Sistema Socio Sanitario
Regione Lombardia
ASST Lecco

Epidemiologia di *Enterobacterales* MDR in Italia oggi

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Milano, 18 ottobre 2021

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

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant

World Health Organization

Milano, 18 ottobre 2021

ecdc

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

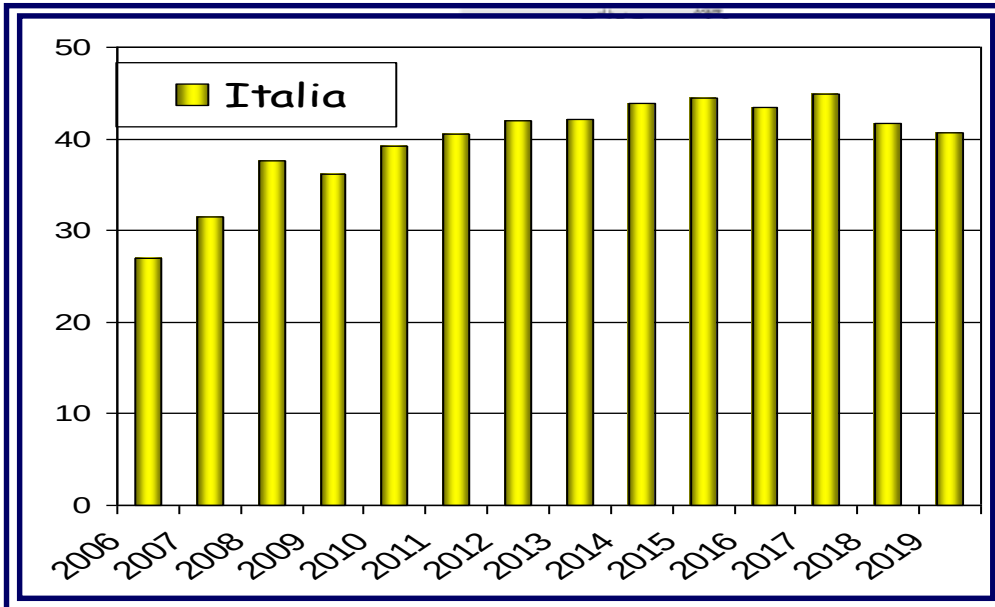
SURVEILLANCE REPORT

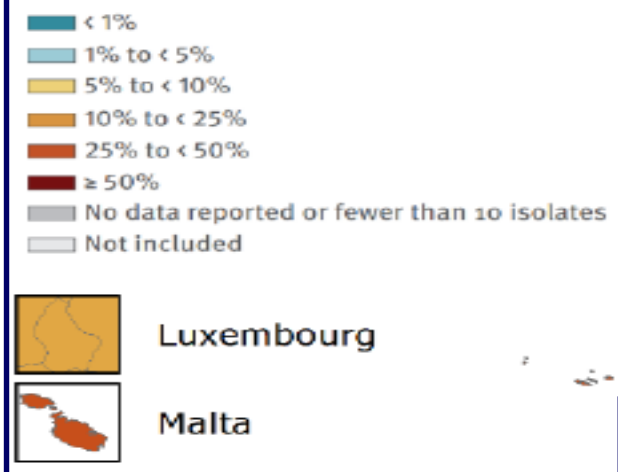
Antimicrobial resistance in the EU/EEA (EARS-Net)

Annual Epidemiological Report for 2019

Milano, 18 ottobre 2021

Escherichia coli: resistenza ai fluorochinoloni (2006-2019)





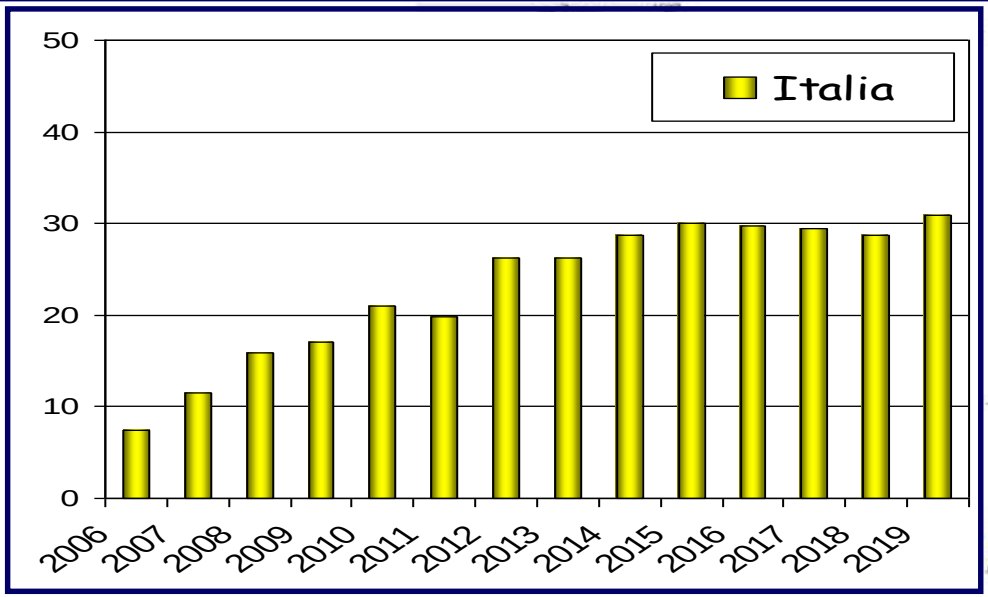
Italia: 40.6%

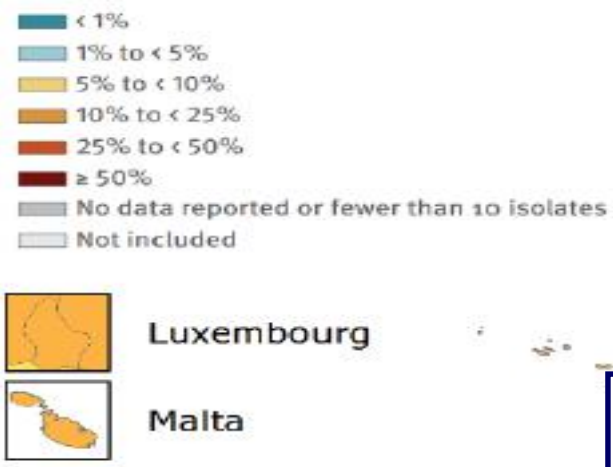
Figura 1

EARS-NET 2019

Milano, 18 ottobre 2021

Escherichia coli: resistenza alle cefalosporine 3G (2006-2019)





Italia: 30.9%

Figura 2

EARS-NET 2019

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Escherichia coli: resistenza ai carbapenemi

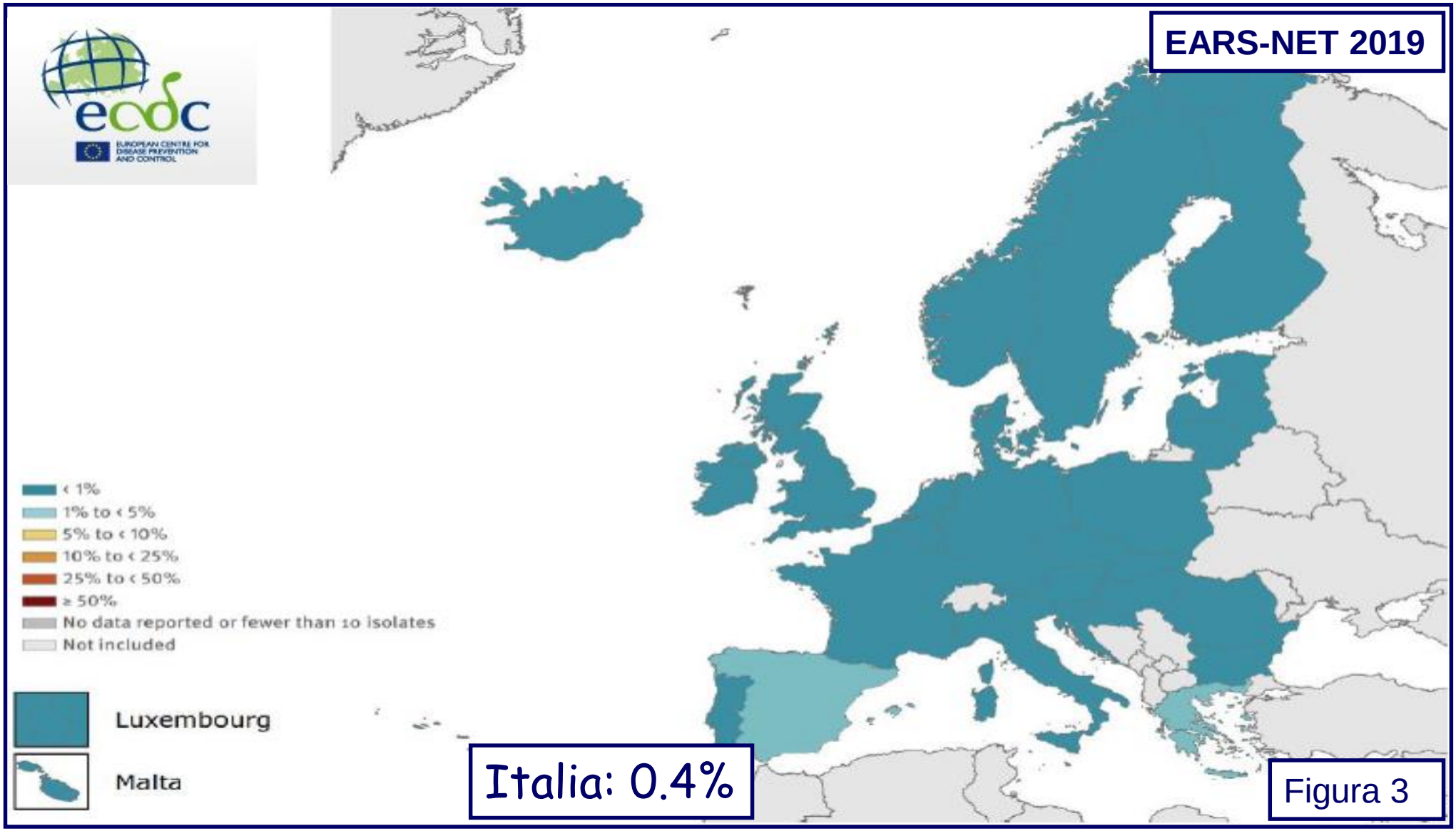

Figura 3

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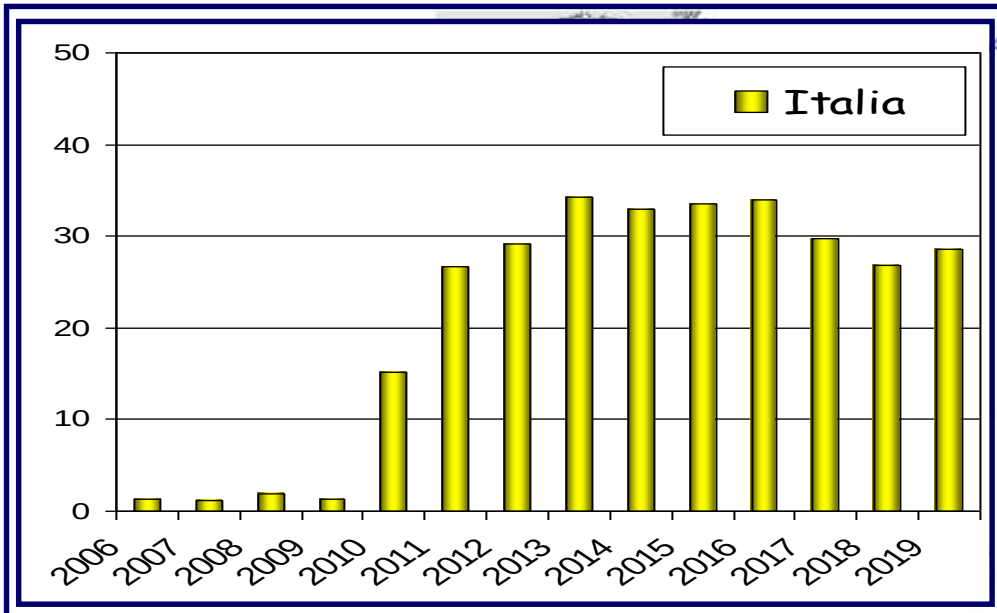
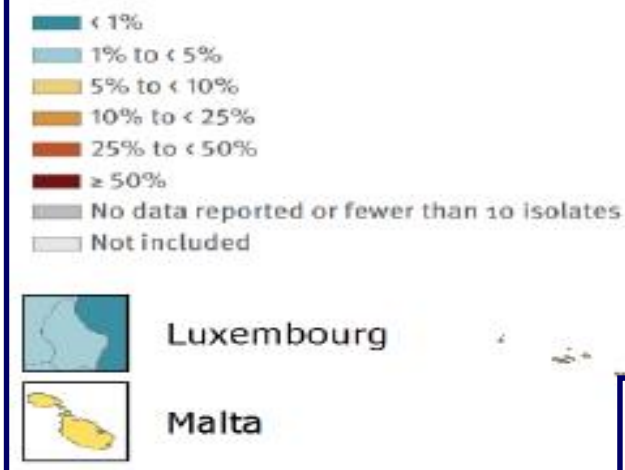
Klebsiella pneumoniae: resistenza ai carbapenemi (2006-2019)





Italia: 28.5%

Figura 5

EARS-NET 2019

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Meccanismi di resistenza ai carbapenemi negli enterobatteri

Perdita di porine associata a produzione di ESBL / AmpC +++

Produzione di carbapenemasi:

- Metallo-beta-lattamasi (IMP, VIM, NDM)
- Carbapenemasi a serina (KPC)
- Carbapenemasi di tipo OXA (OXA-48)

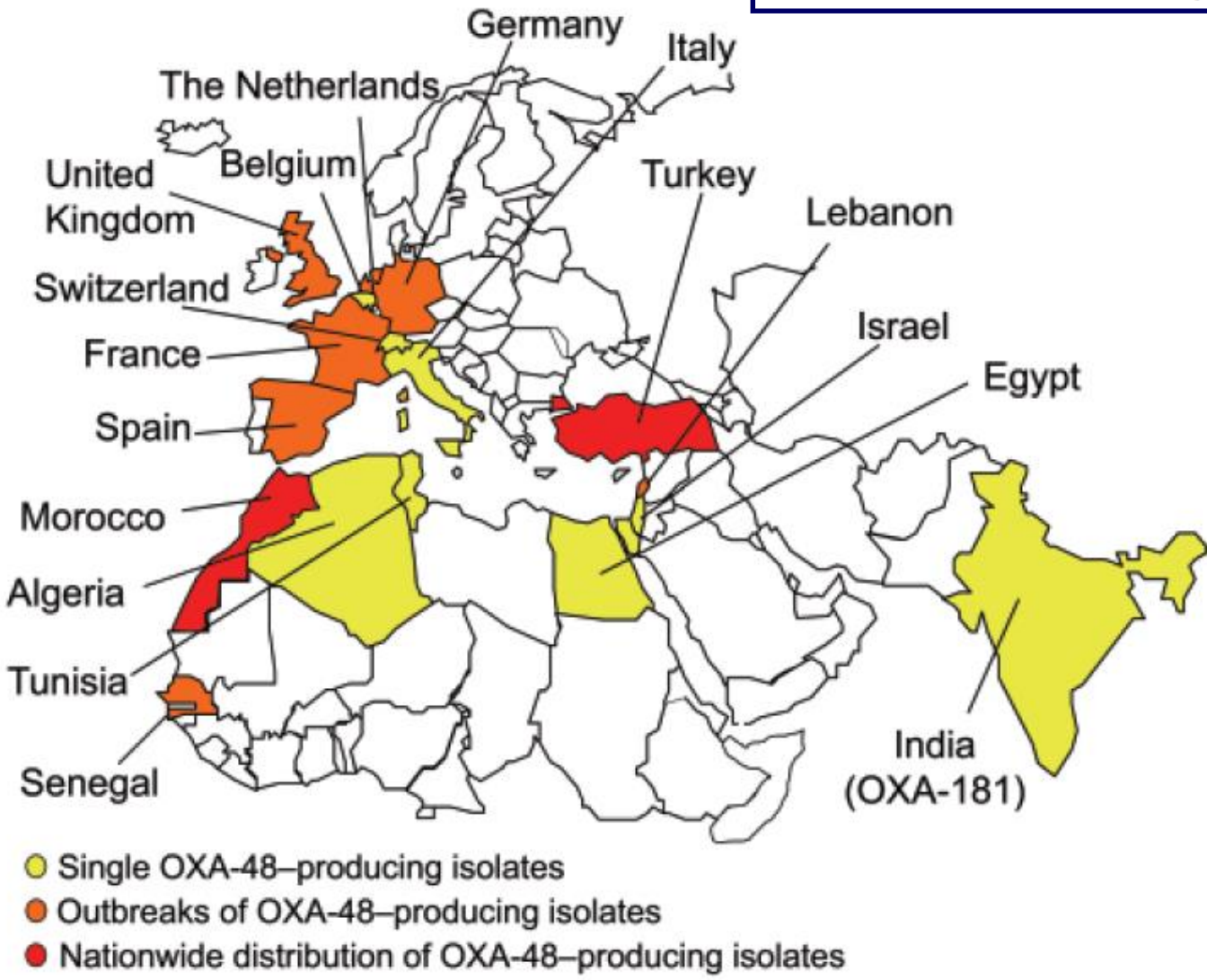
CRE: Carbapenem Resistant *Enterobacterales*

CPE: Carbapenemase Producing *Enterobacterales*

- ❖ Più alto livello di resistenza ai carbapenemi
- ❖ Resistenza trasferibile
- ❖ Episodi epidemici di grandi dimensioni (cloni ad alto rischio)

Global Spread of Carbapenemase-producing *Enterobacteriaceae*

Patrice Nordmann, Thierry Naas, and Laurent Poirel



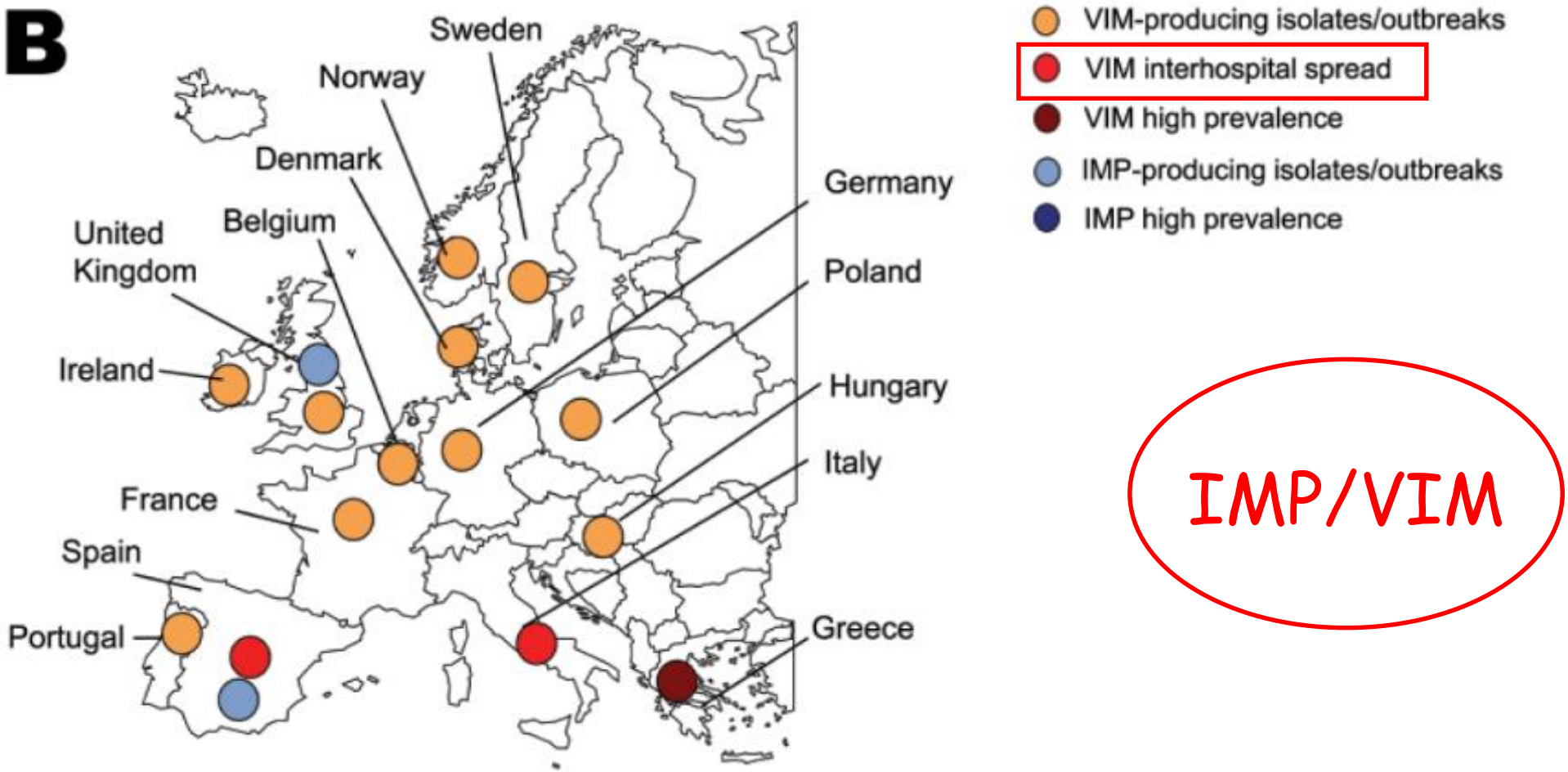
OXA-48

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

Milano, 18 ottobre 2021

Global Spread of Carbapenemase-producing *Enterobacteriaceae*

Patrice Nordmann, Thierry Naas, and Laurent Poirel



IMP/VIM

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

Milano, 18 ottobre 2021

Global Spread of Carbapenemase-producing *Enterobacteriaceae*

Patrice Nordmann, Thierry Naas, and Laurent Poirel

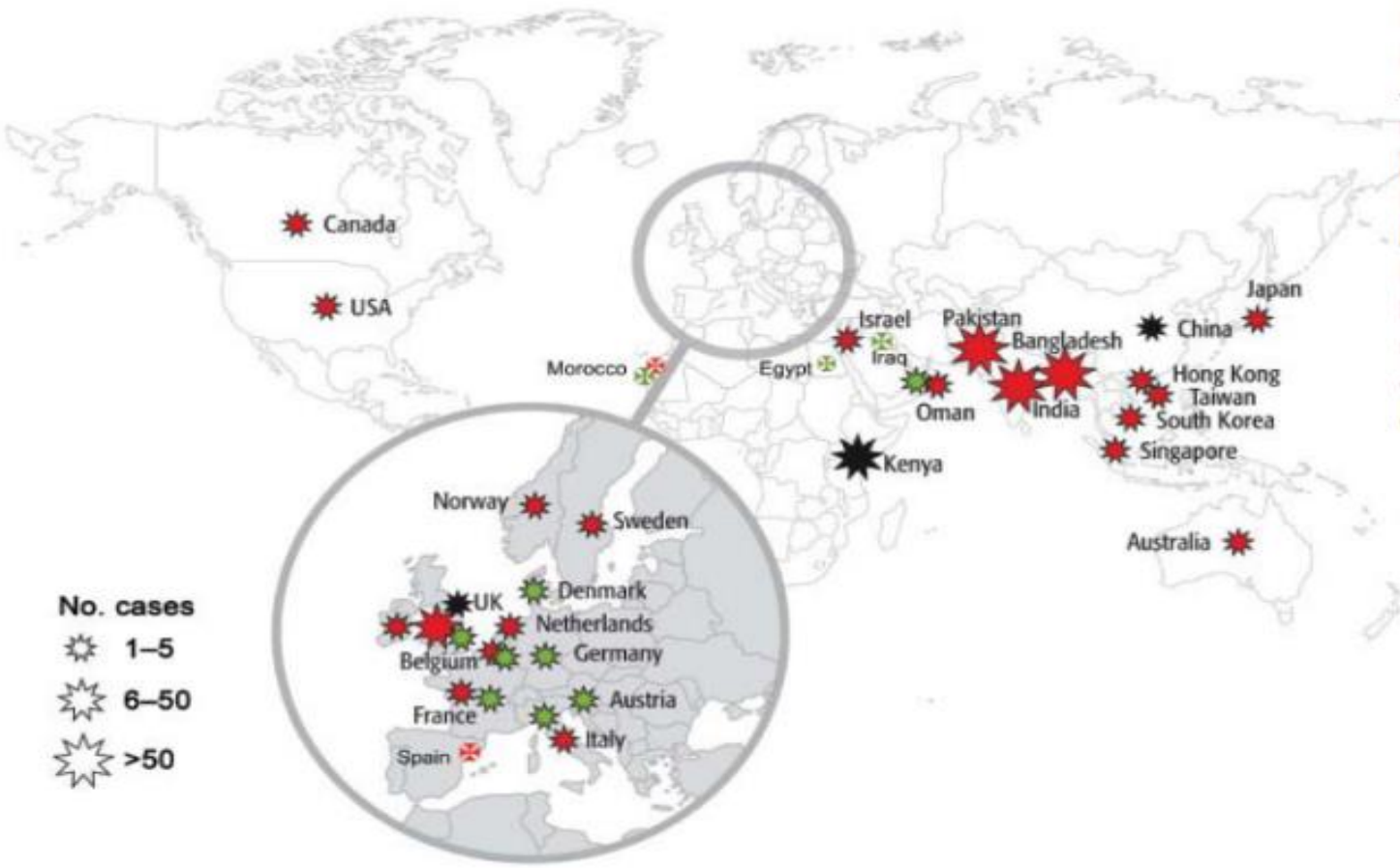


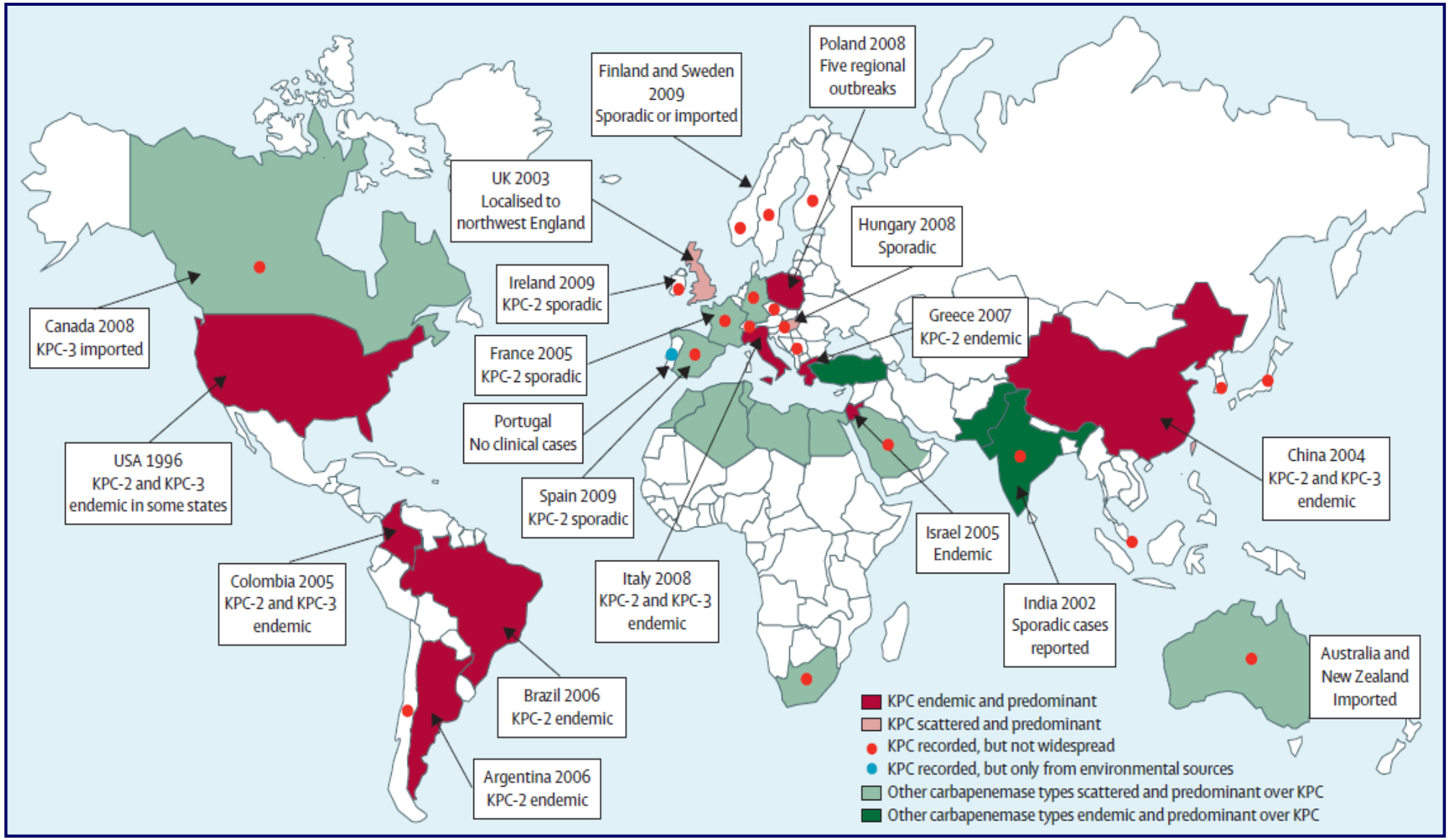
Figure 4. Geographic distribution of New Delhi metallo-β-lactamase-1 producers, July 15, 2011. Star size indicates number of cases reported. Red stars indicate infections traced back to India, Pakistan, or Bangladesh; green stars indicate infections traced back to the Balkan states or the Middle East; and black stars indicate contaminations of unknown origin. (Most of the information corresponds to published data; other data are from P. Nordmann.)

NDM

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

Milano, 18 ottobre 2021

Diffusione globale di *Klebsiella pneumoniae* produttore di KPC



Munoz-Price LS, *Lancet Infect Dis*, 2013

Milano, 18 ottobre 2021

JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2009, p. 3793–3794 Vol. 47, No. 11
0095-1137/09/$12.00 doi:10.1128/JCM.01773-09

Emergence in Italy of *Klebsiella pneumoniae* Sequence Type 258 Producing KPC-3 Carbapenemase▽

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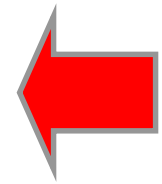
TABLE 1. Antimicrobial susceptibility profiles of *K. pneumoniae* FIPP-1 and the *E. coli* XL-1 transformant XL-1(pFIPP-1) carrying the bla_{KPC-3} gene[a]

Antibiotic	MIC (mg/liter) for strain		
	FIPP-1	XL-1(pFIPP-1)	XL-1
Ampicillin-sulbactam	>32	256	4
Piperacillin-tazobactam	>128	32	0.25
Ceftriaxone	>64	16	0.125
Ceftazidime	>64	32	0.25
Cefepime	>64	16	0.125
Aztreonam	>64	128	<0.125
Imipenem*	>32	2	0.25
Meropenem*	>32	8	<0.125
Ertapenem*	>32	8	<0.125
Ciprofloxacin	>4	0.064	0.064
Amikacin	>64	2	1
Tobramycin	>16	0.50	0.50
Gentamicin	2	<0.125	<0.125
Trimethoprim-sulfamethoxazole	>320	0.012	0.08
Tigecycline	1.5	ND[b]	ND
Colistin*	0.38	ND	ND



Milano, 18 ottobre 2021

SURVEILLANCE AND OUTBREAK REPORTS

Epidemic diffusion of KPC carbapenemase-producing *Klebsiella pneumoniae* in Italy: results of the first countrywide survey, 15 May to 30 June 2011

T Giani[1], B Pini[2], F Arena[1], V Conte[1], S Bracco[2], R Migliavacca[3], the AMCLI-CRE Survey Participants[4], A Pantosti[5], L Pagani[3], F Luzzaro[2], G M Rossolini (gianmaria.rossolini@unisi.it)[1,6,7]

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Citation style for this article:
Giani T, Pini B, Arena F, Conte V, Bracco S, Migliavacca R, the AMCLI-CRE Survey Participants, Pantosti A, Pagani L, Luzzaro F, Rossolini GM. Epidemic diffusion of KPC carbapenemase-producing Klebsiella pneumoniae in Italy: results of the first countrywide survey, 15 May to 30 June 2011. Euro Surveill. 2013;18(22):pii=20489. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20489

Article submitted on 07 September 2012 /published on 30 May 2013

Sorveglianza nazionale 2011

Milano, 18 ottobre 2021

SURVEILLANCE AND OUTBREAK REPORT

Evolving beta-lactamase epidemiology in *Enterobacteriaceae* from Italian nationwide surveillance, October 2013: KPC-carbapenemase spreading among outpatients

T Giani [1,2], A Antonelli [2,3], M Caltagirone [4], C Mauri [5], J Nicchi [3], F Arena [1], E Nucleo [4], S Bracco [5], A Pantosti [6], The AMCLI-CoSA survey participants [7], F Luzzaro [5], L Pagani [4], GM Rossolini [1,3,8]

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7. The AMCLI-CoSA survey participants are listed at the end of the article
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Sorveglianza nazionale 2013

Milano, 18 ottobre 2021

Tabella 2: Enzimi responsabili della resistenza ai carbapenemi nel 2018

Carbapenemasi	*K. pneumoniae*		*E. coli*		Totale	
	n	%	n	%	n	%
KPC	1300	94,3	12	40,0	1312	93,1
MBL*	37	2,7	11	36,7	48	3,4
KPC+MBL**	6	0,4	0	0,0	6	0,4
OXA-48	26	1,9	5	16,7	31	2,2
MBL*** + OXA-48	2	0,1	0	0,0	2	0,1
KPC + OXA-48	1	0,1	0	0,0	1	0,1
N.D.	7	0,5	2	6,7	9	0,6
non indicato	778		20		798	
Totale	**2157**		**50**		**2207**	

KPC: K. pneumoniae carbapenemasi; MBL: metallo-beta-lattamasi; OXA-48: oxacillinasi-48 con attività carbapenemasica; VIM: Verona integron-encoded metallo-beta-lattamasi; NDM: New Delhi metallo beta lattamasi
**Genotipo disponibile per 34 MBL: 15 VIM (12 in K. pneumoniae; 3 in E. coli) e 19 NDM (14 in K. pneumoniae; 5 in E. coli)*
***Genotipo disponibile per 4 MBL: 4 VIM (solo in K. pneumoniae)*
****Genotipo disponibile per 2 MBL: 2 NDM (solo in K. pneumoniae)*
§ N.D.: Non interpretabile (discrepanza tra risultato genotipico e fenotipico)

Milano, 18 ottobre 2021

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

RAPID RISK ASSESSMENT

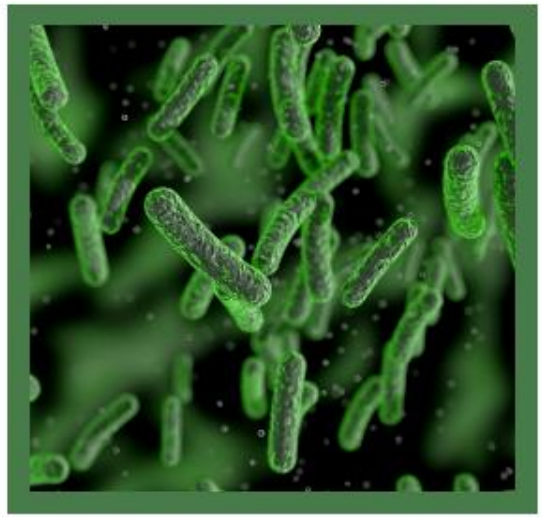
Regional outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacteriaceae, Italy, 2018–2019

4 June 2019

Milano, 18 ottobre 2021

CPE:
sorveglianza nazionale delle batteriemie da enterobatteri produttori di carbapenemasi

Dati 2019



ISTITVTO SVPERIORE DI SANITÀ

Milano, 18 ottobre 2021

Il patogeno maggiormente diffuso è *Klebsiella pneumoniae* produttore di carbapenemasi di tipo KPC (*Klebsiella pneumoniae* carbapenemasi), tuttavia nel 2019 si osserva un consistente aumento di ceppi produttori di carbapenemasi di tipo NDM (New Delhi metallo beta-lattamasi), aumento già osservato in misura minore nel 2018.

Tabella 2. Enzimi responsabili della resistenza ai carbapenemi nel 2019

Carbapenemasi	*K. pneumoniae*		*E. coli*		Totale	
	n.	%	n.	%	n.	%
KPC	1.384	86,4	25	62,5	1.409	85,9
MBL*	178	11,1	9	22,5	187	11,4
KPC+MBL**	3	0,2	0	0,0	3	0,2
OXA-48	17	1,1	5	12,5	22	1,3
MBL*** + OXA-48	2	0,1	1	2,5	3	0,2
KPC + OXA-48	1	0,1	0	0,0	1	0,1
ND	16	1,0	0	0,0	16	1,0
Non indicato	792		24		816	
Totale	2.393		64		2.457	

KPC: *K. pneumoniae* carbapenemasi; MBL: metallo-beta-lattamasi; OXA-48: oxacillinasi-48 con attività carbapenemasica; VIM: Verona integron-encoded metallo-beta-lattamasi; NDM: New Delhi metallo beta lattamasi

Increased Risk of Acquisition of New Delhi Metallo-Beta-Lactamase-Producing Carbapenem-Resistant Enterobacterales (NDM-CRE) among a Cohort of COVID-19 Patients in a Teaching Hospital in Tuscany, Italy

Andrea Davide Porretta [1,2,*], Angelo Baggiani [1,2], Guglielmo Arzilli [1], Virginia Casigliani [1], Tommaso Mariotti [1], Francesco Mariottini [1], Giuditta Scardina [1], Daniele Sironi [1], Michele Totaro [1], Simona Barnini [3] and Gaetano Pierpaolo Privitera [1,2]

Abstract: We describe the epidemiology of New Delhi Metallo-Beta-Lactamase-Producing Carbapenem-Resistant Enterobacterales (NDM-CRE) colonization/infection in a cohort of COVID-19 patients in an Italian teaching hospital. These patients had an increased risk of NDM-CRE acquisition versus the usual patients (75.9 vs. 25.3 cases/10,000 patient days). The co-infection significantly increased the duration of hospital stay (32.9 vs. 15.8 days).

Coorte di pazienti ospedalizzati con COVID-19:
- aumentato rischio di acquisizione di *Enterobacterales* produttori di carbapenemasi di tipo NDM (75.9 vs 25.3 casi/10.000 giornate di degenza)
- la co-infezione aumentava significativamente la durata della degenza ospedaliera (32.9 vs 15.8 giorni)

Pathogens **2020**, *9*, 635

Milano, 18 ottobre 2021

K. pneumoniae KPC+

Antibiotico	MIC mg/L (S/I/R)
Ampicillina	> 16 (R)
Amoxi-Clav	> 16 (R)
Pipera-Tazo	> 64 (R)
Cefotaxime	> 32 (R)
Ceftazidime	> 32 (R)
Cefepime	> 32 (R)
Imipenem	> 8 (R)
Meropenem	> 8 (R)
Ertapenem	> 4 (R)
Colistina	<= 0.5 (S)
Tigeciclina	1 (-)
Gentamicina	1 (S)
Ciprofloxacina	> 4 (R)

K. pneumoniae MBL+

Antibiotico	MIC mg/L (S/I/R)
Ampicillina	> 16 (R)
Amoxi-Clav	> 16 (R)
Pipera-Tazo	> 64 (R)
Cefotaxime	> 32 (R)
Ceftazidime	> 32 (R)
Cefepime	> 32 (R)
Imipenem	8 (I)
Meropenem	> 8 (R)
Ertapenem	> 4 (R)
Colistina	<= 0.5 (S)
Tigeciclina	1 (-)
Gentamicina	> 4 (R)
Ciprofloxacina	> 4 (R)

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NUOVI ANTIBIOTICI E SPETTRO D'AZIONE

Antibiotico	ESBL	CRE	MDR Pseudomonas	MDR Acinetobacter
Ceftolozano/Tazobactam	SI	NO	SI	NO
Ceftazidime/Avibactam	SI	KPC e OXA-48	SI	NO
Meropenem/Vaborbactam	SI	KPC	NO	NO
Imipenem/Relebactam	SI	KPC	NO	NO
Cefiderocol	SI	KPC, MBL, OXA-48	SI	SI
Plazomicina	SI	KPC	NO	NO
Eravaciclina	SI	KPC	NO	SI

Milano, 18 ottobre 2021

NUOVI ANTIBIOTICI E SPETTRO D'AZIONE

Antibiotico	ESBL	CRE	MDR Pseudomonas	MDR Acinetobacter
Ceftolozano/Tazobactam	SI	NO	SI	NO
Ceftazidime/Avibactam	SI	KPC e OXA-48	SI	NO
Meropenem/Vaborbactam	SI	KPC	NO	NO
Imipenem/Relebactam	SI	KPC	NO	NO
Cefiderocol	SI	KPC, MBL, OXA-48	SI	SI
Plazomicina	SI	KPC	NO	NO
Eravaciclina	SI	KPC	NO	SI

Cefiderocol: A Review in Serious Gram-Negative Bacterial Infections

Yahiya Y. Syed[1]

Published online: 24 August 2021

Table 2 In vitro activity of cefiderocol against selected clinical isolates by β-lactamase genotype in SIDERO-WT and SIDERO-CR

Pathogen/β-lactamase genotypes (no. of isolates)	MIC_{90} (mg/L) [% susceptible[a]]						
	FDC	FEP	CZA	C/T	CIP	CST	MEM
Enterobacterales							
KPC (644) [18, 45]	2–4 [98.1]	> 64 [0]	4 [96]	> 64 [0]	> 8 [5.3]	> 8	> 64 [0]
NDM (162) [44, 45]	8 [84–87.2]	> 64	> 64	> 64	> 8	1 to > 8	> 64
VIM (174) [44, 45]	4 [98.0]	> 64	> 64	> 64	> 8	2 to > 8	≥ 64
OXA-48 (168) [18, 45]	4 [100]	> 64 [12.5]	4 to > 64 [90.6]	> 64 [3.1]	> 8 [3.1]	> 8 [78.1]	≥ 64 [0]
VIM (174) [44, 45]	4 [98.0]	> 64	> 64	> 64	> 8	2 to > 8	≥ 64
P. aeruginosa							
VIM (256) [44, 45]	0.5–1 [100]	> 64	> 64	> 64	> 8 to > 64	1–2	> 8 to > 64
IMP (16) [44]	1	> 64	> 64	> 64	> 64	2	> 8
A. baumannii							
OXA-23 (775) [18, 45]	1–2 [92.2]	> 64.7 [1.7]	> 64	> 64	> 8 [0]	1 to > 8 [79.6]	> 64 [0]
OXA-24 (237) [18, 45]	1–8 [89.4]	> 64.7 [11.3]	> 64	> 64	> 8 [0]	1 [96.8]	> 64 [0]
OXA-58 (14) [18]	1	> 64 [0]	> 64	> 64	> 8 [0]	1 [92.9]	16 [0]

Drugs https://doi.org/10.1007/s40265-021-01580-4

Review

The Revival of Aztreonam in Combination with Avibactam against Metallo-β-Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases

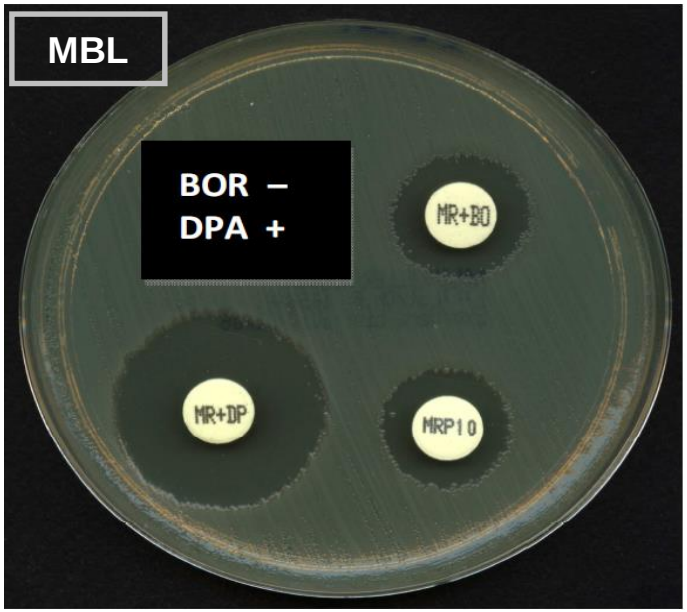
Carola Mauri [1,†], Alberto Enrico Maraolo [2,†], Stefano Di Bella [3], Francesco Luzzaro [1] and Luigi Principe [4,*]

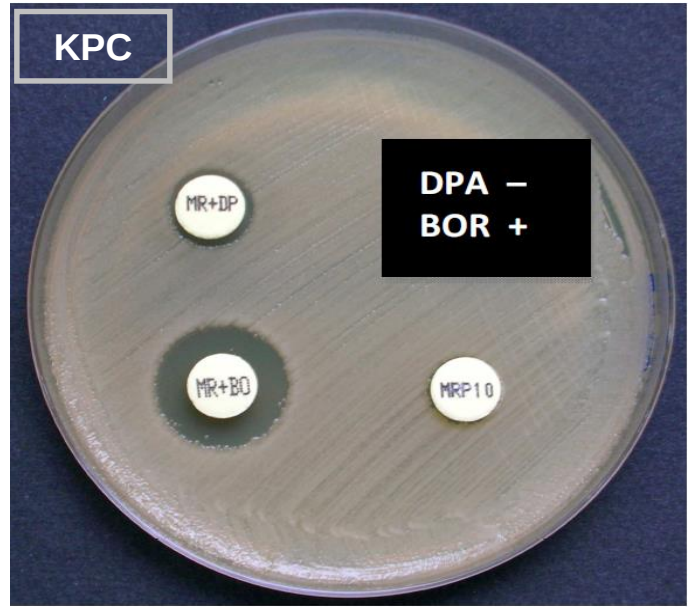
Abstract: Infections caused by metallo-β-lactamase (MBL)-producing *Enterobacterales* and *Pseudomonas* are increasingly reported worldwide and are usually associated with high mortality rates (>30%). Neither standard therapy nor consensus for the management of these infections exist. Aztreonam, an old β-lactam antibiotic, is not hydrolyzed by MBLs. However, since many MBL-producing strains co-produce enzymes that could hydrolyze aztreonam (e.g., AmpC, ESBL), a robust β-lactamase inhibitor such as avibactam could be given as a partner drug. We performed a systematic review including 35 in vitro and 18 in vivo studies on the combination aztreonam + avibactam for infections sustained by MBL-producing Gram-negatives. In vitro data on 2209 Gram-negatives were available, showing the high antimicrobial activity of aztreonam (MIC ≤ 4 mg/L when combined with avibactam) in 80% of MBL-producing *Enterobacterales*, 85% of *Stenotrophomonas* and 6% of MBL-producing *Pseudomonas*. Clinical data were available for 94 patients: 83% of them had bloodstream infections. Clinical resolution within 30 days was reported in 80% of infected patients. Analyzing only patients with bloodstream infections (64 patients), death occurred in 19% of patients treated with aztreonam + ceftazidime/avibactam. The combination aztreonam + avibactam appears to be a promising option against MBL-producing bacteria (especially *Enterobacterales*, much less for *Pseudomonas*) while waiting for new antimicrobials.

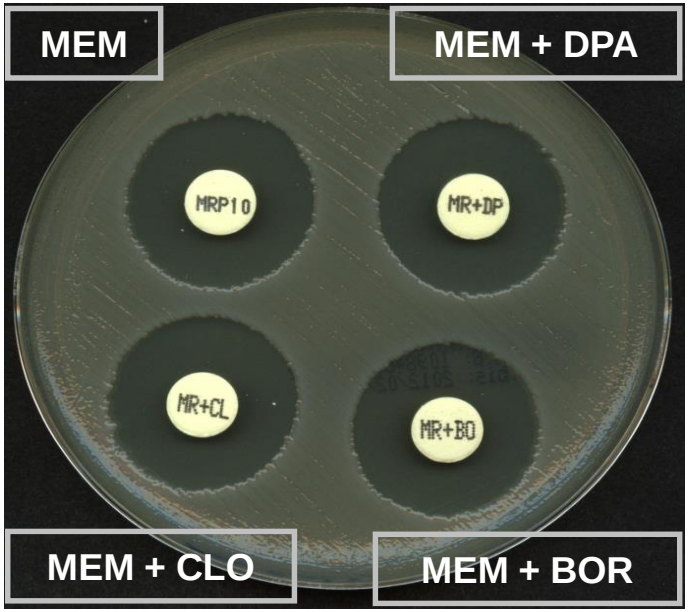
Antibiotics **2021**, *10*, 1012. https://doi.org/10.3390/antibiotics10081012

Milano, 18 ottobre 2021

Carbapenemasi: test fenotipici di conferma







Test di sinergia
mediante dischi di combinazione

- MBL: BOR -, DPA +
- KPC: DPA -, BOR +
- OXA-48: DPA -, BOR – CLO -

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Cepheid – GeneXpert Carba-R Assay

Risultato in circa 1 ora

bla_{KPC}	KPC
bla_{VIM}	VIM
bla_{NDM-1}	NDM

bla_{OXA-48}		
OXA-48	bla_{IMP-1}	
OXA-162	IMP-1 subgroup	
OXA-163	IMP-1	IMP-6
OXA-181	IMP-3	IMP-25
OXA-204	IMP-10	IMP-30

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CTX-M-1

CPE:

- KPC
- VIM
- IMP
- NDM
- OXA-48

MCR-1

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Nanosphere

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TARGETS

Species

- *Escherichia coli*[1]
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Genus

- *Acinetobacter* spp.
- *Citrobacter spp.*
- *Enterobacter* spp.
- *Proteus* spp.

Resistance

- CTX-M (ESBL)
- IMP (carbapenemase)
- KPC (carbapenemase)
- NDM (carbapenemase)
- OXA (carbapenemase)
- VIM (carbapenemase)

...RE TEST

The Verigene® Gram-Negative Blood Culture Test (BC-GN) identifies genus, species, and genetic resistance determinants for a broad panel of gram-negative bacteria directly from positive blood culture bottles.

While conventional microbiological methods may require 2-4 days to produce bacterial identification and resistance results, Verigene BC-GN provides results within 2 hours of blood culture positivity.

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The BioFire® FilmArray® Blood Culture Identification Panels

Early identification and treatment of sepsis are essential to combat one of the leading causes of hospital patient deaths.[1] With 43 targets, the newly expanded and FDA-cleared BioFire® Blood Culture Identification 2 (BCID2) Panel detects pathogens and antimicrobial resistance genes directly from positive blood cultures.

BioFire BCID2 Panel: 43 Targets. 1 Test. About 1 Hour.

The BioFire BCID2 Panel tests for 43 targets associated with bloodstream infections, including gram-negative bacteria, gram-positive bacteria, yeast, and 10 antimicrobial resistance genes—all with one test and with results available in about an hour from positive blood culture.

The BioFire BCID2 Panel features broadened inclusivity for *Enterobacterales*, new assays for fungal and anaerobic pathogens, and additional identification of coagulase-negative *Staphylococcus* species. The BioFire BCID2 Panel menu includes seven additional resistance genes, including carbapenemases and colistin resistance genes. An MREJ assay allows for more specific MRSA identification.

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The BioFire BCID2 Panel Menu

Overall 99% Sensitivity and 99.8% Specificity[2]

Sample Type: Positive blood culture

GRAM-NEGATIVE BACTERIA:

- *Acinetobacter calcoaceticus-baumannii* complex
- *Bacteroides fragilis**
- *Enterobacterales*
  - *Enterobacter cloacae* complex
  - *Escherichia coli*
  - *Klebsiella aerogenes**
  - *Klebsiella oxytoca*
  - *Klebsiella pneumoniae* group
  - *Proteus*
  - *Salmonella**
  - *Serratia marcescens*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia**

GRAM-POSITIVE BACTERIA:

- *Enterococcus faecalis**
- *Enterococcus faecium**
- *Listeria monocytogenes*
- *Staphylococcus*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis**
  - *Staphylococcus lugdunensis**
- *Streptococcus*
  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*

YEAST:

- *Candida albicans*
- *Candida auris**
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*
- *Cryptococcus neoformans/gattii**

ANTIMICROBIAL RESISTANCE GENES:

- **Carbapenemases**
  - IMP*
  - KPC
  - OXA-48-like*
  - NDM*
  - VIM*
- **Colistin Resistance**
  - *mcr-1**
- **ESBL**
  - CTX-M*
- **Methicillin Resistance**
  - *mecA/C*
  - *mecA/C* and MREJ (MRSA)*
- **Vancomycin Resistance**
  - *vanA/B*

*Indicates a new target on the BioFire BCID2 Panel

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Sistema Socio Sanitario
Regione Lombardia
ASST Lecco

Grazie per l'attenzione !

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