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The difficult-to-control spread of carbapenemase producers among *Enterobacteriaceae* worldwide

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Abstract

The spread of carbapenemase producers in *Enterobacteriaceae* has now been identified worldwide. Three main carbapenemases have been reported; they belong to three classes of β-lactamases, which are KPC, NDM, and OXA-48. The main reservoirs of KPC are *Klebsiella pneumoniae* in the USA, Israel, Greece, and Italy, those of NDM are *K. pneumoniae* and *Escherichia coli* in the Indian subcontinent, and those of OXA-48 are *K. pneumoniae* and *Escherichia coli* in North Africa and Turkey. KPC producers have been mostly identified among nosocomial isolates, whereas NDM and OXA-48 producers are both nosocomial and community-acquired pathogens. Control of their spread is still possible in hospital settings, and relies on the use of rapid diagnostic techniques and the strict implemention of hygiene measures.

Keywords: Carbapenemase, *Enterobacteriaceae*, KPC, NDM, OXA-48
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Introduction

Although they were rarely reported a decade ago, carbapenemase-producing *Enterobacteriaceae* are now being extensively reported. Different groups of enzymes possessing carbapenemase properties have emerged, and are spreading worldwide. Some of these enzymes hydrolyse carbapenems very efficiently, whereas others show weak activity against carbapenems. Some include broad-spectrum cephalosporins in their hydrolytic pattern, and some do not. Some have activity that may be inhibited (at least partially) by β-lactamase inhibitors (such as clavulanic acid and tazobactam), whereas most are not inhibited by clinically available inhibitors. However, these significant differences do not really explain the successful spread of specific enzymes in specific countries or areas [1].

The main features related to the epidemiology of these enzymes are as follows:

1. The first parameter is the primary reservoir. Indeed, it is very likely that a specific enzyme will emerge in a given geographical area where many favourable conditions exist, such as a high-density population, poor hygiene, and high selective pressure linked to overuse and misuse of antibiotics.
2. The second parameter concerns the genetics of the carbapenemase gene, as some genetic structures are prone to enhance gene plasticity and mobility. Some integron or transposon structures and plasmids may indeed favour horizontal gene transfer. Some plasmids possess a broad host range for replication, and can therefore enhance interspecies dissemination, whereas some others possess a narrow host range. Some plasmids replicate very efficiently and are self-conjugative, whereas others are not self-conjugative or conjugate at very low rate. The genetic background of the strain harbouring the carbapenemase gene may also play an important role, as the emergence of one gene in a so-called successful clone (being, for instance, more likely to disseminate from patient to patient, or more able to survive on dry surfaces) can favour the initial spread of a carbapenemase through the spread of the corresponding bacterial host.

3. The third main parameter concerns the level of human population exchanges once a reservoir has been constituted. If the emergence of a carbapenemase occurs in a geographical area where the population is mobile (an important worldwide-located diaspora, tourism, or medical tourism), then the likelihood of seeing that resistance determinant emerging worldwide is high.

The spread of carbapenemase genes is explained by a combination of these three parameters. Among the four molecular classes according to the Ambler classification [2], carbapenemases can be found in classes A, B, and D.

The Class A Carbapenem-hydrolysing β-lactamases

The first carbapenemase (NmcA; non-metallo-carbapenemase of class A) was identified >20 years ago in an *Enterobacter cloacae* isolate. Since then, the SME enzymes (*Serratia marcescens* enzymes) have been identified in *S. marcescens*. This family includes five variants (SME-1 to SME-5), all of which are chromosomally encoded [3] and have been recovered sporadically throughout the USA and Canada [4–6] (M. Mulvey, unpublished). The IMI enzymes (imipenem-hydrolysing β-lactamases) have been detected in rare isolates of *Enterobacter* in the USA [7], France [8], Croatia [9], Finland [10], and Argentina[11], and, more recently, a colistin-resistant *Enterobacter asburiae* isolate was recovered in Ireland [12]. The genes encoding these carbapenemases are mostly chromosomally located and associated with AmpC-type regulation (LysR-dependent), limiting their spread and their expression at a high level. However, genes encoding the IMI-2 variant have been found to be plasmid-located in environmental *E. asburiae* strains recovered from several US rivers [13] and in a single *E. cloacae* isolate in China [14].

The first variant of the GES family (for 'Guiana extended-spectrum β-lactamase'), i.e. GES-1, which is not a carbapenemase, was reported in 2000. The GES family now includes 24 variants (http://www.lahey.org/Studies/other.asp#table 1) [15]. All GES variants possess the ability to hydrolyse broad-spectrum cephalosporins, but, as a result of specific amino acid substitutions inside the active site, extension of their spectrum of activity towards carbapenems has been identified for several variants [16]. Among these variants, GES-2, GES-4, GES-5, GES-6, GES-11, GES-14 and GES-18 hydrolyse imipenem efficiently [17]. Although they are quite rare, GES enzymes have been identified worldwide. Among those GES variants for which significant carbapenemase activity has been noted are the following: GES-2 identified in *Pseudomonas aeruginosa*, with one clone being the cause of a nosocomial outbreak in South Africa [18]; and GES-5 identified in *Enterobacteriaceae* and *P. aeruginosa*, which has been widely reported in South America (Brazil) [19,20], and for which there are some scattered reports in Turkey [21] and South Korea [22]. GES-11 and GES-14 have been identified only in *Acinetobacter baumannii* [23], and GES-18 has been identified in *P. aeruginosa* but not in *Enterobacteriaceae* [24].

It is noteworthy that this GES-5 variant possessing significant carbapenemase activity has disseminated quite widely, being found not only in nosocomial settings but also in the environment in South America [25], and being the main carbapenem-hydrolysing GES-type enzyme identified in *Enterobacteriaceae*. The high rate of GES-5 producers in South America and, in particular, in Brazil [26] might be a consequence of the occurrence of the non-carbapenemase GES-1 variant in the same geographical area [27]. It might be speculated that selective pressure resulting from the use of carbapenems has resulted in the emergence of GES-5.

KPC enzymes (*Klebsiella pneumoniae* carbapenemases) are currently the most clinically significant enzymes among the class A carbapenemases. They have been mainly identified in *K. pneumoniae*, which is an important nosocomial pathogen, and confer high levels of resistance not only to carbapenems but also to most β-lactams, including broad-spectrum cephalosporins. The first KPC producer (a KPC-2-positive *K. pneumoniae*) was identified in 1996 on the eastern coast of the USA [28], and since then a series of variants have been identified, even though KPC-2 remains the most commonly identified variant. There are now 19 KPC variants, all being point-mutant derivatives of a common amino acid sequence. Within a few years, KPC producers spread globally and were identified in many Gram-negative species, even though KPC enzymes have been mostly identified in *K. pneumoniae* [29] (Fig. 1). In Latin America, KPC producers are endemic in some areas, such as in Colombia and Argentina [29]. Some reports have also shown the occurrence of KPC producers in Puerto Rico and Mexico [30,31] (Fig. 1).

In Europe, KPC producers have been found almost everywhere, mostly being being linked to importation from endemic areas [29]. Those endemic areas in Europe are Greece and Italy, and probably Poland, where nosocomial outbreaks caused by KPC-producing *K. pneumoniae* often occur [32]. In Israel, endemicity of KPC producers has been demonstrated by many studies, with a large number of nosocomial reports, but also, noticeably, some cases occurring in the community [29,33].

The extent of the diffusion of KPC in Southeast Asia is not well known, even though China is considered to be a country where some areas are facing endemic situations [29]. In India,

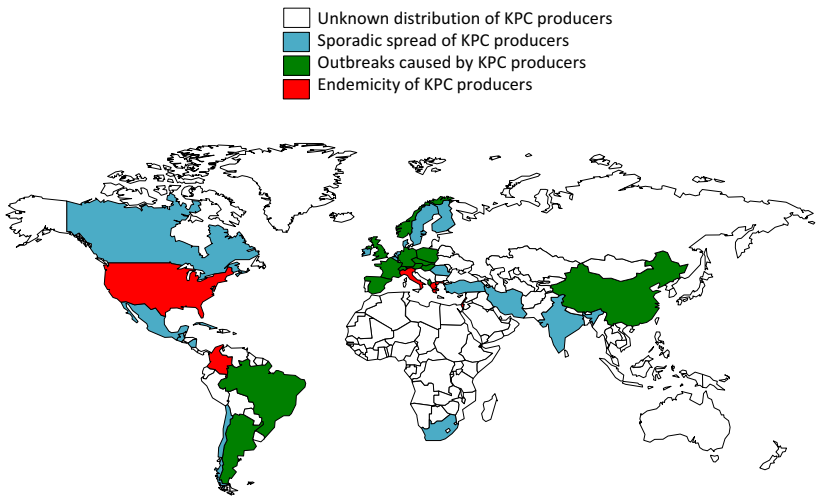

FIG. 1. Geographical distribution of KPC producers.

there are very few reports on KPC-producing isolates, the most commonly identified carbapenemases being NDM and OXA-48-like enzymes (see below). However, there are some reports showing that KPC producers are occurring in India [34,35].

It is noteworthy that one specific KPC-2-producing or KPC-3-producing *K. pneumoniae* clone (sequence type 258) has been extensively identified worldwide [36], indicating that it has significantly contributed to the spread of this resistance trait.

The Class B Metallo-β-lactamases (MBLs)

MBLs, which are known to be intrinsic in many environmental and opportunistic bacterial species, have been identified as acquired enzymes since the early 1990s, either in *Pseudomonas* or in *Enterobacteriaceae* [37]. The most common families of acquired class B MBLs identified in *Enterobacteriaceae* include the VIM and IMP groups [37], together with the emerging NDM group (see below), whereas others, such as GIM-1 and KHM-1, have been found only sporadically [38,39]. Although they have been reported worldwide, the VIM producers among *Enterobacteriaceae* are highly prevalent in the southern part of Europe and around the Mediterranean Sea (first reported in Italy by Cornaglia *et al.*), whereas the IMP producers remain mostly located in Asia [37].

IMP-type β-lactamases were the first acquired MBLs to be identified, and have been detected in a series of clinically important Gram-negative bacilli, such as *Enterobacteriaceae*, *Pseudomonas*, and *Acinetobacter*. Among *Enterobacteriaceae*, IMP-1 was found in an *S. marcescens* isolate in Japan in 1991 [40]. So far, 48 IMP variants have been assigned, and IMP-type carbapenemase producers have spread worldwide. However, the frequency of IMP-producing isolates worldwide is much less than that of KPC, VIM, NDM or OXA-48 producers. The wide spread of IMP-type enzymes has been demonstrated mainly in Japan, Taiwan, and eastern China, although there are single reports from many other countries, and isolates producing these enzymes have sometimes caused nosocomial outbreaks. Another type of MBL corresponds to the VIM-type enzymes (Verona integron-encoded MBLs). VIM-1 was first identified in Italy in 1997 [41,42], and VIM-2 was then reported in France in a *P. aeruginosa* isolate dating from 1996 [43]. Currently, the VIM family includes 41 variants, which have been mainly identified in *P. aeruginosa* but also in enterobacterial isolates. VIM-2 is actually the most commonly reported MBL worldwide [1], with endemic spread in southern Europe (Greece, Spain, and Italy) and Southeast Asia (South Korea and Taiwan), but has also caused outbreaks in Africa, in particular in the Ivory Coast [44], South Africa [45], Tunisia [46], and some European countries, such as Germany [47], The Netherlands [48], and France [49,50]. These outbreaks have mainly involved VIM-producing *P. aeruginosa*, and rarely enterobacterial species. In Europe, Greece is known to be endemic for VIM-1-producing *Enterobacteriaceae*. Many Greek studies have reported the spread of VIM-1-producing *K. pneumoniae* at a national level, but this enzyme has also been identified in *Escherichia coli*, *Citrobacter freundii*, *Morganella morganii*, *Serratia* species, and *Klebsiella oxytoca* [51,52].

Recently, the KHM-1 β-lactamase was identified in Japan in a single *C. freundii* clinical isolate that had been recovered in 1997 [39]. The GIM-1 MBL (which stands for 'German imipenemase'), which was first identified in a *P. aeruginosa* isolate from Germany [38], has since been identified in other *P. aeruginosa* isolates [53], and also in *S. marcescens* [54], *E. cloacae* [55], and *Acinetobacter pittii* [56]. Worringly, GIM-1 was recently identified in many enterobacterial species,

including *Escherichia coli*, *C. freundii*, and *K. oxytoca*, always in Germany [53]. The other described acquired MBLs include SPM-1 [57], SIM-1 [58], DIM-1 [59], TMB-1 [60], and AIM-1 [61], but they have not been identified in *Enterobacteriaceae*, being found either in *Pseudomonas* or *Acinetobacter*.

One of the most most clinically significant carbapenemase is NDM-1 (New Delhi metallo-β-lactamase), which was described in 2009, the corresponding *K. pneumoniae* and *Escherichia coli* isolates being from a Swedish patient of Indian origin hospitalized in Örebro, Sweden, after a hospital stay in New Delhi [62,63]. NDM-1 shares very little identity with other MBLs, the most similar being VIM-1/VIM-2, with only 32.4% amino acid identity. NDM-1 efficiently hydrolyses a broad range of β-lactams, including penicillins, cephalosporins, and carbapenems, but sparing monobactams such as aztreonam [62]. Since the first description of NDM-1, eight variants of this enzyme have been published (NDM-1 to NDM-8), and 12 have been assigned (http://www.lahey.org); most of them originated from Asia [64–66]. As compared with NDM-1, the NDM-4, NDM-5 and NDM-7 variants possess increased activity towards carbapenems [67–70]. A detailed analysis of the resistance patterns shows their systematic association with other antibiotic resistance determinants, such as plasmid-mediated AmpC cephalosporinases, clavulanic acid-inhibited expanded-spectrum β-lactamases, other types of carbapenemases (OXA-48, VIM and KPC types), and enzymes conferring broad-spectrum resistance to aminoglycosides (16S RNA methylases), to quinolones (Qnr), to macrolides (esterases), to rifampicin (rifampicin-modifying enzymes), to chloramphenicol, and to sulphamethoxazole [71,72]. Consequently, many of the NDM-1 producers remain susceptible only to colistin, fosfomycin, and tigecycline [73].

The main identified reservoir of NDM-producing *Enterobacteriaceae* is the Indian subcontinent (Pakistan, India, and Sri Lanka) [63] (Fig. 2). The spread of NDM producers has been extensively identified not only among patients from the Indian subcontinent, but also in the soil [74,75]. Therefore, it is likely that the environment is already heavily contaminated with NDM producers. The prevalence of carriage is estimated to be 5–15% in that part of the world [76,77]. Significant spread of NDM producers has also been identified in the UK, which has close relationships with India and Pakistan [65]. Subsequently, NDM producers among *Enterobacteriaceae* have been reported in almost all of world, including many countries in Asia, Africa, Australia, the Americas, and Europe [78]. NDM producers are now on top of the list of carbapenemase producers in European countries such as the UK and France [63,65].

Other particularly important sources of NDM producers (or established secondary reservoirs) are the Balkan states [79,80], the Arabian peninsula [81,82], and North African countries [64]. The impact of intercontinental travel as a source of spread of NDM producers has been extensively reported. NDM producers have been extensively identified in countries where many Indians and Pakistanis live, such as Canada, the USA, the UK, Ireland, South Africa, Saudi Arabia, the Gulf countries, and Australia. It is noteworthy that the identification of NDM producers is not always associated with an Indian subcontinental origin, supporting the hypothesis of established secondary reservoirs [83–87].

All NDM-producing enterobacterial species have been found to be involved in infections, but *K. pneumoniae* and *Escherichia coli* are the main causes of hospital and community-acquired infections, respectively. The frequent identification of NDM-producing *Escherichia coli* is of concern, considering that *Escherichia coli* is the main pathogen responsible for urinary tract infections, community-acquired infections, and diarrhoea [88]. In fact, antibiotic resistance occurring in community settings is, by definition, very difficult to contain, and diarrhoea is the source of further spread of NDM producers in the environment, at least in Southeast Asia.

It may therefore be expected that outbreaks caused mostly by NDM-producing *K. pneumoniae* will be increasingly reported worldwide and, concomitantly, a slow but progressive increase in the prevalence rate of NDM-producing *Escherichia coli* will be observed, mirroring the spread of CTX-M producers that we have observed in community setttings since the 2000s. It is noteworthy that outbreaks caused by NDM-1-producing *Escherichia coli* or *E. cloacae* have been reported in Bulgaria and Turkey, respectively [89,90]. However, it is difficult to evaluate the time that it will take to obtain prevalence rates of NDM-producing *Escherichia coli* comparable to those observed for CTX-M producers (15–70%, depending on the countries). Long-term persistence of NDM producers in the human gut will contribute to further human-to-human transfer [91], leading to some autochthonous cases in non-endemic areas, as observed in France [92].

The Carbapenem-hydrolysing Class D β-lactamases (CHDLs)

Class D β-lactamases, which are also named OXAs (for 'oxacillinases'), now include >400 enzymes, among which only some variants actually possess carbapenemase activity [93]. With the exception of rare OXA enzymes (such as OXA-163; see below), the CHDLs do not hydrolyse (or very poorly hydrolyse) expanded-spectrum cephalosporins. Notably, all CHDLs possess weak carbapenemase activity, which does not confer high-level resistance to carbapenems if it is not

associated with other factors, such as permeability defects [94].

Although most of the CHDL variants have been identified in *Acinetobacter*, OXA-48 and its derivatives have been identified in *Enterobacteriaceae* [95]. The first OXA-48 producer to be identified was a *K. pneumoniae* isolate recovered in Turkey in 2003 [96]. Since then, OXA-48 producers have been extensively reported in Turkey, often being the causes of nosocomial outbreaks [96–99]. OXA-48-producing isolates have now widely disseminated throughout European countries, and it is highly probable that one of the main reservoirs, apart from Turkey, corresponds to North African countries [95]. Indeed, most countries in the Mediterranean area frequently report the occurrence of OXA-48-producing *Enterobacteriaceae* [95]. Hospital outbreaks involving OXA-48-producing *K. pneumoniae*, *Escherichia coli* and *E. cloacae* have been reported in many countries, including France, Germany, Switzerland, Spain, The Netherlands, and the UK [100–105]. One of the main factors sustaining the successful spread of the bla_{OXA-48} gene among a variety of enterobacterial species is the high transfer efficiency of the plasmid on which bla_{OXA-48} is located [106]. This self-conjugative plasmid, which is considered to be epidemic, does not carry any additional resistance determinants, and conjugates at a very high frequency to any enterobacterial species [107].

OXA-48-producing isolates have been reported in the Middle East, in countries such as Lebanon, the Sultanate of Oman, Saudi Arabia, and Kuwait [108–114] (Fig. 3). In Africa, they have been mainly identified in the northern countries (Morocco, Algeria, Tunisia, Egypt, and Libya) [101,115–126], but OXA-48 producers have also been identified in Senegal and South Africa [127,128] (Fig. 3).

The same OXA-48-producing *K. pneumoniae* isolate of sequence type 395 has been identified in Morocco, France, and The Netherlands, indicating clonal dissemination in some instances [101]. It is noteworthy that the recently identified occurrence of OXA-48 producers in Israel was demonstrated to be linked with medical tourism, involving patients who had been transferred from Georgia or Jordan [129]. Also noticeable is the fact that OXA-48 is still considered to be almost completely absent from the Americas, even though recent reports have shown the emergence of OXA-48-producing *K. pneumoniae* in the USA [30].

A point-mutant derivative of OXA-48, namely OXA-181, sharing the same hydrolytic properties, has been identified in enterobacterial isolates from India and from patients with a link with the Indian subcontinent [130]. The genetic structure surrounding $bla_{OXA-181}$ was found to be distinct from that associated with bla_{OXA-48}, indicating that the current disseminations are not related to each other. The $bla_{OXA-181}$ gene has been identified in different countries, such as France, the UK, Norway, Romania, the Sultanate of Oman, Canada, Australia, New Zealand, Singapore, and Sri Lanka, and a link with India has been systematically observed [95,128,131].

OXA-204 was recently identified in a series of *K. pneumoniae* isolates recovered from patients having a link with Algeria or Tunisia. OXA-204 has two amino acid substitutions as compared with OXA-48, and preliminary data indicate a substrate profile that is very similar to that of OXA-48 [132]. OXA-232 has recently been identified in *K. pneumoniae* isolates in France, from patients who had been transferred from Mauritius or India [133]. It has five amino acid substitutions as compared with OXA-48, but is just a point-mutant derivative of OXA-181. OXA-232 possesses a weaker ability to hydrolyse carbapenems than OXA-48, but was recently found to be co-associated with NDM-1 in a carbapenem-resistant *K. pneumoniae* isolate obtained very recently in the USA from a patient who had been previously identified in India [134].

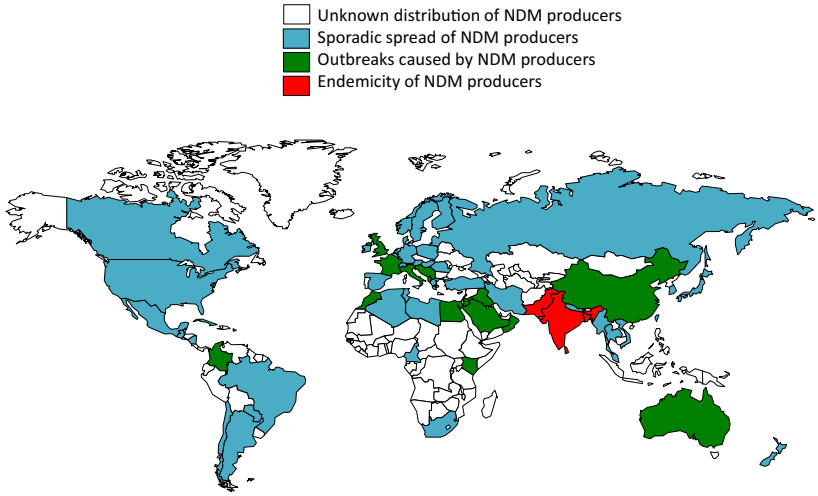

FIG. 2. Geographical distribution of NDM producers.

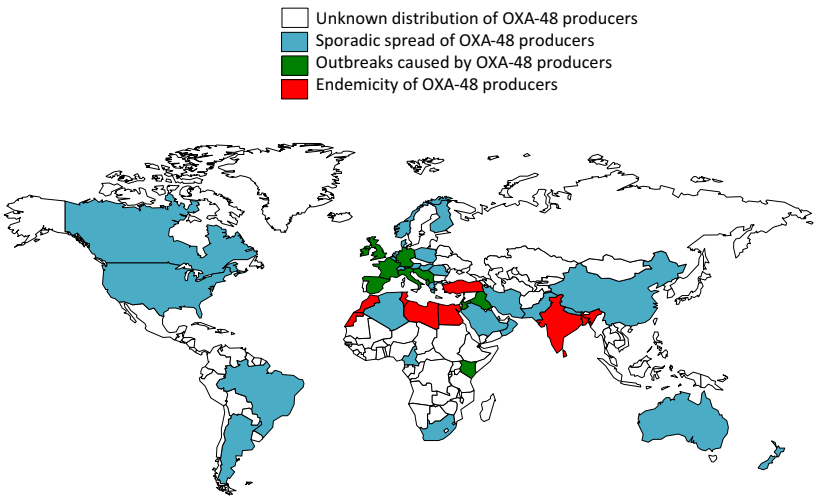

FIG. 3. Geographical distribution of OXA-48-like producers.

Finally, another OXA-48-like enzyme, namely OXA-163, has been recently identified in enterobacterial isolates recovered in Argentina [135]. OXA-163 differs from OXA-48 by a single amino acid substitution and a four amino acid deletion [95,135]. Interestingly, although its carbapenemase activity is lower than that of OXA-48, its substrate profile includes broad-spectrum cephalosporins, and its activity is partially inhibited by clavulanic acid, thus conferring on the corresponding enterobacterial recipient strains a resistance phenotype very similar to that of an expanded-spectrum β-lactamase producer. OXA-163 was originally identified in enterobacterial isolates (*E. cloacae* and *K. pneumoniae*) recovered in Argentina [135], and then in Egypt [136]. Other studies confirmed that OXA-163 producers were frequently identified in Argentina [30], and one single amino acid mutant (OXA-247) sharing the same hydrolytic properties was identified in that country [137].

Conclusion

Although the spread of carbapenemases appears to be quite recent, the 'big players', which are NDM, KPC, and OXA-48, are now widely distributed. Important reservoirs have been identified: the Indian subcontinent for NDM, the USA, Israel, Greece and Italy for KPC, and Turkey and North Africa for OXA-48. The Indian subcontinent actually acts as a reservoir of all three types of carbapenemases: KPC, NDM, and OXA-181. KPC producers are still mostly identified in nosocomial *K. pneumoniae* isolates. In contrast, NDM and OXA-48 are being extensively identified in nosocomial and community-acquired *K. pneumoniae* and *Escherichia coli* isolates, respectively. Interestingly KPC and NDM have been identified in unrelated Gram-negative species, whereas OXA-48 has been identified only in enterobacterial species. However, genetic analysis indicates that the OXA-48 gene has a propensity to spread among enterobacterial species at a much higher rate than KPC and NDM genes.

The important reservoirs of these carbapenemase producers that have been identified act as significant sources for their dissemination worldwide. Indeed, it is extremely common to see the occurrence of a carbapenemase-producing isolate in a geographical area where there is no endemicity or an epidemic situation linked to a patient who has a previous history of hospitalization or a travel in an endemic area. This indicates that very early identification of carbapenemase producers, at least in hospital settings, may contribute to limitating their spread. The use of rapid diagnostic techniques is key to their diagnosis, and should be followed by the implementation of strict hygiene measure to limit their spread.

Transparency Declaration

None.

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