REVIEW 10.1111/j.1469-0691.2012.03821.x

Rapid evolution and spread of carbapenemases among *Enterobacteriaceae* in Europe

R. Cantón[1,2], M. Akóva[3], Y. Carmeli[4], C. G. Giske[5], Y. Glupczynski[6], M. Gniadkowski[7], D. M. Livermore[8,9], V. Miriagou[10], T. Naas[11], G. M. Rossolini[12], Ø. Samuelsen[13], H. Seifert[14], N. Woodford[9] and P. Nordmann[11]; the European Network on Carbapenemases*

1) Servicio de Microbiología and CIBER en Epidemiología y Salud Pública (CIBERESP), Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) and Hospital Universitario Ramón y Cajal, 2) Unidad de Resistencia a Antibióticos y Virulencia Bacteriana asociada al Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain, 3) Department of Medicine, Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey, 4) Division of Epidemiology, Tel-Aviv Sourasky Medical Centre, Tel-Aviv, Israel, 5) Clinical Microbiology MTC, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, 6) National Reference Laboratory for Antibiotic Resistance Monitoring in Gram-negative Bacteria, CHU Mont-Godinne, Université Catholique de Louvain, Yvoir, Belgium, 7) Department of Molecular Microbiology, National Medicines Institute, Warsaw, Poland, 8) Norwich Medical School, University of East Anglia, Norwich, UK, 9) Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency, London, UK, 10) Laboratory of Bacteriology, Hellenic Pasteur Institute, Athens, Greece, 11) Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, K.-Bicêtre, France, 12) Dipartimento di Biotecnologie, Sezione di Microbiologia, Università di Siena, Siena, Italy, 13) Reference Centre for Detection of Antimicrobial Resistance, Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø, Norway and 14) Institute for Medical Microbiology, Immunology and Hygiene, Cologne University, Cologne, Germany

Abstract

Plasmid-acquired carbapenemases in *Enterobacteriaceae*, which were first discovered in Europe in the 1990s, are now increasingly being identified at an alarming rate. Although their hydrolysis spectrum may vary, they hydrolyse most β-lactams, including carbapenems. They are mostly of the KPC, VIM, NDM and OXA-48 types. Their prevalence in Europe as reported in 2011 varies significantly from high (Greece and Italy) to low (Nordic countries). The types of carbapenemase vary among countries, partially depending on the cultural/population exchange relationship between the European countries and the possible reservoirs of each carbapenemase. Carbapenemase producers are mainly identified among *Klebsiella pneumoniae* and *Escherichia coli*, and still mostly in hospital settings and rarely in the community. Although important nosocomial outbreaks with carbapenemase-producing *Enterobacteriaceae* have been extensively reported, many new cases are still related to importation from a foreign country. Rapid identification of colonized or infected patients and screening of carriers is possible, and will probably be effective for prevention of a scenario of endemicity, as now reported for extended-spectrum β-lactamase (mainly CTX-M) producers in all European countries.

Keywords: Carbapenemases, cross-border transmission, *Enterobacteriaceae*, Europe, extended-spectrum β-lactamases, polyclonal spread
Article published online: 26 March 2012
Clin Microbiol Infect 2012; **18:** 413–431

Corresponding author: R. Cantón, Servicio de Microbiología, Hospital Universitario Ramón y Cajal, 28034-Madrid, Spain
E-mail: rcanton.hrc@salud.madrid.org

*Members of The European Network on Carbapenemases are as follows: M. Akóva (Ankara, Turkey); V. Miriagou (Athens, Greece); T. Naas, P. Nordmann, L. Poirel (Bicêtre, Paris); H. Seifert (Köln, Germany); D.M. Livermore, N. Woodford (London, UK); P. Bogaerts, Y. Glupczynski (Yvoir, Belgium); R. Cantón (Madrid, Spain); G. M. Rossolini (Sienna, Italy); C. G. Giske (Stockholm, Sweden); Y. Carmeli, S, Navon-Venezia (Tel-Aviv, Israel); Ø. Samuelsen (Tromsø, Norway); G. Cornaglia (Verona, Italy); M. Gniadkowski (Warsaw, Poland).

Introduction

Carbapenemases are enzymes that are able to hydrolyse nearly all β-lactam antibiotics, including carbapenems. They are classified into different molecular classes (A, B and D), and have become epidemiologically important in different parts of the world, including Europe, in recent years [1–4]. Most carbapenemases are plasmid-mediated, and have been mainly reported in *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Table 1).

In 2005, Walsh *et al.* [5] published a review article entitled 'Metallo-β-lactamases: the quiet before the storm?' Although they specifically reviewed the biochemical and genetic characterization of metallo-β-lactamases (MBLs), they also pointed out that the continued spread of carbapenemases worldwide would result in a clinical catastrophe and could cause a future public health crisis. Unfortunately, the current epidemiological situation in Europe confirms this prediction at a level that is even worse than expected. At the time of that review, most of the carbapenemases were confined to *P. aeruginosa*, only anecdotal reports of currently important carbapenemases such as KPCs belonging to class A [6] or OXA-48 belonging to class D [7] had been published, and NDM-1 belonging to class B had not been described [8].

In this review, we describe the evolving situation of carbapenemase-producing *Enterobacteriaceae* (CPE) in Europe, highlighting epidemiological data from representative countries.

From Extended-spectrum β-Lactamases (ESBLs) to Carbapenemases

The interest in β-lactam resistance in *Enterobacteriaceae* during the 2000s was dominated by the increase in the number of *Enterobacteriaceae* producing ESBLs, particularly the CTX-M enzymes [9]. Characterization of the genetic environment of the $bla_{CTX\text{-}M}$ genes and the respective plasmid carriers revealed the existence of efficient genetic machineries contributing to the spread of these resistance determinants. In addition, data obtained from epidemiological typing tools such as multilocus sequence typing revealed the spread of specific *Escherichia coli* and *Klebsiella pneumoniae* clones expressing ESBL phenotypes, even in the community setting [10–12]. Cumulative experience with ESBL producers supports the idea that, once the prevalence surpasses a critical threshold, their eradication from bacterial communities is nearly impossible.

At present, the interest in β-lactamases has turned to carbapenemases, particularly in *Enterobacteriaceae* [1,3,4,13]. The emergence of ESBLs and that of carbapenemases have had different epicentres, but lately they have spread to different parts of the world. ESBLs appeared almost simultaneously in Europe (Germany) and South America (Argentina), whereas carbapenemases appeared mainly in Asia (Japan and India) and North America (USA) [4]. With ESBLs, it seems that, after quiet and continuous spread, outbursts occurred in many parts of the world, including Europe [14]. This could also have been the

TABLE 1. General classification of carbapenemases and frequency of isolation

Molecular class[a] (functional group[b])	Enzymes	Inhibited by		ATM	Organisms	Gene location	Epidemiological relevance
		CLA	EDTA				
A (2f)	Sme-1 to Sme-3, IMI-1 to IMI-3, NmcA, SFC-1	±	–	R	*Serratia marcescens* and *Enterobacter cloacae*	Ch	±
	KPC-2[c] to KPC-13	±	–	R	*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*	Pl	++++
	GES-1 to GES-20	+	–	S/R	*Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii*	Pl	+
B (3)	IMP-1 to IMP-33, VIM-1 to VIM-33, NDM-1 to NDM-6, SPM-1, SIM, GIM, IND-1 to IND-7, AIM, DIM, KHM	–	+	S	*Enterobacteriaceae*, *P. aeruginosa*, and other GNNFB	Pl/Ch	±/+++
D (2df)[d]	OXA-23 group (OXA-23, OXA-27, OXA-49) OXA-24 group (OXA-24, OXA-25, OXA-26, OXA-40, OXA-72) OXA-40 group (OXA-40, OXA-143) OXA-58 OXA-48 group (OXA-48, OXA-54, OXA-181)	±	–[e]	S	*A. baumannii*, *P. aeruginosa*, *Enterobacteriaceae*	Pl/Ch	++

ATM, aztreonam; Ch, chromosomal; CLA, clavulanate; GNNFB, gram-negative non fermentative bacilli; Pl, plasmid; R, resistant; S, susceptible.
[a]Ambler classification.
[b]Bush, Jacoby and Medeiros classification.
[c]KPC-1 was later found to be identifical to KPC-2.
[d]Only class D carbapenemases representative of different groups have been included.
[e]Some OXA enzymes may be slightly inhibited by EDTA.

case with carbapenemases. Within the *Enterobacteriaceae* family, class A carbapenemases (KPC enzymes) emerged in North Carolina (USA) in 1996 and later spread to Europe; class B emerged as VIM-1 in *E. coli* in Greece, but rapidly spread in *K. pneumoniae*, becoming endemic in that country as well as in other European countries; and OXA-48 belonging to class D emerged in Turkey in *K. pneumoniae*, and later spread to other Mediterranean countries [4,15,16].

Currently, carbapenemases in *Enterobacteriaceae* are mainly found in *K. pneumoniae*, and to a much lesser extent in *E. coli* and other enterobacterial species, with a higher prevalence in southern Europe and Asia than in other parts of the world. It has recently been suggested that the future global spread of CPE will be dominated in the hospital setting by *K. pneumoniae* expressing all types of carbapenemase, mainly KPC, VIM, NDM, and OXA-48, and in the community by *E. coli* expressing NDM or OXA-type (OXA-48 and OXA-181) enzymes [4]. Moreover, as these enzymes are able to hydrolyse nearly all β-lactam antibiotics, and CPE isolates are normally resistant to non-β-lactam antibiotics, selection pressure is high, increasing the probability of persistence [17], even though efficient clones (high-risk clones) express these carbapenemases, increasing the likelihood of spread and endemicity [18].

Carbapenemases in Europe: a north–south distribution?

In a summary from a meeting on carbapenem-non-susceptible *Enterobacteriaceae* published in 2010 [16], European countries were classified into a numerical staging system according to the epidemiological situation. This scale includes: 0, no cases reported; 1, sporadic occurrence; 2a, single-hospital outbreaks; 2b, sporadic hospital outbreaks; 3, regional outbreaks; 4, interregional spread; and 5, endemic situation. At the time of that summary, July 2010, two countries each were graded 5 (Greece and Israel) and 4 (Italy and Poland), three were graded 3 (France, Germany, and Hungary), three were graded 2a (Belgium, Spain, and England/Wales), and five were graded 2b (Cyprus, The Netherlands, Norway, Scotland, and Sweden). Other European countries were graded 1 or 0. The situation changed during 2011, as the number of reports from different European countries increased dramatically. Fig. 1 shows the current situation in different European countries according to this epidemiological scale, and carbapenemase types in different countries or geographical areas.

According to the EARS-Net surveillance study (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx), antimicrobial resistance in northern European countries is lower than in southern European countries. This is true for ESBL-producing organisms as well as for methicillin-resistant *Staphylococcus aureus*, but only partially true for carbapenemase-producing *E. coli* and *K. pneumoniae* (Fig. 2). These figures indicate that different factors might be influencing the emergence and spread of carbapenemases than that of ESBLs and/or methicillin-resistant *S. aureus*. Antimicrobial use and different policies and/or implementation of infection control measures can be only partly responsible for these differences. Importation of carbapenemases from specific areas in Europe as a

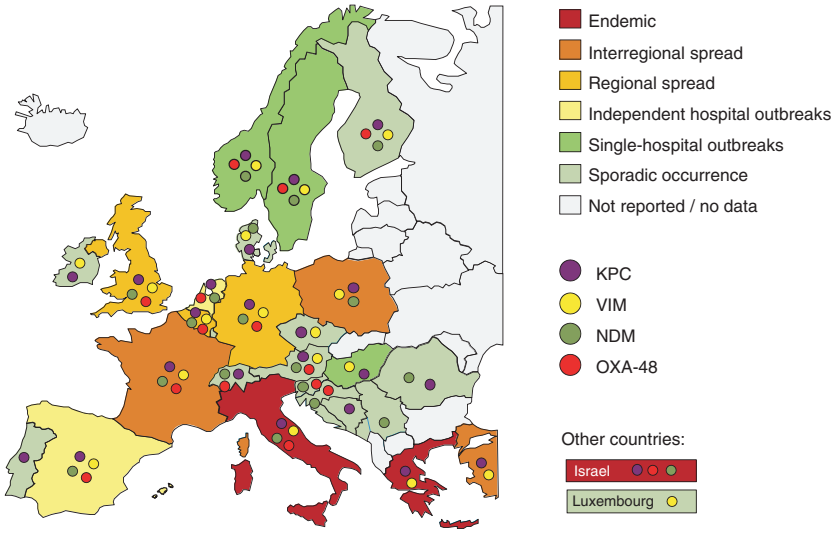

FIG. 1. European situation regarding carbapenemase-producing *Enterobacteriaceae*, using an epidemiological scale of nationwide expansion (data have been updated from reference 17) and carbapenemase types in different countries or geographical areas known until January 2012.

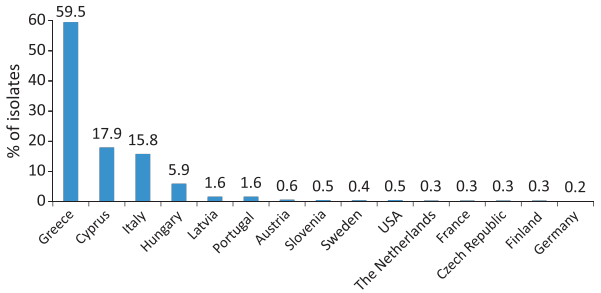

FIG. 2. Rates of non-susceptibility (intermediate plus resistant) of *Klebsiella pneumoniae* to carbapenems in European countries. Data were obtained from the EARS-Net database (2010). (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx). Only those countries with non-susceptible isolates are included.

consequence of cross-border transfer of patients, travel, medical tourism and refugees might play also an important role in this outburst [15,19,20]. This has been clearly demonstrated for carbapenemases of different molecular classes, including KPC [21,22], NDM-1 [23], and OXA-48 [24–26].

Emergence and Spread of CPE in Different European Countries

Most CPE data for Europe have come from microbiological studies carried out during the emergence of these isolates in specific countries or when describing outbreaks. These data are not always in agreement with local and supranational surveillance reports. For these studies, clinical breakpoints are used, and they do not introduce concepts to discriminate non-wild-type populations from those with high-level or low-level resistance mechanisms. This can be the case for enterobacterial isolates with low-level expression of carbapenemases [27,28].

Implementation of national guidelines for reporting multidrug-resistant (MDR) organisms may influence communication and publishing on the emergence of CPE. Some European countries have frequently reported the emergence of these isolates, whereas in others no epidemiological information is available. Nevertheless, in these countries information has became available when patients have been transferred to the former countries. This has been, for instance, the case for the detection of NDM-1 in the Balkans [15]. Moreover, countries with very active investigators have a large number of reports, despite their countries having a lower prevalence than others. This is, for instance, the case for France and UK as compared with other countries. The current information on CPE in Europe is presented below.

Greece

According to the data of the EARS-Net, Greece is the European country with the highest incidence of CPE isolates, and has been considered to be the epicentre of the spread of VIM-producing *Enterobacteriaceae*, mainly *K. pneumoniae*, to other EU countries [29,30]. Recent reports of the EARS-Net database (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx) show that up to 49% of *K. pneumoniae* invasive isolates in Greece exhibit resistance to carbapenems, but this percentage can be even higher in intensive-care units (ICUs) [31].

In November 2001, an *E. coli* strain exhibiting decreased susceptibility to carbapenems was isolated from a hospitalized patient [32]. This strain was the first CPE isolate obtained in Europe. The strain carried a self-transferable plasmid coding for VIM-1. The bla_{VIM-1} gene, along with the *aacA7*, *dhfrI* and *aadA* genes, was included as a gene cassette in a class 1 integron (In-e541). Soon, VIM-1-producing *E. coli* strains were isolated in Crete [33] with bla_{VIM-1} genes located in a class 1 integron that was different from the initially characterized one. In 2002, distinct VIM-1-producing *K. pneumoniae* strains exhibiting various carbapenem resistance levels were recovered from ICU patients in three tertiary-care institutions in Athens [34]. Since then, polyclonal outbreaks of VIM-positive *K. pneumoniae* isolates have been described in hospitals throughout the country [31,35]. The majority of the VIM producers harboured variants of a self-transmissible plasmid of the IncN family that contained In-e541[36]. Nevertheless, the bla_{VIM-1} gene was increasingly found in other replicons as well as chromosomes of enterobacterial species other than *K. pneumoniae* and *E. coli*. Also, reshuffling of the bla_{VIM} gene cassette in various class 1 integrons and the emergence of novel bla_{VIM} variants have occurred over time [37–39].

KPC-2-producing *K. pneumoniae* was first reported in Greece in 2008 [40], although the introduction of KPC-2-producing *K. pneumoniae* in this country started 1 year before, as the first outbreak occurred in Crete in 2007 [41]. Since then, the continuous spread of these isolates, later demonstrated to belong to the sequence type (ST)258 lineage [42], has led to a nationwide epidemic. The bla_{KPC-2} gene is commonly carried by plasmids of similar size (*c.* 100 kb) belonging to the FII_k incompatibility group and associated mainly with the Tn*4401*a isoform, whereas the Tn*4401*b isoform has been sporadically detected.

Today, ST258 is still predominant among KPC-positive *K. pneumoniae* isolates, but additional KPC-producing clones (ST147, ST383, ST133, ST274, and ST323, among others)

have emerged. It is of note that ongoing monitoring of carbapenem-non-susceptible *K. pneumoniae* has revealed the emergence of clones expressing both VIM and KPC enzymes, but at present their frequency of isolation is low. Also, resistance to colistin has already emerged, and pan-drug resistant isolates are being increasingly reported [43–45]. Finally, outbreaks caused by *E. coli* strains producing KPC-2 in long-term-care facilities have recently been reported [46]. These findings show the potential of the KPC-positive *Enterobacteriaceae* isolates to spread outside the hospital environment and to circulate in the community, as has occurred with VIM producers in Spain [47] (R. Cantón and P. Ruiz-Garbajosa, unpublished data). Unlike in other European countries, KPC-3, NDM and OXA-48 producers have not yet been reported in Greece.

Turkey

Resistance in Turkey is not currently recorded in the EARS-Net database. Nevertheless, in the last available data from this surveillance study before transition to the ECDC (formerly the EARSS) and corresponding to 2008, carbapenem resistance in *K. pneumoniae* was 3%, similar to that in Italy and the Balkan countries (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx). This situation, as that in other European countries, might have changed in the last few years with the increasing prevalence of CPE.

The most important carbapenemase in Turkey is OXA-48. First detected in 2001 in Istanbul in *K. pneumoniae* [7], it is now well disseminated in the Mediterranean and western European countries [4]. This class D carbapenemase has been found in different *Enterobacteriaceae*, such as *Citrobacter freundii* [48], *Providencia rettgeri*, and *Enterobacter cloacae* [49], and even in *E. coli* [50,51]. Although the majority of these descriptions were associated with single cases, important outbreaks have also been described [52]. In addition, OXA-48 has been found in patients transferred from Turkey to other European countries [24]. Further analysis of the OXA-48-producing isolates demonstrated that this enzyme was not exclusively linked with a single clone, and that the bla_{OXA-48} gene was associated with either transposon Tn*1999* or transposon Tn*1999.2* within transferable non-typeable plasmids of 70 or 150 kb [53]. Despite these observations, recent data on OXA-48-producing *K. pneumoniae* isolates in western European countries showed the dissemination of a single clone that is also found in Morocco [53]. OXA-48 producers might be also circulating in the community in Turkey (P. Nordmann, unpublished data).

MBLs in *Enterobacteriaceae* were reported in Turkey in 2003, and correspond to a VIM-5-producing *K. pneumoniae* isolate (Midilli *et al.*, KLIMIK Congress, Istanbul, Turkey, Abstract, 2003, S-21). This five amino acid substitution variant of VIM-1 might have spread rapidly, as it was also found in *Enterobacter cloacae* [54] and in *P. aeruginosa* [55] during this period. Moreover, it might have coexisted with the VIM-1 that was later reported in *P. aeruginosa* [56] and in *K. pneumoniae* [57]. Remarkably, VIM-1-producing and SHV-12-producing *K. pneumoniae* isolates were identified in Norway in a patient with a recent history of hospitalization in Turkey [58]. Other MBL detected in *Enterobacteriaceae* was IMP-1 in *K. pneumoniae* in 2003 [59] and in *Enterobacter cloacae* in 2003 and in 2004 [60]. NDM enzymes have not yet been reported in Turkey.

Israel

Before 2006, carbapenemases were rarely identified in Israel. They included a single case of VIM-producing *P. aeruginosa* in 2001 (Y. Carmeli, unpublished data), and a few cases of KPC-2 in *Enterobacter* spp. and *E. coli* [61,62]. Importation of KPC producers from the USA could not be demonstrated. In a large survey in all major Israeli hospitals conducted between 2004 and 2005, 1011 *E. coli* and *Klebsiella* isolates were tested, and none of them contained a carbapenamase [63,64]. In early 2006, small polyclonal outbreaks of KPC-2-producing *K. pneumoniae* occurred in Israeli hospitals, shortly followed by a multicentre outbreak caused primarily by a single KPC-3 clone termed clone Q as assessed by pulsed-field gel electrophoresis [65,66]. The epidemic clone Q was later shown to have a similar pattern to that of isolates implicated in large US outbreaks since the early 2000s [67], and has been shown to belong to the pandemic clone ST258, suggesting importation from the USA [68]. The nationwide nature of this outbreak was identified only in early 2007, and a national intervention to limit the spread of KPC-producing *Enterobacteriaceae* was initiated only after 1275 cases had already occurred in 27 acute-care hospitals (175 cases per million population). At the peak of the outbreak, 186 new cases were identified monthly. Indeed, the EARSS reports documented a rise of carbapenem resistance in *Klebsiella* isolates causing bacteraemia from 0% to 22% between 2005 and 2008. Following the intervention, the incidence of clinical cases of carbapenem-resistant *Enterobacteriaceae* in acute-care hospitals stabilized at 40 cases per month by mid-2008 (5.3 cases per million population per month). The outbreak and the national intervention are described in detail elsewhere [69]. In parallel, it was observed that a large reservoir

of carbapenem-resistant *Enterobacteriaceae* carriers was created in long-term-care facilities [70]. Currently, carbapenem-resistant *Enterobacteriaceae* rarely spread in the community. In almost all Israeli acute-care hospitals, the risk of acquiring CPE during a hospital stay is minimal (*c.* 1/1000 admissions); however, the endemicity is maintained by the large reservoir created in the long-term-care setting. KPC enzymes have not been detected in Gram-negative non-fermenters in Israel.

Apart from KPC, a few cases of OXA-48 and NDM-1 have been introduced into Israel by tourism [71], and single cases have been detected with no apparent foreign travel relationship.

Italy, Croatia, and Slovenia

Italy was the first European country to report acquired carbapenemases in Gram-negatives during the late 1990s. These early reports included IMP-2 from *A. baumannii* [72,73] and VIM-1 from *P. aeruginosa* [74] and *Achromobacter xylosoxidans* isolates [75], and represented the first descriptions of these enzymes. Recently, the bla_{VIM-1} determinant has been detected in a stored strain of *Pseudomonas mosselii* isolated in Italy in 1994 [76], suggesting that the influx of this carbapenemase gene in the clinical setting dates back to least the early 1990s.

The first report of CPE from Italy dates back to the early 2000s, with sporadic isolates of *K. pneumoniae* and *Enterobacter cloacae* producing VIM-4 [77]. Since then, several reports have documented the presence of various *Enterobacteriaceae* (mostly *K. pneumoniae*, *Enterobacter*, and *E. coli*) producing VIM-1-like enzymes [78–85]. However, such VIM-producing *Enterobacteriaceae* have not undergone wide dissemination, unlike that observed in Greece during the same period, and their spread remains low overall and mostly limited to sporadic cases or small clonal outbreaks, as was documented by a recent nationwide survey (G. M. Rossolini, unpublished data). Nevertheless, VIM enzymes have been associated with *E. coli* that are also associated with dissemination of ESBLs, such as ST131 [86].

A different evolution has been observed with *K. pneumoniae* producing KPC-type enzymes. Reported for the first time in late 2008, where the likely source was a medical trainee from Israel [87], KPC-producing *K. pneumoniae* has since undergone rapid and extensive dissemination in this country, with several reports of hospital outbreaks [88–95]. The abrupt and remarkable increase in carbapenem resistance rates in *K. pneumoniae* recently reported by the EARS-Net surveillance system for Italy (from 1% to 2% during the period 2006–2009 to 15% in 2010) (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx) appears to be mostly related to the countrywide dissemination of KPC-producing *K. pneumoniae*, as shown by results from a recent countrywide survey (G. M. Rossolini, unpublished data). As in Greece, multifocal emergence of colistin-resistant isolates of KPC-producing *K. pneumoniae* has been observed [92] (Giani *et al.*, 51st ICAAC, 2011, Abstract C2669b), which is a matter of major concern, as colistin is among the few drugs that retain activity against these organisms, and is a cornerstone of antimicrobial chemotherapy for infections caused by these organisms.

Most recently, isolates of *E. coli* and *K. pneumoniae* producing NDM-1 [96,97] and OXA-48 [98], of likely cross-border origin, have also been reported in Italy, but the dissemination of these carbapenemases appears to be still very limited.

Few data are available on the dissemination of acquired carbapenemases in countries bordering the eastern coast of the Adriatic Sea. Most of them are associated with *P. aeruginosa* and *Acinetobacter* [99–102], but a case of OXA-48-producing *K. pneumoniae* imported from Libya has recently been found in Slovenia [103]. It is of note that dissemination of NDM-1 is highly suspected in this area, as there are different reports of the isolation of NDM-1-producing *Enterobacteriaceae* in patients from Balkan countries but admitted to other European countries [15,104].

Spain and Portugal

As in other Mediterranean countries (Greece, Italy, and France), the first description of CPE in Spain concerned the VIM type, and was published in 2005 [105]. In this study, an *E. coli* isolate from a urinary tract infection and a *K. pneumoniae* isolate, recovered in 2003 during a surveillance study of faecal ESBL carriers in Barcelona, were shown to produce VIM-1. Since then, continuous penetration of different carbapenemases from different molecular classes has been observed, and both sporadic cases and important outbreaks have been described [106–110].

The first outbreak involving VIM-1 occurred at Ramón y Cajal University Hospital (Madrid) in 2005 and 2006 [106]. Twenty-five patients (52% from the ICU) were infected and/or colonized with single or multiple MBL-producing *Enterobacteriaceae* isolates, including *K. pneumoniae*, *E. cloacae*, *E. coli*, and *Klebsiella oxytoca*). Clonal analysis revealed a complex population structure, as all *K. pneumoniae* isolates belonged to the same clone but different patterns were found among the *Enterobacter cloacae* isolates. This complexity was even higher when the genes and plasmids surrounding

the bla_{VIM-1} gene were characterized. The bla_{VIM-1} gene was detected within a 4.0-kb class 1 integron (In113, bla_{VIM-1}–*aacA4*–*dfrII*–*aadA1*–*catB2*) in *K. pneumoniae* and *E. coli*, and within a 2.5-kb class 1 integron (In110, bla_{VIM-1}–*aacA4*–*aadA1*) in *E. cloacae* and *K. oxytoca* isolates. A 60-kb plasmid belonging to the IncI1 group was detected in the epidemic VIM-1-producing *K. pneumoniae* clone, whereas plasmids of 300 or 435 kb belonging to the IncH12 group were found among *E. cloacae* isolates. Interestingly, the *K. pneumoniae* and *E. coli* isolates also produce the ESBL SHV-12. Moreover, class 1 integrons were associated with defective Tn*402* variants also found in VIM-1-producing *P. aeruginosa* isolates from the same institution, indicating potential interspecies spread of different genetic determinants [111].

In 2009, the Spanish Network Research of Infectious Disease (REIPI) performed a surveillance study involving 35 hospitals, with the aim of investigating the epidemiology of CPE isolates in Spain (Miró *et al.*, XIV Congress of the Spanish Society of Infectious Diseaeses and Clinical Microbiology, 2010, Abstract 706). Only class B carbapenemase producers were found (VIM-1 and IMP-22) in specific areas (Madrid, Catalonia, Andalusia, and Balearic Islands), with a local prevalence of <0.2% of tested isolates. This situation might have changed, as several descriptions of outbreaks caused by VIM producers have been published since then, as well as sporadic cases affecting non-hospitalized patients [47,110–115]. One of these outbreaks was associated with the ST15 clone previously associated with the spread of CTX-M-15 in central Europe [110]. In addition, KPC-3 in *K. pneumoniae* [107], but not belonging to ST258, and KPC-2 in *C. freundii* [108], and NDM-1 in *E. coli* and *K. pneumoniae* [26,109,116] have also emerged. Very recently, an outbreak caused by a porin-deficient *K. pneumoniae* isolate co-producing OXA-48 and CTX-M-15 was recognized [26]. The index case was a patient transferred from an ICU in a hospital in Marrakech (Morocco) to Barcelona. Sequence typing study revealed that the OXA-48-producing, CTX-M-15-producing *K. pneumoniae* isolate belonged to the ST101 clone that was previously found in North African countries and that was responsible from the spread of this enzyme in other European countries [117]. All of these descriptions confirmed the dissemination of carbapenemase-producing isolates in Spain, which can even be found in hospital sewage water [118].

In Portugal, with the exception of one report of a VIM-2-producing *K. oxytoca* isolate, reports of VIM enzymes are restricted to *P. aeruginosa* [119]. KPC enzymes have not been described in clinical *Enterobacteriaceae* isolates, but a KPC-producing *E. coli* isolate was very recently found in the aquatic environment [120].

France and Switzerland

The first description of CPE in France was in 1993, i.e. NmcA in *E. cloacae* [121], the first carbapenemase to be identified in *Enterobacteriaceae*. Then, a VIM-1-producing *K. pneumoniae* isolate also co-producing SHV-5 was reported in 2004 and subsequently in a nosocomial outbreak [29,122]. The bla_{VIM-1} gene was part of a class 1 integron that also included the *aac6*, *dhfrI* and *aadA* genes, and was similar to those reported from strains isolated in Greece. The index case was a patient transferred from Greece and identified on admission as a CPE faecal carrier. This isolate spread to other patients, but was not longer isolated after implementation of infection control barrier precautions. Also, VIM-19 with extended carbapenemase activity was isolated from *E. coli* and *K. pneumoniae* from a patient transferred from Algeria [123]. VIM-1-producing isolates have rarely been reported, and have always been associated with patients transferred from Greece, whereas IMP-producing *Enterobacteriaceae* have only been isolated once in France. However, a study performed in 2010 showed penetration of VIM-1 and IMP-1 [124]. This study addressed the prevalence of MDR Gram-negative bacilli and ESBL-producing isolates in stool specimens obtained from patients hospitalized for acute diarrhoea in a university hospital during a non-outbreak situation. Surprisingly, it revealed a high prevalence of CPE faecal carriers (2.6% of patients). All isolates were *E. cloacae* with VIM-1 or IMP-1.

The first identification of NDM-1 in France was in April 2009. It corresponded to an imported *E. coli* isolate from India [125]. Subsequently, most NDM-1 cases were of Indian origin, but there were also cases from Iraq and Serbia [126,127]. In addition, in 2011, the first reported case of community-acquired NDM-1 producing CPE was identified in the southern part of France [128], and this was followed by another possible case of autochthonous acquisition [129]. NDM-1 has been found in *K. pneumoniae* by the use of real-time PCR directly in clinical samples [130,131], and with both phenotypic and molecular methods in different *E. coli* strains [132].

The first KPC-producing isolate was identified from a patient transferred directly from New York in February 2005 [21]. After that, several reports were published related to KPC importation from the USA, Israel, and Greece [30,133,134]. In France, KPC-producing *K. pneumoniae* isolates remain rare, and, to date, have always been linked to patients transferred from a country where KPC enzymes are endemic (Israel, Greece, the USA and, recently, Italy) [135]. In some cases, hospital outbreaks have been described [135],

but nosocomial regional interhospital dissemination mediated by a contaminated duodenoscope has also been reported [136,137]. Most KPC producers have been nosocomial *K. pneumoniae* ST258 isolates and, to a lesser extent, *E. coli* and other enterobacterial species [135,138]. Recently, the *E. coli* ST131 clone, the main clone responsible for CTX-M-15 diffusion in the community, was shown to harbour the bla_{KPC-2} gene along with the narrow-spectrum TEM-1 and OXA-9 β-lactamases, and the CTX-M-9 ESBL [139]. It was isolated from a urinary tract infection from a 64-year-old bedridden woman hospitalized in the gerontology ward of Lille University Hospital (France) [139]. Other class A carbapenemases have rarely been described in France. One IMI-1-producing *E. cloacae* [140] isolate and three IMI-2-producing *Enterobacter asburiae* isolates have recently been described (P. Nordmann, unpublished data).

Finally, the first OXA-48-producing isolate was a *K. pneumoniae* isolate identified in Paris in 2009 from the sputum of a patient transferred from Tunisia [141]. Subsequently, other OXA-48-producing *K. pneumoniae* isolates were found in patients transferred from countries around the Mediterranean sea (Turkey, Egypt, Algeria, Libya, Tunisia and, mostly, Morocco) [24,59,117,142–144]. They were associated with several outbreaks [145]. OXA-48 is mainly found in unrelated *K. pneumoniae* clones detected across Europe and in *E. coli* isolates associated with clones previously linked with ESBLs in patients without a history of prior hospitalization [25]. However, very recently, an identical or clonally related *K. pneumoniae* OXA-48 producer was identified in France, The Netherlands, and Morocco [53]. A point mutant derivative, OXA-181, has been isolated from patients transferred from India [146].

Since August 2001, France has implemented a mandatory national nosocomial infection notification system. The baseline reporting requires the use of strict criteria; one of them is about rare or noticeable microorganisms, depending on virulence and/or antimicrobial susceptibility (Coignard *et al.*, SHEA 15th Annual Scientific Meeting, 2005, Abstract B306). Notification of CPE to the French Institute of Health (InVS) is recommended. From 2004 to 2009, only isolated CPE cases were notified to the health authorities. Since 2009, the number of notifications per year has increased (six in 2009; 28 in 2010, and 62 in the first 9 months of 2011). A total of 104 cases have been notified (http://www.invs.sante.fr/content/download/21883/128402/version/3/file/Bilan+EPC_270911.pdf). These CPE isolates were mostly *K. pneumoniae* (59%), *E. coli* (22%), *E. cloacae* (12%), and various other enterobacterial species. The most prevalent carbapenemases were OXA-48 (51%), KPC (25%), VIM (9%), NDM (13%), IMI-1 (1%), and IMI-2 (1%). A link to foreign countries (patients transferred from foreign hospitals, previously hospitalized in a foreign country, and having undertaken recent travel to a foreign country) has been established for 76 of the cases (73%). These countries are mostly Greece, Morocco, and India. For 28 episodes, no link to a foreign country could be established, and among these, 21 involved OXA-48-like producers. These latter isolates were recovered in several parts of France, suggesting intra-country dissemination of these isolates, probably linked to the difficulty in detection of OXA-48-producing CPE isolates or to community dissemination from North Africa. These 104 episodes involved a total of 249 patients; 68 of them (29%) were infected and 170 (71%) were colonized. Most of the notifications related to single isolation of CPE, but epidemics involving up to 44 patients have also been described.

As the number of CPE cases in France remains low, in December 2010 the French health authorities implemented (Circulaire DGS/DGOS 06/12/2010 Contrôle des cas importés d'EPC; http://www.circulaires.gouv.fr/pdf/2010/12/cir_32240.pdf) guidelines in order to build a 'line of defence' based on systematic screening for MDR bacteria for every patient transferred from foreign hospitals, or with a previous hospitalization in a foreign country, or who had undertaken a recent trip to a country with high prevalence, and to maintain contact isolation and strict hygiene measures for these patients, until screening results are available. Compliance with these rules would allow the containment of many episodes to a single case.

In Switzerland, the first CPE isolate was an SME-2-producing *Serratia marcescens* strain isolated in May 2006 at the University Hospital of Lausanne, Switzerland [147]. SME-2 is a clavulanic acid-inhibited class A carbapenemase, and its gene, bla_{SME-2}, is chromosomally encoded. Subsequently, a few cases of imported KPC producers have been described. A *K. pneumoniae* isolate producing KPC-2 was probably imported as a result of the transfer of a patient from Sicily, Italy, to the Neuchâtel public hospital in Switzerland in mid-2000 [148]. Four epidemiologically unrelated cases of KPC-producing *K. pneumoniae* were identified in Switzerland between May 2009 and November 2010; three cases were transferred from Italy (two KPC-3; one KPC-2) and one from Greece (KPC-2) [149]. During analysis of the mechanisms responsible for decreased susceptibility or resistance to carbapenems in several enterobacterial isolates recovered in 2009–2010 in Geneva University Hospitals, Switzerland, three patients were found to be positive for NDM-1-producing enterobacterial isolates (one with *E. coli* and *K. pneumoniae*, one with *K. pneumoniae* only, and one with *Proteus mirabilis*) [150]. This study constitutes the first identification of NDM-1 producers in Switzerland. Interestingly, patients from whom these NDM-1-producing isolates were recov-

ered had a link to the Indian subcontinent or the Balkans. Finally, a few cases of OXA-48-producing *K. pneumoniae* identified in Geneva University Hospitals were probably transferred from North African countries (P. Nordmann and J. Schrenzel, unpublished data).

Belgium, Luxembourg, and The Netherlands

Although there is currently no mandatory reporting of carbapenem-resistant Gram-negative bacilli in Belgium, the National Reference Centre for MDR *Enterobacteriaceae* has been recording the proportion of CPE isolates detected. In 2007, only two isolates (8%) of those referred to this centre that were not susceptible to carbapanems were CPE, VIM-2 being the single carbapenemase found at that time. In 2010 and 2011, this situation rapidly changed, with 18 isolates of 94 (19.1%) referred in 2010 and 60 of 197 (30.5%) in referred 2011 being confirmed as CPE by the National Reference Centre. A variety of enzymes were found in these isolates, mainly OXA-48, VIM, and KPC. In 2010, sporadic NDM-producing isolates were detected for the first time in Belgium. The most frequent *Enterobacteriaceae* species by far was *K. pneumoniae* (69%), followed by *Enterobacter cloacae* (15%) and *E. coli* (6%). These isolates were found all over the country [151]. Although initial sporadic occurrence of CPE in Belgium was reported in patients returning from travel abroad [41,104], the majority of patients (70%) carrying CPE did not have a history of travel abroad or cross-border transfer, demonstrating potential secondary or autochthonous acquisition.

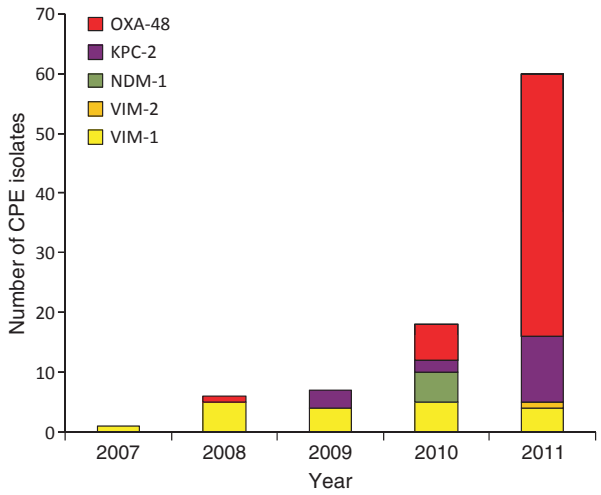

FIG. 3. Evolution of the carbapenemase-producing *Enterobacteriaceae* (CPE) isolates in Belgium (92 isolates referred to the National Reference Centre, Belgium, January 2007–December 2011) (data have been updated from reference 150).

Today, the most prevalent carbapenemase in *Enterobacteriaceae* in Belgium by far is OXA-48 (Fig. 3)[151]. Although most OXA-48-producing isolates have been found to represent asymptomatic cases in the urinary tract in elderly patients, a few cases of bacteraemia and of systemic infections have been recorded among patients in ICUs, and independent local outbreaks were reported in at least three hospitals in Belgium in 2010 and in 2011 [151–153]. In this country, carbapenemases were first detected in *Acinetobacter* (OXA-58), and later, in 2008, in *K. pneumoniae* (VIM-1), and were implicated in different nosocomial outbreaks, as in France and The Netherlands [41,151–153]. A recent study highlighted this situation, with OXA-48 enterobacterial isolates also producing ESBLs (CTX-M-9, CTX-M-15, or SHV variants) [154]. Other carbapenemases from Belgium include KPC-2, which emerged within ST258 *K. pneumoniae* in 2009 in a patient transferred from Greece [104], and NDM-1, which emerged in 2010 in non-clonally related *Enterobacteriaceae* from three patients who had been hospitalized in Pakistan, Montenegro, and Serbia/Kosovo [152]. NDM-1 was detected in all of the isolates, in addition to several ESBLs (CTX-M-15 and SHV-12), acquired AmpCs (CMY-16 and CMY-58), 16S rRNA methylases (ArmA and RmtB), and Qnr genes (*qnrA6*, *qnrB1*, and *qnrB2*). Screening for intestinal carriage of carbapenemases and strict infection control measures prevented secondary cases [152].

The situation in The Netherlands is probably similar to that in Belgium, with OXA-48 now being one of the most prevalent carbapenemases [53,155]. This enzyme was associated with an important outbreak at one hospital in Rotterdam, and was linked to a widespread ST395 *K. pneumoniae* clone also producing CTX-M-15 found in France that may have its origin in North Africa [156]. This clone has been found in a hospital in Morocco and also in the environmental setting [156]. Other carbapenemases found in The Netherlands are KPC-2 and NDM-1, both of them in *K. pneumoniae* isolates from patients with a history of travel to Greece and India, respectively [157]. In Luxembourg, as in Belgium and The Netherlands, sporadic cases of VIM-type carbapenemases (VIM-1 and VIM-27) have also been found in patients repatriated from hospitals in Greece [158] (Y. Glpczynski, unpublished data).

Germany and Austria

In the 2010 Annual report of the European Antimicrobial Resistance Surveillance Network (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx), one case was reported from Germany of invasive

infection caused by carbapenem-resistant *Enterobacteriaceae*. In 2009, the German National Reference Laboratory for Multidrug-Resistant Gram-negative Bacteria was inaugurated (Nationales Referenzzentrum für gramnegative Krankenhauserreger, Institute for Medical Microbiology, Ruhr-University Bochum; heads, S. G. Gatermann and M. Kaase). Since August 2009, microbiological laboratories in Germany have been encouraged to send Gram-negative bacilli with suspected carbapenem resistance to the national reference centre, which offers molecular characterization of resistance mechanisms of the submitted isolates. No systematic data are collected, and the data obtained do not allow prevalence rates to be determined for Germany; likewise, no denominator data and no clinical data are obtained. In 2010, the national reference centre received 808 Gram-negative bacilli with elevated carbapenem MICs, and 621 of these isolates were analysed for the presence of a carbapenemase (405 *Enterobacteriaceae*; 127 *P. aeruginosa*; 86 *A. baumannii*). Two hundred and eighty-nine of them were found to harbour a carbapenemase, whereas reduced carbapenem susceptibility in the remaining isolates was conferred by porin loss combined with either ESBL or AmpC enzymes (http://www.rki.de/cln_109/nn_2030884/DE/Content/Infekt/EpidBull/Archiv/2011/32/Tabelle.html?__nnn=true). Among CPE isolates, the majority were *K. pneumoniae* (n = 111), followed by *E. coli* (18), *Enterobacter cloacae* (17), *K. oxytoca* (6), and *C. freundii* (5). The predominant carbapenemases in the different species were as follows: in *K. pneumoniae*, OXA-48 (43%), KPC-2 (23%), and KPC-3 (23%); in *E. coli*, OXA-48 (44%) and VIM-1 (28%); in *Enterobacter cloacae*, VIM-1 (71%); and in *K. oxytoca*, VIM-1 (83%). NDM-1 was found in only two *K. pneumoniae* isolates and in two *E. coli* isolates.

Despite the dominance of OXA-48, for outbreaks in Germany only KPC-producing *K. pneumoniae* isolates have been reported, one of them also co-producing VIM-1 [159,160].

In Austria, few reports have recognized the presence of CPE [161–163]. One of them records emergence in the year 2005, with a remarkable increase in the number of involved patients in 2010. Carbapenem-resistant *Enterobacteriaceae* comprise *K. pneumoniae*, *K. oxytoca* and *E. coli* isolates with NDM, VIM, IMP, and KPC enzymes, showing the complexity of CPE. NDM-1 producers have been related to a Balkan origin.

Poland, the Czech Republic, Hungary, and Romania

According to the surveillance data collected by the National Reference Centre for Susceptibility Testing (NCRST) in Warsaw, most of the CPE isolates detected in Poland so far have been KPC producers. The first KPC-positive *K. pneumoniae* isolates reported were recovered in May 2008 in Warsaw. The isolates belonged to the ST258 clone, and produced KPC-2 together with the ESBL SHV-12. As the patient had not travelled for a long period before that time but had a history of previous hospitalization in Warsaw, it is likely that KPC producers had been present before this first report [164].

Soon thereafter, the next organisms suspected of being KPC producers were sent to the NRCST by several hospitals, and by the end of 2008, 33 unique KPC-positive isolates from 32 patients in total had been confirmed. These were 30 *K. pneumoniae* and three *K. oxytoca* isolates, and were recovered in five Warsaw hospitals, three of which experienced outbreaks. The situation developed further in 2009, with 86 non-duplicate isolates from 82 patients, these being 84 *K. pneumoniae* and two *E. coli* isolates (the *E. coli* isolates were co-isolated with *K. pneumoniae* from a single patient). Most of the patients were hospitalized in 12 centres in the Warsaw area; moreover, three outpatients and one nursing home resident were diagnosed there as well. KPC producers were also identified in six other cities, in three cases following patient transfer from Warsaw, and in one case following patient transfer from New York. The molecular analysis of all isolates collected in 2008–2009 [165] revealed that 97.4% of the *K. pneumoniae* isolates were ST258, and only sporadic isolates belonged to ST11 or ST23. The two *E. coli* strains, being likely recipients of bla_{KPC}-carrying plasmids from *K. pneumoniae*, were ST93 and ST224. Almost all of the isolates produced KPC-2; the only two exceptions, including the isolate from New York, expressed KPC-3. In all but one case, the bla_{KPC} genes were located in the Tn*4401*a transposon [166], carried by plasmids ranging from *c.* 48 to 250 kb. The most prevalent plasmids were conjugative $IncFII_K$ (*c.* 110–160 kb), identical or similar to the pKpQIL plasmid characterized in Israel [167]. The other prevalent plasmid was the non-typeable pETKp50 of *c.* 50 kb [168], with low transfer potential. Significant groups of the isolates produced the ESBLs SHV-12 and/or CTX-M-3. In general, the analysis revealed a major role of *K. pneumoniae* ST258 and pKpQIL-like molecules in the early spread of KPC-positive organisms. The diversity of the strains was attributed to several possible introductions of these into the country, their evolution during clonal dissemination, and transfer of plasmids [165].

In 2010, the NRCST confirmed 153 unique KPC-producing isolates, mostly *K. pneumoniae* (one *E. coli*). This increase was mostly attributable to the continuous spread in central Poland (region Mazowsze, including Warsaw), from where 126 isolates from 32 healthcare institutions were collected (106 isolates from 26 sites in the Warsaw area alone). Of

note was a local outbreak in another region (Świętokrzyskie) involving five hospitals in four locales, from which 19 unique isolates were confirmed in 2010. It is possible that wider implementation of the national guidelines for infection control (http://www.korld.edu.pl) helped to reduce the total number of cases confirmed to 104 in 2011. The Warsaw area continued to be the most affected; however, even more concern has been caused recently by a new outbreak in the region Podlasie (northeastern Poland), which started in February (possibly with a patient from the USA). By the end of 2011, the NRCST had confirmed 29 unique isolates from ten hospitals, including six centres in the main city Białystok, and, despite many efforts of the infection control specialists, the increase has been continuing to date (M. Gniadkowski, A. Baraniak, D. Żabicka, E. Tryniszewska, W. Hryniewicz, unpublished data).

Considering all of the data, it is clear that KPC spread has become the major issue in Poland. The total number of patients confirmed from 2008 to 2011 was 371, and it has been certainly underestimated. At least 58 hospitals in 34 locales have faced the problem, and even though the majority of these have apparently managed to control the situation, the notable number of institutions constitutes a reservoir for further spread. Of the three regional outbreaks observed, those with epicentres in Warsaw and Białystok are far from being successfully controlled.

There has been much less information concerning MBL-producing *Enterobacteriaceae* in Poland. The first such isolate reported, *K. pneumoniae* with VIM-4, was identified in 2006 in a hospital in Bydgoszcz [169] (I. Kern-Zdanowicz, M. Gniadkowski, unpublished data). In 2006–2008, the NRSCT confirmed eight MBL-positive isolates; however, in 2009, 2010, and 2011, these numbers were 22, 23, and 31, respectively (all of the isolates were collected from 39 hospitals in 24 cities). This increase may have been caused by the growing awareness of hospital laboratories regarding carbapenem resistance in enterobacteria and/or the actual dissemination of these organisms. Interestingly, the predominant species have been *Enterobacter cloacae* (50.0%), followed by *S. marcescens* (17.9%), *K. oxytoca* (16.7%), and *K. pneumoniae* (11.9%). Most of the isolates analysed so far have produced VIM-type MBLs (93.8%); three isolates had IMP types, and recently the first *E. coli* isolate with an NDM-like enzyme was recovered in Warsaw from a patient who had been moved from a hospital in the Congo (M. Gniadkowski, J. Fiett, D. Żabicka, K. Filczak, W. Hryniewicz, unpublished data).

In the Czech Republic, the situation regarding CPE is much better than in Poland; however, in 2011, the National Reference Laboratory for Antibiotics in Prague observed significant increases in the numbers of both MBL-positive and KPC-positive cases (J. Hrabák, P. Urbášková, H. Žemličková, personal communication). Regarding MBL producers, from 2009 to 2010, five VIM-1-producing isolates (four *S. marcescens* and one *Enterobacter cloacae*) were recovered from sporadic infections in Opava, Havířov (the area of Ostrava), and from a large hospital in Prague (three cases). Interestingly, in 2011, this Prague hospital recorded eight new cases, but most of these involved *K. pneumoniae* isolates with another bla_{VIM-1}-carrying integron, indicating the new emergence of VIM-1 producers in that centre. Additionally, two other hospitals reported MBL-positive *K. pneumoniae*, including one VIM-1 producer imported by a patient from Greece. Also from Greece, the first Czech patient infected with a *K. pneumoniae* ST258 KPC-2 producer was admitted to the Havířov hospital in July 2009 [170]. In 2011, 11 unique KPC-producing *K. pneumoniae* isolates were identified in five hospitals in Prague, including six isolates from an outbreak in one hospital with a patient returning from Italy. Of the remaining five cases, three were linked to the previous hospitalization in Greece.

In Hungary, a local outbreak of KPC-2-producing and SHV-12-producing *K. pneumoniae* ST258 was reported in 2008–2009 in the north-eastern part of the country; this started with a patient who had been hospitalized in Greece [171]. In 2009, single isolates of *K. pneumoniae* ST11 and *K. oxytoca* carrying the same integron with the bla_{VIM-4} gene cassette were identified in two different hospitals [145]. KPC-producing *Enterobacteriaceae* have been recently detected in Romania (Y. Carmeli, unpublished data), as well as cases of NDM producers abroad associated with travellers to this country (Ø. Samuelsen, unpublished data).

UK and the Republic of Ireland

There is no mandatory reporting of carbapenem-resistant Gram-negative bacilli in the UK. However, the Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) of the Health Protection Agency (HPA) encourages referral (see http://www.hpa.org.uk/ProductsServices/InfectiousDiseases/LaboratoriesAndReferenceFacilities/AntibioticResistanceMonitoringAndReferenceLaboratory/), and seeks carbapenemases in these: (i) if they are confirmed to be resistant to at least one carbapenem; and (ii) if that resistance cannot be attributed to a non-carbapenemase mechanism by interpretative reading of the complete antibiogram. The HPA, together with the UK Government's ARHAI Committee, has issued 'Advice on Carbapenemase Producers: recognition, infection control and treatment' (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1294740725984).

The first confirmed isolate in the UK with an acquired carbapenemase was an *Acinetobacter* isolate with IMP-1 in 2000 [172], but this genus has not proved to be a frequent host of metalloenzymes in the UK. The first confirmed CPE isolates were referred to the ARMRL in 2003. These were an isolate of *Enterobacter* with KPC-4, and two isolates of *Klebsiella* with IMP-type and VIM-type enzymes. Fewer than five CPE isolates were confirmed in the UK in each of the next 4 years (2004–2007). They were mostly isolated from patients with a history of travel and hospitalization, often following road traffic accidents, in endemic areas, e.g. KPC producers from Greece or Israel [173], VIM-positive klebsiellae from Greece, and an OXA-48 producer from Turkey.

From 2008, the numbers of confirmed CPE increased dramatically: 23 in 2008, 73 in 2009, 333 in 2010, and 561 in 2011 (at the time of writing, the 2011 database is not yet closed). Most producers were *Klebsiella* (80%), mainly *K. pneumoniae*, followed by *E. coli* (10%) and *Enterobacter* (8%), with the remaining 2% comprising occasional isolates of *Citrobacter*, *Morganella*, *Providencia*, *Raoultella* and *Serratia*. The enzymes produced included KPC (62%), NDM (14%), VIM (12%), OXA-48-like (9%) and IMP (2%) types. A single isolate of *Klebsiella* produced both KPC and VIM enzymes. Three isolates of *Enterobacter* with IMI/NMC-A enzymes were detected in 2010–2011, each from a different hospital.

Although *Enterobacteriaceae* with KPC enzymes were most commonly referred, the numbers are skewed by an ongoing problem in north-western England, which involves the transmission of pKpQIL-like plasmids [167], encoding KPC-2 among different bacterial strains, principally of *K. pneumoniae*, but with spread also to *E. coli* and *Enterobacter* (N. Woodford and D. M. Livermore, unpublished data). Referrals from this region accounted for *c.* 75% of the UK's total number of KPC-positive isolates, with many of these isolates being obtained from faecal screens rather than infections. Similarly, a small number of hospitals in one region shared an ongoing outbreak of VIM-positive klebsiellae, which also extended to the community, and these accounted for the majority of the UK total with this carbapenemase. In 2008, there was an outbreak, centred on a London renal unit, caused by *K. pneumoniae* with OXA-48; there was a dominant outbreak strain, but with horizontal transfer of an OXA-48-encoding plasmid to other strains (Thomas *et al.*, 49th ICAAC, 2009, Abstract C2-648).

Although less numerous than KPC producers, bacteria with NDM enzymes [8,23] have the widest distribution in the UK; 55 laboratories referred at least one producer after the enzyme was first detected in 2008, as compared with 42 referring isolates with KPC enzymes and 22 with VIM types (Fig. 4).

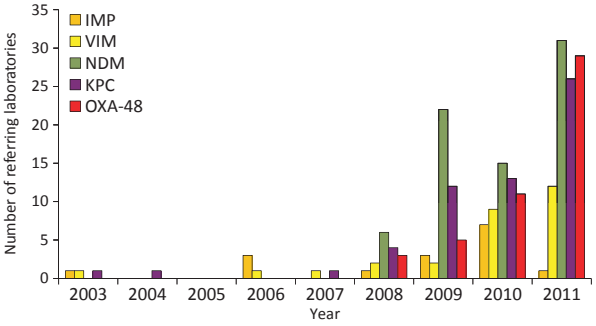

FIG. 4. Numbers of UK laboratories referring at least one carbapenemase-producing *Enterobacteriaceae* (CPE) isolate to the Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) (Health Protection Agency). Additionally, in 2010 and 2011, two and one laboratories, respectively, referred IMI-producing CPE isolates, respectively. In 2011, one laboratory referred at least one CPE isolate producing both KPC and VIM enzymes.

The UK has recorded more NDM cases than any other European country [116], and, to the end of 2011, genes encoding NDM enzymes had been detected in 138 isolates of *Enterobacteriaceae* and also in 11 *A. baumannii* isolates, collectively from 115 patients. Multiple species with NDM enzymes were isolated from several patients, which is consistent with either *in vivo* transfer of a resistance plasmid or initial colonization/infection by more than one species.

There is no coordinated epidemiological follow-up for these cases, and the HPA has a travel history, albeit limited, for only 53/115 (46%) patients with NDM-positive isolates, 32 (60%) of whom were known to have travelled to or had healthcare contact in India (n = 25) or Pakistan (n = 7).

The antibiograms of carbapenemase producers are highly variable, and range from extreme multiresistance to resistance only to β-lactams. Many *K. pneumoniae* isolates from the large KPC cluster in north-western England remain susceptible to aminoglycosides and ciprofloxacin, and, as noted earlier, producers of OXA-48-like enzymes may remain susceptible to oxyimino-cephalosporins unless they have other co-resident mechanisms, such as ESBLs or AmpC enzymes. In 2011 analyses, only colistin was active against >90% of all UK carbapenemase producers. Tigecycline was active against some producers, notably vs. *E. coli*, but a breakthrough bacteraemia caused by an NDM-positive *E. coli* isolate that became resistant to tigecycline during on-label use of the drug has been described [174]. In short, therapy of patients infected by carbapenemase-producing bacteria must be guided by the resistance profile of the causative isolate, which may remain susceptible to less commonly tested agents [175].

The first published report of CPE in Ireland was of a KPC enzyme in a *K. pneumoniae* isolate recovered in 2009

from a sputum sample collected 48 h after hospital admission in a patient with exacerbation of chronic obstructive pulmonary disease. No association with travel abroad was demonstrated in this patient [176]. The second one reported the emergence of a VIM-1-producing *K. pneumoniae* isolate in 2010 in a patient transferred from Greece [177]. Subsequently, there has been regional spread of KPC producers (Condon *et al.*, 21st ECCMID, 2011, Abstract P73), with isolates being detected in four hospitals (D. Morris, personal communication). It is of note that KPC-2 has also been detected in an *E. coli* isolate belonging to the uropathogenic ST131 clone [178]. *K. pneumoniae* isolates with OXA-48-like enzymes have also been obtained from at least four Irish hospitals (D. Morris, personal communication). The only 'OXA-48' outbreak reported to date was caused by a strain that belonged to ST221 [179] (B. Crowley, personal communication). OXA-48 has also been detected in a single *E. coli* isolate (D. Morris, personal communication). Although not formally a reference laboratory for Ireland, the ARMRL has confirmed 30 CPE isolates from Irish laboratories since 2009. Consistent with the above reports, most referred isolates were KPC producers, but isolates of *K. pneumoniae* with OXA-48 and of *Enterobacter cloacae* with a VIM-type enzyme were also referred. Ireland's first NDM-1 producer—a *K. pneumoniae* strain—was recently isolated from a urine specimen of a child who had moved to Ireland from India (R. Cunney, personal communication).

Nordic and Baltic Countries

During the early 2000s, there were no reports on CPE from any of the Nordic countries. Approaching the end of the decade, and particularly in the last 3 years, the number of cases has increased rapidly, but still remains very low. In most of the countries, laboratories are encouraged to send suspected CPE isolates to reference laboratories, but the number of cases is too low for it to be meaningful to consider denominator data. In all of the Nordic countries, there were, in total, 41 cases of CPE in 2011. There have been few cases of invasive infections caused by CPE, although one case of invasive VIM-producing *K. pneumoniae*, one case of KPC-producing *K. pneumoniae* and one case of invasive NDM-1-producing *E. coli* have been observed over a 5-year period [42,58,180].

There have been no reports so far of CPE from the Baltic countries and from Iceland, whereas all of the other Nordic countries have experienced cases. In general, the awareness of CPE is high in Nordic hospitals, and active faecal screening is conducted in many locations on patients with a history of recent travel or hospitalization abroad.

The most prevalent class of carbapenemases observed in the Nordic countries has been KPC, and almost exclusively in *K. pneumoniae*. In total, 14 cases have been identified in Norway, 14 cases in Sweden, three cases in Denmark, and five cases in Finland. KPC-2 has most commonly been identified, but cases of KPC-3 have also been demonstrated. The cases have mostly been associated with strain imports from Greece, Israel, the USA, or Italy; however, subsequent cases of nosocomial transfer and a small long-term outbreak have been observed [42] (Ø. Samuelsen, unpublished data). Mostly, KPC enzymes have been found in *K. pneumoniae* of ST258 or in STs belonging to the same clonal complex [42,181–184]. The plasmid epidemiology has been less well characterized, and at present it has not been established which plasmid types are mainly associated with the spread of KPC. Finally, of the minor class A carbapenemases, GES-14 and IMI-1/2 have been detected in Finland in *K. pneumoniae* (GES-14) and *Enterobacter cloacae* (IMI-1/-2).

MBLs are the second most common group of enzymes produced by CPEs, and, historically, VIM has been the most common variant. Since the first case of NDM-1 in Sweden in 2008 [8], this MBL has become as common as VIM, especially in Sweden (C. G. Giske, upublished data). The cases have usually been associated with recent travel to India [8,145] or the Balkan region [182], or have been connected to Middle Eastern countries or even Thailand (C. G. Giske, unpublished data) and Romania (Ø. Samuelsen, unpublished data). Many of the VIM-producing *K. pneumoniae* isolates belong to international clonal complexes such as ST147, and association with IncN-type plasmids is common [58]. The NDM-producing *K. pneumoniae* isolates have been associated with ST14, ST11, and ST525 [8,177] (Ø. Samuelsen unpublished data), whereas the plasmid epidemiology has been less well studied, with the exception of the identification of NDM-1 on an IncA/C plasmid in an isolate from Denmark [181]. The number of cases identified in the Nordic countries so far are as follows: Norway, seven cases (four VIM and three NDM-1); Sweden, 16 cases (six VIM and ten NDM-1); Denmark, six cases (three VIM and three NDM-1); and Finland, seven cases (four VIM and three NDM-1).

OXA-48-like enzymes are emerging as an important third group of carbapenemases. In the Nordic countries, most of the cases with OXA-48 or OXA-48-like enzymes have been associated with travel or hospitalization in North Africa and Middle Eastern countries, similar to what has been reported from other European countries. No published data are available on STs and plasmid characterization so far. OXA-48-like enzymes have been detected so far in Finland (n = 10),

Denmark (n = 7), Sweden (n = 4), and Norway (n = 1), including several cases in *E. coli* (C. G. Giske, Ø. Samuelsen, A. M. Hammerum, J. Jalava, unpublished data).

Conclusions

Carbapenemases in *Enterobacteriaceae* are mostly plasmid-encoded, which largely explains their common association with other resistance markers and their multidrug resistance patterns. The prevalence of the CPE is variable across Europe; a high prevalence can be found in Greece, Italy, Turkey, and Israel, whereas a low prevalence is still reported in Nordic countries, Switzerland, Germany, and the Czech Republic. The type of CPE depends on the country, and might be associated with historical/cultural relationships and exchange of populations with other countries of high prevalence. Cross-border transfer of patients, travel, medical tourism and refugees might also play an important role. This is particularly true for the spread of OXA-48 in France and in Belgium from North Africa, and in Germany, probably from Turkey, or the identification in UK of NDM-1 producers of Indian origin. The clearly increasing frequency of CPE in recent last years could be related to the increasing prevalence of OXA-48 producers in many European countries and the exportation of KPC producers from Greece and Italy to other European countries. In many cases, the spread of CPE results from hospitalization abroad. More important are the cases without importation links, which may represent community-acquired and/or autochthonous cases. In addition, although a polyclonal situation has been observed for CPE in many countries, some widespread clones have also been detected across Europe (KPC-2-producing *K. pneumoniae* ST258 or OXA-48-producing *K. pneumoniae* ST395).

The future trend of this CPE epidemic will be one of increase, as the reservoirs of carbapenemase producers are growing worldwide. Although dissemination of CPE mainly occurs among hospitalized patients (*K. pneumoniae*), community acquisition is increasing (especially for OXA-48 producers). A well-concerted effort all over Europe is clearly needed to prevent the further spread of CPE, and hence to avoid an uncontrollable situation as can now be observed worldwide for CTX-M ESBL producers.

Funding

This work was partially funded by grants from INSERM (U914), the European Commission (LSHMCT-2008-223031), and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), who sponsored the first meeting of the European Network on Carbapenemases held in Paris, September 2011.

Transparency Declaration

The authors declare no conflict of interest.

References

1. Walsh TR. Emerging carbapenemases: a global perspective. *Int J Antimicrob Agents* 2010; 36: S8–S14.
2. Patel G, Bonomo RA. Status report on carbapenemases: challenges and prospects. *Expert Rev Anti Infect Ther* 2011; 9: 555–570.
3. Queenan AM, Bush K. Carbapenemases: the versatile β-lactamases. *Clin Microbiol Rev* 2007; 20: 440–458.
4. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing *Enterobacteriaceae*. *Emerg Infect Dis* 2011; 17: 1791–1798.
5. Walsh TR, Toleman MA, Poirel L *et al.* Metallo-β-lactamases: the quiet before the storm? *Clin Microbiol Rev* 2005; 18: 306–325.
6. Yigit H, Queenan AM, Anderson GJ *et al.* Novel carbapenem-hydrolyzing β-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2001; 45: 1151–1161.
7. Poirel L, Héritier C, Tolün V *et al.* Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2004; 48: 15–22.
8. Yong D, Toleman MA, Giske CG *et al.* Characterization of a new metallo-β-lactamase gene, bla_{NDM-1}, and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009; 53: 5046–5054.
9. Cantón R, Coque TM. The CTX-M β-lactamase pandemic. *Curr Opin Microbiol* 2006; 9: 466–475.
10. Rodríguez-Baño J, Pascual A. Clinical significance of extended-spectrum β-lactamases. *Expert Rev Anti Infect Ther* 2008; 6: 671–683.
11. Valverde A, Coque TM, García-San Miguel L *et al.* Complex molecular epidemiology of extended-spectrum β-lactamases in *Klebsiella pneumoniae*: a long-term perspective from a single institution in Madrid. *J Antimicrob Chemother* 2008; 61: 64–72.
12. Peirano G, Pitout JD. Molecular epidemiology of *Escherichia coli* producing CTX-M β-lactamases: the worldwide emergence of clone S-T131 O25:H4. *Int J Antimicrob Agents* 2010; 35: 316–321.
13. Poirel L, Pitout JD, Nordmann P. Carbapenemases: molecular diversity and clinical consequences. *Future Microbiol* 2007; 2: 501–512.
14. Cantón R, Novais A, Valverde A *et al.* Prevalence and spread of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in Europe. *Clin Microbiol Infect* 2008; 14: 144–153.
15. Nordmann P, Poirel L, Toleman MA *et al.* Does broad-spectrum β-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria? *J Antimicrob Chemother* 2011; 66: 689–692.
16. Grundmann H, Livermore DM, Giske CG *et al.* Carbapenem-non-susceptible *Enterobacteriaceae* in Europe: conclusions from a meeting of national experts. *Euro Surveill* 2010; 15: pii: 19711.
17. Cantón R, Ruiz-Garbajosa P. Co-resistance: an opportunity for the bacteria and resistance genes. *Curr Opin Pharmacol* 2011; 11: 477–485.

18. Woodford N, Turton JF, Livermore DM. Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. *FEMS Microbiol Rev* 2011; 35: 736–755.
19. Pitout JD. The latest threat in the war on antimicrobial resistance. *Lancet Infect Dis* 2010; 10: 578–579.
20. European Centre for Disease Prevention and Control. *Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities*. Stockholm: ECDC; 2011.
21. Naas T, Nordmann P, Vedel G *et al.* Plasmid-mediated carbapenem-hydrolyzing β-lactamase KPC in a *Klebsiella pneumoniae* isolate from France. *Antimicrob Agents Chemother* 2005; 49: 4423–4424.
22. Potron A, Poirel L, Verdavaine D *et al.* Importation of KPC-2-producing *Escherichia coli* from India. *J Antimicrob Chemother* 2012; 67: 242–243.
23. Kumarasamy KK, Toleman MA, Walsh TR *et al.* Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; 10: 597–602.
24. Levast M, Poirel L, Carrër A *et al.* Transfer of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* from Turkey to France. *J Antimicrob Chemother* 2011; 66: 944–945.
25. Poirel L, Bernabeu S, Fortineau N *et al.* Emergence of OXA-48-producing *Escherichia coli* clone ST38 in France. *Antimicrob Agents Chemother* 2011; 55: 4937–4938.
26. Pitart C, Solé M, Roca I *et al.* First outbreak of a plasmid-mediated carbapenem-hydrolyzing OXA-48 β-lactamase in *Klebsiella pneumoniae* in Spain. *Antimicrob Agents Chemother* 2011; 55: 4398–4401.
27. Miriagou V, Cornaglia G, Edelstein M *et al.* Acquired carbapenemases in Gram-negative bacterial pathogens: detection and surveillance issues. *Clin Microbiol Infect* 2010; 16: 112–122.
28. Thomson KS. Extended-spectrum-β-lactamase, AmpC, and carbapenemase issues. *J Clin Microbiol* 2010; 48: 1019–1025.
29. Kassis-Chikhani N, Decré D, Gautier V *et al.* First outbreak of multidrug-resistant *Klebsiella pneumoniae* carrying bla_{VIM-1} and bla_{SHV-5} in a French university hospital. *J Antimicrob Chemother* 2006; 57: 142–145.
30. Cuzon G, Naas T, Demachy MC *et al.* Plasmid-mediated carbapenem-hydrolyzing β-lactamase KPC-2 in *Klebsiella pneumoniae* isolate from Greece. *Antimicrob Agents Chemother* 2008; 52: 796–797.
31. Vatopoulos A. High rates of metallo-β-lactamase-producing *Klebsiella pneumoniae* in Greece—a review of the current evidence. *Euro Surveill* 2008; 13: pii: 8023.
32. Miriagou V, Tzelepi E, Gianneli D *et al. Escherichia coli* with a self-transferable, multiresistant plasmid coding for metallo-β-lactamase VIM-1. *Antimicrob Agents Chemother* 2003; 47: 395–397.
33. Scoulica EV, Neonakis IK, Gikas AI, Tselentis YJ. Spread of *bla*(VIM-1)-producing *E. coli* in a university hospital in Greece. Genetic analysis of the integron carrying the *bla*(VIM-1) metallo-beta-lactamase gene. *Diagn Microbiol Infect Dis.* 2004; 48: 167–172.
34. Giakkoupi P, Xanthaki A, Kanelopoulou M *et al.* VIM-1 metallo-β-lactamase-producing *Klebsiella pneumoniae* strains in Greek hospitals. *J Clin Microbiol* 2003; 41: 3893–3896.
35. Ikonomidis A, Tokatlidou D, Kristo I *et al.* Outbreaks in distinct regions due to a single *Klebsiella pneumoniae* clone carrying a *bla* VIM-1 metallo-β-lactamase gene. *J Clin Microbiol* 2005; 43: 5344–5347.
36. Miriagou V, Papagiannitsis CC, Kotsakis SD *et al.* Sequence of pNL194, a 79.3-kilobase IncN plasmid carrying the bla_{VIM-1} metallo-β-lactamase gene in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2010; 54: 4497–4502.
37. Tokatlidou D, Tsivitanidou M, Pournaras S *et al.* Outbreak caused by a multidrug-resistant *Klebsiella pneumoniae* clone carrying blaVIM-12 in a university hospital. *J Clin Microbiol* 2008; 46: 1005–1008.
38. Ikonomidis A, Spanakis N, Poulou A *et al.* Emergence of carbapenem-resistant *Enterobacter cloacae* carrying VIM-4 metallo-β-lactamase and SHV-2a extended-spectrum β-lactamase in a conjugative plasmid. *Microb Drug Resist* 2007; 13: 221–226.
39. Galani I, Souli M, Koratzanis E *et al.* Emerging bacterial pathogens: *Escherichia coli*, *Enterobacter aerogenes* and *Proteus mirabilis* clinical isolates harbouring the same transferable plasmid coding for metallo-β-lactamase VIM-1 in Greece. *J Antimicrob Chemother* 2007; 59: 578–579.
40. Tsakris A, Kristo I, Poulou A *et al.* First occurrence of KPC-2-possessing *Klebsiella pneumoniae* in a Greek hospital and recommendation for detection with boronic acid disc tests. *J Antimicrob Chemother* 2008; 62: 1257–1260.
41. Maltezou HC, Giakkoupi P, Maragos A *et al.* Outbreak of infections due to KPC-2-producing *Klebsiella pneumoniae* in a hospital in Crete (Greece). *J Infect* 2009; 58: 213–219.
42. Samuelsen Ø, Naseer U, Tofteland S *et al.* Emergence of clonally related *Klebsiella pneumoniae* isolates of sequence type 258 producing plasmid-mediated KPC carbapenemase in Norway and Sweden. *J Antimicrob Chemother* 2009; 63: 654–658.
43. Giakkoupi P, Papagiannitsis CC, Miriagou V *et al.* An update of the evolving epidemic of bla_{KPC-2}-carrying *Klebsiella pneumoniae* in Greece (2009–10). *J Antimicrob Chemother* 2011; 66: 1510–1513.
44. Pournaras S, Protonotariou E, Voulgari E *et al.* Clonal spread of KPC-2 carbapenemase-producing *Klebsiella pneumoniae* strains in Greece. *J Antimicrob Chemother* 2009; 64: 348–352.
45. Kontopoulou K, Protonotariou E, Vasilakos K *et al.* Hospital outbreak caused by *Klebsiella pneumoniae* producing KPC-2 β-lactamase resistant to colistin. *J Hosp Infect* 2010; 76: 70–73.
46. Mavroidi A, Miriagou V, Malli E *et al.* Emergence of *Escherichia coli* sequence type 410 (ST410) with KPC-2 β-lactamase. *Int J Antimicrob Agents* 2012; 39: 247–250.
47. Oteo J, Hernández-Almaraz JL, Gil-Antón J *et al.* Outbreak of vim-1-carbapenemase-producing *Enterobacter cloacae* in a pediatric intensive care unit. *Pediatr Infect Dis J* 2010; 29: 1144–1146.
48. Nazic H, Poirel L, Nordmann P. Further identification of plasmid-mediated quinolone resistance determinant in *Enterobacteriaceae* in Turkey. *Antimicrob Agents Chemother* 2005; 49: 2146–2147.
49. Carrër A, Poirel L, Eraksoy H *et al.* Spread of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in Istanbul, Turkey. *Antimicrob Agents Chemother* 2008; 52: 2950–2954.
50. Gülmez D, Woodford N, Palepou MF *et al.* Carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolates from Turkey with OXA-48-like carbapenemases and outer membrane protein loss. *Int J Antimicrob Agents* 2008; 31: 523–526.
51. Kilic A, Aktas Z, Bedir O *et al.* Identification and characterization of OXA-48 producing, carbapenem-resistant *Enterobacteriaceae* isolates in Turkey. *Ann Clin Lab Sci* 2011; 41: 161–166.
52. Carrër A, Poirel L, Yilmaz M *et al.* Spread of OXA-48-encoding plasmid in Turkey and beyond. *Antimicrob Agents Chemother* 2010; 54: 1369–1373.
53. Potron A, Kalpoe J, Poirel L *et al.* European dissemination of a single OXA-48-producing *Klebsiella pneumoniae* clone. *Clin Microbiol Infect* 2011; 17: E24–E26.
54. Gacar GG, Midilli K, Kolayli F *et al.* Genetic and enzymatic properties of metallo-β-lactamase VIM-5 from a clinical isolate of *Enterobacter cloacae*. *Antimicrob Agents Chemother* 2005; 49: 4400–4403.
55. Bahar G, Mazzariol A, Koncan R *et al.* Detection of VIM-5 metallo-beta-lactamase in a *Pseudomonas aeruginosa* clinical isolate from Turkey. *J Antimicrob Chemother* 2004; 54: 282–283.
56. Ozgumus OB, Caylan R, Tosun I, Sandalli C, Aydin K, Koksal I. Molecular epidemiology of clinical *Pseudomonas aeruginosa* isolates carrying IMP-1 metallo-β-lactamase gene in a university hospital in Turkey. *Microb Drug Resist* 2007; 13: 191–198.

57. Yildirim I, Ceyhan M, Gur D *et al.* First detection of VIM-1 type metallo-β-lactamase in a multidrug-resistant *Klebsiella pneumoniae* clinical isolate from Turkey also producing the CTX-M-15 extended-spectrum β-lactamase. *J Chemother* 2007; 19: 467–468.
58. Samuelsen Ø, Toleman MA, Hasseltvedt V *et al.* Molecular characterisation of VIM-producing *Klebsiella pneumoniae* from Scandinavia reveals genetic relatedness with international clonal complexes encoding transferable multidrug resistance. *Clin Microbiol Infect* 2011; 17: 1811–1816.
59. Aktas Z, Bal C, Midilli K *et al.* First IMP-1-producing *Klebsiella pneumoniae* isolate in Turkey. *Clin Microbiol Infect* 2006; 12: 695–696.
60. Deshpande LM, Jones RN, Fritsche TR, Sader HS. Occurrence and characterization of carbapenemase-producing *Enterobacteriaceae*: report from the SENTRY Antimicrobial Surveillance Program (2000–2004). *Microb Drug Resist* 2006; 12: 223–230.
61. Navon-Venezia S, Chmelnitsky I, Leavitt A *et al.* Plasmid-mediated imipenem-hydrolyzing enzyme KPC-2 among multiple carbapenem-resistant *Escherichia coli* clones in Israel. *Antimicrob Agents Chemother* 2006; 50: 3098–3101.
62. Marchaim D, Navon-Venezia S, Schwaber MJ *et al.* Isolation of imipenem-resistant *Enterobacter* species: emergence of KPC-2 carbapenemase, molecular characterization, epidemiology, and outcomes. *Antimicrob Agents Chemother* 2008; 52: 1413–1418.
63. Colodner R, Samra Z, Keller N *et al.* First national surveillance of susceptibility of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp. to antimicrobials in Israel. *Diagn Microbiol Infect Dis* 2007; 57: 201–205.
64. Leavitt A, Chmelnitsky I, Colodner R *et al.* Ertapenem resistance among extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* isolates. *J Clin Microbiol* 2009; 47: 969–974.
65. Leavitt A, Navon-Venezia S, Chmelnitsky I *et al.* Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. *Antimicrob Agents Chemother* 2007; 51: 3026–3029.
66. Samra Z, Ofir O, Lishtzinsky Y *et al.* Outbreak of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-3 in a tertiary medical centre in Israel. *Int J Antimicrob Agents* 2007; 30: 525–529.
67. Navon-Venezia S, Leavitt A, Schwaber MJ *et al.* First report on a hyperepidemic clone of KPC-3-producing *Klebsiella pneumoniae* in Israel genetically related to a strain causing outbreaks in the United States. *Antimicrob Agents Chemother* 2009; 53: 818–820.
68. Kitchel B, Raseheed JK, Pate JB *et al.* Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258. *Antimicrob Agents Chemother* 2009; 53: 3365–3370.
69. Schwaber MJ, Lev B, Israeli A *et al.* Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* 2011; 52: 848–855.
70. Ben-David D, Masarwa S, Navon-Venezia S *et al.* Carbapenem-resistant *Klebsiella pneumoniae* in post-acute-care facilities in Israel. *Infect Control Hosp Epidemiol* 2011; 32: 845–853.
71. Adler A, Shklyar M, Schwaber MJ *et al.* Introduction of OXA-48-producing *Enterobacteriaceae* to Israeli hospitals by medical tourism. *J Antimicrob Chemother* 2011; 66: 2763–2766.
72. Cornaglia G, Riccio ML, Mazzariol A *et al.* Appearance of IMP-1 metallo-β-lactamase in Europe. *Lancet* 1999; 353: 899–900.
73. Riccio ML, Franceschini N, Boschi L *et al.* Characterization of the metallo-β-lactamase determinant of *Acinetobacter baumannii* AC-54/97 reveals the existence of bla_{IMP} allelic variants carried by gene cassettes of different phylogeny. *Antimicrob Agents Chemother* 2000; 44: 1229–1235.
74. Lauretti L, Riccio ML, Mazzariol A *et al.* Cloning and characterization of bla_{VIM}, a new integron-borne metallo-β-lactamase gene from a *Pseudomonas aeruginosa* clinical isolate. *Antimicrob Agents Chemother* 1999; 43: 1584–1590.
75. Riccio ML, Pallecchi L, Fontana R *et al.* In70 of plasmid pAX22, a bla_{VIM-1}-containing integron carrying a new aminoglycoside phosphotransferase gene cassette. *Antimicrob Agents Chemother* 2001; 45: 1249–1253.
76. Giani T, Marchese A, Coppo E *et al.* VIM-1-producing *Pseudomonas mosselii* isolated in Italy, pre-dating known VIM-producing index strains. *Antimicrob Agents Chemother* 2012. Jan 30 [Epub ahead of print].
77. Luzzaro F, Docquier JD, Colinon C *et al.* Emergence in *Klebsiella pneumoniae* and *Enterobacter cloacae* clinical isolates of the VIM-4 metallo-β-lactamase encoded by a conjugative plasmid. *Antimicrob Agents Chemother* 2004; 48: 648–650.
78. Aschbacher R, Doumith M, Livermore DM *et al.* Linkage of acquired quinolone resistance (*qnrS1*) and metallo-β-lactamase (bla_{VIM-1}) genes in multiple species of *Enterobacteriaceae* from Bolzano, Italy. *J Antimicrob Chemother* 2008; 61: 515–523.
79. Perilli M, Mezzatesta ML, Falcone M *et al.* Class 1 integron-borne bla_{VIM-1} carbapenemase in a strain of *Enterobacter cloacae* responsible for a case of fatal pneumonia. *Microb Drug Resist* 2008; 14: 45–47.
80. Rossolini GM, Luzzaro F, Migliavacca R *et al.* First countrywide survey of acquired metallo-β-lactamases in gram-negative pathogens in Italy. *Antimicrob Agents Chemother* 2008; 52: 4023–4029.
81. Cagnacci S, Gualco L, Roveta S *et al.* Bloodstream infections caused by multidrug-resistant *Klebsiella pneumoniae* producing the carbapenem-hydrolysing VIM-1 metallo-β-lactamase: first Italian outbreak. *J Antimicrob Chemother* 2008; 61: 296–300.
82. Castanheira M, Debbia E, Marchese A *et al.* Emergence of a plasmid-mediated bla_{VIM-1} in *Citrobacter koseri*: report from the SENTRY Antimicrobial Surveillance Program (Italy). *J Chemother* 2009; 21: 98–100.
83. Falcone M, Mezzatesta ML, Perilli M *et al.* Infections with VIM-1 metallo-β-lactamase-producing *Enterobacter cloacae* and their correlation with clinical outcome. *J Clin Microbiol* 2009; 47: 3514–3549.
84. Falcone M, Perilli M, Mezzatesta ML *et al.* Prolonged bacteraemia caused by VIM-1 metallo-β-lactamase-producing *Proteus mirabilis*: first report from Italy. *Clin Microbiol Infect* 2010; 16: 179–181.
85. Aschbacher R, Pagani L, Doumith M *et al.* Metallo-β-lactamases among *Enterobacteriaceae* from routine samples in an Italian tertiary-care hospital and long-term care facilities during 2008. *Clin Microbiol Infect* 2011; 17: 181–189.
86. Mantengoli E, Luzzaro F, Pecile P *et al. Escherichia coli* ST131 producing extended-spectrum β-lactamases plus VIM-1 carbapenemase: further narrowing of treatment options. *Clin Infect Dis* 2011; 52: 690–691.
87. Giani T, D'Andrea MM, Pecile P *et al.* Emergence of *Klebsiella pneumoniae* sequence type 258 producing KPC-3 carbapenemase, Italy. *J Clin Microbiol* 2009; 47: 3793–3794.
88. Fontana C, Favaro M, Sarmati L *et al.* Emergence of KPC-producing *Klebsiella pneumoniae* in Italy. *BMC Res Notes* 2010; 3: 40.
89. Ambretti S, Gaibani P, Caroli F *et al.* A carbapenem-resistant *Klebsiella pneumoniae* isolate harboring KPC-1 from Italy. *New Microbiol* 2010; 33: 281–282.
90. Marchese A, Coppo E, Barbieri R *et al.* Emergence of KPC-2 carbapenemase-producing *Klebsiella pneumoniae* strains and spread of an isolate of sequence type 258 in the neuro-rehabilitation unit of an Italian hospital. *J Chemother* 2010; 22: 212–214.
91. Gaibani P, Ambretti S, Berlingeri A *et al.* Rapid increase of carbapenemase-producing *Klebsiella pneumoniae* strains in a large Italian hospital: surveillance period 1 March–30 September 2010. *Euro Surveill* 2011; 16: 19800.
92. Mezzatesta ML, Gona F, Caio C *et al.* Outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals. *Clin Microbiol Infect* 2011; 17: 1444–1447.

93. Agodi A, Voulgari E, Barchitta M *et al.* Containment of an outbreak of KPC-3-producing *Klebsiella pneumoniae* in Italy. *J Clin Microbiol* 2011; 49: 3986–3989.
94. Richter SN, Frasson I, Bergo C *et al.* Transfer of KPC-2 carbapenemase from *Klebsiella pneumoniae* to *Escherichia coli* in a patient: first case in Europe. *J Clin Microbiol* 2011; 49: 2040–2042.
95. Di Carlo P, Pantuso G, Cusimano A *et al.* Two cases of monomicrobial intraabdominal abscesses due to KPC-3 *Klebsiella pneumoniae* ST258 clone. *BMC Gastroenterol* 2011; 11: 103.
96. Mammina C, Palma DM, Bonura C *et al.* Outbreak of infection with *Klebsiella pneumoniae* sequence type 258 producing *Klebsiella pneumoniae* carbapenemase 3 in an intensive care unit in Italy. *J Clin Microbiol* 2010; 48: 1506–1507.
97. Gaibani P, Ambretti S, Berlingeri A *et al.* Outbreak of NDM-1-producing *Enterobacteriaceae* in northern Italy, July to August 2011. *Euro Surveill* 2011; 16: 20027.
98. Giani T, Conte V, Di Pilato V *et al.* OXA-48 carbapenemase-producing *Escherichia coli* from Italy, encoded by a novel Tn*1999* transposon derivative. *Antimicrob Agents Chemother* 2012. Jan 30 [Epub ahead of print].
99. Sardelic S, Pallecchi L, Punda-Polic V *et al.* Carbapenem-resistant *Pseudomonas aeruginosa*-carrying VIM-2 metallo-β-lactamase determinants, Croatia. *Emerg Infect Dis* 2003; 9: 1022–1023.
100. Bosnjak Z, Bedenić B, Mazzariol A *et al.* VIM-2 β-lactamase in *Pseudomonas aeruginosa* isolates from Zagreb, Croatia. *Scand J Infect Dis* 2010; 42: 193–197.
101. Franolić-Kukina I, Bedenić B, Budimir A *et al.* Clonal spread of carbapenem-resistant OXA-72-positive *Acinetobacter baumannii* in a Croatian university hospital. *Int J Infect Dis* 2011; 15: e706–e709.
102. Goic-Barisic I, Towner KJ, Kovacic A *et al.* Outbreak in Croatia caused by a new carbapenem-resistant clone of *Acinetobacter baumannii* producing OXA-72 carbapenemase. *J Hosp Infect* 2011; 77: 368–369.
103. Pirs M, Andlovic A, Cerar T *et al.* A case of OXA-48 carbapenemase-producing *Klebsiella pneumoniae* in a patient transferred to Slovenia from Libya, November 2011. *Euro Surveill* 2011; 16: pii: 20042.
104. Bogaerts P, Bouchahrouf W, de Castro RR *et al.* Emergence of NDM-1-producing *Enterobacteriaceae* I in Belgium. *Antimicrob Agents Chemother* 2011; 55: 3036–3038.
105. Tórtola MT, Lavilla S, Miró E *et al.* First detection of a carbapenem-hydrolyzing metalloenzyme in two *Enterobacteriaceae* isolates in Spain. *Antimicrob Agents Chemother* 2005; 49: 3492–3494.
106. Tato M, Coque TM, Ruíz-Garbajosa P *et al.* Complex clonal and plasmid epidemiology in the first outbreak of *Enterobacteriaceae* infection involving VIM-1 metallo-β-lactamase in Spain: toward endemicity? *Clin Infect Dis* 2007; 45: 1171–1178.
107. Curiao T, Morosini MI, Ruiz-Garbajosa P *et al.* Emergence of *bla* KPC-3-Tn*4401a* associated with a pKPN3/4-like plasmid within ST384 and ST388 *Klebsiella pneumoniae* clones in Spain. *J Antimicrob Chemother* 2010; 65: 1608–1614.
108. Gómez-Gil MR, Paño-Pardo JR, Romero-Gómez MP *et al.* Detection of KPC-2-producing *Citrobacter freundii* isolates in Spain. *J Antimicrob Chemother* 2010; 65: 2695–2697.
109. Solé M, Pitart C, Roca I *et al.* First description of an *Escherichia coli* strain producing NDM-1 carbapenemase in Spain. *Antimicrob Agents Chemother* 2011; 55: 4402–4404.
110. Sánchez-Romero I, Asensio A, Oteo J *et al.* Nosocomial outbreak of VIM-1-producing *Klebsiella pneumoniae* isolates of multilocus sequence type 15: molecular basis, clinical risk factors, and outcome. *Antimicrob Agents Chemother* 2012; 56: 420–427.
111. Tato M, Coque TM, Baquero F *et al.* Dispersal of carbapenemase *bla*VIM-1 gene associated with different Tn*402* variants, mercury transposons, and conjugative plasmids in *Enterobacteriaceae* and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2010; 54: 320–327.
112. Miró E, Segura C, Navarro F *et al.* Spread of plasmids containing the *bla*(VIM-1) and *bla*(CTX-M) genes and the qnr determinant in *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* isolates. *J Antimicrob Chemother* 2010; 65: 661–665.
113. Cendejas E, Gómez-Gil R, Gómez-Sánchez P *et al.* Detection and characterization of *Enterobacteriaceae* producing metallo-β-lactamases in a tertiary-care hospital in Spain. *Clin Microbiol Infect* 2010; 16: 181–183.
114. Treviño M, Navarro D, Barbeito G *et al.* Molecular and epidemiological analysis of nosocomial carbapenem-resistant *Klebsiella* spp. using repetitive extragenic palindromic-polymerase chain reaction and matrix-assisted laser desorption/ionization-time of flight. *Microb Drug Resist* 2011; 17: 433–442.
115. Sorlí L, Miró E, Segura C *et al.* Intra- and inter-species spread of carbapenemase genes in a non-hospitalized patient. *Eur J Clin Microbiol Infect Dis* 2011; 30: 1551–1555.
116. Struelens MJ, Monnet DL, Magiorakos AP *et al.* New Delhi metallo-β-lactamase 1-producing *Enterobacteriaceae*: emergence and response in Europe. *Euro Surveill* 2010; 15: pii: 19716.
117. Cuzon G, Ouanich J, Gondret R *et al.* Outbreak of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in France. *Antimicrob Agents Chemother* 2011; 55: 2420–2423.
118. Scotta C, Juan C, Cabot G *et al.* Environmental microbiota represents a natural reservoir for dissemination of clinically relevant metallo-β-lactamases. *Antimicrob Agents Chemother* 2011; 55: 5376–5379.
119. Conceição T, Brízio A, Duarte A *et al.* First isolation of *bla*(VIM-2) in *Klebsiella oxytoca* clinical isolates from Portugal. *Antimicrob Agents Chemother* 2005; 49: 476.
120. Poirel L, Barbosa-Vasconcelos A, Simões RR *et al.* Environmental KPC-producing *Escherichia coli*, Portugal. *Antimicrob Agents Chemother* 2012; 56: 1662–1663.
121. Naas T, Nordmann P. Analysis of a carbapenem-hydrolyzing class A beta-lactamase from *Enterobacter cloacae* and of its LysR-type regulatory protein. *Proc Natl Acad Sci USA* 1994; 91: 7693–7697.
122. Lartigue MF, Poirel L, Nordmann P. First detection of a carbapenem-hydrolyzing metalloenzyme in an *Enterobacteriaceae* isolate in France. *Antimicrob Agents Chemother* 2004; 48: 4929–4930.
123. Rodriguez-Martinez JM, Nordmann P, Fortineau N, Poirel L. VIM-19, a metallo-beta-lactamase with increased carbapenemase activity from *Escherichia coli* and *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2010; 54: 471–476.
124. Vidal-Navarro L, Pfeiffer C, Bouziges N *et al.* Faecal carriage of multidrug-resistant Gram-negative bacilli during a non-outbreak situation in a French university hospital. *J Antimicrob Chemother* 2010; 65: 2455–2458.
125. Poirel L, Hombrouck-Alet C, Freneaux C *et al.* Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* 2010; 10: 597–602.
126. Poirel L, Ros A, Carricajo A *et al.* Extremely drug-resistant *Citrobacter freundii* isolate producing NDM-1 and other carbapenemases identified in a patient returning from India. *Antimicrob Agents Chemother* 2011; 55: 447–448.
127. Poirel L, Fortineau N, Nordmann P. International transfer of NDM-1-producing *Klebsiella pneumoniae* from Iraq to France. *Antimicrob Agents Chemother* 2011; 55: 1821–1822.
128. Nordmann P, Couard JP, Sansot D, Poirel L. Emergence of an autochthonous and community-acquired NDM-1-producing *Klebsiella pneumoniae* in Europe. *Clin Infect Dis* 2012; 54: 150–151.
129. Denis C, Poirel L, Carricajo A *et al.* Nosocomial transmission of NDM-1-producing *Escherichia coli* within a non-endemic area in France. *Clin Microbiol Infect* 2012. Jan 2 [Epub ahead of print].
130. Diene M, Bruder N, Raoult D, Rolain JM. Real-time PCR assay allows detection of the New Delhi metallo-β-lactamase (NDM-1)-encoding gene in France. *Int J Antimicrob Agents* 2011; 37: 544–546.

131. Naas T, Ergani A, Carrër A, Nordmann P. Real-time PCR for detection of NDM-1 carbapenemase genes from spiked stool samples. *Antimicrob Agents Chemother* 2011; 55: 4038–4043.
132. Birgy A, Doit C, Mariani-Kurkdjian P *et al.* Early detection of colonization by VIM-1-producing *Klebsiella pneumoniae* and NDM-1-producing *Escherichia coli* in two children returning to France. *J Clin Microbiol* 2011; 49: 3085–3087.
133. Petrella S, Ziental-Gelus N, Mayer C *et al.* Genetic and structural insights into the dissemination potential of the extremely broad-spectrum class A β-lactamase KPC-2 identified in an *Escherichia coli* strain and an *Enterobacter cloacae* strain isolated from the same patient in France. *Antimicrob Agents Chemother* 2008; 52: 3725–3736.
134. Dortet L, Radu I, Gautier V *et al.* Intercontinental travels of patients and dissemination of plasmid-mediated carbapenemase KPC-3 associated with OXA-9 and TEM-1. *J Antimicrob Chemother* 2008; 61: 455–457.
135. Cuzon G, Naas T, Demachy MC, Nordmann P. Nosocomial outbreak of *Klebsiella pneumoniae* harboring *bla*KPC-3 in France subsequent to a patient transfer from Italy. *Int J Antimicrob Agents*, 2012. Mar 13 [Epub ahead of print].
136. Naas T, Cuzon G, Babics A *et al.* Endoscopy-associated transmission of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-2 beta-lactamase. *J Antimicrob Chemother* 2010; 65: 1305–1306.
137. Carbonne A, Thiolet JM, Fournier S *et al.* Control of a multi-hospital outbreak of KPC-producing *Klebsiella pneumoniae* type 2 in France, September to October 2009. *Euro Surveill* 2010; 15: pii: 19734.
138. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis* 2009; 9: 228–236.
139. Naas T, Cuzon G, Gaillot O *et al.* When carbapenem-hydrolyzing β-lactamase KPC meets *Escherichia coli* ST131 in France. *Antimicrob Agents Chemother* 2011; 55: 4933–4934.
140. Naas T, Cattoen C, Bernusset S *et al.* First identification of *bla*IMI-1 in an *Enterobacter cloacae* clinical isolate from France. *Antimicrob Agents Chemother*. 2012; 56: 1664–1665.
141. Cuzon G, Naas T, Lesenne A, Benhamou M, Nordmann P. Plasmid-mediated carbapenem-hydrolysing OXA-48 beta-lactamase in *Klebsiella pneumoniae* from Tunisia. *Int J Antimicrob Agents* 2010; 36: 91–93.
142. Decre D, Birgand G, Geneste D *et al.* Possible importation and subsequent cross-transmission of OXA-48-producing *Klebsiella pneumoniae*, France, 2010. *Euro Surveill* 2010; 15: pii: 197.
143. Poirel L, Ros A, Carrër A *et al.* Cross-border transmission of OXA-48-producing *Enterobacter cloacae* from Morocco to France. *J Antimicrob Chemother* 2011; 66: 1181–1182.
144. Ruppé E, Armand-Lefèvre L, Lolom I *et al.* Development of a phenotypic method for detection of fecal carriage of OXA-48-producing *enterobacteriaceae* after incidental detection from clinical specimen. *J Clin Microbiol* 2011; 49: 2761–2762.
145. Kristóf K, Tóth A, Damjanova I *et al.* Identification of a bla_{VIM-4} gene in the internationally successful *Klebsiella pneumoniae* ST11 clone and in a *Klebsiella oxytoca* strain in Hungary. *J Antimicrob Chemother* 2010; 65: 1303–1305.
146. Potron A, Nordmann P, Lafeuille E *et al.* Characterization of OXA-181, a carbapenem-hydrolyzing class D beta-lactamase from *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2011; 55: 4896–4899.
147. Poirel L, Wenger A, Bille J *et al.* SME-2-producing *Serratia marcescens* isolate from Switzerland. *Antimicrob Agents Chemother* 2007; 51: 2282–2283.
148. Poirel L, Lienhard R, Potron A *et al.* Plasmid-mediated carbapenem-hydrolysing β-lactamase KPC-2 in a *Klebsiella pneumoniae* isolate from Switzerland. *J Antimicrob Chemother* 2011; 66: 675–676.
149. Babouee B, Widmer AF, Dubuis O *et al.* Emergence of four cases of KPC-2 and KPC-3-carrying *Klebsiella pneumoniae* introduced to Switzerland, 2009–10. *Euro Surveill* 2011; 16: pii: 19817.
150. Poirel L, Schrenzel J, Cherkaoui A *et al.* Molecular analysis of NDM-1-producing enterobacterial isolates from Geneva, Switzerland. *J Antimicrob Chemother* 2011; 66: 1730–1733.
151. Huang TD, Bogaerts P, Berhin C *et al.* Rapid emergence of carbapenemase-producing *Enterobacteriaceae* isolates in Belgium. *Euro Surveill* 2011; 16: pii: 19900.
152. Bogaerts P, Montesinos I, Rodriguez-Villalobos H *et al.* Emergence of clonally related *Klebsiella pneumoniae* isolates of sequence type 258 producing KPC-2 carbapenemase in Belgium. *J Antimicrob Chemother* 2010; 65: 361–362.
153. Bogaerts P, Naas T, Wybo I *et al.* Outbreak of infection by carbapenem-resistant *Acinetobacter baumannii* producing the carbapenemase OXA-58 in Belgium. *J Clin Microbiol* 2006; 44: 4189–4192.
154. Glupczynski Y, Huang TD, Bouchahrouf W *et al.* Rapid emergence and spread of OXA-48-producing carbapenem-resistant *Enterobacteriaceae* isolates in Belgian hospitals. *Int J Antimicrob Agents* 2012; 39: 168–172.
155. Kalpoe JS, Al Naiemi N, Poirel L *et al.* Detection of an Ambler class D OXA-48-type β-lactamase in a *Klebsiella pneumoniae* strain in The Netherlands. *J Med Microbiol* 2011; 60: 677–678.
156. Potron A, Poirel L, Bussy F *et al.* Occurrence of the carbapenem-hydrolyzing β-lactamase gene bla_{OXA-48} in the environment in Morocco. *Antimicrob Agents Chemother* 2011; 55: 5413–5414.
157. Leverstein-van Hall MA, Stuart JC, Voets GM *et al.* Carbapenem-resistant *Klebsiella pneumoniae* following foreign travel. *Ned Tijdschr Geneeskd* 2010; 154: A2013.
158. Bogaerts P, de Castro RR, Deplano A *et al.* Detection of a VIM-27-producing *Klebsiella pneumoniae* isolate in a patient following surgical tourism in Greece. *Antimicrob Agents Chemother* 2011; 55: 4488–4489.
159. Steinmann J, Kaase M, Gatermann S *et al.* Outbreak due to a *Klebsiella pneumoniae* strain harbouring KPC-2 and VIM-1 in a German university hospital, July 2010 to January 2011. *Euro Surveill* 2011; 16: pii: 19944.
160. Wendt C, Schütt S, Dalpke AH *et al.* First outbreak of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in Germany. *Eur J Clin Microbiol Infect Dis* 2010; 29: 563–570.
161. Heller I, Grif K, Orth D. Emergence of VIM-1-carbapenemase-producing *Enterobacter cloacae* in Tyrol, Austria. *J Med Microbiol* 2012; 61: 567–571.
162. Zarfel G, Hoenigl M, Würstl B *et al.* Emergence of carbapenem-resistant *Enterobacteriaceae* in Austria, 2001–2010. *Clin Microbiol Infect* 2011; 17: E5–E8.
163. Zarfel G, Hoenigl M, Leitner E *et al.* Emergence of New Delhi metallo-β-lactamase, Austria. *Emerg Infect Dis* 2011; 17: 129–130.
164. Baraniak A, Izdebski R, Herda M *et al.* The emergence of *Klebsiella pneumoniae* ST258 with KPC-2 in Poland. *Antimicrob Agents Chemother* 2009; 53: 4565–4567.
165. Baraniak A, Grabowska A, Izdebski R *et al.* Molecular characteristics of KPC-producing *Enterobacteriaceae* at the early stage of their dissemination in Poland, 2008–2009. *Antimicrob Agents Chemother* 2011; 55: 5493–5499.
166. Naas T, Cuzon G, Villegas MV *et al.* Genetic structures at the origin of acquisition of the β-lactamase bla_{KPC} gene. *Antimicrob Agents Chemother* 2008; 52: 1257–1263.
167. Leavitt A, Chmelnitsky I, Carmeli Y *et al.* Complete nucleotide sequence of KPC-3-encoding plasmid pKpQIL in the epidemic *Klebsiella pneumoniae* sequence type 258. *Antimicrob Agents Chemother* 2010; 54: 4493–4496.
168. Zacharczuk K, Piekarska K, Szych J *et al.* Emergence of *Klebsiella pneumoniae* coproducing KPC-2 and 16S rRNA methylase ArmA in Poland. *Antimicrob Agents Chemother* 2011; 55: 443–446.
169. Sękowska A, Hryniewicz W, Gniadkowski M *et al.* Antimicrobial susceptibility of metallo-beta-lactamase positive and negative *Klebsiel-*

la pneumoniae strains isolated from intensive care unit patients. *Pol J Microbiol* 2010; 59: 67–69.
170. Hrabák J, Niemczyková J, Chudáčková E *et al.* KPC-2-producing *Klebsiella pneumoniae* isolated from a Czech patient previously hospitalized in Greece and *in vivo* selection of colistin resistance. *Folia Microbiol (Praha)* 2011; 56: 361–365.
171. Tóth A, Damjanova I, Puskás E *et al.* Emergence of a colistin-resistant KPC-2-producing *Klebsiella pneumoniae* ST258 clone in Hungary. *Eur J Clin Microbiol Infect Dis* 2010; 29: 765–769.
172. Henwood CJ, Gatward T, Warner M *et al.* Antibiotic resistance among clinical isolates of *Acinetobacter* in the UK, and *in vitro* evaluation of tigecycline (GAR-936). *J Antimicrob Chemother* 2002; 49: 479–487.
173. Woodford N, Zhang J, Warner M *et al.* Arrival of *Klebsiella pneumoniae* producing KPC carbapenemase in the United Kingdom. *J Antimicrob Chemother* 2008; 62: 1261–1264.
174. Stone NRH, Woodford N, Livermore DM *et al.* Breakthrough bacteraemia due to tigecycline-resistant *Escherichia coli* with New Delhi metallo-b-lactamase (NDM)-1 successfully treated with colistin in a patient with calciphylaxis. *J Antimicrob Chemother* 2011; 66: 2677–2678.
175. Livermore DM, Warner M, Mushtaq S *et al.* What remains against carbapenem-resistant *Enterobacteriaceae*? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. *Int J Antimicrob Agents* 2011; 37: 415–419.
176. Roche C, Cotter M, O'Connell N, Crowley B. First identification of class A carbapenemase-producing *Klebsiella pneumoniae* in the Republic of Ireland. *Euro Surveill* 2009; 14: pii: 19163.
177. Prior AR, Roche C, Lynch M, Kelly S, O'Rourke K, Crowley B. First identified case of VIM-producing carbapenem-resistant *Klebsiella pneumoniae* in the Republic of Ireland associated with fatal outcome. *Euro Surveill* 2010; 15: pii: 19752.
178. Morris D, Boyle F, Ludden C *et al.* Production of KPC-2 carbapenemase by an *Escherichia coli* clinical isolate belonging to the international ST131 clone. *Antimicrob Agents Chemother* 2011; 55: 4935–4936.
179. O'Brien DJ, Wrenn C, Roche C *et al.* First isolation and outbreak of OXA-48-producing *Klebsiella* 271 *pneumoniae* in an Irish hospital, March to June 2011. *Euro Surveill* 2011; 16: pii: 19921.
180. Samuelsen Ø, Thilesen CM, Heggelund L *et al.* Identification of NDM-1-producing *Enterobacteriaceae* in Norway. *J Antimicrob Chemother* 2011; 66: 670–672.
181. Österblad M, Kirveskari J, Koskela S *et al.* First isolations of KPC-2-carrying ST258 *Klebsiella pneumoniae* strains in Finland, June and August 2009. *Euro Surveill* 2009; 14: pii: 19349.
182. Tegmark Wisell K, Haeggman S, Gezelius L *et al.* Identification of *Klebsiella pneumoniae* carbapenemase in Sweden. *Euro Surveill* 2007; 12: E071220.3.
183. Hammerum AM, Hansen F, Lester CH *et al.* Detection of the first two *Klebsiella pneumoniae* isolates with sequence type 258 producing KPC-2 carbapenemase in Denmark. *Int J Antimicrob Agents* 2010; 35: 610–612.
184. Hammerum AM, Toleman MA, Hansen F *et al.* Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* 2010; 10: 829–830.