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Carbapenemase-Producing Enterobacteriaceae in Spain in 2012

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43

44 **Abstract**

45 We report the epidemiological impact of carbapenemases-producing  
46 *Enterobacteriaceae* (CPE) in Spain in 2012. Of the 237 carbapenemases detected 163  
47 were OXA-48 group, 60 VIM-1, 8 KPC-2, 5 IMP group, and one NDM-1. Inter-hospital  
48 spread of carbapenemase-producing *K. pneumoniae* was due to a limited number of  
49 MLST and carbapenemases types including ST15/VIM-1, ST11/OXA-48, ST405/OXA-  
50 48, ST101/KPC-2 and ST11/VIM-1. The number of CPE in Spain has increased sharply  
51 in recent years mainly due to the emergence of OXA-48.

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57           In recent years, *Enterobacteriaceae* isolates, mainly *Klebsiella pneumoniae*,  
58 have increased their potential to become extensively-drug resistant by acquiring  
59 resistance to carbapenems (1-3), mainly due to the production of carbapenemases.

60           In general, carbapenemases hydrolyze all  $\beta$ -lactam antibiotics (1-3). The most  
61 clinically important carbapenemases produced by *Enterobacteriaceae* are the class B  
62 metallo- $\beta$ -lactamases (MBLs), represented by VIM, IMP and NDM types; the class A  
63 enzymes of the KPC type; and the class D enzymes, represented by the OXA-48-type  
64 (3). In Spain, the number of reports on carbapenemase-producing *Enterobacteriaceae*  
65 (CPE) has increased in recent years (4-10). However comprehensive assessment of the  
66 impact of CPE in Spain is still missing.

67           Our Institute runs an active and unrestricted Antibiotic Resistance Surveillance  
68 Program at the national level since 2009. When this program was launched, all Spanish  
69 clinical microbiology laboratories and health-associated professionals were personally  
70 contacted and encouraged to submit their carbapenem-resistant *Enterobacteriaceae* to  
71 our antibiotic reference lab for molecular and epidemiological characterization.

72           *Enterobacteriaceae* isolates were identified by standard microbiological methods  
73 and MicroScan semiautomated system (MicroScan, Siemens Healthcare Diagnostics,  
74 Deerfield, IL, USA). If necessary, species identification was confirmed by 16S  
75 ribosomal DNA sequencing.

76           Antibiotic susceptibility testing was carried out by broth microdilution (Panel  
77 type Neg MIC 31, MicroScan) and by the disc diffusion method according to the  
78 EUCAST guidelines (11). Isolates were considered as non-susceptible to carbapenems  
79 if they were either resistant or intermediate to at least one of the three carbapenem  
80 antibiotics tested (imipenem, meropenem, and ertapenem) according to EUCAST

81 breakpoints (11). A modified Hodge test using an ertapenem disk was performed on all  
82 isolates. Inhibition of carbapenemase activity was carried out by comparing the  
83 inhibition zones obtained from ertapenem disks, with or without EDTA (10 µL 0.5 M  
84 solution) and phenyl-boronic acid (400 µg).

85 The presence of genes encoding carbapenemases *bla*<sub>KPC</sub>, *bla*<sub>VIM</sub>, *bla*<sub>IMP</sub>, and  
86 *bla*<sub>NDM</sub> was confirmed by PCR and DNA sequencing (5,12,13). Specific primers for  
87 PCR amplification and sequencing of *bla*<sub>OXA-48 like</sub> genes were designed according to  
88 GenBank (National Center for Biotechnology Information, National Institutes of Health,  
89 Bethesda, MD, USA) database entry AY236073 (OXA-48-TOT-F 5' -  
90 TGCGTGTATTAGCCTTATCG- 3'; OXA-48-TOT-R: 5' -  
91 TTTTTCCTGTTTGAGCACTTC- 3').

92 Multi-locus sequence type (MLST) was determined in all carbapenemase-  
93 producing *K. pneumoniae* according to the Institut Pasteur scheme  
94 (<http://www.pasteur.fr/recherche/genopole/PF8/mlst/Kpneumoniae.html>; May 2013,  
95 data last accessed). *E. coli* isolates were typed by MLST according to the University  
96 College Cork (Cork, Ireland) scheme (<http://mlst.ucc.ie/mlst/dbs/Ecoli>; May 2013, data  
97 last accessed).

98 During 2012, 357 isolates of *Enterobacteriaceae* non-susceptible to  
99 carbapenems were studied in detail, only one isolate per patient was considered. They  
100 came from 49 Spanish hospitals (about 20% of all Spanish microbiology laboratories)  
101 located in 24 geographic areas. The estimated catchment population was about 21.5%,  
102 corresponding to approximately 10.5 millions. Of these 357 isolates, 237 (66.4%) had a  
103 carbapenemase gene positively identified and distributed as follows: 203 (74.4%)  
104 carbapenemases identified in 273 carbapenems non-susceptible *K. pneumoniae* isolates;  
105 6 (75%) in 8 *Klebsiella oxytoca*; 16 (36.4%) in 44 *Enterobacter cloacae*; 2 (25%) in 8

106 *Enterobacter aerogenes*; 4 (22.2%) in 18 *Escherichia coli*; and 6 (100%) in 6 single  
107 isolates of *Serratia marcescens*, *Morganella morganii*, *Citrobacter freundii* and  
108 *Enterobacter* spp (Table 1).

109 One hundred and forty-nine (62.9%) isolates were from males and 76 (32.1%)  
110 from patients  $\geq$  65 years old. Of the 237 CPE, 162 (68.4%) produced clinical infections:  
111 71 (43.8%) urinary tract infections (UTI), 37 (22.8%) blood infections, 28 (17.3%)  
112 respiratory tract infections, 13 (8%) wound infections, and 13 (8%) other infections.  
113 The remaining 75 isolates (31.6%) were obtained from carriers, mainly from rectal  
114 samples.

115 The carbapenemases detected were: 163 OXA-48 group (84 OXA-48 and 79  
116 OXA-245), 60 VIM-1, 8 KPC-2, 5 IMP group (2 IMP-22 and 3 IMP-8), and one NDM-  
117 1 (Table 1). These CPE came from 30 Spanish hospitals (average of 8.1 CPE per  
118 hospital, range 1-83) located in 14 geographic areas. Six hospitals had more than 10  
119 CPE cases; the remaining 24 hospitals had between one and nine cases.

120 Susceptibility to carbapenem antibiotics is depicted in Table 2; all  
121 carbapenemase-producing isolates were ertapenem non-susceptible, but of the OXA-48  
122 like and VIM-1 producers, 66.3% and 15% were susceptible to imipenem, respectively.

123 From 2009 to 2012, we observed an increase in the number of CPE isolates  
124 submitted to the surveillance program: 15 isolates in 2009, 38 in 2010, 112 in 2011 and  
125 237 in 2012 (sixteen-fold increase). The number of hospital submitting cases increased  
126 from 6 in 2009 to 30 in 2012 (five-fold increase) (Figure 1). Although VIM-1 was the  
127 first carbapenemase described in Spain (14), its frequency has been widely surpassed by  
128 the abrupt emergence of OXA-48 in the last two years (Figure 1).

129 The frequency and distribution of carbapenemases are distinct in different  
130 countries. A rapid dissemination of KPC-producing *K. pneumoniae* was first noticed in

131 the United States (3). Later, isolates producing KPC-2 and KPC-3 also emerged in Latin  
132 America, Israel and Greece (1,3). A recent study showed that KPC enzymes were the  
133 most common (89.5%) found in Italy (15). Outbreaks caused by OXA-48-producing *K.*  
134 *pneumoniae* have been described in several countries (1,3,16).

135 According to our data, OXA-48 is by far the most common carbapenemase type  
136 circulating in Spain in *K. pneumoniae* (75.4% in this study), followed by VIM (19.7%).  
137 (Table 1). The carbapenemase-producing *K. pneumoniae* belonged to 12 different  
138 sequence types (STs) (Table 3), although most of them (88.7%) were carried by four  
139 major clones: ST11, ST15, ST16 and ST405. ST11, ST15, and ST16 have been  
140 described previously associated to different outbreaks due to ESBLs or carbapenemase-  
141 producing *K. pneumoniae* (1,7,9,17). ST405 was recently associated with OXA-48  
142 production in Spain and Belgium (7,8,16), and was found in this study in eight hospitals  
143 from three geographic regions. These data may suggest that ST405 has been established  
144 in Spain and contributes to the dissemination of OXA-48.

145 The most common ST/carbapenemase associations found are detailed in Table 3.  
146 Only two STs carried more than one type of carbapenemase: ST11 (OXA-48, OXA-  
147 245, VIM-1, KPC-2 and NDM-1) and ST15 (VIM-1 and OXA-48). It should be  
148 emphasised the apparent capacity of ST11 to carry and disseminate different types of  
149 carbapenemases (1,7,17).

150 The four carbapenemases-producing *E. coli* belonged to four different STs:  
151 ST10, ST226 and ST1152 with one case each of VIM-1, and ST131 that produced  
152 OXA-48.

153 Our results are based on a large representative sample of Spanish CPE cases, but  
154 reporting of CPE is not mandatory in this country so far. Recent global data about the



155 spread of CPE in Spain are not available; one multicenter study carried out in 2009 in  
156 Spain detected only 43 CPE, mainly VIM-1 and IMP-22 (5).

157         Only 13.5% of the isolates producing carbapenemases in this study were *K.*  
158 *pneumoniae* or *E. coli* isolated from blood suggesting that EARS-Net  
159 ([http://www.ecdc.europa.eu/en/activities/surveillance/EARS-](http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx)  
160 [Net/database/Pages/database.aspx](http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx)) may underestimate the occurrence of carbapenem-  
161 resistant *Enterobacteriaceae*. From 2011 to 2012, imipenem-non susceptible *K.*  
162 *pneumonia* has increase from <1% to 1.7% according to Spanish EARS-Net databases  
163 (unpublished data); similarly, according to Surveillance Program data depicted in Figure  
164 1, the number of carbapenemase-producing *Enterobacteriaceae* more than doubled  
165 between 2011 and 2012.

166         It is remarkable that, from 2009 to 2012, the number of hospitals reporting CPE  
167 increased five times. This fact that may suggest that a recent epidemiological change  
168 may have occurred in this country, characterised by a rapid increase in the number of  
169 cases of CPE causing both nosocomial outbreaks and single infections (Table 3). A  
170 second significant factor explaining this trend may be that hospitals have increased  
171 awareness of CPE.

172         In summary, our data suggest that the impact of CPE in Spain has dramatically  
173 increased in the last years. Inter-hospital spread of several *K. pneumoniae*  
174 clone/carbapenemase combinations have been detected in this study, mainly  
175 ST15/VIM-1, ST11/OXA-48, ST405/OXA-48, ST101/KPC-2 and ST11/VIM-1. To  
176 address the emergence and spread of CPE, urgent measures are required, including early  
177 detection and the rapid implementation of control measures.

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179

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266 **Table 1.** Distribution of carbapenemase-producing *Enterobacteriaceae* in 2012 in Spain  
 267 according to the national surveillance program of the Instituto de Salud Carlos III.

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<b>Species</b>	<b>Isolates with CBP<sup>a</sup></b>	<b>OXA-48- group</b>	<b>VIM group</b>	<b>KPC group</b>	<b>IMP group</b>	<b>NDM group</b>
<i>K. pneumoniae</i>	203 (85.6)	153	40	6	3	1
<i>K. oxytoca</i>	6 (2.5)	0	6	0	0	0
<i>E. cloacae</i>	16 (6.8)	7	6	1	2	0
<i>E. aerogenes</i>	2 (0.8)	2	0	0	0	0
<i>E. coli</i>	4 (1.7)	1	3	0	0	0
<i>S. marcescens</i>	1 (0.4)	0	0	1	0	0
<i>M. morgannii</i>	1 (0.4)	0	1	0	0	0
<i>C. freundii</i>	1 (0.4)	0	1	0	0	0
<i>Enterobacter spp.</i>	3 (1.3)	0	3	0	0	0
<b>Total</b>	<b>237</b>	<b>163</b>	<b>60</b>	<b>8</b>	<b>5</b>	<b>1</b>

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 271  
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<sup>a</sup>CBP: carbapenemases

273 **Table 2.** Susceptibility to carbapenem antibiotics in carbapenemase-producing  
 274 *Enterobacteriaceae* isolated in Spain (2012).

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Carbapenemase type	Carbapenem	Range <sup>a</sup>	MIC <sub>50</sub> <sup>a</sup>	MIC <sub>90</sub> <sup>a</sup>	%S	%I	%R
<b>OXA-48 like</b>							
<b>(n=163)</b>							
	Ertapenem	2->4	4	>4	0	0	100
	Imipenem	≤1->8	2	>8	66.3	20.2	13.5
	Meropenem	≤1->8	4	>8	30	47.9	22.1
<b>VIM-1</b>							
<b>(n=60)</b>							
	Ertapenem	1->4	4	>4	0	10	90
	Imipenem	≤1->8	4	>8	15	55	30
	Meropenem	≤1->8	8	>8	18.3	40	41.7
<b>IMP-like</b>							
<b>(n=5)</b>							
	Ertapenem	4->4	>4	>4	0	0	100
	Imipenem	≤1-2	2	2	100	0	0
	Meropenem	2->8	8	>8	20	60	20
<b>KPC-like</b>							
<b>(n=8)</b>							
	Ertapenem	>4->4	>4	>4	0	0	100
	Imipenem	4->8	4	>8	0	75	25
	Meropenem	2->8	8	>8	25	25	50

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277 <sup>a</sup> Expressed in µg/mL.

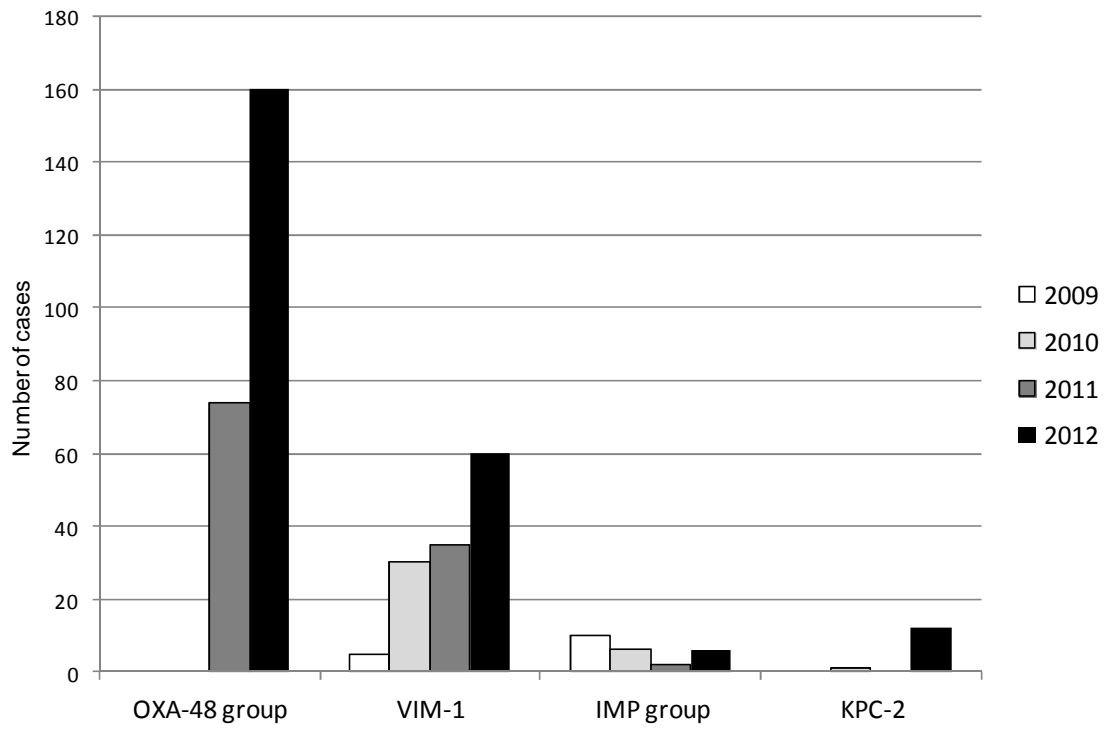
278 %S: Percentage of susceptible isolates according to EUCAST breakpoints.

279 %I: Percentage of intermediate isolates according to EUCAST breakpoints.

280 %R: Percentage of resistant isolates according to EUCAST breakpoints.

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282 **Figure 1.** Yearly evolution (2009-2012) of carbapenemase-producing  
283 *Enterobacteriaceae* in Spain and number of individual hospitals reporting cases to the  
284 national surveillance program of the Instituto de Salud Carlos III.



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291 **Table 3.** Distribution of *Klebsiella pneumoniae* MLST clones producing  
292 carbapenemases in Spain in 2012 according to the national surveillance program of the  
293 Instituto de Salud Carlos III.

294

<b>ST</b>	<b>Carbapenemase</b>	<b>Number of Cases</b>	<b>Number of Hospitals</b>	<b>Geographic sources</b>
11	OXA-245	76	1	Málaga
	VIM-1	14	6	Madrid, Guadalajara
	OXA-48	12	7	Madrid
	KPC-2	3	3	Madrid, Ciudad Real
	NDM-1	1	1	Alicante
15	VIM-1	15	4	Madrid, Barcelona, Ávila
	OXA-48	4	2	Madrid, Málaga
405	OXA-48	38	8	Madrid, Barcelona, Guadalajara
16	OXA-48	17	2	Asturias
147	VIM-1	5	1	Alicante
340	VIM-1	5	1	Madrid
437	OXA-245	3	1	Málaga
101	KPC-2	3	2	Madrid
464	IMP-8	3	1	Almeria
846	OXA-48	2	1	Madrid
13	OXA-48	1	1	Barcelona
1235	VIM-1	1	1	Guadalajara

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