Eur J Clin Microbiol Infect Dis (2018) 37:587–604
https://doi.org/10.1007/s10096-017-3112-7

REVIEW

OXA-48-like carbapenemases producing *Enterobacteriaceae* in different niches

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Received: 5 September 2017 / Accepted: 15 September 2017 / Published online: 8 October 2017

Abstract The emergence of carbapenem-resistant enterobacterial species poses a serious threat to public health worldwide. OXA-48-type carbapenem-hydrolyzing class D β-lactamases are widely distributed among *Enterobacteriaceae*, with significant geographical differences. To date, 11 OXA-48-like variants have been identified, with classical OXA-48 being the most widespread. These enzymes show high-level hydrolytic activity against penicillins and low-level hydrolysis towards carbapenems. Since the first description of the OXA-48 carbapenemase in Turkey, bacterial strains producing the enzyme have been extensively reported in nosocomial and community outbreaks in many parts of the word, particularly in the Mediterranean area and European countries. The rapid spread of *Enterobacteriaceae* producing OXA-48-like enzymes in different ecosystems has become a serious issue recently. The number of reservoirs for such organisms is increasing, not only in hospitals, but also in the community, among animals (e.g., livestock, companion animals, and wildlife) and in the environment. This review aims to summarize the main characteristics of the OXA-48-type carbapenemases, covering genetic and enzymatic traits, their epidemiology, clonality and associated genes, correlation with extended-spectrum β-lactamases (ESBLs) or plasmidic AmpC (pAmpC) in different bacterial species worldwide.

Keywords Carbapenemase · *Enterobacteriaceae* · Environment · Niches · OXA-48-like · Persistence

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-017-3112-7) contains supplementary material, which is available to authorized users.

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β-lactam resistance and enterobacteria

Enterobacteriaceae are opportunistic pathogens that are found as commensals in the intestinal tract of humans and animals, and are frequently associated with a variety of community and hospital-acquired infections [1]. β-lactams including penicillins, cephalosporins, aztreonam, and carbapenems are the principal therapeutic choices for the treatment of *Enterobacteriaceae* infections, and constitute approximately 60% of all clinically used antibiotics in human and veterinary medicine [2]. Consumption of antibiotics has risen over recent years in many countries [3], both in humans and animals, and has contributed to an increase of antibiotic residues in the environment. The presence of antibiotic residues in the environment and many if not all reservoirs of life exerts selective pressure leading to the emergence and dissemination of bacterial resistance [4].

Gram-negative bacteria, including *Enterobacteriaceae*, have developed multiple strategies to overcome antibiotic effects by employing several resistance mechanisms (alteration of the antibiotics by production of enzymes, modification of the bacterial envelope by decreasing the porin production or increasing the expression of efflux pump systems, changes in cellular permeability of antibiotics, and reduction of the antibiotic affinity by the modification of drug targets) [5]. These

phenomena are encountered in various clinical isolates showing a multidrug-resistant (MDR) phenotype [6].

Production of β-lactamases constitutes the principal mechanism of bacterial resistance to β-lactam antibiotics among enterobacteria [7]. The first described β-lactamase in Gram-negative bacteria was TEM-1 (for TEMONEIRA) isolated from *Escherichia coli* in 1963 in Greece [8]. In turn, the pharmaceutical industry developed novel β-lactam compounds resistant to hydrolysis by large spectrum β-lactamases (TEM-1/2 and SHV-1) that were popularly known as third-generation cephalosporins (3GCs). The further selection of resistant mutants by overproduction of chromosomal AmpC through acquisition of either extended-spectrum β-lactamases (ESBLs) or plasmidic AmpC (pAmpC) has compromised the use of 3GCs for the treatment of serious infections caused by Gram-negative bacteria [9]. Among the ESBLs genes described, *bla*TEM genes, *bla*SHV genes, and particularly *bla*CTX-M genes are the most frequently reported [10]. In parallel, pAmpC, including *bla*CMY and *bla*DHA, have increased over the last decade [11], but are less frequently reported compared to ESBLs genes [12].

To counter this situation, carbapenems were developed and introduced into the therapeutic arsenal through the 1990s [8]. These molecules are extremely stable to degradation by ESBLs and pAmpC, and are used to treat severe infections caused by ESBLs and pAmpC producers [13]. In 1988, the first plasmidic carbapenemase, IMI-1, was reported in Japanese *Pseudomonas aeruginosa* isolate [14]. However, the first carbapenemase producer in *Enterobacteriaceae* (NmcA) was not identified until 1993 in a clinical isolate of *Enterobacter cloacae* [15]. This class A carbapenemase was chromosomally encoded, but has rarely been reported since. Subsequently, numerous carbapenemase-producing *Enterobacteriaceae* (CPE) have been identified [16]. Nowadays, carbapenemases described in *Enterobacteriaceae* are divided into three classes according to the Ambler classification: (i) class A β-lactamases (*Klebsiella pneumoniae* carbapenemase (KPC), NmcA, IMI, Sme, and GES-type which are inhibited by clavulanic acid or boronic acid, (ii) class B metallo-β-lactamases [New Delhi metallo-β-lactamase (NDM), imipenemase (IMP), and Verona integron-encoded metallo-β-lactamase (VIM)] hydrolyzing all β-lactams except aztreonam and inhibited by chelating agents such as EDTA and dipicolinic acid, and (iii) class D β-lactamases (oxacillinases), including OXA-48-like enzymes hydrolyzing carbapenems but only weakly (or not) hydrolyzing cephalosporins and not inhibited by classical inhibitors [17, 18]. The carbapenemase genes in *Enterobacteriaceae* have been shown to be associated with mobile genetic elements such as plasmids or transposons, thereby facilitating their dissemination into the community and the environment [19].

In recent years, an increasing number of studies that include OXA-48-like carbapenemase-producing *Enterobacteriaceae* have been published including humans and veterinary practices, animal production, food chain, companion animals, wild animals, agriculture, and environments across different countries.

Biochemical and genetic properties of OXA-48-like

The OXA-48 carbapenemase was first reported in a *Klebsiella pneumoniae* isolate from a 54-year-old man with a urinary tract infection and skin burns from Istanbul (Turkey) in 2001 [20]. Since then, it has been identified as a source of nosocomial outbreaks in this country [21].

Analysis of the enzyme kinetics of OXA-48 showed that it has high-level hydrolytic activity against penicillins and low-level hydrolysis towards carbapenems [22]. Among carbapenems, OXA-48 has a low level of hydrolytic activity for both imipenem and meropenem compared to ertapenem, which represents the best substrate for this enzyme [23].

Since the discovery of OXA-48, several variants have emerged including OXA-162 (single substitution at Thr213Ala), identified from *K. pneumoniae* isolates in Turkey [24], OXA-163 (single substitution at Ser212Asp and four deletions at Arg214, Ile215, Glu216, and Pro217), identified in *K. pneumoniae* and *Enterobacter cloacae* isolates in Argentina [25], OXA-181 (four substitutions at Thr104Ala, Asn110Asp, Glu168Gln, and Ser171Ala), identified from a *K. pneumoniae* isolate in India [26], OXA-204 (two substitutions at Gln98His Thr99Arg), identified in *K. pneumoniae* isolates in patients having a link with North Africa [27], OXA-232 (single substitution at Arg214Ser), identified in France from a *K. pneumoniae* isolate recovered from a patient who had been transferred from India to Mauritius [28], OXA-244 (single substitution at Arg214Gly) and OXA-245 (single substitution at Glu125Tyr), collected from *K. pneumoniae* isolates in Spain [29], OXA-247 (two substitutions at Tyr211Ser and Asp212Asn), identified from a *K. pneumoniae* isolate recovered in Argentina [30], OXA-370 (single substitution at Gly220Glu), reported from an *Enterobacter hormaechei* isolate in Brazil [31], and OXA-405 (four deletions at Thr213 to Glu216), identified from *Serratia marcescens* isolates in France [32]. These variants differ from OXA-48 by one to five amino acid substitutions and/or by a four-amino-acid deletion, which results in a modified β-lactam hydrolysis spectrum (Table 1, Fig. S1) [18].

While OXA-163 appears to be a very poor hydrolyser of the carbapenems, OXA-181 and OXA-232 are broadly similar to OXA-48 in their activity; OXA-232 has a reduced ability to hydrolyze carbapenems but possesses higher hydrolysis activity against penicillins [25, 28]. Interestingly, OXA-163 and OXA-405 have marginal carbapenem hydrolytic activity, but

Table 1 Variants of OXA-48-like enzyme and degree of homology (%)

OXA-48-like variants	OXA-48	OXA-162	OXA-163	OXA-181	OXA-199	OXA-204	OXA-232[a]	OXA-244	OXA-245	OXA-247[b]	OXA-370	OXA-405
OXA-48	100	99	98	98	99	99	98	99	99	98	99	98
OXA-162	99	100	98	98	98	99	98	99	99	97	99	98
OXA-163	98	98	100	98	98	98	98	98	98	99	98	99
OXA-181	98	98	98	100	98	98	99	98	98	98	98	98
OXA-199	99	98	98	98	100	99	99	99	99	99	99	99
OXA-204	99	99	98	98	99	100	99	99	99	99	99	99
OXA-232[a]	98	98	98	99	99	99	100	98	98	98	98	98
OXA-244	99	99	98	98	99	99	98	100	99	99	99	99
OXA-245	99	99	98	98	99	99	98	99	100	99	99	99
OXA-247[b]	98	97	99	98	99	99	98	99	99	100	98	99
OXA-370	99	99	98	98	99	99	98	99	99	98	100	98
OXA-405	98	98	99	98	99	99	98	98	98	98	98	100

OXA-48-like variants deposited and compared percentages of identity in NCBI website (http://www.ncbi.nlm.nih.gov/pubmed/)

[a] OXA-232: A mutant derivative of OXA-181, not derived from OXA-48

[b] OXA-247: Two amino acid derivatives of OXA-163, not originating from OXA-48

showed capacity to hydrolyze ceftazidime and aztreonam, and they share an increased ability to hydrolyze cefotaxime and cefepime over OXA-48, making these enzymes more similar to ESBL enzymes than to carbapenemase [25, 33].

It has been proposed that the progenitor gene of OXA-48 is a property of *Shewanella* spp., a waterborne bacterium. *Shewanella oneidensis* strain MR-1 has been found to naturally harbor the *bla*OXA-54 gene, which is closely related to the *bla*OXA-48 gene [34]. *Shewanella xiamenensis* is a recently validated species that has been reported in different parts of the world [35]. The *bla*OXA-181 gene seems likely to have originated from *S. xiamenensis* [36]. In addition, several other variants of *bla*OXA-48 genes have been identified in *S. xiamenensis* strains including *bla*OXA-48, *bla*OXA-199 [37], and *bla*OXA-204 [38]. Mobile genetic elements might have been involved in the mobilization of *Shewanella* chromosomal carbapenemases to plasmids, which have then spread to other bacterial species [39].

The emergence of the OXA-48 enzyme is mediated by the rapid spread of a broad host-range conjugative plasmid harboring the *bla*OXA-48 gene located within a composite transposon, namely *Tn*1999, that flanks the carbapenemase gene and cooperates in mobilizing an intervening DNA segment [40, 41]. Sequence analysis of plasmid pOXA-48 demonstrated that the *bla*OXA-48 gene is flanked by two copies of *IS*1999 [40]. In addition, the *bla*OXA-48 gene could be inserted into the second variant *Tn*1999.2 which was identified in clinical *K. pneumoniae* isolates from Turkey. The *Tn*1999.2 differs to *Tn*1999 by the insertion of *IS*1R within the *IS*1999 located upstream of *bla*OXA-48. The *Tn*1999.3 has been identified in an *E. coli* isolate from Italy, with a second copy of *IS*1R located downstream of *bla*OXA-48 [21, 42]. Recently, the *bla*OXA-48 gene was identified as a part of a novel transposon variant, named *Tn*1999.4. This transposon has been recovered in *E. coli* and *E. cloacae*, composed of *Tn*1999.2 truncated by another transposon, *Tn*2015 (Fig. 1). This latter is comprised of IS*Ecp1*, *bla*CTX-M-15, and a truncated *Tn*2-type transposase gene [43]. Finally, the *bla*OXA-48 gene was found in *Tn*1999.5, a novel variant of the *Tn*1999.2 transposon in which the *lysR* gene encoding a transcriptional regulator was truncated by the IS*Kpn19* element [44].

*IS*1999 was initially reported in clinical *Pseudomonas aeruginosa* isolates from Thailand [45]. In these strains, *IS1999* was inserted into an integron-specific recombination site, *attI1*, upstream of the integron-borne *bla*VEB-1 gene that encodes an ESBL [40].

The *bla*OXA-48-like genes are most frequently observed in the IncL/M plasmids which carry no additional resistance genes and are 60–70 Kb [46]. The IncL/M plasmids are currently one of the six major resistance plasmid families identified in clinically relevant *Enterobacteriaceae*, and are now commonly identified among environmental and clinical isolates, together with several IncF variants, IncA/C, IncI, IncHI2, and IncX3 and ColE-like replicons [47]. The high transfer efficiency of the epidemic IncL/M plasmid to any enterobacterial species is the reason proposed for the successful spread of *bla*OXA-48 [48].

A chromosomal location of *bla*OXA-48 was recently reported by Turton et al. [49]. Two *E. coli* isolates carrying a chromosomally integrated *bla*OXA-48 shared a similar arrangement, with a plasmid fragment containing *bla*OXA-48 flanked by *IS*1R elements integrated into the chromosome,

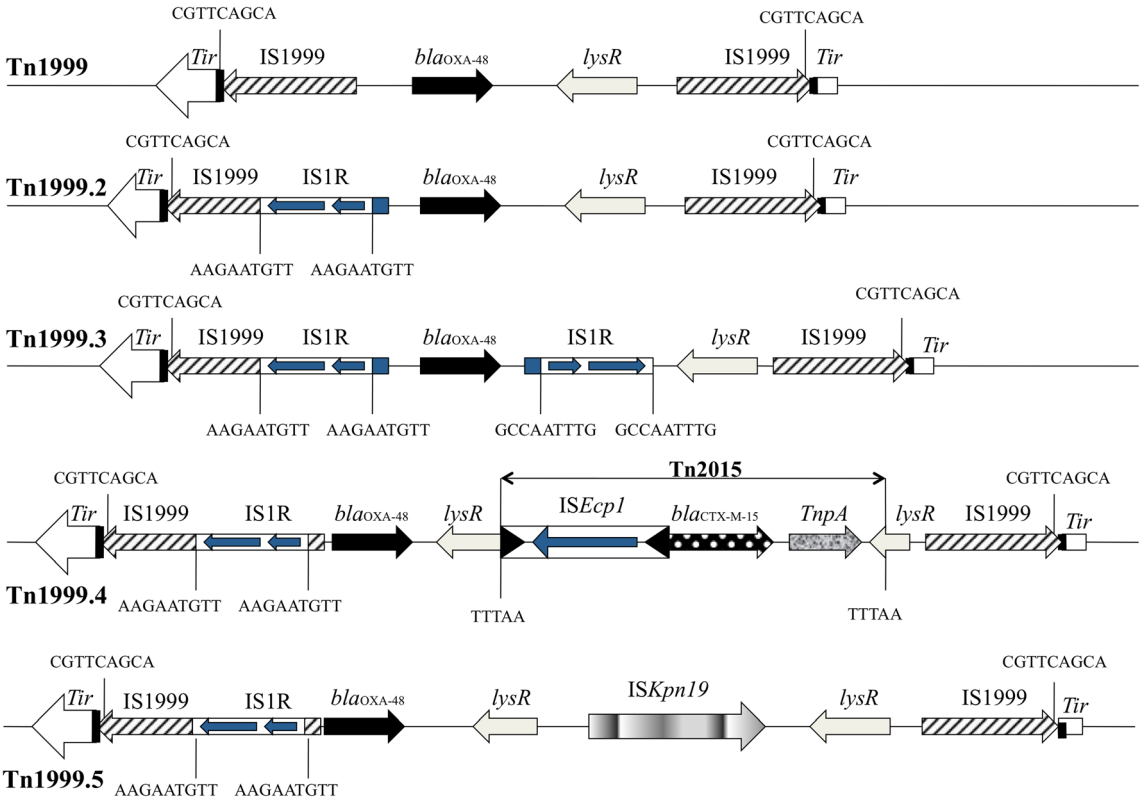

Fig. 1 Genetic environments of the *bla*OXA-48-bearing *Tn*1999-like transposon structures in *Enterobacteriaceae* isolates

although the length of the plasmid fragment and the insertion site differed between the two isolates. Beyrouthy et al. showed that the insertion of the *bla*OXA-48 gene into the *E. coli* chromosome is not a rare event and may occur at different sites, and that the DNA fragments harboring the *bla*OXA-48 gene originated in a pOXA-48a-type plasmid [41]. In another study, Beyrouthy et al. indicated that plasticity of the OXA-48 genetic environment was mediated by *IS*1R insertion sequences. The insertion sequences can induce the transfer of the OXA-48 encoding gene into *E. coli* chromosomes and thereby promote its persistence and expression at low levels [50]. The same was also described for the *bla*OXA-181 gene in *K. pneumoniae* [51].

OXA-48-like and associated genes

ESBL and pAmpC

A significant proportion of OXA-48-like producers have been found to co-express ESBLs and pAmpC genes on additional plasmids (Fig. 2). Several studies describing ESBLs in association with OXA-48 in *Enterobacteriaceae* have been reported, including *bla*TEM, *bla*SHV, and *bla*CTX-M-like genes. The association with *bla*CTX-M-like gene was the most frequently detected, including CTX-M-1 [52], CTX-M-8 [53], CTX-M-9 [52], CTX-M-14 [54], CTX-M-15 [55], CTX-M-24 [56], CTX-M-27 [57], and CTX-M-123 variants [58].

Among SHV enzymes, different variants have been identified: SHV-11 and SHV-12 have been reported in *E. coli* and *K. pneumoniae* in many European countries and in the Mediterranean area; SHV-27 was detected in one *K. pneumoniae* isolate in Morocco [59]; SHV-28 was identified in *K. pneumoniae* from Germany, India, Kuwait, Morocco, and Tunisia [60–64]; SHV-85 and SHV-133 were found in one isolate of *K. pneumoniae* in Algeria [65]; and SHV-134 was described in Spain [66].

The TEM-type ESBL determinants were also reported in OXA-48-producing isolates: TEM-5 in *E. coli* from USA [58]; TEM-31 in *K. pneumoniae* from Taiwan; and TEM-198 in *E. cloacae* from Algeria [67, 68].

Furthermore, some studies reported co-production both of OXA-48-like and pAmpC genes. CMY-2 has been recovered in *K. pneumoniae* and *E. coli* from Algeria, Denmark, Germany, India, Tunisia, and the USA [58, 64, 69–72]; CMY-4 in *K. pneumoniae* isolates from Singapore, Thailand and Tunisia [54, 73–76]; CMY-6 in a single *K. pneumoniae* isolate from India [77]; and DHA-1 in *K. pneumoniae* from Greece, Morocco, Sri Lanka, Thailand, and Tunisia [33, 59, 62, 71, 78].

In addition, VEB-8 was identified in a single *K. pneumoniae* isolate from Tunisia that co-produced the CMY-2 and CTX-M-15 enzymes [79].

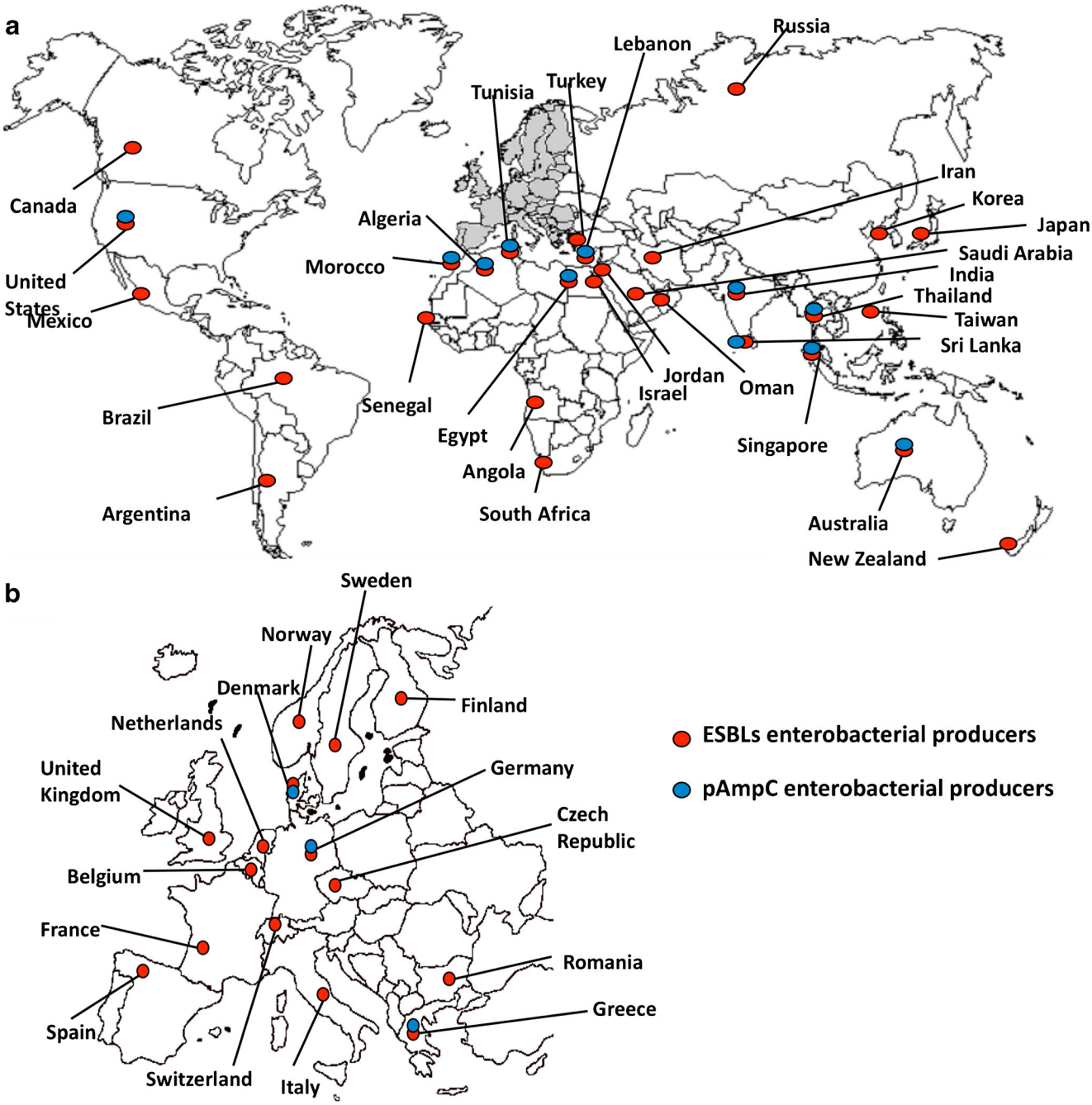

Fig. 2 Distribution of OXA-48-like-producers co-producing ESBLs and pAmpC genes. *(A)* Global distribution outside of Europe; *(B)* European distribution

Association with other carbapenemase-encoding genes

Several studies have reported the association between OXA-48-like and NDM-1 in enterobacterial species from different countries [60, 78, 80–92]: NDM-5 in *K. pneumoniae* from South Korea and the USA [51, 93]; NDM-7 in *K. pneumoniae* from India, Iran, and Spain [77, 92, 94]; KPC-2 in *K. pneumoniae* from Belgium and Malaysia [83, 95]; VIM-1 in different enterobacteria from Egypt and France [84, 87, 96]; VIM-5 in *K. pneumoniae* from Turkey [82]; and IMP-1 in *E. coli* from India [88].

Additional co-located resistance genes

Other plasmidic resistance genes were also associated with OXA-48-like-production in enterobacteria.

The plasmid-mediated resistance markers to quinolones (PMQR) *qnrA, qnrB, qnrS* and *aac (6')-Ib-cr* have usually been associated with OXA-48-producers in clinical

isolates. These genes have been described from Germany in *E. cloacae* [97], from Morocco in *K. pneumoniae* and *E. coli* [61], from North America in *K. pneumoniae* [98], from Saudi Arabia in *K. pneumoniae* and *E. coli* [99], from Senegal in *E. coli*, *E. cloacae*, *E. sakazakii*, and *K. pneumoniae* [100], from Tunisia in *Providencia rettgeri* [101], and from Turkey in *C. freundii* [102]. The associations between OXA-48-producers and PMQR markers were not exclusively found in humans, with Stolle et al. reporting *qnrB* and *aac(6')-Ib-cr* associated with *bla*CTX-M-1, *bla*SHV-12, *bla*TEM-1, *bla*OXA-2, *bla*CMY-2 genes, recovered in *E. coli*, and *K. pneumoniae* in German dogs [64].

An OXA-232-producing *K. pneumoniae* was reported in a clinical strain from India, including β-lactamases (CTX-M-15, SHV-28 and OXA-1-like), aminoglycoside resistance genes (*armA* and *aacC*), and fluoroquinolone resistance determinants (*qnrB* and *aac(6')-Ib-cr*) [60]. Additionally, OXA-181-producing *K. pneumoniae* and *E. coli* were associated with *qnrS* or *qnrB* and *aac(6')-Ib-cr* in Australia, Canada, and Thailand [71, 76, 103].

Finally, plasmid-mediated 16S rRNA methylase aminoglycoside resistance determinants *armA, rmtB, rmtC*, and *rmtF* were also combined with OXA-48-like producers. They were observed in Australia, Greece, India, Morocco, North America, and Thailand [60, 76, 80, 98, 103, 104]. In addition, *aac(3)-II* determinant were recovered in *K. pneumoniae* in Morocco [61].

Epidemiology of OXA-48-like from human sources

Different studies have been published reporting the emergence and dispersal of OXA-48 genes and the bacterial strains harboring such genes in a worldwide fashion. A search in PubMed using OXA-48 in humans as a keyword showed an increasing number of reports of OXA-48 producers for the period 2004 to 2017 (from two between 2004 and 2007 to 73 between 2016 and 2017). Although *bla*OXA-48-like genes have been most often found in *K. pneumoniae*, the plasmids harboring this resistance are now widespread in multiple species such as *E. coli*, *Klebsiella oxytoca*, *E. cloacae*, *Enterobacter aerogenes*, *Enterobacter sakasakii*, *Citrobacter freundii*, *Citrobacter koseri*, *Citrobacter braakii*, *Providencia rettgeri*, *Serratia marcescens*, *Salmonella enterica*, *Morganella morganii*, and *Raoultella planticola* [21, 41, 61, 84, 97, 100, 105–108]. Figure S2 shows the distribution of OXA-48-producing *Enterobacteriaceae* species over the period 2004–2017. The clonal distribution of OXA-48 carbapenemase-producing *Enterobacteriaceae* isolates is reported in Fig. 3.

Worldwide dissemination of OXA-48-like enzymes

Since the first description of the OXA-48 carbapenemase in Turkey, the enzyme has been extensively reported as a source of nosocomial and community outbreaks in many parts of the world, particularly in the Mediterranean area [109] (Fig. 4). It has been described in Algeria [65, 110–114], Argentina [98], Belgium [83, 85, 115–117], Bulgaria [118], China [119], Columbia [120], Croatia [121], the Czech Republic [44], Denmark [69, 122, 123], Egypt [87, 96], Finland [120], France [56, 84, 124–129], Germany [130, 131], Greece [104, 132], Hungary [133], India [88, 134], Iran [92, 135–137], Ireland [138, 139], Israel [140, 141], Italy [42, 142, 143], Jordan [144], Kuwait [63], Lebanon [41, 145–149], Libya [150, 151], Morocco [59, 61, 152, 153], the Netherlands [9, 154–157], Romania [158], Russia [159], Saudi Arabia [89, 160], Senegal [100], Singapore [161], South Africa [162], Spain [94, 100, 106, 163–169], Sultanate Oman [170], Sweden [171], Switzerland [172, 173], Taiwan [68], Thailand [71], Tunisia [62, 79, 81, 101, 174–178], Turkey [20, 55, 102, 179–183], Brazil [184], Poland [185], Malaysia [95], the UK [52, 186], and the USA [187].

The OXA-48 producers were reported from hospitalized patients with diverse infections including UTIs, wound infections, and bloodstream infections. Furthermore, fecal carriage represents an important problem and a high risk factor for infection [61].

OXA-48-like isolates and multilocus sequence typing (ST)

Among *K. pneumoniae*, *bla*OXA-48-like genes are found in multiple STs. However, some dominant clones, including ST101, ST395, ST405, ST11, ST14, and ST15, have successfully emerged. OXA-48-positive *K. pneumoniae* belonging to ST101 was the most commonly observed ST in the Mediterranean area [126, 188]. It has been implicated in different outbreaks in Morocco, Spain, and Tunisia [177, 189]. This clone has now spread widely and has been recovered from many countries including European countries (the Czech Republic, Denmark, France, Germany, Ireland, Italy, Romania, Sweden, the UK), Africa (Egypt, Algeria), South East Asia (Malaysia), and the Middle East (Israel, Kuwait) [42, 52, 95, 96, 113, 115, 123, 130, 138, 158, 171, 190, 191]. ST395 and ST405 have been widely described in European outbreaks (e.g., Belgium, France, and Spain) involving strains from North Africa [66, 117, 157, 188, 192]. ST11 has been reported in outbreaks in Spain and Tunisia [81, 168]. This ST is now found throughout Europe and also in South Africa [66, 117, 132]. ST14 was recently characterized as the most prevalent clone in the UK [193]. Finally, OXA-48 enzymes were found in

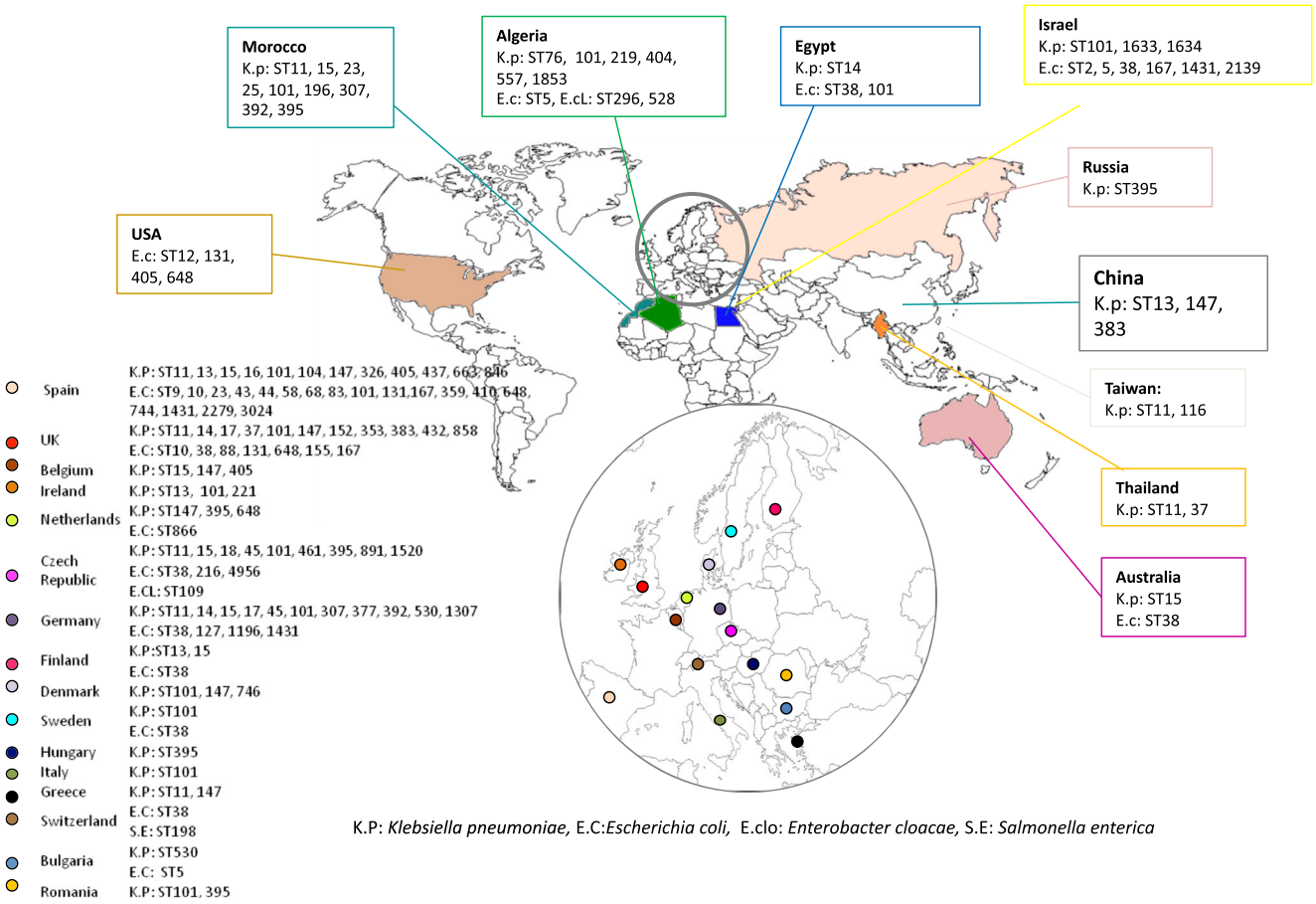

Fig. 3 Clonal distribution of OXA-48-like producing *Enterobacteriaceae*

ST15 which corresponds to a disseminated worldwide clone carrying ESBL and carbapenemases, notably in Europe [106, 126, 169, 194, 195].

This relatively high number of global clones illustrates the wide spread of OXA-48-producing *K. pneumoniae* in the Mediterranean area (Turkey, North Africa, and the Middle East) and in Europe. Interestingly, plasmids harboring the new variants such as *bla*OXA-181 were found in ST11, ST61, ST25, ST307, and ST709, or *bla*OXA-232 in ST14, ST15, ST16, ST147, ST231, ST307, and ST395 [193]. Some differences in the repartition of the STs could be explained by their different geographical associations, with the new variants often arising on the Indian subcontinent.

The dissemination of OXA-48-producing *E. coli* is polyclonal, with multiple STs reported. In many studies, OXA-48-producing *E. coli* isolates have been described from patients after initial isolation of epidemic clone of *K. pneumoniae*, suggesting horizontal transfer of pOXA-48a from *K. pneumoniae* to commensal *E. coli* in the intestine of the patient [52, 126, 156, 191, 196]. Of concern is the fact that the acquisition of OXA-48 by successful *E. coli* clones has already occurred. Indeed, the most prevalent OXA-48-producing *E. coli* in Spain belongs to ST131 (Warwick scheme) [197], which is known for its role in the global dissemination of ESBLs, especially CTX-M-15, including in community settings [198]. We could note that multiple ST schemes exist for this species (e.g., Warwick scheme, Pasteur scheme…). Similarly, ST38, another emerging global epidemic clone, is dominant in North Lebanon, in the UK, in Finland [41, 193, 194], and in France [56]. ST410 and ST88 were also identified [52, 193].

More recently, a chromosomal location of *bla*OXA-48 was reported from isolates in Egypt, France, Lebanon, Switzerland, and the UK [41, 52, 188]. Interestingly, chromosomal location of *bla*OXA-48 was mostly associated with *E. coli* ST38 co-harboring *bla*CTX-M-24 and *bla*TEM-1. This resistance and the ST are not only found among humans but also in fowl [199].

Since the development of the *Enterobacter cloacae* MLST scheme is recent, very few data are available for this species. The most prevalent OXA-48-positive clones belong to ST89 (in Poland) [185], ST108 (in the UK) [193], ST114 (in the South of France, personal data), and ST296 (in Algeria) [111].

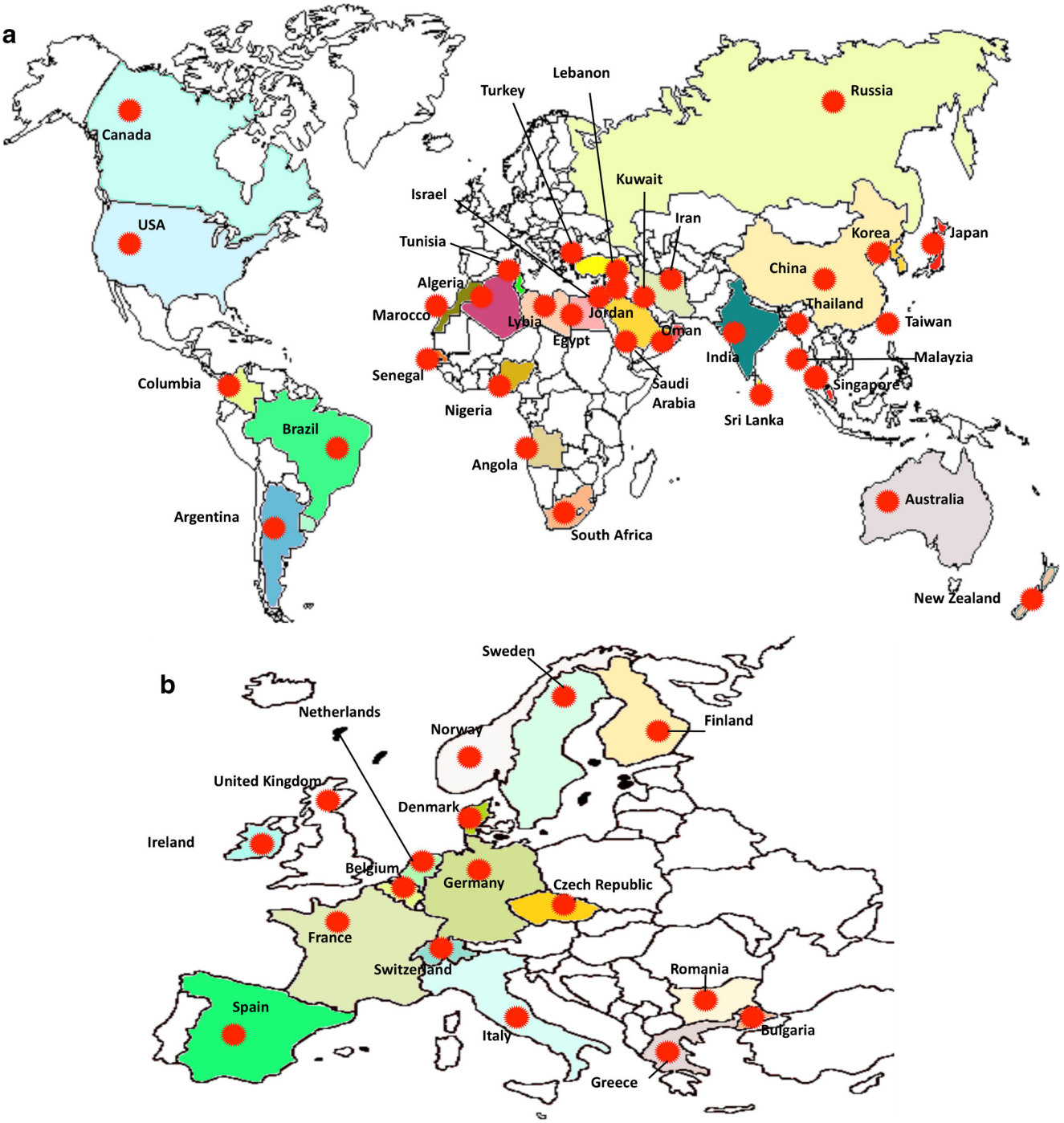

Fig. 4 Worldwide dissemination of OXA-48-like producers

Risk factors of OXA-48-like acquisition/carriage

There is a paucity of data with regard to risk factors predisposing to gut colonization with OXA-48-like. The gastrointestinal tract represents an important reservoir for these strains. The main risk factors identified were intensive care unit (ICU) stays of > 72 h, ventilator use [200], treatment with antibiotics [201] (notably carbapenems or aminoglycosides [200]), use of antacids [201], and foreign travel, in particular to Asia, Africa, and Northern America [201]. Healthy travelers to countries where CPE are endemic might be at risk, even without contact with the local healthcare system. A CPE was identified in three tourists returning to France from a trip to India (two OXA-181-producing *E. coli* and one NDM-1-producing *E. coli*), none of whom had been in contact with health-care institutions while in India [202]. Some other risk factors have been identified such as male gender, age, and previous use of fluoroquinolones, identified during a large Dutch hospital

outbreak [203]. Prolonged length of stay in hospital represents another risk factor for CRE acquisition [204]. In this case, other colonized patients, health-care workers, and the ICU environment could increase this risk [205].

Epidemiology of OXA-48-like CPE in non-human sources

Some studies have reported the presence of OXA-48-like producers from non-human sources (Fig. S3).

OXA-48-like producers in the environment

Several publications have described CPE in the hospital environment [114, 206–208]. However, there is currently little information available with regard to the dissemination of these isolates into the hospital environment. One study has reported the presence of OXA-48-producing *E. cloacae* and *K. pneumoniae* isolates from environmental surfaces in an Algerian hospital in 2014 [111]. In addition, these authors reported cases of colonization by the same OXA-48-strains in the same period. This finding may indicate that surfaces in hospitals can play a role in the nosocomial acquisition of these isolates. In France, the contamination of patients and the persistence of OXA-48-producing *K. pneumoniae* for many months were observed in an ICU due to presence of the bacteria in mattresses and sinks [128]. A similar case was reported in Belgium where an OXA-48-producing *C. freundii* was isolated from a contaminated sink in an ICU [83].

Both the antimicrobial agents used for treating infected patients in hospital and multidrug-resistant bacteria may end up in the hospital effluent or in wastewater. The presence of antibiotics in the environment exerts a selective pressure for MDR pathogens. As a result, hospital effluents represent an important pathway for the dissemination of both resistance genes and antibiotic resistant bacteria into the natural environment [209]. Recently, insufficient wastewater management by bulk drug manufacturing facilities in India has led to contamination of water resources with antimicrobial agents, associated with the selection and dissemination of OXA-48 producers [88]. Even after treatment of urban wastewater, a significant number of carbapenemase-producing bacteria can still survive and are then released into aquatic environments such as rivers, lakes, estuaries, or oceans [210]. In this context, OXA-48-producing *S. marcescens* was recovered from water (puddles) in 2011 in Morocco [105]. Galler et al. reported OXA-48-producing *E. coli* and *K. pneumoniae* from Australian wastewater between 2011 and 2012 [211]. Notably, the use of sewage in agriculture can act as a possible route for the dissemination of carbapenemase genes into the natural environment and subsequently into the food chain [211]. Nasri et al. reported OXA-48-producing *Enterobacteriaceae* from Tunisian wastewater [212]. Recently, in Algeria, OXA-48-like-producing *Enterobacteriaceae* (e.g., OXA-48- and OXA-244-producing *E. coli*) were isolated from river water. These strains belonged to a diverse ST (ST559, ST38, ST212, ST3541, ST1972, ST2142, and ST3541), with no ST observed in human infections [213]. However, in Algeria, two ST296 *E. cloacae* strains were isolated during the same period in the environment and in health-care workers [111], and *E. coli* ST38 and *K. pneumoniae* ST15 were recovered from wastewater [211], showing that transmission between environment and humans is clearly possible.

OXA-48-like producers in companion animals

Companion animals can serve as reservoirs of zoonotic bacteria and resistance genes [214]. Evaluation of multiresistance in pets is difficult because there are few surveillance programs compared to data available for livestock, and the data available are generally from retrospective studies of clinical isolates [215].

The emergence of carbapenem-resistant organisms in pets is a worrying trend. This situation may be due to the increasing prescription to pets of antimicrobial substances that are critical to human medicine, but also due to the close contact between pets and their human co-habitants [216]. Although carbapenems are not used in animals in any major jurisdiction, a case of use of these molecules has been reported in dogs for the treatment of urinary tract infection and postoperative infection caused by MDR *E. coli* when no other class of antibiotic was available [217]. The first report of OXA-48 from companion animals found in *K. pneumoniae* and/or *E. coli* isolates, recovered from six diseased dogs with several comorbidity factors, admitted to a veterinary clinic in Germany in 2012 [64]. Shortly after this episode, in the same region, OXA-48 enzyme was reported in *K. pneumoniae* and/or *E. cloacae* from dogs, cats, and a horse in 2009 and 2011 [218]. A study from the US identified *E. coli* strains harboring $bla_{\mathrm{OXA-48}}$ gene originating in dogs and cats between 2009 and 2013 [60]. In Algeria, five OXA-48-producing *E. coli* were detected in healthy pets (dogs and cats) and a diseased cat (submitted for diagnostic investigation) in one veterinary office and private owners between 2014 and 2015 [72]. Recently, OXA-48-producing *E. coli* were recovered in a large set of healthy cats and dogs in France [219]. Pets harboring $bla_{\mathrm{OXA-48}}$ gene were associated with diverse STs: ST12, ST131, ST372, ST405, ST648, ST1088, ST1196, ST1431, and ST1800 were found in *E. coli* isolates, and ST1196 and ST1431 in *K. pneumoniae* isolates [58, 64, 219].

The possible transfer of bacteria from pets is an emerging problem and constitutes a serious threat for public health.

OXA-48-like producers in livestock and production animals

The current level of intensification of animal production systems leaves production animals vulnerable to disease outbreaks [220]. Thus, various antimicrobial drugs have been administered as veterinary therapeutics in farmed animals [221]. These practices provide favorable conditions for selection, persistence, and spread of MDR bacteria at the farm level [220]. Currently, livestock animals are a source of MDR enterobacteria, and represent risks for public health associated with economic losses in livestock production [222].

The first CPE described from livestock were reported by Fischer et al., from poultry and swine in German farms where VIM-1-producing *E. coli* and *Salmonella enterica* were isolated [223, 224]. However, there are only limited and sporadic findings on OXA-48-producing *Enterobacteriaceae* in livestock. The first report concerned OXA-48-producing *E. coli* strains isolated from fowl species *Gallus domesticus* in eight livestock farms in 2013 in Lebanon [199]. Another report from Egypt identified $bla_{\text{OXA-48}}$ and $bla_{\text{OXA-181}}$ in different *E. coli* isolates recovered from healthy dairy cattle [222]. Recently, the worrying association of $bla_{\text{OXA-181}}$, $bla_{\text{CMY-2}}$, and *armA* with the colistin resistance determinant *mcr-1* was characterized in an *E. coli* strain from pigs in Italy [225]. This raises the question of how the potentially contaminated feces are disposed of. As dung is often used as a fertilizer, the $bla_{\text{OXA-48}}$ gene might enter the food chain, either directly through consumption of meat, or indirectly from cattle grazing on fertilized pasture. In addition, the use of manure in agriculture can cause the spread of resistance genes in the environment.

Indeed, another study reported coproduction of OXA-48 and/or KPC and/or NDM-producing *K. pneumoniae* in broiler chickens collected from five different poultry farms in Egypt. In the same study, carbapenemase genes were described in drinking water and in the farmers themselves, suggesting possible transmission between broilers and humans [226]. Thus livestock represents a zoonotic risk for people working in close contact to animals [227], although this relatively limited number of reports about CPEs from livestock may suggest that such bacteria are currently present in livestock at only a very low prevalence. This may reflect the lack of a direct selective pressure, as carbapenems must never be used for livestock animals. A change in this trend might be anticipated as predicted by Poirel et al. who raised a concern of co-selection of these carbapenemase genes under the selective pressure imposed by the use of aminopenicillins or penicillin–β-lactamase inhibitor combinations in livestock [228].

OXA-48-like producers in the food chain

The food chain has recently attracted attention because it can serves as reservoir of resistance genes, related to the use of antimicrobial drugs in the livestock sector [229]. Nevertheless, several studies have investigated food products colonized with ESBL/AmpC producers [230]. Few publications have reported CPE detected in food animal products [231–233]. Even better, no studies have reported OXA-48-producers in food animal products. However, OXA-181 enzymes were recovered in *Klebsiella variicola* in fresh vegetables imported from Asia to Switzerland in 2015 [108]. This suggests that vegetables may be contaminated through insufficiently treated water and fertilizers, or may be compromised by the use of biocides during cultivation. This represents a great concern, since these products would not necessarily be cooked to sterilization.

Recently, OXA-48-producing *K. pneumoniae* was recovered in fresh vegetables from Algeria [234]. Furthermore, this indicates that the food chain could become a reservoir of MDR bacteria and contribute to the spread of these bacteria, but lack of reliable data makes it difficult to assess the attributable risk of different food sources.

OXA-48-like producers in wildlife

Researchers have suggested that wildlife can play an important role in the dissemination of resistant bacteria [235]. In this respect, the presence of MDR bacteria, including CPE, has recently been reported in wild animals with no apparent prior exposure to antimicrobials. Indeed, NDM-1-producing *Salmonella* were isolated from wild birds in Germany [236], VIM-1-producing *E. coli* from yellow-legged gulls in France, and IMP-4 *Salmonella* from silver gulls in Australia [237]. Wild birds could act as important environmental bio-indicators, as they do for the influenza virus [238]. They could participate in the transmission of resistance mechanism types and the potential intercontinental spread of these antibiotic resistance determinants [239]. Otherwise, no published reports of OXA-48 CPE have so far been isolated, although OXA-48-producing *E. coli* isolates were detected in our laboratory from wild boars in Algeria [240].

Insects may also act as potential vectors for the spread of MDR bacteria to different environments [241]. One study has described OXA-48-producing *E. cloacae* belonging to ST296 from cockroaches species *Blattella germanica* collected in 2015 from the burn unit of Batna University Hospital in Algeria [113]. Within the same period, the same authors identified the emergence of OXA-48-producing *K. pneumoniae* in the same hospital, and hypothesized that these cockroaches can be a source of OXA-48 transmission [113]. The same observation was reported by Davari et al. in houseflies collected in hospitals and slaughterhouses [242].

Conclusion

The emergence and the worldwide spread of CPE is a concern. The reservoirs of these bacteria continue to grow in size and numbers, not only in hospitals, but also in the community, the environment, the food chain, and in animals including pets, livestock, and wild animals. The OXA-48-like enzymes are a good example of how these enzymes evolve continuously. Several publications have reported the appearance of the same resistance genes in animals and humans and the possible transfer of inter-species clonal spread. In addition, these resistant bacteria could have a public health impact if zoonotic transfer occurs. It is clear that the presence of resistance genes in bacteria is associated with the uncontrolled use of antibiotics in human and veterinary medicine. The incidence of resistant bacteria in some sources needs to be closely monitored. Monitoring of antibiotic resistance in animals is mainly concerned with detecting the emergence and preventing possible spread of bacteria that can be pathogenic to humans or animals.

Similarly, the absence of environmental barriers between humans and animals contributes to the spread of antimicrobial resistance in various interconnected ecological niches. Resistance, once developed, is not confined to the limits of the ecological niche where it primarily emerged. If such a scenario occurs, initiatives need to be taken to limit antimicrobial resistance in various environments, for the preservation of human health.

Acknowledgments We thank Sarah Kabani for her help in the preparation and editing of the manuscript.

Funding This work was supported by the National Institute of Health and Medical Research (INSERM).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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