



Hospital Universitario La Paz



Servicio de
Microbiología
y Parasitología

IdiPAZ
Instituto de Investigación
Hospital Universitario La Paz

Carbapenemases in UTI: a view from the bench

Jesús Mingorance



OXA-48-like carbapenemases: the phantom menace

Laurent Poirel*, Anaïs Potron and Patrice Nordmann

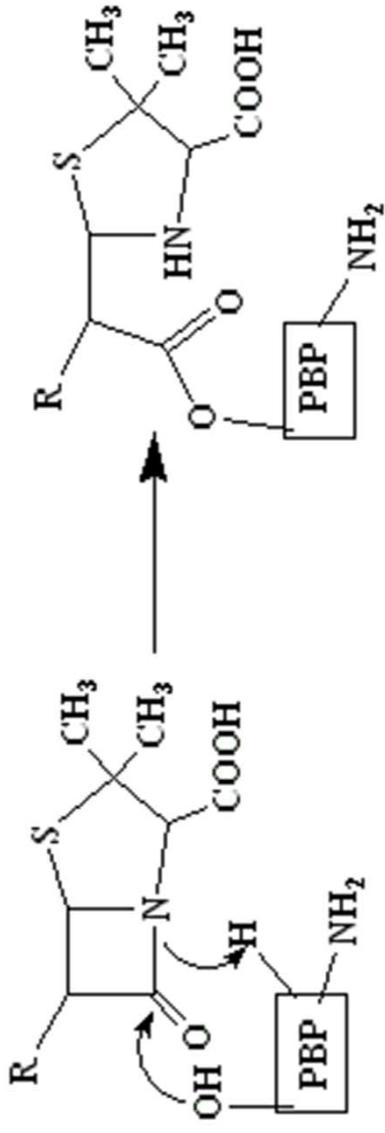
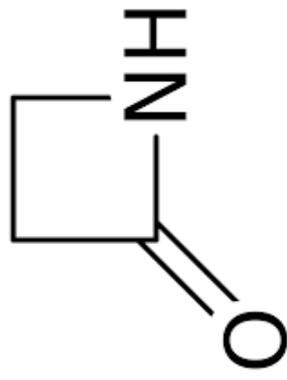


Clinical Microbiology Reviews p. 682–707
October 2012 Volume 25 Number 4

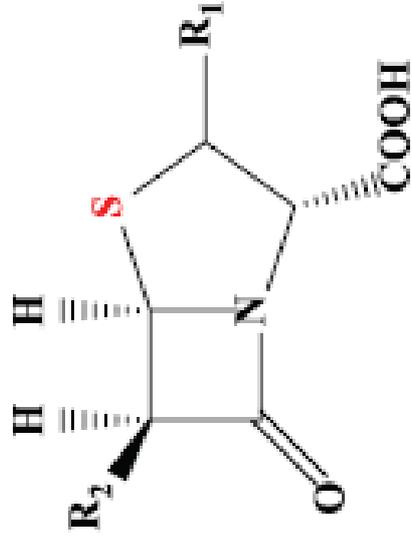
Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

L. S. Tzouvelekis,^a A. Markogiannakis,^b M. Psychogiou,^c P. T. Tassios,^a and G. L. Daikos^c

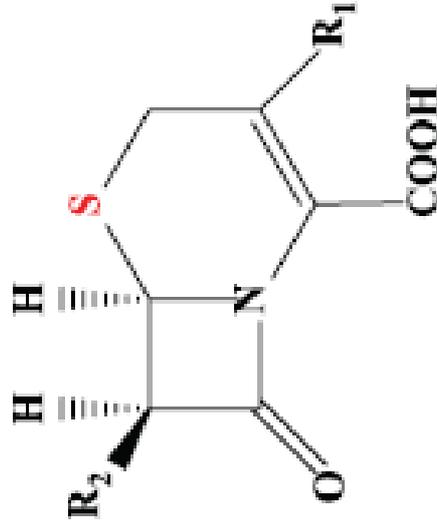
Department of Microbiology^a and First Department of Propaedeutic Medicine,^c School of Medicine, University of Athens, and Department of Pharmacy, Laiko General Hospital,^b Athens, Greece



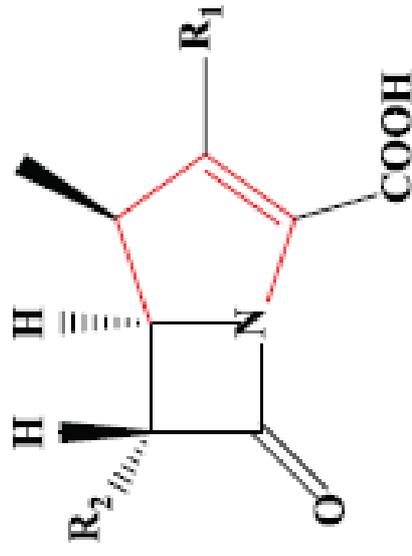
Penicillin



Cephalosporin



Carbapenem



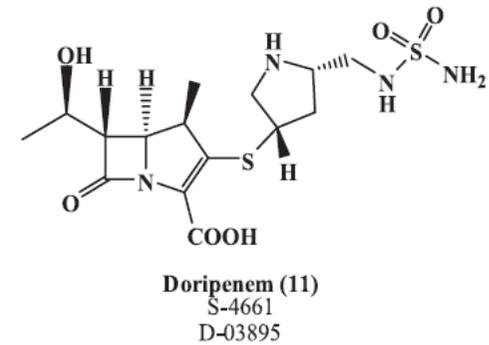
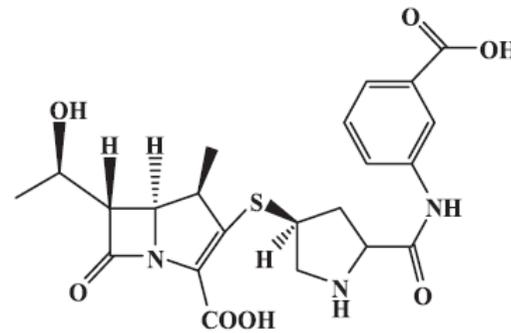
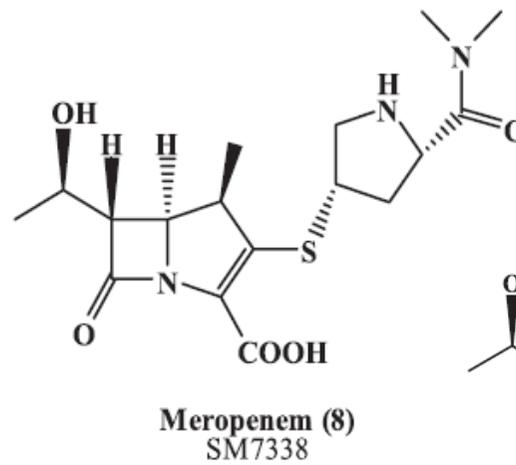
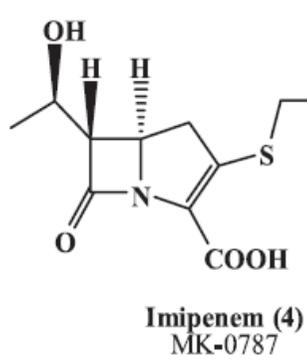
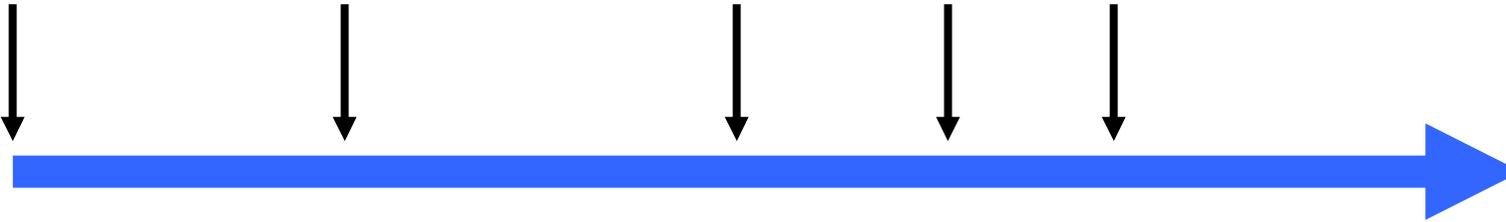
1976
tienamicina

1985
imipenem

1995
meropenem

2001
ertapenem

2005
doripenem



Broad-spectrum of activity:

- G+ cocci and G- rods
- Aerobic and anaerobic
- Multi-resistant
(including pneumococci, *Pseudomonas*, *Acinetobacter*)
- ESBL+

No activity against:

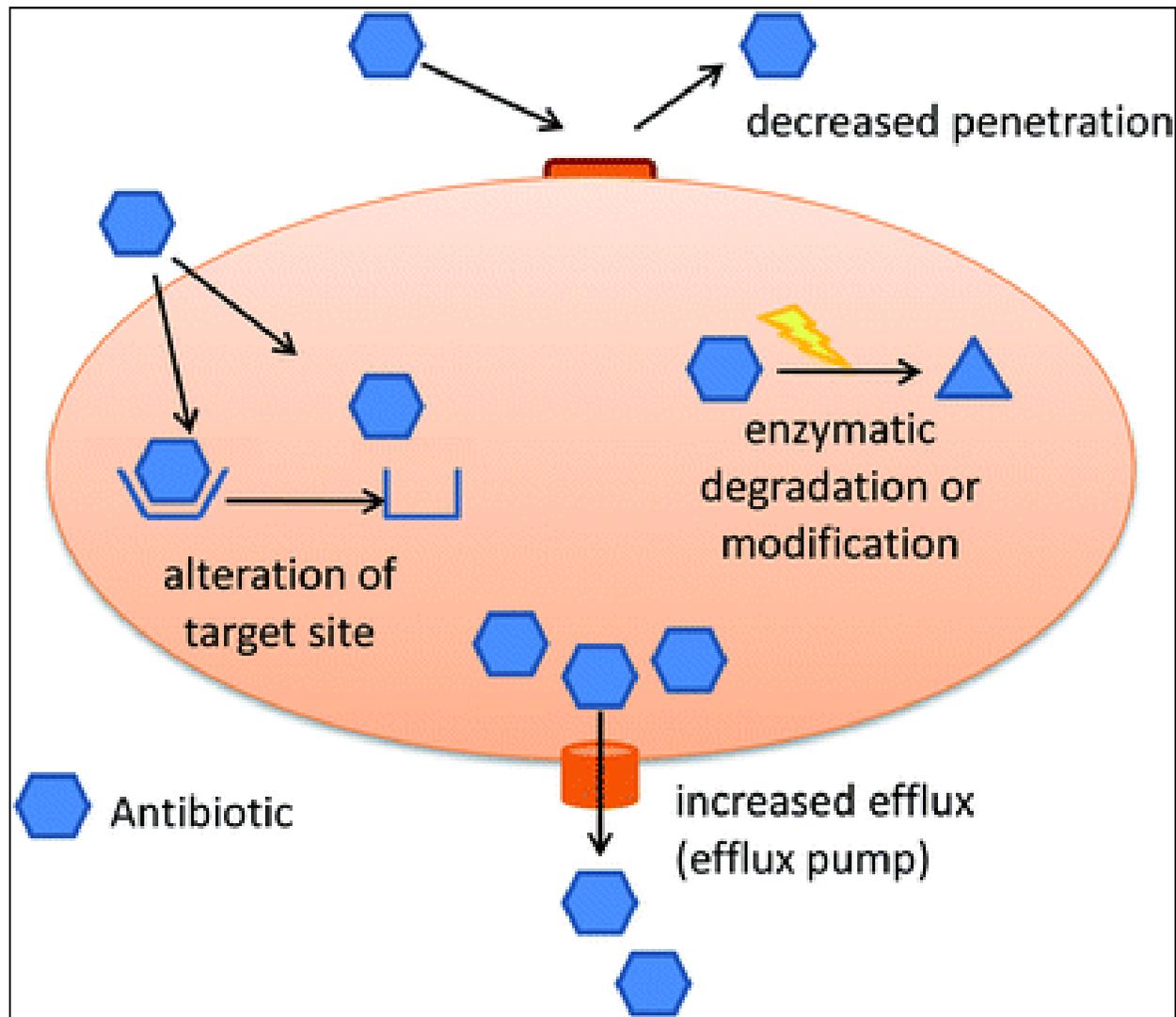
- MRSA
- Enterococci
- Stenotrophomonas maltophilia*

Clinical Indications

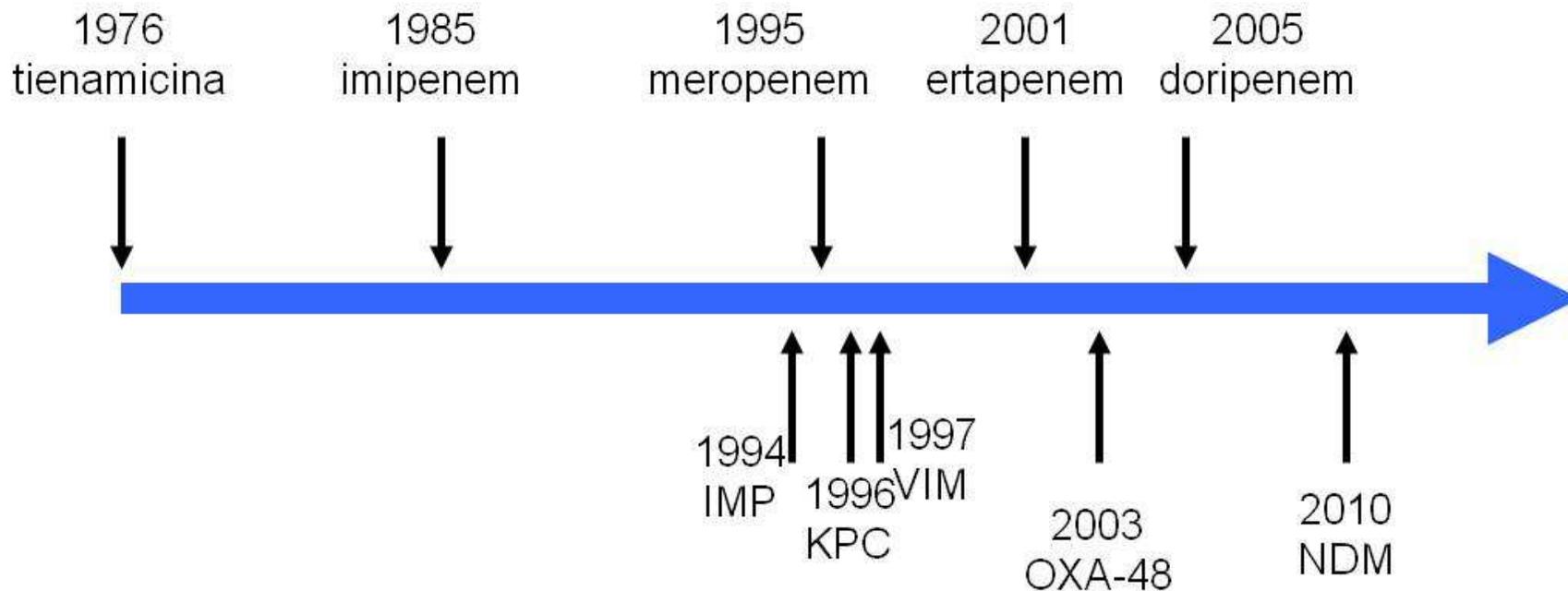
- Lower Respiratory Tract infection
- Urinary Tract Infection
- Intra abdominal infection
- Gynaecological infection
- Bacterial septicemia
- Bone & joint infection
- Skin & soft tissue infection
- Endocarditis
- Polymicrobial infections
- Skin & soft tissue infection
- Bacterial meningitis

- Community acquired pneumonia requiring hospitalization (Ertapenem)

Mechanisms of resistance to Carbapenems



Rise of the Carbapenemases



KPC: class A

IMP, VIM, NDM: class B (metallobetalactamases)

OXA-48: class D

Most carbapenemases hydrolyze
MOST β -lactams

Antibiogram of an OXA-48 producing *Klebsiella pneumoniae*

Ampicilina	R
Piperacilina	R
Amoxicilina/Clavulánico	R
Piperacilina/Tazobactam	R
Cefalotina	R
Cefuroxima	R
Cefoxitina	R
Cefotaxima	R
Ceftazidima	R
Cefepime	R
Aztreonam	R
Ertapenem	R
Imipenem	R
Meropenem	R
Doripenem	R

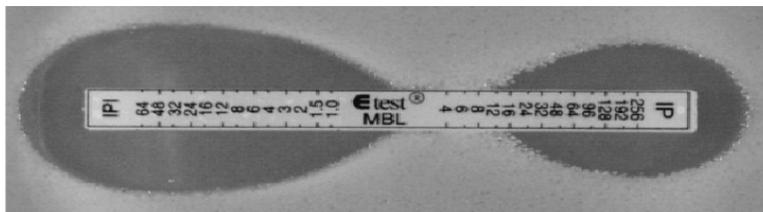
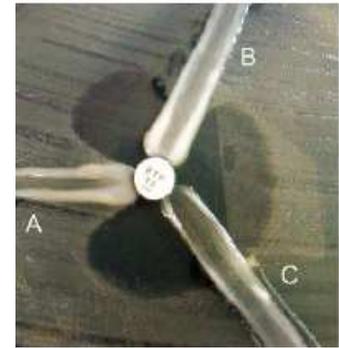
Cotrimoxazol	R
Ciprofloxacino	R
Gentamicina	R
Tobramicina	R
Amikacina	S
Colistina	S
Fosfomicina	S
Tigeciclina	S

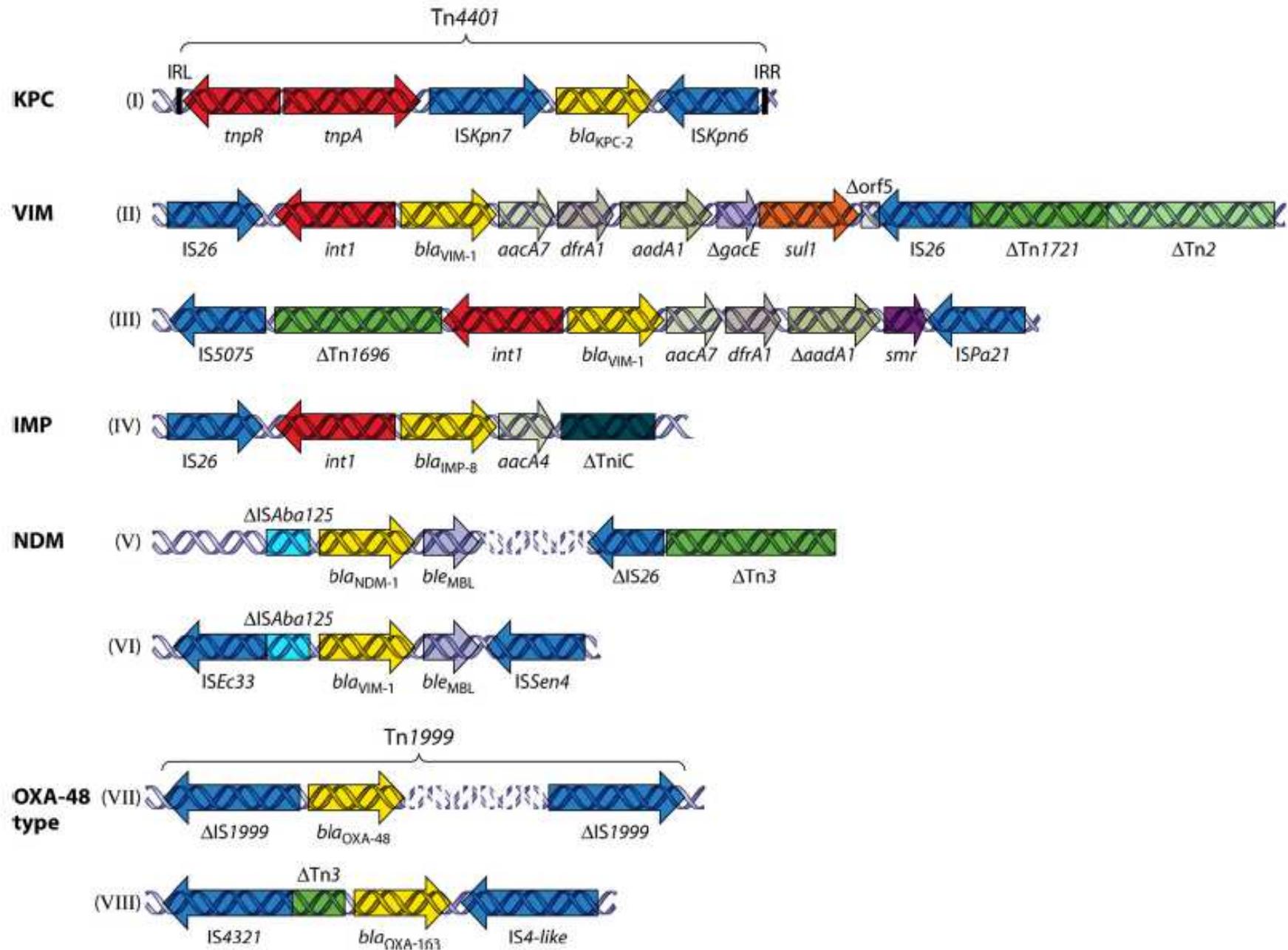
3-5% R
12.5% R
48% R
33% R

Phenotypic detection: carbapenem
MIC

Phenotypic confirmation: Modified
Hodge Test, Double Disk Synergy
Test, EDTA inhibition, boronic acid
inhibition, commercial tests, MALDI-
TOF

Genotypic assays: PCR and
sequencing

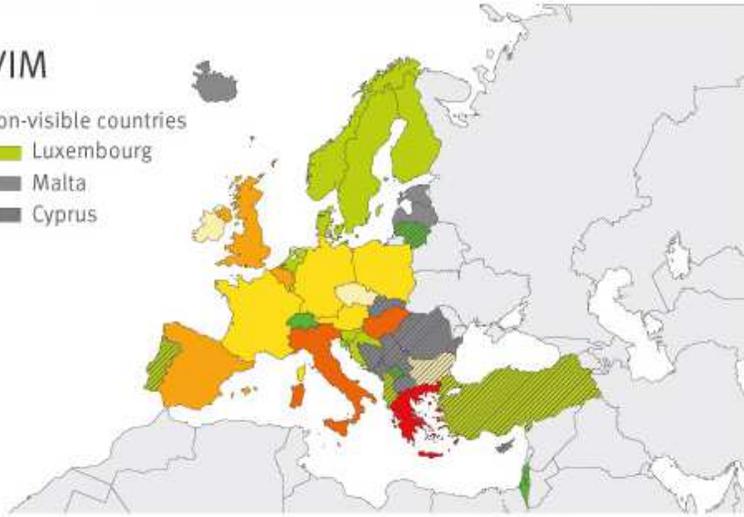




VIM

Non-visible countries

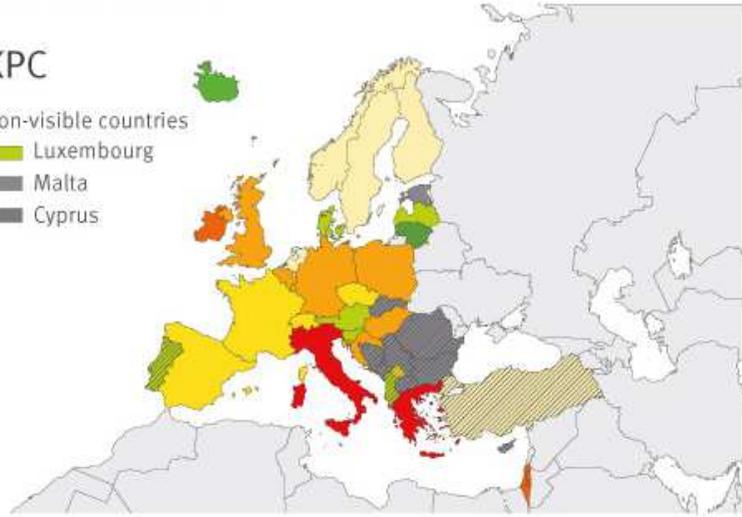
-  Luxembourg
-  Malta
-  Cyprus



KPC

Non-visible countries

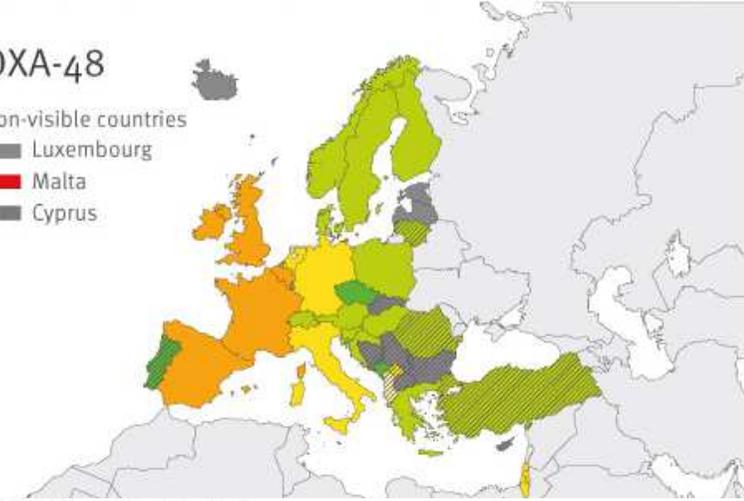
-  Luxembourg
-  Malta
-  Cyprus



OXA-48

Non-visible countries

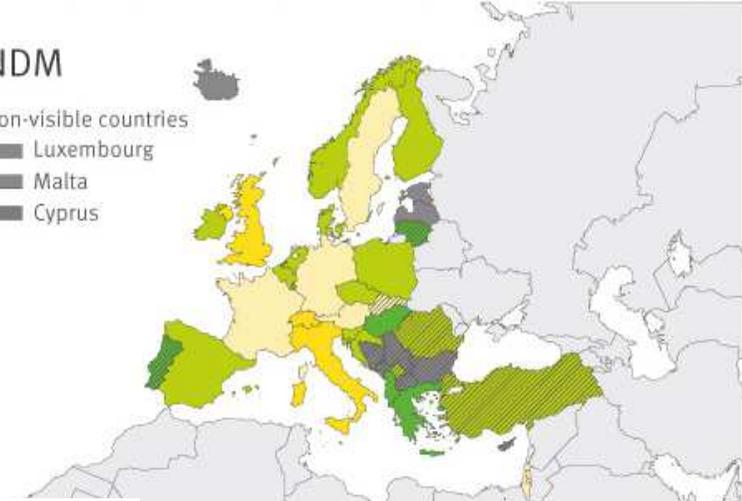
-  Luxembourg
-  Malta
-  Cyprus



NDM

Non-visible countries

-  Luxembourg
-  Malta
-  Cyprus



Epidemiological stages

- | | |
|---|---|
|  No cases reported |  Data not available |
|  Sporadic occurrence |  Not participating countries |
|  Single hospital outbreak | |
|  Sporadic hospital outbreaks | |
|  Regional spread | |
|  Inter-regional spread | |
|  Endemic situation | |
|  Uncertain | |

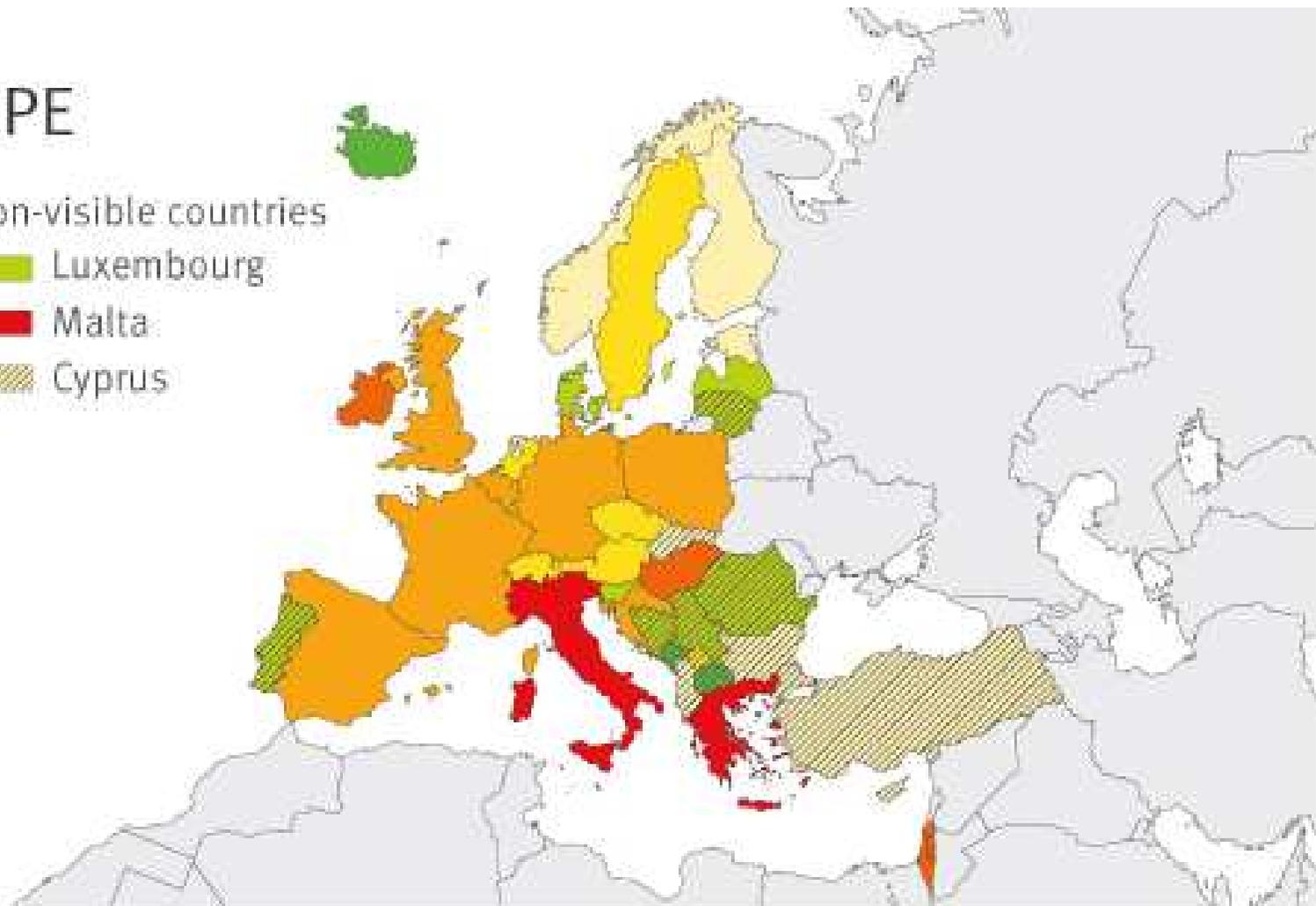
CPE

Non-visible countries

 Luxembourg

 Malta

 Cyprus



Epidemiological stages

 No cases reported

 Sporadic occurrence

 Single hospital outbreak

 Sporadic hospital outbreaks

 Regional spread

 Inter-regional spread

 Endemic situation

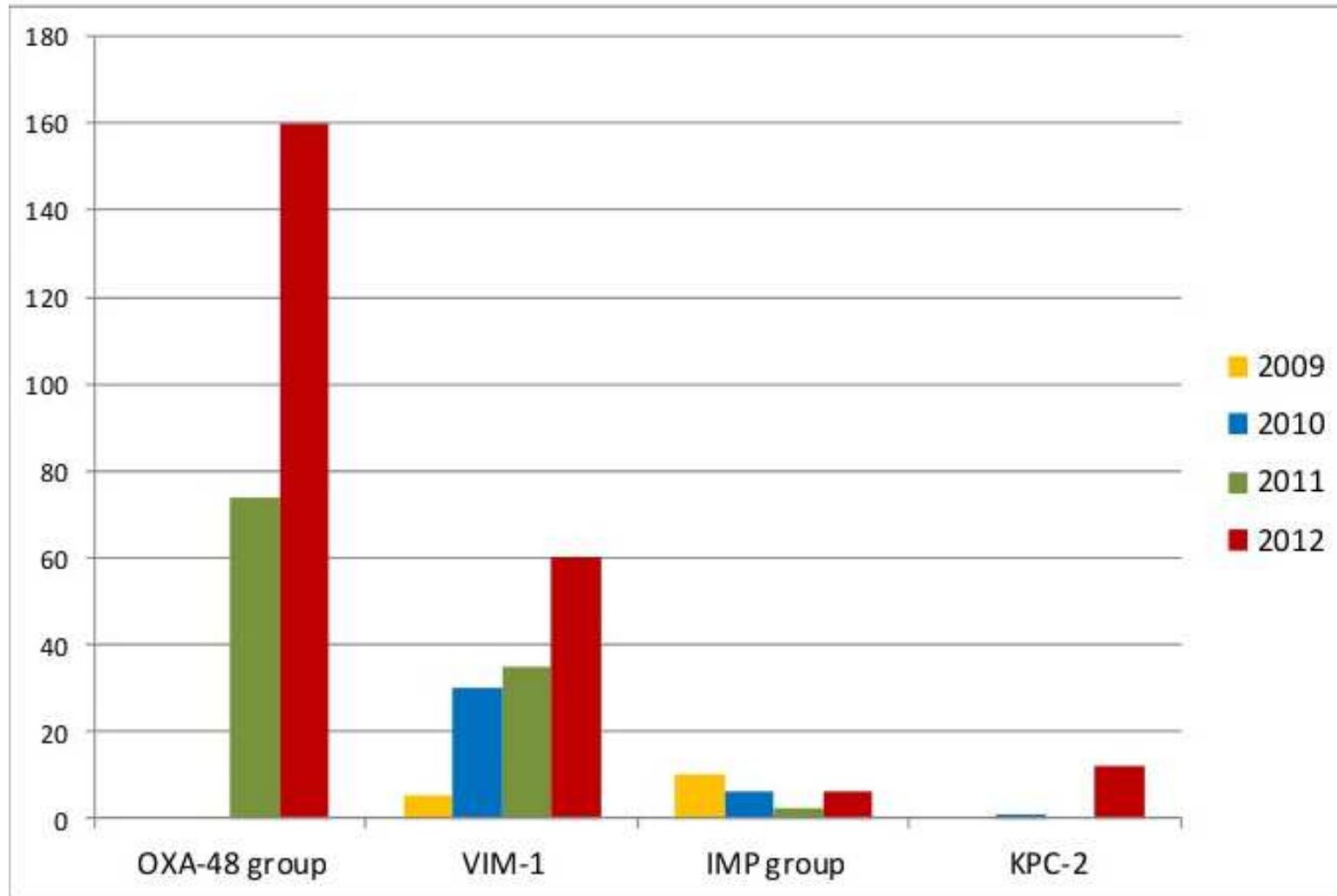
 Uncertain

 Data not available

 Not participating countries

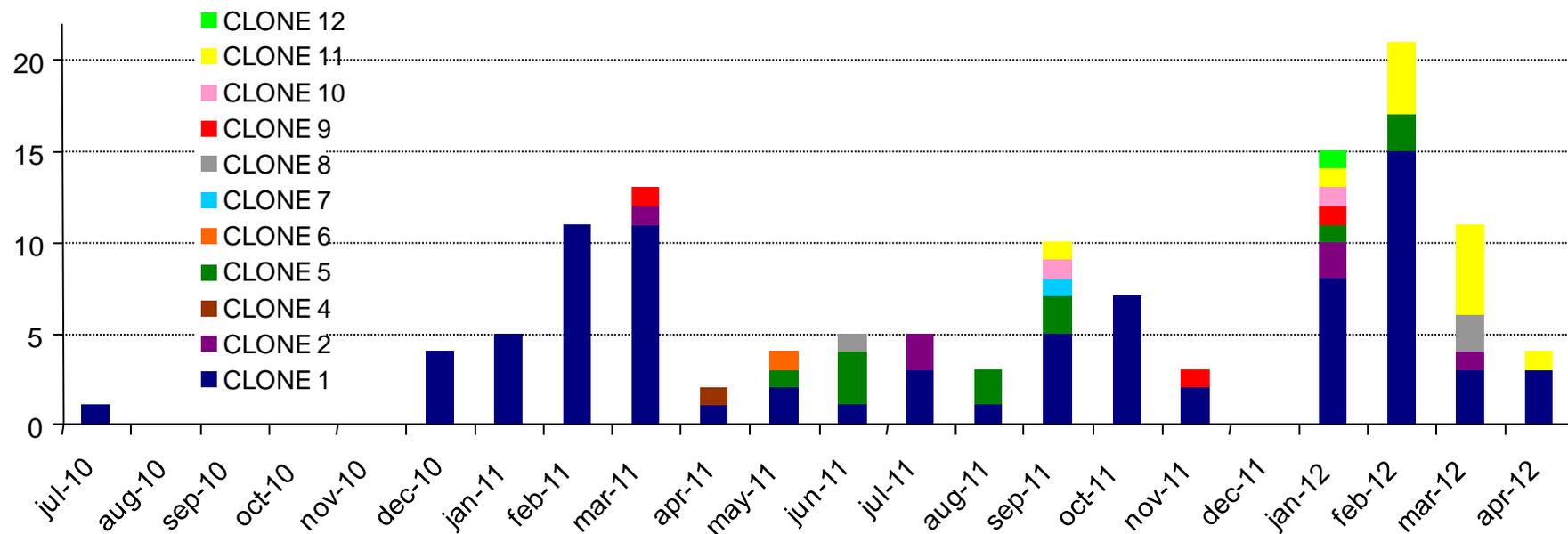
Carbapenemase-producing enterobacteria in Spain, 2009-2012

J. Oteo, Centro Nacional de Microbiología



Infections caused by OXA-48-producing *Klebsiella pneumoniae* in a tertiary hospital in Spain in the setting of a prolonged, hospital-wide outbreak

José Ramón Paño-Pardo^{1,2*}, Guillermo Ruiz-Carrascoso³, Carolina Navarro-San Francisco^{1,2}, Rosa Gómez-Gil³, Marta Mora-Rillo^{1,2}, María Pilar Romero-Gómez³, Natalia Fernández-Romero³, Julio García-Rodríguez³, Verónica Pérez-Blanco⁴, Francisco Moreno-Ramos⁵ and Jesús Mingorance³



OXA-48 in HULP

	2011	2012	2013	2014
New cases	105	185	407	410
In clinical samples (%)	65 (62)	80 (43)	96 (23)	56 (14)
More frequent samples	Rectal 38%	Rectal 56%	Rectal 76%	Rectal 86%
	Urine 21%	Urine 17%	Urine 13%	Urine 7.5%
	Blood 12%	Blood 11%	Blood 2%	Blood 2%
Mortality (%)	28%	22%	21%	16%
Age (Mean \pm SD)	71 \pm 15	62 \pm 25	70 \pm 5	73 \pm 15

2014

448 OXA-48 producing enterobacteria



410 related to healthcare in HULP



354 colonization



29 infections



16 (55%) UTI

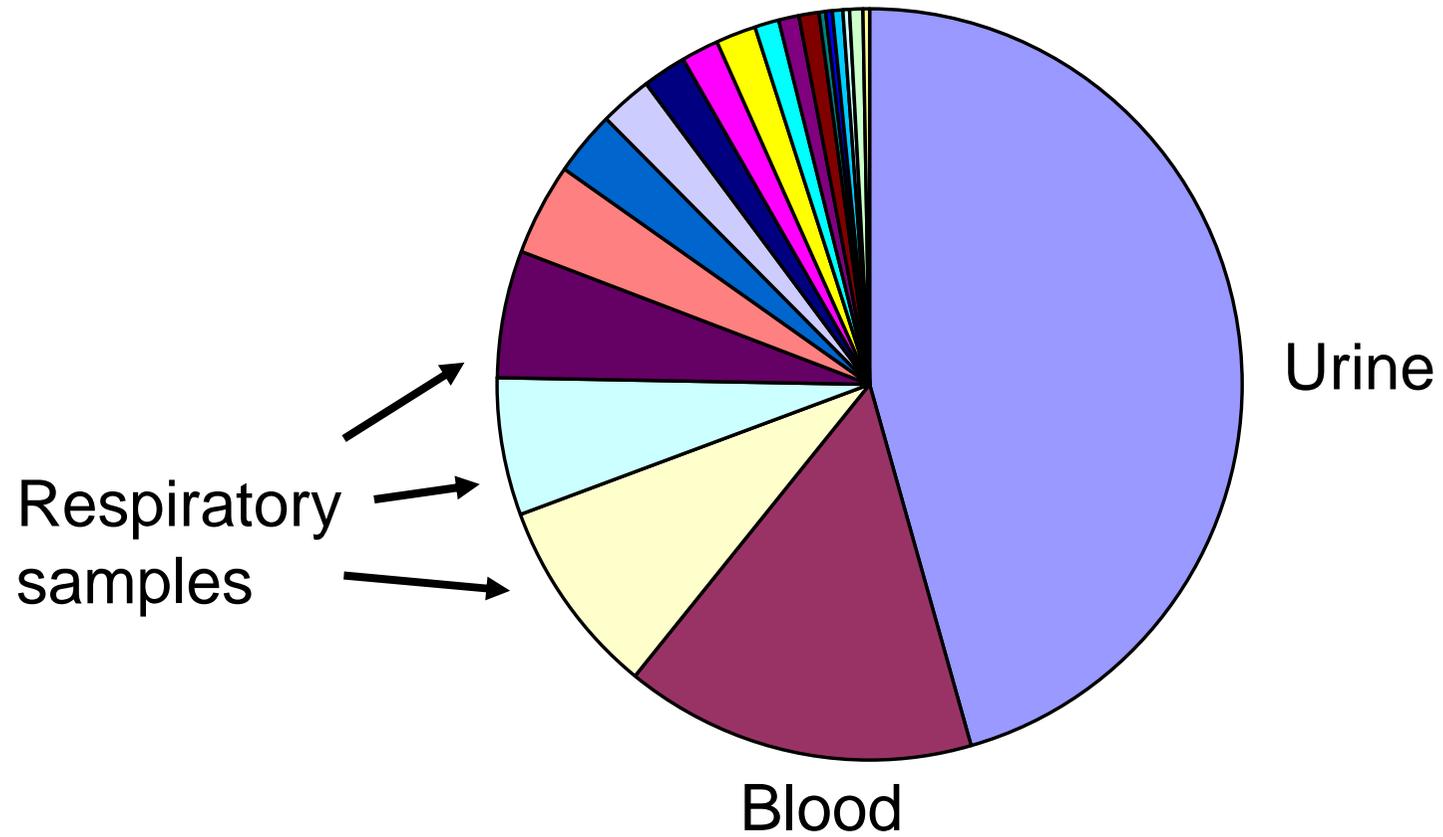


56 infections

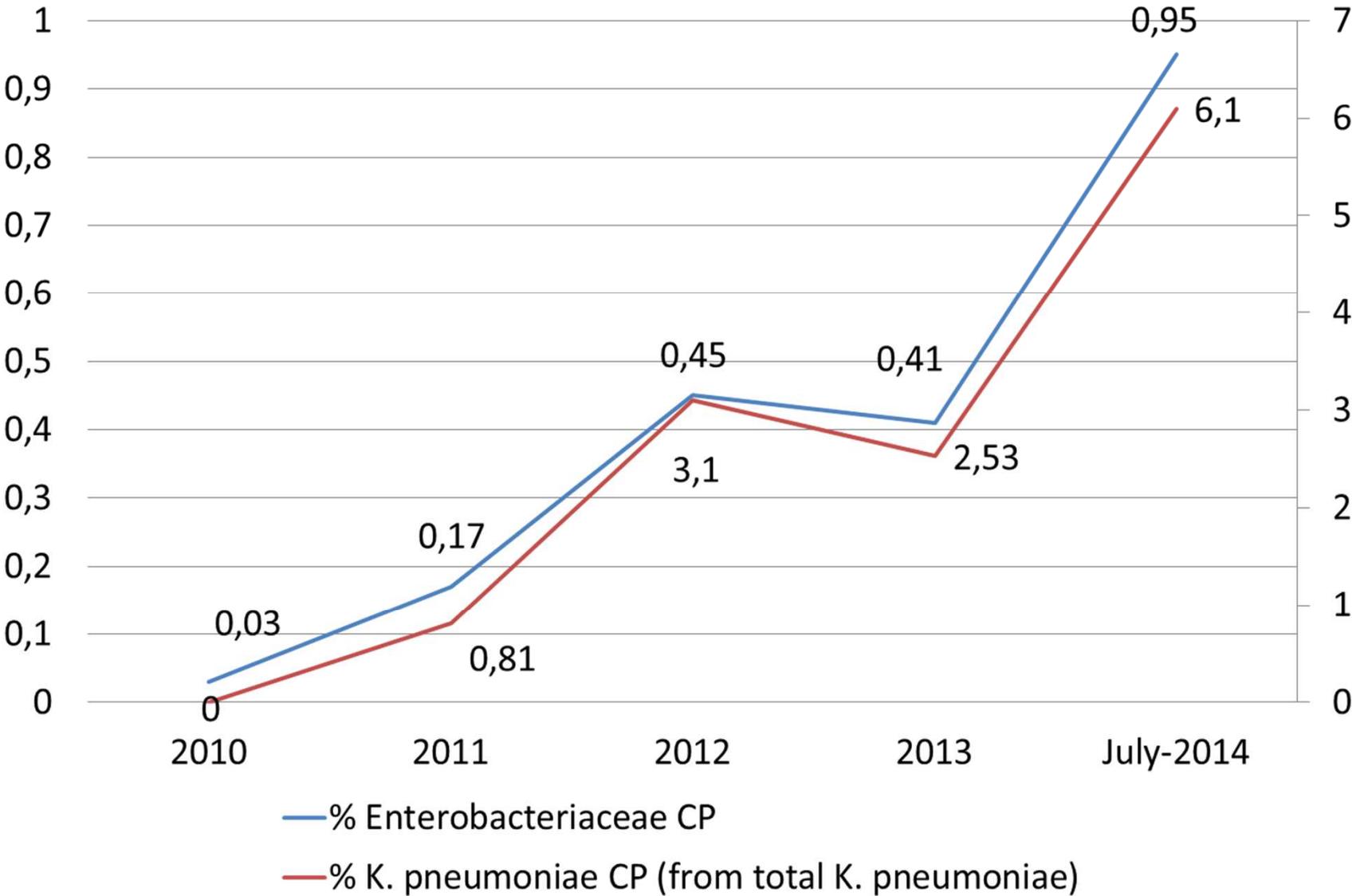


31 (55%) UTI

OXA-48 in clinical samples

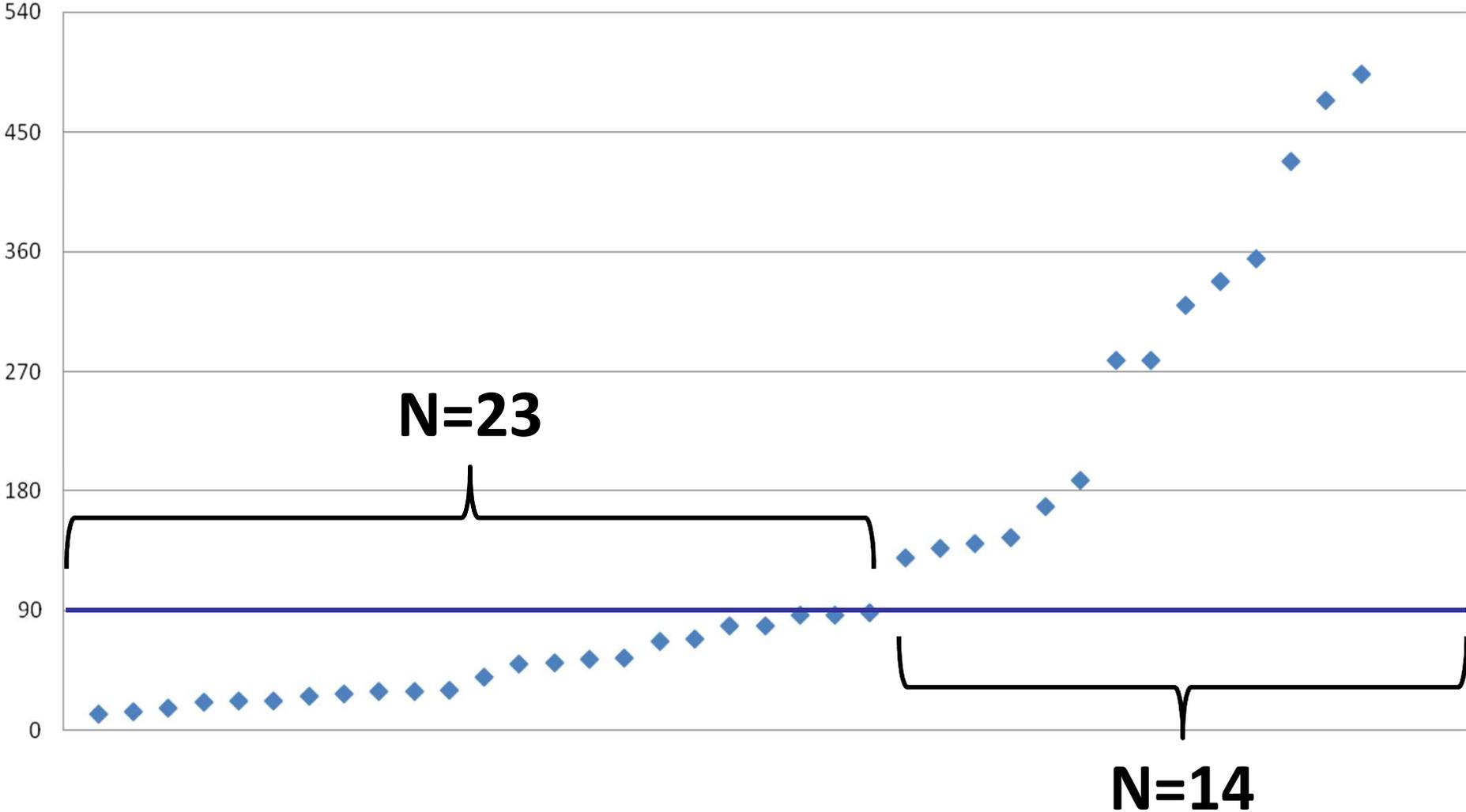


Infections caused by carbapenemase producing Enterobacteriaceae (CPE) in ambulatory care

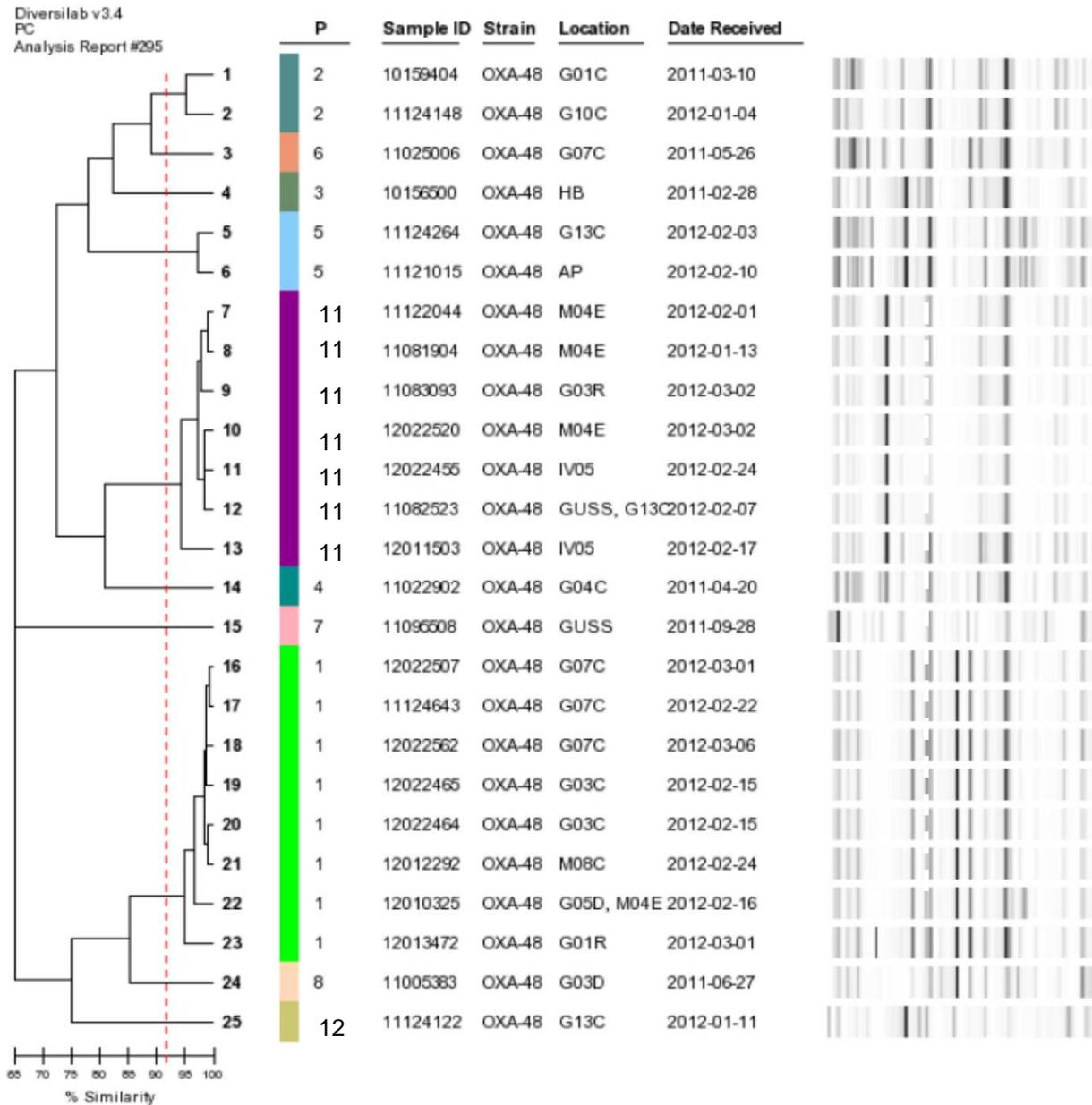


Infections caused by carbapenemase producing Enterobacteriaceae (CPE) in ambulatory care

Days from hospital discharge to clinical isolation



Clonality of *K. pneumoniae* OXA-48



Genome Sequence of OXA-48 Carbapenemase-Producing *Klebsiella pneumoniae* KpO3210

Jan-Jaap Wesseling,^a Elena López-Camacho,^b Santiago de la Peña,^a Ricardo Ramos-Ruiz,^c Guillermo Ruiz-Carrasco,^b Silvia Lusa-Bernal,^a Victor M. Fernández-Soria,^c Rosa Gómez-Gil,^b Paulino Gomez-Puertas,^d and Jesús Mingorance^b

Biomol-Informatics, S.L., Campus Universidad Autónoma de Madrid, Madrid, Spain^a; Servicio de Microbiología, Hospital Universitario La Paz, IdIPAZ, Madrid, Spain^b; Parque Científico de Madrid, Campus Universidad Autónoma de Madrid, Madrid, Spain^c; and Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Campus Universidad Autónoma de Madrid, Madrid, Spain^d



Genome Announcements
July/August 2014 Volume 2 Issue 4 e00737-14

Draft Whole-Genome Sequence of OXA-48-Producing Multidrug-Resistant *Klebsiella pneumoniae* KP_ST11_OXA-48

Jennifer Villa,^a Esther Viedma,^{a,b} Patricia Brañas,^a Jesús Mingorance,^{b,c} Fernando Chaves^{a,b}

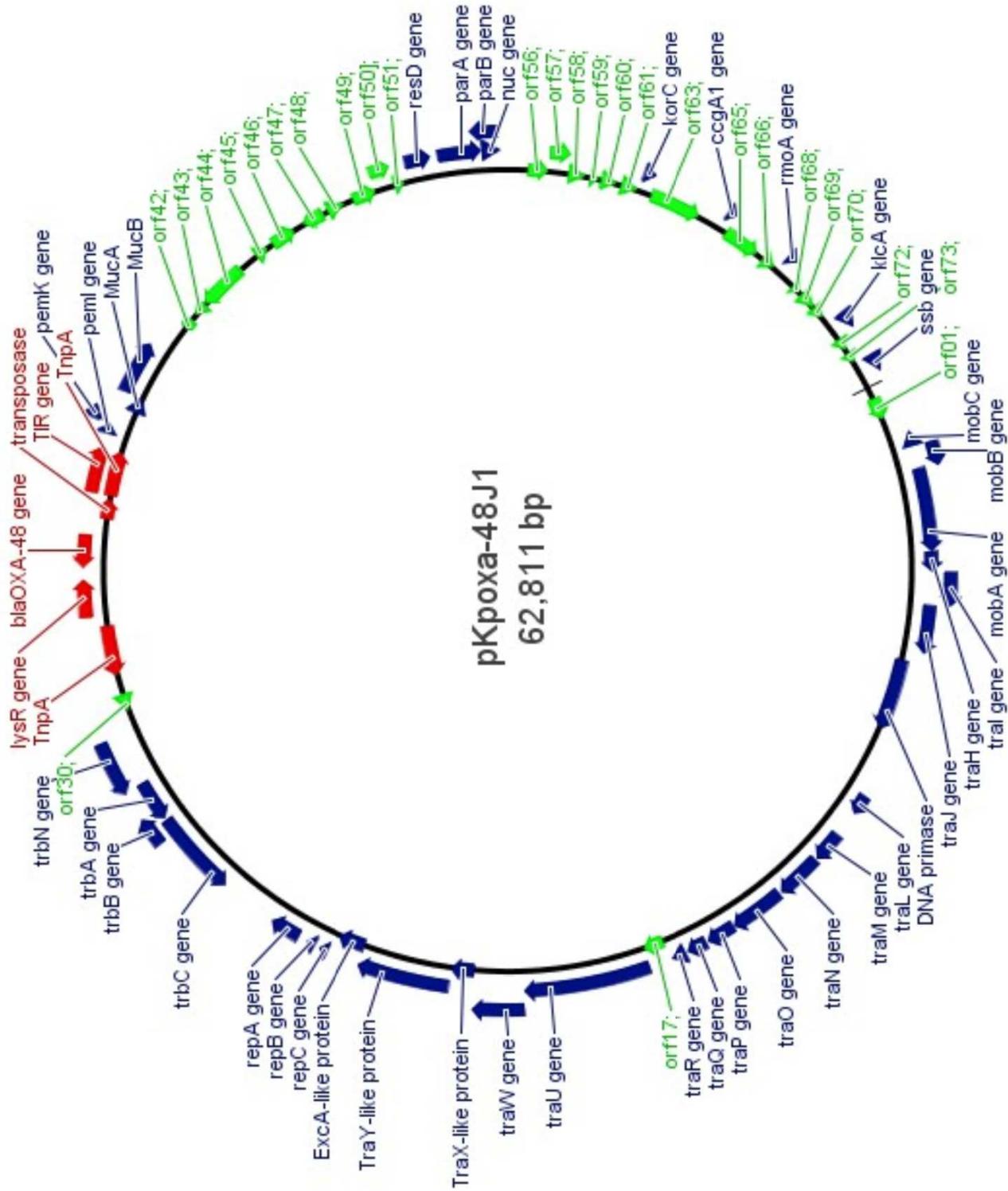
Servicio de Microbiología Clínica, Hospital Universitario 12 de Octubre, Madrid, Spain^a; Spanish Network for Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain^b; Hospital Universitario la Paz, IdIPAZ, Madrid, Spain^c

Genome Sequence of OXA-48 Carbapenemase-Producing *Klebsiella pneumoniae* KpO3210

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Biomol-Informatics, S.L., Campus Universidad Autónoma de Madrid, Madrid, Spain^a; Servicio de Microbiología, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain^b; Parque Científico de Madrid, Campus Universidad Autónoma de Madrid, Madrid, Spain^c; and Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Campus Universidad Autónoma de Madrid, Madrid, Spain^d

Cromosome	5.8 Mb	5278 genes
Plasmid 1	230 Kb	222 genes
pOXA -48	62 Kb	79 genes
Plasmid 3	34 Kb	44 genes
Plasmid 4	4 Kb	4 genes



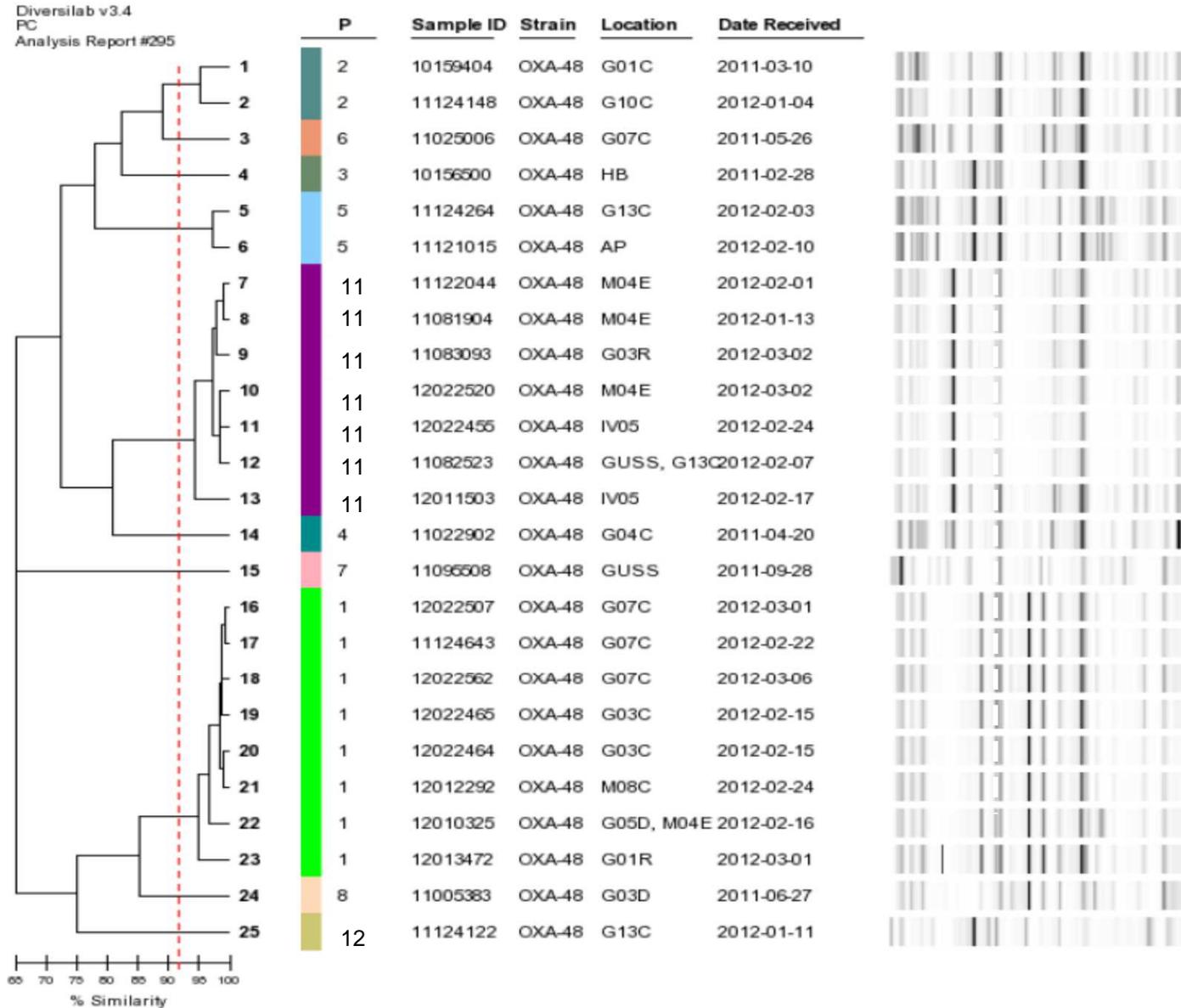
KpO3210
(ST405)

ANTIBIOTIC	GENES
β -lactams	<i>bla</i> _{SHV-76} , <i>bla</i> _{TEM} , <i>bla</i> _{OXA-1} , <i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-48}
Aminoglycosides	<i>aac(6')Ib-cr</i> , <i>aac(3)-IIa</i> , <i>aph(3'')-Ib</i> , <i>aph(6)-Id</i>
Fluoroquinolones	<i>qnrB6</i>
Phenicol	<i>catB3</i>
Sulphonamide-trimethoprim	<i>sul2</i> , <i>dfrA14</i>

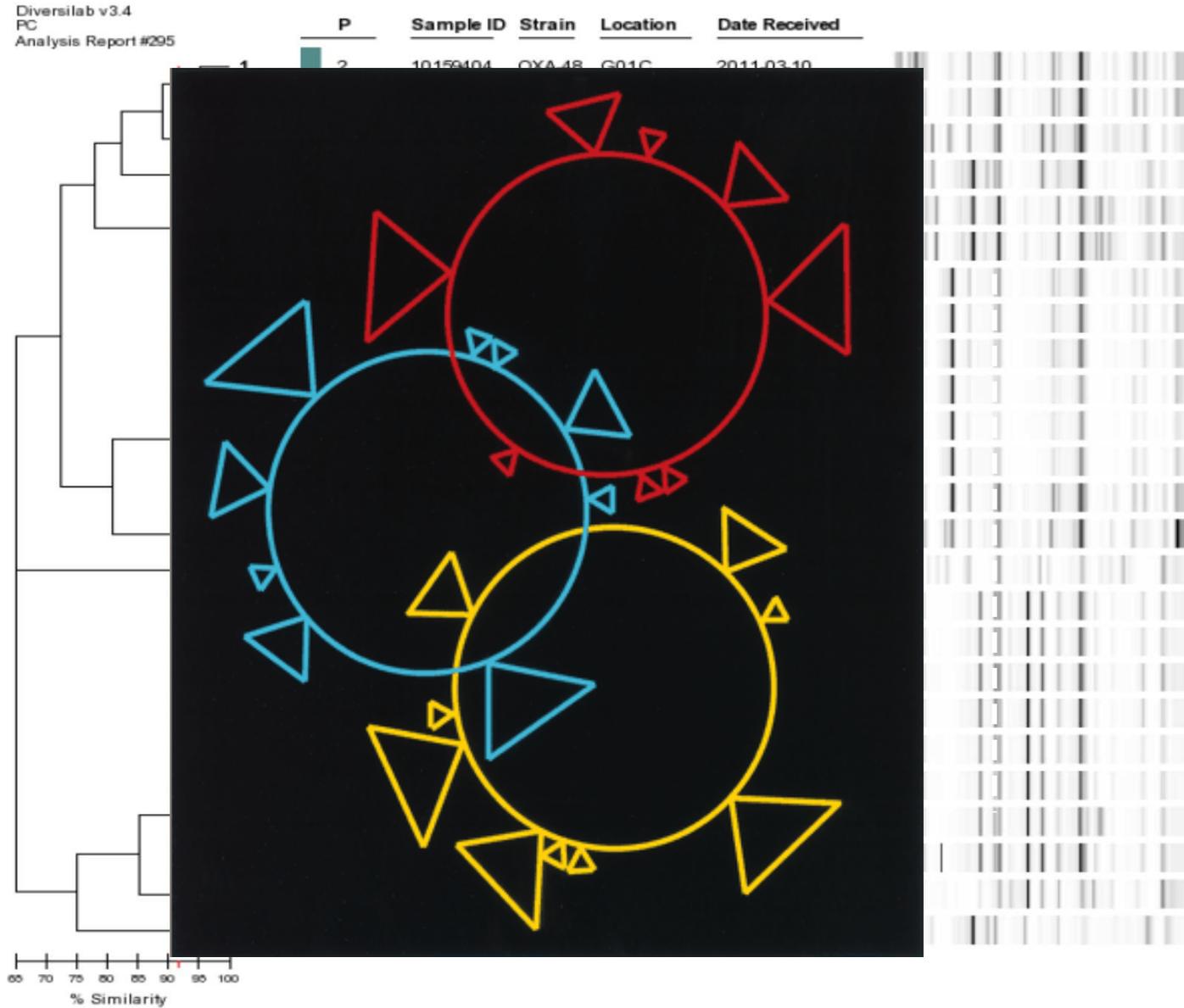
Kp_ST11_OXA-48 :

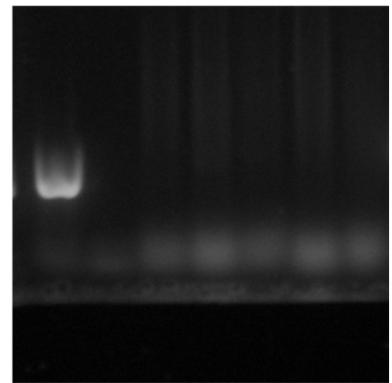
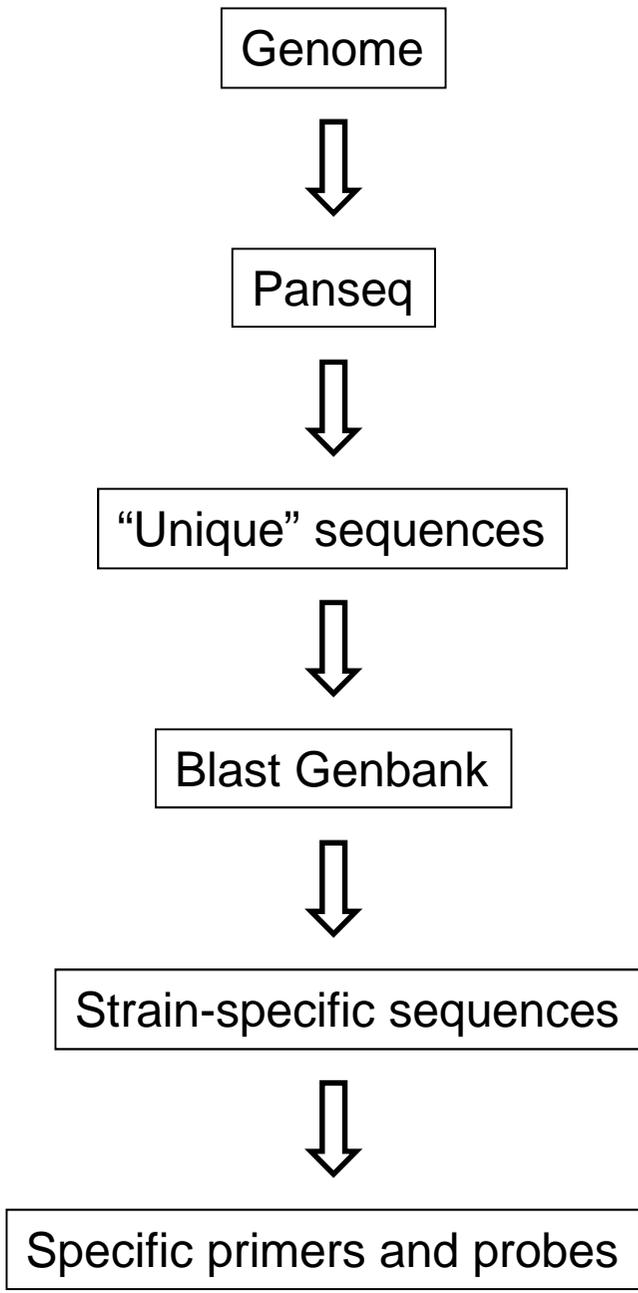
	GENES
β -lactams	<i>bla</i> _{SHV-11} , <i>bla</i> _{OXA-1} , <i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-48}
Aminoglycosides	<i>aac(6')Ib-cr</i> , <i>aac(3)-IIa</i> , <i>aadA2</i> , <i>aph(3')-Ia</i>
Fluoroquinolones	<i>gyrA</i> S83F, D87A, <i>parC</i> S80I, <i>qnrB1</i>
Macrolides	<i>mph-A</i>
Phenicol	<i>catA1</i> , <i>catB2</i>
Sulphonamide-trimethoprim	<i>sul1</i> , <i>dfrA12</i>

Design of strain-specific assays for rapid typing

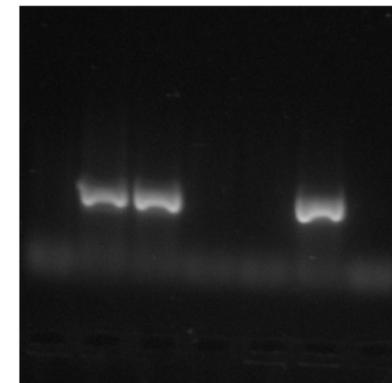


Design of strain-specific assays for rapid typing

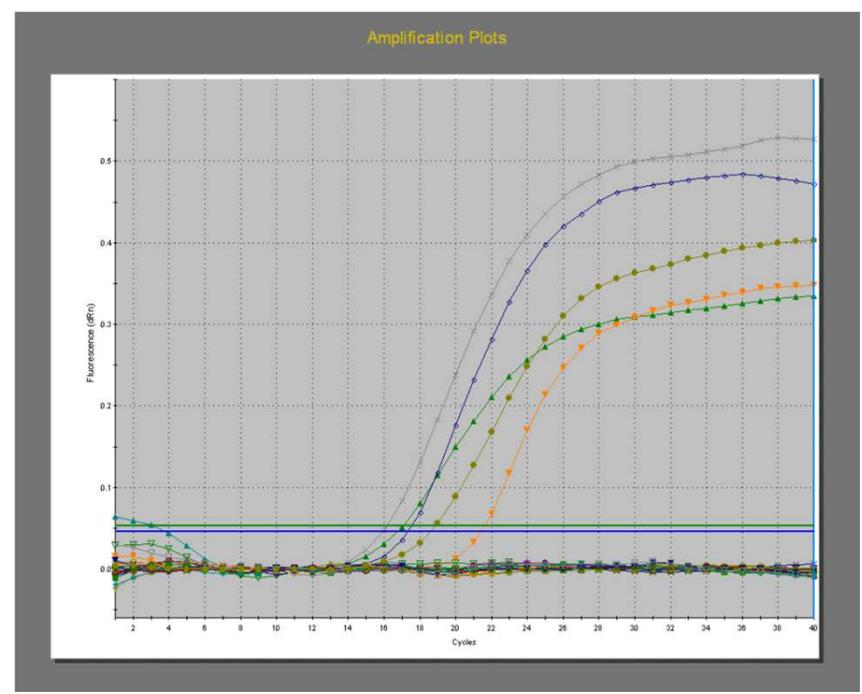




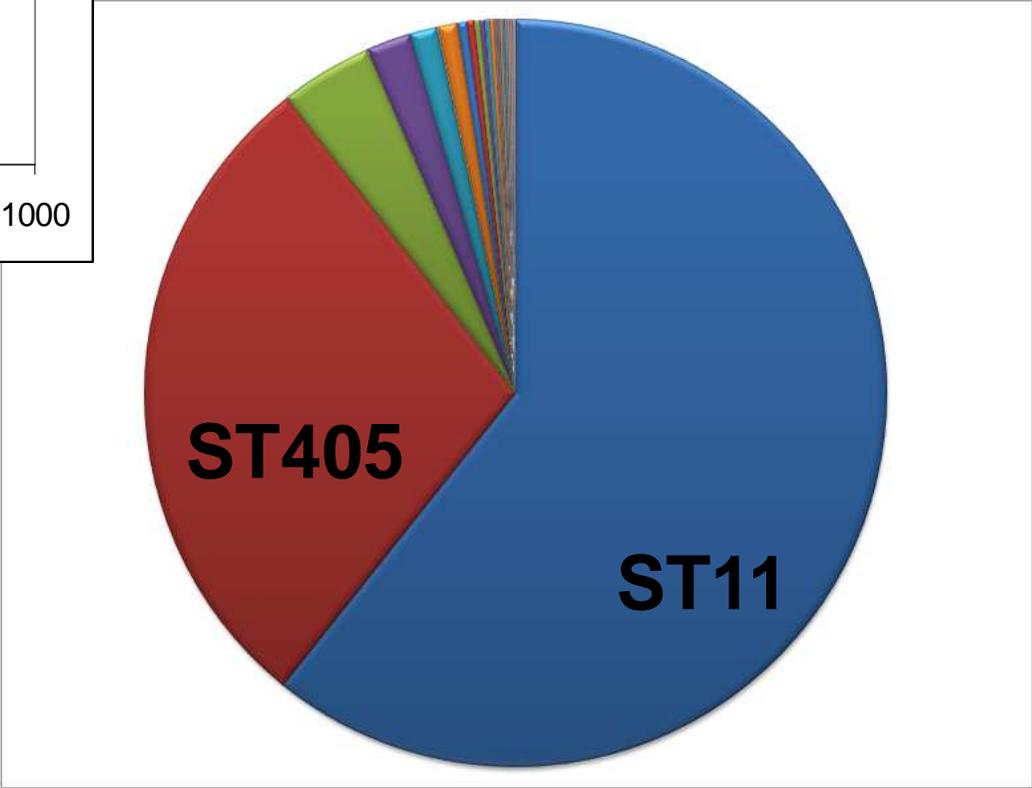
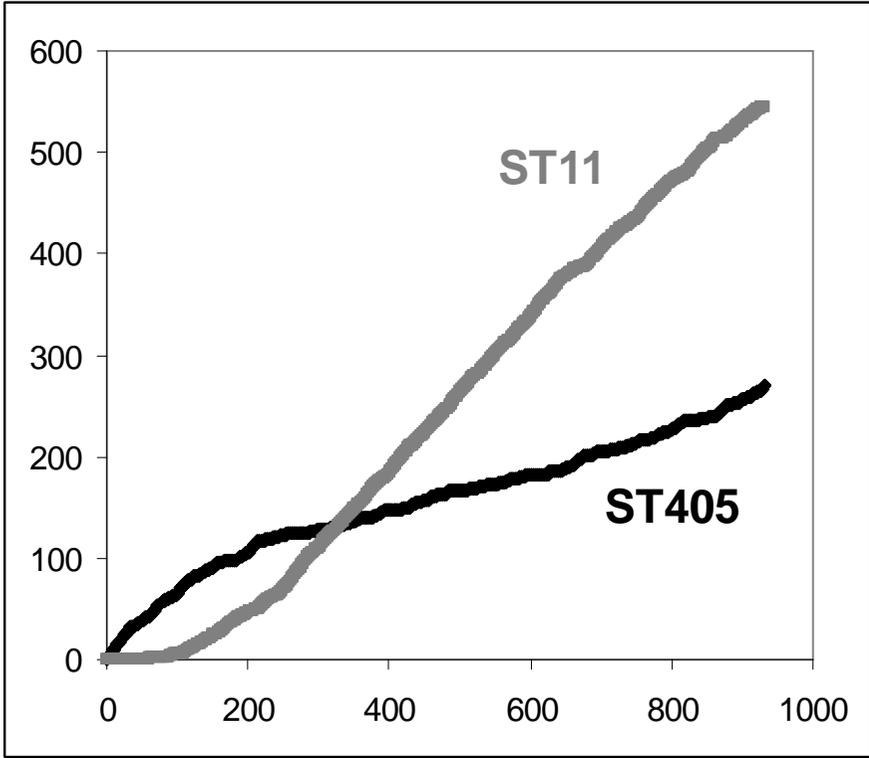
ST405



ST11

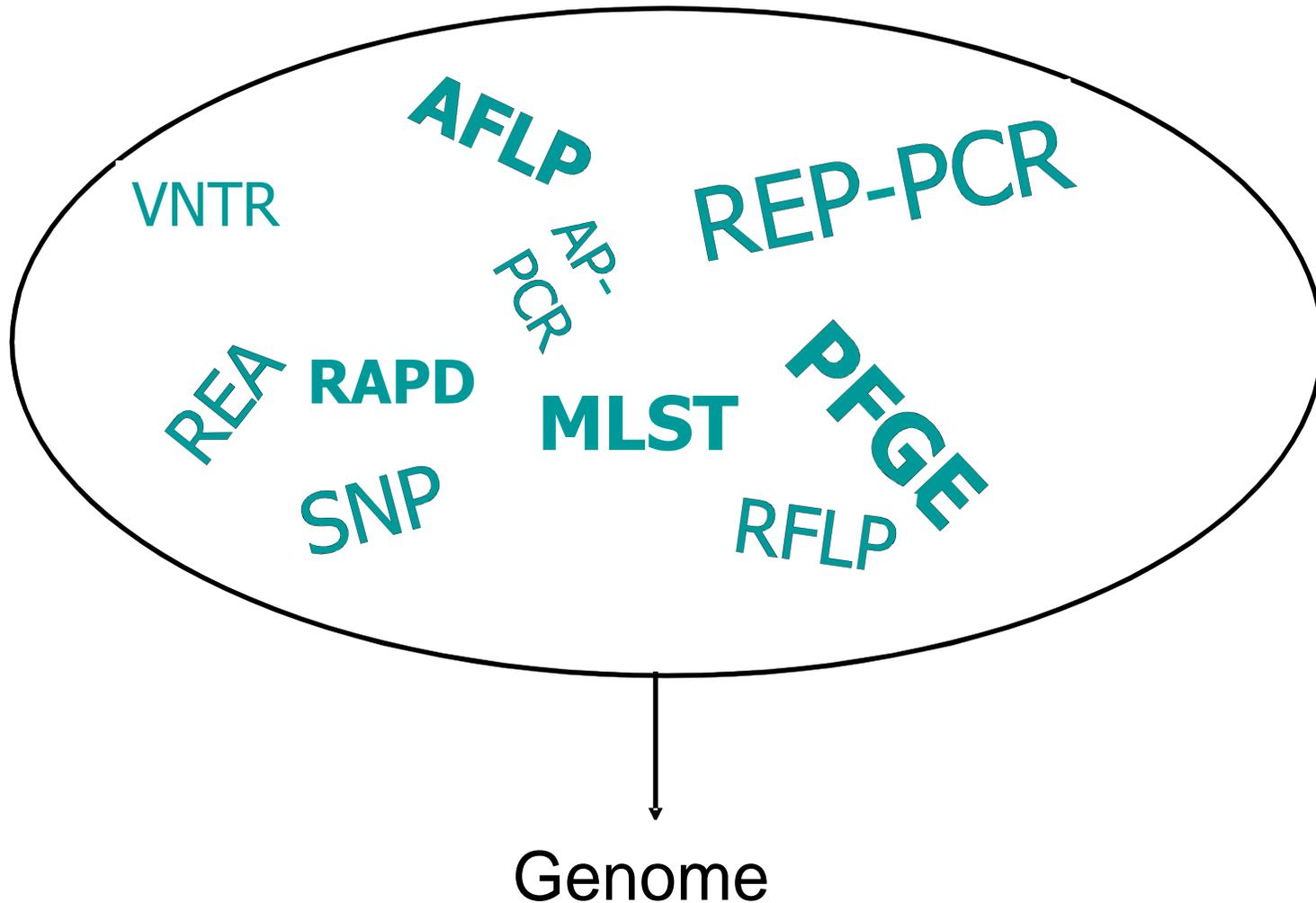


2015

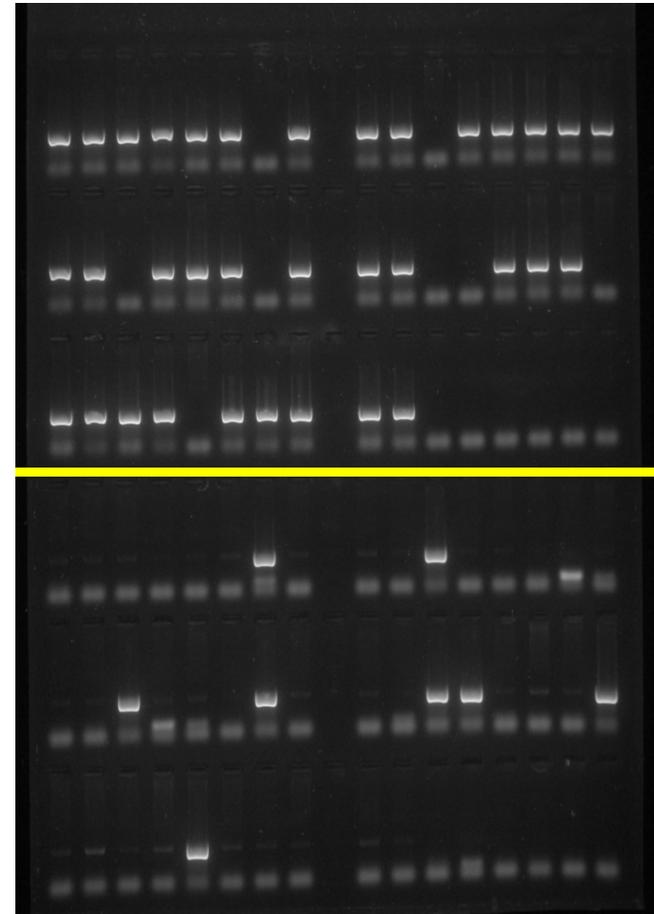
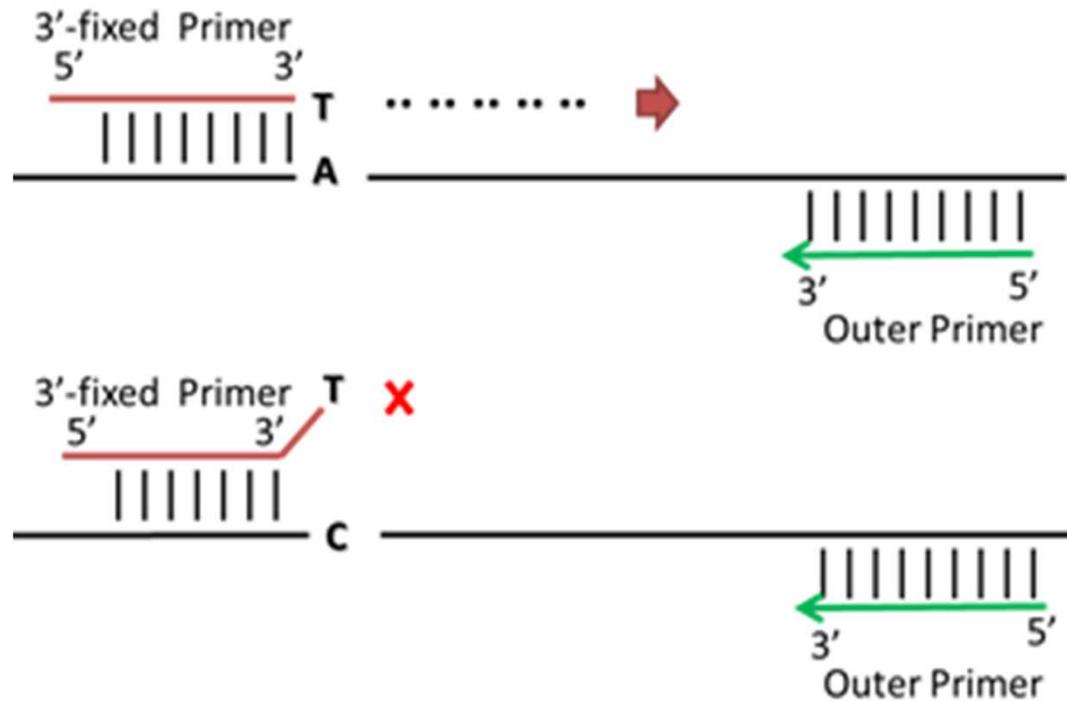


60% ST11
28% ST405
12% other STs (18)

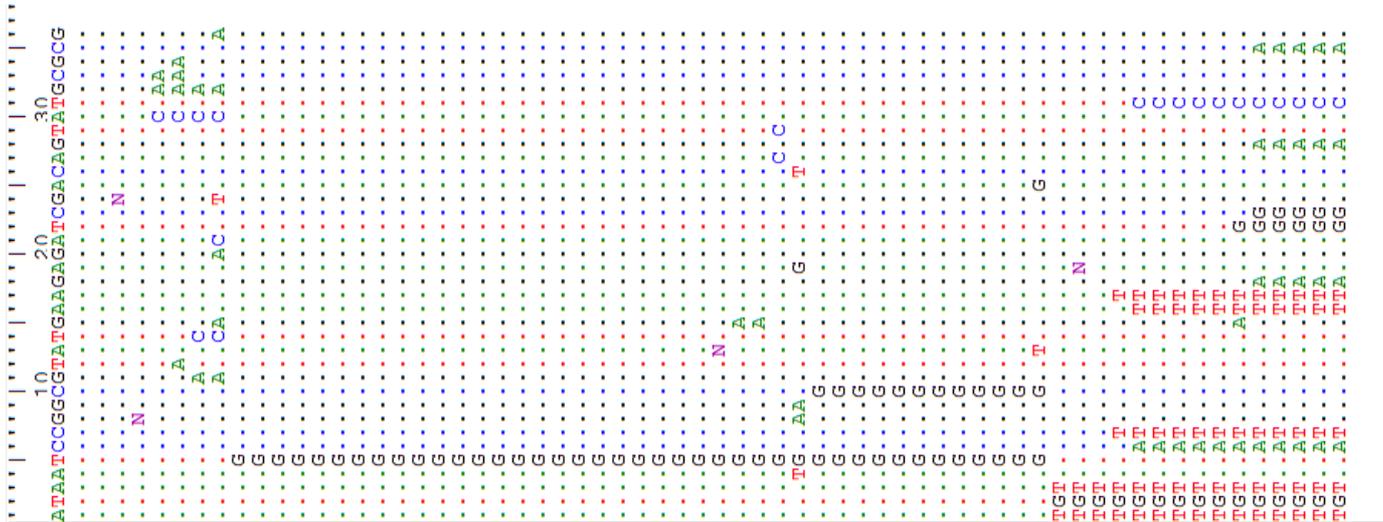
High resolution typing by SNP analysis



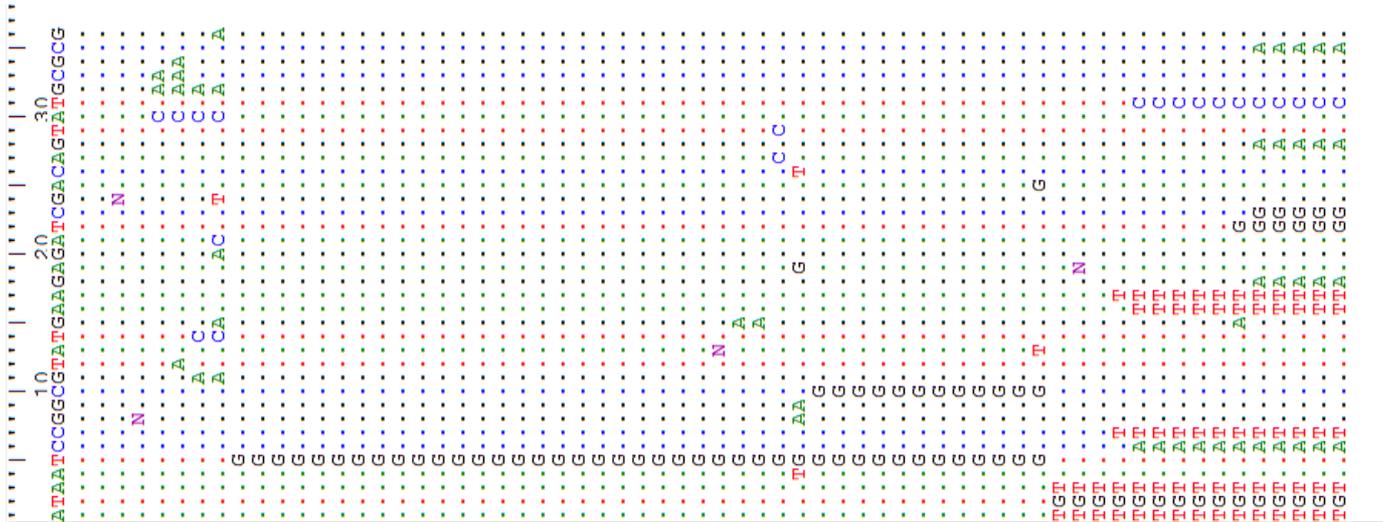
Allele-specific PCR



	10	20	30
I670 (29/04/10) GUSS Ancestral	A	T	T
7823 (21/01/11) M08C	A	T	T
0789 (23/02/11) G10C	A	T	T
RVC (02/07/12)	T	T	T
8535 (07/11/11) G03D	C	C	C
7106 (29/07/11) T01C	C	C	C
Kp9 (3472) (01/03/12) G01R	C	C	C
0104 (04/05/12) T03C	C	C	C
Kp5 (1562) (07/03/12) G06D	C	C	C
1215 (28/12/10) G13C	C	C	C
8678 (29/12/10) G05C	C	C	C
5047 (10/01/11) T01C	C	C	C
9430 (25/01/11) G03D	C	C	C
0001 (07/02/11) G06D	C	C	C
1637 (08/02/11) GUSS	C	C	C
5334 (15/11/12) G03D	C	C	C
1396 (16/03/11) G01R	C	C	C
5869 (21/03/11) GUSS	C	C	C
5728 (31/05/11) HB	C	C	C
1541 (02/09/11) AP	C	C	C
5737 (28/09/11) GUSS	C	C	C
0025 (18/10/11) GUSS	C	C	C
2241 (27/01/12) G03D	C	C	C
0325 (16/02/12) G05D	C	C	C
K956 (23/01/12)	C	C	C
K1035 (13/03/12)	C	C	C
K1059 (09/04/12)	C	C	C
K1075 (25/04/12)	C	C	C
K1115 (15/05/12)	C	C	C
Kp8 (2307) (10/01/12) T05C	C	C	C
Kp10 (6219) (11/01/11) T03C	C	C	C
K1202 (25/06/12)	C	C	C
K946 (26/12/11)	C	C	C
5383 (27/06/2011) G03D	C	C	C
5475 (25/01/11) T04C	C	C	C
K1288 (20/07/12)	C	C	C
Kp7 (2292) (24/02/12) M08C	C	C	C
Kp2 (8517) (30/10/11) G14C	C	C	C
2661 (30/06/11) M08C	C	C	C
8436 (04/06/12) GUSS	C	C	C
2734 (03/09/12) Q00R	C	C	C
2837 (10/09/12) G06C	C	C	C
3278 (27/09/12) G02C	C	C	C
3771 (22/10/12) G04C	C	C	C
3781 (22/10/12) H13LA	C	C	C
5173 (07/11/12) G01C	C	C	C
5202 (08/11/12) T02C	C	C	C
5364 (16/11/12) G04C	C	C	C
1077 (28/12/12) CBGE	C	C	C
Kp4 (1439) (17/03/11) G07C	C	C	C
Kp1 (3210) (21/12/10) G14C	C	C	C
Belga	C	C	C
1546 (22/03/11) G02C	C	C	C
K1257 (13/07/12)	C	C	C
4926 (05/08/11) AP	C	C	C
5914 (24/10/11) HB	C	C	C
0800 (23/02/11) G05C	C	C	C
5761 (02/02/11) Q00R	C	C	C
Kp3 (0568) (23/11/11) G05C	C	C	C
K1057 (04/04/12)	C	C	C
3212 (16/04/12) T03C	C	C	C
9799 (12/04/12) G07C	C	C	C
6286 (15/12/12) G02C	C	C	C
5895 (29/10/12) GUSS	C	C	C
Kp6 (2009) (03/02/12) Q00R	C	C	C



	10	20	30
I670 (29/04/10) GUSS Ancestral	A	T	T
7823 (21/01/11) M08C	A	T	T
0789 (23/02/11) G10C	T	C	C
RVC (02/07/12)	G	G	G
8535 (07/11/11) G03D	N	N	N
7106 (29/07/11) T01C	N	N	N
Kp9 (3472) (01/03/12) G01R	A	A	A
0104 (04/05/12) T03C	A	C	C
Kp5 (1562) (07/03/12) G06D	A	C	A
1215 (28/12/10) G13C	A	C	A
8678 (29/12/10) G05C	G	G	G
5047 (10/01/11) T01C	G	G	G
9430 (25/01/11) G03D	G	G	G
0001 (07/02/11) G06D	G	G	G
1637 (08/02/11) GUSS	G	G	G
5334 (15/11/12) G03D	G	G	G
1396 (16/03/11) G01R	G	G	G
5869 (21/03/11) GUSS	G	G	G
5728 (31/05/11) HB	G	G	G
1541 (02/09/11) AP	G	G	G
5737 (28/09/11) GUSS	G	G	G
0025 (18/10/11) GUSS	G	G	G
2241 (27/01/12) G03D	G	G	G
0325 (16/02/12) G05D	G	G	G
K956 (23/01/12)	G	G	G
K1035 (13/03/12)	G	G	G
K1059 (09/04/12)	G	G	G
K1075 (25/04/12)	G	G	G
K1115 (15/05/12)	G	G	G
Kp8 (2307) (10/01/12) T05C	G	G	G
Kp10 (6219) (11/01/11) T03C	G	G	G
K1202 (25/06/12)	G	G	G
K946 (26/12/11)	G	G	G
5383 (27/06/2011) G03D	G	G	G
5475 (25/01/11) T04C	G	G	G
K1288 (20/07/12)	G	G	G
Kp7 (2292) (24/02/12) M08C	G	G	G
Kp2 (8517) (30/10/11) G14C	T	T	T
2661 (30/06/11) M08C	G	G	G
8436 (04/06/12) GUSS	G	G	G
2734 (03/09/12) Q00R	G	G	G
2837 (10/09/12) G06C	G	G	G
3278 (27/09/12) G02C	G	G	G
3771 (22/10/12) G04C	G	G	G
3781 (22/10/12) H13LA	G	G	G
5173 (07/11/12) G01C	G	G	G
5202 (08/11/12) T02C	G	G	G
5364 (16/11/12) G04C	G	G	G
1077 (28/12/12) CBGE	G	G	G
Kp4 (1439) (17/03/11) G07C	G	G	G
Kp1 (3210) (21/12/10) G14C	T	T	T
Belga	T	T	T
1546 (22/03/11) G02C	T	T	T
K1257 (13/07/12)	T	T	T
4926 (05/08/11) AP	T	T	T
5914 (24/10/11) HB	T	T	T
0800 (23/02/11) G05C	T	T	T
5761 (02/02/11) Q00R	T	T	T
Kp3 (0568) (23/11/11) G05C	T	T	T
K1057 (04/04/12)	T	T	T
3212 (16/04/12) T03C	T	T	T
9799 (12/04/12) G07C	T	T	T
6286 (15/12/12) G02C	T	T	T
5895 (29/10/12) GUSS	T	T	T
Kp6 (2009) (03/02/12) Q00R	T	T	T



Carbapenemases are broad spectrum β -
lactamases

Dynamics of Hospital outbreaks with large
colonized patient populations

Few Klebsiella pneumoniae clones

UTI account for half of the infections by
carbapenemase-producing *Klebsiella*
pneumoniae (>90% of extrahospitalary
infections)



Hospital Universitario La Paz



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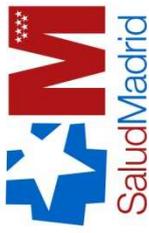
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5 May 2015

World Hand Hygiene Day

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