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Evolution of carbapenemase-producing Enterobacteriaceae at the global and national level: What should be expected in the future?

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ABSTRACT

Keywords:

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In recent years, Enterobacteriaceae isolates have increased their potential to become highly drug resistant by acquiring resistance to carbapenems, primarily due to the production of acquired carbapenemases. The carbapenemases detected in Enterobacteriaceae are largely of the KPC, VIM, NDM, IMP and OXA-48 types. Although the epidemiological origin and geographic distribution of carbapenemases are clearly different, they all first appeared in the late 20th Century. Only a decade later, these enzymes have already become established and have expanded globally.

An important epidemiological change has occurred in Spain in recent years, characterized by a rapid increase in the number of cases of carbapenemase-producing Enterobacteriaceae (CPE), causing both nosocomial outbreaks and single infections. The impact of CPE in Spain is primarily due to OXA-48-producing and VIM-1-producing *Klebsiella pneumoniae* isolates, although other species such as *Escherichia coli* and *Enterobacter cloacae* are also increasing.

The emergence of CPE as a cause of community-onset infections is a matter of great concern. Taking into account recent experience, and considering the fact that increasing numbers of patients are becoming infected by CPE and reservoirs of carbapenemases are growing globally, the trend of the CPE epidemic points toward a rise in its incidence.

To prevent a massive CPE pandemic, a well-coordinated response from all health professionals and national and supranational authorities is clearly needed.

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Evolución de las enterobacterias productoras de carbapenemasas a nivel global y nacional: ¿qué deberíamos esperar en el futuro?

RESUMEN

Palabras clave:

Carbapenemasas
Enterobacterias
Diseminación

En los últimos años, los aislamientos clínicos de enterobacterias resistentes a múltiples antibióticos, incluyendo los antibióticos carbapenémicos, han aumentado debido principalmente a la producción de carbapenemasas. Las principales carbapenemasas detectadas en enterobacterias pertenecen a los tipos KPC, VIM, NDM, IMP y OXA-48. Aunque el origen epidemiológico y la distribución geográfica de las diferentes carbapenemasas son diversos, todas aparecieron en los últimos años del siglo XX. Solo una década más tarde, estas enzimas ya se han establecido y expandido a nivel mundial.

En España se ha producido un importante cambio epidemiológico en los últimos años caracterizado por un aumento rápido del número de casos de enterobacterias productoras de carbapenemasas (EPC), causando tanto brotes nosocomiales como infecciones esporádicas. En la actualidad, el mayor impacto de las EPC en España es debido a las cepas de *Klebsiella pneumoniae* productoras de OXA-48 o VIM-1, aunque la prevalencia de otras especies como *Escherichia coli* y *Enterobacter cloacae* también está aumentando.

La aparición de EPC como causa de infecciones de inicio en la comunidad es un asunto de gran preocupación. Teniendo en cuenta las últimas tendencias detectadas y el aumento de los reservorios de carbapenemasas a nivel mundial, la evolución futura de la incidencia de las EPC no parece ser otra que la del aumento tanto en infecciones nosocomiales como en las adquiridas en la comunidad.

Para prevenir una pandemia por EPC es necesaria una respuesta rotunda, bien coordinada y protocolizada de todos los profesionales sanitarios y autoridades nacionales y supranacionales implicadas.

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Evolution of beta-lactam resistance in Enterobacteriaceae

Since beta-lactam antibiotics became available for the treatment of Gram-negative infections, the greatest threat to these antibiotics has been beta-lactamase production. At the beginning of 21st Century, the primary concern regarding antimicrobial resistance in Enterobacteriaceae was the development and spread of resistance to third-generation cephalosporins due to the increase of extended-spectrum beta-lactamase (ESBL). ESBL producers now exist globally and have a great clinical impact because they frequently show co-resistance to other antibiotic families such as aminoglycosides and fluorquinolones.¹

According to the European Antibiotic Resistance Net (EARS-Net), resistance to third-generation cephalosporins in invasive isolates of *Escherichia coli* has increased in Spain from 0.5% in 2001 to 13.9% in 2013 (http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx). ESBLs have expanded globally through both mobile genetic elements and clonal expansion, making the eradication of these enzymes difficult. A mechanism of resistance, once it has widely spread and has exceeded a certain threshold, appears impossible to eradicate.² In recent years, concern has resurfaced due to the emergence of enzymes capable of degrading carbapenems, the only remaining beta-lactams effective against ESBL-carrying bacteria.

Carbapenems have been considered one of the first-line antibiotics for the treatment of severe infections due to ESBL-producing Enterobacteriaceae. Consequently, the burden of third-generation resistance in these bacteria has been followed by a significant increase in carbapenem use.³⁻⁶ Growing carbapenem use has selected for resistance to these antibiotics, leading to the emergence of extensively drug-resistant (XDR) strains. The emergence of carbapenem resistance during treatment has been reported due to the combination of ESBLs and/or cephalosporinases and decreased drug permeability.⁷ Most of these isolates are unique, with limited clonal dissemination, making them less competitive in the absence of antibiotics. However, the greatest current threat concerning antimicrobial resistance is the rapid dissemination of XDR Enterobacteriaceae, primarily *Klebsiella pneumoniae* strains, producing carbapenemases encoded by transmissible plasmids.⁸ We have recently observed the evolution from sporadic and anecdotal cases to a universal spread of various enzymes from diverse genetic origins able to hydrolyze carbapenems.

This article aims to describe the global evolution of carbapenemase-producing Enterobacteriaceae (CPE), focusing particularly on Spain (Figs. 1 and 2). The tracking of carbapenemase expansion by type has been developed according to published data; the rates of resistance in some countries might be underestimated due to the lack of organized reporting structures and limited resources.⁹ In addition, the frequent epidemic nature of these CPE strains can significantly influence the local prevalence data.

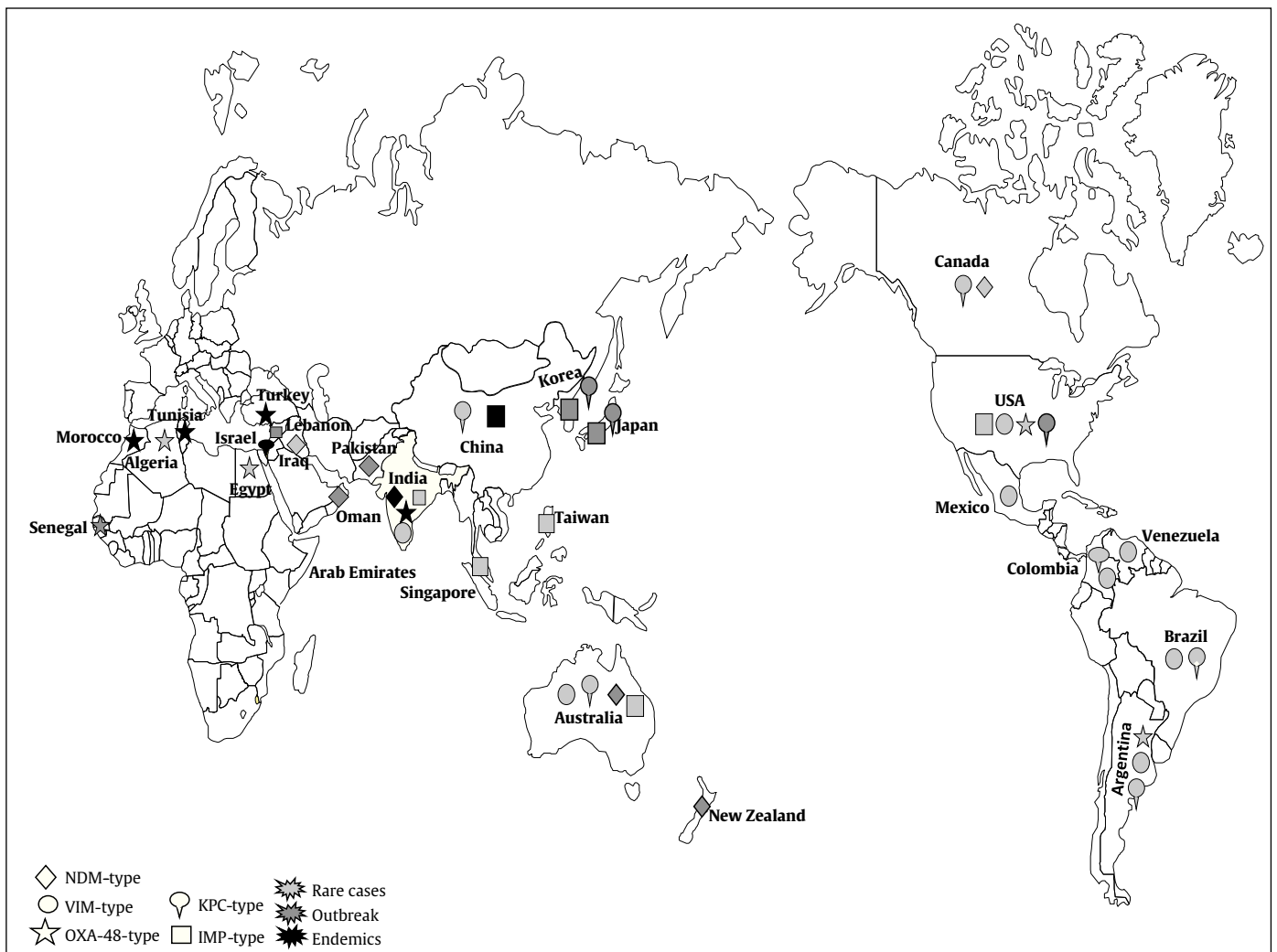


Figure 1. Representation of the global distribution of carbapenemase-producing Enterobacteriaceae. European data are shown in Figure 2.

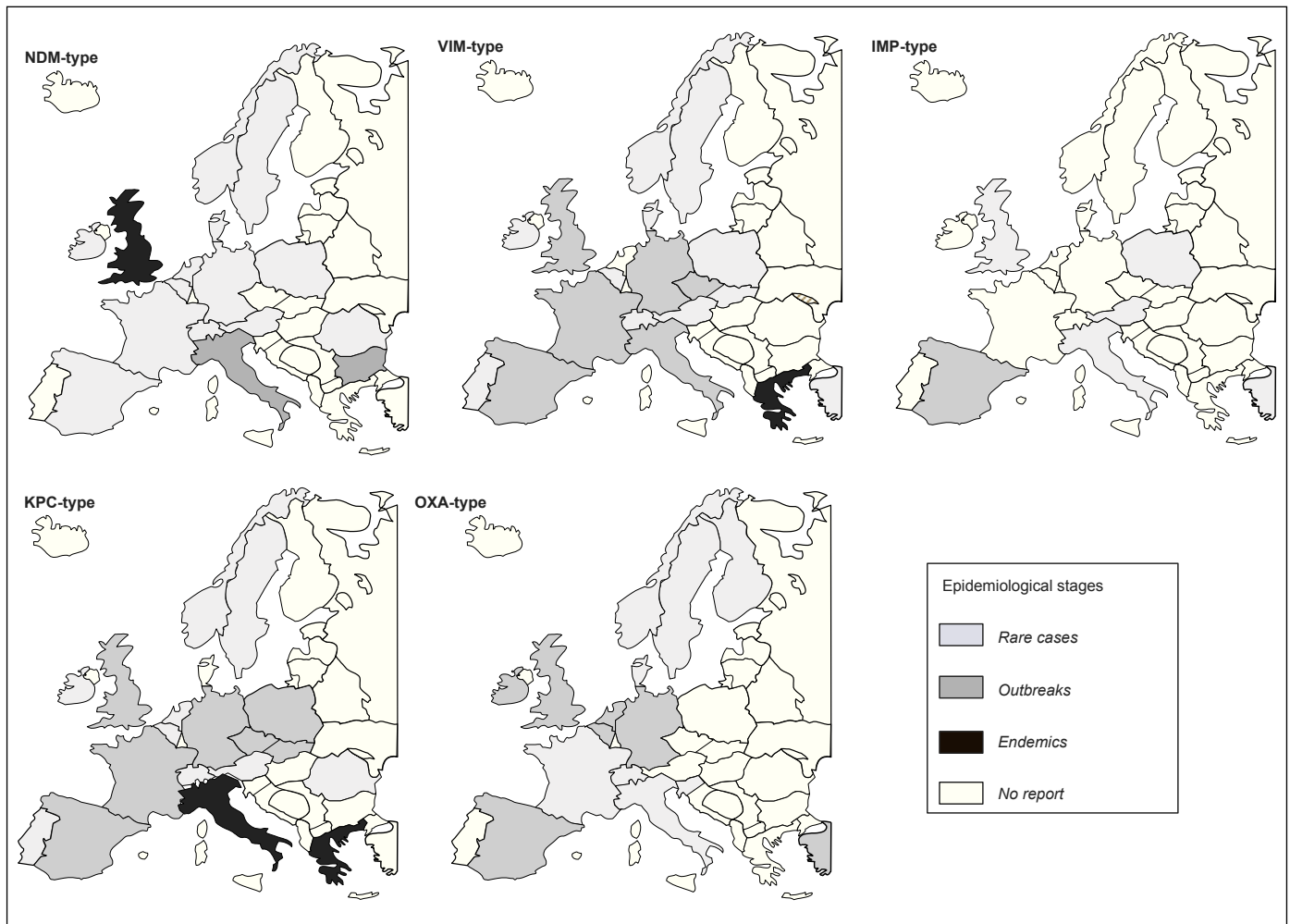


Figure 2. Representation of the European distribution of carbapenemase-producing Enterobacteriaceae.

Global evolution of class A carbapenemase-producing Enterobacteriaceae

Among the various types of class A carbapenemases described (KPC, GES, NMC-A, IMI, SME, SFC and BIC), only 2, the KPC and GES enzymes, have become an important epidemiological issue. They have been reported in various plasmids, clones and enterobacterial species. Genes encoding the remaining class A carbapenemases appear to have only a chromosomal location, and they have been reported in such species as *Enterobacter* spp. (bla_{NMC-A} and bla_{IMI}), *Serratia* spp. (bla_{SME} and bla_{SFC}), and *Pseudomonas* spp. (bla_{BIC}).^{8,9}

Sixteen subtypes of KPC carbapenemases have been reported. KPC-2 and KPC-3 have been the types most frequently found in Enterobacteriaceae, primarily in *K. pneumoniae*. KPC enzymes have been detected in a large number of *K. pneumoniae* sequence types (ST), although the majority belongs to ST14 or ST258.^{9,10}

The first KPC-producing *K. pneumoniae* strain was reported in the northeastern part of the United States in 2001.^{2,11} Five years later, various hospitals in the New York area reported nosocomial outbreaks of KPC-producing *K. pneumoniae*, with one finding a prevalence rate as high as 24%; whereas, in the same area, 0.5% of *E. coli* strains acquired this enzyme.^{9,11} At the same time, isolates carrying KPC were reported in South America, Israel and China. In Colombia, the prevalence of KPC-producing strains has been increasing since 2006, including nosocomial outbreaks in which 30% of hospital patients have been affected.^{12,13} In Brazil, Monteiro et al¹⁴

reported the first KPC-2-producing *K. pneumoniae* strain in 2006, and only two years later the expansion of this enzyme had affected various hospitals in different areas, with a prevalence of approximately 6%.¹⁵ In Israel, Leavitt et al¹⁶ studied 51 carbapenem-resistant *K. pneumoniae* isolates collected from January 2004 to December 2006. The pulsed-field gel electrophoresis results of this study revealed a major clone (affecting 31 cases, 60%), with a pattern similar to the pandemic clone ST258 described in the USA outbreaks.¹⁶ These data suggest importation from the USA to Israel, but it could not be proven.² In contrast, the prevalence of KPC remained low in Argentina¹⁷ and China¹⁸ in 2007.

In Europe, the first KPC-producing strain was reported in Greece in 2008,¹⁹ where KPC-carbapenemases have since become endemic.^{2,20} In fact, 89.5% of 270 carbapenem-resistant Enterobacteriaceae isolates were KPC producers according to a national survey carried out in 2011.²¹ Multihospital outbreaks have also been reported in Italy, where KPC-producing *K. pneumoniae* have had a rapid and extensive dissemination.^{22,23} In Northern and Western European countries, KPC prevalence remains low. In these countries, most reports concern sporadic outbreaks introduced by patients from high-prevalence areas.^{10,24}

GES enzymes with carbapenemase activity (GES-2, GES-5, GES-6, GES-12, GES-13, GES-14, GES-16, GES-18 and GES-20) have primarily been recovered from *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.^{25,26} Nevertheless, few Enterobacteriaceae strains carrying these enzymes have been reported. Jeong et al²⁷ noted in 2004 a

nosocomial outbreak due to GES-5-producing *K. pneumoniae* in the Republic of Korea.

Global evolution of metallo-beta-lactamase-producing (MBL) Enterobacteriaceae

The more geographically widespread MBLs include IMP, VIM and NDM.⁹

To date, 48 IMP variants have been reported (<http://www.lahey.org/Studies/>), primarily in *P. aeruginosa* from Asia. The first IMP-producing Enterobacteriaceae strain was a *Serratia marcescens* strain carrying *bla*_{IMP-1}, isolated in Japan in 1991.²⁸ Also in Japan, IMP-1 and IMP-2 enzymes have been described in various Enterobacteriaceae species such as *Citrobacter freundii*, *Morganella morganii* and *Enterobacter cloacae*, with a prevalence of approximately 5%.²⁹ IMP-producing Enterobacteriaceae strains have also been reported in Australia, where in 2004 a prospective study revealed 19 isolates recovered from 16 patients: *S. marcescens* (10 isolates), *K. pneumoniae* (4 isolates), *P. aeruginosa* (3 isolates), *E. coli* (1 isolate) and *E. cloacae* (1 isolate).³⁰ A number of sporadic cases of IMP-1- and IMP-4-*K. pneumoniae*-producing strains have been reported in Singapore and China, respectively¹⁰. In Europe, IMP-producing Enterobacteriaceae strains have been found in Turkey (*K. pneumoniae* and *E. cloacae*),³¹ the United Kingdom (*K. pneumoniae*), and Poland (*K. pneumoniae*).² Among the IMP-producing *K. pneumoniae* isolates, the predominant ST was ST11, related to IMP-1 and IMP-8.^{32,33} ST11 is frequent in *K. pneumoniae*, primarily in ESBL –or plasmid-AmpC– producing strains. Nevertheless, other STs of *K. pneumoniae* have been reported to carry IMP enzymes; for example, IMP-35 was reported in strains with sequence type ST622.³⁴

Verona integron-encoded MBLs (VIM) are reported globally, with the exception of Northern Europe and the United States, where outbreak rates remain low.²⁹ Nevertheless, VIM-producing Enterobacteriaceae isolates were frequently found in the Mediterranean area, primarily in Greece.^{2,10} The most frequently found enzymes were VIM-1 in Enterobacteriaceae and VIM-2 in *P. aeruginosa*.

The most significant public health impact due to MBLs is disease caused by NDM-producing Enterobacteriaceae, primarily the *E. coli* and *K. pneumoniae* species. This enzyme was first described in New Delhi,¹⁰ where these MBLs are now endemic.^{10,29,35} The enzyme was later reported in the Middle East.¹⁰ It is now observed sporadically in Europe, except in Great Britain, where is endemic, and Italy and the Balkans with sporadic hospital outbreaks described.^{20,35,36} Only a few cases have been reported on the American continent.³⁶ In contrast to KPC-producing *K. pneumoniae*, there are no predominant clones related to the rapid dissemination of NDM-producing strains. A variety of studies showed a great diversity of *E. coli* strains harboring the *bla*_{NDM-1} gene, although ST101 and ST131 appear to be the most frequent sequence type identified.³⁷⁻³⁹ A high number of resistance genes have been associated with NDM, including OXA-48 types, VIM-type genes, plasmid-mediated AmpC genes, ESBL genes, aminoglycoside resistance genes and sulfamethoxazole resistance genes.²⁸

Global evolution of OXA-48-like carbapenemase-producing Enterobacteriaceae

The class D carbapenemases present in Enterobacteriaceae reduce to OXA-48-related enzymes. The *bla*_{OXA-48} gene has always been reported in Enterobacteriaceae, and never in *Pseudomonas* or *Acinetobacter*; *bla*_{OXA-48} gene has primarily been found in *K. pneumoniae*, but it has also been found in *E. coli* and *E. cloacae*. The first OXA-48 producer was a *K. pneumoniae* strain isolated in Turkey in 2001, where this enzyme has persisted and caused significant nosocomial outbreaks.⁴⁰ After Turkey, the OXA-48 enzyme spread throughout the Mediterranean area, including Lebanon, Tunisia,

Egypt, Morocco and Senegal.⁴¹⁻⁴⁴ The prevalence of these enzymes is increasing in Europe (France, Germany, Spain, the Netherlands and the United Kingdom), where an increasing number of outbreaks have been reported.² The SENTRY antimicrobial surveillance program showed an increase from 3% in 2007 to 27% in 2009.⁴⁵ Only a few cases have been reported in North America,⁴⁶ however, and no OXA-48 producers have been reported in Canada.²⁸ The OXA-181 enzyme is the variant of OXA-48 most prevalent in India: among the 1445 Enterobacteriaceae strains studied between 2006 and 2007 in India, 10 (0.7%) harbored *bla*_{OXA-181}.⁴⁷ In 2008, two *bla*_{OXA-163}-producing isolates of *K. pneumoniae* and *E. cloacae* were identified in Argentina.⁴⁸ Two cases of infection caused by two genetically unrelated OXA-163-carrying *K. pneumoniae* strains were reported in Cairo, Egypt, in 2009 and 2010.⁴⁹ Another OXA-48-derivative is OXA-204 carbapenemase, thus far only reported in one *K. pneumoniae* strain isolated in Tunisia.⁵⁰

The OXA-48 enzyme has been detected in various clones of *K. pneumoniae*; however, ST101 was the sequence type most frequently described, followed by ST14, ST15, ST147 and ST395. ST395 was reported in Morocco, France and the Netherlands, indicating a clonal dissemination.⁴⁰ In the USA, the first clinical cases were associated with ST199 and ST43.⁵¹

Emergence and spread of CPE in Spain

The first cases of CPE in Spain were VIM-1-producing isolates reported in a study performed in Barcelona in 2003.⁵² One strain of *E. coli* from a urinary tract infection and one strain of *K. pneumoniae* from a fecal carrier were detected among 4,345 clinically relevant isolates and 2,398 isolates from stools, respectively.⁵²

Since this first discovery, both sporadic cases and significant outbreaks of MBL-producers, primarily concerning the VIM type, have been reported.⁵³⁻⁶¹

In 2007, the first Spanish outbreak involving VIM-1 was reported in a hospital in Madrid.⁵⁴ The *bla*_{VIM-1} gene was detected in various species, including *K. pneumoniae*, *E. cloacae*, *E. coli* and *Klebsiella oxytoca*. The clonal analysis revealed a complex population structure, including clonal and polyclonal dissemination.⁵⁴ A wide clonal spread of the VIM-1-producing *K. pneumoniae* strain belonging to ST15 was detected in another Spanish hospital in 2009.⁵⁹ Fifty-five patients from surgical wards and medical ICUs were infected and/or colonized by this clonal strain, which also produced the new ESBL SHV-134.⁵⁹ A total of 14 pediatric patients were infected by VIM-1-producing Enterobacteriaceae in 2 Spanish hospitals in Madrid (8 cases of *K. pneumoniae*, 2 of *E. coli* and 1 of *K. oxytoca*)⁵⁷ and Vizcaya (3 cases of *E. cloacae*).⁵³ VIM-1 Enterobacteriaceae producers have been progressively increasing in recent years and now constitute the second most frequent type of carbapenemase in Spain.^{62,63}

Other MBL carbapenemase types, such as IMP and NDM, are much less frequent than the VIM type, and only single cases and a few small outbreaks have been reported.^{55,62-68}

In a national multicenter survey performed in Spain in 2009, Miró et al⁵⁵ detected 10 IMP-producing Enterobacteriaceae: 9 clonal *K. pneumoniae* isolates producing IMP-22 and 1 *K. oxytoca* producing IMP-28, first described in this study.^{54,64} Conejo et al⁶⁵ described a prolonged clonal outbreak of nosocomial infections due to a strain of IMP-8-producing *K. oxytoca* in a community hospital in Seville, emphasizing that identifying and isolating the environmental reservoir was essential for eradicating this outbreak.⁶⁹ According to data from the Spanish Antibiotic Resistance Surveillance Program of the National Center of Microbiology (PVRA-CNM), the IMP-producing Enterobacteriaceae isolates submitted in 2012 were 3 IMP-8-producing *K. pneumoniae* isolates and 2 IMP-22-producing *E. cloacae* isolates (2.1% of the total CPE submitted).⁶²

Despite the concern generated by the worldwide spread of NDM-type carbapenemases, few cases have been detected in Spain.^{62,66-68}

All had an established origin in India: an *E. coli* isolate recovered from a stool specimen from a Spanish patient with diarrhea who had traveled to India;⁶⁶ an abdominal abscess due to *K. pneumoniae* in a Spanish patient after hospitalization in India for a perforated appendix;⁶⁷ and a *K. pneumoniae* isolated from urine in a three-month-old child adopted from India.⁶⁸

The emergence of the KPC type in Spain was first detected between September 2009 and February 2010 in ST384 and ST388 *K. pneumoniae* clones isolated from a tertiary hospital in Madrid, both harboring *bla*_{KPC-3}.⁷⁰ At approximately the same time, there were 3 clonally related *C. freundii* isolates detected in a nearby hospital that harbored *bla*_{KPC-2}.⁷¹ All the strains were isolated in different patients with no apparent epidemiological links. In a recent study concerning the PVRA-CNM data,⁶² 8 KPC-producing isolates were studied in 2012 (3.4% of the total CPE submitted). Six were *K. pneumoniae* belonging to ST101 and ST11 from Madrid and Ciudad Real, and the 2 remaining cases were *E. cloacae* and *S. marcescens*; all produced KPC-2 carbapenemase.⁶² The majority of the KPC-producing *K. pneumoniae* in Spain do not belong to the epidemic *K. pneumoniae* ST258 high-risk clone.^{62,70,72} A single ST258 isolate producing KPC-2 has recently been collected from a patient in Spain who had previously been hospitalized in the intensive care unit of a hospital in Greece.⁷³ In Spain, KPC prevalence in Enterobacteriaceae is low, although a few hospital outbreaks have been detected. A significant outbreak due to a KPC-3-producing *K. pneumoniae* belonging to ST512 has recently been reported in a hospital in Córdoba; the index case was a patient transferred from an Italian hospital.⁷⁴ Dissemination to other community hospitals in the same province has occurred. The current epidemiological status of KPC-producers in Spain can be characterized as "sporadic hospital outbreaks".²⁰

The greatest clinical and epidemiologic impact of CPE in Spain is due to OXA-48-producing isolates. Since their emergence in *K. pneumoniae* in 2009,⁷⁵ multidrug-resistant *K. pneumoniae* isolates producing OXA-48 carbapenemase are emerging as significant pathogens in Spain due to intra- and inter-hospital, clonal and non-clonal dissemination.^{62,75-79} The first report was of an outbreak due to the ST101 *K. pneumoniae* strain coproducing OXA-48 and CTX-M-15; the index case was a patient transferred from an ICU in a hospital in Marrakech (Morocco) to Barcelona.⁷⁵

Subsequently, several outbreaks due to various *K. pneumoniae* sequence types (primarily ST11, ST405, ST15 and ST16) were detected in various hospitals throughout the country,^{62,63,76,77} including prolonged and widespread outbreaks associated with significantly high in-hospital mortality.⁷⁷ In addition, 2 novel variants of the OXA-48-type carbapenemase, OXA-244 and OXA-245, have been reported in a single hospital in Malaga in the context of a nosocomial outbreak.⁷⁶ In 2012, 68.8% of the 237 CPE isolates submitted to the PVRA-CNM were OXA-48-like producers,⁶² and 93.8% were *K. pneumoniae*. According to this study, the OXA-48-producing Enterobacteriaceae isolates submitted to the PVRA-CNM have increased from no cases in 2010 to 160 in 2012⁶² and 523 in 2013 (unpublished data, Oteo et al).

A multicenter study performed in hospitals in the Catalonia region of Spain showed a prevalence of *K. pneumoniae* strains producing OXA-48 of approximately 2.2% (87/3.901). Clonal studies revealed five pulse types (A to E, with 76% homology). The 2 most prevalent clones were ST405 (78%) and ST101 (19%), whose strains coexpressed the *bla*_{CTX-M-15} and *bla*_{SHV-76} genes and showed resistance to aminoglycosides and fluoroquinolones.⁸⁰

Considering all the carbapenemase types, the CPE cases in Spain have quickly increased. One multicenter study performed in 2009 in 35 Spanish hospitals detected only 43 CPE cases (0.04%), primarily VIM-1 and IMP-22.⁵⁵ The data obtained from a recent Spanish study performed in 2013 with 83 hospitals participating showed a significant evolution, with a total of 379 CPE cases, chiefly OXA-48- and VIM-producing *K. pneumoniae* isolates (62% and 11.3%, respectively).⁶³

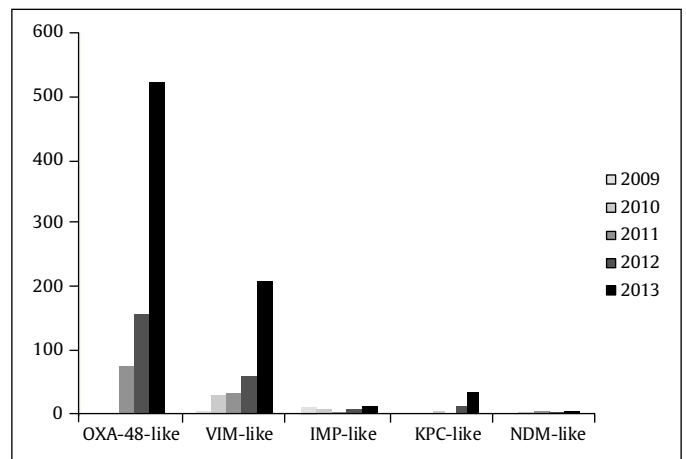


Figure 3. Yearly evolution (2009-2013) of the number of cases of carbapenemase-producing Enterobacteriaceae submitted to the Spanish Antibiotic Resistance Surveillance Program of the National Center of Microbiology. (Updated from reference 62.)

According to data from the PVRA-CNM, the number of CPE isolates submitted to this program increased from 15 in 2009 to 237 in 2012,⁶² including clinical isolates (68.4%) and isolates from carriers (31.6%). The number of hospitals submitting cases also increased from 6 in 2009 to 30 in 2012 [62]. In 2013, the CPE isolates studied by this surveillance program, including both clonal and single isolates, significantly rose to 777 CPE isolates in 57 hospitals located in 19 geographic areas (Spanish provinces) (unpublished data, Oteo et al) (Fig. 3).

Multiple epidemiologically related outbreaks occurred early in 2014 in various health districts, suggesting an inter-regional autochthonous spread and inter-institutional transmission (Table 1). This epidemiological stage of inter-regional spread is primarily due to OXA-48-producing *K. pneumoniae*, and it has quickly evolved since 2011² and February 2013,²⁰ when the Spanish situation regarding CPE was classified as "independent hospital outbreaks" and "regional spread," respectively.^{2,20}

What should be expected in the future?

The public health threat due to the global spread of CPE isolates has caught us unprepared, despite recent and similar experiences with ESBL producers. Taking into account this previous experience, and considering that infections of patients by CPE and reservoirs of carbapenemases are growing globally, the future trend of the CPE epidemic will be to increase its incidence.

Thus far, the greatest epidemiological and clinical impact of CPE has been due to nosocomial infections produced by *K. pneumoniae*. However, the prevalence of carbapenemases in *E. coli*, primarily

Table 1 Occurrence of carbapenemase-producing Enterobacteriaceae (CPE) in Spain (April 2014)

Carbapenemase types	Epidemiological stage
VIM-type	Regional spread
IMP-type	Sporadic hospital outbreaks
NDM-type	Sporadic occurrence
KPC-type	Sporadic hospital outbreaks
OXA-48-type	Inter-regional spread
All types	Inter-regional spread

According to the epidemiological scale described in reference 20.

OXA-48-producers, is increasing (PVRA-CNM unpublished data, Oteo et al).⁶³ A massive transfer of carbapenemases to *E. coli* could introduce a new situation in which a fast clonal and polyclonal spread, including in community settings, would greatly increase the threat of CPE. Of concern is the acquisition of carbapenemases by successful *E. coli* clones such as ST131, as has already occurred.^{38,81}

The ESBL situation changed greatly with the emergence of CTX-M-type beta-lactamases as a significant cause of community-onset infections. Similarly, the emergence of CPE as a major cause of community-onset infections, primarily due to OXA-48 producers, may be changing the epidemiology of CPE.

The co-production of 2 or more carbapenemases in a same isolate is increasing^{21,60} making the diagnosis and treatment of these infections more difficult.

Finally, the consumption of the few antibiotics available against infection by CPE (e.g., colistin, amikacin, tigecycline, susceptible carbapenems) is rising. The emergence of CPEs with increased MICs to carbapenems, and/or resistance to colistin and/or tigecycline could limit the therapeutic options in the near future even further.

The geographic distribution of CPE shows significant variation. Multiple factors could contribute to this varying dispersion of the carbapenemases, among which we find the genetic structures of the microorganisms themselves and human relations (mobility for economic, commercial, political or recreational purposes).

A well-coordinated and prompt response from all health professionals and national and supranational authorities is clearly needed to prevent a massive global dissemination of CPE. We have not avoided the CTX-M pandemic; will we be able to avoid a pandemic caused by CPE?

Conflicts of interest

The authors have no conflicts of interest to declare.

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