which should be cited to refer to this work.

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

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Spread of carbapenemase producers in Enterobacteriaceae is now identified worldwide. Three main carbapenemases are reported which belong to three classes of ß-lactamases that are KPC, NDM and OXA-48. The main reservoirs of KPC are Klebsiella pneumoniae in the USA, Israel, Greece and Italy, of NDM are K. pneumoniae and Escherichia coli in the Indian subcontinent, and of OXA-48 are K. pneumoniae and E. coli in North Africa

and Turkey. KPC producers remain mostly identified in 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 strict implemention of hygiene measures.

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

The main features related to the epidemiology of those enzymes are as follows;

i) The first parameter is the primary reservoir. Indeed it is very likely that a specific enzyme emerges in a given geographical area where many favorable conditions exist such as high-density population, poor hygiene, high selective pressure linked to over- and misuse of antibiotics.

ii) The second parameter corresponds to the genetics of the carbapenemase gene, since some genetic structures are prone to enhance gene plasticity and mobility. Some integron or transposon structures and plasmids may indeed favorize horizontal gene transfer. Some plasmids possess broad-host range of replication, and can therefore enhance the inter-species dissemination, while some others possess narrow-host range. Some plasmids replicate very efficiently and are self-conjugative, while 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, since the emergence of one gene in a so-called successful clone (being for instances more prompt to disseminate from patient to patient, or more prompt to resist on dry surfaces) can favorize the initial spread of a carbapenemase through the spread of the corresponding bacterial host.

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

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

The class A carbapenem-hydrolyzing ß-lactamases

The first carbapenemase (NmcA, Non metallo-carbapenemase of class A) had been identified more that 20 years ago in an *Enterobacter cloacae* isolate. Then the SME enzymes (*Serratia marcescens* enzyme) have been identified in *S. marcescens*. This family includes 5 variants (SME-1 to -5), all being chromosomally-encoded [3] and recovered sporadically throughout the United States and Canada [4-6, M. Mulvey, unpublished]. The IMI enzymes (IMIpenem-hydrolyzing ß-lactamase) have been detected in rare isolates of *Enterobacter* spp. in 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 those carbapenemases are mostly chromosomally-located and associated to an AmpC type regulation (LysR dependant), thus limiting their spread and their expression at a high level. However, genes encoding the IMI-2 variant have been found plasmid-located in environmental *Enterobacter 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 ß-lactamase") which is 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#table1) [15]. All the GES variants possess the ability to hydrolyze broad-spectrum cephalosporins, but through specific amino acid substitutions inside the active site, the extension of their spectrum of activity towards carbapenems has been identified for several variants [16]. Among these variants, the GES-2, -4, -5, -6, -11, -14, and -18 hydrolyze imipenem efficiently [17]. Although quite rare, GES enzymes have been identified worldwide. Among those GES variants for which a significant carbapenemase activity is noticed, there are; GES-2 identified in *Pseudomonas aeruginosa*, with one clone being the source of a nosocomial outbreak in South Africa [18];

GES-5 identified in *Enterobacteriaceae* and *P. aeruginosa*, being widely reported in South America (Brazil) [19,20], and some scattered reports in Turkey [21] and South Korea [22]. The GES-11 and -14 variants have been identified in *Acinetobacter baumannii* only [23], and GES-18 identified in *P. aeruginosa* and not in *Enterobacteriaceae* [24].

Noteworthy, this GES-5 variant possessing a 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-hydrolyzing GES-type enzyme to be 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 a selective pressure with carbapenems selected GES-5 along the years is at the origin of the emergence of that carbapenemase.

KPC enzymes (*Klebsiella pneumoniae* carbapenemases) are currently the most clinically-significant enzymes among the class A carbapenemases. Indeed, they are mainly identified in *K. pneumoniae* which is an important nosocomial pathogen, and confer high

level of resistance not only to carbapenems but also to most ß-lactams including broad-spectrum cephalosporins. The first KPC producer (a KPC-2-positive *K. pneumoniae*) was identified in 1996 in the Eastern coast of the USA [28] and then a series of variants have been identified, eventhough KPC-2 remains the most commonly identified variant. There are now nineteen KPC variants assigned, all being point-putant derivatives of a common amino acid sequence. Within a few years, KPC producers went global and identified in many Gram negative species eventhough KPC enzymes are mostly identified in *K. pneumoniae* [29]. In Latin America, KPC producers are endemic in some areas, such as in Colombia, and Argentina [29]. Some reports also showed the occurrence of KPC producers in Puerto Rico and Mexico [30,31].

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

The extent of the diffusion of KPC in South East Asia is not well known, even if China is considered as a country where some areas are facing out endemic situations [29]. In India, very few reports on KPC-producing isolates do exist, 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].

Noteworthy, one specific KPC-2- or KPC-3-producing *K. pneumoniae* clone (ST258) has been extensively identified worldwide [36], indicating that it has significantly contributed to the spread of this resistance trait.

The class B metallo ß-lactamases (MBL)

MBLs which are known to be intrinsic in many environmental and opportunistic bacterial species have been identified as acquired enzymes since the early 1990's, 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 are sporadic [38,39]. Although reported worldwide, the VIM producers in Enterobacteriaceae are

highly prevalent in Southern part of Europe and around the Mediterranean sea (first reported in Italy by Cornaglia and colleagues) whereas the IMP producers remain mostly located in Asia [37].

IMP-type ß-lactamases have been the first acquired MBLs to be identified and detected in a series of clinically important Gram-negative bacilli, such as in *Enterobacteriaceae, Pseudomonas* spp., *Acinetobater* spp.. In *Enterobacteriaceae*, IMP-1 was reported from a *Serratia 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 occurrence of IMP-producing isolates worldwide is much less than that of KPC-, VIM-, NDM-, or OXA-48 producers. Wide spread of IMP-type enzymes has been demonstrated mainly in Japan, Taiwan, and Eastern China, although single reports have been reported in many other countries, being sometimes at the origin of nosocomial outbreaks. Another type of MBL corresponds to the VIM-type enzymes (Verona Integron-encoded Metallo-ß-lactamase). VIM-1 was first identified in Italy in 1997 [41,42] and then the VIM-2 variant was reported in France from a *P. aeruginosa* isolate dating from 1996 [43]. Currently, the VIM family includes 41 variants, mainly identified from *P. aeruginosa* but also from

enterobacterial isolates. VIM-2 is actually the most reported MBL worldwide [1], with an endemic spread in Southern Europe (Greece, Spain, Italy) and Southeast Asia (South Korea, Taiwan), but also found as causing outbreaks in Africa, and in particular in the Ivory Coast [44], South Africa [45], Tunisia [46], or some European coutries such as Germany [47], the Netherlands [48], and France [49,50]. Those outbreaks are most of the time involving VIM-producing *P. aeruginosa*, and rarely enterobacterial species. In Europe, Greece is known to be an endemic place for VIM-1-producing Enterobacteriaceae. Many Greek studies report the spread of VIM-1-producing *K. pneumoniae* at a national scale, but this enzyme is also identified in *E. coli*, *Citrobacter freundii*, *Morganella morganii*, *Serratia* spp., and *Klebsiella oxytoca* [51,52].

Recently, the KHM-1 ß-lactamase has been identified in Japan from a single *C. freundii* clinical isolate that had been recovered in 1997 [39]. The GIM-1 MBL (that stands for "German Imipenemase") which has been firstly identified from a *P. aeruginosa* isolate from Germany [38] has been then identified in other *P. aeruginosa* isolates [53] but also in *Serratia marcescens* [54], *Enterobacter cloacae* [55] and *Acinetobacter pittii* [56]. Worringly, it was recently shown that GIM-1 was identified in many enterobacterial species, including *E.*

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 either from *Pseudomonas* spp. or *Acinetobacter* spp

One of the most most clinically-significant carbapenemase is NDM-1 (New Delhi metallo-β-lactamase) described in 2009, the corresponding *K. pneumoniae* and *E. 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, just sparing monobactams such as aztreonam [62]. Since the first description of NDM-1, eight variants of this enzyme have been published (NDM-1 to -8) and twelve have been assigned (http://www.lahey.org), most of them originated from Asia [64-66]. Compared to 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 show their systematic association with other antibiotic resistance determinants such as plasmid-mediated AmpC cephalosporinases,

clavulanic-acid inhibited expanded-spectrum ß-lactamases (ESBLs), other types of carbapenemases (OXA-48-, VIM-, KPC-types), broad spectrum resistance to aminoglycosides (16S RNA methylases), to quinolones (Qnr), to macrolides (esterases), to rifampicin (rifampicin-modifying enzymes), to chloramphenicol and to sulfamethoxazole [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, Sri Lanka) [63]. Spread of NDM producers has been not only extensively identified among patients from the Indian subcontinent but also from the soil [74,75]. Therefore, it is likely that there the environment is already heavily contaminated by NDM producers. The prevalence of carriage is estimated at 5 to 15 % in that part of the world [76,77]. A significant spread of NDM producers has been identified also in the Great Britain with tight relationships with India and Pakistan [65]. Subsequently, NDM producers in *Enterobacteriaceae* have been reported almost worldwide including many countries in Asia, Africa, Australia, America, and Europe [78]. NDM producers are now on the top list of carbapenemase producers in European countries such as in the UK and in France [63,65].

Another particularly important source of NDM producers (or established secondary reservoirs) is constituted by the Balkan states [79,80], the Arabic peninsula [81,82] and the North African countries [64]. The impact of intercontinental travels as a source of spread of NDM producers has been extensively reported. NDM producers are heavily identified in countries where many Indian and Pakistani live such as Canada, the USA, Great Britain, Ireland, South Africa, Saudi Arabia, Gulf countries, Australia etc... Noteworthy, the identification of NDM producers is not always associated with an Indian subcontinent origin, sustaining the hypothesis of established secondary reservoirs [83-87].

All types of NDM-producing enterobacterial species have been found involved in infections, but mostly *K. pneumoniae* and *E. coli* are sources of hospital and community acquired infections, respectively. The frequent identification of NDM-producing *E. coli* is of concern considering that *E. coli* is the first pathogen responsible for urinary tract infections, community-acquired infections, and diarrhea [88]. In fact, antibiotic resistance occurring in community settings are by definition very difficult to be contained and diarrhea is the source of a further spread of NDM producers in the environment at least in South East Asia.

It may therefore be expected that outbreaks due mostly to NDM-producing *K. pneumoniae* will be increasingly reported worldwide and concomitantly, a slow but progressive increase in the prevalence rate of NDM-producing *E. coli* will be observed, mirrorring the spread of CTX-M producers we have observed in community setttings since the 2000's. Noteworthy, outbreaks with NDM-1-producing *E. coli* or *E. cloacae* have been reported in Bulgaria and Turkey, respectively [89,90]. It is however difficult to evaluate the time (years) it will take to obtain similar prevalence rates of NDM-producing *E. coli* comparable to those observed for CTX-M producers (15-70% depending of 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 area as observed in France [92].

The carbapenem-hydrolysing class D ß-lactamases

Class D ß-lactamases, also named OXAs (for “oxacillinases”) include now more than 400 enzymes, among which only some variants actually possess a carbapenemase activity [93]. With the exception of rare OXA-enzymes (such as OXA-163, see further), the carbapenem-hydrolysing class D ß-lactamases (CHDLs) do not hydrolyse (or very poorly)

expanded-spectrum cephalosporins. Noticeably, all CHDLs possess a weak carbapenemase activity which, by itself, does not confer high level resistance to carbapenems if not associated to other factors, such as permeability defects [94].

Although most of the CHDLs variants have been identified in *Acinetobacter* spp., OXA-48 and its derivatives are identified in *Enterobacteriaceae* [95]. The firstly identified OXA-48 producer was a *K. pneumoniae* isolate recovered in Turkey in 2003 [96]. Then, OXA-48 producers have been extensively reported from Turkey, being often the sources 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 reservoir, apart from Turkey, corresponds to North African countries [95]. Indeed most countries from the Mediterranean area frequently report the occurrence of the OXA-48-producing Enterobacteriaceae [95]. Hospital outbreaks involving OXA-48-producing *K. pneumoniae*, *E. coli*, and *E. cloacae* have been reported in many countries including France, Germany, Switzerland, Spain, the Netherlands, and UK [100-105]. One of the main factors sustaining the successful spread of the $bla_{\text{OXA-48}}$ gene among a variety of enterobacterial species corresponds to the high transfer efficiency of the plasmid on which $bla_{\text{OXA-48}}$ is located [106].

That self-conjugative plasmid, which is considered as epidemic, does not carry any additional resistance determinant, and conjugates at very high frequency from an to any enterobacterial species [107].

OXA-48-producing isolates have been reported in the Middle East, such as in Lebanon, Sultanate of Oman, Saudi Arabia, and Kuwait [108-114]. In Africa, they are mainly identified in the Northern countries (Morocco, Algeria, Tunisia, Egypt, Libya) [115-127], but occurrence of OXA-48 producers has also been identifeid in Senegal and South Africa [128,129].

The same OXA-48-producing *K. pneumoniae* of sequence type (ST) ST395 has been identified in Morocco, in France, and in the Netherlands, indicating a clonal dissemination in some instances [120]. Noteworthy, the recently identified occurrence of OXA-48 producers in Israel was demonstrated to be linked with medical tourism, that involved patients who had been transferred from Georgia or in Jordania [130]. Also noticeable is the fact that OXA-48 is still considered almost absent from the Americas, even though recent reports showed the emergence of OXA-48-producing *K. pneumoniae* in the US [30].

A point-mutant derivative of OXA-48, namely OXA-181, sharing the same hydrolytic properties, has been identified in enterobacterial isolates from India or from patients with a link with the Indian subcontinent [131]. The genetic structure surrounding the $bla_{\text{OXA-181}}$ gene was found to be distinct from that associated to $bla_{\text{OXA-48}}$, thus indicating their respective current disseminations are not related to each other. The $bla_{\text{OXA-181}}$ gene has been identified in different countries such as France, UK, Norway, Romania, Sultanate of Oman, Canada, Australia, New Zealand, Singapore, and Sri Lanka, and a link with India is quite systematically observed [95,129,133].

OXA-204 was recently identified from a series of *K. pneumoniae* isolates recovered from patients having a link with Algeria or Tunisia. OXA-204 exhibits two amino acid substitutions compared to OXA-48, and preliminary data indicate a substrate profile very similar to that of OXA-48 [134] (Figure 2). OXA-232 has been recently identified from *K. pneumoniae* isolates in France, from patients who had been transferred from Mauritius or India [134]. It exhibits five amino acid substitutions compared to OXA-48, but is just a point mutant derivative of OXA-181. OXA-232 possesses a weaker ability to hydrolyze carbapenems as compared to OXA-48, but was recently found co-associated to NDM-1 in a

carbapenem-resistant *K. pneumoniae* isolate in the US very recently from a patient who had been previously identified in India [135].

Finally, another OXA-48-like enzyme, namely OXA-163, has been recently identified from enterobacterial isolates recovered in Argentina [136]. OXA-163 differs from OXA-48 by a single amino acid substitution together with a four amino-acid deletion [95,136]. 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 to the corresponding enterobacterial recipient strains an resistance phenotype very similar to that of an ESBL producer. OXA-163 was originally identified from enterobacterial isolates (*E. cloacae* and *K. pneumoniae*) recovered in Argentina [136], and then in Egypt [137]. 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 [138].

Conclusion

Although the spread of carbapenemases appear to be quite recent, the "big players" which are NDM, KPC, and OXA-48 are widely distributed worldwide nowadays. Important reservoirs have been identified, being the Indian subcontinent for NDM, the US, 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. By contrast NDM and OXA-48 enzymes are extensively identified in nosocomial and community-acquired *K. pneumoniae* and *E. coli* isolates, respectively. Interestingly KPC and NDM have been identified in unrelated Gram negatives species wheras OXA-48 remains identified only in enterobacterial species. However genetic analysis indicates that the OXA-48 gene will has a propensy to spread among enterobacterial species at a much higher rate than KPC and NDM genes.

The identifed important reservoirs of those carbapenemase producers significantly act as sources for their dissemination worldwide. Indeed, it is extremely frequent to see that occurrence of a carbapenemase-producing isolate in a geographical area where there is no

endemicity or an epidemic situation linked to a patient who had a previous history of hospitalization or a travel in an endemic area. This indicates that a very early identification of carbapenemase producers at least in hospital settings may contribute to the limitation of their spread. Use of rapid diagnostic techniques is the key issue for their diagnosis followed by implementation of strict hygiene measure to limit their spread.

Legends to Figures.

Figure 1. Geographical distribution of KPC producers.

Figure 2. Geographical distribution of NDM producers.

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

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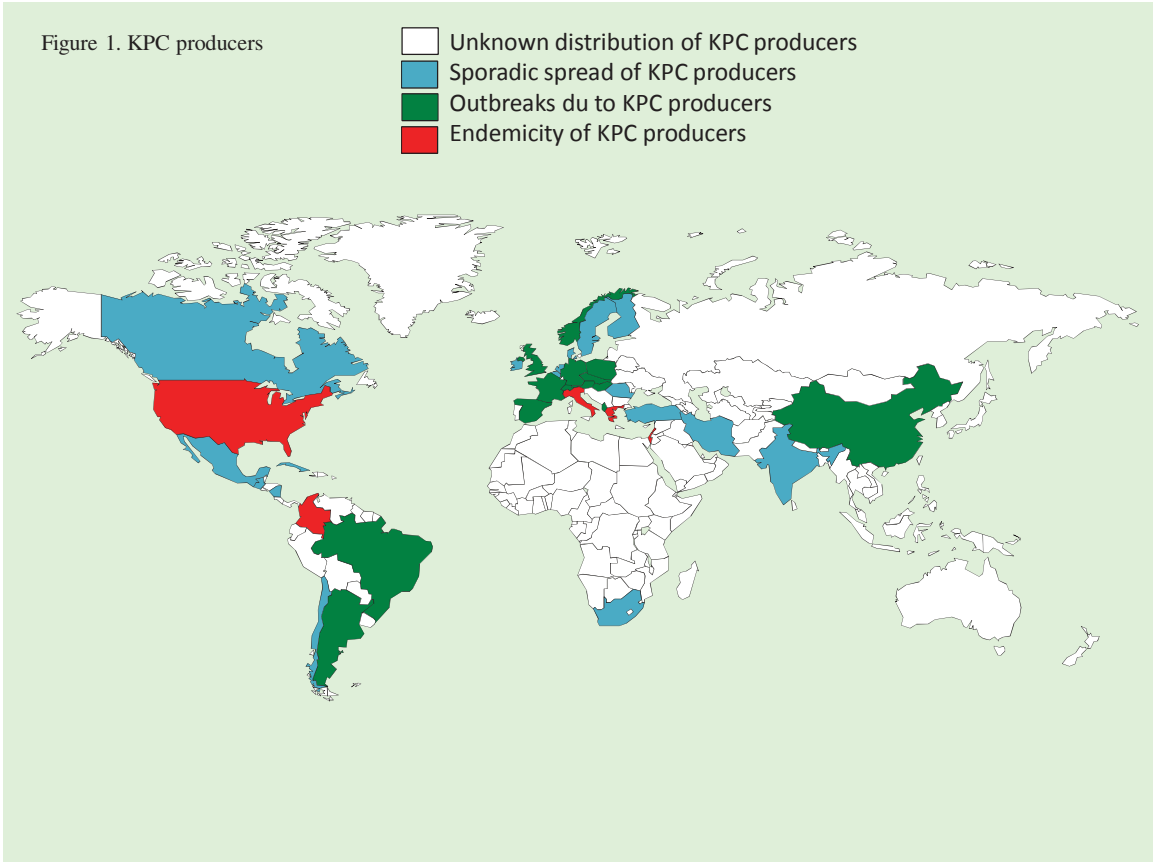

Figure 1. KPC producers

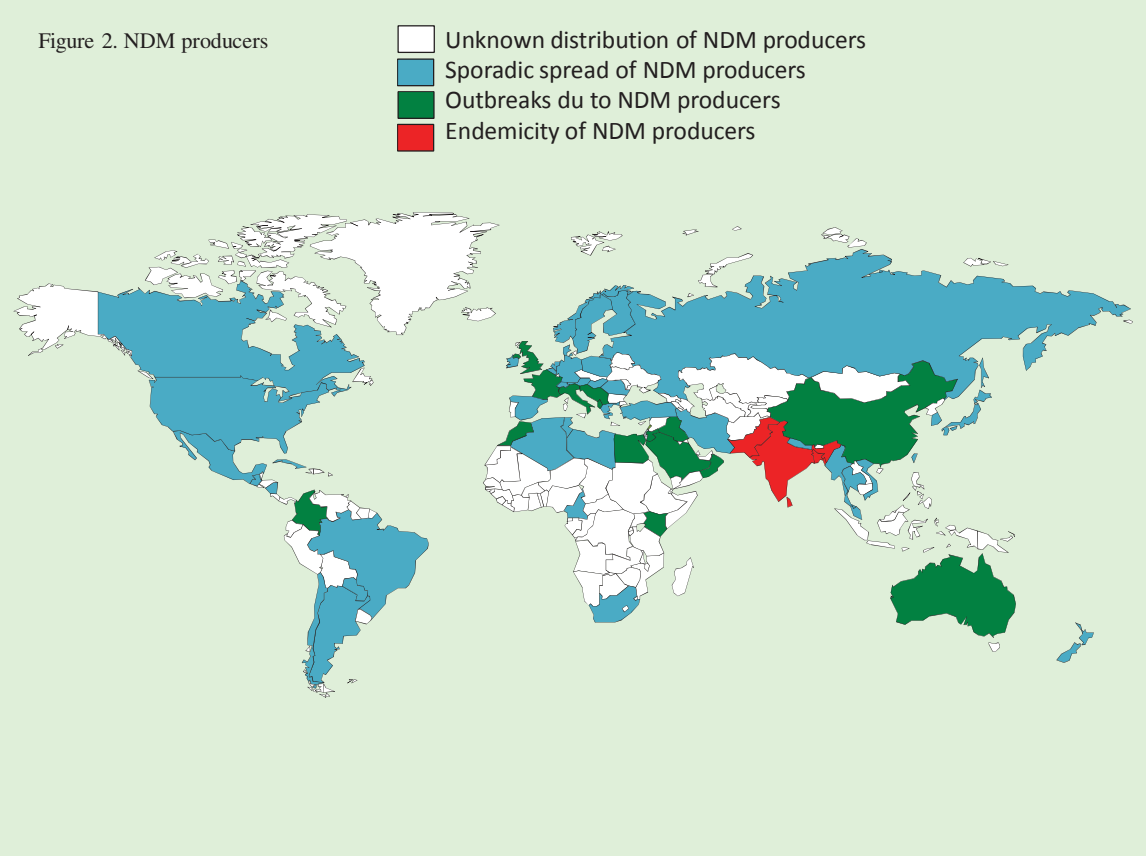

Figure 2. NDM producers

Figure 3. OXA-48 producers