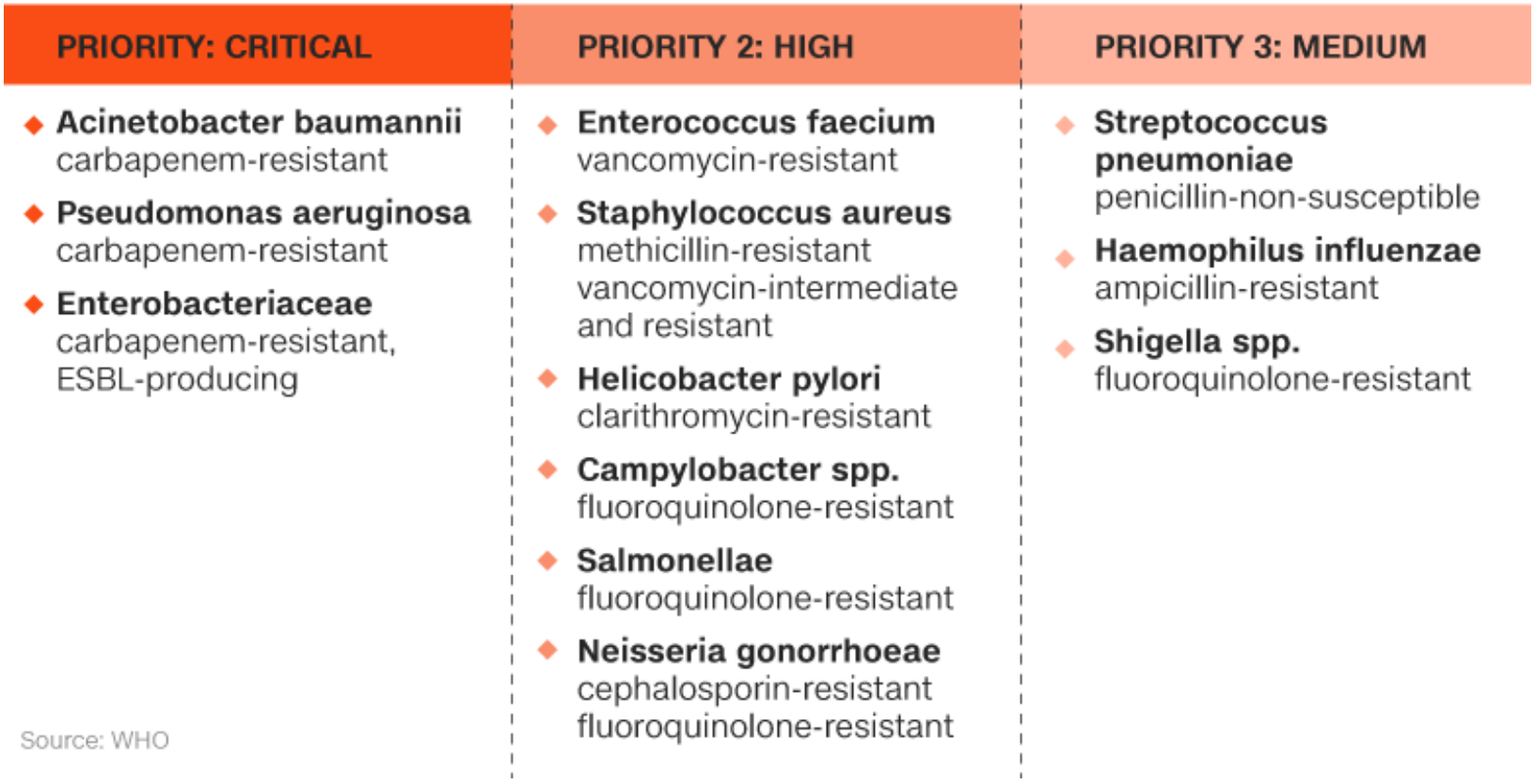
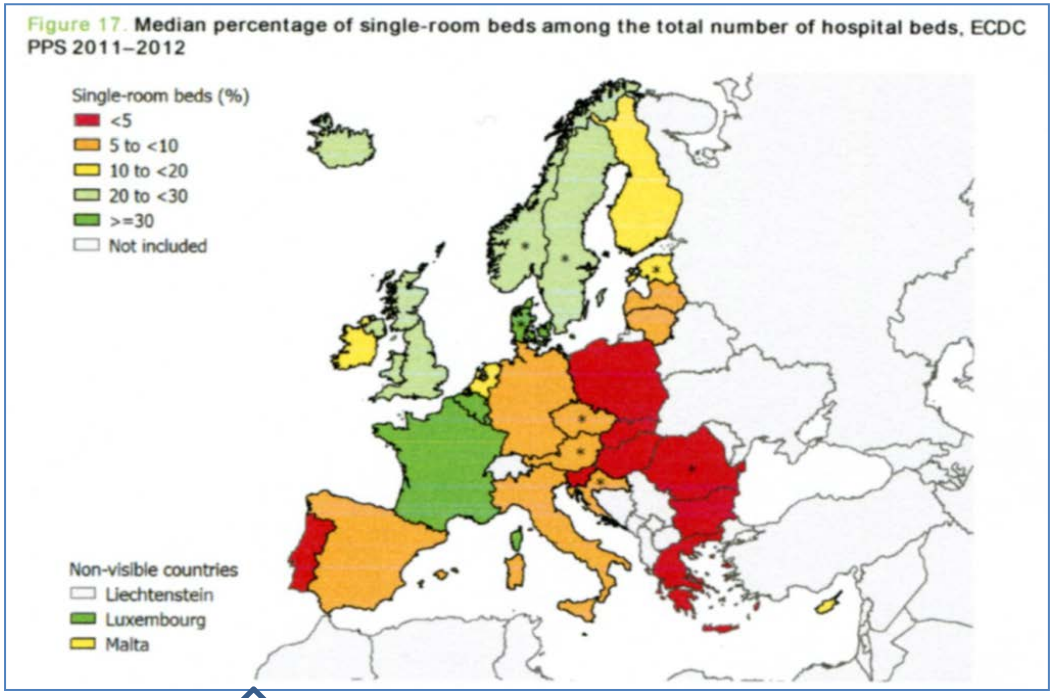
# The WHO priority list

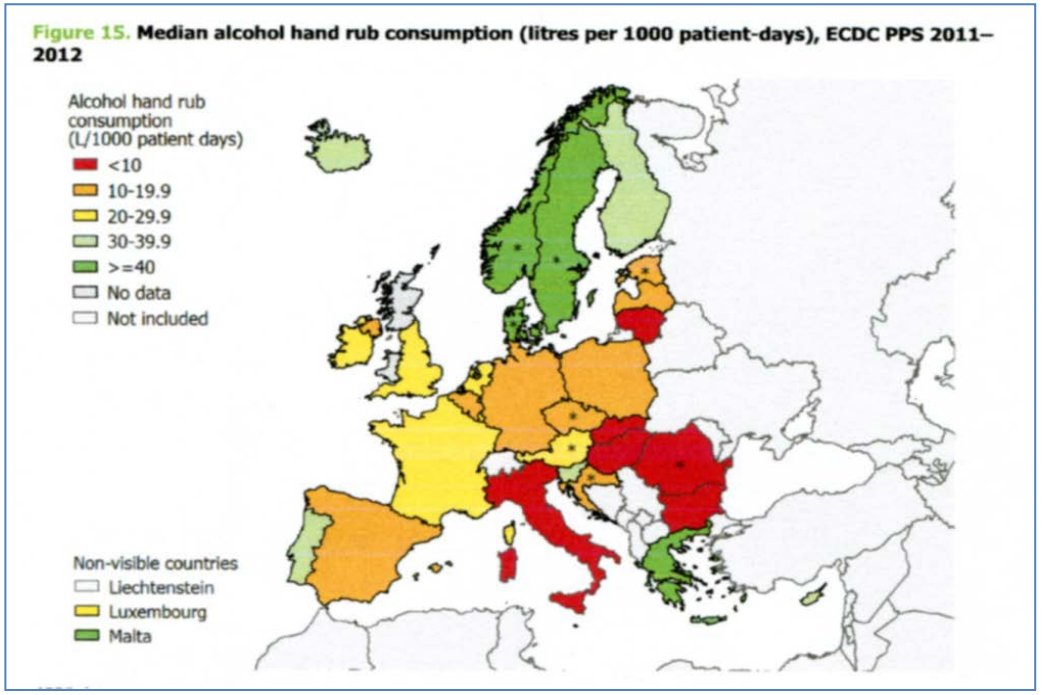



Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. WHO. 2017.

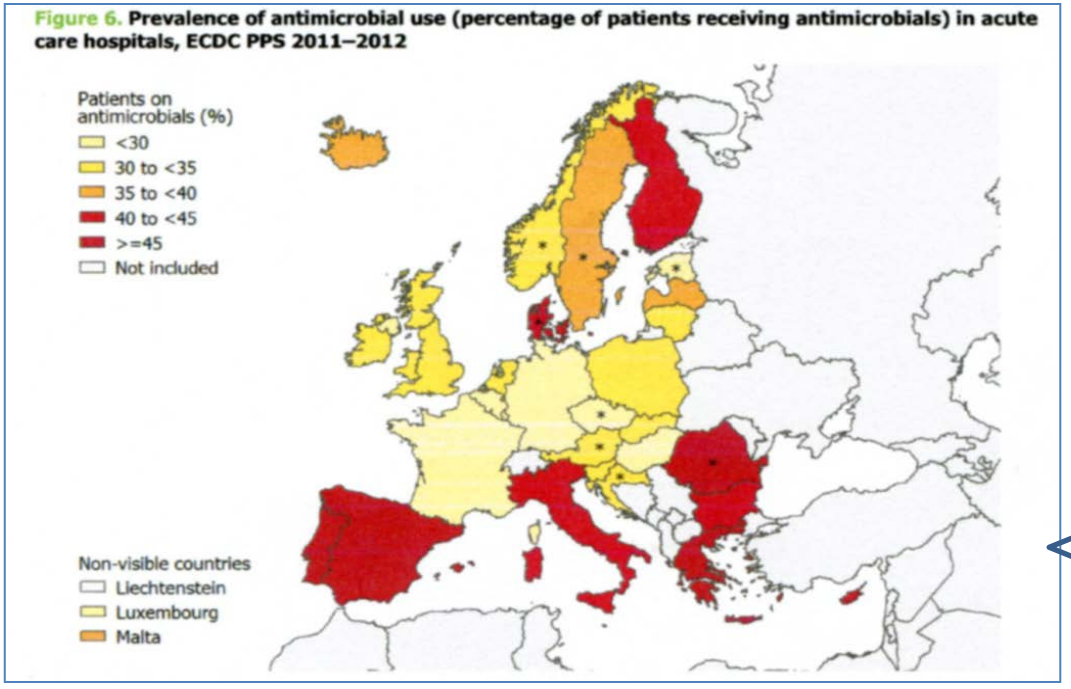
# Point prevalence survey 2011-2012




Low % of single bed-rooms




Low alcohol hand-rub consumption




Antibiotics abuse

*ECDC 2013*

*Tabella 1: Frequenza di resistenze in isolamenti da emocolture in Italia, dati EARS-net 2015 e trend 2006-2015*

| | **Italia 2015** (%) (categoria)[§] | Media europea 2015 (%) (categoria)[§] | **Trend 2012-15**[*] |
|---|---|---|---|
| *Klebsiella pneumoniae* | | | |
| resistente a cefalosporine 3° generazione | 55,9 (6) | 30,3 (5) | > |
| resistente agli aminoglicosidi | 34,0 (5) | 22,5 (4) | |
| resistente ai carbapenemi | 33,5 (5) | 8,1 (3) | |
| MDR (R a cefalosporine di 3° generazione + aminoglicosidi + fluorochinoloni) | 29,7 (5) | 18,6 (4) | |
| | | | |
| *Escherichia coli* | | | |
| resistente a cefalosporine 3° generazione | 30,1 (5) | 13,1 (4) | > |
| resistente a fluorochinoloni | 44,4 (5) | 22,8 (4) | > |
| resistente agli aminoglicosidi | 20,2 (4) | 10,4 (4) | |
| MDR (R a cefalosporine di 3° generazione + aminoglicosidi + fluorochinoloni) | 14,6 (4) | 5,3 (3) | |
| | | | |

| | | | |
|---|---|---|---|
| *Pseudomonas aeruginosa* | | | |
| resistente a piperacillina-tazobactam | 29,5 (5) | 18,1 (4) | |
| resistente a ceftazidime | 21,7 (4) | 13,3 (4) | |
| resistente agli aminoglicosidi | 17,2 (4) | 13,3 (4) | < |
| resistente a carbapenemi | 23,0 (4) | 17,8 (4) | |
| | | | |
| *Acinetobacter spp.* | | | |
| resistente a carbapenemi | 78,3 (7) | Non riportata | |
| | | | |
| *Staphylococcus aureus* | | | |
| resistente alla meticillina | 34,1 (5) | 16,8 (4) | |
| | | | |
| *Streptococcus pneumoniae* | | | |
| NS alla penicillina | 12,3 (4) | Non riportata | |
| NS ai macrolidi | 24,5 (4) | Non riportata | <# |
| | | | |
| *Enterococcus faecium* | | | |
| resistente ai glicopeptidi (VRE) | 11,2 (4) | 8,3 (3) | > |

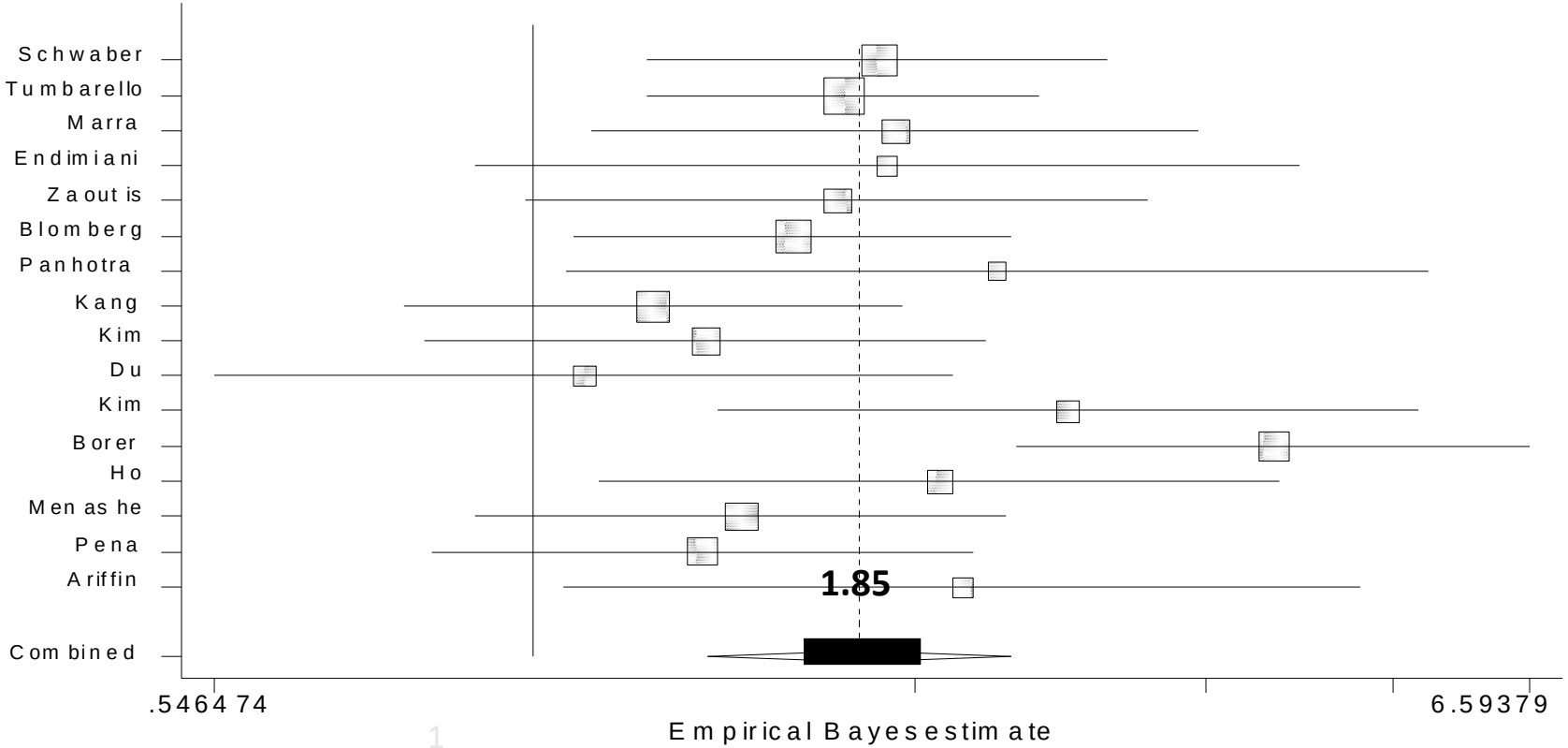
Legenda

# COME SIAMO MESSI RISPETTO AGLI ALTRI PAESI EUROPEI ?

| PATOGENO RESISTENTE | POSIZIONE IN CLASSIFICA |
|---|---|
| E.Coli FQ R | 2° su 30 |
| E. Coli CEF R | 2° su 30 |
| K. pneumoniae Carba R | 2° su 30 |
| K. pneumoniae FQ R | 5 su 30 |
| K. pneumoniae CEF R | 6 su 30 |
| XDR Acinetobacter | 6 su 30 |
| MRSA | 6 su 30 |
| P. aeruginosa MDR | 9 su 30 |
| VRE | 15 su 30 |
| MDR Pneumococchi | 15 su 30 |

# MORTALITY DUE TO BACTEREMIA:

# META-ANALYSIS OF STUDIES COMPARING ESBLS AND NON-ESBLS




**Odds Ratio**

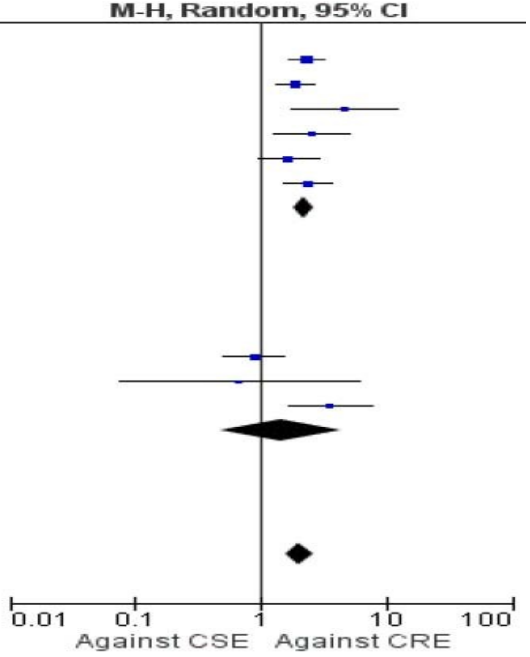
Schwaber M. JAC 2007

# Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections

Matthew E. Falagas,[1] Giannoula S. Tansarli,[1] Drosos E. Karageorgopoulos,[1] and Konstantinos Z. Vardakas[1]

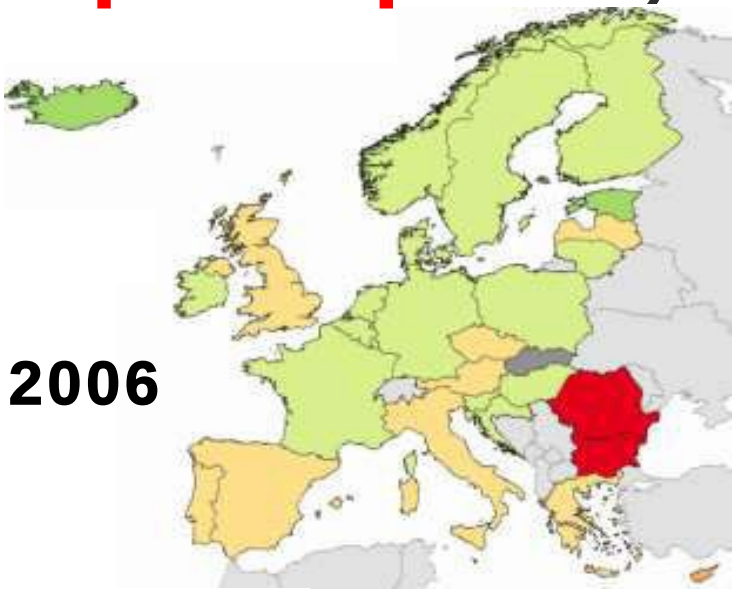
**CRE Bacteremia mortality 131/222= 60%**

| Study or Subgroup | Carba-resistant Events | Total | Carba-susceptible Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Bacteremia** | | | | | | |
| Ben-David 2012 | 29 | 42 | 45 | 150 | 18.4% | 2.30 [1.68, 3.16] |
| Chang 2011 | 16 | 17 | 17 | 34 | 17.3% | 1.88 [1.32, 2.69] |
| Daikos 2007 | 7 | 13 | 5 | 43 | 6.0% | 4.63 [1.76, 12.16] |
| Daikos 2009 | 6 | 14 | 25 | 148 | 9.3% | 2.54 [1.26, 5.12] |
| Mouloudi 2010 | 25 | 37 | 9 | 22 | 12.2% | 1.65 [0.95, 2.86] |
| Patel 2008 | 48 | 99 | 20 | 99 | 14.9% | 2.40 [1.54, 3.73] |
| **Subtotal (95% CI)** | | **222** | | **496** | **78.1%** | **2.19 [1.82, 2.63]** |
| Total events | 131 | | 121 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.53$, df = 5 (P = 0.48); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 8.30 (P < 0.00001) | | | | | | |
| **1.1.2 Bacteremia or other infections** | | | | | | |
| Falagas 2007 | 16 | 53 | 18 | 53 | 12.1% | 0.89 [0.51, 1.55] |
| Gaviria 2011 | 1 | 19 | 3 | 38 | 1.4% | 0.67 [0.07, 5.99] |
| Schwaber 2008 | 21 | 48 | 7 | 56 | 8.4% | 3.50 [1.63, 7.51] |
| **Subtotal (95% CI)** | | **120** | | **147** | **21.9%** | **1.46 [0.47, 4.49]** |
| Total events | 38 | | 28 | | | |
| Heterogeneity: $Tau^2 = 0.68$; $Chi^2 = 8.68$, df = 2 (P = 0.01); $I^2 = 77\%$ | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.51) | | | | | | |
| **Total (95% CI)** | | **342** | | **643** | **100.0%** | **2.05 [1.56, 2.69]** |
| Total events | 169 | | 149 | | | |
| Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 16.49$, df = 8 (P = 0.04); $I^2 = 51\%$ | | | | | | |
| Test for overall effect: Z = 5.17 (P < 0.00001) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.49$, df = 1 (P = 0.49), $I^2 = 0\%$ | | | | | | |



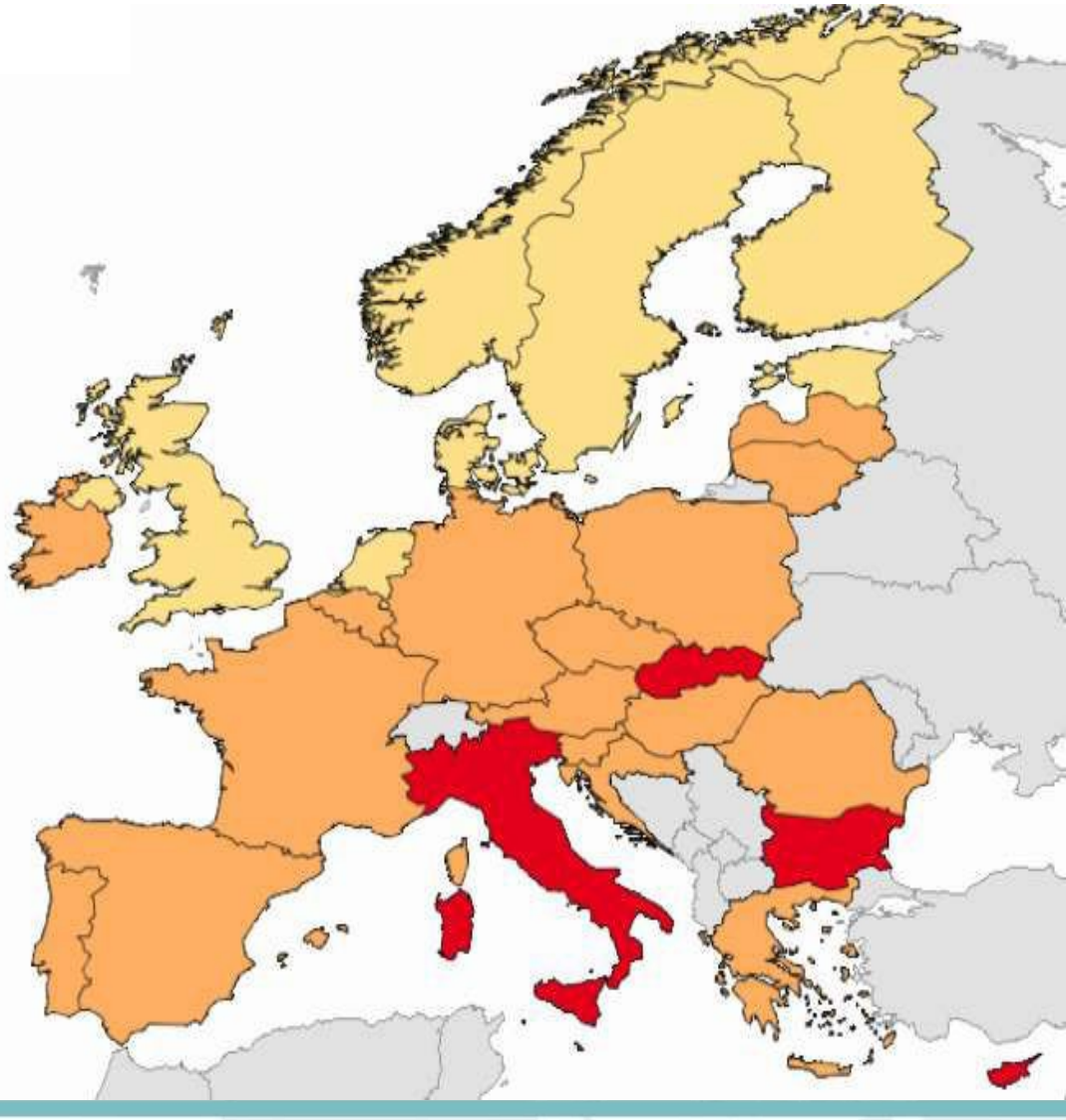
# ESCHERICHIA COLI

# Escherichia coli: percentage of invasive isolates resistant to third-generation cephalosporins, EU/EEA, 2006 & 2016



2006

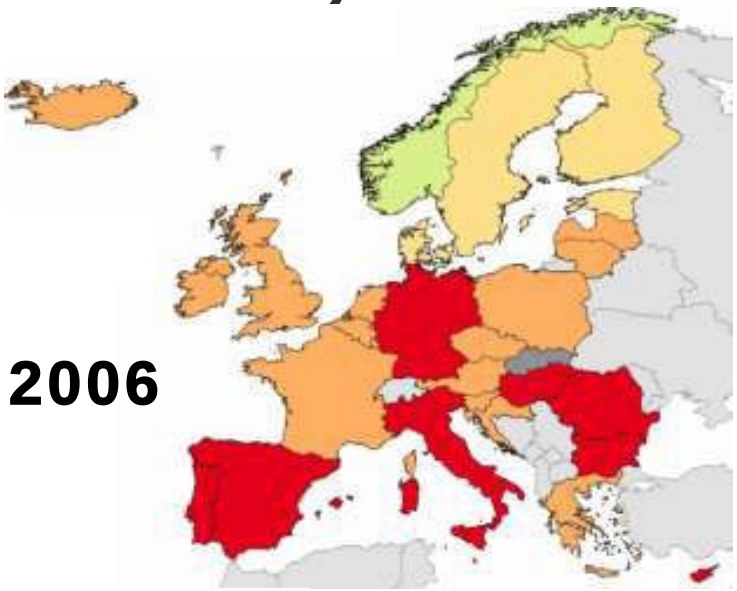
2016



- <1%
- 1-<5%
- 5-<10%
- 10-<25%
- 25-<50%
- 50-<75%
- >=75%
- Not calculated

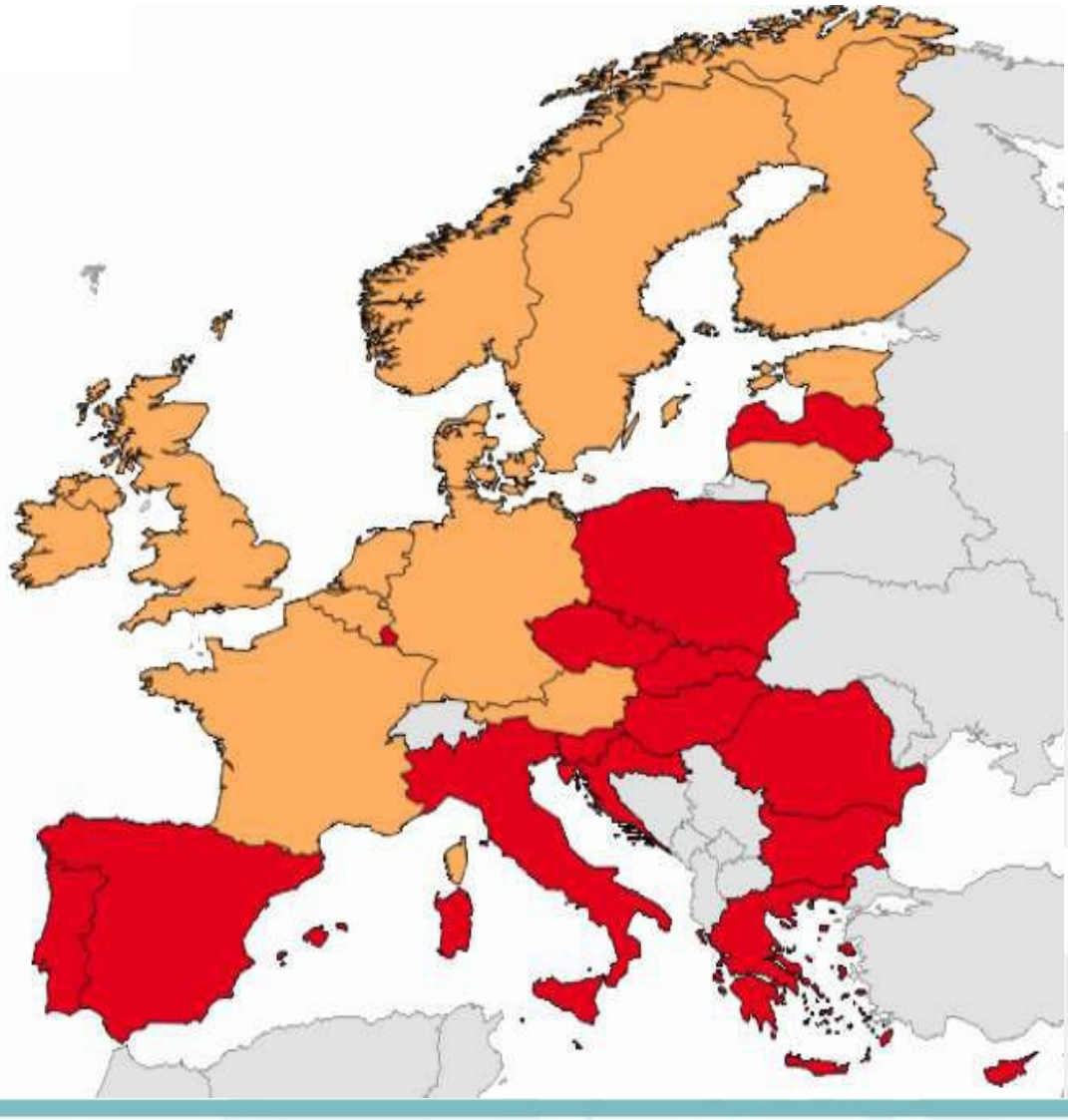
Source: EARS/EARS-Net, 2017 (https://atlas.ecdc.europa.eu).

# Escherichia coli: percentage of invasive isolates resistant to fluoroquinolones, EU/EEA, 2006 & 2016



2006

2016



- <1%
- 1-<5%
- 5-<10%
- 10-<25%
- 25-<50%
- 50-<75%
- >=75%
- Not calculated

Source: EARS/EARS-Net, 2017 (https://atlas.ecdc.europa.eu).

# ESBL AOUI VERONA

ATTENZIONE: DAL 2013 CAMBIATI CRITERI DI SELEZIONE

| ESBL** | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018(feb) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B. TRENTO | 219 | 197 | 269 | 224 | 177 | 277 | 366 | 446 | 517 | 473 | 68 |
| B. ROMA | 106 | 133 | 160 | 149 | 141 | 223 | 279 | 291 | 376 | 409 | 75 |
| TOTALE | 325 | 330 | 429 | 373 | 318 | 500 | 645 | 737 | 893 | 828 | 143 |

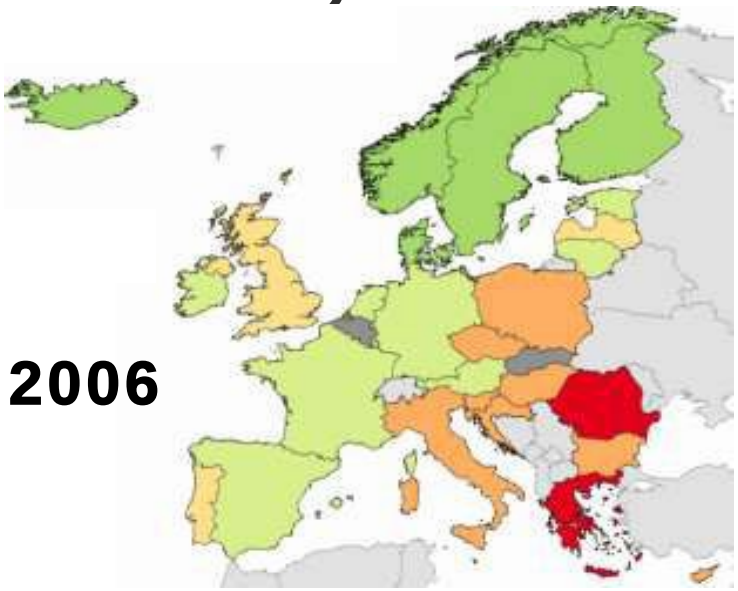
| TOTALE |
|---|
| 3233 |
| 2342 |
| 5575 |

** Enterobatteriacee resistenti alle Cefalosporine di terza generazione. Microrganismi ricercati: Escherichia Coli, Klebsiella Pneumoniae, Morganella morgani, Proteus mirabilis, Providencia alcalifaciens, Providencia rettgeri, Providencia spp., Providencia stuarti

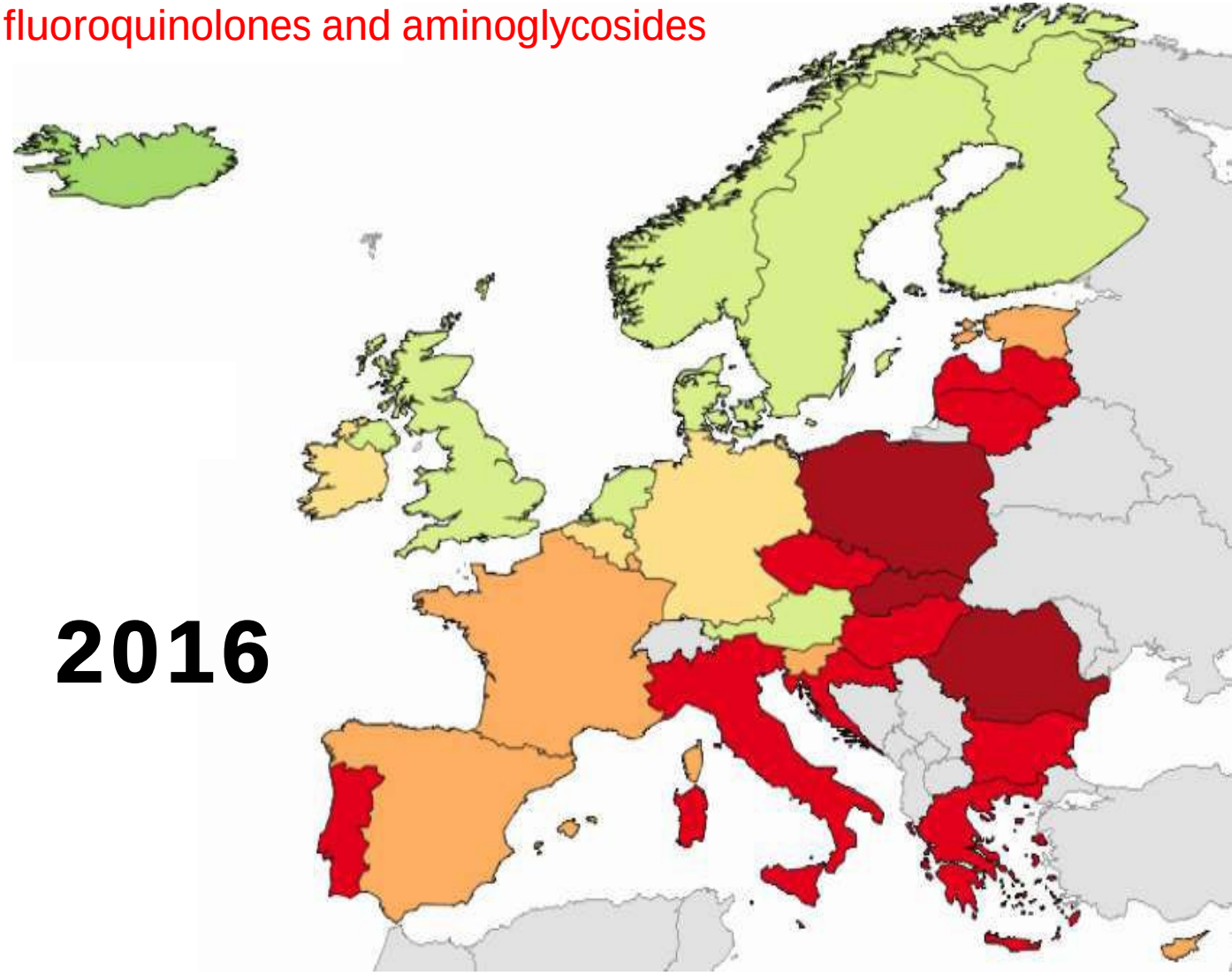
# KLEBSIELLA PNEUMONIAE

# Klebsiella pneumoniae: % of invasive isolates with combined resistance*, EU/EEA, 2006 & 2016

*Third-generation cephalosporins, fluoroquinolones and aminoglycosides



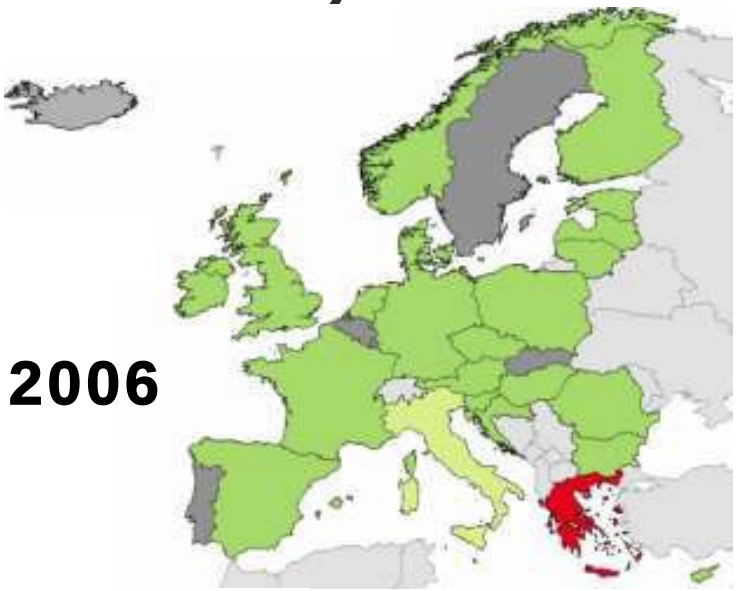
2006



2016

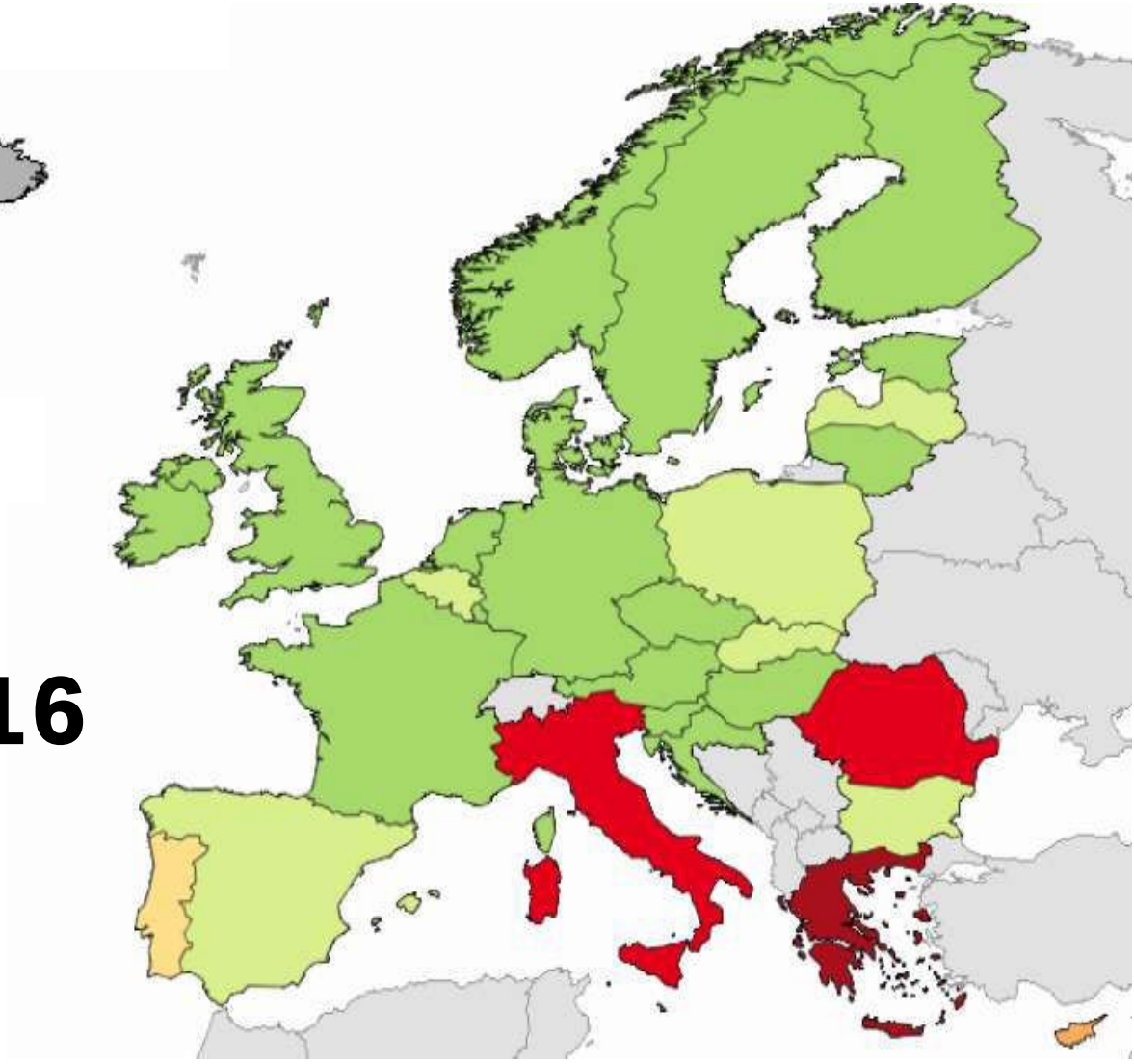
- <1%
- 1-<5%
- 5-<10%
- 10-<25%
- 25-<50%
- 50-<75%
- >=75%
- Not calculated

# Klebsiella pneumoniae: % of invasive isolates with resistance to carbapenems, EU/EEA, 2006 & 2016



2006

2016



- <1%
- 1-<5%
- 5-<10%
- 10-<25%
- 25-<50%
- 50-<75%
- >=75%
- Not calculated

# Azienda Osp. Univ. Verona: KPC

| AREA | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017[1] | Totale |
|---|---|---|---|---|---|---|---|---|
| MEDICA | 149 | 127 | 156 | 116 | 178 | 143 | 156 | 1025 |
| CHIRURGICA | 40 | 42 | 65 | 46 | 79 | 88 | 85 | 445 |
| ONCOEMATOLOGICA | 1 | 2 | 8 | 5 | 10 | 13 | 6 | 45 |
| CRITICA | 46 | 45 | 52 | 59 | 121 | 122 | 94 | 539 |
| ALTRO | 0 | 0 | 1 | 2 | 1 | 2 | 3 | 9 |
| Totale | 236 | 216 | 282 | 228 | 389 | 368 | 121 | 2063 |

1: valori aggiornati al 28 MARZO 2017

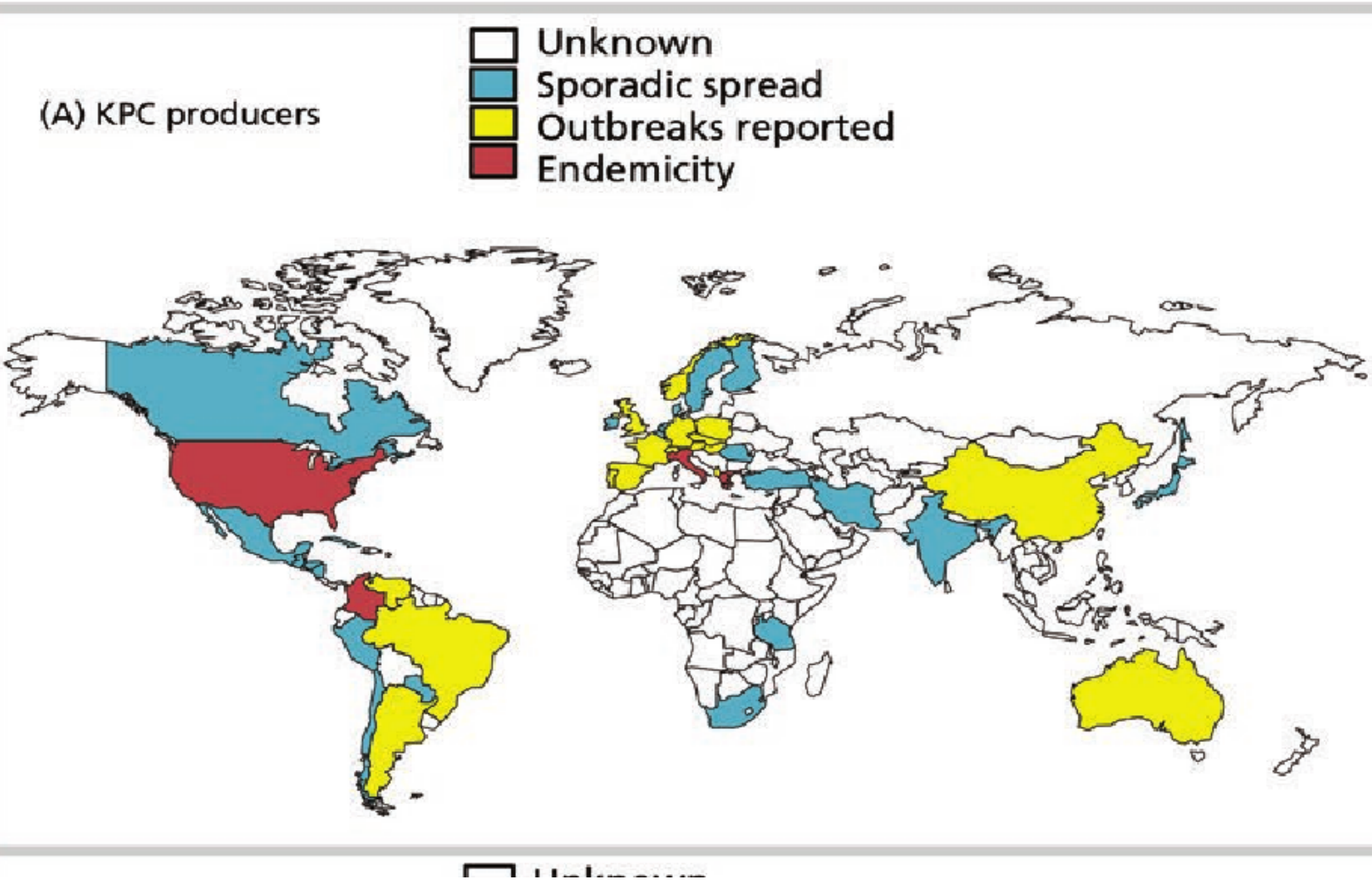
| | ITALIA | ARS Toscana |
|---|---|---|
| VRE | 11 % | 21 % (0-72 %) |
| KPC | 34 % | 37 % (6-60 %) |

G. Rossolini

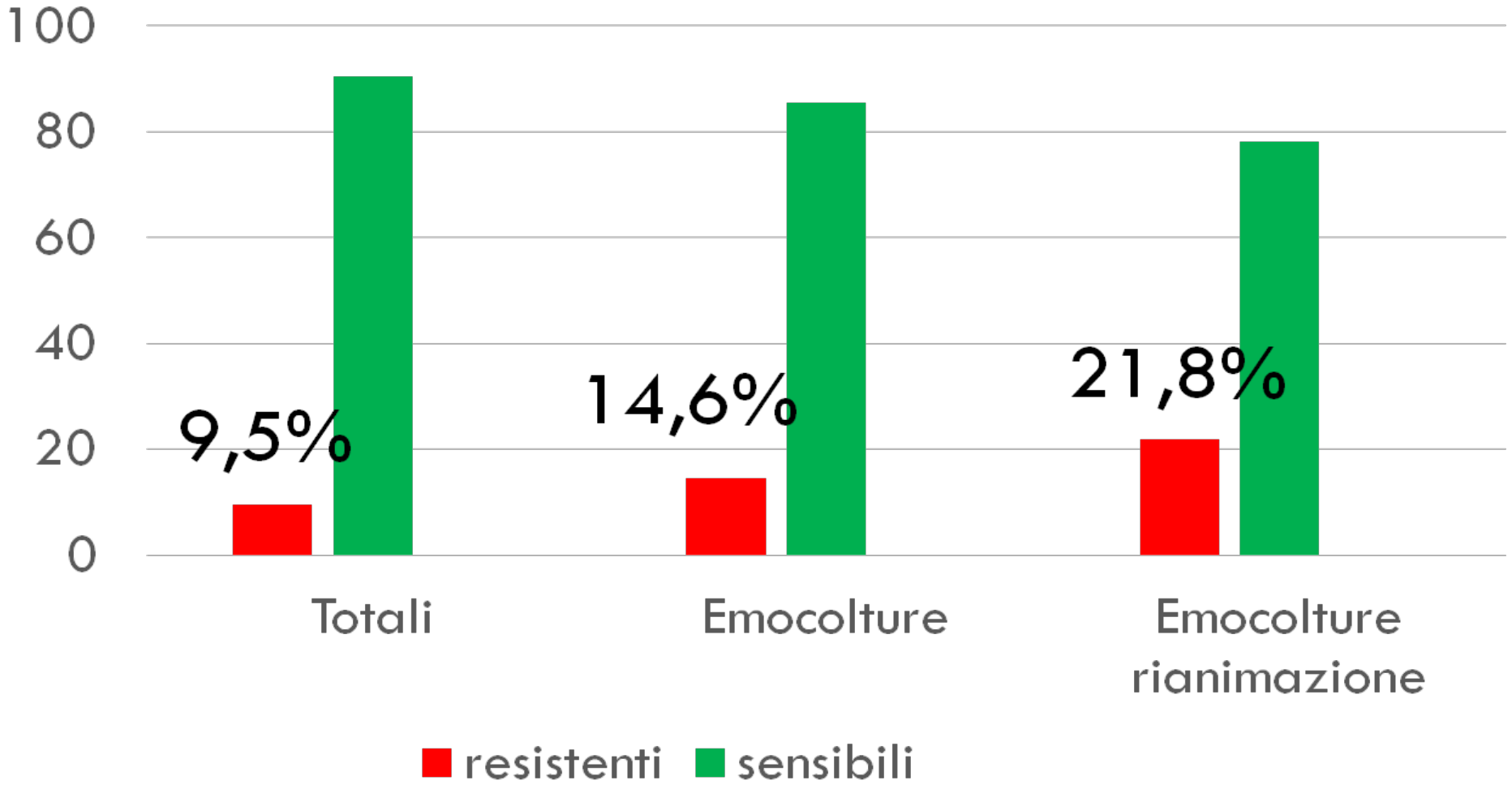
| | Hospitals submitting carbapenem non-susceptible *K pneumoniae* isolates (n) | Number of submitted carbapenem non-susceptible *K pneumoniae* isolates | Confirmed carbapenemase-producing *K pneumoniae* isolates | | | | | Other (n, %)* |
|---|---|---|---|---|---|---|---|---|
| | | | KPC (n, %) | NDM (n,%) | OXA-48-like (n, %) | VIM (n, %) | Total (n, %) | |
| Albania | 3 | 8 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 8 (100) |
| Austria | 6 | 15 | 6 (40·0) | 2 (13·3) | 2 (13·3) | 0 (0) | 10 (66·7) | 5 (33·3) |
| Belgium | 11 | 48 | 13 (27·1) | 2 (4·2) | 18 (37·5) | 0 (0) | 33 (68·8) | 15 (31·3) |
| Bulgaria | 3 | 4 | 0 (0) | 2 (50·0) | 0 (0) | 0 (0) | 2 (50·0) | 2 (50·0) |
| Croatia | 14 | 48 | 1 (2·1) | 0 (0) | 1 (2·1) | 5 (10·4) | 7 (14·6) | 41 (85·4) |
| Cyprus | 1 | 1 | 0 (0) | 0 (0) | 1 (100) | 0 (0) | 1 (100) | 0 (0) |
| Czech Republic | 5 | 26 | 0 (0) | 1 (3·8) | 1 (3·8) | 0 (0) | 2 (7·7) | 24 (92·3) |
| Denmark | 3 | 8 | 1 (12·5) | 3 (37·5) | 2 (25·0) | 0 (0) | 6 (75·0) | 2 (25·0) |
| Estonia | 1 | 9 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 9 (100) |
| Finland | 1 | 1 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (100) |
| France | 11 | 27 | 1 (3·7) | 0 (0) | 10 (37·0) | 0 (0) | 11 (40·7) | 16 (59·3) |
| Germany | 13 | 36 | 8 (22·2) | 2 (5·6) | 12 (33·3) | 0 (0) | 22 (61·1) | 14 (38·9) |
| Greece | 10 | 86 | 56 (65·1) | 12 (14·0) | 2 (2·3) | 9 (10·5) | 79 (91·9) | 7 (8·1) |
| Hungary | 7 | 36 | 0 (0) | 0 (0) | 0 (0) | 26 (72·2) | 26 (72·2) | 10 (27·8) |
| Ireland | 7 | 12 | 2 (16·7) | 2 (16·7) | 2 (16·7) | 0 (0) | 6 (50·0) | 6 (50·0) |
| Israel | 7 | 39 | 31 (79·5) | 2 (5·1) | 1 (2·6) | 0 (0) | 34 (87·2) | 5 (12·8) |
| Italy | 22 | 195 | 187 (95·9) | 1 (0·5) | 1 (0·5) | 3 (1·5) | 192 (98·5) | 3 (1·5) |
| Latvia | 1 | 4 | 0 (0) | 0 (0) | 0 (0) | 2 (50·0) | 2 (50·0) | 2 (50·0) |
| Lithuania | 4 | 4 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (100) |
| Luxembourg | 3 | 10 | 4 (40·0) | 0 (0) | 2 (20·0) | 2 (20·0) | 8 (80·0) | 2 (20·0) |
| Malta | 1 | 9 | 0 (0) | 0 (0) | 9 (100) | 0 (0) | 9 (100) | 0 (0) |
| Montenegro | 1 | 10 | 0 (0) | 10 (100) | 0 (0) | 0 (0) | 10 (100) | 0 (0) |
| Norway | 4 | 5 | 0 (0) | 1 (20·0) | 0 (0) | 0 (0) | 1 (20·0) | 4 (80·0) |
| Poland | 10 | 34 | 2 (5·9) | 2 (5·9) | 0 (0) | 0 (0) | 4 (11·8) | 30 (88·2) |
| Portugal | 17 | 61 | 36 (59·0) | 0 (0) | 0 (0) | 0 (0) | 36 (59·0) | 25 (40·9) |
| Romania | 8 | 68 | 4 (5·9) | 5 (7·4) | 50 (73·5) | 2 (2·9) | 61 (89·7) | 7 (10·3) |
| Serbia | 11 | 67 | 1 (·5) | 33 (49·3) | 9 (13·4) | 0 (0) | 43 (64·2) | 24 (35·8) |
| Slovakia | 5 | 22 | 1 (4·5) | 0 (0) | 0 (0) | 0 (0) | 1 (4·5) | 21 (95·5) |
| Slovenia | 4 | 12 | 0 (0) | 1 (8·3) | 1 (8·3) | 1 (8·3) | 3 (25·0) | 9 (75·0) |
| Spain | 20 | 116 | 9 (7·8) | 0 (0) | 81 (69·8) | 12 (10·3) | 102 (87·9) | 14 (12·1) |
| Macedonia | 1 | 3 | 2 (66·7) | 0 (0) | 0 (0) | 0 (0) | 2 (66·7) | 1 (33·3) |
| Turkey | 17 | 124 | 0 (0) | 9 (7·3) | 98 (79·0) | 5 (4·0) | 112 (90·3) | 12 (9·7) |
| UK-England and Northern Ireland | 15 | 47 | 14 (29·8) | 3 (6·4) | 7 (14·9) | 1 (2·1) | 25 (53·2) | 22 (46·8) |
| UK-Scotland | 4 | 8 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 8 (100) |
| Total | 251 | 1203 | 379 (31·5) | 93 (7·7) | 310 (25·8) | 68 (5·7) | 850 (70·7) | 353 (29·3) |

Iceland, Kosovo, and Sweden did not find any *K pneumonia* isolates that were suspected non-susceptible to carbapenems during the study period. *Other mechanism of carbapenem non-susceptibility, since none of the genes coding for the four major types of carbapenemases (KPC, NDM, OXA-48-like and VIM) were detected. All data are n, except where otherwise indicated.

***Table 2: Klebsiella pneumoniae* clinical isolates submitted as non-susceptible to carbapenems, confirmed as producing a carbapenemase and type of carbapenemase, by country**


(A) KPC producers
Unknown
Sporadic spread
Outbreaks reported
Endemicity

# K. pneumoniae resistenti alla colistina Verona 2016

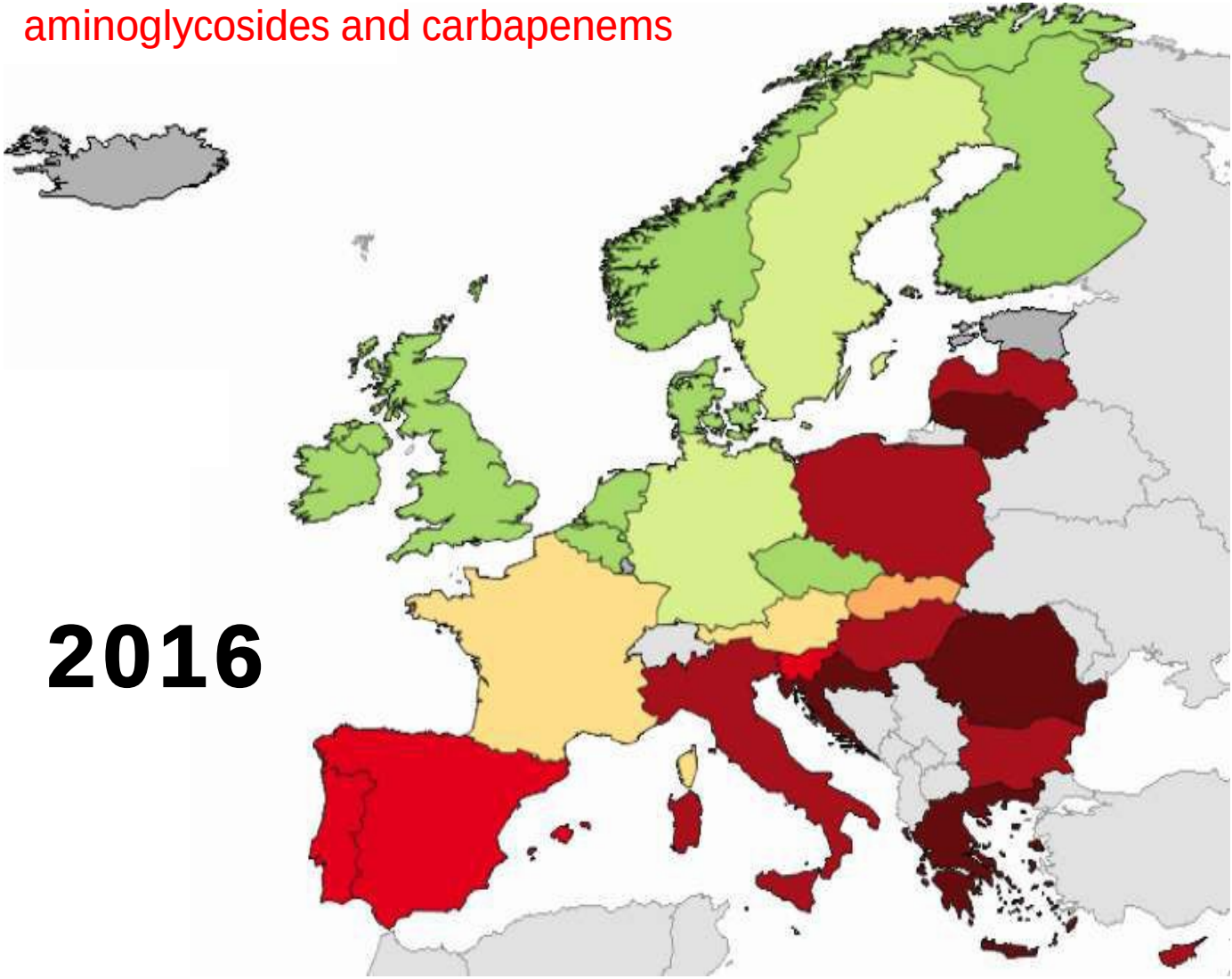


# Acinetobacter spp.: % of invasive isolates with combined resistance*, EU/EEA, 2012 & 2016

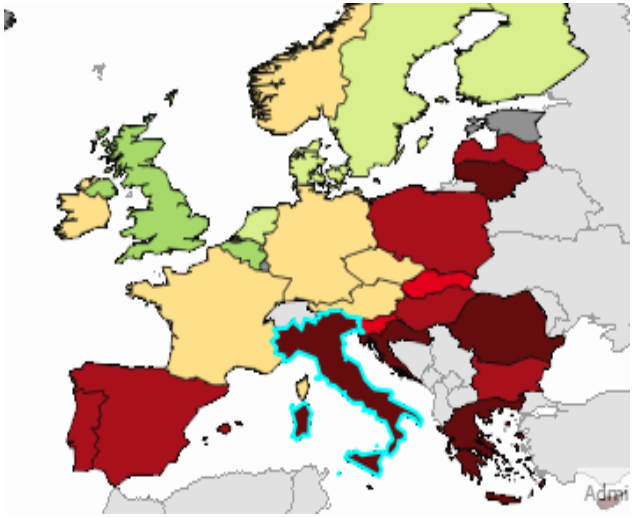
*Fluoroquinolones, aminoglycosides and carbapenems

**2012**

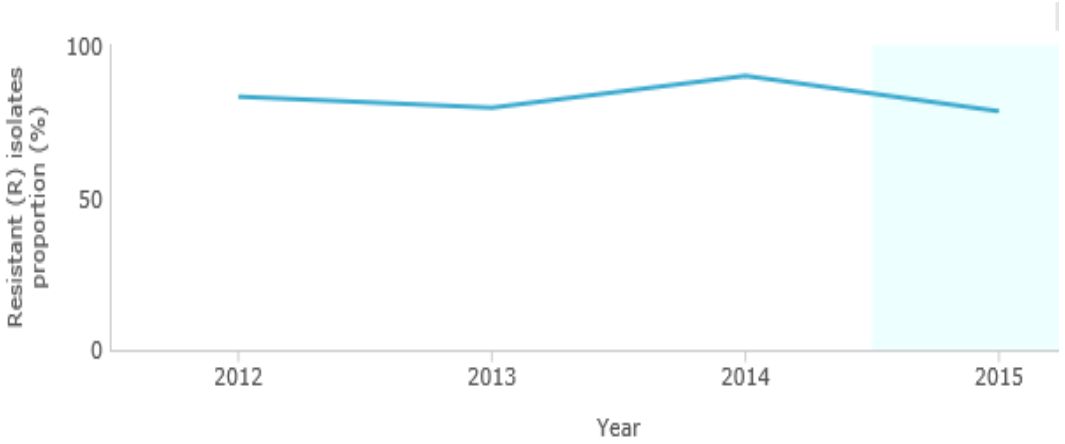
- <1%
- 1-<5%
- 5-<10%
- 10-<25%
- 25-<50%
- 50-<75%
- >=75%
- Not calculated

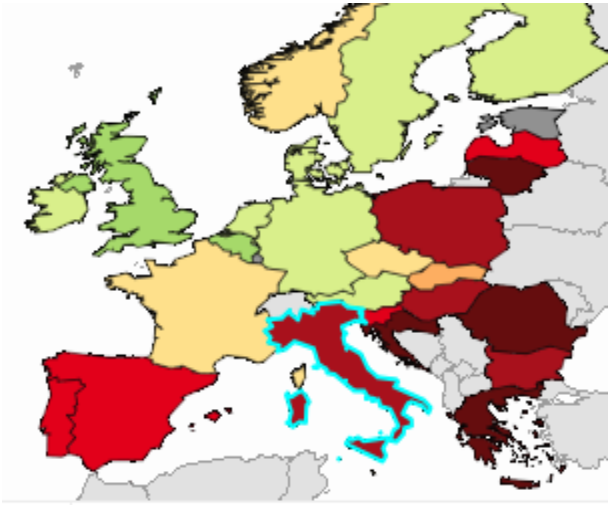


**2016**

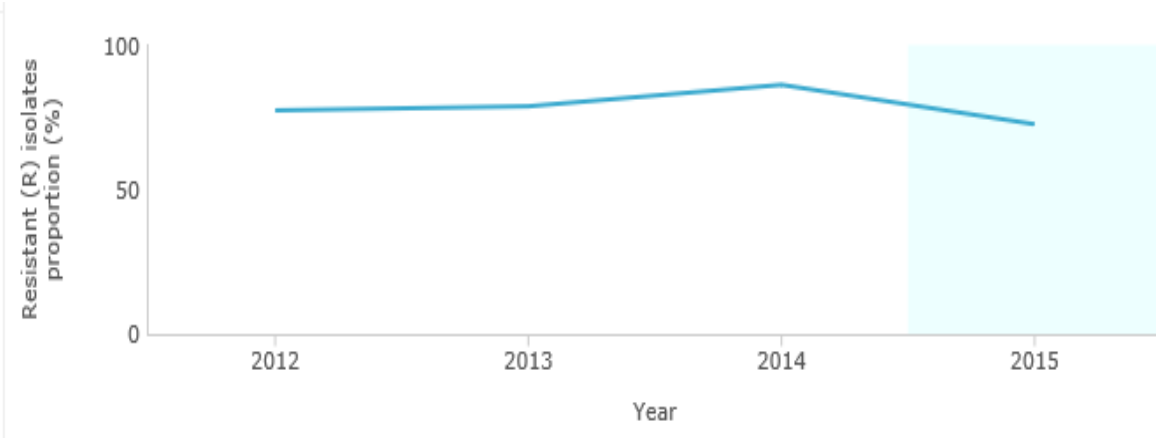


Carbapenem-resistant A. baumannii



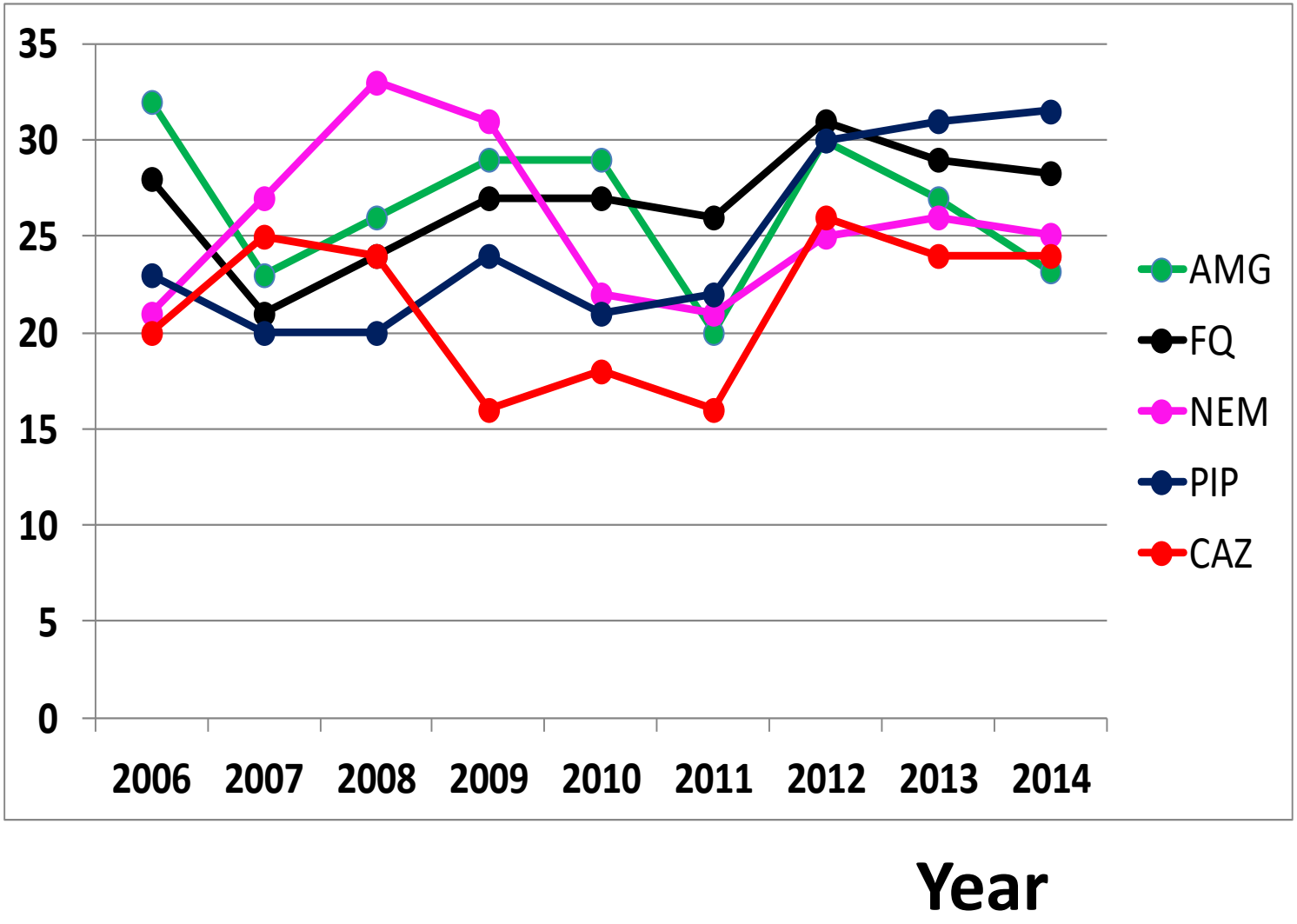



Combined resistance (FQ-Carba-Aminog) A. baumannii



# PSEUDOMONAS AERUGINOSA

# *Pseudomonas aeruginosa* resistance trends, Italy




**2016**:

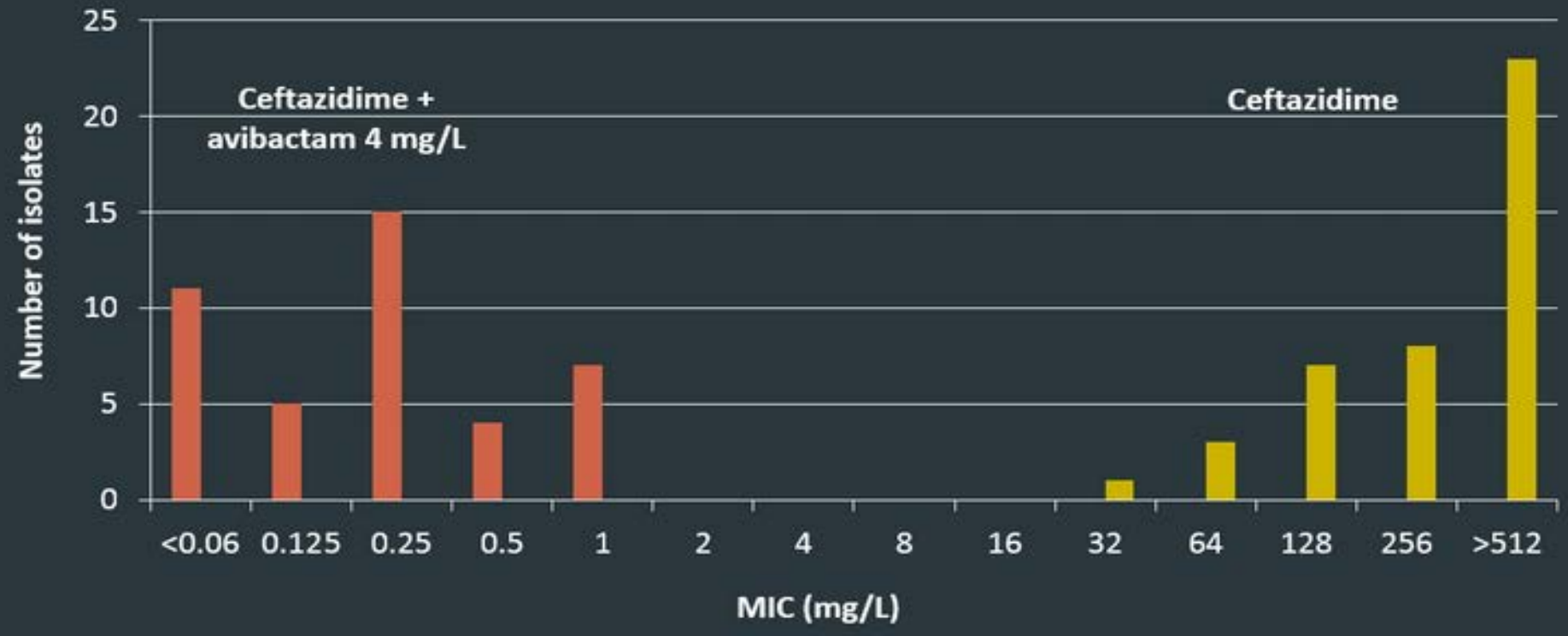
| | |
|---|---|
| FQ | 24,7 % |
| PIP/TAZ | 20,7 % |
| CEFTAZ | 23,0 % |
| AMINOS | 19,1 % |
| CARBAP | 23,5 % |

# CEFTAZIDIME/AVIBACTAM: POTENZIALITA’

**Table 2** In vitro activity[a] of ceftazidime-avibactam and comparators against Gram-negative aerobes [47–66]

| Gram negative aerobe | Ceftazidime | | | Ceftazidime-avibactam[a] | | | Ceftazidime-avibactam $MIC_{90}$ reduction (fold) | Cefepime | | Ceftriaxone | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | $MIC_{50}$ | $MIC_{90}$ | Range | | $MIC_{50}$ | $MIC_{90}$ | $MIC_{50}$ | $MIC_{90}$ |
| *Citrobacter freundii* | 0.5 | >32 | ≤0.25–>64 | 0.25 | 0.5 | ≤0.06–2 | >64 | ≤1 | ≤1 | ≤1 | 32 |
| *Citrobacter* spp. | 0.25 | >32 | NA | 0.12 | 0.5 | ≤0.06–4 | >64 | ≤0.12 | 4 | NA | NA |
| Ceftazidime non-susceptible | 32 | >32 | NA | 0.25 | 1 | ≤0.06–4 | >32 | 1 | >16 | NA | NA |
| *Enterobacter aerogenes* | ≤0.5 | >32 | ≤0.25–>32 | 0.25 | 0.5 | ≤0.06–2 | >64 | ≤1 | ≤1 | ≤1 | 16 |
| *Enterobacter cloacae* | 0.5 | >32 | ≤0.25–>32 | 0.25 | 1 | ≤0.06–2 | >32 | ≤1 | 1 | ≤0.25 | 64 |
| *Enterobacter* spp. | 0.25 | >32 | NA | 0.25 | 1 | ≤0.03–>32 | >32 | ≤0.12 | 2 | NA | NA |
| Ceftazidime-resistant[b] | 32 | >32 | NA | 0.5 | 2 | 0.06–>32 | >16 | 2 | >16 | NA | NA |
| AmpC producing + porin loss | 256 | 256 | 64–256 | 1 | 1 | 0.25–1 | 256 | NA | NA | NA | NA |
| *Escherichia coli* | 0.25 | 2 | ≤0.03–>32 | 0.12 | 0.25 | ≤0.03–2 | 8 | ≤0.12 | 1 | ≤0.25 | ≤0.25 |
| ESBL producing | 16 | 32 | 0.5–>64 | 0.12 | 0.25 | <0.008–2 | 128 | 8 | 32 | 64 | >64 |
| AmpC hyper-producing | 16 | 64 | 0.12–>64 | 0.12 | 0.5 | ≤0.004–4 | 128 | 0.25 | 0.5 | 8 | 32 |
| ESBL producing and AmpC hyper-producing | 32 | >64 | 2–>64 | 0.12 | 0.12 | 0.015–0.12 | >512 | 16 | 32 | >64 | >64 |
| *Klebsiella oxytoca* | ≤0.25 | 0.5 | ≤0.25–>64 | 0.12 | 0.5 | ≤0.06–1 | 1 | ≤1 | ≤1 | ≤0.25 | 0.5 |
| *Klebsiella pneumoniae* | ≤0.25 | 1 | ≤0.5–>32 | 0.12 | 0.5 | ≤0.06–2 | 2 | ≤1 | ≤1 | ≤0.25 | ≤0.25 |
| ESBL producing | 64 | >64 | 0.12–256 | 0.5 | 1 | 0.06–2 | >64 | 8 | 64 | >64 | >64 |
| OXA-48 carbapenemase-producing | 256 | 512 | ≤0.12–512 | 0.25 | 0.5 | <0.008–1 | 1024 | 32 | 512 | NA | NA |
| KPC-producing | ≥512 | ≥512 | 32–≥512 | 0.25 | 1 | ≤0.06–1 | ≥512 | 32 | 128 | NA | NA |
| ESBL-producing plus porin loss | 256 | 512 | 126–512 | 1 | 1 | 0.5–2 | 512 | NA | NA | NA | NA |
| *Klebsiella* spp. | 0.12 | 32 | NA | 0.12 | 0.5 | ≤0.03–32 | 64 | ≤0.12 | 16 | 0.06 | 32 |
| ESBL | >32 | >32 | NA | 0.5 | 2 | ≤0.03–32 | >16 | >16 | >16 | NA | NA |
| Carbapenem non-susceptible[c] | >32 | >32 | NA | 0.5 | 2 | ≤0.03–32 | >16 | >16 | >16 | NA | NA |
| *Morganella morganii* | 0.12 | 8 | NA | 0.06 | 0.12 | ≤0.06–8 | 64 | ≤0.12 | 0.25 | 0.12 | 8 |
| *Proteus mirabilis* | 0.06 | 0.12 | ≤0.25–32 | 0.06 | 0.12 | ≤0.03–0.25 | 1 | ≤0.12 | 0.25 | ≤0.25 | ≤0.25 |
| Indole-positive *Proteus* spp. | 0.12 | 8 | NA | 0.06 | 0.25 | ≤0.03–2 | 32 | ≤0.12 | 0.25 | NA | NA |
| *Salmonella* spp. | 0.25 | 0.5 | NA | 0.25 | 0.5 | ≤0.03–0.5 | 1 | ≤0.12 | 0.25 | 0.06 | 0.125 |
| *Serratia marcescens* | 0.12 | 2 | ≤0.25–16 | 0.25 | 0.5 | ≤0.06–>8 | 4 | ≤0.12 | 2 | ≤0.25 | 1 |
| *Serratia* spp. | 0.25 | 0.5 | N | 0.25 | 0.5 | 0.06–8 | 1 | ≤0.12 | 0.5 | NA | NA |
| *Burkholderia cepacia* | 64 | >128 | 8–>128 | 8 | >128 | ≤1–>128 | 1 | NA | NA | NA | NA |
| *Pseudomonas aeruginosa* | 4 | 32 | ≤0.25–256 | 2 | 8 | ≤0.06–>128 | 4 | 4 | 16 | 32 | >64 |
| MDR[d] | | | NA | 8 | 32 | ≤1–>128 | NA | NA | NA | NA | NA |
| AmpC-derepressed | 64 | >128 | 8–>128 | 4 | 8 | ≤1–64 | >16 | NA | NA | NA | NA |
| Intrinsic MexA/OprM | 4 | 8 | ≤1–16 | 4 | 8 | ≤1–16 | 1 | NA | NA | NA | NA |
| *Acinetobacter baumannii* | 8 | 32 | 1–>512 | 8 | >16 | 1–256 | NA | 64 | 128 | 8 | 64 |
| OXA carbapenemase-producing | 128 | >128 | 4–>128 | 8 | >128 | 4–>128 | 1 | NA | NA | NA | NA |

# MICs of 42 KPC-producing *K. pneumoniae* collected in the US




Endimiani A et al. *Antimicrob Agents Chemother.* 2009;53:3599–3601

# Avibactam has a broader spectrum of activity than currently available β-lactamase inhibitors

| | | Clavulanic acid | Tazobactam | Avibactam |
|---|---|---|---|---|
| Class A | TEM, SHV | ✓ | ✓ | ✓ |
| | CTX-M | ✗ | ✓ | ✓ |
| | KPC | ✗ | ✗ | ✓ |
| Class B | IMP, VIM, NDM1 | ✗ | ✗ | ✗ |
| Class C | Chromosomal Enterobacteriaceae AmpC | ✗ | ✗ | ✓ |
| | Chromosomal *Pseudomonas* AmpC | ✗ | ✗ | ✓ |
| | Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT | ✗ | ✗ | ✓ |
| Class D | Carbapenemase-type OXA 48 | ✗ | ✗ | ✓ |

Lagacé-Wiens P, et al. Core Evid 2014;9:13–25.

# Avibactam: a broader spectrum of β-lactamase inhibition[1]

IC50 (nM) for inhibition of β-lactamase activity

| | Avibactam | Clavulanic acid | Tazobactam |
|---|---|---|---|
| **Class A** | | | |
| **TEM-1** | 8 | 130 | 40 |
| **TEM-1** | 8 | 58 | 32 |
| **SHV-4** | 1.5 | 5 | 120 |
| **SHV-4** | 3 | 4 | 55 |
| **KPC-2** | 38 | 6,500 | 80,000 |
| **KPC-2** | 170 | >100,000 | 50,000 |
| **CTX-M-15** | 5 | 12 | 6 |
| **CTX-M-15** | 5 | 12 | 6 |
| **Class C** | | | |
| **P99** | 80 | $1 \times 10^6$ | 5,000 |
| **P99** | 100 | >100,000 | 1,300 |
| **AmpC** | 128 | >100,000 | 4,600 |

**Avibactam potency is 10 to >100 times that of currently available therapeutic inhibitors[2]**

IC50, half maximal inhibitory concentration.

1. Zhanel GG, et al. Drugs 2013;73:159–177 2. Coleman K. Curr Opin Microbiol 2011;14:550–555.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

# *Pseudomonas aeruginosa* Antimicrobial Susceptibility Results from Four Years (2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States

Helio S. Sader, Michael D. Huband, Mariana Castanheira, Robert K. Flamm
JMI Laboratories, North Liberty, Iowa, USA

March 2017

**TABLE 1** Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* isolates from U.S. medical centers (2012 to 2015)[d]

| Isolate group (*n*) and antimicrobial agent(s) | $MIC_{50}$ (mg/liter) | $MIC_{90}$ (mg/liter) | CLSI[a] | | | EUCAST[b] | | |
|---|---|---|---|---|---|---|---|---|
| | | | % S | % I | % R | % S | % I | % R |
| All isolates (7,452) | | | | | | | | |
| Ceftazidime-avibactam | 2 | 4 | 97.0 | | 3.0[c] | 97.0 | | 3.0 |
| Ceftazidime | 2 | 32 | 84.3 | 4.0 | 11.7 | 84.3 | | 15.7 |
| Cefepime | 2 | 16 | 85.4 | 8.4 | 6.2 | 85.4 | | 14.6 |
| Piperacillin-tazobactam | 4 | >64 | 80.5 | 9.1 | 10.3 | 80.5 | | 19.5 |
| Meropenem | 0.5 | 8 | 82.0 | 5.9 | 12.1 | 82.0 | 11.9 | 6.2 |
| Ciprofloxacin | 0.12 | >4 | 77.5 | 5.3 | 17.2 | 71.8 | 5.7 | 22.5 |
| Levofloxacin | 0.5 | >4 | 74.9 | 6.6 | 18.5 | 66.0 | 8.9 | 25.1 |
| Gentamicin | ≤1 | 8 | 88.3 | 3.7 | 8.1 | 88.3 | | 11.7 |
| Amikacin | 2 | 8 | 97.0 | 1.2 | 1.8 | 93.0 | 4.0 | 3.0 |
| Colistin | 1 | 2 | 99.4 | 0.6 | 0.1 | 99.9 | | 0.1 |
| MDR isolates (1,151) | | | | | | | | |
| Ceftazidime-avibactam | 4 | 16 | 82.1 | | 17.9[c] | 82.1 | | 17.9 |
| Ceftazidime | 32 | >32 | 27.6 | 16.0 | 56.4 | 27.6 | | 72.4 |
| Cefepime | 16 | >16 | 26.5 | 39.5 | 34.0 | 26.5 | | 73.5 |
| Piperacillin-tazobactam | >64 | >64 | 15.5 | 34.0 | 50.6 | 15.5 | | 84.5 |
| Meropenem | 8 | >8 | 21.4 | 18.1 | 60.6 | 21.4 | 44.4 | 34.2 |
| Ciprofloxacin | >4 | >4 | 21.3 | 12.3 | 66.5 | 12.4 | 8.9 | 78.7 |
| Levofloxacin | >4 | >4 | 14.8 | 14.6 | 70.6 | 8.4 | 6.3 | 85.2 |
| Gentamicin | 4 | >8 | 51.1 | 10.3 | 38.7 | 51.1 | | 48.9 |
| Amikacin | 8 | 32 | 87.1 | 5.0 | 8.0 | 74.5 | 12.6 | 12.9 |
| Colistin | 1 | 2 | 99.1 | 0.6 | 0.3 | 99.7 | | 0.3 |
| XDR isolates (698) | | | | | | | | |
| Ceftazidime-avibactam | 8 | 32 | 75.8 | | 24.2[c] | 75.8 | | 24.2 |
| Ceftazidime | 32 | >32 | 18.9 | 16.0 | 65.0 | 18.9 | | 81.1 |
| Cefepime | 16 | >16 | 14.3 | 42.0 | 43.7 | 14.3 | | 85.7 |
| Piperacillin-tazobactam | >64 | >64 | 5.7 | 34.4 | 59.9 | 5.7 | | 94.3 |
| Meropenem | 8 | >8 | 7.6 | 17.6 | 74.8 | 7.6 | 46.3 | 46.1 |
| Ciprofloxacin | >4 | >4 | 10.2 | 12.2 | 77.7 | 3.3 | 6.9 | 89.8 |
| Levofloxacin | >4 | >4 | 4.2 | 14.2 | 81.7 | 2.1 | 2.0 | 95.8 |
| Gentamicin | >8 | >8 | 38.1 | 11.5 | 50.4 | 38.1 | | 61.9 |
| Amikacin | 8 | >32 | 83.2 | 6.2 | 10.6 | 68.1 | 15.2 | 16.8 |
| Colistin | 1 | 2 | 99.1 | 0.6 | 0.3 | 99.7 | | 0.3 |

# *Pseudomonas aeruginosa* Antimicrobial Susceptibility Results from Four Years (2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States

Helio S. Sader, Michael D. Huband, Mariana Castanheira, Robert K. Flamm

| Resistance group | No. of isolates (%) susceptible to drug(s): | | | |
|---|---|---|---|---|
| | CAZ-AVI | CAZ | MEM | PT |
| All ($n$ = 7,452) | 7,228 (97.0) | 6,284 (84.3) | 6,096 (82.0) | 5,996 (80.5) |
| CAZ-NS (≥16 mg/liter; $n$ = 1,168) | 946 (81.0) | 0 (0.0) | 516 (44.3) | 95 (8.1) |

AAC 2017

## Activity of novel beta-lacam/inhibitors

| | ESBL | Carbapenemases | | | Pseudomonas spp. | Acinetobacter | Phase |
|---|---|---|---|---|---|---|---|
| | | Serine (KPC) | Oxa 48- like | MBL | | | |
| Ceftolozane-tazobactam* | + + | - | - | - | ++ | - | FDA approved |
| Ceftazidime-avibactam* | ++ | ++ | + | - | ++ | - | FDA approved |
| Aztreonam-avibactam | ++ | ++ | + | ++ | + | - | 2 |
| Imipenem-relebactam (MK7655) | ++ | ++ | | - | + | - | 3 |
| Meropenem-vaborbactam (RPX7009) | ++ | ++ | | - | + | - | 3 |
| Cefepime-zidebactam (WCK5222) | ++ | ++ | ++ | ++ | ++ | - | 2 |
| Cefiderocol (S49266) | ++ | ++ | ++ | ++ | ++ | + | 3 |

# Ceftazidime–avibactam: therapeutic indications

1. Complicated intra-abdominal infection (cIAI)
2. Complicated urinary tract infection (cUTI), including pyelonephritis
3. Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
4. For the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (after consultation with a physician with appropriate experience)

Zavicefta SmPC. 2018

# Posology and method of administration

| Type of infection | Dose ceftazidime–avibactam | Frequency | Infusion time | Duration of treatment |
|---|---|---|---|---|
| Complicated IAI | 2 g/0.5 g | 8 hours | 2 hours | 5–14 days |
| Complicated UTI, including pyelonephritis | 2 g/0.5 g | 8 hours | 2 hours | 5–10 days |
| Hospital-acquired pneumonia, including VAP | 2 g/0.5 g | 8 hours | 2 hours | 7–14 days |
| Infections due to aerobic Gram-negative organisms in patients with limited treatment options | 2 g/0.5 g | 8 hours | 2 hours | Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress |

IAI, invasive intra-abdominal infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
Zavicefta SmPC. 2018

# PK/PD TARGET ATTAINMENT ANALYSES TO DETERMINE OPTIMAL DOSINGOF CEFTAZIDIME-AVIBACTAM FOR THE TREATMENT OF ACUTE PULMONARY EXACERBATIONS IN PATIENTS WITH CYSTIC FIBROSIS

Bensman TJ et al. *Antimicrob Agent Chemother* 2017 Oct; 61: e00988-17

CUMULATIVE RESPONSE PROBABILITY OF CEFTAZIDIME AVIBACTAM 2.5 G Q8H vs. P. aeruginosa CF ISOLATES

| | CRP | | | |
|---|---|---|---|---|
| Infusion time (h) | Stasis ($fT_{>MIC}$, 40%) | 1- to 2-log drop ($fT_{>MIC}$, 50%) | Nearly maximal response ($fT_{>MIC}$, 65%) | Maximal response ($fT_{>MIC}$, 100%) |
| 0.5 | 0.824 | 0.805 | 0.76 | 0.449 |
| 2 | 0.836 | 0.815 | 0.788 | 0.554 |
| 5 | 0.844 | 0.829 | 0.814 | 0.757 |
| 8 | 0.825 | 0.825 | 0.825 | 0.825 |

RECOMMENDED DOSES FOR PATIENTS WITH VARYING DEGREES OF RENAL IMPAIRMENT

| Creatinine clearance, ml/min | Dosage recommendation |
|---|---|
| > 50 | Ceftazidime 2 g–avibactam 0.5 g every 8 hrs |
| 31–50 | Ceftazidime 1 g–avibactam 0.25 g every 8 hrs |
| 16–30 | Ceftazidime 0.75 g–avibactam 0.19 g every 12 hrs |
| 6–15 | Ceftazidime 0.75 g–avibactam 0.19 g every 24 hrs |
| ≤ 5 | Ceftazidime 0.75 g–avibactam 0.19 g every 48 hrs |

Zasowski EJ et al. *Pharmacotherapy* 2015; 35(8): 755–770

# Phase III clinical trials of ceftazidime–avibactam

**RECLAIM 1, 2 and 3[1-2]: Adults with cIAI**

- **Double-blind randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g + metronidazole 0.5 g IV q8h *or*
  - Meropenem 1 g IV + placebo q8h
- **Primary objective:**
  - RECLAIM 1 and 2: Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations)
  - RECLAIM 3: Proportion of patients with clinical cure at TOC visit (CE populations)

**RECAPTURE 1 and 2[3]: Adults with cUTI (including acute pyelonephritis)**

- **Double-blind randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g q8h IV *or*
  - Doripenem 0.5 g + placebo q8h IV
- **Primary objective:**
  - Assess non-inferiority of CAZ-AVI on co-primary endpoints in mMITT analysis set:
    - Resolution of UTI-specific symptoms
    - Resolution/improvement of flank pain
    - Per-patient microbiological eradication and symptomatic resolution

**REPRISE[4] Adults with CAZ-resistant bacteria**

- **Open-label randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g + metronidazole 0.5 g q8h IV *or*
  - Best available therapy
- **Primary objective:**
  - Estimate per-patient clinical response to CAZ-AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative bacteria

**REPROVE[5] Adults with HAP (including VAP)**

- **Double-blind randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g q8h IV *or*
  - Meropenem 1 g q8h IV
- **Primary objective:**
  - Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

AVI, avil ab
IV, intra ter
1. Mazuski JE, et al. Clin Infect Dis 2016;62:1380–9; 2. C
Dis 2016;16:661–73; 5. Torres A, et al. OS0603: abstrac

on; cMMIT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection;
UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
ner F, et al. Clin Infect Dis 2016;63:754–62; 4. Carmeli Y, et al. Lancet Infect
. 22–25 April 2017.

# TERAPIA DELLE INFEZIONI DA ENTEROBATTERI PRODUTTORI DI ESBL (BetaLattamasi a Spettro Esteso)

1. **IMIPENEM**
   **MEROPENEM**
   **ERTAPENEM**

2. (TIGECICLINA) **(non attiva su Proteus mirabilis e Proteus indolo**

***4.*** ***FOSFOMICINA EV*** *(sempre in associazione)*

*5.* *FOSFOMICINA os NITROFURANTOINA os (UTI)*

***6.*** ***CEFTOLOZANE/TAZOBACTAM***

***7.*** ***(CEFTAZIDIME/AVIBACTAM)***

# TERAPIE DELLE INFEZIONI DA KPC

- COLIMICINA + MEROPENEM + TIGECICLINA
- COLIMICINA + MEROPENEM + FOSFOMICINA

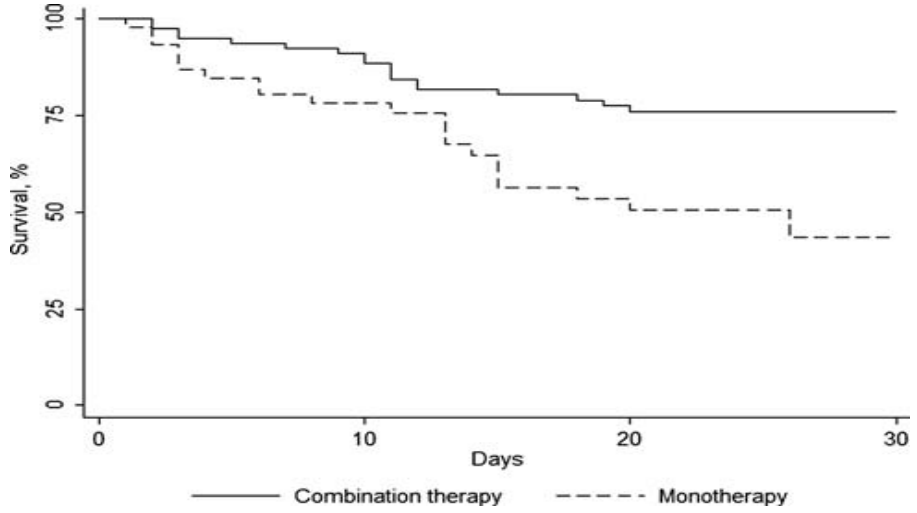
- GENTAMICINA + MEROPENEM + TIGECICLINA
- GENTAMICINA + MEROPENEM + FOSFOMICINA

- COLIMICINA o GENTAMICINA + TIGECICLINA
- COLIMICINA o GENTAMICINA + FOSFOMICINA

- **CEFTAZIDIME/AVIBACTAM**
- **CEFTAZIDIME/AVIBACTAM + GENTAMICINA**
- **CEFTAZIDIME/AVIBACTAM + FOSFOMICINA**

# KPC producing KP

- 125 patients with BSI
- The overall 30-day mortality rate was 41.6%.
  - Monotherapy: 54.3%
  - Combination: 34.1%
  - KPC-Kp BSIs are associated with high mortality.




Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by KPC-producing Klebsiella pneumoniae: importance of combination therapy. Clin Infect Dis 2012; 55:943–50.

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

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

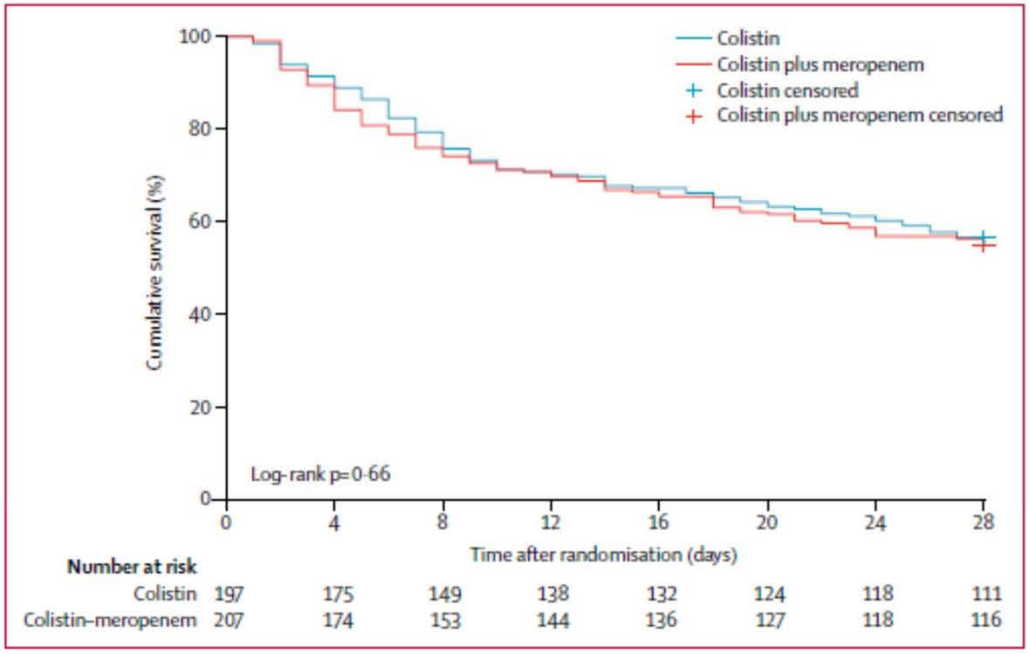



*Figure 2:* **Survival analysis to day 28 after randomisation**

# Ceftazidime avibactam

**CEFTAZIDIME AVIBACTAM 2,5 g (2 g ceftazidime, 0,5 avibactam) ogni 8 ore (2 h di infusione)**

**monoterapia ?**
**associazione ?**
**con quali farmaci ? (gentamicina**
**fosfomicina**
**colimicina**
**……..)**

**DOSE 2,5 x 3 ? (HAP,VAP, Osteomieliti…….) INFUSIONE PROLUNGATA ?**

**Terapia solo delle KPC o anche ESBL, Pseudomonas**

# Terapia delle infezioni da Pseudomonas aeruginosa MDR

1. COLIMICINA ( 9 milioni dose da carico poi 4,5 milioni x 2 / die)

   +

   RIFAMPICINA 600 -900 mg /die (l'uso prescinde dalla sensibilità in vitro)

2. COLIMICJNA (dose come sopra)

   +

   FOSFOMICINA (4 gr x 4-6 / die) (solo se è dimostrata una sensibilità in vitro)

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3. **CEFTOLOZANE /TAZOBACTAM**

4. **CEFTAZIDIME/AVIBACTAM**

# CRE real world experience

- Several large scale reported on the experience treating CRE severe infections often in immunocompromised patients
  - Overall good success rate relative to severity of the infection (60-70%), double than the success in the comparison groups
  - Several cases of emergence of ceftazidime-avibactam resistance emerged in a transplant center, usually resulting in decrease in carbapenem susceptibility
    - de-novo mutations often accompanied by reduction in carbapenem MICs

# Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

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**TABLE 1** Patient characteristics and clinical outcomes across treatment groups

| Characteristic[a] | Treatment group[b] | | | | *P* value |
|---|---|---|---|---|---|
| | C-A (*n* = 13) | CB+AG (*n* = 25) | CB+COL (*n* = 30) | Other[c] (*n* = 41) | |
| Patient demographics | | | | | |
| Male (*n* [%]) | 7 (54) | 16 (64) | 18 (60) | 21 (51) | 0.75 |
| Age (median [range]) | 66 (32–91) | 57 (32–87) | 59 (26–84) | 62 (25–90) | 0.63 |
| Underlying disease | | | | | |
| Diabetes (*n* [%]) | 4 (31) | 8 (32) | 8 (27) | 15 (37) | 0.85 |
| Chronic liver disease (*n* [%]) | 0 (0) | 9 (36) | 9 (30) | 13 (32) | 0.11 |
| Chronic respiratory disease (*n* [%]) | 5 (38) | 5 (20) | 8 (27) | 8 (20) | 0.51 |
| Immunocompromised (*n* [%]) | 5 (38) | 13 (52) | 14 (47) | 22 (54) | 0.78 |
| Solid-organ transplant recipient (*n* [%]) | 3 (23) | 11 (44) | 9 (30) | 17 (41) | 0.46 |
| Severity of illness | | | | | |
| ICU at time of bacteremia (*n* [%]) | 6 (46) | 13 (52) | 12 (40) | 25 (61) | 0.36 |
| RRT (*n* [%]) | 2 (15) | 7 (28) | 7 (23) | 8 (20) | 0.79 |
| Pitt bacteremia score (median [range]) | 4 (1–6) | 4 (0–9) | 4 (0–9) | 4 (0–9) | 0.74 |
| APACHE II score (median [range]) | 20 (16–33) | 17 (8–38) | 16 (7–36) | 19 (4–34) | 0.46 |

| | | | | | |
|---|---|---|---|---|---|
| Strain characteristic | | | | | |
| Presence of KPC (*n* [%]) | 13 (100) | 24 (96) | 30 (100) | 39 (95) | 0.56 |
| KPC-2 | 9 | 19 | 24 | 29 | |
| KPC-3 | 4 | 5 | 6 | 10 | |
| Primary bacteremia (*n* [%]) | 3 (23) | 6 (24) | 5 (17) | 14 (34) | 0.41 |
| Secondary bacteremia (*n* [%]) | 10 (77) | 19 (76) | 25 (83) | 27 (66) | 0.41 |
| Abdominal | 2 | 12 | 16 | 20 | |
| Respiratory | 3 | 2 | 6 | 3 | |
| Urinary tract | 5 | 2 | 2 | 4 | |
| Soft tissue | 0 | 3 | 1 | 0 | |
| Treatment characteristic | | | | | |
| ≥2 active agents[d] (*n* [%]) | 5 (38)[e] | 10 (40)[f] | 9 (30) | 8 (20) | 0.28 |
| Time to active treatment (median [IQR]) | 55.7 (25–67) | 52.5 (28–64) | 67.9 (30–133) | 65.0 (35–95) | 0.23 |
| Duration of treatment (median days [range]) | 13 (5–23) | 12 (3–28) | 14 (3–96) | 10 (3–47) | 0.31 |

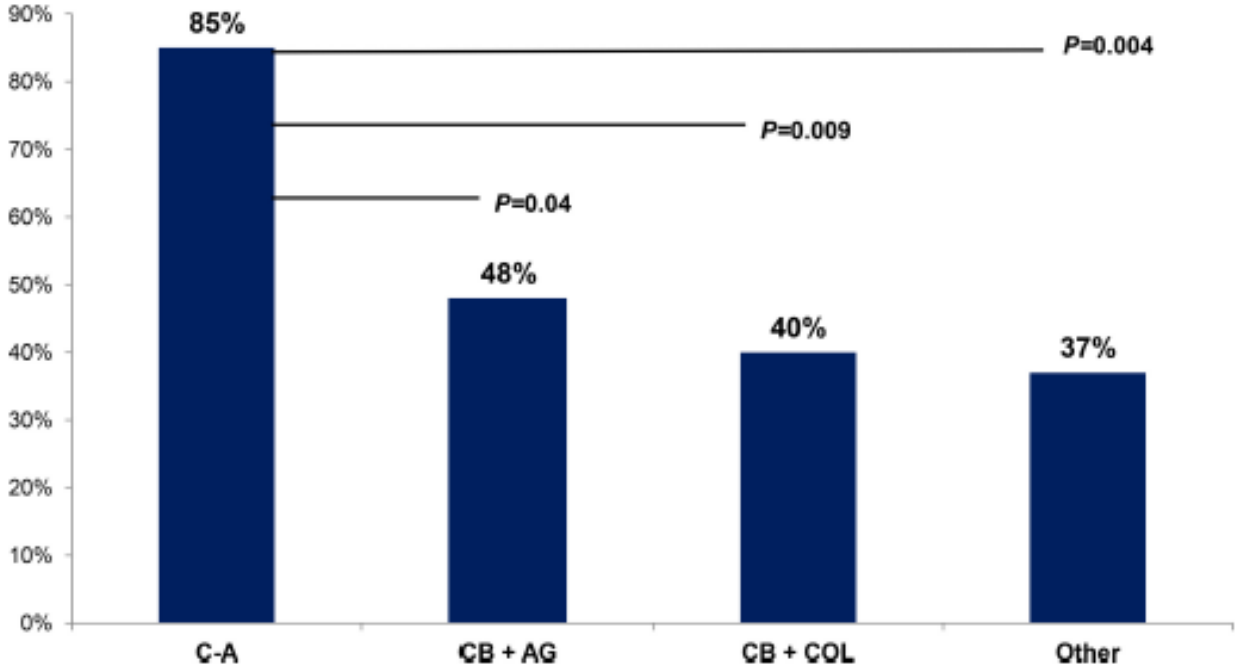



**FIG 1** Rates of 30-day clinical success across treatment regimens. Among patients with carbapenem-resistant

Shields AAC 2017

# Colistin vs. Ceftazidime-avibactam in the Treatment of Infections due to Carbapenem-Resistant Enterobacteriaceae

Figure 1.A. ceftazidime-avibactam (n=38)

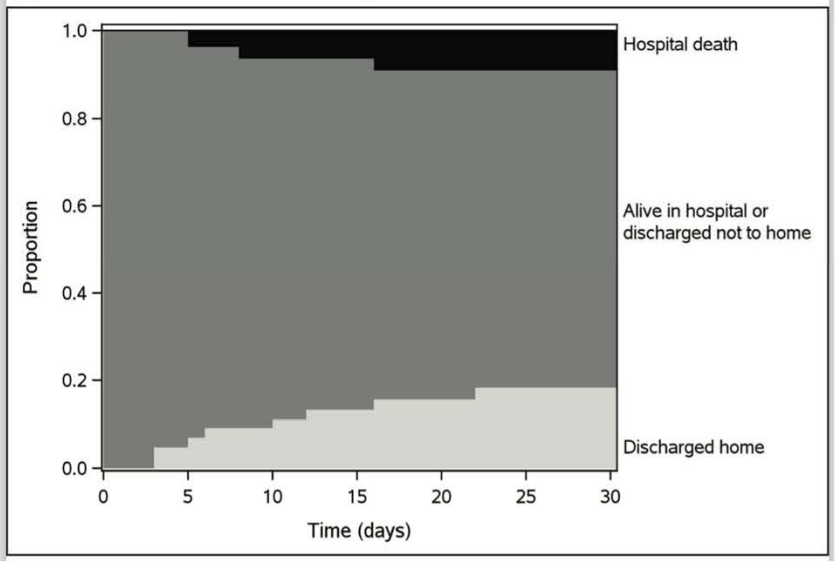
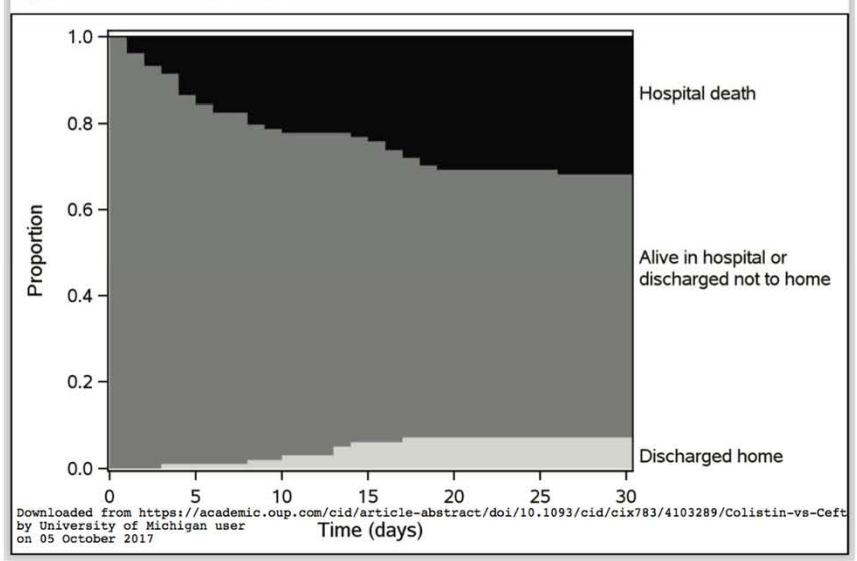



Figure 1.B. colistin (n=99)






**IPTW adjusted mortality at 30-days after starting treatment was 9% vs. 32%, respectively (Difference 23% [95% bootstrap CI: 9-35%], p=0.0012).**

Van Duin et al Clin Infect Dis 2018

# Terapia delle infezioni da Acinetobacter multiresistente

1. COLIMICINA 9 milioni dose da carico

   poi 4,5 milioni x 2

   +

   RIFAMPICINA 600-900 mg / die

   +/-

   Imipenem o Meropenem**

   anche se resistenti ma con CMI relativamente basse

---

2 COLIMICINA dose come sopra

   +

   TIGECICLINA 100 mg poi 50 mg x 2 ***

   (la dose può essere aumentata sino a 100/150 mg x 2 / die)

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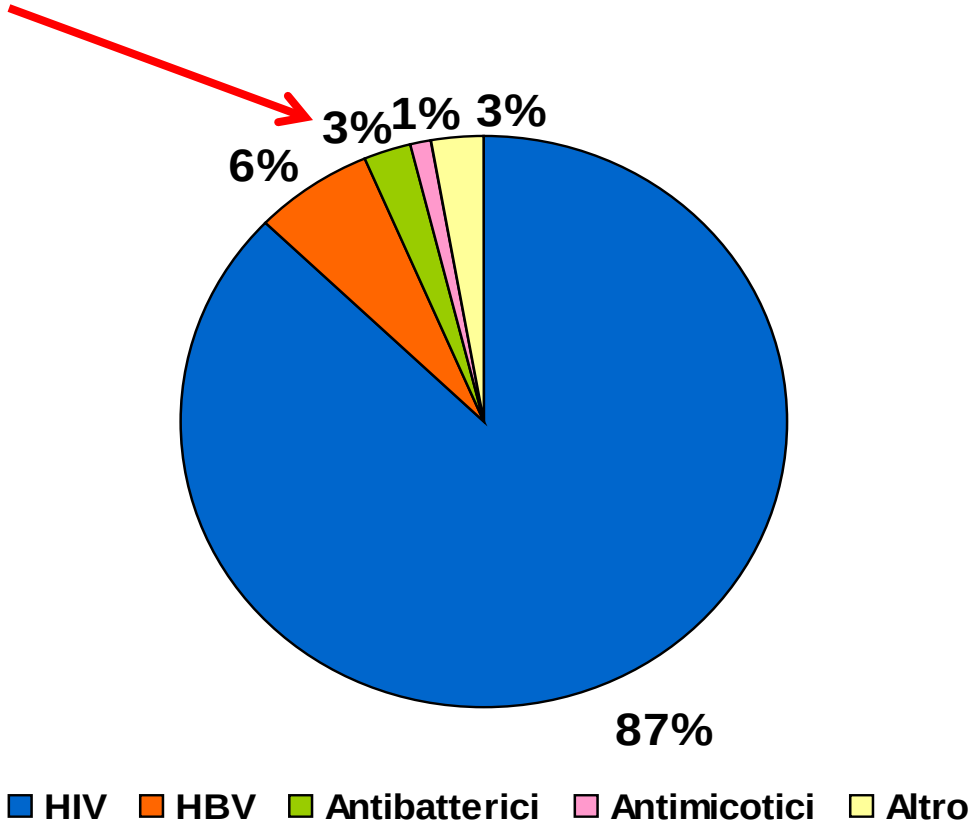
**3 MINOCICLINA ev**

**4 COLIMICINA + TEICOPLANINA COLIMICINA + VANCOMICINA**

** **La triplice terapia (colimicina + rifampicina + carbapenemico è consigliabile nel caso di un grave quadro settico).**

*** **L'associazione colimicina + tigeciclina non è consigliata nel caso di HAP o VAP**

# Spesa Farmaci per categoria




| Farmaci | spesa 2015 | spesa 2016 | differenza | Diff % |
|---|---|---|---|---|
| HIV | 6.554.666 | 6.624.607 | 69.941 | 1,1% |
| HBV | 379.279 | 466.435 | 87.156 | 23,0% |
| Antibatterici | 237.315 | 201.671 | -35.645 | -15,0% |
| Antimicotici | 180.580 | 73.919 | -106.660 | -59,1% |
| Altro | 282.502 | 217.659 | -64.844 | -23,0% |
| **Totale** | **7.634.342** | **7.584.290** | **-50.052** | **-0,7%** |

## COSTO/GIORNATA TERAPIA PER ANTIBIOTICI CATEGORIE TERAPEUTICHE AD ELEVATO IMPATTO ECONOMICO

| CLASSE | Principio attivo | Dosaggio | UP/die | costo/die (IVA esclusa) | Note |
|---|---|---|---|---|---|
| J01AA: TETRACICLINE | tigeciclina | 100 mg 1 somministrazione poi 50 mg/bid - 100 mg/bid terapie intens. | 2-4 fl | € 98-197 | |
| J01DH: CARBAPENEMI | meropenem | 2-6 g/die | 2-6 fl 1 g | € 6-18 | prezzo può variare per carenza di mercato € 16-48 |
| | ertapenem | 1 g/die | 1 fl | € 36 | |
| | imipenem+cilastatina | 2 - 4 g/die | 4 - 8 fl | € 10,5 -21 | |
| J01DF: MONOBATTAMI | aztreonam | 3-6 g/die | 3-6 fl | € 60-120 | |
| J01XA: GLICOPEPTIDI | vancomicina | 2 g/die | 4 fl | € 3 | |
| | teicoplanina | 800 mg/die | 4 fl | € 74 | |
| J01BX: POLIMIXINE | colistina | 4000000 - 9000000 /die | 4 - 9 fl | € 13 - 29 | |
| J07XX:ALTRI ANTIBATTERICI | daptomicina | 4 - 6 mg/kg/die | 1 fl 350 mg - 1 fl 500 mg | € 72 - 98 | |
| | linezolid | 600 mg/bid | 2 sacche o 2 cpr | € 13.5(sacche) € 17.38(cpr) | |
| A07AA: ANTIINFETTIVI INTESTINALI | fidaxomicina | 200 mg/bid | 2 cpr | € 113 | |

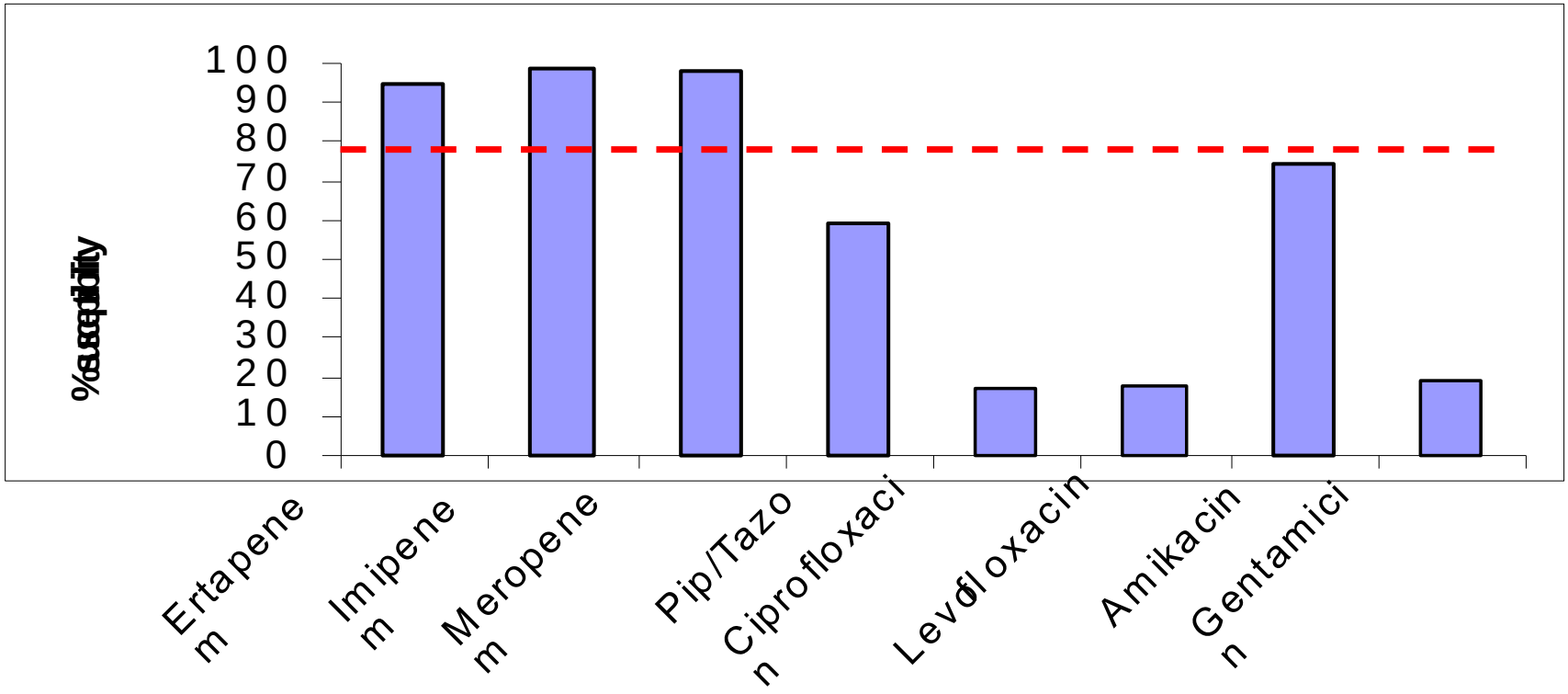
**Ceftazidime/avibactam**: **74 x 3 = 220/die**

**Ceftolozane/Tazobactam**: **70 x 3= 210/die o 140 x 3 = 420/die**

**Fosfomicina ev** 16-24g/die: **122/183**

Coli+Mer+Tige = 188
Coli+Mer+Fosfo= 353

# The end results MDR organisms: Susceptibilities of 1030 ESBL producing *E. coli* & *Klebsiella spp.*




Colodner R. DMID 2007

**Table 2. In Vitro Susceptibility of Selected Subsets of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* to Ceftazidime/Avibactam**

| | Ceftazidime/Avibactam | | | |
|---|---|---|---|---|
| Isolates (No.) | $MIC_{50}$ | $MIC_{90}$ | % S | Reference |
| KPC-producing Enterobacteriaceae (129) | 0.5 | 2 | 100 | [21] |
| KPC-producing Enterobacteriaceae (120) | 0.25 | 1 | 97.5 | [22] |
| *Escherichia coli* (6486) | 0.06 | 0.12 | 100 | [22] |
| *E. coli* (375) | 0.06 | 0.12 | 100 | [23] |
| ESBL-producing *E. coli* (90) | 0.12 | 0.25 | 100 | [23] |
| Gentamicin-resistant *E. coli* (166) | 0.12 | 0.25 | 100 | [24] |
| *Klebsiella pneumoniae* (4421) | 0.12 | 0.25 | 99.9 | [22] |
| *K. pneumoniae* (254) | 0.12 | 0.5 | 100 | [23] |
| ESBL-producing *K. pneumoniae* (84) | 0.25 | 1 | 100 | [23] |
| *Pseudomonas aeruginosa* (5328) | 2 | 4 | 96.8 | [25] |
| Meropenem-nonsusceptible[a] *P. aeruginosa* (396) | 8 | 32 | 67.4 | [25] |
| Non-ICU *P. aeruginosa* (2240) | 2 | 4 | 97.5 | [21] |
| ICU *P. aeruginosa* (842) | 2 | 8 | 95.6 | [21] |
| Meropenem-nonsusceptible *P. aeruginosa* (537) | 4 | 16 | 87.0 | [21] |
| Ceftazidime-nonsusceptible *P. aeruginosa* (482) | 4 | 16 | 80.7 | [21] |
| *P. aeruginosa* (3902) | 2 | 4 | 97 | [26] |
| MDR *P. aeruginosa* (580) | 4 | 16 | 81 | [26] |
| XDR *P. aeruginosa* (338) | 8 | 32 | 74 | [26] |
| *P. aeruginosa* (1743) | 2 | 8 | 96.3 | [27] |
| *P. aeruginosa* (881)[b] | 2 | 8 | 95.8 | [28] |
| Gentamicin-resistant *P. aeruginosa* (131) | 4 | 16 | 88 | [24] |
| β-lactam–resistant *P. aeruginosa* (55) | 2 | 32 | 84 | [29] |

van Duin D. & Bonomo RA. CID 2016

# Phase III clinical trials of ceftazidime–avibactam

**RECLAIM 1, 2 and 3[1-2]: Adults with cIAI**

- **Double-blind randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g + metronidazole 0.5 g IV q8h *or*
  - Meropenem 1 g IV + placebo q8h
- **Primary objective:**
  - RECLAIM 1 and 2: Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations)
  - RECLAIM 3: Proportion of patients with clinical cure at TOC visit (CE populations)

**RECAPTURE 1 and 2[3]: Adults with cUTI (including acute pyelonephritis)**

- **Double-blind randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g q8h IV *or*
  - Doripenem 0.5 g + placebo q8h IV
- **Primary objective:**
  - Assess non-inferiority of CAZ-AVI on co-primary endpoints in mMITT analysis set:
    - Resolution of UTI-specific symptoms
    - Resolution/improvement of flank pain
    - Per-patient microbiological eradication and symptomatic resolution

**REPRISE[4] Adults with CAZ-resistant bacteria**

- **Open-label randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g + metronidazole 0.5 g q8h IV *or*
  - Best available therapy
- **Primary objective:**
  - Estimate per-patient clinical response to CAZ-AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative bacteria

**REPROVE[5] Adults with HAP (including VAP)**

- **Double-blind randomisation (1:1):**
  - CAZ 2 g + AVI 0.5 g q8h IV *or*
  - Meropenem 1 g q8h IV
- **Primary objective:**
  - Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

AVI, avil… IV, intra… on; cMMIT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

1. Mazuski JE, et al. Clin Infect Dis 2016;62:1380–9; 2. … Dis 2016;16:661–73; 5. Torres A, et al. OS0603: abstrac… ner F, et al. Clin Infect Dis 2016;63:754–62; 4. Carmeli Y, et al. Lancet Infect … 22–25 April 2017.