

Emergence of carbapenemase-producing Enterobacteriaceae in France, 2004 to 2011

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Emergence of carbapenemase-producing Enterobacteriaceae (CPE) is currently a major public health concern worldwide. This study showed that 53 episodes of CPE infection or colonisation have been notified by French healthcare facilities since 2004. A sharp increase in the number of notifications was observed in the last three years. Oxacillinase (OXA)-48 and *Klebsiella pneumoniae* carbapenemase (KPC) beta-lactamases were the most frequent enzymes reported in these episodes. The index cases in most episodes were patients with a history of hospitalisation abroad within the previous year. Around a third of the episodes (n=18) led to secondary transmission in hospitals but most of them were controlled due to reinforced measures. Reinforcement of screening and control measures at national level when there is cross-border transfer of patients, along with overall reinforcement of infection control and antimicrobial stewardship worldwide, is urgently needed to contain the spread of CPE.

Introduction

As Enterobacteriaceae become increasingly resistant to antibiotics, carbapenems are among the few last-line drugs available for therapy against serious infections, such as pyelonephritis or bacteraemia, caused by multidrug-resistant strains, particularly those expressing extended-spectrum beta-lactamases. Resistance to carbapenems, resulting from carbapenemases, reduces the possibility of treating infections of multidrug-resistant strains. Carbapenemase-producing Enterobacteriaceae (CPE) have been reported increasingly worldwide and are becoming a major clinical and public health concern, as they constitute the last step towards a therapeutic dead end.

Carbapenemases belong to three molecular classes of beta-lactamases (A, B and D). Chromosome-encoded class A carbapenemases were first reported in 1994 [1]. The first plasmid-encoded class A carbapenemase, *Klebsiella pneumoniae* carbapenemase (KPC), was discovered in 1996 and reported for the first time in 2001

from the United States in a *K. pneumoniae* clinical isolate [2]. Since then, KPC-producing isolates have spread worldwide, notably in Greece and Israel, where they are now endemic [3,4]. The metallo-beta-lactamases (class B), such as Verona integron-encoded metallo-beta-lactamase (VIM) and imipenemase (IMP), are currently prevalent in Greece, Italy, Japan and Spain. Belonging to the same class, New Delhi metallo-beta-lactamase (NDM)-1 has recently emerged in India, Pakistan and the United Kingdom [5,6]. NDM-1 represents a serious threat of rapid dissemination of multiple antibiotic resistance since the majority of NDM 1-producing Enterobacteriaceae have been reported to remain susceptible only to colistin and tigecycline [5]. The first of the class D beta-lactamases with carbapenemase activity was described in 1995 [1]. Among this class, oxacillinase (OXA)-48, which was discovered in a clinical *K. pneumoniae* isolate in 2004, has been identified mostly in Mediterranean countries, especially Turkey [1,7].

In France, resistance of Enterobacteriaceae to carbapenems remains uncommon. According to data from the European Antimicrobial Resistance Surveillance Network (EARS-Net), the proportion of carbapenem-resistant strains among strains isolated from patients with invasive infections in 2009 was 0.03% (2 of 7,731) for *Escherichia coli* and 0.16% (2 of 1,268) for *K. pneumoniae* [8]. However, CPE isolates have already been described in France and were involved in sporadic cases or limited outbreaks [3,9-15].

Since 2001, a national Healthcare-Associated Infections Early Warning and Response System (HAI-EWRS) has been implemented in France to quickly detect unusual and emerging events in hospitals, promote outbreak investigations and implement control measures [16]. Healthcare facilities are mandatorily obliged to notify such events to interregional infection control coordinating centres (CCLins), so they can receive technical assistance and to regional health authorities for the follow up of control measures. Notifications are then forwarded to the French Institute for Public Health

Surveillance (Institut de Veille Sanitaire, InVS) for second-line assistance and the monitoring of trends. For microbiological expertise, healthcare facilities can rely on a network of national reference centres (NRCs), funded and coordinated by InVS [17] or expert laboratories located in major university hospitals or research centres.

The objectives of this study were to review, quantify and describe the characteristics of CPE episodes reported to InVS during February 2004 (when the first CPE cases were notified) to 11 April 2011.

Methods

Definitions

We defined a case as a patient infected or colonised by a CPE that was confirmed by a reference or expert laboratory. The clinical diagnosis of infection or colonisation was made by the physician in charge of the patient.

An episode was defined as one sporadic case or several cases related by an identified chain of transmission. A chain of transmission was established between two or more cases if they had been in contact, i.e. they shared the same healthcare workers (nurse, auxiliary staff or physician).

Epidemiological investigation

We included all the episodes that were notified by healthcare facilities through the French HAI-EWRS. We also included other episodes that were retrospectively identified through a survey of French microbiologists known to have an interest and expertise in Enterobacteriaceae beta-lactamases, conducted by InVS by email in August 2010. Follow-up data on each

notified episode were provided to InVS by CClins or laboratories.

For each episode, we documented the patients' demographic characteristics, number of infected or colonised patients, site of infection/colonisation, number of reported deaths, bacterial species, types of carbapenemase (as identified by the Antimicrobial Resistance NRC, based at the Institut Pasteur in Paris, or expert laboratories), existence of an epidemiological link between the index case and a foreign country, name of this country and the nature of the link (previous stay or hospitalisation abroad within one year of hospitalisation in France).

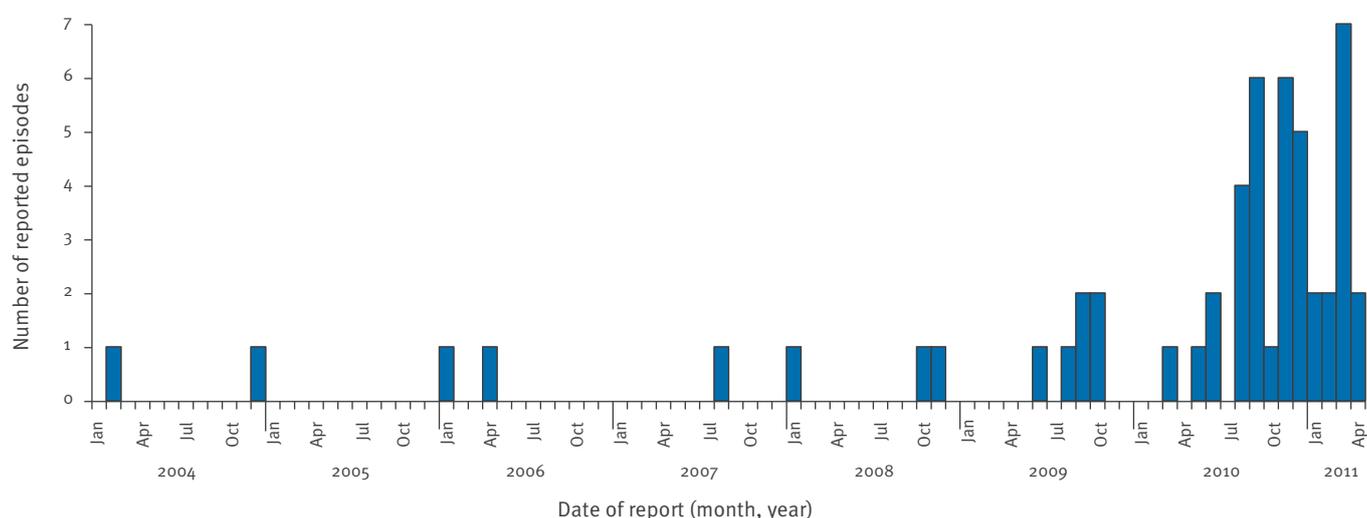
Microbiological investigations

Antibiotic susceptibility was tested by disc diffusion on Mueller-Hinton agar according to standards of the Antibiogram Committee of the French Microbiology Society [18].

In carbapenem-resistant strains, carbapenemase production was detected using Hodge test, and synergy test between carbapenems and ethylenediaminetetraacetic acid (EDTA) (for class B metallo beta-lactamases) or clavulanic acid (for class A beta-lactamases) [19]. The genes encoding carbapenemases were identified by the Antimicrobial Resistance NRC or 13 expert laboratories using PCR and sequencing of the amplified product [20]. In every PCR analysis, a positive control strain was included. All expert laboratories were located in major university hospitals or research centres and were involved in external quality assessment at the national level (through the French Health Products Safety Agency, Afssaps) or international level (through EARS-Net). The Antimicrobial Resistance NRC follows Institut Pasteur quality control policies.

FIGURE

Monthly number of episodes of carbapenemase-producing Enterobacteriaceae infection or colonisation, France, 1 January 2004–11 April 2011 (n=53)



Results

Number and location of CPE episodes

The first reported CPE episode occurred in France in February 2004 [12]. The yearly number of episodes remained low (1–3 episodes) until 2009, when a sharp increase was observed: 6, 26 and 13 episodes in 2009, 2010 and the first four months of 2011, respectively (Figure). A total of 53 CPE episodes were identified in France between February 2004 and April 2011, most of which (n=50) were reported through the HAI-EWRS.

These 53 episodes were reported in the following areas of France: Paris and the north of the country (n=36), south-east (n=8), east (n=4), west (n=3) and south-west (n=2).

Bacteria and resistance mechanisms

The CPE that were reported were mainly *K. pneumoniae* (n=33 episodes), but also *E. coli* (n=14), *Enterobacter cloacae* (n=6), *Enterobacter aerogenes* (n=3), *Citrobacter freundii* (n=2), *Serratia marcescens* (n=1) or *Proteus mirabilis* (n=1). Two or three species of Enterobacteriaceae were isolated in six episodes.

The carbapenemases involved in the 53 episodes were OXA-48 (n=23), KPC (n=16), VIM (n=6), NDM-1 (n=7) and VIM plus IMP (n=1) (Table 1).

Epidemiological description of the CPE episodes

The 53 episodes accounted for a total of 169 cases, comprising 52 infections and 112 colonisations (data available for 164 cases). Among the 169 cases, 43 deaths were reported, giving an estimated crude lethality rate (deaths of all cases, whether infected or colonised) of 25%.

Of the 53 episodes, 36 included a single, sporadic case. Secondary cases were reported in 18 episodes: the total number of cases in these 18 episodes ranged from 2 (in six episodes) to 32 (one episode). The mean number of cases by cluster was seven (median: four cases).

A total of 54 index cases were identified. In one episode, two co-index cases (two members of the same family repatriated at the same time) were reported. Of the 54 index cases with available information, 37 were found to be colonised, at least at one site: digestive tract (n=27 episodes), urinary tract (n=5), skin (n=2), respiratory tract (n=3) abdominal tract (n=1) or gynaecological tract (n=1). A total of 16 were infected at least at one site: urinary tract (n=6), respiratory tract (n=3), abdominal or gastrointestinal tract (n=5), bloodstream (n=3) and skin or soft tissue (n=1). The clinical diagnosis of infection or colonisation was not available for one index case and the clinical site was not available for two colonised and one infected index cases.

Episodes of particular importance

Several episodes were of particular importance, considering their impact on healthcare activities. In 2004, an outbreak of eight cases with VIM-1-producing *K. pneumoniae* (including five infections) occurred after the transfer of a patient from a Greek hospital. This outbreak, which lasted six months, was finally controlled after implementation of extended control and screening measures and led to the screening of 277 contact-patients [9,12]. In 2009, 13 cases with KPC-producing *K. pneumoniae* (two infections) were associated with a contaminated endoscope and transmission from patient to patient during healthcare in three hospitals. Controlling this outbreak also required implementation of extended control and screening measures and led to

TABLE 1

Bacterial species and carbapenemase type in 53 episodes of carbapenemase-producing Enterobacteriaceae infection or colonisation, France, 1 January 2004–11 April 2011

Bacterial species	Number of episodes by type of carbapenemase					Total
	OXA-48	KPC	NDM-1	VIM	VIM and IMP	
<i>Klebsiella pneumoniae</i>	12	14	3	4	0	33
<i>Escherichia coli</i>	9	1	3	1	0	14
<i>Enterobacter cloacae</i>	4	1	0	1	0	6
<i>Enterobacter aerogenes</i>	2	0	0	0	1	3
<i>Citrobacter freundii</i>	1	0	1	0	0	2
<i>Proteus mirabilis</i>	0	0	1	0	0	1
<i>Serratia marcescens</i>	1	0	0	0	0	1
Total	23^a	16	7^b	6	1	53^c

IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Delhi metallo-beta-lactamase; OXA: oxacillinase; VIM: Verona integron-encoded metallo-beta-lactamase.

^a OXA-48 was involved in four episodes with two bacterial species and in one episode with three species.

^b NDM-1 was involved in one episode with two bacterial species isolated from patients with a possible epidemiological link.

^c Five episodes involved two species with the same carbapenemase and one episode involved three species with the same carbapenemase.

the screening of 341 contact-patients in five healthcare facilities. The index case was a patient transferred from Greece [14,21]. In 2010, an outbreak of 13 cases with OXA-48-producing *K. pneumoniae* (seven infections) led to the screening of more than 280 contact-patients in 15 healthcare facilities. Interestingly, the index case in this episode did not report any travel abroad [22]. In addition, an ongoing episode of OXA-48-producing *K. pneumoniae*, which was notified in November 2010, has included 32 cases (infections or colonisations) to date and has led to the screening of contact-patients in more than 10 healthcare facilities.

Seven episodes were associated with NDM-1-mediated carbapenem-resistance: five were reported in 2010 and two during the first three months of 2011. In these seven episodes, there were six index cases who reported travel within the previous year to India and one to Iraq [23-25]. Five were hospitalised abroad before their transfer to a French hospital. Two lived in India and had received healthcare in France, but had no reported hospitalisation in India within the previous year. Nine cases were associated with these episodes; the bacterial species involved are reported in Table 1. No deaths were reported.

Association with cross-border transfer

Of the 53 episodes, 42 were associated with cross-border transfers: the index cases had been transferred directly from a foreign hospital to a French hospital (n=27 episodes), or had been hospitalised in a foreign hospital a few days (n=1), a few weeks (n=1), between one and six months (n=4) or one year (n=1) before their hospitalisation in France. In three additional episodes, the index cases lived abroad and had no reported

hospitalisation in the previous year (two of the index cases were colonised; the other was infected). In the other five episodes, the index cases had spent weeks or months in a foreign country before their hospitalisation in France, but without any reported hospitalisation abroad. These five index cases were colonised.

In the 42 episodes associated with cross-border transfers, the countries where index cases had travelled, been hospitalised or had lived were Greece (n=14 episodes), Morocco (n=7), India (n=6), Italy (n=4), Algeria (n=3), Tunisia (n=2), Egypt (n=2), Turkey (n=2), United States (n=1) and Iraq (n=1). Of the 14 episodes involving cross-border transfer with North Africa (Morocco, Algeria, Tunisia and Egypt), 12 were associated with OXA-48-producing bacteria (Table 2).

In 11 of the 53 episodes, the index cases had not travelled, been hospitalised or lived in a foreign country, before their hospitalisation in France. Among these index cases, one was reported from Réunion. The majority of these episodes (n=9) were associated with OXA-48 carbapenemase (Table 2).

Discussion and conclusion

Although national surveillance data demonstrate that Enterobacteriaceae resistance to carbapenems remains rare in France, our study, based on HAI-EWRS notifications and a survey among French microbiologists, strongly suggests that CPE are emerging in French healthcare facilities and have an important impact on the organisation of health care. It also demonstrates the ability of the French HAI-EWRS to detect unusual and emerging events in hospitals, since a large majority of CPE episodes have been reported through this

TABLE 2

Carbapenemase type in 53 episodes of carbapenemase-producing Enterobacteriaceae infection or colonisation, France, 1 January 2004–11 April 2011, by country where index cases had been hospitalised or stayed abroad

Country	Number of episodes ^a by type of carbapenemase					Total
	OXA-48	KPC	NDM-1	VIM	VIM and IMP	
Greece	0	11 (2007)	0	3 (2004)	0	14
Morocco	7 (2010)	0	0	0	0	7
India	0	0	6 (2010)	0	0	6
Italy	0	2 (2010)	0	2 (2008)	0	4
Algeria	1 (2010)	1 (2010)	0	1 (2008)	0	3
Tunisia	2 (2011)	0	0	0	0	2
Egypt	2 (2009)	0	0	0	0	2
Turkey	2 (2010)	0	0	0	0	2
Iraq	0	0	1 (2010)	0	0	1
United States	0	1 (2006)	0	0	0	1
No stay or hospitalisation abroad reported	9 (2010)	1 (2010)	0	0	1 (2004)	11
Total	23	16	7	6	1	53

IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Delhi metallo-beta-lactamase; OXA: oxacillinase; VIM: Verona integron-encoded metallo-beta-lactamase.

^a The years in parentheses are the year the first case in this study was reported.

system. The effectiveness of HAI-EWRS has also been demonstrated with other emerging pathogens in the recent past [26-28].

In this survey of CPE episodes notified in France, most of the reported episodes comprised sporadic cases and were related to cross-border transfer, mainly after hospitalisation in countries abroad where CPE are endemic. OXA-48 was the most frequent type of carbapenemase and was often associated with index cases who had been previously hospitalised in North Africa and Turkey. The second most frequent carbapenemase was KPC, which was often associated with index cases previously hospitalised in Greece. The types of carbapenemase observed by country of origin for index cases are highly consistent with those previously described in these countries: NDM-1 in the Indian sub-continent [5,23], KPC notably in Greece and the United States [3,4], OXA-48 in Turkey [29,30], Tunisia [31] and Morocco [32]. In Greece, the proportion of carbapenem-resistant strains among *K. pneumoniae* increased from 27.8% to 43.5% during 2005 to 2009 [8]. Interestingly, the origin of index cases was also highly consistent with population migration routes and countries most frequently visited by French tourists [33].

As cross-border transfer and globalisation are major trends in the world today, awareness of the risk of spread of multidrug resistance, such as carbapenemase-mediated resistance of Enterobacteriaceae by cross-border transfer of patients, needs to be emphasised. Furthermore, appropriate control measures need to be strongly reinforced in countries where carbapenemase-producing Enterobacteriaceae are endemic [34,35]. In addition, in order to prevent or to delay emergence of carbapenemase-mediated resistance in countries with low prevalence, such as France, it is essential to rapidly identify CPE by screening carriers among patients transferred from hospitals in countries with high prevalence of these organisms and to implement adequate control measures.

In response to the trends observed, the French Healthcare Safety Advisory Committee issued in 2010 national recommendations for screening and presumptive isolation with contact precautions of patients transferred from or hospitalised abroad. These recommendations target two multidrug-resistant pathogens with a low prevalence in France (vancomycin-resistant enterococci, VRE, and CPE). Healthcare facilities are requested to notify immediately CCLins and regional health authorities about any suspected episodes of VRE or CPE infection/colonisation and laboratories should send strains to the Antimicrobial Resistance NRC or an expert laboratory for confirmation [36]. If a case is confirmed, adequate control measures should be rapidly implemented: reinforcement of standard and contact precautions, contact tracing and cohorting of patients into three distinct sectors (one for cases, one for contact-patients and one for newly admitted VRE- or CPE-free patients) [36,37]. Such a strict strategy of

cohorting patients – which had been developed and field-tested in healthcare facilities that experienced the first CPE outbreaks and was later disseminated through national recommendations – has limited the number of secondary cases and has led to the control of CPE outbreaks [9,21].

In 11 of the 53 reported episodes, the index cases had not crossed any border. Nine of the 11 were due to OXA-48 carbapenemase. Although a chain of transmission resulting from contact with an unknown traveller from abroad could have been missed, the beginning of autochthonous circulation of CPE in France cannot be excluded. Almost all of these 11 episodes (n=10) have been reported since 2010: this recent trend emphasises the need for sustained vigilance when carbapenem resistance is suspected in Enterobacteriaceae isolated from any patient. Moreover, it also underlines the need for better antimicrobial stewardship in France. In French healthcare facilities, carbapenem consumption increased from 2.0 defined daily doses per 1,000 bed-days in 1999 to 4.8 per 1,000 in 2009 (P. Cavalié, Afssaps, personal communication, November 2010) and is most probably related to the spread of Enterobacteriaceae producing extended-spectrum beta-lactamases [8].

Our study has some limitations. First, the completeness of reporting cannot be guaranteed since (i) all French healthcare facilities do not have the capacity to identify patients with CPE and should therefore rely on the help of the Antimicrobial Resistance NRC or an expert laboratory, (ii) some healthcare facilities may not report them (despite reporting being mandatory and strongly encouraged) and (iii) data collected through HAI-EWRS could be incomplete. Conversely, recent emphasis on CPE in the scientific literature, national recommendations and media reports could have triggered better reporting and may partly explain the sharp increase in the number of reported episodes observed in 2010.

Second, the impact of CPE on patients' morbidity or mortality is difficult to assess. The crude mortality rate of cases in this study was high, as was reported in outbreaks with extended-spectrum beta-lactamase-producing Enterobacteriaceae [38,39]. However, crude estimates of lethality are not easy to interpret because of the difficulties in ascertaining retrospectively the cause of deaths in patients with multiple pathologies, and as it is not known whether the patients who died had been infected or colonised.

Last, six episodes involved more than one bacteria species with the same resistance mechanism, but no microbiological data were available that could account for this. Such bacteria could have been identified among the same or different patients and, as reported previously, interspecies transmission of carbapenemase genes by transposons or by self-transferable plasmids could have occurred [40].

Improving coordination between the Antimicrobial Resistance NRC and expert laboratories, healthcare facilities and InVS in the surveillance of CPE should allow episodes to be better documented, future trends to be monitored and the impact of current national recommendations to be assessed.

In conclusion, emergence of CPE in France, Europe and worldwide is nowadays a major medical and public health concern because it may lead to therapeutic dead-ends. The French HAI-EWRS demonstrated to be an effective tool to detect and monitor CPE emergence and to promote adequate recommendations for control. To date, most of episodes reported in France have been associated with a sporadic case who had been hospitalised, had travelled or had lived in foreign countries where CPE are prevalent.

The need to contain CPE emergence in France justifies reinforcing control measures when there is cross-border transfer. However, such measures might have a limited impact in the long term if no similar measures are implemented to control the sources abroad. Increasing laboratories' capacities, infection control and antimicrobial stewardship at a global level is therefore urgently needed for a successful fight against this new type of antimicrobial resistance.

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