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REVIEW

The Global Ascendency of OXA-48-Type Carbapenemases

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SUMMARY Surveillance studies have shown that OXA-48-like carbapenemases are the most common carbapenemases in *Enterobacterales* in certain regions of the world and are being introduced on a regular basis into regions of nonendemicity, where they are responsible for nosocomial outbreaks. OXA-48, OXA-181, OXA-232, OXA-204, OXA-162, and OXA-244, in that order, are the most common enzymes identified among the OXA-48-like carbapenemase group. OXA-48 is associated with different Tn*1999* variants on IncL plasmids and is endemic in North Africa and the Middle East. OXA-162 and OXA-244 are derivatives of OXA-48 and are present in Europe. OXA-181 and OXA-232 are associated with IS*Ecp1*, Tn*2013* on ColE2, and IncX3 types of plasmids and are endemic in the Indian subcontinent (e.g., India, Bangladesh, Pakistan, and Sri Lanka) and certain sub-Saharan African countries. Overall, clonal dissemination plays a minor role in the spread of OXA-48-like carbapenemases, but certain high-risk clones (e.g., *Klebsiella pneumoniae* sequence type 147 [ST147], ST307, ST15, and ST14 and *Escherichia coli* ST38 and ST410) have been associated with the global dispersion of OXA-48, OXA-181, OXA-232, and OXA-204. Chromosomal integration of bla_{OXA-48} within Tn*6237* occurred among *E. coli* ST38 isolates, especially in the United Kingdom. The detection of *Enterobacterales* with OXA-48-like enzymes using phenotypic methods has improved recently but remains challenging for clinical laboratories in regions of nonendemicity. Identification of the specific type of OXA-48-like enzyme requires sequencing of the corresponding genes. Bacteria (especially *K. pneumoniae* and *E. coli*) with bla_{OXA-48}, $bla_{OXA-181}$, and $bla_{OXA-232}$ are emerging in different parts of the world and are most likely underreported due to problems with the laboratory detection of these enzymes. The medical community should be aware of the looming threat that is posed by bacteria with OXA-48-like carbapenemases.

KEYWORDS carbapenemases, *Enterobacteriaceae*, OXA-48-like

INTRODUCTION

The global spread of antimicrobial-resistant organisms (AROs) was recently identified by the World Health Organization, the European Union, the U.S. Government, and the Centers for Disease Control and Prevention (USA) as one of the most significant

threats to human health (1). The spread of AROs in general is troublesome for medical practitioners at large, since infections due to such bacteria are often responsible for increased patient mortality and morbidity due to the delayed administration of suitable antibiotics (2, 3).

β-Lactam antibiotics, such as penicillins, cephalosporins, monobactams, and carbapenems, are among the most frequently prescribed antibiotics worldwide. These agents bind to and inhibit bacterial enzymes (referred to as penicillin binding proteins [PBPs]) responsible for cell wall synthesis (4).

Resistance to β-lactam antibiotics involves different mechanisms, summarized as follows (4). (i) Mutational changes in the active site of PBPs lower the affinity for β-lactams and lead to decreased binding between antibiotic and enzymes. This is a common mechanism among Gram-positive organisms, and penicillin resistance in *Streptococcus pneumoniae* due to mutations in PBPs is a good example of decreased affinity. (ii) Alterations in outer membrane permeability are mediated by decreased expression and subsequent loss of outer membrane proteins. The loss of OprD in *Pseudomonas aeruginosa* leads to the decreased entry of imipenem into the periplasmic space, with subsequent resistance to this carbapenem. (iii) Membrane efflux pumps that are capable of removing antibiotics from the periplasmic space to the external environment are upregulated. The increased expression of the MexA-MexB-OprD pump system in *P. aeruginosa* can decrease the periplasm levels of several drugs, including the cephalosporins and carbapenems. (iv) Enzymes, such as β-lactamases, that bind to and inactivate different β-lactam antibiotics are produced.

The aim of this article is to provide a brief overview on β-lactamases (including a section on the OXA-type β-lactamases) and then to review in detail the characteristics, evolution, molecular epidemiology, and laboratory diagnosis of bacteria with acquired OXA-48-like β-lactamases.

β-Lactamases

β-Lactamases are bacterial enzymes that inactivate β-lactam antibiotics by hydrolysis, which results in ineffective compounds (5). The first enzyme with the ability to hydrolyze penicillin was described nearly 70 years ago for *Escherichia coli* (6).

In Gram-negative bacteria, β-lactamase production remains the most important contributing factor to β-lactam resistance, and their increasing frequency and their continuous evolution are directly linked to selection by the use of different β-lactam agents (7). β-Lactamases differ from each other in their substrate profiles (i.e., the different types of β-lactam antibiotics they inactivate), inhibitor profiles (i.e., which compounds inactivate them), and sequence homologies (i.e., amino acid compositions of these enzymes) (5). Using these different characteristics, two classification systems have been created to divide β-lactamases into Ambler classes (i.e., classes A, B, C, and D, based on amino acid sequence homology) and the Bush-Jacoby-Medeiros groups (i.e., groups 1, 2, 3, and 4, based on substrate and inhibitor profiles) (8, 9). The Ambler classification system is more commonly used in published literature.

Enzymes that belong to classes A, C, and D share the amino acid serine as part of their respective active sites, while the class B β-lactamases (also known as metallo-β-lactamases [MBLs]) contain zinc ions in their active sites (10).

One of the most pressing current ARO concerns is the expeditious growth and global spread of carbapenem-resistant Gram-negative bacteria (11). Carbapenems are some of the last efficacious antibiotic therapies available for treating serious infections due to Gram-negative AROs. β-Lactamases that specifically target the carbapenems are known as the carbapenemases, and they are the most important causes of carbapenem resistance among Gram-negative bacteria (12). The main reason is because genes encoding carbapenemases are typically part of mobile genetic elements (MGEs) that have the ability to move between different Gram-negative species, especially among members of the *Enterobacterales* (13).

Carbapenemases belong to Ambler class A (i.e., KPC types), class B (i.e., MBLs: VIM, IMP, and NDM types), and class D (OXA β-lactamases) (11). The KPC, NDM, IMP, and VIM

and certain OXA-type enzymes are the most common global carbapenemases among Gram-negative bacteria.

OXA β-Lactamases

The class D β-lactamases are also referred to as oxacillinases or OXA β-lactamases due to their capacity for hydrolyzing oxacillin more efficiently than benzylpenicillin (14). These enzymes were first recognized in the 1960s and 1970s and showed hydrolytic activity against the penicillins and oxacillin (15, 16). Later on, certain OXA β-lactamases were described that also inactivate the cephalosporins and carbapenems (17). Currently, more than 750 types of OXA β-lactamases have been reported. It is important to remember that the OXA β-lactamases, as a group, show heterogeneous substrate profiles that are confusing to medical practitioners, even those with a special interest in infectious disease and microbiology. A general principle does exist: OXA enzymes are resistant to inhibition by β-lactam inhibitors such as clavulanate, sulbactam, and tazobactam, and they confer resistance to the amino-, carboxy-, and ureidopenicillins (18).

The OXA β-lactamases hydrolyze β-lactam antibiotics by a unique method that features a carbamylated lysine (5). The OXA enzymes use this carbamylated lysine to activate and anchor the serine active site, removing the steric hindrances from the deacylating water molecule pathway and leading to tighter binding and more efficient hydrolysis of β-lactam agents.

According to the class D β-lactamase numbering scheme, OXA β-lactamases possess a serine residue at position 70 and a carbamoylated lysine at position 73 (5). The Tyr-Gly-Asn motif at positions 144 to 146 and Lys-Thr-Gly motif at positions 216 to 218 are mostly conserved among the class D β-lactamases. In some instances, the Tyr-Gly-Asn motif can be replaced by a Phe-Gly-Asn motif. Mutations in the omega loop of the β-lactamases can change an enzyme's specific function and substrate profile and are responsible for enhanced activity to the cephalosporins and carbapenems.

In 2010, Poirel and colleagues divided the OXA β-lactamases into the following 4 groups (19). Group I is the acquired narrow-spectrum class D β-lactamases that do not have significant activity against the cephalosporins or the carbapenems. This group consists of the OXA-1, OXA-2, and OXA-101 subgroups. Group II is the acquired extended spectrum class D β-lactamases that are able to hydrolyze certain extended-spectrum cephalosporins (especially ceftriaxone and cefepime). Group II members are often point mutants of the narrow-spectrum class D β-lactamases, while certain extended-spectrum OXA enzymes are not structurally related to the narrow-spectrum group I OXA β-lactamases. Group III is acquired carbapenem-hydrolyzing class D β-lactamases with weak activity against the carbapenems that do not significantly hydrolyze the extend-spectrum cephalosporins. One subgroup of the acquired carbapenem-hydrolyzing class D β-lactamases, named the OXA-23-like enzymes, is a very important cause of carbapenem resistance among *Acinetobacter* spp. (17). Another subgroup, named the OXA-48-like enzymes, has found a niche among the *Enterobacterales* (20) and is the main topic of this review. Group IV is naturally occurring class D β-lactamases that form parts of the chromosomes of various non-fermenting Gram-negative bacteria and includes the OXA-51-like subgroup in the *Acinetobacter baumannii* complex.

OXA Carbapenemases

The carbapenem-hydrolyzing class D carbapenemases are principal causes of carbapenem resistance among *A. baumannii* isolates and the *Enterobacterales* (21). These enzymes have activity against the penicillins (especially the amino-, carboxy- and ureidopenicillins) and narrow-spectrum cephalosporins (e.g., cephalothin), weakly hydrolyze the carbapenems, and have limited activities against the broad-spectrum cephalosporins (especially ceftazidime) and most β-lactam inhibitors (e.g., clavulanate, sulbactam, and tazobactam).

They are divided phylogenetically into two groups (21). Group I is present mainly in *A. baumannii* and includes 4 subgroups. Subgroup Ia is named the OXA-23-like β-lactamases (examples include OXA-23, -27, -49, -73, -102, -103, -133, -146, -165, -166, -167, -168, -169, -170, -171, -225, -239, -366, -398, -422, -423, -435, -440, -481, -482, -483, and -565). Subgroup Ib is named the OXA-24/40-like β-lactamases, and examples include OXA-24, -25, -26, -72, -139, -160, -207, and -437. Subgroup Ic is named the OXA-51-like β-lactamases, with numerous examples, and subgroup Id is named the OXA-58-like β-lactamases (examples include OXA-58, -96, -97, -164, -397, -420, and -512).

The group II OXA carbapenemases consist of the OXA-48-related variants and is named OXA-48-like β-lactamases. The encoded OXA-48-like enzymes are weakly related to other class D β-lactamases, sharing less than 50% amino acid identity to the other OXA members (e.g., 46%, 36%, and 21% amino acid identity exists with OXA-10, OXA-23, and OXA-1, respectively). OXA-48-like enzymes share 87% amino acid identity within the OXA-48-like group (the outlier being OXA-436; please refer to "Enzyme Characteristics for OXA-48-Like Carbapenemases" below for details).

Global genomic surveillance and clinical studies as well as several case reports suggest that *Enterobacterales* with OXA-48-like carbapenemases are endemic in certain parts of the world and are being introduced on a regular basis into regions of nonendemicity where they are responsible for nosocomial outbreaks. The laboratory detection of *Enterobacterales* with OXA-48-like carbapenemases is challenging for some clinical laboratories, especially for those that are situated in regions of nonendemicity. The medical community at large, especially individuals interested in antimicrobial resistance, should be aware of the looming threat that is posed by OXA-48-like carbapenemases.

THE OXA-48-LIKE β-LACTAMASES

Acquired OXA-48-type carbapenemases are important causes of nonsusceptibility to the carbapenems among the *Enterobacterales* and include the following enzymes: OXA-48 (22), OXA-162 (23), OXA-181 (24), OXA-204 (25), OXA-232 (26), OXA-244 (27), OXA-245 (27), OXA-247 (28), OXA-436 (29), OXA-484 (30) and OXA-519 (31). Other OXA-48 variants, such as OXA-163 (32), OXA-252 (listed on GenBank only), and OXA-405 (33), do not have sufficient activity against the carbapenems to be considered carbapenemases (34). *Klebsiella pneumoniae* and *Enterobacter* spp. with $bla_{OXA-163}$ were first obtained during 2008 in Argentina and are presently widely dispersed in that country (20). *Serratia marcescens* with $bla_{OXA-405}$ was reported in France in 2012. OXA-163 and OXA-405 hydrolyze the extended-spectrum cephalosporins and show limited activities against the carbapenems. These enzymes are not addressed in detail in this article.

Enterobacter hormaechei with OXA-370 (35) showed high MICs to ertapenem and meropenem, but it is unclear if this enzyme is a true carbapenemase since its hydrolytic profile has not yet been determined (36). The sequences of certain OXA-48-variants (e.g., OXA-438, OXA-439, OXA-505, OXA-517, OXA-566, and OXA-567) are listed only in GenBank, and it is currently uncertain if these enzymes have carbapenemase activities.

OXA-54, OXA-199, OXA-252, OXA-416, and various others listed in GenBank and on the β-Lactamase DataBase (BLDB; http://bldb.eu) (37) form parts of the *Shewanella oneidensis* and *Shewanella xiamenensis* chromosomes and shares more than 90% amino acid identity with OXA-48-like β-lactamases, indicating that aquatic *Shewanella* spp. are likely the ancestors of OXA-48-like enzymes (please refer to "Origin and Evolution of OXA-48-Like Carbapenemases" below for more details on the origin and evolution of OXA-48 β-lactamases) (38–40). Chromosomal OXA-48-like β-lactamases are also not specifically addressed in this review.

OXA-48, OXA-181, OXA-232, OXA-204, OXA-162, and OXA-244, in that order, are the most common enzymes identified among the OXA-48-like carbapenemases. OXA-436, OXA-245, OXA-484, and OXA-519 are less often reported group (please see below for more details).

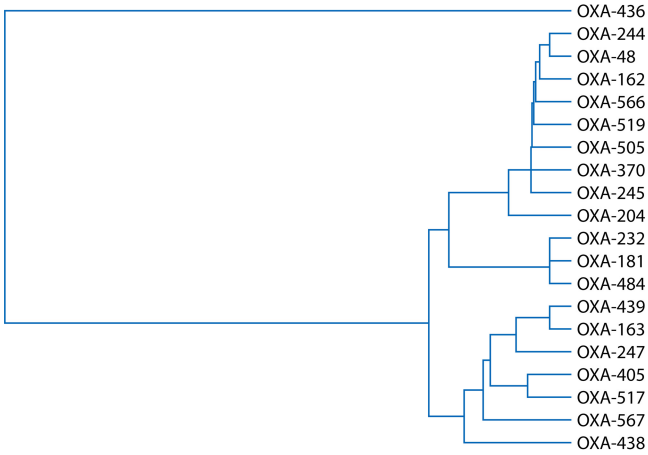

FIG 1 UPGMA (unweighted pair group method using average linkages) phylogenetic tree of OXA-48-producing *Enterobacterales* using amino acid alignments. The tree calculation was performed with the ClustalW2 multiple-sequence alignment program.

Enzyme Characteristics for OXA-48-Like Carbapenemases

OXA-48-like β-lactamases consist of 261 to 265 amino acids encoded by the bla_{OXA} open reading frame (ORF), consisting of 798-bp nucleotides (22). Overall, the carbapenemase activities of OXA-48-like enzymes are low, and the production of extended-spectrum β-lactamases (ESBLs) and/or porin mutations are often required to provide the high levels of carbapenem resistance (41, 42).

The crystal structure of OXA-48 and hydrolysis assays showed that the carbapenem hydrolysis is different from that of other non-48 OXA carbapenemases. Hydrolytic efficiency of OXA-48 against imipenem is approximately 10-fold higher than that of the OXA carbapenemases (OXA-23-like, etc.) from *Acinetobacter* spp. (17). OXA-48 has the highest k_{cat} value for imipenem, 2 s^{-1}, which represented the highest hydrolysis rate of all of the published kinetic parameters among the OXA-48-like enzymes (22). For OXA-48, hydrolysis relies on the rotation of the carbapenem-hydroxyethyl group within the active site of the enzyme in a manner that allows movement of the deacylating water molecules toward the acylated serine residue (43). Consequently, OXA-48-producing *K. pneumoniae* isolates exhibit elevated MICs to the carbapenems (especially to imipenem). OXA-48 efficiently hydrolyzes the amino-, carboxy-, and ureidopenicillins and narrow-spectrum cephalosporins (e.g., cephalothin), but not the extended-spectrum cephalosporins (e.g., ceftriaxone, ceftazidime, and cefepime) (22).

Figure 1 shows a phylogenetic tree of the amino acid alignment of the different OXA-48-like enzymes using the ClustalW2 sequence alignment program. OXA-48-like carbapenemases can be broadly divided into 3 clusters, namely, the OXA-48 cluster (which shows more than 95% amino acid homology and consists of OXA-48, -162, -204, -244, -245, and -519), the OXA-181 cluster (which shows more than 98% amino acid homology and consists of OXA-181, -232 and -484), and OXA-436, which has significantly different amino acid alignment than other OXA-48-like carbapenemases (showing 76% amino acid homology with the OXA-48 and OXA-181 clusters). Please note that the OXA-48-like noncarbapenemases (e.g., OXA-163 and OXA-204) formed a separate cluster from the OXA-48, OXA-181, and OXA-436 clusters (Fig. 1).

Tables 1 and 2 show the amino acid differences and kinetic parameters of certain OXA-48-like β-lactamases. Most of the differences are located within the $\beta5$-$\beta6$ loop, which is important for the substrate specificity of OXA-48-like enzymes. Some OXA-48 variants have hydrolytic activities similar to that of OXA-48 (e.g., OXA-204 and OXA-181); others have slightly increased carbapenem-hydrolyzing activities (e.g., OXA-162) or slightly reduced carbapenem- and temocillin-hydrolyzing activities (e.g., OXA-232 and OXA-244). In contrast, OXA-48 variants with a 4-amino-acid deletion within the

TABLE 1 Amino acid divergences among OXA-48-like β-lactamases

OXA-48-like enzyme	Species	NCBI protein accession number	Divergence from OXA-48
OXA-162	*K. pneumoniae*	ACZ73269	Single substitution: Thr213Ala
OXA-163	*E. cloacae*	ADY06444	Single substitution: Ser212Asp Four deletions: Arg214, Ile215, Glu216, Pro217
OXA-181	*K. pneumoniae*	AEP16366	Four substitutions: Thr104Ala, Asn110Asp, Glu168Gln, Ser171Ala
OXA-204	*E. coli*	AJF39128	Two substitutions: Gln98His, Thr99Arg
OXA-232	*E. coli*	AGD91915	Five substitutions: Thr104Ala, Asn110Asp, Glu168Gln, Ser171Ala, Arg214Ser
OXA-244	*E. coli*	AKJ18768	Single substitution: Arg214Gly
OXA-245	*K. pneumoniae*	AGC60013	Single substitution: Glu125Tyr
OXA-247	*K. pneumoniae*	AGC70814	Two substitutions: Tyr211Ser, Asp212Asn
OXA-370	*E. hormaechei*	AHW47891	Single substitution: Gly220Glu
OXA-405	*S. marcescens*	AJA30430	Four deletions: Thr213, Arg214, Ile215, Glu216
OXA-436	*C. freundii*	ALN39145	23 substitutions: Val3Ala, Phe10Leu, Leu11Met, Ala13Thr, Ser14Thr, Ile15Met, Thr36Ser, Ser40Thr, Lys51Thr, Asn58Asp, Thr104Ala, Asn110Asp, Val153Leu, Glu168Gln, Ser171Ala, Gly201Ala, Thr213Val, Val226Ile, Met237Thr, Ser244Ala, Asp245Glu, Ala252Thr, Glu256Ala
OXA-438	*E. coli*	AKL59521	Four substitutions: Ser212Gly, Ile215Tyr, Glu216Asp, Pro217Thr Two deletions: Thr213, Arg214
OXA-439	*E. coli*	AKR53961	Two substitutions: Tyr123His, Ser212Asp Four deletions: Arg214, Ile215, Glu216, Pro217
OXA-484	*K. pneumoniae*	ALI16502	Five substitutions: Thr104Ala, Asn110Asp, Glu168Gln, Ser171Ala, Arg214Gly
OXA-505	*K. pneumoniae*	ALZ40809	Single substitution: Ala8Thr
OXA-517	*K. pneumoniae*	AMO66558	Single substitution: Arg214Lys Two deletions: Ile215, Glu216
OXA-519	*K. pneumoniae*	ANI25017	Single substitution: Val120Leu
OXA-566	*E. coli*	ACS55290	Single substitution: Ala141Asp
OXA-567	*K. pneumoniae*	ATJ25944	Three substitutions: Ser212Asp, Arg214Lys, Glu216Gly Single deletion: Pro217

β5-β6 loop (e.g., OXA-163 and OXA-405) have lost their carbapenem-hydrolytic activity and gained the capacity to hydrolyze extended-spectrum cephalosporins (44).

Origin and Evolution of OXA-48-Like Carbapenemases

The OXA-54 gene is present on the chromosome of *S. oneidensis* and was reported around the same time as OXA-48. It shares 92% amino acid identity with OXA-48, suggesting that this genus is most likely the progenitors of OXA-48 (39). *S. xiamenensis* type strain S4, isolated in China, harbored an OXA-48 gene variant, namely, $bla_{\text{OXA-48b}}$, on its chromosome that differs by four nucleotides but results in the same amino acids as $bla_{\text{OXA-48}}$ (40). *S. xiamenensis* with $bla_{\text{OXA-48b}}$ was also found in Portugal (45).

Mobile genetic elements, especially the composite transposon Tn*1999*, were likely responsible for the capture and mobilization of OXA-48-like β-lactamases from the chromosome of *Shewanella* spp. onto conjugative plasmids and then spread to members of the *Enterobacterales*. The $bla_{\text{OXA-48}}$-like genes on the chromosomes of several *Shewanella* species are flanked by a gene encoding the peptidase C15 and *lysR-acc* (*lysR* is a transcriptional regulator and *acc* encodes acetyl coenzyme A [acetyl-CoA] carboxylase). The *lysR* sequence in *S. xiamenensis* S4 showed 99% nucleotide identity and the *acc* sequences were identical to that of Tn*1999* (GenBank accession numbers JX644945 and AY236073, respectively). It is thus more than likely that two copies of IS*1999* mobilized $bla_{\text{OXA-48}}$–*lysR*–Δ*acc* from the chromosome of *Shewanella* spp. to an IncL plasmid that was then transferred to *Enterobacterales* (Fig. 2).

S. xiamenensis, obtained from Indian seepage water during 2010, was identified as the progenitor of the OXA-181 gene, with chromosomal genetic structures similar to those described for the ColE-type OXA-181-containing plasmid (46). The $bla_{\text{OXA-181}}$ gene and its flanking regions (i.e., a 128-bp fragment downstream of IS*Ecp1* and a 378-bp fragment upstream of Δ*lysR* and partial *ere*) are identical to regions on the chromosome of *S. xiamenensis* strains S12 and Sh5 (46). The initial capture of the OXA-181 gene was mediated via IS*Ecp1* and the gene was then incorporated into Tn*2013*, which found its way onto ColE2, IncX3, IncN1, and IncT plasmids (Fig. 2) (46).

TABLE 2 Kinetic parameters of certain OXA-48-like β-lactamases[a]

Antibiotic and parameter	Value for indicated β-lactamase								
	OXA-48	OXA-162	OXA-163	OXA-181	OXA-204	OXA-232	OXA-245	OXA-436	OXA-519
Benzylpenicillin									
k_{cat} (s^{-1})	245	123	23	444	353	125	NE	900	NE
K_m (μM)	40	35	13	90	90	60	NE	200	NE
k_{cat}/K_m (mM^{-1}/s^{-1})	6,100	3,400	1,800	5,000	4,100	2,100	NE	4,500	NE
Ampicillin									
k_{cat} (s^{-1})	955	269	23	218	389	132	1,200	600	131
K_m (μM)	400	315	315	170	450	220	35	5	776
k_{cat}/K_m (mM^{-1}/s^{-1})	2,400	830	70	1,300	860	600	3,428	120,000	169
Oxacillin									
k_{cat} (s^{-1})	130	3	34	90	56	156	NE	NE	8
K_m (μM)	95	75	90	80	100	130	NE	NE	338
k_{cat}/K_m (mM^{-1}/s^{-1})	1,400	40	370	1,100	540	1,200	NE	NE	23
Piperacillin									
k_{cat} (s^{-1})	75	NE	8	NE	NE	380	NE	NE	36
K_m (μM)	410	NE	70	NE	NE	540	NE	NE	109
k_{cat}/K_m (mM^{-1}/s^{-1})	180	NE	110	NE	NE	700	NE	NE	330
Temocillin									
k_{cat} (s^{-1})	0.3	0.7	NH	0.3	0.5	0.03	NE	3	>12
K_m (μM)	45	170	NH	60	75	60	NE	200	>1,000
k_{cat}/K_m (mM^{-1}/s^{-1})	6	4	ND	5	7	0.5	NE	15	8.8
Imipenem									
k_{cat} (s^{-1})	5	11	0.03	7.5	4	0.2	4.4	6	2.1
K_m (μM)	13	25	530	13	9	9	11	20	982
k_{cat}/K_m (mM^{-1}/s^{-1})	370	420	0.06	550	420	20	400	300	2.138
Meropenem									
k_{cat} (s^{-1})	0.07	0.1	>0.1	0.1	0.05	0.03	0.11	0.14	3.4
K_m (μM)	10	80	>2,000	70	60	100	2	3	358
k_{cat}/K_m (mM^{-1}/s^{-1})	6	1.3	0.03	1.5	0.8	0.3	55	4,666	9.497
Ertapenem									
k_{cat} (s^{-1})	0.13	0.3	0.05	0.2	0.1	0.04	0.29	0.4	1.1
K_m (μM)	100	30	130	100	90	110	80	160	83
k_{cat}/K_m (mM^{-1}/s^{-1})	1	9	0.3	2	1	0.4	3,625	2.5	13.25
Cefotaxime									
k_{cat} (s^{-1})	>9	3	10	>62	12	>6.5	NE	6	>1.3
K_m (μM)	>900	310	45	>1,000	990	>1,000	NE	130	>1,000
k_{cat}/K_m (mM^{-1}/s^{-1})	10	10	230	13	12	6	NE	46.15	0.39
Ceftazidime									
k_{cat} (s^{-1})	NH	ND	8	ND	ND	>0.6	0.3	7	0.02
K_m (μM)	NH	NH	>1,000	NH	NH	>1,000	110	150	373
k_{cat}/K_m (mM^{-1}/s^{-1})	NH	ND	3	ND	ND	0.1	2,727	4,666	0.05
Cefepime									
k_{cat} (s^{-1})	1	NE	2	NE	NE	13	NE	NE	>1.3
K_m (μM)	160	NE	350	NE	NE	1,200	NE	NE	>1,000
k_{cat}/K_m (mM^{-1}/s^{-1})	6	NE	6	NE	NE	10	NE	NE	0.31
Cephalothin									
k_{cat} (s^{-1})	44	12	3	13	12	13	NE	NE	>13
K_m (μM)	195	180	10	250	270	125	NE	NE	>1,000
k_{cat}/K_m (mM^{-1}/s^{-1})	255	70	300	50	45	105	NE	NE	3.5

[a]Kinetic parameter values for OXA-48 are from reference 44, except those for benzylpenicillin, piperacillin, and cefepime, which are from reference 22. Values for OXA-163 are from reference 44, except those for piperacillin and cefepime, which are from reference 32. Values for OXA-232 are from reference 44, except those for piperacillin and cefepime, which are from reference 26. All values for OXA-162, OXA-181, and OXA-204 are from reference 44. All values for OXA-245 are from reference 307. All values for OXA-436 are from reference 214. All values for OXA-519 are from reference 31. k_{cat}, number of times each enzyme site converts substrate to product per unit time; K_m, inverse measure of affinity; NE, not evaluated; ND, not determined; NH, not detectable.

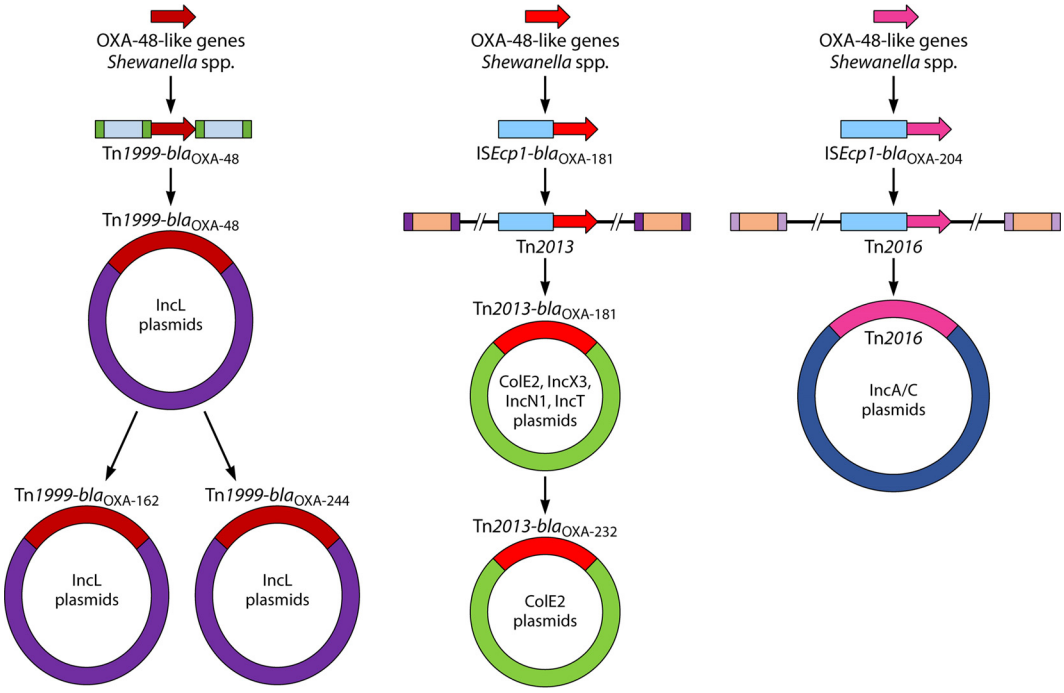

FIG 2 Origin and evolution of OXA-48-like carbapenemases, namely, OXA-48, OXA-162, OXA-181, OXA-204, OXA-232, and OXA-244.

OXA-232 differs from OXA-181 by a single amino acid substitution, and the genetic environment surrounding the $bla_{OXA-232}$ is very similar to the environment surrounding $bla_{OXA-181}$ (Table 1 and Fig. 2; see "Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-232}$" below for details). This suggests that OXA-232 is a derivative of OXA-181.

The OXA-204 gene has a genetic environment similar to that of $bla_{OXA-181}$, but OXA-204 differs from OXA-181 by 6 amino acid substitutions (Table 1 and Fig. 2; see "Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-204}$" below for details). The origin of $bla_{OXA-204}$ is most likely the chromosome of *S. xiamenensis* (45), and the capture of $bla_{OXA-204}$ was most likely due to distinct transposition processes independently from $bla_{OXA-181}$ (Fig. 2).

OXA-162 and OXA-244 differ from OXA-48 by a single amino acid substitution and the genetic environments surrounding the $bla_{OXA-162}$ and $bla_{OXA-244}$ are very similar to the environment surrounding $bla_{OXA-48.}$ (Table 1 and Fig. 2; see "Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-162}$" and "Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-244}$" below for details). This suggests that OXA-162 and OXA-244 are derivatives of OXA-48.

In summary, the nucleotide similarities and genetic structures flanking the carbapenemase genes suggest that bla_{OXA-48}, $bla_{OXA-181}$, and $bla_{OXA-204}$ were derived from different *S. xiamenensis* isolates through distinct transposition processes and that OXA-232, OXA-162, and OXA-244 are derivatives of OXA-181 (i.e., OXA-232) and OXA-48 (i.e., OXA-162 and OXA-244) (Fig. 2).

Global Surveillance for OXA-48-Like Carbapenemases

Surveillance studies that use molecular methodologies to identify carbapenemases have shown that OXA-48-like β-lactamases are the 2nd or 3rd most common carbapenemases among global *Enterobacterales* (47, 48). Data from the SMART (2008 to 2014) and INFORM (2012 to 2014) global surveillance programs show that 27% of carbapenemase-producing *Enterobacterales* (CPE; $n = 1,615$) were positive for OXA-48-like carbapenemases (compared to 55% KPCs and 26% NDMs). In certain areas (e.g., the Middle East, North Africa, and European countries such as Belgium and Spain),

OXA-48-like enzymes were the most common carbapenemases among the *Enterobacterales*. OXA-48-like carbapenemases was mainly present in *K. pneumoniae* isolates submitted from hospitals sites and were increasing toward the end of the surveillance periods (47, 48).

OXA-48

OXA-48 is currently the most common global OXA-48-like enzyme and was first reported in 2004 from a clinical isolate obtained in Istanbul, Turkey (22). *K. pneumoniae* 11978 was responsible for lower urinary tract infection and tested nonsusceptible to all β-lactam antibiotics (including imipenem and ertapenem), the aminoglycosides, chloramphenicol, nalidixic acid, ciprofloxacin, rifampin, sulfonamides, and tetracycline. *K. pneumoniae* 11978 produced five different β-lactamases, and the enzyme with a pI of 7.2 turned out to be OXA-48. OXA-48 was distantly related to other oxacillinases and hydrolyzed the penicillins, cephalothin, and imipenem. The insertion sequence element IS*1999* was found up- and downstream of the bla_{OXA-48} gene harbored on a 70-kb plasmid named pA-1 (22). *K. pneumoniae* with bla_{OXA-48} quickly became endemic in Istanbul, causing several nosocomial outbreaks at the University Hospital of Istanbul (49), while *K. pneumoniae* and *E. coli* with this enzyme gradually spread to other parts of Turkey (50).

Geographical Distribution of OXA-48

The 1st report of *K. pneumoniae* with OXA-48 outside Turkey occurred in Brussels, Belgium, in 2010 when a patient, with no apparent connection with Turkey, underwent chemotherapy for lymphoma (51). This was followed by a study that described different *Enterobacterales* (i.e., *K. pneumoniae*, *Enterobacter cloacae*, *Providencia rettgeri*, *Citrobacter freundii*, and *E. coli*) with the OXA-48 gene situated on similar 70-kb plasmids, recovered from Turkey and Lebanon (52) and Egypt, France, and Belgium (53) and described in reports from France (54) and North Africa, namely, Tunisia (55, 56) and Morocco (57, 58).

In 2011, reports of OXA-48-producing *Enterobacterales* appeared from Israel (59), Senegal (60), the Netherlands (61), Spain (62), Ireland (63), and Slovenia (64). The reports from France (65, 66), Slovenia (64), Spain (62), and Israel (59) were due to patients that had previously visited or were transferred from hospitals in Turkey or North Africa (especially Morocco). Nosocomial outbreaks with OXA-48-producing *Enterobacterales* (especially due to *K. pneumoniae*) occurred early after their introduction into France (67), Belgium (68), Ireland (63), and Spain (62).

Enterobacterales with bla_{OXA-48} are currently endemic in Turkey, other Middle Eastern countries (i.e., Lebanon, Jordan, Oman, Iran, and Saudi Arabia), and North Africa (Morocco, Algeria, Tunisia, and Egypt) and are important causes of nosocomial outbreaks in these regions and countries (69) (Fig. 3). Health care-associated outbreaks have also been described in various other countries, including Greece (70, 71), Australia (72), Israel (73, 74), the United Kingdom (75, 76), the Netherlands (77, 78), Ireland (79, 80), Spain (81–85), France (86–88), Germany (89, 90), Mexico (91), China (92), Belgium (93), Norway (94), Poland (95), Taiwan (96), South Africa (97), Croatia (98), and Slovenia (99).

Currently, *Enterobacterales* with bla_{OXA-48} have a truly global distribution, and reports of imported and nonimported cases have described from all continents except Antarctica, including the Americas (e.g., Colombia [100] and Mexico [91]), various European and North American countries (69), Sub-Saharan Africa (e.g., Tanzania [101], South Africa [97], and Senegal [60]), Asia (e.g., Japan [102], Singapore [103], Taiwan [104], and Malaysia [105]), Oceania (e.g., New Zealand [106]), and the Caribbean islands (107).

Bacteria Producing OXA-48

OXA-48 was first described for *K. pneumoniae*, and it remains the most common global bacterium associated with health care-associated infections due to organisms

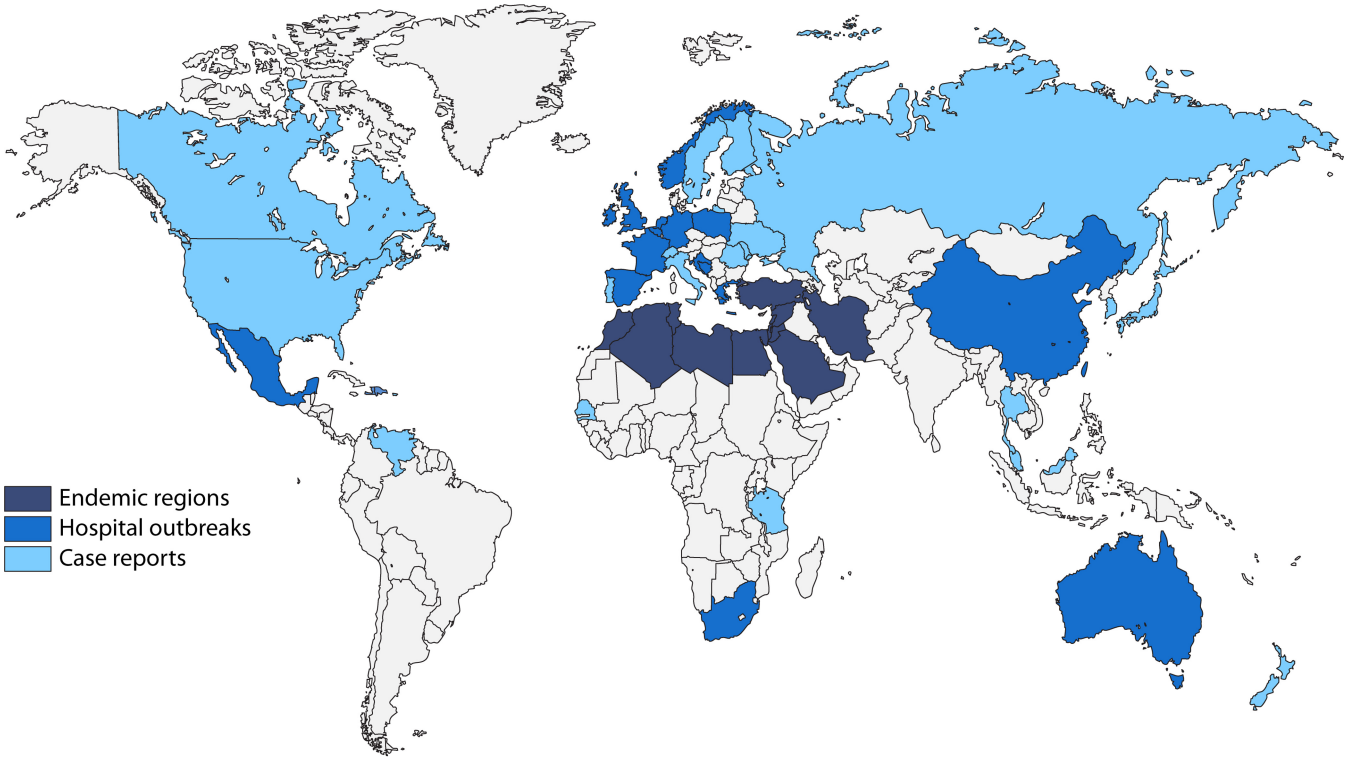

FIG 3 Global distribution of *Enterobacterales* with OXA-48.

with bla_{OXA-48} (47, 48). Subsequently OXA-48 was reported from several members of the *Enterobacterales*, especially *E. coli* (108), the *E. cloacae* complex (109), *Citrobacter freundii* (98), *Serratia marcescens* (74), *Proteus mirabilis* (110), *Kluyvera* spp. (111), *Klebsiella oxytoca* (112), and *Salmonella* spp. (113). *Klebsiella* spp. and *Enterobacter* spp. tend to be responsible for health care-associated infections, while *E. coli* with bla_{OXA-48} is an important cause of community-acquired infections due to carbapenemase-producing bacteria (114). The wide distribution of OXA-48 among different species in hospitals and especially in community settings remains one of the reasons why it is so difficult to limit and control the spread of bacteria with these enzymes. Plasmids containing bla_{OXA-48} have the ability to easily and widely disperse between various bacterial species via horizontal transmission. Different bacteria obtained from the same patient (either as colonizers or as clinical isolates) often contain identical plasmids harboring OXA-48 (115).

Enterobacterales with OXA-48 have been obtained from humans, animals (companion, other domestic, farm, and wildlife) and various types of environmental specimens from different parts of the world (69).

Molecular Epidemiology of *Enterobacterales* with bla_{OXA-48}

The current international and interspecies spread of bla_{OXA-48} is mainly driven by the composite transposon Tn*1999* and its variants situated on pOXA-48a-like IncL conjugative plasmids (116).

Genetic Environments Surrounding bla_{OXA-48}

Tn*1999* variants. Tn*1999*, also named Tn*1999.1*, consists of two copies of the insertion sequence IS*1999*; one copy is inserted 26 bp upstream of bla_{OXA-48} and another copy is inserted downstream of bla_{OXA-48}–*lysR*–Δ*acc* (Fig. 4) (116). IS*1999* was first identified in *Pseudomonas aeruginosa* from Thailand and was inserted into the integron-specific recombination site, *attI1*, upstream of bla_{VEB-1} (117). The bla_{OXA-48}-like genes on the chromosomes of several *Shewanella* species are flanked by a gene

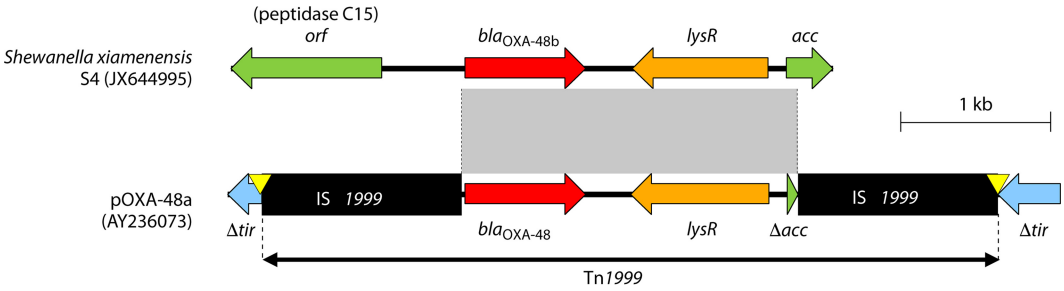

FIG 4 Similarities between Tn*1999* with bla_{OXA-48} within the pOXA-48a plasmid and the *Shewanella xiamenensis* chromosome. Genes from background plasmids are indicated with cyan, and chromosomal genes of *Shewanella* are indicated with green. Yellow triangles indicate target site duplications.

encoding the peptidase C15 and *lysR-acc* (*lysR* is a transcriptional regulator and *acc* encodes acetyl-CoA carboxylase), which is similar to regions surrounding IS*1999* (Fig. 4) (40).

Tn*1999.2* and Tn*1999.3* are Tn*1999* variants with an IS*1R* insertion into IS*1999* upstream of bla_{OXA-48} creating a strong hybrid promoter (−35 box from IS1R and −10 box from IS*1999*), leading to a 2-fold-higher enzymatic activity than with Tn*1999* (Fig. 5) (49). Tn*1999.2* was first described in Turkey in 2006 to 2007 (49) and then among clinical isolates from France, Turkey, Lebanon, Belgium, and Egypt situated on pOXA-48a-like plasmids (53, 68). Inverted copies of Tn*1999.2* were found on pOXA-48a-like plasmids from *K. pneumoniae*, *Klebsiella aerogenes*, *E. cloacae*, *Citrobacter koseri*, and *Raoultella planticola* obtained in Lebanon (118). Tn*1999.3* differs from Tn*1999.2*, with a second copy of IS*1R* located just downstream of bla_{OXA-48} (Fig. 5), and has been identified in an *E. coli* isolate from Italy (119).

Tn*1999.4* is a Tn*1999.2* variant with Tn*2015* inserted downstream of bla_{OXA-48} within *lysR* and was described for *E. coli* and *E. cloacae* from France situated on a pOXA-48a-like plasmid (Fig. 5) (120). Tn*2015* included IS*Ecp1* with the $bla_{CTX-M-15}$ ESBL gene, which contributes to reduced susceptibility to the cephalosporins and carbapenems (120). Tn*1999.5* is another variant of Tn*1999.2* in which *lysR* is truncated by IS*Kpn19* (Fig. 5) found in *K. pneumoniae* sequence type 891 (ST891) from the Czech Republic, also situated on a pOXA-48a-like plasmid (121).

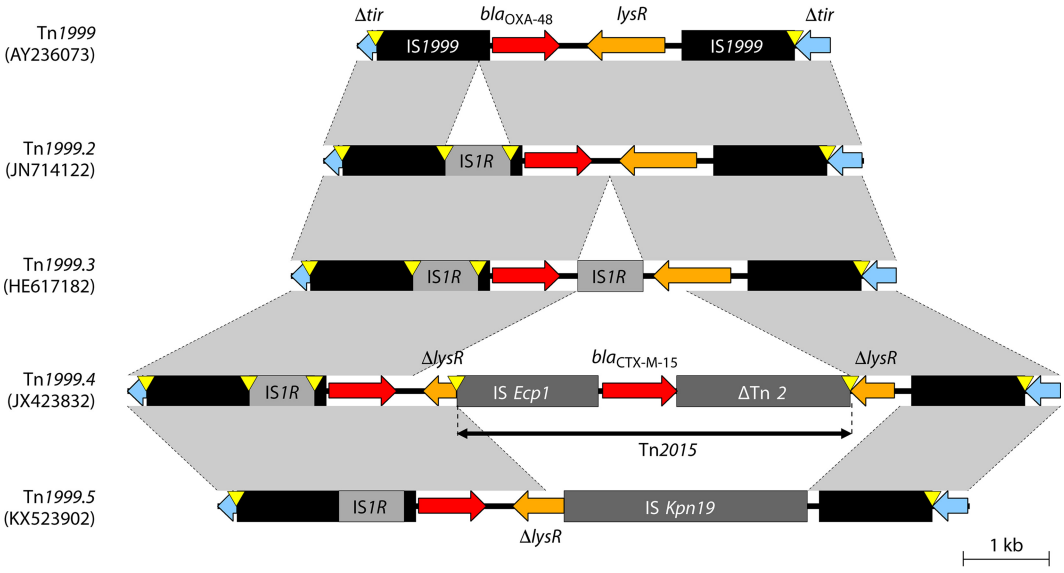

FIG 5 Genetic environments of Tn*1999* and its variants within pOXA-48a-like plasmids. Mobile elements are indicated with black (e.g., IS*1999*) or gray (others). Genes from background plasmids are indicated with cyan. Yellow triangles indicate target site duplications.

All the Tn*1999* variants were integrated into the *tir* site of pOXA-48a-like plasmids, suggesting that they originated from Tn*1999* by stepwise insertion of different MGEs.

Tn*2016*-like element. Izdebski et al. in 2018 described a bla_{OXA-48} gene among *K. pneumoniae* ST15 and ST11 isolates obtained from Poland that was located downstream of IS*Ecp1*, situated within Tn*2016*, that had previously been reported for $bla_{OXA-204}$ (95) (please refer to the OXA-204 section for details). The Tn*2016*-like element was situated on nontypeable plasmids ranging in size from 90 to 160 kb, suggesting a different event for mobilization of bla_{OXA-48} from *Shewanella* spp.

Plasmids harboring bla_{OXA-48}. The most common plasmids that harbor Tn*1999* variants associated with bla_{OXA-48} belong to the pOXA-48a-like IncL (IncL/M) replicon types (122). The IncL/M replicon type is currently one of the seven major plasmid families together with IncF, A/C type (IncA/C), IncI, IncHI, IncX, and IncN associated with antimicrobial resistance (AMR) among *Enterobacterales* (123). Recent molecular analyses have divided IncL/M plasmids into IncL, IncM1, and IncM2 subgroups based on incompatibility, differences in IncRNA (long noncoding RNA), and entry exclusion systems (122). IncL plasmids (e.g., pOXA-48a) and its variants have been mainly associated with bla_{OXA-48} (122).

pOXA-48a-like IncL plasmids do not contain additional AMR genes other than bla_{OXA-48}, which differs from IncM plasmids (116, 121, 122, 124). pOXA-48a is highly similar to the IncM2 plasmid named pCTX-M3 (122), except for IS*Ecp1*–$bla_{CTX-M-3}$, which was inserted close to Tn*1999* and a 27-kb AMR island near the *trb* transfer locus (116). The pOXA-48a-like IncL plasmids are conjugative and have been described for *E. coli*, *E. cloacae*, *K. pneumoniae*, *Klebsiella oxytoca*, *Citrobacter freundii*, and *R. planticola* (53, 116, 118). Transformation assays were unsuccessful for transferring pOXA-48a into *A. baumannii* and *P. aeruginosa* (116), and it seems that the host range is limited to the *Enterobacterales* (125).

pOXA-48a is highly transmissible, exhibiting a transfer frequency 50 times higher than those of the similar pNDM-OM IncL plasmids with bla_{NDM-1}. This is likely due to the insertion and disruption of Tn*1999* variants into the *tir* regions of pOXA-48a (the *tir* gene encodes a protein that inhibits transfer) (126). The insertion of Tn*1999* variants into *tir* in pOXA-48a-like plasmids plays an important role in the mobility of these plasmids.

The PCR-based replicon typing scheme developed by Carattoli et al. was unable to detect pOXA-48a-like plasmids (127). Poirel et al. designed three primer pairs for the detection of pOXA-48a-like plasmids that amplified the *repA*, *traU*, and *parA* genes (116). The presence of Tn*1999* variants and these three genes suggests the presence of pOXA-48a-like plasmids, but these genes are not specific markers, since they are also present in other IncL/M group plasmids.

Non-IncL plasmids have rarely been associated with bla_{OXA-48}, but Tn*1999* (without bla_{OXA-48}) has been translocated to other plasmids, e.g., a nontypeable 29-kb plasmid in *K. pneumoniae* ST530 from Bulgaria (128), an A/C-type 150-kb plasmid in *Providencia rettgeri* from Turkey (129), and a 160-kb IncF plasmid in *E. coli* ST963 from France (129).

Chromosomal insertion of bla_{OXA-48}. Tn*6237* is a 21.9-kb IS*1R*-based composite transposon consisting of an inverted ΔTn*1999.2* and a fragment from pOXA-48a (stretching from Δ*tir-pemI* to *korC*-*orf25*) (Fig. 6). Tn*6237* has been integrated into different chromosomal insertion sites among several *E. coli* and *K. pneumoniae* STs obtained from Lebanon and the Czech Republic (118, 121). Tn*6237* most likely originated when the pOXA-48_4963 plasmid (with Tn*1999.2*) and the pRA35 plasmid (with inverted Tn*1999.2* and IS*1R* insertion in *orf25*) underwent IS*1R*-mediated transposition and recombination and was then inserted into the chromosome of *E. coli* and *K. pneumoniae* STs (Fig. 6) (118).

E. coli ST38 without OXA-48-containing plasmids emerged in different hospitals throughout the United Kingdom in 2014 to 2015, as a common host of bla_{OXA-48} (130). Tn*6237* variants with different plasmid-derived sequences (9.7 kb or 11.2 kb) and different insertion sites were identified among sequenced isolates. The sequences and insertion sites identified in the UK *E. coli* ST38 were different than those characterized

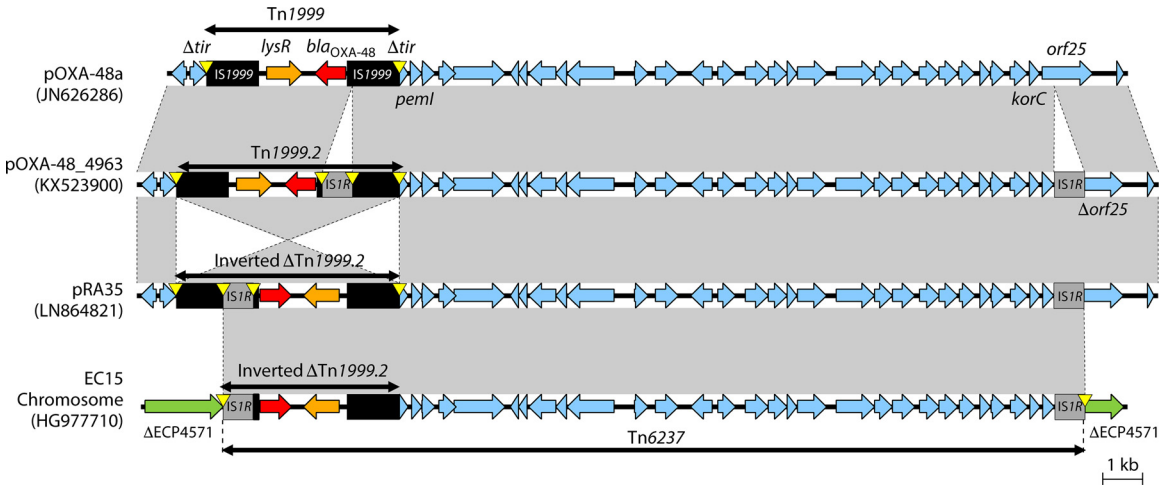

FIG 6 Genetic environments of Tn*1999* within pOXA-48a, Tn*1999.2* in pOXA-48_4963, inverted Tn*1999.2* in pRA35, and Tn*6237* containing inverted ΔTn*1999.2* in the *E. coli* chromosome. In the *E. coli* EC15 chromosome, Tn*6237* was inserted into a gene coding histidine kinase-like ATPase (ECP4571 in *E. coli* 536 [GenBank accession number CP000247]). Mobile elements are indicated with black (e.g., IS*1999*) or gray (others). Genes from background plasmids are indicated with cyan, and those from the chromosome are indicated with green. Yellow triangles indicate target site duplications.

from Lebanon (118). The Lebanese study included 3 *E. coli* ST38 isolates with chromosomal insertion of bla_{OXA-48} and was obtained from hospital patients and the stool of a healthy child. The chromosomal integration of bla_{OXA-48} into Tn*6237* among *E. coli* ST38 isolates and the subsequent clonal dissemination across different UK sites have contributed to the increase of OXA-48-producing *E. coli*.

Tn*6237* has also been described on an IncC plasmid of 117 kb obtained from *K. pneumoniae* ST147 (131), suggesting that IS*1R*-mediated transposition from pOXA-48a-like plasmids played an important role in the mobilization of bla_{OXA-48} among various plasmid and chromosomal genetic backgrounds.

Clonal dissemination of *Enterobacterales* with bla_{OXA-48}. *K. pneumoniae*, followed by *E. coli* and *E. cloacae*, is a common vehicle for bla_{OXA-48} (129, 132). Potron et al. conducted a molecular epidemiological study characterizing 107 OXA-48-producing *Enterobacterales* obtained mainly from Europe and North Africa between 2001 and 2011 (129). The bla_{OXA-48} gene was situated on pOXA-48a-like IncL plasmids among 93% of isolates. Different Tn*1999* variants were associated with bla_{OXA-48} in all isolates, with Tn*1999.2* being the most common (79%), followed by Tn*1999* (20%) (129). Coproduction of ESBLs (most often CTX-M-15) was observed in 75% of isolates.

Among *K. pneumoniae* isolates, diverse sequence types have been reported, with global AMR high-risk clones such as ST101, ST395, ST15, and ST147 being the most common (129). The most common STs identified in nationwide surveillances were ST101 in the United Kingdom (30) and ST395 in Poland (95). Regional nosocomial outbreaks of different *K. pneumoniae* STs have been reported from various countries, including the following: ST11, ST101, and ST405 in Spain (84), ST147 in Germany (131) and Slovenia (99), and ST11 in Croatia (98) and Spain (133). The analysis of the *K. pneumoniae* ST147 outbreak in Germany showed that bla_{OXA-48} was harbored on pOXA-48a-like IncL plasmids, while $bla_{CTX-M-15}$ and other antimicrobial resistance genes were situated within IncR and IncC plasmids (131). Tn*1999.2* on pOXA-48a-like plasmids was common among the ST147 isolates from the United Kingdom (134). Colistin-resistant *K. pneumoniae* ST11 with bla_{OXA-48} and $bla_{CTX-M-15}$ caused nosocomial outbreaks in France (135), while pan-drug-resistant *K. pneumoniae* ST147 and extensively-drug resistant *K. pneumoniae* ST101 with bla_{OXA-48} and $bla_{CTX-M-15}$ caused nosocomial outbreaks in Spain (70).

Among *E. coli* isolates, diverse STs, including international AMR high-risk clones (e.g., ST38 [130], ST131 [136], ST410 [137], and ST648 [95]), have been associated with

OXA-48. *E. coli* ST38 is characteristic for the chromosomal location of bla_{OXA-48} within Tn*6237* and has been reported from Canada, the Czech Republic, Egypt, Finland, France, Lebanon, Switzerland, and the United Kingdom (118, 121, 129, 130, 134). A single ST38 isolate with bla_{OXA-48} on a plasmid (pOXA-48a-like) has also been described (129). In the United Kingdom, 16% of OXA-48-producing *Enterobacterales* referred to the national reference laboratory between 2013 and 2015 were *E. coli* ST38 with Tn*6237* (130). *E. coli* ST38 isolates were collected across the country, often without clear epidemiological links. *E. coli* ST38 isolates from the Czech Republic and Lebanon also contained chromosomal insertions of Tn*6237* (118, 121). These epidemiological data show that *E. coli* ST38 with chromosomal Tn*6237* harboring bla_{OXA-48} was responsible for international spread of OXA-48-producing *E. coli*.

Enterobacter species isolates with OXA-48 were collected by two global surveillance programs between 2008 and 2014 (109). Three global clones (i.e., *Enterobacter xiangfangensis* ST114, *Enterobacter hormaechei* subsp. *steigerwaltii* ST93, and *E. cloacae* Hoffmann cluster III ST78) from Europe, Africa, the Middle East, and Asia were associated with bla_{OXA-48} situated within Tn*1999.2* (109).

OXA-48-producing *Enterobacterales* have also been identified in nonhuman sources. For example, *E. coli* ST38 with Tn*1999.2* was isolated from poultry in Lebanon (138). *K. pneumoniae* ST15 and *E. coli* ST1431 and ST1196 with Tn*1999.2* on pOXA-48a-like plasmids were isolated from dogs from veterinary clinics in Germany (139).

In summary, pOXA-48a-like IncL plasmids with Tn*1999.2* and Tn*1999* have been the main sources of the current global distribution of bla_{OXA-48} into multiple *Enterobacterales* members. Clonal outbreaks caused by specific AMR high-risk clones such as *K. pneumoniae* STs (e.g., ST101, ST395, ST15, and ST147) with pOXA-48a-like plasmids and *E. coli* ST38 with chromosomally carried bla_{OXA-48} within Tn*623* also have contributed to the international spread of bla_{OXA-48} into various hospitals, regions, and countries.

OXA-181

OXA-181 is currently the 2nd most common global OXA-48-like derivative and was first described in Indian hospitals in 2006 to 2007 (140), was followed by reports from France (141), the Netherlands (61), Oman (24), and New Zealand (142) in 2011. The Indian publication was from the Sentry Antimicrobial Surveillance program and described 10 *K. pneumoniae* isolates and 1 *E. cloacae* complex isolate with OXA-181 obtained from blood and respiratory specimens from hospitals in Kolkata, New Delhi, and Mumbai (140). The French, Dutch, New Zealand, and Oman studies characterized *Citrobacter freundii* and *K. pneumoniae* isolates, resistant to all β-lactams (including the carbapenems), isolated from patients that had been transferred from India or Tanzania to France, the Netherlands, New Zealand, and the Sultanate of Oman. *C. freundii* STE from France was isolated from urine, was resistant to the aminoglycosides, sulfonamides, tetracycline, tigecycline, nitrofurantoin, and fluoroquinolones, and coproduced NDM-1, VIM-4, CTX-M-15, OXA-1, OXA-9, and TEM-1 (141). $bla_{OXA-181}$ was situated downstream of the insertion element IS*Ecp1* harbored within Tn*2013* located on an 84-kb mobile IncT-type plasmid (143). *K. pneumoniae* KP3 from Oman had a resistance profile similar to that of *C. freundii* STE and coproduced CTX-M-15, OXA-1, and TEM-1, and the $bla_{OXA-181}$ gene was also incorporated within Tn*2013* but located on a 7.6-kb ColE-type plasmid (24).

Geographical Distribution of OXA-181

Over the next 3 years (i.e., 2012 to 2014), OXA-181 was reported for *Enterobacterales* obtained from the United Kingdom (134), Singapore (144), South Africa (97), Norway (145), Romania (146), Canada (147), and Sri Lanka (148). The majority of these isolates were associated with coproduction of NDM-1 and previous travel to the Indian subcontinent.

Since 2014, the description of OXA-181 has escalated on a global scale, with reports from Asia (e.g., Japan [149], South Korea [150], China [151], Thailand [152], Pakistan [153], and Myanmar [154]), North America (e.g., the United States [155–157] and Canada

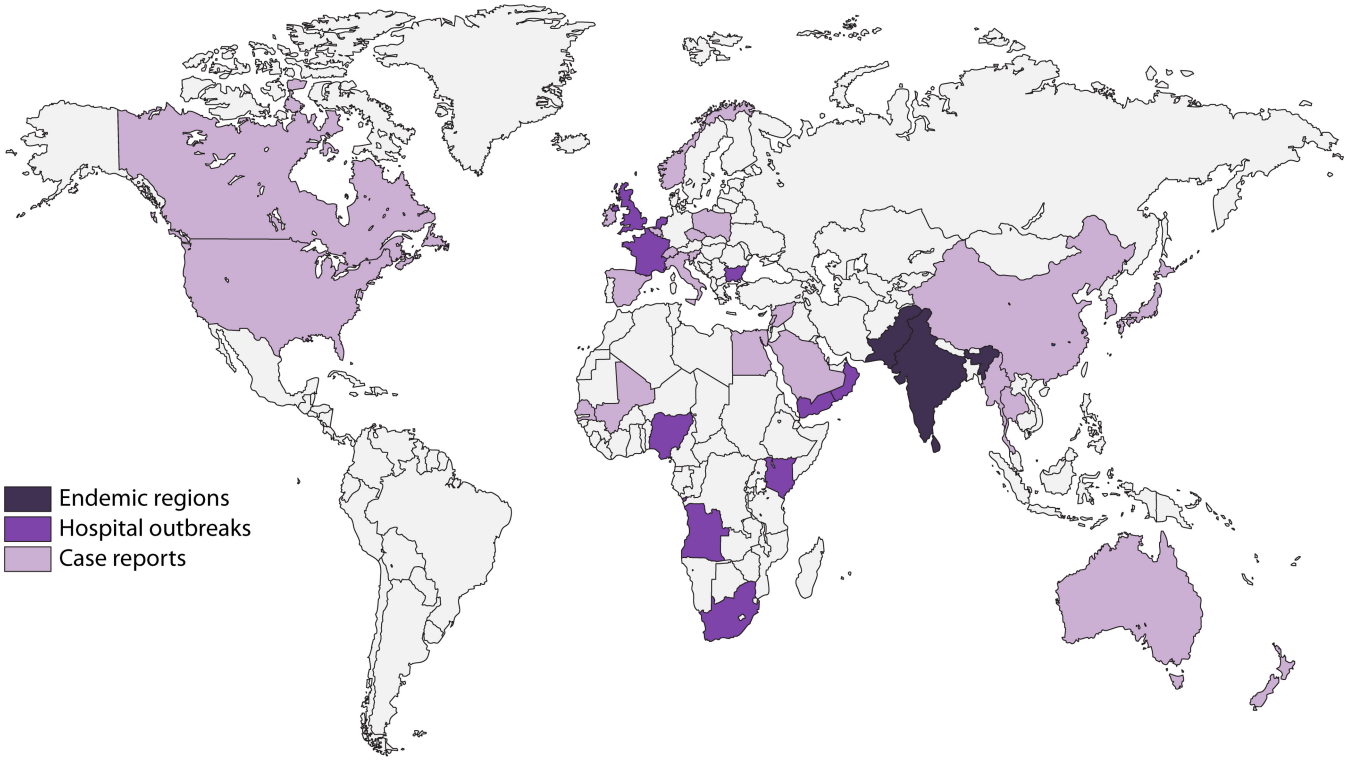

FIG 7 Global distribution of *Enterobacterales* with OXA-181.

[158]), Europe (e.g., Denmark [159], Austria [160], Switzerland [161], the Czech Republic [121], France [162], Poland [95], Italy [163], and Spain [164]), Africa (Burkina Faso [165], Egypt [166], Angola [167], Mali [168], Nigeria [169], and São Tomé and Príncipe [170]), the Middle East (e.g., Lebanon [171] and Saudi Arabia [172]), and Oceania (e.g., Australia [173]). Previous travel to India (147), Nigeria (174), and the Middle East (150) was identified as a risk factor of infection with OXA-181-producing bacteria.

Currently, *Enterobacterales* with $bla_{OXA-181}$ are endemic in the Indian subcontinent (e.g., India, Pakistan, Bangladesh, and Sri Lanka) and are important causes of nosocomial outbreaks in India (175, 176) and Bangladesh (177). Nosocomial outbreaks have also been described in Angola (167), South Africa (178), São Tomé and Príncipe (170), and the United Arab Emirates (179) (Fig. 7).

Bacteria Producing OXA-181

OXA-181 was first described for *K. pneumoniae*, and *K. pneumoniae* remains the most common global bacterium associated with $bla_{OXA-181}$ (153, 158, 164, 180). OXA-181 has also been reported among *E. coli* isolates (151, 155, 158, 167), followed by other members of the *Enterobacterales* such *Morganella morganii* (156), *Proteus mirabilis* (160), *Citrobacter freundii* (141), and the *E. cloacae* complex (30). OXA-181 has also been detected in *Aeromonas caviae* (181) and *P. aeruginosa* (182).

Enterobacterales with OXA-181 have been obtained from humans and animals (69) and from fresh Swiss vegetables imported from Asia (161).

Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-181}$

The current international and interspecies spread of $bla_{OXA-181}$ among *Enterobacterales* is mainly driven by the insertion element IS*Ecp1*, which is situated within Tn*2013* located on various plasmid backbones.

Genetic environments surrounding $bla_{OXA-181}$. Tn*2013* is composed of $bla_{OXA-181}$, IS*Ecp1* (located upstream), and Δ*lysR*-Δ*ere* (located downstream) (Fig. 8) (24). IS*Ecp1* includes promoter sequences near the inverted repeat right (IRR) (at positions −35 and

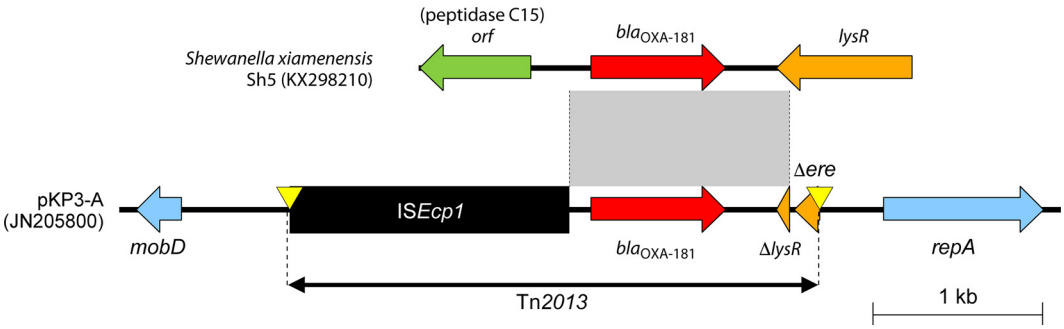

FIG 8 Similarities between *S. xiamenensis* chromosome with $bla_{OXA-181}$ and Tn*2013* within the pKP3-A plasmid. Genes from background plasmids are indicated with cyan, and chromosomal genes of *Shewanella* are indicated with green. Yellow triangles indicate target site duplications.

−10), uses one-sided transposition for mobilizing AMR genes, and is often associated with other β-lactamase genes, including $bla_{CTX-M-15}$ (117). In addition to the original inverted repeat left (IRL) and the IRR of IS*Ecp1*, Tn*2013* also contains a second IRR named IRR2 (24). Tn*2013* was initially inserted into a noncoding region of ColE2-type plasmid pKP3-A, with a target site duplication of 5 bp (ATATA) (Fig. 8). *In vitro* experiments showed that Tn*2013* can be integrated into the *E. coli* chromosome (24).

The origin of $bla_{OXA-181}$ is most likely the chromosome of *S. xiamenensis* (Fig. 2) (46). The $bla_{OXA-181}$ gene and its flanking regions (i.e., a 128-bp fragment downstream of IS*Ecp1* and a 378-bp fragment upstream of Δ*lysR* and partial *ere*) are identical to regions on the chromosome of *S. xiamenensis* strains S12 and Sh5 (Fig. 8) (46).

Plasmids harboring $bla_{OXA-181}$. The OXA-181 gene is harbored on mainly on 4 different plasmid types belonging to the ColE2, IncX3, IncN1, and IncT replicon types. *K. pneumoniae* KP3 from Oman belonged to ST11 and contained pKP3-A, which is a 7.6-kb ColE2-type (also referred to as ColKP3-type) plasmid harboring Tn*2013* with $bla_{OXA-181}$. The backbone of pKP3-A consisted of the *repA* replicase and *mob* mobilization genes (Fig. 9), and this plasmid is not self-transmissible but is mobilizable with the aid of other plasmids (24, 134). Electrotransformation assays have shown that pKP3-A can be introduced into and maintained within *P. aeruginosa* (24).

E. coli ST410 from China contained pOXA181_EC14828, a 51-kb self-transmissible, mobile IncX3 plasmid with $bla_{OXA-181}$ and *qnrS1* (151). IncX plasmids are narrow-host-range *Enterobacterales* plasmids (183) that are difficult to detect using PCR-based replicon typing schemes (127). IncX3 plasmids are associated with several types of bla_{NDM} genes (184), and the 26-kb backbone of pOXA181_EC14828 was similar to other IncX3 backbones with bla_{NDM-1} previously described in China (151). The immediate genetic environment of $bla_{OXA-181}$ (i.e., ΔIS*Ecp1*–$bla_{OXA-181}$–Δ*lysR*–Δ*ere*–Δ*repA*) situated within pOXA181_EC14828 is similar to the structure described for pKP3-A (Fig. 9). The *repA* gene from pKP3-A is interrupted and two parts are located upstream of IS*Ecp1* and downstream of Δ*lysR*-Δ*ere*, which are flanked by a 5-bp AT-rich duplicate sequence (ATCTT). These events might explain the insertion of an additional IS*Ecp1* with the subsequent homologous recombination between two copies of IS*Ecp1* (151). pOXA181_EC14828 contains IS*Kpn19* and *qnrS1* downstream of $bla_{OXA-181}$ and IS*3000* upstream of $bla_{OXA-181}$ and is flanked by a composite transposon consisting of two copies of the insertion sequence IS*26* (Fig. 9). Similar IncX3 plasmids with identical genetic environments surrounding $bla_{OXA-181}$ have also been described for *K. pneumoniae* isolates from the Czech Republic (121), Angola (167), and South Africa (185).

The 58-kb conjugative IncN1 plasmid named pMR3-OXA181 with $bla_{OXA-181}$ was identified in *Morganella morganii* MRSN 22709 and *E. coli* ST131 obtained from a U.S. patient with a history of travel to Germany and Afghanistan (Fig. 9) (156). pMR3-OXA181 contained a pKP3-A-like fragment with $bla_{OXA-181}$, flanked by IS*Kpn19*, IS*3000*, and two copies of IS*26*, showing high similarity to pOXA181_EC14828 (151), the IncX3 plasmid obtained in China (Fig. 9). The main difference between plasmids pMR3-

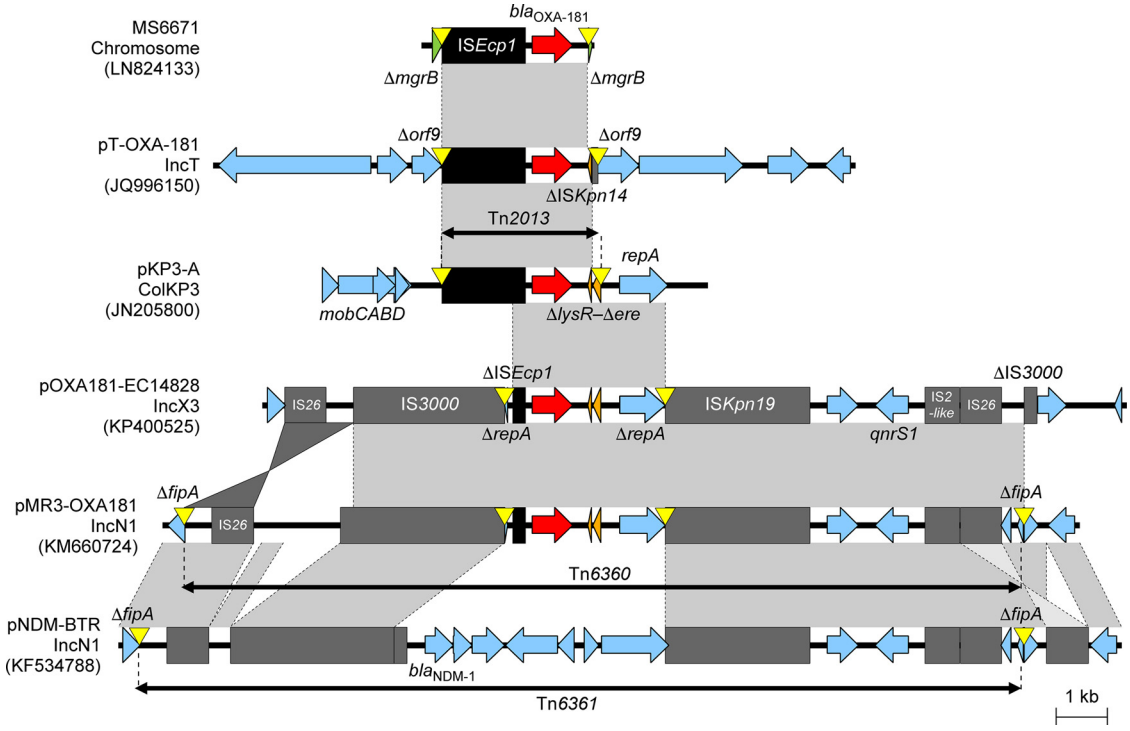

FIG 9 Genetic environments of $bla_{OXA-181}$ in the *K. pneumoniae* chromosome, IncT plasmid, Tn*2013* (pKP3-A plasmid), IncX3 plasmid, and IncN1 plasmid. Tn*6361* with bla_{NDM-1} in the IncN1 plasmid pNDM-BTR was also shown for comparison with Tn*6360* in the IncN1 plasmid pMR3-OXA181. Mobile elements are indicated with black (IS*Ecp1*) or gray (others). Genes from background plasmids are indicated with cyan, and those from the chromosome are indicated with green. Yellow triangles indicate target site duplications.

OXA181 and pOXA181_EC14828 is situated in the target duplication site that flanks the pKP3-A-like fragment. The pMR3-OXA181-like plasmids, obtained from the different U.S. *E. coli* ST131 isolates mentioned before, contained a second copy of IS*Kpn19* that was inserted upstream of Δ*rep*–ΔIS*Ecp1*–$bla_{OXA-181}$ and was flanked by a 9-bp target repeat region (156).

pMR3-OXA181 is also similar to an IncN1 plasmid with bla_{NDM-1}, named pNDM-BTR, obtained from a Chinese *E. coli* isolate (186). The main difference between these two plasmids occurs in the bla_{NDM-1} flanking region (i.e., Tn*6360* with $bla_{OXA-181}$ in pMR3-OXA181 and Tn*6361* with bla_{NDM-1} in pNDM-BTR) (Fig. 9). This is most likely due to IS*3000*-mediated transposition.

C. freundii isolate STE harbored an 84-kb IncT plasmid with a Tn*2013* variant, named pT-OXA-181 (Fig. 9). This plasmid is non-self-transmissible but is mobilizable with the help of two other plasmids (143). pT-OXA-181 is highly similar to a 217-kb IncT-type plasmid named Rts1 (187), and a large portion of the IncT plasmid backbone (including the transfer system) is deleted in pT-OXA-181. The Tn*2013*-like element of pT-OXA-181 lacked IS*26*, IS*3000*, the *ere* gene and IRR2 (24) and contained IS*Kpn14* (as opposed to IS*Kpn19*, found in pMR3-OXA181 and pOXA181_EC14828) (Fig. 9). The presence of a 5-bp target site duplication (ATTTA) flanking the Tn*2013*-like element suggested that this mobile genetic element was also acquired through transposition (143).

Chromosomal insertion of $bla_{OXA-181}$. The integration of $bla_{OXA-181}$ into the chromosome of *K. pneumoniae* ST147 was reported from several U.S. patients that had previously visited India (157), the United Arab Emirates (179, 188), and Pakistan (153). Three copies of a partial Tn*2013* element (IS*Ecp1*–$bla_{OXA-181}$) were described for the isolates obtained from the patient that visited the United Arab Emirates (179, 188). The insertion of one of these copies into *mgrB* conferred colistin resistance (179). Among *K. pneumoniae* ST14 isolates from Canada, the chromosomal integration of Tn*2013* with $bla_{OXA-181}$ (or $bla_{OXA-232}$) occurred in 39% of OXA-48-like isolates, while the remaining

isolates harbored pKP3-A-like plasmids (158). In this Canadian study, the most common site of integration was an intergenic region between *tRNA* and *lysR*. Tn*2013* was also integrated into a different chromosomal position on *K. pneumoniae* ST43 obtained from Japan (149).

Clonal dissemination of *Enterobacterales* with $bla_{OXA-181}$. The National Microbiology Reference in Canada reported on 35 OXA-181-producing *Enterobacterales* obtained from 2011 to 2014. The *K. pneumoniae* isolates belonged to ST14, ST147, and ST1847 and harbored $bla_{OXA-181}$ on ColE2-type plasmids, whereas the *E. coli* isolates belonged to ST410, ST940, and ST1284 and harbored $bla_{OXA-181}$ on IncX3 plasmids, showing clear association between the species and plasmids (158). *K. pneumoniae* ST14 was the most common clone in this Canadian study. *K. pneumoniae* ST11 with $bla_{OXA-181}$ situated in Tn*2013* on pKP3-A-like plasmids was described in the United Kingdom (134). *K. pneumoniae* ST147, an international AMR high-risk clone (11, 184) with chromosomal Tn*2013*, was responsible for interhospital outbreaks and was obtained from North America (157, 158) and the Middle East (153, 179). In the United States, *K. pneumoniae* ST34 and ST43 were the most common clones associated with $bla_{OXA-181}$ (155). A large-scale country-wide outbreak occurred in South Africa from 2014 to 2016 due to the high-risk clone *K. pneumoniae* ST307 with OXA-181, involving 350 patients across 42 hospitals from 23 cities (185). $bla_{OXA-181}$ was part of Tn*2013* that was housed on a 51-kb IncX3 plasmid identical to pOXA181_EC14828.

Among *E. coli* isolates, ST410 is the most common high-risk global clone associated with $bla_{OXA-181}$, usually situated within pOXA181_EC14828-like IncX3 types of plasmids. ST410 has been described in Canada (158), the Czech Republic (121), China (151), France (108), and Poland (95).

In summary, Tn*2013*, which contains IS*Ecp1* upstream of $bla_{OXA-181}$ and harbored on different plasmids belonging to the ColE2, IncX3, IncN1, and IncT replicon types, has been mainly responsible for the global dispersion of OXA-181. Clonal outbreaks (e.g., *K. pneumoniae* ST147 and ST307 and *E. coli* ST410) have also contributed to the international spread of bla_{OXA-48} into various hospitals, regions, and countries.

OXA-232

OXA-232 is currently the 3rd most common global OXA-48-like derivative and was described in 2013 from *E. coli* (1 isolate) and *K. pneumoniae* (2 isolates) from rectal swabs obtained from three French patients who had recently visited India (26). One of the patients was hospitalized during the visit to India. The *E. coli* isolate tested nonsusceptible to all β-lactams (excluding imipenem, ertapenem, and meropenem), fluoroquinolones, aminoglycosides, sulfonamides, and tetracycline, while the *K. pneumoniae* isolates had similar susceptibility patterns but were also resistant to the carbapenems. The $bla_{OXA-232}$ gene was situated downstream of IS*Ecp1* harbored within Tn*2013* located on a 6.1-kb ColE-type plasmid (a scenario previously described with $bla_{OXA-181}$) (26).

This was followed by a publication from a Singapore hospital that reported OXA-232 from eight *K. pneumoniae* isolates obtained from several types of clinical specimens (189). Interestingly, the $bla_{OXA-232}$ was also harbored on a 6.1-kb ColE-type plasmid.

Geographical Distribution of OXA-232

In 2014 to 2015, OXA-232-producing *K. pneumoniae* and *E. coli* were reported in the United States (190), Malaysia (191), South Korea (192), and Mexico (91). The majority of these reports were associated with the coproduction of NDM-1 and previous travel to the Indian subcontinent.

Since 2015, OXA-232 has been reported from Europe (e.g., Germany [193], the Czech Republic [121], Italy [194], Switzerland [195], Poland [95], and the United Kingdom [30]), Asia (e.g., Brunei [196], China [197], and Thailand [198]), and Africa (e.g., Tunisia [199]).

Published evidence suggests that *Enterobacterales* with $bla_{OXA-232}$ are endemic in India, and nosocomial outbreaks have been described in South Korea (192, 200), Mexico (91), the United States (201), Brunei (196), and China (197).

Bacteria Producing OXA-232

OXA-232 was first described for *K. pneumoniae* and *E. coli* from humans, and these organisms remain the most common bacteria associated with $bla_{OXA-232}$ (193, 194, 196, 197).

Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-232}$

The $bla_{OXA-232}$ gene was first identified in 2012 from *E. coli* ST2968 and two *K. pneumoniae* ST14 isolates from French patients who had returned from India (26). OXA-232 was associated with IS*Ecp1* within a truncated Tn*2013* that was situated within a ColKP3-type plasmid named pOXA-232.

Genetic environments surrounding $bla_{OXA-232}$. The genetic environment surrounding $bla_{OXA-232}$ is very similar to the environment surrounding $bla_{OXA-181}$ except that Tn*2013* contains a large deletion on the 5′ end of IS*Ecp1* (26). The deletion which disrupted the IS*Ecp1* transposase activity most likely stabilized $bla_{OXA-232}$ onto pOXA-232-like plasmids. Tn*2013* is the only reported genetic environment associated with $bla_{OXA-232}$ to date.

Plasmids harboring $bla_{OXA-232}$. The ColE2-type pOXA-232 plasmid is 6,141 bp in length, and its backbone is identical to pKP3-A with $bla_{OXA-181}$, except for the 5′-end deletion of IS*Ecp1* within Tn*2013* (26). $bla_{OXA-232}$ differs from $bla_{OXA-181}$ by one nucleotide substitution (A642T) that leads to one amino acid alteration (Arg214Ser). The pOXA-232 plasmid was nonconjugative but transformative. Almost all isolates with $bla_{OXA-232}$ harbored pOXA-232-like plasmids (i.e., with plasmids highly similar or identical to pOXA-232) and have been described globally, including in Brunei (196), Canada (158), China (197, 202), France (26), Germany (193), South Korea (192), Italy (203), Singapore (189), Switzerland (195), and the United States (201). A *K. pneumoniae* ST15 isolate from the Czech Republic harbored a pOXA-232-like plasmid named pOXA-232_30929, which contained a 5,981-bp segment insertion consisting of Tn*1000* situated between Tn*2013* and *repA* (121). The similarities of the genes, transposons, and plasmids between $bla_{OXA-181}$ and $bla_{OXA-232}$ suggest a common origin and transposition followed by subsequent evolution of OXA-232 from OXA-181 (Fig. 2).

A large (110-kb) nontypeable plasmid containing a truncated Tn*2013* that included $bla_{OXA-232}$ was reported from Poland (95). Detailed analysis and sequencing of this plasmid have not yet been performed.

Chromosomal insertion of $bla_{OXA-232}$. A single *K. pneumoniae* ST14 isolate from Canada that lacked a ColKP3 plasmid showed chromosomal integration of $bla_{OXA-232}$ (158).

Clonal dissemination of *Enterobacterales* with $bla_{OXA-232}$. Hospital outbreaks due to *K. pneumoniae* strains with $bla_{OXA-232}$ on pOXA-232-like plasmids have been reported worldwide and include the following: ST14 in Western Canada (158) and in a burn intensive care unit in South Korea (192), ST15 in an intensive care unit (202) and in a neonatal intensive care unit in China (197), ST16 from three institutions in Italy (203), ST17 in a U.S. hospital (201), and ST231 in two hospitals in Switzerland (195), two hospitals in Brunei (196), and two hospitals in Singapore (189). *K. pneumoniae* ST14 and ST16 were the most common U.S. STs associated with $bla_{OXA-232}$ obtained from the United States (155). The majority of *K. pneumoniae* isolates with $bla_{OXA-232}$ coproduced CTX-M-15 (26, 121, 155, 189, 192, 195–197, 201–203), and NDM-1 (26, 121, 155, 190, 193, 203) or contained the *rmtF* 16S rRNA methyltransferase (195, 201, 202) situated on different plasmids than those that contained the $bla_{OXA-232}$. *K. pneumoniae* ST15 responsible for a NICU outbreak in China also contained a hypervirulent plasmid (i.e., pLVPK-like IncHI1B/IncFIB plasmid) containing different virulence-associated genes, including *rmpA2* (202).

Sporadic global appearances of *E. coli* with $bla_{OXA-232}$ on pOXA-232-like plasmids have been reported, and the isolates belonged to the following clones: ST131, ST167, ST448, ST457, ST2003, and ST2968 (26, 112, 158, 190, 193).

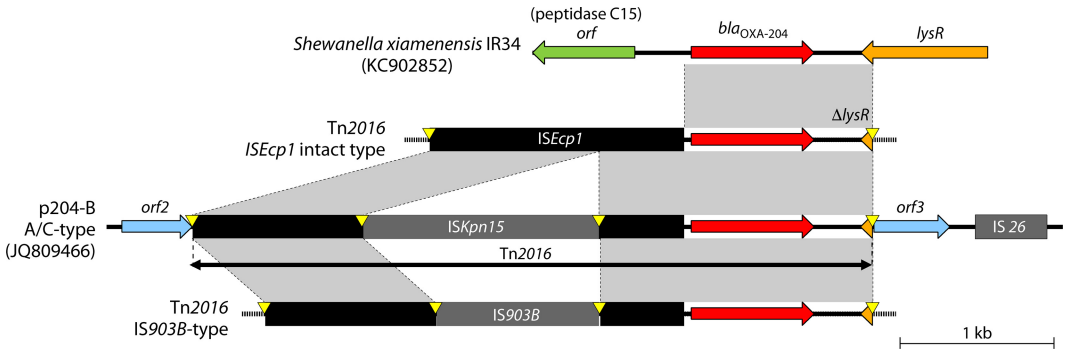

FIG 10 Genetic environments of $bla_{OXA-204}$ in the *S. xiamenensis* chromosome, Tn*2016* (p204-B plasmid), and Tn*2016* variants. Only partial sequences of Tn*2016* IS*Ecp1* intact type (pKP49) and Tn*2016* IS*903B* type (pEC25) were available (GenBank accession numbers KP027886 and KP027885, respectively), but the whole structures of the transposons are drawn. Mobile elements are indicated with black (IS*Ecp1*) or gray (others). Genes from background plasmids are indicated with cyan, and those from the chromosome are indicated with green. Yellow triangles indicate target site duplications.

OXA-204

OXA-204 is a rarely reported OXA-48-like carbapenemase and was first described in 2013 when a *K. pneumoniae* strain with reduced susceptibility to ertapenem was isolated from a urine of a Tunisian patient (25). The isolate, *K. pneumoniae* 204, also tested nonsusceptible to the penicillins, the β-lactamase inhibitor combinations, broad-spectrum cephalosporins, aminoglycosides, fluoroquinolones, sulfonamides, and tetracycline but remained susceptible to meropenem and imipenem. *K. pneumoniae* 204 coproduced SHV-1, CTX-M-14, OXA-1, and CMY-4. The $bla_{OXA-232}$ gene was situated downstream of IS*Ecp1* harbored within Tn*2016* located on a 150-kb IncA/C-type plasmid that also contained bla_{CMY-4} (25). Subsequently OXA-204 has also been found in *E. coli* obtained in Tunisia (204).

Geographical Distribution of OXA-204

Enterobacterales with OXA-204 outside Tunisia have been described only in France, where it is often associated with the coproduction of CMY-4, Tn*2016*, and previous travel to Tunisia (87, 108, 115).

Bacteria Producing OXA-204

OXA-204 was first described for *K. pneumoniae* and *E. coli* from humans, and these organisms remain the most common bacteria associated with $bla_{OXA-204}$ (25, 204). This carbapenemase has also been found in *P. mirabilis*, *C. freundii*, and *S. marcescens* (87).

Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-204}$

The $bla_{OXA-204}$ gene was first reported in 2012 from a *K. pneumoniae* ST383 isolate from a Tunisian patient (25). It was associated with Tn*2016* that was located on a 150-kb A/C-type plasmid named p204-B.

Genetic environments surrounding $bla_{OXA-204}$. The genetic environment of the 4,420-bp transposon Tn*2016* is similar to that of Tn*2013* associated with $bla_{OXA-181}$, but it differs in that IS*Kpn15* was inserted within IS*Ecp1* upstream of $bla_{OXA-204}$ and Tn*2013* and does not contain the Δ*ere* downstream of $bla_{OXA-204}$ (Fig. 10) (25). Interestingly, the segment separating $bla_{OXA-204}$ from the IS*Ecp1* element was 46 bp in length (as opposed to 128 bp for $bla_{OXA-181}$), suggesting that $bla_{OXA-204}$ and $bla_{OXA-181}$ had been mobilized independently through two distinct transposition processes from their natural progenitor (Fig. 2). In addition to the original IRL and IRR of IS*Ecp1*, Tn*2016* contains IRR2, which is responsible for one-sided transposition. Tn*2016* was inserted into the IncA/C-type p204-B plasmid within a target site duplication of 5 bp (AAATA) (Fig. 10). IS*Kpn15* did not disrupt promoter sequences of IS*Ecp1*, and it is likely involved in the expression of $bla_{OXA-204}$ (25). However, the IS*Ecp1* transposase was disrupted by IS*Kpn15*, and this may have stabilized $bla_{OXA-204}$ onto p204-B-like A/C plasmids (25).

IS*Kpn15* is flanked by the 8-bp target site duplication, which indicates a transposition event that occurred after mobilization of Tn*2013*-like IS*Ecp1*–$bla_{OXA-204}$–Δ*lysR* element onto the p204-B plasmid. This functional genetic structure has also been described for OXA-204-producing *E. coli*, *K. pneumoniae*, and *P. mirabilis* from France (87) and Tunisia (204). A Tn*2016* variant that contained IS*903B* instead of IS*Kpn15* was reported from an *E. coli* ST617 isolate in Tunisia (Fig. 10). IS*903B* also did not disrupt promoter sequences of IS*Ecp1*.

The origin of $bla_{OXA-204}$ is most likely the chromosome of *S. xiamenensis* (Fig. 2) (45). The $bla_{OXA-204}$ gene on the chromosome of *S. xiamenensis* strain IR34 was flanked by a gene encoding peptidase C15 and *lysR*, a transcriptional regulator (45) (Fig. 10).

Plasmids harboring $bla_{OXA-204}$. *K. pneumoniae* ST383 strain 204 contained a 150-kb A/C-type plasmid named p204-B, which contained Tn*2016* (40). A/C-type plasmids (formerly called IncA/C) can be divided into IncA (A/C_1), IncA (A/C_2), and IncC plasmids (205). IncC plasmids have two antimicrobial resistance islands (ARI-A and ARI-B) which harbor various antimicrobial resistance genes (205). IncC type 1 plasmids frequently have the IS*Ecp1*-bla_{CMY} element inserted downstream of *traA* (205). The exact plasmid type of p204-B is unknown because the complete sequence has not yet been reported. The p204-B plasmid also contains bla_{CMY-4} (40). A/C-type plasmids are broad-range plasmids (123), and this was confirmed with p204-B by electrotransformation using *A. baumannii* and transconjugation using *E. coli* and *P. aeruginosa* (40). *K. pneumoniae* 204 also contained an approximately 70-kb IncL/M-type conjugative plasmid, named p204-A, that harbors $bla_{CTX-M-14}$ (40).

Studies from France and Tunisia have shown the predominance of p204-B-like A/C-type plasmids with Tn*2016* or variants that contain bla_{CMY-4} (87, 206) among OXA-204-producing *Enterobacterales*, including *K. pneumoniae*, *E. coli*, *C. freundii*, *P. mirabilis*, and *S. marcescens* (87). The Tn*2016* variant containing the intact IS*Ecp1* is associated with the functional transposon, suggesting that $bla_{OXA-204}$ can disperse among various bacterial species.

A *K. pneumoniae* ST11 isolate and an *E. coli* ST617 isolate from Tunisia harbored 2 nontypeable plasmids containing $bla_{OXA-204}$; one plasmid was approximately 180 kb, while the other plasmid was approximately 150 kb (204).

Clonal dissemination of *Enterobacterales* with $bla_{OXA-204}$. An endoscopy-related outbreak involving 10 health institutions occurred in France between 2012 and 2014 (87) that was due to *E. coli* ST90 and *K. pneumoniae* ST147 harboring p205-B-like A/C plasmids with bla_{CMY-4} and $bla_{CTX-M-15}$ (87). *K. pneumoniae* ST147 and ST11 with $bla_{OXA-204}$ on A/C plasmids have also been detected in Tunisia (204, 206).

OXA-162

OXA-162 is a rarely reported OXA-48-like carbapenemase and was first described for a *K. pneumoniae* isolate from Turkey in 2008 (23). This was followed by a German report in 2012 when carbapenem-nonsusceptible *Enterobacterales* with OXA-162 (including *E. coli*, *Raoultella ornithinolytica*, and *C. freundii*) were recovered in 2008 to 2009 from different patients without recent travel history (207). The $bla_{OXA-162}$ gene was situated downstream of IS*1999* located on a 60-kb IncL/M-type plasmid (similar to bla_{OXA-48}). *R. ornithinolytica* and *C. freundii* coproduced SHV-5.

Geographical Distribution of OXA-162

Since 2012, OXA-162 has been reported in *K. pneumoniae* from Turkey (23), Hungary (208), and Greece (209). The Hungarian isolates coproduced CTX-M-15, and the Greek isolates coproduced DHA-1.

Bacteria Producing OXA-162

OXA-162 has been described in different *Enterobacterales*, including *K. pneumoniae*, *E. coli*, *R. ornithinolytica*, and *C. freundii* (207, 209).

Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-162}$

The $bla_{OXA-162}$ gene was first identified in a *K. pneumoniae* isolate in Turkey in 2008

(23). Compared with bla_{OXA-48}, $bla_{OXA-162}$ has only one nucleotide substitution (A637G), resulting in one amino acid alteration (Thr213Ala). The $bla_{OXA-162}$ was situated in Tn*1999.2* (Tn*1999* variant with disruption of IS*1999* by IS*1R*) (23, 207) and was harbored on a 60-kb pOXA-48a-like IncL conjugative plasmid (207–209). Tn*1999.2* with $bla_{OXA-162}$ was identical to Tn*1999.2* with bla_{OXA-48}, except one nucleotide difference in $bla_{OXA-162}$, suggesting that OXA-162 originated from OXA-48 through a point mutation (Fig. 2) (23, 207).

The following *Enterobacterales* with $bla_{OXA-162}$ have been reported: *K. pneumoniae* ST15 isolates from two patients in a pediatric intensive care unit in Hungary (208), *K. pneumoniae* ST11 from a patient in Greece (209), *K. pneumoniae* (ST unknown) from a patient in Turkey (23), *E. coli*, *R. ornithinolytica*, and *C. freundii* from a patient in Germany (207). Identical pOXA-48a-like plasmids with $bla_{OXA-162}$ were identified among three German *Enterobacterales* species obtained from the same patient, indicating that horizontal transfer had occurred *in vivo* (207).

OXA-244

OXA-244 is a rarely reported OXA-48-like carbapenemase and was first described in 2011 from a *K. pneumoniae* isolate from ascitic fluid from a patient in Malaga, Spain (27). The $bla_{OXA-244}$ gene was located on a 60-kb IncL type plasmid, and the *K. pneumoniae* isolate coproduced CTX-M-15.

Geographical Distribution of OXA-244

Subsequently, OXA-244 has been described in Germany (210), Russia (41), France (211), the Netherlands (212), and the United Kingdom (30). A French report described OXA-244-producing *E. coli* from a patient with epidemiological links to Egypt (42), while Dutch travelers returning from Indonesia were colonized with OXA-244-producing *E. coli* (212).

Bacteria Producing OXA-244

OXA-244 has been described for different *Enterobacterales* species, including *K. pneumoniae*, *E. coli*, and *K. aerogenes* isolates (27, 30, 41).

Molecular Epidemiology of *Enterobacterales* with $bla_{OXA-244}$

The $bla_{OXA-244}$ gene was first identified in a *K. pneumoniae* ST392 isolate from Spain (27). Compared with bla_{OXA-48}, $bla_{OXA-244}$ contains a single nucleotide substitution (A640G) that leads to one amino acid alteration (Arg214Gly) (27). The $bla_{OXA-244}$ gene is also situated within Tn*1999* on a ca. 60-kb IncL plasmid, suggesting that OXA-244 originated from OXA-48 through a point mutation (Fig. 2). A Russian study described *P. mirabilis* and *K. aerogenes* isolates with $bla_{OXA-244}$ on identical 60-kb IncL plasmids, suggesting that horizontal transfer of the conjugative plasmids had occurred (41).

Tn*51098* is a 21.9-kb IS*1R*-based composite transposon that includes an inverted ΔTn*1999.2* with $bla_{OXA-244}$ and a plasmid-derived fragment of pOXA-48a (stretching from Δ*tir-pemI* to *korC*-*orf25*), which is 99.9% identical to Tn*6237* with bla_{OXA-48} (Fig. 11). Tn*51098* was described in 4 different *E. coli* clones (namely, ST38, ST361, ST1722, and ST3541) obtained from French patients with epidemiological links to Egypt. Tn*51098* was integrated into the same chromosomal position among the different STs (42, 211). Genetic analysis revealed that the genes upstream of Tn*51098* was identical to those of Tn*6237* containing bla_{OXA-48} previously described in the United Kingdom among epidemic *E. coli* ST38 cluster 2 isolates (130) (Fig. 11). *E. coli* ST38 with $bla_{OXA-244}$ was also found in fecal samples of two Dutch travelers that had returned from Indonesia (212) as well as ST38 obtained in Canada (158). The association of Tn*51098* and Tn*6237* with *E. coli* ST38 suggests that the evolution of bla_{OXA-48} to $bla_{OXA-244}$ through a point mutation most likely occurred after the mobilization of Tn*6237* onto the *E. coli* ST38 chromosome.

A community fecal surveillance study for ESBL-producing *E. coli* in Germany detected an isolate with $bla_{OXA-244}$ (210). The UK national AMR surveillance program detected $bla_{OXA-244}$ among 10 out of 114 *E. coli* isolates with OXA-48-like enzymes (30).

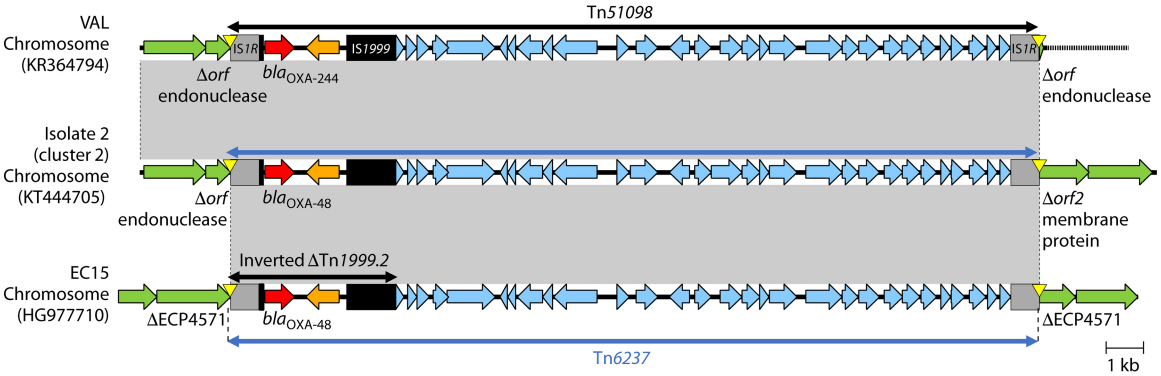

FIG 11 Genetic environments of $bla_{OXA-244}$ in Tn*51098* (*E. coli* chromosome) and bla_{OXA-48} in Tn*6237* (*E. coli* chromosome). Mobile elements are indicated with black (IS*1999*) or gray (others). The upstream regions of Tn*51098* and Tn*6237* in isolate 2 are identical, whereas the downstream regions are different. The Tn*6237* flanking regions in isolate 2 and EC15 are different. Genes from background plasmids are indicated with cyan, and those from the chromosome are indicated with green. Yellow triangles indicate target site duplications.

OTHER OXA-48-LIKE CARBAPENEMASES (e.g., OXA-245, OXA-436, OXA-484, AND OXA-519)

OXA-245 was first reported in 2011 from a *K. pneumoniae* isolate obtained from a surveillance culture in Malaga, Spain (27). OXA-245 differs from OXA-48 by a single amino acid substitution: Glu125Tyr. Similar to the OXA-244 gene, $bla_{OXA-245}$ was located upstream of IS*1999* situated on a 60-kb IncL/M-type plasmid (27). In Spain, OXA-245 has been associated with *K. pneumoniae* ST11 (213) and the coproduction of CTX-M-15 (84). OXA-245 has also been reported from the United Kingdom (30).

OXA-436 was first reported in 2017 from *Enterobacter asburiae*, *C. freundii*, and *K. pneumoniae* obtained from 4 Danish patients without recent travel history (214). The $bla_{OXA-436}$ gene was harbored on a 314-kb IncHI2 plasmid. *Shewanella bicestrii* sp. nov. has been identified as the most likely the progenitor of OXA-436 (29).

K. pneumoniae isolates with OXA-484 and OXA-519 were, respectively, obtained from the United Kingdom (30) and Belgium (31). OXA-519 differed from OXA-48 by a Val120Leu substitution and was located within Tn*1999* harbored on a 60.7-kb IncL plasmid.

LABORATORY DETECTION OF *ENTEROBACTERALES* WITH OXA-48-LIKE CARBAPENEMASES

The detection of carbapenemase-producing *Enterobacterales* (CPE) normally consists of a two-step approach, namely, a screening process using the appropriate screening agents followed by a phenotypic or genotypic confirmation test to detect the presence of a carbapenemase. *Enterobacterales* with OXA-48-like enzymes can test susceptible to the carbapenems and the extended-spectrum cephalosporins (e.g., 3rd- and 4th-generation cephalosporins). *Enterobacterales* with OXA-48-like enzymes often coproduce ESBLs of the CTX-M types that cause resistance to the extended-spectrum cephalosporins and increase the MICs to carbapenems (20). Clinical laboratories are more likely to identify and report *Enterobacterales* coproducing OXA-48-like and CTX-M enzymes, while the detection of those isolates with only bla_{OXA-48}-like genes remains challenging. It is important to remember that the majority of diagnostic tests are evaluated against bacteria producing OXA-48 and OXA-181 (to a lesser extent) and often do not include other OXA-48-like enzymes. This might be one of the reasons why OXA-48 enzymes are more commonly reported than other OXA-48-like enzymes in the published literature. The laboratory detection of bacteria with different OXA-48-like enzymes is problematic for some clinical laboratories, especially those in regions of nonendemicity.

Screening Agents

CPE in general test nonsusceptible to carbapenems, and this approach still remains

a simple initial screen for the presence of carbapenemases among *Enterobacterales*. However, the OXA-48-like producers often show only slight increases in the carbapenem MICs (215, 216), which makes the strategy of considering nonsusceptibility to carbapenems more problematic. The lowering of the carbapenem breakpoints did increase the sensitivity for the detection CPE but decreased the specificity because the production of ESBLs or AmpC enzymes combined with decreased permeability is also responsible for nonsusceptibility to the carbapenems. Thus, screening criteria using other antimicrobial agents (such as temocillin) have been studied (see below for details). Temocillin, as a treatment option, is not currently available in the United States.

The Clinical and Laboratory Standards Institute (CLSI) in 2010 revised the carbapenem breakpoints. For epidemiological or infection control purposes, isolates that test nonsusceptible to one or more carbapenems should be tested for the presence of carbapenemases (217). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) uses different carbapenem screening breakpoints for carbapenemases than for clinical purposes. The latest EUCAST guidelines (breakpoint tables version 9.0, 2019 [218], and guidelines on detection of resistance mechanisms version 2.0, 2017 [219]) state the following: *Enterobacterales* with meropenem MICs of $>$0.125 μg/ml or disk diameter $<$28 mm should be tested for carbapenemase production. Isolates with meropenem zones sizes between 25 and 27 mm should be tested for carbapenemase production if they are coresistant to piperacillin-tazobactam and/or temocillin (218). The disk diameter of $<$25 mm was stated in the previous version of the EUCAST guidelines (220), but this criterion was not able to detect 25% of OXA-48 producers in Europe (216). The combination of the disk zone diameter cutoffs for piperacillin-tazobactam ($\leq$16 mm) and temocillin ($\leq$12 mm) with meropenem zones of 25 to 27 mm showed excellent negative predictive value (99.2%) for the detection of OXA-48-like carbapenemases (216). A Canadian study investigated 189 CPE, including 30 OXA-48-like producers, to determine the best MIC screening criteria (221). That study, using meropenem (i.e., $>$1 μg/ml) as a screening agent, was able to capture 86% of carbapenemase-producing isolates, including only 40% of OXA-48-like producers, whereas application of EUCAST recommendations detected 98.4% of CPE isolates, including 93% of OXA-48 producers (221).

Meropenem, as a single screening agent, provides the best balance between sensitivity and specificity for the detection of OXA-48-like carbapenemases (215, 219, 222, 223). Ertapenem has a high sensitivity but lacks specificity (215, 217, 219, 222–224), while imipenem cannot reliably distinguish between wild-type isolates and carbapenemase producers in species such as *Proteus* spp., *Providencia* spp., and *M. morganii* (215). The EUCAST guidelines no longer support imipenem as a sole screening agent (219). Faropenem is an oral penem antibiotic, and a UK study evaluated its use as a potential screening agent for CPE (224). Growth up to the edge of a 10-μg faropenem disk showed 99% sensitivity and 94% specificity for the detection of CPE, including 90% of OXA-48-like producers ($n = 21$) that were flagged as possible CPE (224). French investigators published algorithms with faropenem and temocillin disks that showed mixed results for detecting OXA-48-like CPE (225, 226). Further evaluation of faropenem as a screening agent that includes a large number of OXA-48-like carbapenemases is needed.

The most challenging aspect for the successful screening of CPE with OXA-48-like enzymes is the difference in results obtained with automated susceptibility platforms. A multicenter Nordic study found significant variations in carbapenem MICs among CPE that included OXA-48 and OXA-181 producers (227), while a UK study showed that susceptibility profiles generated with BD Phoenix, MicroScan, and Vitek 2 were poor at detecting CPE with OXA-48-like enzymes (228). Currently, BD Phoenix CPO Detect panels are available for clinical use, including integrated phenotypic tests for the detection of carbapenemase (229).

Phenotypic Confirmation Methods

Phenotypic methods for the specific detection of carbapenemase activity will be

able (in theory at least) to identify all types of OXA-48-like derivatives. The characteristics of these tests are summarized in Table 3. For the detection of carbapenemase activity specifically for infection and prevention or surveillance purposes, the Carba NP and modified carbapenem inactivation method (mCIM) tests are endorsed by the CLSI for use in clinical laboratories (for details, please see "Carba NP test" and "Carbapenem inactivation method" below). Other methods, including improved Carba NP or CIM-based methods, spectrophotometry, electrochemical assays, and matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS)-based methods, are also available. For the rapid, easy, and specific detection of CPE with OXA-48-like enzymes, the lateral flow immunoassay methodologies are promising. The specific details of these methods are described below.

Inhibitor-based synergy tests. Inhibitor-based synergy tests are based on the ability of certain substrates to inhibit the action of carbapenemases (230). This process involves the testing of a carbapenem with and without the addition of an inhibitor with the ability to inhibit different types of carbapenemase. The inhibitor-based methods often use disk susceptibility testing principles (e.g., the double-disk synergy test [DDST] and combined disk test [CDT]). The interpretation is subjective with the DDST but is standardized with the CDT (e.g., zone diameter difference of *x* mm is indicative of a positive test) (12). The main disadvantage with these methods is the long turnaround time, between 18 and 24 h. The inhibitors most often used include boronic acid derivatives for inhibition of KPCs and metal chelators such as EDTA and dipicolinic acid for inhibition of metallo-β-lactamases (MBLs) (230). They are often used in combination with AmpC inhibitors, such as cloxacillin, to distinguish carbapenemases from isolates with porin mutations that produce high levels of AmpC enzymes.

Chemical compounds with specific inhibition properties for OXA-48-like enzymes are not yet available for clinical use. OXA-48-like enzymes confer high-level resistance to temocillin (216). Temocillin resistance is not specific for OXA-48-type carbapenemases, as other resistance mechanisms, including certain non-OXA-48-like carbapenemases, ESBLs, and AmpCs combined with porin loss, can also cause resistance to temocillin (231, 232). When combined with negative results obtained with inhibitor-based tests for carbapenemases, temocillin resistance has the ability to predict the presence of OXA-48-like enzymes (219, 232). The EUCAST guidelines advocate that in the absence of synergy for KPC, AmpC, and MBLs, high-level temocillin resistance ($>$128 μg/ml or disk zone diameter of $<$11 mm) is suggestive for the presence of OXA-48-like enzymes (219). However, EUCAST recommended that the presence of OXA-48-like enzymes be confirmed with other methods (219). More complicated algorithms for routine workflow that aimed for a higher sensitivity and specificity for detection different types of carbapenemases (including OXA-48-like enzymes) have been published (223, 233). Maurer et al. recently proposed an extensive algorithm that includes synergy tests using disks containing cloxacillin supplemented agar with boronic acid, EDTA, and temocillin, which resulted in 100% sensitivity and specificity for detecting CPE, including OXA-48 (other OXA-48 variants were not included for evaluation) (223). The authors do recommend that molecular testing be performed for confirmation of OXA-48-like enzymes.

Commercial disk kits that use inhibitors combined with temocillin are available from 3 companies: the MASTDISCS *Combi Carba plus* (Mast Group Ltd., Merseyside, UK), the KPC/MBL and OXA-48 Confirm kit (Rosco Diagnostica, Taastrup, Denmark), and the KPC&MBL&OXA-48 disk kit (Liofilchem, Roseto degli Abruzzi, Italy). All of them were based on the EUCAST recommendation (220) and contained 5 disks with carbapenem, carbapenem with MBL inhibitor, carbapenem with AmpC inhibitor, carbapenem with KPC inhibitor, and temocillin. The combinations of carbapenems and inhibitors differ among the different methodologies. MASTDISCS *Combi Carba plus* was reported to have 100% sensitivity and 91.1% specificity for CPE, including 5 OXA-48 and 1 OXA-181/NDM-1 producers (234). The other kits have not been extensively evaluated, but promising results have been published (235).

Avibactam is a recently developed non β-lactam β-lactamase inhibitor that inhibits

TABLE 3 Characteristics of phenotypic tests for carbapenemase detection[a]

Test method	Specific detection of OXA-48	Sensitivity/specificity (%)	Sensitivity for OXA-48 (%)	Com	Special equipment	Interpretation	Exper	TAT	Cost (U.S. dollars)	Ref
Inhibitor-based, MASTDISCS Combi Carba plus	Indirectly	100/91.1	100	Yes	No	Disk zone diam	Low	18–24 h		234
Carba NP test, RAPIDEC CARBA NP	No	97.8–99/98.5–100	93–96.3	Yes	No	Color change	Low	2.5 h	$10	244
Colorimetric, β-CARBA test	No	85.1/92.7	80.5[b]	Yes	No	Color change	Low	35 min[b]		258
mCIM, CLSI	No	97/99	100	No	No	Disk zone diam	Low	22 h	$1	244
rCIM	No	99/100	97.4	No	No	Disk zone diam	Low	2.5 h	$0.25	260
Lateral flow immunoassay, O.O.K. *K*-SeT	Yes[c]	OXA-48 and KPC only	100	Yes	No	Visible lines	Low	20 min	$11	
Lateral flow immunoassay, NG-Test CARBA5	Yes	97.3/99.8	100	Yes	No	Visible lines	Low	20 min		268
Electrochemical assay, BYG Carba v2.0	No	96.3/99.7	97.2	No	Homemade potentiostat	Conductance signal with cutoff value	High	30 min	$2.5	270
Spectrophotometry	No	100/98.5	100	No	UV spectrophotometer	Absorbance slope with cutoff value	High	12–24 h	$2–3	271
MALDI-TOF MS, MBT STAR-Carba IVD	No	100/98.2	100	Yes	MALDI-TOF MS (Bruker)	Automatic interpretation by software	Low	55 min	?	280

[a]Com, commercially available; Exper, expertise needed; TAT, turnaround time; Ref, reference.
[b]A higher sensitivity for OXA-48 producers was reported when an extended incubation time (60 min) was used.
[c]OXA-48 groups and OXA-163 groups can be separately detected.

class A, C, and selected D β-lactamases (including OXA-48-like enzymes) (236, 237). Huang et al. evaluated an avibactam-supplemented combination disk test approach with a zone diameter difference between temocillin and temocillin-avibactam disks of ≥5 mm for the detection of OXA-48 producers. When this approach was combined with inhibitors specifically for KPCs and MBLs, it yielded a 97% sensitivity and an 84% specificity for the detection of OXA-48 producers (238).

Greek investigators designed an OXA-48 disk verification method that incorporated imipenem disks saturated with EDTA and EDTA with phenylboronic acid (PBA) (239). The evaluation of the test is based on the contortion of zone sizes, and the test is very problematic to read.

Carba NP test. The Carba NP (Nordmann and Poirel) method was initially reported by French investigators in 2012 (240). Since 2015, the CLSI has advocated the use of a modified version of this methodology for the routine verification of carbapenemases among *Enterobacterales* (217). The procedure incorporated an incubation process of a microbe within a solution containing imipenem, zinc sulfate, and phenol red, and carbapenemase activity is shown by a color change from red to orange or yellow due to imipenem breakdown products. The original publication by Nordmann and Poirel documented 100% sensitivity and specificity for identifying different carbapenemases, including *Enterobacterales* with OXA-48-like enzymes. The authors advocated incubating the lysate for at least 2 h to ensure ample time for the detection of OXA-48-like β-lactamases (241). The Carba NP test has been ratified with bacteria obtained from blood agar, Mueller-Hinton agar, and Trypticase soy agar plates (241).

Enterobacterales with OXA-48-like β-lactamases can test false negative with the Carba-NP test, and a sensitivity of 21% has been documented by investigators from Canada (242). The sensitivity of the methodology can be enhanced by enlarging the inoculum of mucoid *K. pneumoniae* (242). Different shades of orange obtained with OXA-48-like microbes make the Carba NP test hard to interpret. In 2015, the CLSI published a modified version and recommended specific bacterial controls for routine clinical use (217). The CLSI approach showed high sensitivities and specificities, and the majority of results were available within 15 min, including for microbes with OXA-48-like enzymes (243). Commercial applications such as RAPIDEC CARBA NP (bioMérieux) and Neo-Rapid CARB (Rosco Diagnostica) have been available and evaluated by several different investigators (243–245). Overall, the commercial versions show results similar to those with the original and CLSI-modified versions. The detection of OXA-48-like bacteria using the Carba NP or Rapidec Carba NP can be significantly improved by using 10-μl bacterial loops as opposed to 1-μl loops.

Further modifications to improve interpretation of color change, accuracy, or procedures have been reported. The Blue-Carba test is a modification of the Carba NP test developed in Portugal by Peixe and colleagues (246). This method uses bromothymol blue as the indicator and imipenem and cilastatin as the antibiotic and substrate, and it can be performed directly on bacterial colonies (246). The performance of the Blue-Carba test is similar to that of the Carba NP test. Sensitivities for CPE with KPCs and MBLs were close to 100%, but this modification has the same issues as the Carba NP test regarding mucoid *K. pneumoniae* and false negatives for OXA-48-like CPE (the sensitivities range from 89 to 100%) (247–249). A commercial version has been recently launched as the Rapid Carb Blue kit (Rosco Diagnostica) (250). The Carba NP test direct (251) can be performed directly on bacterial cultures, as opposed to bacterial extracts, with an enhanced sensitivity for the detection of OXA-48-like enzymes from 83% to 94% (251). The modified paper strip Carba NP method uses filter paper strips with the Carba NP solutions and bacterial cultures (252). The results can be obtained within 5 min, and the strip method had higher overall sensitivity than the CLSI method (86% versus 75%) for the detection of CPEs (252).

Colorimetric test. The β-CARBA test (Bio-Rad, Marne la Coquette, France) is a commercially available, easy-to-use, and rapid chromogenic test (253). This test is based on the change of color of an undisclosed chromogenic substrate in the presence of carbapenem-hydrolyzing enzymes (254). A single colony is suspended in a reaction

mixture and incubated at room temperature for 30 min. A color change from yellow to orange-red or purple is indicative of the presence of carbapenem-hydrolyzing activity. A validation study found that overall sensitivity and specificity of the β-CARBA test for the detection of CPEs (e.g., 85.1% and 92.7%, respectively) were lower than with the Carba NP test (254). OXA-48-like enzymes were detected in only 80.5% of isolates (254). The test gave false-positive results for OXA-163 and OXA-405 producers (254). The extended incubation of 1 h allows the additional detection of some OXA-48 variants (253).

Carbapenem inactivation method. The carbapenem inactivation method (CIM) was described in 2015 and consists of the initial incubation for 2 h of the isolate in water that contains a meropenem disk (255). The meropenem disk is then plated on an agar plate inoculated with a susceptible *E. coli* indicator bacterium and incubated for at least 8 h. If a carbapenemase is present, the activity of the meropenem disk will be inactivated, allowing uninhibited growth of the susceptible *E. coli*. The advantages of CIM included cost-effectiveness, ease of performance, and the availability of reagents in most laboratories. Tijet et al. evaluated the CIM and reported a sensitivity of 98.8% and specificity of 100% for the detection of CPE that also included OXA-48-like-, NDM-, and KPC-producing isolates that previously tested negative with the Carba NP test (256). However, some groups reported lower detection rates for OXA-48-like enzymes (50 to 91%) (257).

The mCIM, which uses tryptic soy broth for incubation and a longer incubation time (4 h), was published by the CLSI (257). The overall sensitivity increased from 82% to 93%, and a validation study involving 9 laboratories confirmed high reproducibility, with a mean sensitivity and specificity of 97% and 99%, respectively (257). A recent evaluation by Tamma et al. of 11 phenotypic assays, including the mCIM, found 100% sensitivity of the mCIM for the detection of OXA-48-like-producing CPE, with 98% sensitivity and 99% specificity for all CPE (258). The interpretation of mCIM results is less subjective than that of the Carba NP test. The mCIM was added to the CLSI M100 document in the 2018 edition (217) as a suitable carbapenemase detection method. However, this test is time-consuming, since the best results are obtained when agar plates are incubated for 12 to 18 h (256). Rapid versions of the CIM have been published recently and include the CIMplus test, which allows for the detection of carbapenemases within 8 h, with an overall sensitivity of 95.7% and specificity of 94.4% for the detection of different carbapenemases, including 38 isolates producing OXA-48-like enzymes (259). Muntean et al. published the rapid carbapenem inactivation method (rCIM), which is rapid (i.e., results are available within 3 h), cost-effective, and accurate for the detection of CPE (i.e., overall sensitivity of 99% and specificity of 100%) (260). Among OXA-48 variants, the rCIM was able to detect isolates with OXA-162, OXA-181, OXA-204, OXA-232, and OXA-372; however, isolates with OXA-244 tested negative (260).

Indirect carbapenemase test. The MAST indirect carbapenemase test is a paper test device that has been recently developed based on the principles of the indirect carbapenemase test (ICT) (261). The ICT method utilizes a cell permeabilizing agent to release carbapenemase enzymes for hydrolyzing a carbapenem. This will allow a carbapenem-susceptible reporter organism to grow, producing a distorted zone of inhibition. The MAST ICT had 100% sensitivity for the detection of the most common carbapemases but was more subjective to interpret than the mCIM test, showing a specificity of 70.3% (262).

Lateral flow immunoassay. The immunochromatographic lateral flow assay is based on an antigen-antibody reaction performed on chromatographic paper and is easy to perform with rapid results, usually within 15 min after an extract solution is applied to a test cartridge. The OXA-48 *K*-SeT assay (Coris Bioconcept, Gembloux, Belgium) was designed to capture two epitopes specific to the OXA-48-like enzyme, including OXA-48, -181, -204, -232, and -244 (263). This assay has been upgraded to a multiplex form (RESIST-3 O.K.N. *K*-SeT assay; Coris BioConcept) that can simultaneously detect the presence of KPC and NDM enzymes. The assay showed 100% sensitivity and 100%

specificity for these carbapenemases (264). The RESIST-4 O.K.N.V. assay, which contains two cassettes (OXA-48-like/KPC and NDM/VIM), is also available (265). Recently, Coris BioConcept developed the RESIST-3 O.O.K. *K*-SeT assay, which detects OXA-48-like and KPC enzymes. This product was developed to distinguish between OXA-48-like enzymes with high (i.e., OXA-48, -162, -181, and -232) and weak (i.e., OXA-163, -108, -247, -405, and -438) carbapenemase activities. The manufacturer claimed 100% sensitivity and 100% specificity, but the performance has not been validated by other researchers.

The Carba5 assay is another immunochromatographic assay that can detect the most common carbapenemases (including OXA-48, -162, -181, -204, -232, -244, -517, -519, and -535) in one cassette with 100% sensitivity and 95.3% specificity (266). Three isolates with OXA-163 and OXA-405 gave false-positive results. These OXA-48-like enzymes have weak carbapenemase activity (267). A commercial version is available as the NG-Test CARBA5 assay (NG Biotech, Guipry, France) (268). All isolates with KPC, NDM, VIM, and OXA-48-like enzymes could be detected, but *Enterobacterales* with IMP-13 and IMP-14 were not detected in the validation study (268).

Electrochemical assay. The BYG Carba test recognizes carbapenem hydrolysis via an electrochemical reaction to show a pH change (269). Results are available within 30 min, and evaluation by different investigators showed sensitivities and specificities of up to 97% and 99%, respectively, for *Enterobacterales* with OXA-48-like β-lactamases (270).

Spectrophotometry. UV spectrophotometry with excellent sensitivities and specificities for showing carbapenem hydrolysis among OXA-48-like bacteria was described in 2012 (271). This methodology is not available for clinical diagnostics (44, 272).

Mass spectrometry. The Bruker MALDI-TOF MS system that incorporates specific software for the detection of carbapenemases within 2 to 3 h has been available in certain microbiology laboratories worldwide (273, 274). *Enterobacterales* with OXA-48-like enzymes can test negative using this approach (275). Imipenem is the best carbapenem for the detection of bacteria with OXA-48-like β-lactamases (276), and adding ammonium bicarbonate to the test lysate will increase the ability of MALDI-TOF to detect *Enterobacterales* with OXA-48-like enzymes (277).

Recently, Bruker Daltonik launched a software module, named MBT STAR-BL, for the automatic analysis of drug hydrolysis mass spectra that has been integrated into the MBT Compass software for species identification (278, 279). The software is accompanied by detailed protocols for the manual preparation of reagents. More recently, the MBT STAR-Carba IVD kit (Bruker Daltonik), the first CE-IVD (*in vitro* diagnostic)-certified mass spectrometric resistance detection assay, was launched and in combination with the MBT STAR-BL showed 100% sensitivity and 98.2% specificity for the detection of CPE, including those with OXA-48 variants of OXA-162, -181, -204, -232, and -244, within a turnaround time of 55 min (280).

Genotypic Methods

Molecular methods are highly sensitive and specific for the detection of OXA-48-like genes among *Enterobacterales* and are considered to be the best confirmatory methods. The basic strategy for the identification of OXA-48-like enzymes is first to amplify the $bla_{\text{OXA-48}}$-like genes, followed by sequencing of the gene for the identification of the specific subtypes (e.g., OXA-48, OXA-181, etc.) (12). For diagnostic purposes, screening for OXA-48-like genes is sufficient, while subtype identification is more relevant for genomic surveillance programs.

Molecular assays are mainly performed on cultured bacterial isolates, and some assays have also been validated for the identification of carbapenemase genes directly on clinical samples. Several in-house PCR, commercial real-time PCR, and DNA microarray methods are available for routine clinical use and usually aimed to identify different carbapenemases simultaneously. It is important to keep in mind that some $bla_{\text{OXA-48}}$-like genes have significant variation in nucleotide sequences (e.g., OXA-181 variants), leading to false-negative results (281), while certain OXA-48 subtypes without carbapenemase activity (i.e., OXA-163, OXA-247, and OXA-405) can produce false-positive

results (282). Disadvantages of molecular methods include the relatively high costs (compared to most phenotypic tests), the ability to only detect carbapenemase genes targeted in the assay (compared to hydrolysis assays), and relatively longer turnaround times (compared to rapid phenotypic tests such as the lateral flow technologies, which have turnaround times of minutes versus hours).

In-house assays. In-house multiplex PCR assays that can simultaneously detect the most common carbapenemase genes (e.g., bla_{OXA-48}, bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{IMP}) are useful and sometimes implemented in clinical laboratories (283). Table 4 shows an up-to-date list of published in-house PCR assays for different carbapenemases. We performed *in silico* PCR (284) to assess the detection performances of these assays for 32 bla_{OXA-48}-like genes as defined in the BLDB website (37), and the results are shown in Table 4. The most extensive multiplex assay available has the ability to identify 11 different carbapenemase genes in three separate reactions (285).

A conventional PCR method includes the following steps: DNA extraction, PCR amplification, and gel electrophoresis, and it usually take 3 to 6 h to get results. Real-time PCR is superior in terms of specificity and speed, is less labor-intensive, but is more expensive than conventional PCR. Monteiro et al. developed a one-reaction assay for bla_{OXA-48}, bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and bla_{GES} using melting-curve analysis (286). Probe-based assays for the simultaneous detection of bla_{OXA-48}, bla_{KPC}, and bla_{NDM} (287) as well as for bla_{OXA-48}, bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{IMP} (288) have also been reported. A probe-based assay specifically for bla_{OXA-48} was developed at the U.S. Centers for Disease Control and Prevention (155) and included 2 sets of bla_{OXA-48} primers/probes combined with a bacterial 16S rRNA gene as an internal control. Peirano et al. recently developed a simple and cost-effective PCR method for the rapid identification of *Enterobacterales* with OXA-181 (306).

Hemarajata et al. developed a real-time PCR assay with LunaProbe-enhanced high-resolution melt analysis using the LightCycler 480 instrument and software (Roche Molecular Systems, Pleasanton, CA) (289). The assay detected the presence of bla_{OXA-48}-like genes, and subsequent data analysis enabled distinction between $bla_{OXA-48/245}$, $bla_{OXA-162}$, $bla_{OXA-244}$, $bla_{OXA-181/204}$, and $bla_{OXA-232}$. The assay is unique for its capability to detect common subtypes without sequencing. However, this approach cannot identify the exact subtypes due to the limited length of probe-binding sequence. For example, the $bla_{OXA-48/245}$ subgroup also includes $bla_{OXA-199}$, $bla_{OXA-505}$, $bla_{OXA-519}$, $bla_{OXA-546}$, $bla_{OXA-547}$, and $bla_{OXA-566}$, and the $bla_{OXA-181}$ subgroup also includes $bla_{OXA-484}$.

Loop-mediated isothermal amplification (LAMP) is a rapid, cost-effective, easy-to-perform alternative nucleic acid amplification methodology that requires only a water bath or heating block to obtain a constant temperature. Results can be interpreted with the naked eye or UV light. Srisrattakarn et al. published a LAMP assay for the detection of bla_{OXA-48}, bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{IMP-14} with a reaction time of 60 min (290).

A novel low-cost molecular method based on the Luminex xTAG assay (Luminex Corp., Austin, TX) that can detect 46 β-lactamases, including bla_{OXA-48} subtypes, within 5 h has been reported (291). The assay utilizes modular multiplex oligonucleotide ligation-PCR and xTAG-compatible probe-based detection using the MAGPIX Dx system (Luminex) to interpret results.

Commercial assays. The commercial multiplex PCR assays for the detection of different carbapenemase genes (including OXA-like genes) that are available for clinical laboratories are listed in Table 5. Advantages of commercial assays include federal/national approval as clinical diagnostic tests, quality controlled materials, and ready-to-use formats. These assays are mainly validated for direct detection of carbapenemase genes on clinical samples. Disadvantages include high cost and uncertain detection performance for bla_{OXA-48} subtypes due to unavailability of targeted oligonucleotide sequences.

Methodologies such as Check-Direct CPE (Checkpoints, Wageningen, the Netherlands) (292), EntericBio CPE (Serosep Limited, Limerick Ireland) (293), Amplidiag CarbaR+VRE assay (Mobidiag Limited, Espoo, Finland) (294), and Amplidiag CarbaR+MCR (Mobidiag) (295) include PCR reagents and use real-time multiplex

TABLE 4 In-house molecular methods for the detection of bla_{OXA-48}-like and other genes

Test method	bla_{OXA-48}-like genes detected[a]	Other genes detected	Reference
Conventional multiplex PCR	All except for bla_{OXA-54}, $bla_{OXA-436}$, and $bla_{OXA-535}$	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{SPM}, bla_{BIC}, bla_{AIM}, bla_{GIM}, bla_{SIM}, and bla_{DIM}	285
	All except for bla_{OXA-54}, $bla_{OXA-436}$, and $bla_{OXA-535}$	bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{IMP}	283
Real-time multiplex PCR, melting-curve analysis	All except for bla_{OXA-54}, $bla_{OXA-436}$, and $bla_{OXA-535}$	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, and bla_{IMP}	286
	All except for bla_{OXA-54}, $bla_{OXA-436}$, and $bla_{OXA-535}$	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and bla_{OXA-23}	300
Real-time multiplex PCR, hydrolysis probe	All except for bla_{OXA-54}, $bla_{OXA-436}$, $bla_{OXA-535}$, and $bla_{OXA-538}$	bla_{KPC} and bla_{NDM}	287
	All except for bla_{OXA-54}, $bla_{OXA-416}$, $bla_{OXA-436}$, and $bla_{OXA-535}$	bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{IMP}	288
	All except for bla_{OXA-54}, $bla_{OXA-436}$, and $bla_{OXA-535}$	16S rRNA (internal control)	155
Real-time multiplex PCR, melting-curve analysis, and LunaProbe	All except for $bla_{OXA-416}$, $bla_{OXA-436}$, and $bla_{OXA-535}$[b]		289
LAMP,[c] visible color change	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-163}$, $bla_{OXA-181}$, $bla_{OXA-199}$, $bla_{OXA-204}$, $bla_{OXA-232}$, $bla_{OXA-244}$, $bla_{OXA-245}$, $bla_{OXA-247}$, $bla_{OXA-370}$, $bla_{OXA-405}$, and $bla_{OXA-438}$	bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{IMP-14}	290
Modular multiplex oligonucleotide ligation-PCR, xTAG probe	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-163}$, $bla_{OXA-181}$, $bla_{OXA-199}$, $bla_{OXA-204}$, $bla_{OXA-232}$, $bla_{OXA-244}$, $bla_{OXA-245}$, and $bla_{OXA-370}$	bla_{KPC}, bla_{GES}, bla_{IMI}, bla_{SEM}, bla_{NDM}, bla_{VIM}, bla_{IMP}, ESBLs, AmpCs	291

[a]*In silico* PCR analysis was performed for the detection of bla_{OXA-48}, $bla_{OXA-48b}$, bla_{OXA-54}, $bla_{OXA-162}$, $bla_{OXA-163}$, $bla_{OXA-181}$, $bla_{OXA-199}$, $bla_{OXA-204}$, $bla_{OXA-232}$, $bla_{OXA-244}$, $bla_{OXA-245}$, $bla_{OXA-247}$, $bla_{OXA-252}$, $bla_{OXA-370}$, $bla_{OXA-405}$, $bla_{OXA-416}$, $bla_{OXA-436}$, $bla_{OXA-438}$, $bla_{OXA-439}$, $bla_{OXA-484}$, $bla_{OXA-505}$, $bla_{OXA-514}$, $bla_{OXA-515}$, $bla_{OXA-517}$, $bla_{OXA-519}$, $bla_{OXA-535}$, $bla_{OXA-538}$, $bla_{OXA-546}$, $bla_{OXA-547}$, and $bla_{OXA-566}$.
[b]Melting-curve analysis followed by data analysis may detect specific bla_{OXA-48} variant groups.
[c]LAMP, loop-mediated isothermal amplification.

TABLE 5 Commercial molecular assays for the detection of bla_{OXA-48}-like and other genes

Test method (name)	bla_{OXA-48}-like genes detected	Other genes detected	Reference
Real-time multiplex PCR, molecular beacon probe (Check-Direct CPE; Checkpoints, Wageningen, the Netherlands)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-163}$, $bla_{OXA-181}$, $bla_{OXA-204}$, $bla_{OXA-232}$, $bla_{OXA-244}$, $bla_{OXA-245}$, and $bla_{OXA\ -370}$	bla_{KPC}, bla_{NDM}, and bla_{VIM} (bla_{KPC}/bla_{NDM} signal cannot be differentiated)	292
Real-time multiplex PCR (EntericBio CPE; Serosep Limited, Limerick, Ireland)	Yes	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, and bla_{IMP}	293
Real-time multiplex PCR, hydrolysis probe (Amplidiag CarbaR+VRE; Mobidiag Limited, Espoo, Finland)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-181}$, $bla_{OXA-204}$, $bla_{OXA-232}$, and $bla_{OXA-244}$	bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, IS*Aba1*-bla_{OXA-51}, $bla_{OXA-23,\ 24/40,\ -58}$, *vanA*, and *vanB*	294
Real-time multiplex PCR, hydrolysis probe (Amplidiag CarbaR+MCR; Mobidiag Limited, Espoo, Finland)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-181}$, $bla_{OXA-204}$, $bla_{OXA-232}$, and $bla_{OXA-244}$	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, bla_{IMP}, IS*Aba1*-bla_{OXA-51}, bla_{OXA-23}, $bla_{OXA24/40}$, bla_{OXA-58}, and *mcr*	295
Conventional PCR, DNA hybridization (AID carbapenemase line probe assay; Autoimmun Diagnostika GmbH, Strassberg, Germany)	Yes	bla_{KPC}, bla_{IMI}, bla_{NCM-A}, bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{SPM}, bla_{BIC}, bla_{AIM}, bla_{GIM}, bla_{SIM}, and bla_{DIM}	223
LAMP, Genie II platform (eazyplex SuperBug CRE; Amplex, Giessen, Germany)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-204}$, and $bla_{OXA-244}$; $bla_{OXA-181}$ and $bla_{OXA-232}$[a]	bla_{KPC}, bla_{NDM}, bla_{VIM}, $bla_{CTX-M-1}$ group, and $bla_{KCTX-M-9}$ group	297
Microarray (Check-MDR CT103 XL; Checkpoints, Wageningen, the Netherlands)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-163}$, $bla_{OXA-181}$, $bla_{OXA-204}$, $bla_{OXA-232}$, $bla_{OXA-244}$, $bla_{OXA-245}$, and $bla_{OXA-370}$	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{SPM}, bla_{GIM}, $bla_{OXA-23-like}$, bla_{OXA-24}-like, bla_{OXA-58}-like genes, ESBLs, and AmpCs	236

[a]These groups were separately detected in different tubes according to the manufacturer. The initial assay could not detect $bla_{OXA-181}$.

PCR instruments (e.g., LightCycler 480 instrument and Applied Biosystems 7500 real-time system [Thermo Fisher Scientific, Waltham, MA]). The AID carbapenemase line probe assay (Autoimmun Diagnostika GmbH, Strassberg, Germany) can detect 13 carbapenemase genes, including bla_{OXA-48}, in a single reaction (296). Line probe assays are tests that use conventional PCR followed by hybridization of labeled PCR products with specific oligonucleotide probes immobilized on a strip. A rapid molecular assay using LAMP has been available as Eazyplex superbug CRE (Amplex Diagnostics, Bahnhof, Germany (297). This assay provides results within 15 min and consists of 8-microtube test strips containing freeze-dried, ready-to-use reagents for the amplification of 7 resistance genes as well as an internal control. The company claims that bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-204}$, $bla_{OXA-244}$, $bla_{OXA-181}$, and $bla_{OXA-232}$ can be detected, but external validation studies have not yet been reported.

The advantage of microarray-based assays is the ability to simultaneously detect a large number of genes. The major limitations are the high cost, turnaround time, and labor associated with the procedure. The Check-MDR CT103 XL (Checkpoints, Wageningen, the Netherlands) kit can simultaneously detect 11 different carbapenemase genes, including bla_{OXA-48}, in approximately 8 h on 16 isolates (298).

Fully automated systems. The use of fully automated commercial PCR systems is easier to incorporate into clinical laboratories and will reduce workload and turnaround time. Unfortunately, they are often more expensive than in-house methods (Table 6). These include the GeneXpert system (Cepheid, CA), which is an easy-to-use cartridge-based system requiring only sample loading. The initial Xpert Carba-R (or MDRO) kit failed to detect $bla_{OXA-181}$ (281). Later the Xpert Carba-R kit, version 2, which can detect $bla_{OXA-181}$ and $bla_{OXA-232}$, was developed (282). The BD MAX system (Becton, Dickinson) has the commercial ready-to-use BD MAX CPE kit (299). The BD MAX system allows user-developed protocols, and several in-house (300) and commercial (301) assays have been reported.

The Verigene system (Luminex, IL) is an automated microarray-based gene detection system. The Verigene BC-GN test has the ability to identify Gram-negative bacteria and detects carbapenemase genes, including bla_{OXA} genes, from positive blood culture bottles within 2 h (302). However, the test cannot distinguish bla_{OXA-48} from other bla_{OXA} genes (e.g., bla_{OXA-23}, bla_{OXA-24}, and bla_{OXA-58}).

Some recent additions on which published data are presently lacking include the following: GenMark's (Steinhausen, Switzerland) ePlex blood culture identification (BCID) test also includes bla_{OXA} genes but cannot distinguish bla_{OXA-48} from bla_{OXA-23}. The BioFire FilmArray pneumonia panel (BioFire Diagnostics, Salt Lake City, UT) contains a bla_{OXA-48}-like target, and the Unyvero LRT panel (Curetis USA, Inc., San Diego, CA) contained several bla_{OXA} targets, including $bla_{OXA-48-like}$. The GenePOC Carba assay was recently released as a point-of-care test for detecting bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA-48}-like genes, and bla_{IMP}.

Whole-genome sequencing. Whole-genome sequencing (WGS) based on next-generation sequencing technology can reconstruct bacterial genomes, enabling the detection of all known carbapenemases and their variants. Recent advances in sequencing technologies and data analysis methods have made WGS more cost-effective and less time-consuming than standard sequencing techniques. WGS is becoming the mainstay for molecular epidemiological studies due to its accuracy and ability for comprehensive analysis, including clonal relatedness, plasmid, virulence genes, mobile genetic elements, and phage types (42, 155, 157).

Resistance gene databases, such as ResFinder (303), ARG-ANNOT (304), and CARD (305), are frequently used for the comprehensive detection of AMR genes. ResFinder has been commonly used by researchers and clinical laboratories due to the availability of an easy-to-use web-based interface (https://cge.cbs.dtu.dk/services/ResFinder/). However, for the definitive identification of the bla_{OXA-48} variants, the reference NCBI database (Bacterial Antimicrobial Resistance Reference Gene Database [https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047]) should be consulted.

TABLE 6 Fully automated systems for the detection of bla_{OXA-48}-like and other genes

Test method (name)	bla_{OXA-48}-like genes detected	Other genes detected	Clinical sample	Turnaround time	Reference
Real-time PCR (Xpert Carba-R version 2; Cepheid, CA)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-163}$, and $bla_{OXA-181}$, $bla_{OXA-204}$, $bla_{OXA-232}$, $bla_{OXA-244}$, and $bla_{OXA-405}$	bla_{KPC}, bla_{GES}, bla_{NDM}, bla_{VIM}, and bla_{IMP-1}	Rectal swabs	50 min	282
Real-time PCR (BD MAX CPE[a]; Becton, Dickinson, NJ)	bla_{OXA-48}, $bla_{OXA-162}$, $bla_{OXA-181}$, $bla_{OXA-199}$, and $bla_{OXA-204}$	bla_{KPC} and bla_{NDM}	Swabs	2.5 h	299
Microarray (Verigene BC-GN; Luminex, IL)	bla_{OXA-48}, bla_{OXA-23}, bla_{OXA-24}, and bla_{OXA-58} were reported as bla_{OXA}	bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and genes for identification of 9 Gram-negative bacteria	Blood culture	2 h	302

[a]Research use only.

CONCLUSIONS

Antimicrobial resistance has become one of the major global health and development challenges of the 21st century. One of the most pressing current AMR concerns is the international spread of carbapenem-resistant Gram-negative bacteria, especially those that produce carbapenemases. Carbapenemases belong to the Ambler class A (i.e., KPC types), class B (i.e., VIM, IMP, and NDM types), and class D OXA β-lactamases.

The OXA β-lactamases with activity against the carbapenems can be divided into those that are mainly present in *A. baumannii* (referred to as OXA-23-like, OXA-24-like, OXA-51-like, and OXA-58-like enzymes) and those that have found a niche among the *Enterobacterales* (referred to as OXA-48-like enzymes). The OXA-48-like enzymes efficiently hydrolyze the amino-, carboxy-, and ureidopenicillins and narrow-spectrum cephalosporins (e.g., cephalothin) and weakly hydrolyze the carbapenems but not the extended-spectrum cephalosporins (e.g., ceftriaxone, ceftazidime, and cefepime).

Global genomic surveillance and clinical studies, as well as several case reports, suggest that *Enterobacterales* with OXA-48-like carbapenemases are endemic in certain parts of the world and are being introduced on a regular basis into regions of nonendemicity, where they are responsible for nosocomial outbreaks.

OXA-48, OXA-181, OXA-232, OXA-204, OXA-162, and OXA-244, in that order, are the most common enzymes identified among the OXA-48-like carbapenemase group. The characteristics (i.e., geographical distribution, bacteria responsible for their production, and molecular epidemiology) of *Enterobacterales* with these β-lactamases are summarized in Table 7. OXA-48 is associated with Tn*1999* on IncL plasmids and is endemic in North Africa and the Middle East. OXA-181 and OXA-232 are associated with IS*Ecp1*, Tn*2013* on IncX3, and ColE2 plasmids and are endemic on the Indian subcontinent (e.g., India, Bangladesh, Pakistan, and Sri Lanka) and certain Sub-Saharan African countries. Overall clonal dissemination plays a minor role, but certain high risk clones (e.g., *K. pneumoniae* ST147, ST307, ST15, and ST14 and *E. coli* ST38 and ST410) have been associated with the global distribution of OXA-48, OXA-181, OXA-232, and OXA-204. Other OXA48-like carbapenemases, such as OXA-436, OXA-245, OXA-484, and OXA-519, are less often reported.

The laboratory detection of *Enterobacterales* with OXA-48-like carbapenemases is challenging for some clinical laboratories, especially for those that are situated in regions of nonendemicity. The detection of OXA-48-like carbapenemases is an essential initial step required for appropriate management of patients during infection prevention and control efforts. Identification is also appropriate for surveillance and epidemiological studies. The detection of OXA-48-like *Enterobacterales* with phenotypic methods has improved recently but remains challenging due to their weak carbapenemase activities. The susceptibility profiles created with automated susceptibility platforms, in general, performed poorly in screening for bacteria with OXA-48-like carbapenemases. Meropenem provides the best balance between sensitivity and specificity, but the ideal single screening agent for screening purposes is still wanting. PCR-based molecular confirmation methods have excellent sensitivities and specificities but are unfortunately rather expensive and time-consuming (compared to some phenotypic tests). Lateral flow immunoassays show promise for the rapid and accurate detection of *Enterobacterales* with OXA-48-like carbapenemases.

In summary, *Enterobacterales* with OXA-48-like carbapenemases are important causes of carbapenem resistance in certain parts of the globe; OXA-48 is associated with Tn*1999* on IncL plasmids and is endemic in North Africa and the Middle East. OXA-181 is associated with IS*Ecp1*, Tn*2013* on IncX3, and ColE2 plasmids and is endemic on the Indian subcontinent (e.g., India, Bangladesh, Pakistan, and Sri Lanka) and certain Sub-Saharan African countries. Bacteria with $bla_{\text{OXA-48}}$ and $bla_{\text{OXA-181}}$ are emerging in different parts of the world and are most likely underreported due to problems with the laboratory detection of these enzymes. The medical community at large, especially those interested in antimicrobial resistance, should be aware of the looming threat that is posed by bacteria with OXA-48-like carbapenemases.

TABLE 7 Summary of the characteristics of Enterobacterales with OXA-48-like carbapenemases

Enzyme	Country and yr of isolation	OXA-48 cluster	Geographical distribution	Bacteria	Genetic environment	Plasmids	Clonal dissemination
OXA-48	Turkey, 2004	48	Regions of endemicity: Middle East (Turkey, Lebanon, Jordan, Oman, Iran, and Saudi Arabia), North Africa (Morocco, Algeria, Tunisia, and Egypt). Hospital outbreaks: Greece, Australia, Israel, UK, Netherlands, Ireland, Spain, France, Germany, Mexico, China, Belgium, Norway, Poland, Taiwan, South Africa, Croatia, and Slovenia. Case reports: global.	*K. pneumoniae*, *E. coli*, *E. cloacae* complex, *C. freundii*, *S. marcescens*, *P. mirabilis*, *K. oxytoca*, *Kluyvera* spp., *Salmonella* spp., *P. aeruginosa*	Tn*1999* variants (1–5, with 2 the most common) Tn*2016*-like (rare)	IncL (common); others (A/C, IncF) very rare	*K. pneumoniae*: global, ST11, ST15, and ST147; UK, ST101; Poland, ST395; Spain, ST405. *E. coli*: global, ST38 with Tn*6237* chromosomal integration, ST410.
OXA-181	India, 2006	181	Region of endemicity: Indian subcontinent (India, Bangladesh, Pakistan, and Sri Lanka). Hospital outbreaks: Nigeria, Angola, South Africa, São Tomé and Príncipe, Romania, and United Arab Emirates. Case reports: global.	*K. pneumoniae*, *E. coli*, *E. cloacae* complex, *C. freundii*, *M. morganii*, *P. mirabilis*, *Aeromonas caviae*	IS*Ecp1* within Tn*2013*	ColE2, IncX3, IncN1, and IncT	*K. pneumoniae*: global, ST147; Canada, ST14; South Africa, ST307; USA, ST34 and ST43. *E. coli*: global, ST410.
OXA-232	France, 2013	181	Region of endemicity: India. Hospital outbreaks: South Korea, Mexico, USA, Brunei, and China. Case reports: global.	*K. pneumoniae*, *E. coli*	IS*Ecp1* within truncated Tn*2013*	ColE2-type	*K. pneumoniae*: Canada, ST14; South Korea, ST14 and ST15.
OXA-204	Tunisia, 2013	48	Tunisia and France	*K. pneumoniae*, *E. coli*, *P. mirabilis*, *C. freundii*, *S. marcescens*	IS*Ecp1* within Tn*2016*	A/C type	*K. pneumoniae* ST147 and *E. coli* ST90
OXA-162	Turkey, 2008	48	Turkey, Germany, Hungary, and Greece	*K. pneumoniae*, *E. coli*, *C. freundii*, *R. ornithinolytica*	Tn*1999.2*	IncL	
OXA-244	Spain, 2011	48	Spain, Germany, Russia, France, Netherlands, UK	*K. pneumoniae*, *E. coli*, *K. aerogenes*	Tn*1999.2* within Tn*51098*	IncL	
OXA-436	Denmark, 2017	436	Denmark	*E. asburiae*, *C. freundii*, *K. pneumoniae*		IncHI2	
OXA-245	Spain, 2011	48	Spain, UK	*K. pneumoniae*	Tn*1999*	IncL	
OXA-484	UK, 2017	181	UK				
OXA-519	Belgium, 2018	48	Belgium	*K. pneumoniae*	Tn*1999*	IncL	

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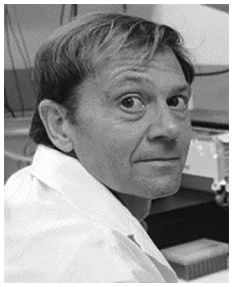

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