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REVIEW

Klebsiella oxytoca Complex: Update on Taxonomy, Antimicrobial Resistance, and Virulence

Jing Yang,[a,b] Haiyan Long,[a] Ya Hu,[a] Yu Feng,[a,c] Alan McNally,[e] Zhiyong Zong[a,c,d]

[a]Center of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, China
[b]Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China
[c]Center for Pathogen Research, West China Hospital, Sichuan University, Chengdu, China
[d]Department of Infection Control, West China Hospital, Sichuan University, Chengdu, China
[e]Institute of Microbiology and Infection, College of Medical and Dental Science, University of Birmingham, Birmingham, United Kingdom

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Address correspondence to Zhiyong Zong, zongzhiy@scu.edu.cn.

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SUMMARY *Klebsiella oxytoca* is actually a complex of nine species—*Klebsiella grimontii*, *Klebsiella huaxiensis*, *Klebsiella michiganensis*, *K. oxytoca*, *Klebsiella pasteurii*, *Klebsiella spallanzanii*, and three unnamed novel species. Phenotypic tests can assign isolates to the complex, but precise species identification requires genome-based analysis. The *K. oxytoca* complex is a human commensal but also an opportunistic pathogen causing various infections, such as antibiotic-associated hemorrhagic colitis (AAHC), urinary tract infection, and bacteremia, and has caused outbreaks. Production of the cytotoxins tilivalline and tilimycin lead to AAHC, while many virulence factors seen in *Klebsiella pneumoniae*, such as capsular polysaccharides and fimbriae, have been found in the complex; however, their association with pathogenicity remains unclear. Among the 5,724 *K. oxytoca* clinical isolates in the SENTRY surveillance system, the rates of nonsusceptibility to carbapenems, ceftriaxone, ciprofloxacin, colistin, and tigecycline were 1.8%, 12.5%, 7.1%, 0.8%, and 0.1%, respectively. Resistance to carbapenems is increasing alarmingly. In addition to the intrinsic bla_{OXY}, many genes encoding β-lactamases with varying spectra of hydrolysis, including extended-spectrum β-lactamases, such as a few CTX-M variants and several TEM and SHV variants, have been found. bla_{KPC-2} is the most common carbapenemase gene found in the complex and is mainly seen on IncN or IncF plasmids. Due to the ability to acquire antimicrobial resistance and the carriage of multiple virulence genes, the *K. oxytoca* complex has the potential to become a major threat to human health.

KEYWORDS β-lactamases, carbapenemases, resistance, *Klebsiella oxytoca*, virulence, taxonomy, *Klebsiella*, antimicrobial resistance

INTRODUCTION

Klebsiella oxytoca is a Gram-negative bacterium of the genus *Klebsiella* within the family *Enterobacteriaceae* and is widely distributed in nature (1–3). In humans, *K. oxytoca* is a member of the normal gut microflora and has been detected in the stool of 8% to 10% of healthy adults by culture-based methods (4). It is also found on the skin and in the oropharynx (5). In addition to being a member of the commensal microflora, *K. oxytoca* is an important human pathogen causing a large variety of infections ranging from mild diarrhea to life-threatening bacteremia and meningitis (5–7) and also causing outbreaks of health care-associated infections. Despite its importance, *K. oxytoca* is relatively under the radar and is largely masked by its notorious relative, *Klebsiella pneumoniae* (8). However, *K. oxytoca* is quite different from *K. pneumoniae* in many respects, such as antimicrobial resistance, virulence, and disease spectrum. Recently, new findings have significantly advanced our knowledge of this important pathogen. For example, genome-based taxonomic studies have shown that *K. oxytoca* is not a single species but in fact a complex comprising at least six species, i.e., *Klebsiella grimontii*, *Klebsiella huaxiensis*, *Klebsiella michiganensis*, *K. oxytoca*, *Klebsiella pasteurii*, and *Klebsiella spallanzanii*. In this review, we provide updates on the taxonomy, antimicrobial resistance, and virulence of the *K. oxytoca* complex and also summarize studies on its epidemiology and infections.

TAXONOMY

In 1886, an organism called "*Bacillus oxytocus perniciosus*" was recovered from old milk by Flugge and then renamed "*Aerobacter oxytocum*" by Bergey in 1923 and *Klebsiella oxytoca* by Lautrop in 1956 (9). *K. oxytoca* is indole positive and was considered a subgroup of *K. pneumoniae* for many years, but the clear distinction between the two species was finally revealed by DNA relatedness studies (9, 10). Through genome sequencing technologies and bioinformatics, *K. oxytoca* has been found to be a heterogeneous complex comprising multiple species (9). Sequence variations of the chromosomally encoded β-lactamase gene bla_{OXY} can assign the *K. oxytoca* complex into phylogroups (9). Currently, nine phylogroups, Ko1 to Ko9, are assigned to reflect the bla_{OXY} variant (bla_{OXY-1} to bla_{OXY-9}) that they carry (Table 1). However, Ko5 is now known to be a sub-phylogroup of Ko1 (11), and Ko9 is a sub-phylogroup of Ko3 (12), while the taxonomic status of Ko7 needs to be determined, as no genome sequence of the strain carrying bla_{OXY-7} is available for analysis (13). *K. oxytoca sensu stricto* belongs to Ko2,

TABLE 1 Species of the *K. oxytoca* complex

Species[a]	Phylogroup	OXY variant(s)	Type or reference strain	Genome accession no.	Reference
K. michiganensis	Ko1	OXY-1, OXY-5	W14^T	GCA_901556995	14
K. oxytoca	Ko2	OXY-2	ATCC 13182^T	GCA_900977765	9
K. spallanzanii	Ko3	OXY-3, OXY-9	SPARK_775_C1^T	ERS3550824	12
K. pasteurii	Ko4	OXY-4	SPARK_836_C1^T	ERS3550825	12
K. grimontii	Ko6	OXY-6	06D021^T	GCA_900200035	17
K. huaxiensis	Ko8	OXY-8	WCHKl090001^T	GCA_003261575	20
Taxon 1		OXY-10	67	QJJG00000000	
Taxon 2		OXY-11	P620	CP046115	
Taxon 3		OXY-12	RHBSTW-00484	CP055481	

[a]Taxa 1, 2, and 3 were identified here.

as it carries bla_{OXY-2}, and the type strain is ATCC 13182 (= NCTC13727 = CIP103434). The taxonomic determination of the Ko1, Ko3, Ko4, Ko6, and Ko8 phylogroups is summarized below according to the timeline of their species designations.

K. michiganensis represents the phylogroup Ko1, which also comprises Ko5 (11). In 2012, strain W14^T of the phylogroup Ko1 was recovered from a toothbrush holder and shared the consistent biochemical profile of the genus *Klebsiella* (14). Analysis based on housekeeping *rpoB*, *gyrB*, and *gyrA* gene sequences showed its close relatedness with *K. oxytoca*. However, the strain was negative in the pectate degradation test and negative by PCR for the polygalacturonase gene *pehX* (involved in pectin degradation), which has been used to differentiate *K. oxytoca* from other *Klebsiella* species (15, 16). The DNA-DNA hybridization (DDH) value between W14^T and the *K. oxytoca* type strain was 55.7% $\pm$ 6.2% (14), below the $\geq$70% cutoff for defining a bacterial species. Isolate W14^T was therefore thought deserving of the status of new species and was named *K. michiganensis* to reflect the state of Michigan in the United States, where the type strain was isolated (14). The type strain is W14 (also designated ATCC BAA-2403 and DSM 25444) (14).

K. grimontii represents the phylogroup Ko6. Six Ko6 strains were found, forming a well-defined sequence cluster based on *rpoB* and *gyrA* sequencing and separate from *K. michiganensis* and *K. oxytoca* (17, 18). The average nucleotide identity (ANI) value of Ko6 was 91.2% with *K. oxytoca* and 93.47% with *K. michiganensis*, both of which were well below the $\geq$95% to 96% ANI cutoff for bacterial species distinction (19). The name *Klebsiella grimontii*, referring to Patrick A. D. Grimont (a French microbiologist), was proposed for the phylogroup Ko6 (19). The type strain is 06D021 (also designated CIP111401 and DSM 105630) (19).

K. huaxiensis represents the phylogroup Ko8. Strain WCHKl090001^T was isolated from human urine in China in 2017 (20). WCHKl090001^T had up to 87.18% ANI and an *in silico* DNA-DNA hybridization (isDDH) value of up to 35.2% with type strains of other *Klebsiella* species (20). Strain WCHKl090001^T therefore belongs to a novel species of the genus *Klebsiella*, named *K. huaxiensis* (Ko8) to refer to West China (Huaxi in Chinese) Hospital, where the strain was isolated (20). The type strain is WCHKl090001 (also designated GDMCC 1.1379 and CNCTC 7650) (20).

K. spallanzanii represents the phylogroup Ko3. Strain SPARK_775_C1^T, a representative Ko3 strain, had the highest ANI value, 90.7%, with *K. huaxiensis* WCHKl090001^T compared with other members of the genus *Klebsiella*. The name *K. spallanzanii*, referring to Lazzaro Spallanzani (an Italian biologist), was proposed for the phylogroup Ko3 (12). The type strain is SPARK_775_C1 (also designated CIP 111695 and DSM 109531) (12).

K. pasteurii represents the phylogroup Ko4. Strain SPARK_836_C1^T, a representative Ko4 strain, had the highest ANI value, 95.5%, with *K. grimontii* 06D021^T, which falls into the 95% to 96% inconclusive zone of defining a bacterial species (21, 22). Nonetheless, the name *K. pasteurii*, commemorating Louis Pasteur, the well-known French microbiologist, was proposed for the Ko4 phylogroup. The type strain is SPARK_836_C1 (also designated CIP 111696 and DSM 109530) (12). We performed an analysis and found that the isDDH between *K. pasteurii* SPARK_836_C1^T and *K. grimontii* 06D021^T was 67.8%, below the 70% cutoff (23). The species status of *K. pasteurii* is therefore confirmed.

In addition to the bla_{OXY} variants bla_{OXY-1} to bla_{OXY-9} reported in the literature (12), bla_{OXY-10}, bla_{OXY-11}, and bla_{OXY-12} have been assigned in the β-lactamase database curated by

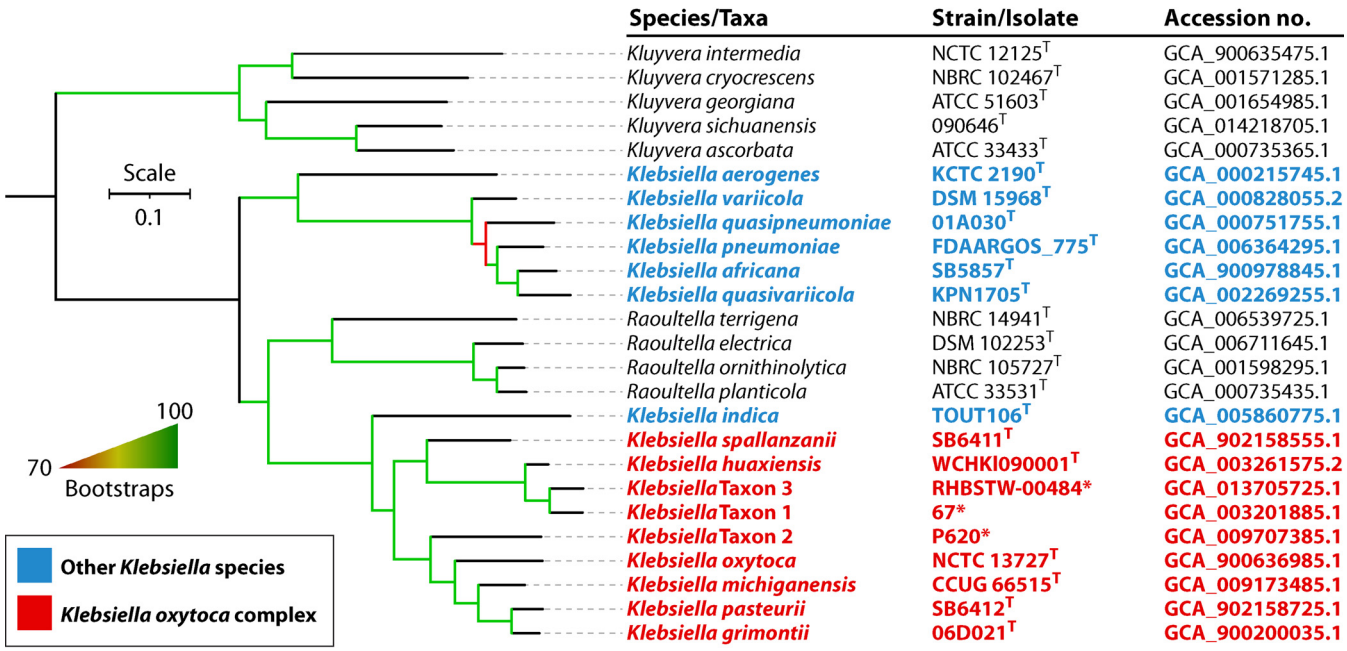

FIG 1 Phylogenomic tree based on the concatenated nucleotide sequence of core genes of *Klebsiella* species. Strains and their nucleotide accession numbers are listed alongside the species names. Species belonging to the *K. oxytoca* complex are in red, while other *Klebsiella* species are in blue. *Raoultella* species that were separated from *Klebsiella* 20 years ago (399) are included, while the genus *Kluyvera*, which is closely related to *Klebsiella* and *Raoultella* (400), is used as an outgroup. The tree was inferred by the core genome identification using PIRATE v1.0.4 (401) and subsequent phylogenetic inference using IQ-TREE v2.1.4 (402) using the GTR+G+ASC model with 10,000 rapid bootstraps. Branches with support over 70% are indicated by gradients. The bar shows nucleotide substitutions per site.

the Institute Pasteur (https://bigsdb.pasteur.fr/cgi-bin/bigsdb/bigsdb.pl?db=pubmlst_klebsiella_seqdef&page=alleleQuery&locus=blaOXY). These three bla_{OXY} genes reflect three new phylogroups and may represent three novel species of the *K. oxytoca* complex. The corresponding genome sequences of strains harboring $bla_{OXY\text{-}10}$, $bla_{OXY\text{-}11}$, and $bla_{OXY\text{-}12}$ were examined for precise species identification as described previously (23, 24). The strains harboring $bla_{OXY\text{-}10}$, $bla_{OXY\text{-}11}$, and $bla_{OXY\text{-}12}$ indeed represent three novel species, which are designated taxa 1 to 3 here (Table 1 and Fig. 1), as the assignation of proper species names needs detailed phenotype characterization (25). Taxa 1 and 3 are most closely related to *K. huaxiensis*, with a 95.62 or 95.18% ANI and a 62.4% or 60.6% isDDH value, while taxon 2 is most closely related to *K. grimontii*, with a 90.42% ANI and a 40.8% isDDH value. The three novel species are therefore members of the *K. oxytoca* complex, which extends the complex to nine species (Table 1 and Fig. 1). Of note, bla_{OXY} has not been found in species other than those of the *K. oxytoca* complex at present; in the chromosomal location corresponding to bla_{OXY} in *K. oxytoca*, there is a gene encoding a myoinosose 2 dehydratase in *K. pneumoniae*, and the genetic context of bla_{OXY} in the *K. oxytoca* complex has no similarities with that of bla_{SHV}, which is intrinsic to *K. pneumoniae*.

Recently, a novel species named *Klebsiella indica* was reported and is most closely related to species of the *K. oxytoca* complex (26). In the phylogenomic tree, *K. indica* is clustered with species of the *K. oxytoca* complex and is phylogenetically separated from other *Klebsiella* species and *Raoultella* species (Fig. 1). However, we found that *K. indica* contains no bla_{OXY} gene, and instead, there is a 1,224-bp gene encoding a putative transporter of the major facilitator superfamily (MFS) in the location of bla_{OXY}. In the phylogenomic tree, *K. indica* is also placed outside species within the *K. oxytoca* complex. The above findings suggest that *K. indica* should not be considered a member of the *K. oxytoca* complex at present.

SPECIES IDENTIFICATION

Phenotypic Tests

Strains of the *K. oxytoca* complex are non-spore forming and nonmotile and form smooth, circular, dome-shaped, glistening colonies on agar plates (12). The classical phenotypic tests

TABLE 2 Phenotypic characteristics of species of the *K. oxytoca* complex[a]

Phenotypic characteristic test	Result for phylogroup (species)					
	Ko1 (*K. michiganensis*)	Ko2 (*K. oxytoca*)	Ko3 (*K. spallanzanii*)	Ko4 (*K. pasteurii*)	Ko6 (*K. grimontii*)	Ko8 (*K. huaxiensis*)
	n = 1	NA	*n* = 3	*n* = 13	*n* = 6	*n* = 1
Motility	−	−	−	−	−	−
Indole	+	+	+	+	+	+
Lysine decarboxylase	+	+	+	+	+	+
Lactose	+	+	+	+	+	+
Mannitol	+	+	+	+	+	+
ONPG	+	+	+	+	+	+
Reduction of nitrate to nitrite	+	+	+	+	+	+
Voges-Proskauer	+	+	−	+	+	−
Malonate	+	+	+	+	+	−
Urease	−	+	+	−	−	−
Ornithine decarboxylase	−	−	−	−	−	−
	n = 7	*n* = 5	*n* = 4	*n* = 5	*n* = 6	*n* = 3
L-Proline	+	+	−	+	+	−
D,L-α-Glycerol-phosphate	+	+	v	+	v	−
α-Ketoglutaric acid	−	−	−	−	+	−
Glyoxylic acid	−	−	−	v	−	−
Melezitose	+	+	+	+	−	v
Tricarballylic acid	+	+	−	+	+	−
Acetyl-β-D-mannosamine	v	+	v	+	+	+
3-*O*-Methyl-glucose	−	−	−	−	−	+
γ-Amino-butyric acid	+	+	−	v	v	−
L-Tartaric acid	v	v	v	+	+	−
Reference(s)	12, 14	9, 12	12	12	12, 17	12, 20

[a]ONPG, *O*-nitrophenyl-β-D-galactopyranoside; +, positive; −, negative; v, between 20 and 80% positive strains; NA, not available.

for identification of *K. oxytoca* include indole, lactose, mannitol, malonate, lysine decarboxylase, ornithine decarboxylase, Voges-Proskauer, and *O*-nitrophenyl-β-D-galactopyranoside (ONPG) tests and the test for reduction of nitrate to nitrite (12). Strains of all six named species of the *K. oxytoca* complex are positive for indole, lactose, lysine decarboxylase, mannitol, ONPG, and reduction of nitrate to nitrite but are negative for ornithine decarboxylase (9, 12). The positive indole test could differentiate species of the *K. oxytoca* complex from *K. pneumoniae*, while the positive ONPG test or the negative ornithine decarboxylase test could differentiate the complex from *Raoultella ornithinolytica* (9, 27–29). A combination of Simmons' citrate agar supplemented with bile salts, inositol, and tryptophan (SCITB agar) and a spot indole test for screening the *K. oxytoca* complex has shown a superior sensitivity (93.8% versus 63.3%) and specificity (99.9% versus 60.4%) and contributed to a reduction in workload and cost compared to the use of MacConkey agar for isolation (30). Conventional phenotypic identification kits such as API 20E and API 50CH and automated phenotypic identification systems such as Vitek II and VITK-JR30 systems are widely used in clinical and scientific laboratories, but they exhibit limited performance for differentiating members of the *K. oxytoca* complex at the species level (17, 31–35).

Based on currently available literature (9, 12), each of the six species of the *K. oxytoca* complex has unique phenotypic features (Table 2), which could help to design phenotypic tests to differentiate these closely related species. For instance, the combination of the Voges-Proskauer, urease, and α-ketoglutaric acid tests could correctly differentiate the six species based on results reported in the literature (Table 2). However, these phenotypic characterizations have been performed for only a very limited number of strains or even on just a single strain (9, 12), and therefore, these discriminatory features are prone to be changed as additional strains of each species are tested. More studies are warranted to investigate the phenotypic differences among species within the *K. oxytoca* complex. At present, it appears that phenotypic tests are more appropriate for screening purposes and preliminary identification to the *K. oxytoca* complex level rather than the individual species level.

TABLE 3 16S rRNA gene sequence identity, ANI, and isDDH values between type strains of each species belonging to the *K. oxytoca* complex

Organism	Identity, ANI, and isDDH (%) for:							
	K. grimontii 06D021^T	*K. huaxiensis* WCHKl090001^T	*K. michiganensis* CCUG 66515^T	*K. oxytoca* NCTC3727^T	*K. pasteurii* SB6412^T	*K. spallanzanii* SB6411^T	Taxon 1	Taxon 2
K. grimontii 06D021^T								
K. huaxiensis WCHKl090001^T	99.8, 88.0, 35.2							
K. michiganensis CCUG 66515^T	99.7, 93.6, 53.8	99.5, 88.0, 35.5						
K. oxytoca NCTC3727^T	97.9, 91.5, 44.7	98.1, 87.6, 34.0	97.9, 92.3, 48.2					
K. pasteurii SB6412^T	99.3, 96.0, 67.8	99.5, 87.7, 34.4	99.4, 93.7, 54.3	98.1, 91.2, 43.9				
K. spallanzanii SB6411^T	98.4, 89.0, 37.7	98.6, 91.2, 44.2	98.5, 89.1, 37.9	98.5, 88.6, 36.3	98.6, 88.7, 36.9			
Taxon 1	98.5, 87.7, 34.2	98.8, 95.1, 62.4	98.6, 87.6, 34.3	99.4, 87.1, 32.8	98.6, 87.4, 33.6	98.9, 89.7, 39.4		
Taxon 2	98.4, 90.2, 40.8	98.2, 87.5, 34.0	98.5, 90.1, 40.9	97.6, 89.6, 39.4	98.7, 89.9, 39.8	97.9, 88.6, 36.4	98.1, 87.0, 32.7	
Taxon 3	98.5, 88.0, 35.1	98.3, 94.8, 60.6	98.5, 88.0, 35.2	98.5, 87.2, 33.5	98.4, 87.5, 34.1	97.9, 89.9, 40.1	98.7, 95.4, 64.0	97.9, 87.1, 33.3

MALDI-TOF MS

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has been increasingly used in clinical microbiology laboratories for identifying microorganisms to the species level (36). It has been attempted for identification of the *K. oxytoca* complex, but misidentification occurs (12). For instance, some *Raoultella* strains have been incorrectly assigned to *K. oxytoca* by MALDI-TOF MS, although this accuracy of identification could be improved by applying a more stringent 10% differential score (37). It is more difficult to differentiate each species within the *K. oxytoca* complex, as most of them were identified very recently, and therefore, most laboratories may not have reference spectra of these new species in their databases (14, 38–40). MALDI-TOF MS patterns of all six species within the *K. oxytoca* complex were analyzed in a study (12) which also updated the data set to improve species identification by MALDI-TOF MS. With the updated data set, the specificity and sensitivity of correct identification for the six named species within the *K. oxytoca* complex by MALDI-TOF MS range from 60 to 100% and from 80 to 100%, respectively (12).

16S rRNA Gene Sequence Analysis

16S rRNA gene sequence analysis has been widely used for bacterial species identification. Typically, the nearly complete 16S rRNA gene sequences of bacterial strains are amplified using PCR with the universal primers 27F and 1492R (41), and the generated amplicons are then subjected to Sanger sequencing (42). Comparison of the 16S rRNA gene sequences can be performed using curated data sets such as EzBioCloud (43). In 1994, a $<$97% similarity was proposed as the cutoff to delineate species (44), and in 2008, it was proposed to update the cutoff to 99% (45). However, as shown in Table 3, type strains of species within the *K. oxytoca* complex have up to 99.9% similarity of the 16S rRNA gene sequences. This suggests that the current scheme of 16S rRNA gene sequence analysis does not have adequate resolution for correct species identifications in the *K. oxytoca* complex as previously demonstrated (12, 14, 17, 20).

Single Gene Markers

All species of the *K. oxytoca* complex carry bla_{OXY}, a β-lactamase-encoding gene intrinsic to the complex, which has not been reported in other species in the literature. In the β-lactamase database curated by the Institute Pasteur (https://bigsdb.pasteur.fr/cgi-bin/bigsdb/bigsdb.pl?db=pubmlst_klebsiella_seqdef&page=alleleQuery&locus=blaOXY; accessed 1 August 2021), there are bla_{OXY} genes encoding 86 distinct OXY enzymes, including 38 that have not been reported in the literature. The pairwise amino acid identity between 12 OXY

TABLE 4 Pairwise amino acid sequence identity between OXY groups

Group	% identity with:										
	OXY-1-1	OXY-2-1	OXY-3-1	OXY-4-1	OXY-5-1	OXY-6-1	OXY-7-1	OXY-8-1	OXY-9-1	OXY-10-1	OXY-11-1
OXY-2-1	88.66										
OXY-3-1	89.35	87.59									
OXY-4-1	96.56	88.28	89.66								
OXY-5-1	97.94	90.00	89.66	97.24							
OXY-6-1	98.97	88.66	89.69	97.60	96.91						
OXY-7-1	97.25	88.28	90.69	97.24	96.21	98.28					
OXY-8-1	88.32	86.90	93.10	87.93	88.62	88.32	88.97				
OXY-9-1	86.94	84.83	94.10	87.24	87.24	87.29	87.93	92.41			
OXY-10-1	89.00	85.86	93.10	87.59	88.62	88.66	88.62	94.48	93.45		
OXY-11-1	86.25	86.60	86.25	86.25	86.25	86.25	86.94	85.57	82.82	84.88	
OXY-12-1	90.03	87.93	94.14	89.31	90.35	89.69	90.35	97.59	93.10	96.55	85.57

groups ranges from 82.82% (between OXY-9-1 and OXY-11-1) to 98.97% (between OXY-1-1 and OXY-6-1) (Table 4). Each of the bla_{OXY} variants matches a species within the complex (Table 1), and therefore, amplification and sequencing of bla_{OXY} genes may be used for species identification within the *K. oxytoca* complex.

The polygalacturonase-encoding gene *pehX* was found to be unique to *K. oxytoca* (15, 16). PCR for *pehX* alone (15, 16, 46–49) or in combination with other housekeeping genes, such as *infB* (50), has been widely used to differentiate *K. oxytoca* from *K. pneumoniae* and *Raoultella* spp. However, it has been reported that *K. michiganensis* is negative by PCR for *pehX* (14). In addition, we found by BLAST analysis that *pehX* was truncated between nucleotides 1,977 and 1,983 in a number of *K. oxytoca* complex genomes, such as *K. michiganensis* strains A10 (342 bp left; accession no. PIDR01001036.1) and A11 (531 bp; accession no. PIDS01000708.1), *K. oxytoca* strain 112_KOXY 226_19650_207590 (288 bp; accession no. WCM01000066.1), and *K. pasteurii* strain FDAARGOS_511 (247 bp; accession no. CP033824.1). These strains may be missed by the currently reported PCR for *pehX*.

The efflux pump-encoding genes *oqxA* and *oqxB* and the fosfomycin resistance gene *fosA* are intrinsic to *K. pneumoniae* (51). *oqxA* and *oqxB* are also intrinsic to some species of the *K. oxytoca* complex (52) but are absent from strains of *K. huaxiensis*, *K. spallanzanii*, taxon 1, and taxon 3 as identified by BLAST. *fosA* is seen in almost all isolates of the *K. oxytoca* complex as identified by BLAST. We found that the nucleotide identities of *fosA* between species of the *K. oxytoca* complex and *K. pneumoniae* are 76.13 to 85.19%. However, the maximum nucleotide sequence identity of *fosA* between different *Klebsiella* species and the minimum nucleotide identity within the same species overlap. For instance, the minimum nucleotide identity within *K. huaxiensis* is 94.93%, while the maximum nucleotide identity between *K. huaxiensis* and *K. spallanzanii* is 99.77%. The presence of *oqxA* and *oqxB* in only some species of the complex and the absence of clear, unified cutoffs of the nucleotide sequence identity for *fosA* suggest that these three genes are not suitable for species identification for the *K. oxytoca* complex.

Whole-Genome Sequencing and Analysis

Whole-genome sequencing provides a maximal level of resolution for precise bacterial species identification (53). Along with the rapidly increased use of whole-genome sequencing and a deluge of bacterial genomes, genome-based species identification has gained in popularity, at least in the research domain, and is usually used as the gold standard for precise species designations and evaluation of other methods, such as phenotypic tests and MALDI-TOF MS (53–55). ANI and isDDH are the two most commonly used algorithms for genome-based species identification (22, 23, 56). The *K. oxytoca* complex has been found to comprise multiple species, and each species has been assigned based on ANI and isDDH (12, 14, 19, 20) with the values shown in Table 3. As currently available phenotypic tests and MALDI-TOF MS are unable to correctly identify species in all cases, genome-based species identification using ANI and isDDH is usually required to determine the precise species for strains of the *K. oxytoca* complex.

EPIDEMIOLOGY, INFECTION, AND ANTIMICROBIAL TREATMENT

As *K. oxytoca* has only recently been identified as an actual complex comprising multiple species, strains called *K. oxytoca* in most studies have not been subjected to precise species identification, and the prevalence of each species of the complex in human colonization and infection remains largely unknown. Due to this absence of precise species identification, organisms referred to as *K. oxytoca* in the literature could actually be any species within the *K. oxytoca* complex. Therefore, "*K. oxytoca*" in this section represents the *K. oxytoca* complex as a whole unless otherwise specified. *K. oxytoca* colonizes the skin, oral cavity, and intestinal and respiratory tracts of both healthy and sick people (5, 57, 58). *K. oxytoca* is also an opportunistic pathogen able to cause a variety of infections, in particular antibiotic-associated hemorrhagic colitis (AAHC) after administration of antimicrobial agents and other health care-associated infections in patients with underlying diseases or immunocompromised conditions (49, 59–61). Of note, studies of antimicrobial susceptibility surveillance or virulence assays that contain information about sample types of the isolates but no clinical information are not included in the analysis here. In general, compared to *K. pneumoniae*, infection due to *K. oxytoca* is much less common, which may be partially due to its relatively low colonization rate, but is associated with relatively better prognoses, with a mortality rate of 7.14 to 23.58% (62–64) versus the 13.52 to 54.30% seen with *K. pneumoniae* (65). In addition, AAHC is commonly caused by *K. oxytoca* but not by *K. pneumoniae*.

Colonization

K. oxytoca is detected from the feces of 1.6 to 9% of healthy subjects, suggesting a relatively low colonization rate (6, 66), which is lower than the 3.9% to 87.7% colonization rate of *K. pneumoniae* (67–69). Nonetheless, the colonization rate is much higher in patients, as *K. oxytoca* was detected in 4.7% of those with inflammatory bowel diseases (IBD) (70), 14% of those with influenza A (71), and 25.5% of infants and neonates in neonatal intensive care units (NICUs) and intermediate care units (72). In addition, the intestinal colonization of *K. oxytoca* producing extended-spectrum β-lactamases (ESBL) has been found in 2.24% of NICU patients and 3.3% of pregnant women (73, 74), while another study reported that 1.4% of adult ICU patients are colonized with carbapenem-resistant *K. oxytoca* (75).

Geological Distribution of Infections

According to published clinical reports (Table 5), infections caused by the *K. oxytoca* complex have been reported mainly in the Asia-Western Pacific region, North America, and Western Europe, with few reports in Africa and South America. All types of infections caused by the *K. oxytoca* complex have been seen in the Asia-Western Pacific region, Europe, or North America, while AAHC appears to be more common in the Asia-Western Pacific region, in particular Iran and Japan (49, 76–79). In contrast, there are no reports of AAHC due to the complex in Africa and South America. However, as reports of infections due to the *K. oxytoca* complex are still limited in the literature, the exact geographical distribution of *K. oxytoca* infections, specifically regarding infection types, incidences, and prognoses, is yet to be elucidated.

AAHC

K. oxytoca can cause various gastrointestinal infections in both children and adults, among which AAHC is particularly common (49). In fact, *K. oxytoca* is recognized and known to clinicians largely due to AAHC, which was first described in 1978 (80). *K. oxytoca* and *Salmonella* are the two pathogens causing AAHC (66), while *K. pneumoniae* has not been reported to cause this disease. In a recent study involving three major hospitals in Iran between 2011 and 2016, *K. oxytoca* was recovered from 50 (9.2%) of 545 patients with AAHC, while no pathogens were reported for the remaining patients (49). There are 22 published studies reporting a total of 161 cases of AAHC due to *K. oxytoca*, but large-scale surveys are lacking, and most of the studies are case reports (6, 30, 49, 66, 76–79, 81–94) (Table 5). The majority of these AAHC cases occurred after the patients received various antimicrobial agents, including β-lactams, fluoroquinolones, clarithromycin, clindamycin, and metronidazole, for 1 to 7 days with sudden onset of bloody diarrhea (6, 30, 66, 76, 93). AAHC due

TABLE 5 Infections due to the *K. oxytoca* complex[a]

Yr	Country	Underlying diseases	Ward or department	Age group	Infection type	No. of cases	Reference
2011–2016	Iran	—	ICU, infectious and internal medicine	1–87 yr	AAHC	50	49
2011–2013	Iran	—	—	Children, adults	AAHC	40	76
—	Austria	—	—	—	AAHC	13	94
2009–2011	China	Chronic cardiopulmonary conditions, malignancy, diabetes	Medical, surgical	1–100 yr	AAHC	12	30
2001–2006	Turkey	Sinusitis, tonsillitis	—	Adults	AAHC	11	93
2007–2009	Nigeria	Pregnancy	Antenatal clinics	Adults	UTI	45	100
2011	Japan	Neurogenic bladder, benign prostatic hyperplasia	Urology	Adults	UTI	42	99
2009–2010	Cameroon	—	Outpatients	2–80 yr	UTI	35	134
2012–2014	India	Pregnant	—	Adults	UTI	35	135
2016–2017	Spain	—	—	Children, adults	UTI	28	96
2001–2010	Australia	Meningitis	—	1 day–16 yr	UTI	26	101
1994–1998	Italy	—	Pediatrics	0–17 yr	UTI	23	102
2009–2010	Bosnia and Herzegovina	—	Inpatients, outpatients	—	UTI	15	103
2014–2016	Tunisia	—	Medical, surgical	Neonates, adults	UTI	10	104
1991–2000	South Korea	Various medical and surgical diseases	—	Adults	BSI	125	62
2003–2008	USA	Various medical and surgical diseases	Medical, surgical	Adults	BSI	68	142
2010–2015	Afghanistan	—	Inpatients	1 day–18 yr	BSI	44	143
1980–1996	China	Hepatobiliary disease, malignancy, diabetes	Medical, surgical and pediatric	5–93 yr	BSI	43	63
1986–1987	USA	COPD, malignancy, diabetes	—	1 day–95 yr	BSI	34	144
1996	Germany	—	PICU	Infants	BSI	28	64
1985	USA	—	ICU	Adults	BSI	15	145
1981–1983	UK	—	NICU	Neonates	BSI	12	146
2016–2017	Spain	—	—	Adults	BSI	11	96
1983	USA	Malignancy, heart disease, COPD, diabetes, alcoholism	Medical, surgical	Adults	Pneumonia	14	108
1979–1981	UK	Chronic bronchitis, malignancy, cryptogenic fibrosing alveolitis	Respiratory, chest	Adults	Pneumonia	11	176
2016–2017	Spain	—	—	Adults	Pneumonia	10	96
2005–2006	Spain	—	—	—	Peritonitis	14	188
2006–2007	Poland	—	Inpatients	—	SSTI	44	210
2001–2011	Australia	Malignancy, postsurgery status	ICU, other wards	Adults	Pleural empyema	19	242

[a]Reports with ≥10 cases are included. —, not available. AAHC, antibiotic-associated hemorrhagic colitis; BSI, bloodstream infection, also containing bacteremia; UTI, urinary tract infection; SSTI, skin and soft tissue infection. COPD, chronic obstructive pulmonary disease. NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

to *K. oxytoca* may develop in critically ill patients who received antimicrobial agents for more than 2 weeks (49). The abdominal cramps and diarrhea symptoms are not mild in AAHC patients but are usually alleviated within 24 to 48 h and resolve within 1 week after withdrawal of antimicrobial agents in nearly all cases (6, 81, 84, 93). This is different from non-AAHC infectious diarrhea caused by other species of the *Enterobacterales*, which often requires antimicrobial treatment to resolve (95).

Urinary Tract Infection

K. oxytoca is a relatively common pathogen of urinary tract infections (UTI) in both children and adults, primarily in pregnant women, immunocompromised patients, or those with genitourinary diseases (20, 96–136) (Table 5). *K. oxytoca* accounted for 1.3% (16/1,235), 0.7% (24/3,103), 1.9% (18/937), and 3.6% (109/3,038) of all UTI isolates in Mexico, China, Spain, and the United States, respectively, between 2009 and 2018 according to the Study for Monitoring Antimicrobial Resistance Trends (SMART) program (137–140). In hospitalized patients, the proportion of *K. oxytoca* in all bacterial uropathogens ranges from 2.5% to 3.5% (59, 101). For pregnant women, *K. oxytoca* appears to be more common in UTI and accounted for 19.4% and 38.1% of bacterial uropathogens, second only to *Escherichia coli*, in two studies (100, 135). Several studies have also reported UTI due to *K. oxytoca* in many patients with immunocompromised conditions, critical illness, or malignancies (97, 98, 115, 136). Most of these patients have a favorable outcome of UTI except for those with critical illness who always have infections at other sites (106, 114, 124, 127). In addition, UTI due to *K. oxytoca* is also common in patients with underlying genitourinary diseases or conditions, such as neurogenic bladder, renal lithiasis, urinary tract surgery, prostatic hyperplasia, and testicular infarction (99, 113, 125). In most of such cases, UTI can be resolved but are prone to recur, as the underlying diseases often continue to exist, and may then lead to long-term colonization with *K. oxytoca* (113, 119, 132).

Bloodstream Infection

Bacteremia refers to viable bacteria in the blood, which can evolve into a bloodstream infection (BSI) when the immune response mechanisms fail or become overwhelmed (141). *K. oxytoca* has not been reported as a common bacteremia pathogen in the past (62), but recently, a number of studies and cases have reported bacteremia or BSI due to *K. oxytoca* in patients across all age groups (62–64, 96, 98, 104, 105, 111, 114, 115, 127, 128, 142–173) (Table 5). In particular, there are three large-scale retrospective studies reporting the proportion of *K. oxytoca* in pathogens causing bacteremia or BSI (60, 62). *K. oxytoca* accounted for 0.57% of all bacteremia cases in South Korea between 1991 and 2001 (62), 3.7% (261/6,754) in Toronto, Canada, between 2006 and 2016 (60), and 4.2% (44/1,040) in Kabul, Afghanistan, between 2010 and 2015 (143).

Most *K. oxytoca* bacteremia or BSI cases are secondary to infections at other sites, such as UTI, skin and soft tissue infections, and pneumonia, and are associated with certain underlying diseases, including diabetes, malignancies, chemotherapy, radiation therapy, hepatobiliary diseases, cerebrovascular accidents, chronic obstructive pulmonary disease, chronic renal insufficiency, congestive heart failure, and various surgeries (63, 115, 144, 148–151, 153, 154). Septic shock, which is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with increased risks of mortality (174), was developed in many BSI cases (152, 156, 159, 160, 173, 175). The mortality of patients with *K. oxytoca* BSI varies significantly in different studies (62, 63, 98, 146), and only one large-scale study reported the mortality rate, which was 23.2% in South Korea (62). More large-scale studies are warranted to investigate the actual mortality of patients with *K. oxytoca* BSI.

Pneumonia

A mortality rate as high as 50% has been seen in pneumonia caused by *Klebsiella* spp. (71). *K. pneumoniae* is the most common *Klebsiella* species causing both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). *K. oxytoca* is also able to cause pneumonia, especially HAP (34, 96, 98, 104, 105, 108, 111, 114–116, 122, 127, 128, 147, 175–186),

although much less commonly than *K. pneumoniae*. One large-scale study in China has reported that *K. oxytoca* constituted 3.6% (70/1,920) of bacterial isolates recovered from patients with pneumonia (138). Another retrospective study has found that *K. oxytoca* accounted for 10% of *Klebsiella* species causing acute respiratory tract infections in the United Kingdom between 1979 and 1981 (176). In Nepal in 2018 and 2019, *K. oxytoca* accounted for 2.86% of all Gram-negative bacteria causing lower respiratory tract infections (177). *K. oxytoca* pneumonia appears to be more commonly seen in patients with underlying respiratory diseases, including chronic bronchitis, small-cell carcinoma, chronic obstructive pulmonary disease (COPD), endobronchial tuberculosis, asthma, and obstructive sleep apnea (98, 108, 115, 128, 176, 186) (Table 5). Several studies have also shown that *K. oxytoca* is a relatively common pathogen causing ventilator-associated pneumonia (VAP) in critically ill patients with mechanical ventilation (116, 127, 186). A possible mechanism of VAP due to *K. oxytoca* is respiratory colonization acquired from hospital staff or equipment surfaces and then subsequent introduction into the lung via the tracheal tube. The prognosis of pneumonia due to *K. oxytoca* appears to be poor, as 12 of the 25 patients with such infection died (108, 176).

Intra-abdominal Infections

Intra-abdominal infections (IAI) are usually caused by *E. coli* and enterococci (187) but can also be due to *K. oxytoca* in some cases (98, 104, 127, 181, 188–209). The proportion of *K. oxytoca* in all pathogens isolated from IAI in the SMART program was 2.0% (54/2,682) in Mexico, 1.7% (65/3,758) in China, 4.8% (69/1,429) in Spain, and 5.9% (209/3,633) in the United States between 2009 and 2018 (137–140). In most cases, peritonitis and liver or spleen abscess due to *K. oxytoca* are secondary to abdominal surgeries or are seen in patients with malignancies, end-stage liver or renal diseases, or immunocompromised conditions, such as diabetes and renal transplantation (189, 194, 208). However, pancreatic abscess due to *K. oxytoca* is seen only in patients with pancreatitis (181, 200). Most patients with IAI due to *K. oxytoca* recovered after a combination of antimicrobial agents and surgeries (194, 199, 206, 207).

Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTIs) due to *K. oxytoca* can be classified into three major types, i.e., wound infection, necrotizing fasciitis, and abscess (16, 96, 105, 108, 118, 128, 186, 210–220) (Table 5). Wound infection is usually secondary to surgeries (16, 96, 186), while necrotizing fasciitis is seen in patients with malignancies or receiving organ transplantations (118, 214, 215). Abscess mainly occurs in diabetic patients and may be due to skin damage (212, 217, 220). Patients usually recover from SSTIs due to *K. oxytoca*, except for those with other severe diseases (212, 214, 217, 219).

Other Infections

K. oxytoca has been found in central nervous system (CNS) infection (221–226), endocarditis (133, 173, 227–231), endophthalmitis (179, 232–237), septic arthritis (238–241), and many other types of infections, such as plueral empyema (242), prostatic infection (243), acute epididymitis (125), nonhemorrhagic diarrhea (244) or colitis (245), and malignant external otitis (246). CNS infections due to *K. oxytoca*, including meningitis, ventriculitis, and brain abscess, have been reported (221, 223–226), some of which are secondary to chronic otitis media (223, 225, 226). Most cases of CNS infections have a good prognosis after antimicrobial therapy and surgical procedures (aspiration or excision) (224–226). In the literature, there are seven cases of adults with endocarditis caused by *K. oxytoca*, six of whom recovered after antimicrobial treatment (133, 173, 227–231). Endophthalmitis, including keratitis, corneal ulcer, and suture abscess, has been reported in six adults and two neonates, and almost all of them recovered after topical antimicrobial drops (179, 232–237). Septic arthritis, an inflammation of the joints secondary to an infectious etiology, is usually caused by *Staphylococcus aureus* or *Kingella kingae* in children and *S. aureus* and *Streptococcus pneumoniae* in adults (247). Four cases of *K. oxytoca* septic arthritis, in two infants and two adults, have been reported (238–241), all of whom recovered after antimicrobial treatment. *K. oxytoca* was also found to be associated with hydropneumothorax in a case report (248).

Antimicrobial Treatment of Infections Due to the *K. oxytoca* Complex

Only few studies have specifically addressed the antimicrobial treatment in patients with infections due to the *K. oxytoca* complex. AAHC due to the *K. oxytoca* complex usually resolves spontaneously after withdrawal of antimicrobial agents that cause AAHC, and there is no need for antimicrobial treatment for AAHC (84, 90). Otherwise, as it is a member of the order *Enterobacterales*, antimicrobial treatment for infections due to the *K. oxytoca* complex is essentially the same as that for infections due to other *Enterobacterales* species, such as *K. pneumoniae* and *E. coli*. It is notable that rates of nonsusceptibility of the *K. oxytoca* complex to commonly used antimicrobial agents such as ceftazidime, carbapenems, amikacin, and levofloxacin are relatively low in surveillance programs such as SENTRY (see "Antimicrobial Resistance and Determinants" for details) and published reports (137, 139, 249). Therefore, many commonly used antimicrobial agents, including β-lactams (e.g., cephalosporins, carbapenems, and piperacillin-tazobactam) and non-β-lactam agents (e.g., amikacin, colistin, quinolones, tigecycline, and trimethoprim-sulfamethoxazole) could be therapeutic options for infections due to the *K. oxytoca* complex according to patient factors such as the disease severity, the immunity status, and the infection site (250). Strains of the complex share carbapenem resistance mechanisms with other *Enterobacterales* species, in particular *K. pneumoniae*. Antimicrobial treatment for carbapenem-resistant strains of the complex is the same as that for carbapenem-resistant *Enterobacterales* (CRE) (250–252). The antimicrobial options against CRE are usually stratified by the infection site (UTI or infections outside the urinary tract), the resistance profile (the susceptibility to meropenem in addition to resistance to ertapenem), and the types of carbapenemases, i.e., serine β-lactamases (e.g., KPC or OXA-48) or metallo-β-lactamases (MBLs, e.g., NDM). For infections outside the urinary tract, combinations containing new non-β-lactam β-lactamase inhibitors, such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, are usually recommended against KPC-producing CRE, while cefiderocol (a novel siderophore cephalosporin) or ceftazidime-avibactam plus aztreonam are the preferred choice against NDM-producing CRE (250).

For cases with endophthalmitis caused by the *K. oxytoca* complex, symptoms disappeared after topical use of antimicrobial agents, including cefazolin, tobramycin, or fluoroquinolones, in combination with dexamethasone when necessary (232, 235). In addition to antimicrobial treatment, most patients with IAI, SSTI, or CNS infection caused by the *K. oxytoca* complex recovered after undergoing surgeries (118, 194, 225).

Outbreaks of Health Care-Associated Infections

To date, 15 outbreaks of health care-associated infections due to the *K. oxytoca* complex have been reported (Table 6), ranging in severity from conjunctivitis to sepsis (50, 175), with the number of cases ranging from 5 to 66 (105, 149). Most of these outbreaks occurred in hospitalized patients mainly in NICUs and several other types of wards, including hematology, neurology, and renal transplantation (40, 50, 97, 114, 115, 175). Microbiological source tracing was performed in most studies; handwashing sinks, drainage systems, humidifiers, blood gas analyzers, enteral feeding, and infusion preparation have been identified as likely sources of the outbreaks (115, 127, 149, 179, 253). This suggests that the *K. oxytoca* complex has environmental sources and may be well adapted to health care environments containing water, but studies examining the ability of the complex to survive and persist in relevant environments are largely lacking. The likely source of some of the outbreaks could not be identified, even though epidemiological and microbiological molecular screening methods were employed (50). Fortunately, all outbreaks with outcomes being reported were controlled by source control, such as sink modifications, and implementing bundles of infection control measures. These measures usually include strengthening hand hygiene, enhancing environment cleaning (particularly sinks and equipment), isolating infected patients, contact precautions, antimicrobial stewardship programs, and performance improvement of standard procedures (38, 50, 97, 115, 175, 253). In addition, there are two studies that reported clusters of NICU or pediatric ICU (PICU) patients with intestinal colonization of the *K. oxytoca* complex but without developing infection (38, 40). The two clusters were controlled after implementing bundles of infection control measures (38, 40).

TABLE 6 Outbreaks due to the *K. oxytoca* complex[a]

Yr	Country	Ward(s)	Age group	Infection type or site	No. of cases (infection/ colonization)	Resistance	Source(s)	Control measures	Mortality	Clonality (ST)	Reference
2016–2017	Norway	NICU	Neonates	IC, pneumonia, necrotizing enterocolitis, conjunctivitis	22 (5/17)	AMP only	—	Bundle: cleaning and disinfection, patient cohorting, hand hygiene, etc.	1/22	M (ST179)	50
2014	Spain	NICU	Neonates	IC, pneumonia, conjunctivitis	20 (4/16)	Carbapenem	Other patients	Bundle: early detection, contact precautions, cohorting patients and HCWs, restricting β-lactams, etc.	0/20	P	175
2013–2016	Tunisia	Hospital-wide	Neonates, adults	UTI, hepatic abscess, pneumonia, sepsis	19 (19/0)	PIP-TAZ, TIC, AMP-SUL	—	—	—	M (ST220)	104
2011–2013	Austria	Hematology	Adults	IC, pneumonia, BSI, abdominal abscess	10 (6/4)	Carbapenem	Handwashing sinks	Isolating colonized patients; enforcing hand hygiene; cleaning the ward, particularly the sinks and equipment	5/10	M (ST4)	115
2009–2011	Spain	ICU	Adults	IC, VAP, BSI, UTI, peritonitis	42 (14/28)	Multidrug resistant	Drainage system	Eliminating the horizontal drainage system	18/42	M	127
2009–2010	Japan	Neurosurgery	17–75 yr	IC, postoperative SSTI, pneumonia	8 (4/4)	PIP-TAZ	—	Enforcing hand hygiene, contact precaution, promoting AMS	0/8	M (ST9)	114
2016–2017	Greece	Oncology chemotherapy outpatient unit	—	CRBSI	7 (7/0)	—	Chemotherapeutical prepn	—	0/7	M	148
2006–2011	Canada	ICU	—	IC, UTI, BSI, SSTI, pneumonia	66 (24/42)	ESBLs	Handwashing sinks	Sink cleaning 3×/day, sink drain modifications, AMS	—	P	105
2005	Argentina	Renal transplant	—	UTI	7 (7/0)	AMX-CLA, FUR, PIP-TAZ, ATM	—	Enhancing standard precautions (i.e., hand hygiene) via education and contact precaution	—	M	97
2003	Turkey	Neurology, ICU	3–65 yr	BSI	5 (5/0)	—	Saline solution during MRA	Changing and discarding saline solution	0/5	M	149
2000	Turkey	NICU	Premature neonates	BSI, pneumonia	10 (10/0)	CAZ, CRO	—	—	—	P	147
1997	South Korea	NICU	Neonates	Endophthalmitis, pneumonia, UTI	6 (6/0)	ATM, CRO	Humidifiers	Humidifiers were thoroughly washed and disinfected	—	M	179

(Continued on next page)

TABLE 6 (Continued)

Yr	Country	Ward(s)	Age group	Infection type or site	No. of cases (infection/ colonization)	Resistance	Source(s)	Control measures	Mortality	Clonality (ST)	Reference
1996–1997	France	Premature baby unit, NICU	Premature neonates	IC, BSI	25 (1/24)	—	Enteral feeding procedures	Using gloves during enteral feeding, hand washing, isolation and cohorting	—	M	253
1996	Germany	NICU, PICU	Infants	BSI	28 (28/0)	—	0.25% disinfectant contaminated	Increasing the concn of disinfectant to 0.5%, replacing plastic pails.	2/28	M	64
1981–1983	UK	NICU	Neonates	BSI	12 (12/0)	GEN	Blood gas analyzer	Disposing wastes from the blood gas analyzer in the lab rather than in the unit.	8/12	—	146
2017–2018	Australia	Neonatal	Neonates	IC	10 (0/10)	ESBLs	Contaminated detergents	Isolating cases, destroying reusable detergent bottles, using prefilled single-use detergent bottles.	—	M	40
2012–2013	Germany	Pediatric center, ICU	Newborns, children	IC	14 (0/14)	ESBLs	Washing machine	Replacing washing machine and sinks, and bundle: environmental monitoring; active patient screening, training HCWs, hand hygiene.	—	M	38

[a]AMS, antimicrobial stewardship; CRBSI, catheter associated bloodstream infection; ESBL, extended-spectrum β-lactamase; HCWs, health care workers; IC, intestinal colonization; MRA, magnetic resonance angiography; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; VAP, ventilator-associated pneumonia; AMP, ampicillin; AMX, amoxicillin; ATM, aztreonam; CAZ, ceftazidime; CLA, clavulanate; CRO, ceftriaxone; FUR, cefuroxime; GEN, gentamicin; PIP, piperacillin; SUL, sulbactam; TAZ, tazobactam; TIC, ticarcillin; M, monoclonal; P, polyclonal; —, not available.

TABLE 7 *In vitro* susceptibility of antimicrobial agents against isolates of the *K. oxytoca* complex in the SENTRY program and other available large-scale (≥100 isolates) national or regional surveillance data in the Asia-West Pacific region and Africa

Antimicrobial agent	% nonsusceptible (no. tested)[a]					
	SENTRY,[b] 2013–2019 (*n* = 5,724)	Japan,[c] 2019 (*n* = 10,551)	China,[d] 2019 (*n* = 30,781)	Thailand,[e] 2019 (*n* = 1,368)	Australia,[f] 2019 (*n* = 239)	Middle East and Africa,[g] 2015–2018 (*n* = 103)
Amikacin	0.2 (5,717)	0.1	2.1 (29,638)	2.4 (1,122)	0 (239)	—
Gentamicin	3.5 (5,723)	1.2	11.9 (26,509)	13.5 (966)	0.4 (239)	—
Tobramycin	3.7 (5,178)	—	—	—	0.4 (239)	—
Amoxicillin-clavulanate	7.5 (3,728)	11	24.9 (11,487)	17.7 (988)	9.3 (215)	—
Ampicillin-sulbactam	51.2 (5,724)	29.1	43.5 (21,537)	33.9 (115)	—	—
Cefoperazone-sulbactam	12.1 (4,714)	—	14.6 (14,697)	17.1 (615)	—	—
Ceftazidime-avibactam	1 (896)	—	—	—	—	—
Ceftolozane-tazobactam	3.9 (894)	—	—	—	—	—
Piperacillin-tazobactam	11 (5,716)	9.1	12.6 (29,731)	11.9 (986)	9.2 (239)	0 (103)
Doripenem	0.8 (4,827)	—	—	—	—	—
Ertapenem	1.8 (2,107)	—	—	4.1 (917)	—	—
Imipenem	1.1 (5,723)	—	6.4 (30,057)	6.1 (917)	—	—
Meropenem	0.9 (5,723)	0.2	5.5 (18,969)	4.5 (1,050)	0 (239)	—
Cefepime	5.3 (5,723)	1.5	11.9 (29,433)	17.9 (380)	0.4 (239)	0 (103)
Cefoperazone	14.6 (1,368)	—	—	—	—	—
Cefoxitin	5.1 (790)	—	15.2 (12,083)	10.1 (513)	—	—
Ceftaroline	17.9 (5,667)	—	—	—	—	3.9 (103)
Ceftazidime	4.1 (5,724)	2.4	12.3 (27,814)	21.2 (1,132)	1.3 (239)	—
Ceftriaxone	12.5 (5,724)	9	20.8 (24,645)	23.2 (858)	7.6 (239)	—
Cefuroxime	28.9 (1,539)	—	27.1 (17,327)	—	—	—
Aztreonam	11.9 (5,723)	8.5	15.8 (22,996)	—	—	0 (103)
Trimethoprim-sulfamethoxazole	7.2 (5,717)	6.9	20.7 (28,690)	—	—	—
Tigecycline	0.1 (5,724)	—	3.3 (8,257)	—	—	0 (103)
Colistin	0.8 (5,656)	—	—	—	—	—
Ciprofloxacin	7.1 (5,710)	—	16.1 (25,604)	30.6 (1,032)	1.7 (239)	—
Levofloxacin	5.4 (5,715)	5.3	12.9 (29,565)	23.4 (444)	—	3.9 (103)
Moxifloxacin	10.7 (4,205)	—	—	—	—	—
Doxycycline	7.6 (4,929)	—	—	—	—	—
Minocycline	5.9 (4,971)	—	—	—	—	—
Tetracycline	7.9 (4,976)	—	—	—	—	—

[a]Nonsusceptible, including intermediate and resistant, is defined using criteria of the Clinical and Laboratory Standards Institute (CLSI) (2019), except for colistin and moxifloxacin, for which the term is defined using criteria of EUCAST (https://www.eucast.org) (2019). For each agent, the number of isolates tested varies and therefore is shown in parentheses except the data from Japan, for which the number is not available. —, not available.
[b]The SENTRY surveillance data are available at https://www.jmilabs.com/sentry-surveillance-program/.
[c]Source: Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) program, comprising 2,223 hospitals (https://j-siphe.ncgm.go.jp/en).
[d]Source: China Antimicrobial Resistance Surveillance System (CARSS), comprising 1,375 hospitals (http://www.carss.cn/).
[e]Source: National Antimicrobial Resistant Surveillance Center, comprising 92 hospitals (http://narst.dmsc.moph.go.th/).
[f]Source: Antimicrobial Use and Resistance in Australia (AURA) Surveillance System (https://www.safetyandquality.gov.au/). These isolates were collected from sepsis patients only.
[g]Source: reference 256. These isolates were collected from patients with SSTI and respiratory tract infections.

Strain Clonal Background

Very few studies have addressed the clonal background of *K. oxytoca* clinical isolates. A multilocus sequencing typing (https://pubmlst.org/organisms/klebsiella-oxytoca) scheme has been developed (254). Using this scheme, 74 isolates from clinical samples or asymptomatic carriers were assigned to 60 sequence types (STs) (254), and in another study (13), 68 isolates (from rectal swabs in hospitals across Europe and Israel) that were not susceptible to expanded-spectrum cephalosporins were assigned to 34 STs. The studies suggest a hugely diverse clonal background within the *K. oxytoca* complex. Among the 359 STs of the *K. oxytoca* complex (https://pubmlst.org/organisms/klebsiella-oxytoca; accessed 1 April 2021), clonal complex 2, comprising ST2, -9, -18, -19, -57, -58, -61, -63, -141, -154, -155, and -176 (13, 254, 255), was the most common type, accounting for 32.4% of the 68 cephalosporin-nonsusceptible carriage isolates (13), and was also the most prevalent type in infants (255). Isolates of clonal complex 2 have been found in many countries in Europe and Israel (8, 13, 254) as well as Australia, China (254), and Japan (114). Clonal complex 2 has also been associated with carbapenem resistance and has caused outbreaks of health care-associated infections. In a

TABLE 8 Antimicrobial resistance genes

Antimicrobial	Antimicrobial resistance gene(s)[a]	References
Carbapenems	bla_{GES-5}, bla_{GIM-1}, $bla_{IMP-1, -4, -6, -8, -28, -29, -34}$, $bla_{KPC-2, -3}$, $bla_{NDM-1, -4, -5}$, $bla_{OXA-48, -181}$, $bla_{VIM-1, -2, -4}$	32, 34, 96, 104, 106, 119–121, 124, 150, 156, 158, 166, 183, 190, 213, 241, 244, 281, 285–287, 296, 299–303, 305–332, 393–398, 403–416
Other β-lactams	bla_{ACC-1}, bla_{ACT-36}, bla_{BEL-1}, bla_{CARB-2}, $bla_{CMY-2, -4, -6, -31}$, $bla_{CTX-M-2, -3, -8, -9, -15}$, bla_{DHA-1}, $bla_{FOX-3, -5}$, bla_{GES-1}, bla_{LAP-2}, $bla_{OXA-1, -2, -4, -9, -10}$, $bla_{SHV-2, -5, -11, -12, -46}$, $bla_{TEM-1, -15, -30}$, bla_{VEB}	32, 34, 40, 96, 106, 119–121, 124, 150, 156, 166, 183, 281, 285–289, 292, 296–303, 309, 310, 316, 319, 322, 323, 337, 338, 354, 393, 397, 406, 411, 414, 415, 417–424
Colistin	*mcr-1*, *-9*	335–338
Aminoglycosides	*aac(3)-I*, *-Ia*, *-Ib*, *-II*, *-IIa*, *-IId*, *-IIg*, *-IV*, *-IVa*, *aac(6′)-30*, *-Ib*, *-Ib3*, *-Ib*-cr, *-Ib*-cr5, *-II*, *-IIa*, *-IIc*, *aacA44*, *aadA1*, *aadA2*, *aadA5*, *aadA13*, *aadB*, *ant(2′′)-Ia*, *ant(3′′)-Ia*, *aph(3′)-Ia*, *-Ib*, *-Ic*, *-VI*, *-XV*, *aph(3′′)-Ib*, *aph(6)-Id*, *armA*, *rmtC*, *sat2*, *strA*, *strB*	31, 32, 40, 96, 119, 150, 166, 169, 213, 244, 286, 287, 292, 296–300, 318–320, 323, 337, 338, 354, 393, 397, 406, 407, 418–420, 425
Quinolones	*oqxA*, *oqxB*, *qnrA1*, *qnrB1*, *qnrB2*, *qnrB4*, *qnrB6*, *qnrB19*, *qnrB32*, *qnrS1*, *qnrS2*	31, 32, 34, 96, 119, 166, 169, 286, 287, 292, 296–298, 300, 306, 319, 323, 336–338, 388, 393, 397, 406, 413, 418, 425–430
Fosfomycin	*fosA3*	34, 323, 337, 388, 393, 427
Sulfonamides	*sul1*, *sul2*, *sul3*	32, 40, 96, 119, 166, 244, 286, 287, 292, 296–298, 300, 323, 337, 393, 397, 418–420
Trimethoprim	*dfrA1*, *dfrA12*, *dfrA14*, *dfrA16*, *dfrA17*, *dfrA19*, *dfrB1*, *dfrII*, *dfrIIIc*	32, 96, 119, 156, 166, 169, 286, 292, 296, 297, 300, 319, 320, 323, 338, 393, 397, 418, 420
Chloramphenicol	*catA1*, *catA2*, *catB2*, *catB3*, *catB11*, *cmlA1*	32, 34, 96, 119, 287, 292, 296–298, 300, 320, 323, 337, 338, 393, 397
Rifampin	*arr-3*, *arr-8*	32, 156, 297, 298, 323, 337, 393
Tetracyclines	*tet*(A), *tet*(B), *tet*(D)	34, 96, 166, 287, 296–298, 323, 338, 393, 418
Macrolides	*ere*(A), *mph*(A), *mph*(E), *msr*(E)	96, 166, 292, 323, 337, 393, 397

[a]All strains of the *K. oxytoca* complex also have intrinsic bla_{OXY} genes.

multicenter study in Spain, eight of the 12 representative strains of carbapenem-resistant the *K. oxytoca* complex belonged to clonal complex 2 (96). In Japan, isolates of clonal complex 2 (ST9) caused an outbreak of various health care-associated infections in a university hospital (114). In the United Kingdom and Ireland, the rapid dissemination of isolates belonging to clonal complex 2 (ST2) has been identified due to clonal expansion (8). In light of the relatively high prevalence, the wide geographical distribution, and the association of carbapenem resistance and outbreaks, clonal complex 2 may have the potential to become a high-risk lineage for mediating the dissemination of antimicrobial resistance, and further studies are warranted.

ANTIMICROBIAL RESISTANCE AND DETERMINANTS

In Vitro Antimicrobial Susceptibility of the *K. oxytoca* Complex

SENTRY (https://www.jmilabs.com/sentry-surveillance-program/) is a worldwide antimicrobial surveillance program and has *in vitro* susceptibility data for 5,724 clinical isolates of the *K. oxytoca* complex from 2013 to 2019 (Table 7). In contrast, the *K. oxytoca* complex is not included in other large-scale international or regional surveillance programs (e.g., European Antimicrobial Resistance Surveillance System [EARSS]) or its overall *in vitro* susceptibility data of all participated regions are not available (e.g., the Assessing Worldwide Antimicrobial Resistance Evaluation [AWARE] global surveillance program and SMART). According to SENTRY data, almost all isolates of the *K. oxytoca* complex are susceptible to tigecycline and colistin, with a <1.0% nonsusceptibility rate, and the vast majority are also susceptible to aminoglycosides, with nonsusceptibility rates of 0.2 to 3.7%. The rates of nonsusceptibility to third-generation cephalosporins ranged from 4.1% (to ceftazidime) to 14.6% (to cefoperazone), while the carbapenem-nonsusceptible rate was 1.8% (to ertapenem) (Table 7). However, the rates of nonsusceptibility of the *K. oxytoca* complex to carbapenems and cephalosporins have been increasing during the past 7 years, although the rates of nonsusceptibility to aminoglycosides and piperacillin-tazobactam have remained stable. The rate of nonsusceptibility of the *K. oxytoca* complex to carbapenems varies across regions. The rate is higher in the Asia-West Pacific region and Europe than in North America, while since 2018, Latin America has shown a faster increase trend and a higher rate. For fluoroquinolones, the rates of nonsusceptibility to levofloxacin, ciprofloxacin, and moxifloxacin were 4%, 7.1%, and 10.7%, respectively, and have remained stable in the past 7 years.

The vast majority of isolates (92.3%) of the *K. oxytoca* complex in the SENTRY program are from North America (61.2%, *n* = 3,501) and Europe (31.1%, *n* = 1,783), while isolates from the Asia-West Pacific region and Latin America accounted for only 4.4% (*n* = 257) and 3.2% (*n* = 183), respectively, and no isolates were from Africa. In the Middle East and Africa, 103 isolates of the *K. oxytoca* complex from patients with SSTI and respiratory tract infections between 2015 and 2018 were reported in the AWARE global surveillance program (256). All of the 103 isolates were susceptible to aztreonam, cefepime, piperacillin-tazobactam, and tigecycline, while the rate of nonsusceptibility to ceftaroline and levofloxacin was 3.9% for both (Table 7) (256).

There are national or large-scale (with 100 or more isolates) surveillance systems, which have reported susceptibility data for clinical isolates of the *K. oxytoca* complex, in several countries (Australia, China, Japan, and Thailand) in the Asia-West Pacific region. In Japan, the rates of nonsusceptibility of the 10,551 clinical isolates of the *K. oxytoca* complex to all tested antimicrobial agents but amoxicillin-clavulanate (https://j-siphe.ncgm.go.jp/en) were lower than those in SENTRY (Table 7). In contrast, clinical isolates of the *K. oxytoca* complex in China (*n* = 30,781, from 1,375 hospitals in 2019; http://www.carss.cn/) and Thailand (*n* = 1,368, from 92 hospitals in 2019; http://narst.dmsc.moph.go.th/) had higher rates of nonsusceptibility to most antimicrobial agents than those in SENTRY and Japan, in particular to carbapenems, ceftazidime, cefepime, and fluoroquinolones (Table 7). For instance, the rates of nonsusceptibility to carbapenems were 6.4% in China and 6.1% in Thailand, which are higher than the 0.9% in SENTRY and the 0.2% in Japan (Table 7). In Australia, 239 clinical isolates of the *K. oxytoca* complex collected from sepsis patients in 2019 had lower rates of nonsusceptibility to almost all tested agents than those in SENTRY and Japan (Table 7), and no carbapenem-nonsusceptible isolates were identified (https://www.safetyandquality.gov.au/).

Antimicrobial Resistance Determinants

The *K. oxytoca* complex carries several intrinsic antimicrobial resistance genes, including the β-lactamase-encoding bla_{OXY} and efflux pump-encoding *oqxA-oqxB*, to mediate low-level resistance to quinolones (52). However, we found that *oqxA-oqxB* was absent from strains of *K. huaxiensis*, *K. spallanzanii*, taxon 1, and taxon 3. In addition, we also found that the fosfomycin resistance gene *fosA* (257) is intrinsic to the *K. oxytoca* complex. Many isolates of the complex have also acquired genes mediating resistance to a variety of antimicrobial agents, including β-lactams (e.g., penicillins, cephalosporins, and carbapenems), aminoglycosides, quinolones, and colistin (258). These antimicrobial resistance genes are listed in Table 8.

Resistance to β-lactams in the *Enterobacteriaceae* is mainly due to the production of β-lactamases. A large number of β-lactamases have been reported and can be divided into four classes, i.e., class A, B, C, and D, according to the molecular structure (259). Narrow-spectrum β-lactamases are able to hydrolyze commonly prescribed penicillins, while broad-spectrum β-lactamases are also capable of hydrolyzing first- and second-generation cephalosporins (260–262). However, it is worth noting that the boundary between narrow- and broad-spectrum β-lactamases is often blurred in the literature and the same β-lactamase may be referred to as either type in different publications. ESBLs have the ability to hydrolyze monobactams (e.g., aztreonam) and the oxyiminocephalosporins (e.g., cefotaxime, ceftazidime, and cefepime) (263). Compared to ESBLs, AmpC-type cephalosporinases are also able to hydrolyze cephamycins (e.g., cefoxitin) but not cefepime, and their hydrolysis mechanism is typically resistance to the inhibition by β-lactam-type β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam) (264). Carbapenemases further extend the hydrolysis spectrum to carbapenems while typically retaining the activities of ESBLs and AmpC. ESBLs are of either class A or D, and AmpC belongs to class C, while carbapenemases can belong to class A, B, or D. In addition, some class A β-lactamases are also resistant to the inhibition of β-lactam-type β-lactamase inhibitors and are called inhibitor-resistant β-lactamases (261).

***bla*$_{OXY}$.** The *K. oxytoca* complex has an intrinsic bla_{OXY} gene encoding the chromosomal class A β-lactamase OXY, which is typically produced at a low level to confer resistance to aminopenicillins (ampicillin and amoxicillin), carboxypenicillins (carbenicillin and ticarcillin), and other penicillins (265, 266). Mutations in the promoter sequences of bla_{OXY} have

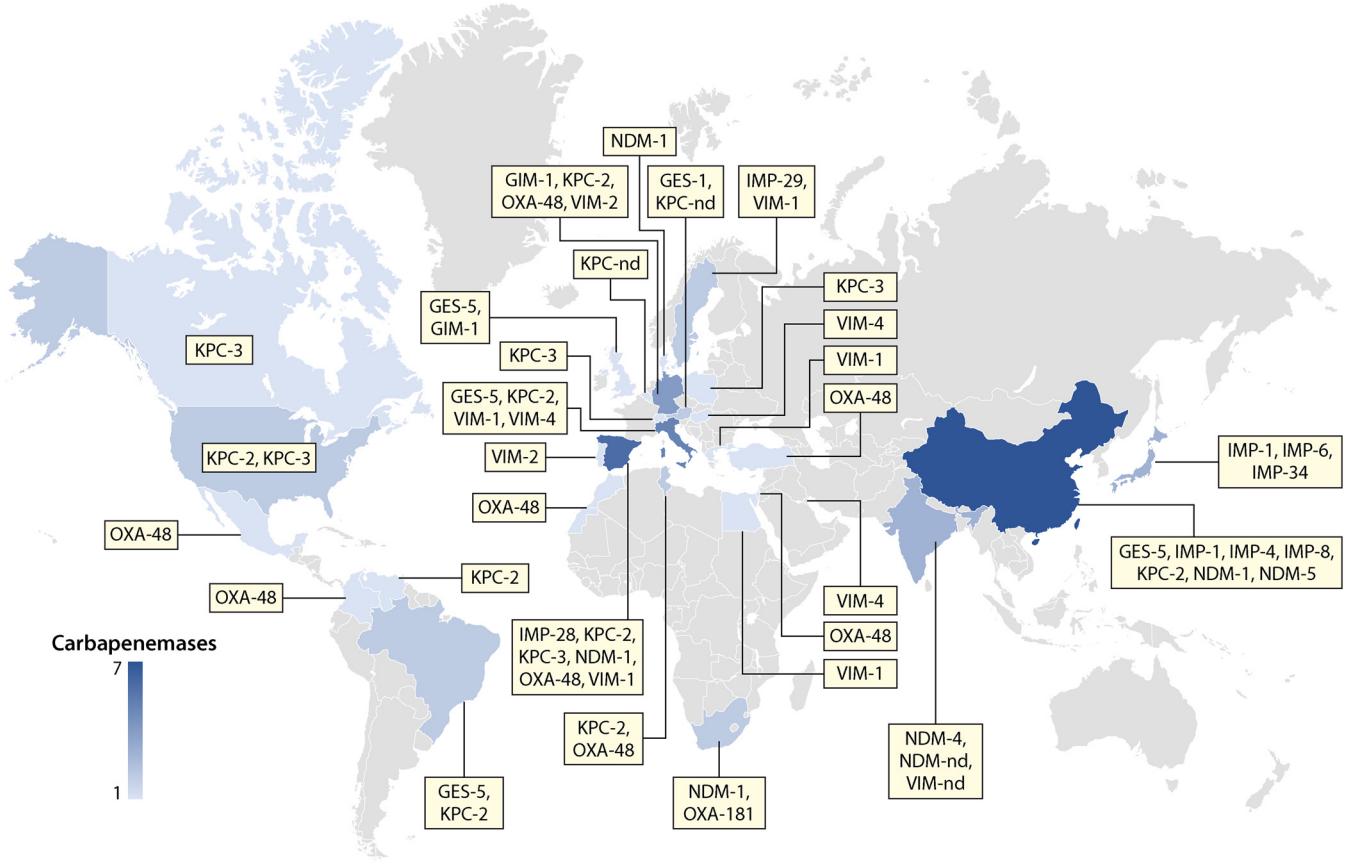

FIG 2 Worldwide distribution of CRKO strains and their carbapenemase types. nd, not determined. The number of carbapenemase variants that have been reported in a given country is indicated by color gradients.

been observed in 10% to 20% of clinical isolates (266–269) and can lead to overexpression of this gene by 73- to 223-fold (268). Five point mutations in the promoter have been mentioned in the literature: four in the −10 consensus sequence (G to T at the first base, G to A at the fifth base, G to A at the eighth base, and G to T at the twelfth base) and a T-to-A mutation at the fourth base of the −35 sequence (267, 270). Compared to the G-to-A mutation at the fifth base (the −10 consensus sequence) and the T-to-A mutation at the fourth base (the −35 sequence), the G-to-T mutation at the first base (the −10 sequence) leads to a stronger promoter (268). bla_{OXY} overexpression confers resistance to penicillins and some extended-spectrum β-lactams, especially aztreonam (265, 269–271), and leads to hydrolysis of ceftriaxone to a greater extent than cefotaxime but typically does not confer resistance to ceftazidime (269–272). Mutations in bla_{OXY} may also extend the resistance spectrum to aztreonam and oxyimino-cephalosporins. The proline-to-serine substitution at Ambler position 167 enhances the ability to hydrolyze ceftazidime (243). At Ambler position 237, the alanine-to-threonine substitution confers resistance to cefotaxime (273), while the alanine-to-glycine substitution increases the hydrolysis of aztreonam and ceftriaxone and increases resistance to the inhibition of clavulanate but decreases the ability to hydrolyze benzylpenicillin, cephaloridine, and cefamandole (274). Amino acid substitutions at Ambler position 237 also reduce susceptibility to ceftazidime (275). Compared with OXY-2-2, OXY-2-15 has a deletion of two amino acids at Ambler positions 168 and 169 and acquires the ability to hydrolyze ceftazidime (201). Some mutations in bla_{OXY}, such as the mutation resulting in a serine-to-glycine substitution at Ambler position 130 of OXY-2, generate an inhibitor-resistant β-lactamase (276). Typically, bla_{OXY} is located on the chromosome of the *K. oxytoca* complex. However, plasmid-borne bla_{OXY} has also been found in certain strains of the complex with the potential to be further transferred to other species, such as *K. pneumoniae* (136).

Class A noncarbapenemase β-lactamase-encoding genes. bla_{TEM-1} appears to be the most common bla_{TEM} variant in the *K. oxytoca* complex and encodes TEM-1, a broad-

spectrum β-lactamase. Several other bla_{TEM} variants have also been found in the *K. oxytoca* complex (Table 8). These variants encode either ESBLs, including TEM-3, TEM-15, TEM-26, and TEM-116 (263, 277), or the inhibitor-resistant β-lactamase TEM-30 (278). bla_{SHV} is intrinsic to *K. pneumoniae* but not *K. oxytoca* (279). Nonetheless, bla_{SHV} variants encoding SHV-2, −5, −7, −11, −12, −14, −30, and −46 have been found in the *K. oxytoca* complex (Table 8). Among these SHV enzymes, all but SHV-11 are ESBLs (263, 280, 281), while SHV-11 is a broad-spectrum β-lactamase (282). CTX-M enzymes are almost always ESBLs (283), and a few bla_{CTX-M} variants have been found in the *K. oxytoca* complex (Table 8). Of note, the presence of OXY β-lactamases may cause false-positive detection of CTX-M by immunological panels (284). Genes encoding other class A β-lactamases, including GES-1 and VEB (the exact variant was not specified), have also been sporadically reported (285).

***ampC* genes.** Unlike many other *Enterobacteriaceae* (such as *Citrobacter* spp., *Enterobacter* spp., and *E. coli*), the *K. oxytoca* complex has no chromosomal *ampC* genes encoding AmpC β-lactamases. Nonetheless, plasmid-borne *ampC* genes, including bla_{ACC} (286), bla_{ACT} (287), bla_{CMY} (106, 121, 288), bla_{DHA} (289, 290), and bla_{FOX} (291, 292), have been found in the *K. oxytoca* complex (Table 8).

Class D noncarbapenemase bla_{OXA} genes. To date, five bla_{OXA} genes encoding OXA-1, OXA-2, OXA-4, OXA-9, and OXA-10, all of which are narrow-spectrum β-lactamases (293–295), have been sporadically found in the *K. oxytoca* complex (96, 119, 150, 286, 296–303). The five OXA β-lactamases can be assigned to four subfamilies, i.e., OXA-1 (OXA-1 and OXA-4), OXA-2, OXA-9, and OXA-10 (295). Of note, OXA-2 and OXA-10 have weak activity against carbapenems (304).

Carbapenemase-encoding genes. Carbapenem-resistant *K. oxytoca* (CRKO) was first reported in 2003, with the strain being isolated from human urine in New York, USA, in 1998 (281). Since then, CRKO carrying a variety of carbapenemase genes has been identified all around the world (Table 8 and Fig. 2). It is worth noting that CRKO strains in most studies were not identified to the precise species level and that "*K. oxytoca*" in these studies could refer to any species of the complex. Therefore, in the following text, CRKO refers to all species within the *K. oxytoca* complex unless otherwise indicated.

Class A carbapenemases KPC-2, KPC-3, and GES-5 have been found in CRKO, including *K. grimontii* (34), *K. michiganensis* (166, 190), and *K. oxytoca* (96, 119, 156, 183, 244, 281, 287, 299, 300, 302, 305–315). KPC-2 appears to be the most common carbapenemase in CRKO strains, and KPC-2-positive CRKO has been identified from patients and clinical environment settings in Brazil (156), China (34, 119, 244, 305, 306, 310), Germany (302), Spain (96), the United States (190, 281, 312), and Venezuela (183), from rivers in Spain (299) and Italy (300), and from a wild bird in Tunisia (287). KPC-3-positive CRKO is usually isolated from patients (166, 190, 314), while GES-5-positive CRKO has been found only in water samples so far (300, 316, 317).

Currently, genes encoding four types of class B MBLs, i.e., GIM, IMP, NDM, and VIM, have been found in CRKO including *K. grimontii*, *K. michiganensis*, and *K. oxytoca*. The first MBL gene reported in CRKO was bla_{VIM-2}, which was found in four isolates from blood cultures of neonates in Portugal in 2005 (150). However, bla_{VIM-1} is the most common bla_{VIM} variant in CRKO, and bla_{VIM-1}-positive CRKO has been widely reported across Europe (96, 286, 299, 318–320) and in Egypt (321). bla_{IMP} is another relatively common MBL gene in CRKO. Seven IMP enzymes encoded by bla_{IMP} genes have been found in CRKO (Table 8), and IMP-4 is the most common one. Three bla_{NDM} variants encoding NDM-1, NDM-4, and NDM-5 have been found in CRKO, including *K. michiganensis* and *K. oxytoca*. In particular, bla_{NDM-1}-positive CRKO has been reported multiple times and all isolates were from patients or hospital environments (32, 96, 244, 296, 305, 322–326). In contrast, bla_{NDM-4} (301) and bla_{NDM-5} (244) have been found only in single isolates. bla_{GIM-1} was originally found in *Pseudomonas aeruginosa* in Germany in 2002 and has been found in one CRKO strain in the United Kingdom recovered in 2010 (327).

bla_{OXA-48} and the closely related $bla_{OXA-181}$ are the two class D carbapenemase-encoding genes that have been found in CRKO, including *K. michiganensis* and *K. oxytoca*. bla_{OXA-48}-positive CRKO has been found in hospital environments in Israel (328),

Mexico (329), Morocco (120), Spain (96), and Turkey (285), from patients in Colombia (330) and Tunisia (104), and from companion animals in Germany (331). $bla_{OXA-181}$ has been reported only in *K. michiganensis* in South Africa from urban hospital effluent (332) and a cancer patient (32).

The coexistence of two or three carbapenemase genes, in particular bla_{NDM-1} plus either bla_{KPC-2} (119, 244, 305), bla_{IMP-4} (119), bla_{NDM-5} (244), or $bla_{OXA-181}$ (32), in the same CRKO strain has also been reported. Other coexistences in the same CRKO strain are bla_{KPC-2} plus either bla_{IMP-4} (119, 305) or bla_{IMP-8} (310).

Plasmid-borne colistin resistance genes. Colistin resistance in the *K. oxytoca* complex is commonly due to the interruption of *mgrB* (158, 333), a negative regulator of the PhoP-PhoQ two-component system (334), or altered expression of this gene (211). Nonetheless, plasmid-borne colistin resistance genes, including *mcr-1* (335, 336) and *mcr-9* (337, 338), have also been seen in the complex. Plasmid-borne *mcr-1* has been found in *K. oxytoca* from the superficial skin swab of a patient in South Africa (335) and from a lake in China (336). Plasmid-borne *mcr-9* has been reported in *K. oxytoca* strains which were recovered from a rectal swab of a patient from Qatar (337) and from horses in Sweden (338).

Other resistance genes. Genes mediating resistance to aminoglycosides, chloramphenicol, fosfomycin, macrolides, quinolones, rifampin, sulfonamides, tetracyclines, and trimethoprim are listed in Table 8. Aminoglycoside resistance in the *K. oxytoca* complex is mainly due to modifications, including acetylation (*aac* and *sat* genes) (339), adenylylation (*ant* and *aad* genes) (339), and phosphorylation (*aph* and *str* genes) (339). Genes (*armA* and *rmtC*) encoding 16S rRNA methylases that confer high-level resistance to all aminoglycosides that are commonly used in clinical settings, including amikacin, gentamicin, and tobramycin, have also been found in the *K. oxytoca* complex (340, 341). Acquired quinolone resistance in the *K. oxytoca* complex is due to plasmid-borne *qnr* genes (*qnrA*, *qnrB*, and *qnrS*). *qnr* genes encode pentapeptide repeat proteins to protect bacterial DNA gyrase and topoisomerase IV from inhibition by quinolones and result in low-level quinolone resistance (342). The sulfonamide resistance genes *sul1*, *sul2*, and *sul3*, encoding dihydropteroate synthases, which are able to catalyze the condensation of *para*-aminobenzoate with 6-hydroxymethyl-7,8-dihydropterin diphosphate (343), are seen in many isolates of the *K. oxytoca* complex. A number of variants of *dfr* trimethoprim resistance genes, which encode dihydrofolate reductases (343), are found in the *K. oxytoca* complex (Table 8). Chloramphenicol resistance in the *K. oxytoca* complex is mainly caused by acetylation of the drug via different types of *cat*-encoding chloramphenicol acetyltransferases (344). In addition, a specific exporter encoded by *cmlA1* also confers chloramphenicol resistance (344) and has been found in the *K. oxytoca* complex. The rifampin resistance gene *arr* encodes ADP-ribosyl transferases able to inactivate rifampin (345) and is also found in the *K. oxytoca* complex. *tet* genes encode energy-dependent membrane-associated proteins to export tetracycline out of bacterial cells (346), and several *tet* genes have been identified in the complex. Macrolide resistance genes seen in the *K. oxytoca* complex include *ere*(A), *mph*(A), *mph*(E), and *msr*(E). *ere*(A) encodes a macrolide esterase, and *mph* genes encode macrolide phosphotransferases, while *msr* encodes an efflux pump able to reduce the intracellular concentration of macrolides (347).

Chromosomal Point Mutation-Associated Antimicrobial Resistance

In addition to intrinsic and acquired antimicrobial genes, nonsynonymous mutations in some chromosomal genes, including *gyrA*, *mgrB*, and *parC*, can also mediate resistance to quinolones (*gyrA* and *parC*) or colistin (*mgrB*).

gyrA and *parC* encode DNA topoisomerase II (gyrase) subunit A (GyrA) and DNA topoisomerase IV subunit A, respectively. Amino acid substitutions in GyrA at positions 83 and 87 and in ParC at position 80 are associated with reduced binding of quinolones to the topoisomerase-DNA complex and lead to quinolone resistance in the *Enterobacteriaceae* (348–350). In the *K. oxytoca* complex, amino acid substitutions of GyrA at position 83 (T83I) or 87 (D87G) and those of ParC at position 80 (S80R or S80I) have been reported to confer quinolone resistance (18, 107, 351–353). In addition, the D87N substitution in GyrA (354) and M157L in ParC (298,

351) have also been found in quinolone-resistant isolates of the *K. oxytoca* complex, but whether these substitutions confer quinolone resistance has yet to be verified.

mgrB is a negative regulator of the PhoP-PhoQ two-component system (334). It has been found that interruption of *mgrB* by insertion sequences (158, 333), altered expression of *mgrB* (211), or the C28Y amino acid substitution in MgrB (333, 355) is able to mediate colistin resistance in the *K. oxytoca* complex.

VIRULENCE FACTORS

Cytotoxins Causing AAHC

K. oxytoca is a well-characterized causative agent of AAHC, caused by the production of cytotoxins. *K. oxytoca*-specific cytotoxin was initially described in 1989 and was thought to be present only in clinical isolates (356). An early study demonstrated that the cytotoxin produced by *K. oxytoca* from an AAHC patient was able to cause fluid accumulation in the ileal and colonic loops and severe ileal mucosal hemorrhage with erosion in rabbits (357). The right-side colon was found to be the main target of *K. oxytoca* using a rat model involving inoculation with *K. oxytoca* or the administration of amoxicillin-clavulanate (6). This finding is consistent with a case report regarding infection sites (86). AAHC associated with *K. oxytoca* happens as a result of the administration of antimicrobial agents, especially penicillins (6, 81, 86), which disturb the normal intestinal microflora, contributing to favorable conditions for the overgrowth of *K. oxytoca* (94). Although *K. oxytoca* also exists in other body sites, such as skin, mouth, upper respiratory tract, and urinary tract, the cytotoxin-producing isolates are more prevalent in the intestinal tract (16, 94). One study reported that 46% (6/13) of isolates from the stool of the asymptomatic carriers exhibited cytotoxicity, while none from the urinary tract ($n = 10$) or respiratory tract ($n = 16$) displayed cytotoxicity (94).

There are two distinct cytotoxins produced by *K. oxytoca*, tilimycin (also known as kleboxymycin or carbinolamine) and tilivalline (generated by nucleophilic attack of free indole on tilimycin [358, 359]), which lead to the pathological changes seen in AAHC (359, 360). Both tilivalline and tilimycin are pyrrolobenzodiazepine (PBD) metabolites and are generated from a bimodular nonribosomal peptide synthetase (NRPS) pathway (359, 360). The kleboxymycin-biosynthetic gene cluster for tilimycin and tilivalline contains the regulators *npsC* and *marR*, an NRPS operon, an *aroX* operon, *mfsX* (encoding a multidrug efflux MFS transporter), and *uvrX* (encoding the excinuclease ABC subunit UvrA) (358, 361, 362). The NRPS operon consists of *npsA* (encoding an amino acid adenylation domain-containing protein), *thdA* (encoding an acyl carrier protein), and *npsB* (encoding a nonribosomal peptide synthetase). The *aroX* operon comprises five genes, *aroX*, *dhbX*, *icmX*, *adsX*, and *hmoX*, encoding a 3-deoxy-7-phosphoheptulonate synthase, a 2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase, an isochorismatase, a 2-amino-2-deoxy-isochorismate synthase, and a 4-hydroxyphenyl acetate-3-monooxygenase, respectively (358, 361, 362).

PBDs are commonly produced by the actinobacteria, and therefore, it is suspected that the gene cluster encoding both toxins in *K. oxytoca* was acquired through horizontal gene transfer (359, 363). In a recent study of 7,170 *Klebsiella* genomes, including 178 belonging to the *K. oxytoca* complex (76 *K. michiganensis*, 66 *K. oxytoca*, 24 *K. grimontii*, 6 *K. pasteurii*, 5 *K. huaxiensis*, and 1 *K. spallanzanii* genome), the complete kleboxymycin gene cluster was found only in *K. grimontii*, *K. michiganensis*, *K. oxytoca*, and *K. pasteurii* (364). As *K. grimontii*, *K. michiganensis*, *K. oxytoca*, and *K. pasteurii* phylogenetically cluster as a lineage separated from other species of the *K. oxytoca* complex (Fig. 1), it is likely that the kleboxymycin gene cluster was acquired in this lineage before species divergence. However, the gene cluster has not been found to be plasmid borne (254).

Tilivalline was the first cytotoxin characterized in detail (360). It has been demonstrated that tilivalline suppresses microtubule-dependent processes in A549 lung carcinoma cells and HT-29 colon cancer cells by binding tubulin directly, making the microtubules stable and resulting in mitotic arrest (361). Tilimycin, also called kleboxymycin, exhibits at least 9-fold-higher toxicity than tilivalline in a cell culture assay based on MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole] and leads to increased virulence in the presence of glucose and lactose (359). Tilimycin is a

genotoxin interacting with double-stranded DNA, inducing cellular DNA damage in host cells *in vitro* and *in vivo* and causing a more serious lesion in cecal enterocytes of colonized mice than in healthy controls (361). Both tilimycin and tilivalline were found to be related to perturbations of the intestinal barrier by decreasing the expression of claudin-1, a barrier-forming tight junction protein, in T84 monolayers (365). However, in the absence of the two toxins, the intestinal barrier damage can also be triggered by reducing the expression of claudin-5 and −8 in *K. oxytoca* in T84 monolayers (365).

CPS and LPS

Capsular polysaccharide (CPS; K antigen) and LPS (containing O antigen) are common virulence factors of *K. pneumoniae* (366–369). Compared to *K. pneumoniae*, K and O antigens of the *K. oxytoca* complex are less studied. Nonetheless, a few K types, including K6, K9, K15, K21, K23, K26, K29, K31, K41, K43, K47, K55, K61, K66, K68, K70, K74, and K79, have been identified in the *K. oxytoca* complex (370–376). In a study containing 150 strains of the *K. oxytoca* complex, K68 was the most prevalent type in human stool samples (371). Currently, no published reports of the O antigen in the *K. oxytoca* complex are available.

Other Virulence Factors in the Literature

Other than AAHC-associated cytotoxins, there are only a limited number of studies addressing virulence factors of the *K. oxytoca* complex, partially due to the fact that most members of the *K. oxytoca* complex were identified in recent years. Nonetheless, a number of *K. pneumoniae* virulence factors have also been reported in the *K. oxytoca* complex, including genes encoding capsules (*matB*) (48, 377, 378), adhesins or biofilm formation (*cf29a*, *fimA*, *fimH*, *mrkABCDF*, and *pilQ*) (48, 377–382), iron uptake (*kfuBC*) (379), and urease (*ureA*) (379, 383). Among these genes, very few have been experimentally tested to explore their association with virulence in the *K. oxytoca* complex. The *mrk* gene cluster (*mrkABCDF*) encodes the mannose-resistant *Klebsiella*-like hemagglutinins (the type 3 fimbriae), allowing attachment to surfaces and thus formation of biofilms in *Klebsiella* spp. (381, 382, 384–386). This operon has been detected in two of 100 *K. oxytoca* isolates (380). The two *mrk*-positive *K. oxytoca* isolates were able to cause type 3 fimbria-specific agglutination in testing on tannic acid-treated red blood cells, but attempts to prove that the expression of type 3 fimbriae leads to the colonization of the mouse urinary tract failed (380). In a study, 70% (35/50) of *K. oxytoca* isolates from AAHC patients produced moderate levels of biofilm with higher expression of *fimA* (encoding a type 1 fimbrial protein facilitating colonization of the epithelium), *pilQ* (encoding type IV pilus biogenesis and competence protein) and *mrkA* than the biofilm-free strains (49). In another study, 78% (156/200) of *K. oxytoca* isolates from patients with colorectal cancer generated moderate levels of biofilm production (377). Virulence genes found in other enteric pathogens, such as *Citrobacter freundii*, *E. coli*, and *Vibrio cholerae* (genes encoding type IV and type VI secretion systems and proteins with partial homology to the cholera toxin), have also been reported in *K. oxytoca*, but their association with virulence in the complex has not been determined (8, 360).

PLASMIDS FOUND IN THE COMPLEX

Replicon Types of Plasmids in the *K. oxytoca* Complex

Plasmids are mobile genetic elements which can replicate independently of the chromosome (387), and many carry genes encoding beneficial phenotypes for the survival of host strains, such as antimicrobial resistance and virulence. A variety of plasmids have been reported in the *K. oxytoca* complex (32, 35, 96, 156, 244, 296, 388, 389). Plasmids seen in the complex belong to various replicon types, but none is specific to the complex.

Plasmids Carrying Carbapenemase-Encoding Genes

No known carbapenemase-encoding genes have originated from the *K. oxytoca* complex, and therefore, plasmids play a pivotal role in introducing carbapenem resistance into the complex. Forty-three plasmids carrying genes encoding class A carbapenemases have been reported in the literature or have been deposited in NCBI (Table 9), most of which carry bla_{KPC-2}.

TABLE 9 Plasmids carrying carbapenemase genes in the *K. oxytoca* complex[a]

Plasmid[b]	Gene	Replicon type[c]	Country	Yr	Host species[d]	Accession no. and/or reference
pJF-789	bla_{GES-5}	Q	NA	NA	Ko	KX912254
pJF-707	bla_{GES-5}	Q	UK	2014–2016	Ko	KX946994 (391)
pKPC-4b66	bla_{KPC-2}	FIA(HI1), N (ST6)	USA	2015	Km	CP026274
pK516_KPC	bla_{KPC-2}	FIA, FII(p14)	China	2016	Km	CP022349 (244)
pK518_KPC	bla_{KPC-2}	FIA, FII(p14)	China	2017	Km	CP023186
pKPC2_020121	bla_{KPC-2}	FII(p14), FII(Yp)	China	2017	Kg	MH192342 (34)
pKPC-f607	bla_{KPC-2}	FII(pKP91)	USA	2015	Km	CP026272
pKPC-55bf	bla_{KPC-2}	FII(pKP91)	USA	2015	Km	CP026280
pKPC-727	bla_{KPC-2}	FII(pKP91), FII(Yp)	USA	2012	Km	CP008791
pKPC_CAV1099	bla_{KPC-2}	FII(S), FII(SARC14)	USA	2009	Ko	CP011595
pKPC_CAV1335	bla_{KPC-2}	FII(S), FII(SARC14)	USA	2010	Ko	CP011615
pKPC_UVA02	bla_{KPC-2}	FII(S), FII(SARC14)	USA	2007	Ko	CP017929 (313)
—	bla_{KPC-2}	FIIK/FIB	Poland	2008–2009	Ko	311
pKPC_CAV1374	bla_{KPC-2}	HI1A(NDM-CIT), HI1B(pNDM-CIT)	USA	2010	Km	CP011635
pKO13459-1_KPC2	bla_{KPC-2}	N (ST15)	Germany	2017	Km	VKMF01000347
pKO17045_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNC01000072
pKO16290_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKND01000090
pKO16162_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNM01000153
pKO14657_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNN01000158
pKO14641_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNO01000140
pKO13137_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNP01000116
pKO13048_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNQ01000128
pKO13047_KPC2	bla_{KPC-2}	N (ST15)	Germany	2014	Km	VKNR01000115
pKPC-8bc0	bla_{KPC-2}	N (ST6)	USA	2015	Km	CP026277
pKm38_N	bla_{KPC-2}	N (ST6)	USA	1997	Ko	KY128483
pKm58_N	bla_{KPC-2}	N (ST6)	USA	1997	Km	KY128484
—	bla_{KPC-2}	N	Germany	2016	Ko	302
(RK 171170-1)	bla_{KPC-2}	N	Germany	2016	Ko	302
(131SC04)	bla_{KPC-2}	N	Spain	2013	Ko	390
(YDC736-2)	bla_{KPC-2}	N	USA	2015	Km	190
(121SC72)	bla_{KPC-2}	P6	Spain	2012	Ko	390
(121SC85)	bla_{KPC-2}	P6	Spain	2012	Ko	390
(121SC07)	bla_{KPC-2}	P6	Spain	2012	Ko	390
p5-KPC	bla_{KPC-2}	P6	China	2013	Ko	KY913901 (119)
pKPC-cd17	bla_{KPC-2}	P6	Spain	2016–2017	Ko	CP026224 (96)
(KPN106)	bla_{KPC-2}	W	Brazil	2008	Ko	156
(131SC24)	bla_{KPC-2}	X3	Spain	2013	Ko	390
pLSCH-KOX18040	bla_{KPC-2}	NA	NA	NA	Ko	MN401418
(8-CAR)	bla_{KPC-2}, bla_{VIM-1}	N	Spain	2014	Ko	299
pCR14_3	bla_{KPC-3}	FIB	Spain	2016–2017	Ko	CP015395 (96)
pKMISG1	bla_{KPC-3}	FIB(pQil), FII(pKP91)	Switzerland	2017	Km	CM011641 (166)
unitig_2	bla_{KPC-3}	FII(p14)	NA	NA	Km	CP020359
(YD358)	bla_{KPC-3}	N	USA	2009	Km	190
p7121-IMP	bla_{IMP-1}	N (ST ua)	China	2014	Ko	KX784502 (395)
pKOI-34	bla_{IMP-34}	M	Japan	NA	Ko	AB715422 (394)
p4-IPM	bla_{IMP-4}	N (ST20)	China	2013	Ko	KY913900 (119)
pC52_003	bla_{IMP-4}	N (ST ua)	Australia	2014	Km	CP042548
pKOX7525_1	bla_{IMP-4}, bla_{NDM-1}	FIA(HI1), R	China	2020	Km	CP065475
(THC5)	bla_{IMP-6}	N	Japan	2011	Ko	124
pMRY14-187KOX_2	bla_{IMP-6}	N (ST5), R	Japan	2013	Ko	AP019199–AP019209 (396)
pMRY14-192KOX_2	bla_{IMP-6}	N (ST5), R	Japan	2013	Ko	AP019216–AP019229 (396)
pMRY14-247KOX_2	bla_{IMP-6}	N (ST5), R	Japan	2014	Ko	AP019274–AP019290 (396)
(8-CAR)	bla_{KPC-2}, bla_{VIM-1}	N	Spain	2014	Ko	299
(K310)	bla_{NDM}	X3	India	2011–2013	Ko	303
(K3682)	bla_{NDM}	X3	India	2011–2013	Ko	303
(K3739)	bla_{NDM}, bla_{VIM}	X3	India	2011–2013	Ko	303
(IR5344)	bla_{NDM-1}	A/C	China	2014	Ko	326
unnamed5 (K9455)	bla_{NDM-1}	A/C_2	Spain	2016–2017	Ko	CP029118 (96)
(AMA942)	bla_{NDM-1}	A/C_2	Denmark	2015	Ko	296
pK516_NDM1	bla_{NDM-1}	FIB(pB171), FII(Yp)	China	2016	Ko	CP022350 (244)
pK518_NDM1	bla_{NDM-1}	FIB(pB171), FII(Yp)	China	2017	Km	CP023187
pKOX_NDM1	bla_{NDM-1}	FIB(pB171), FII(Yp)	China: Taiwan	2010	Ko	JQ314407 (323, 393)

(Continued on next page)

TABLE 9 (Continued)

Plasmid[b]	Gene	Replicon type[c]	Country	Yr	Host species[d]	Accession no. and/or reference
pKOX_NDM	bla_{NDM-1}	FIB(pB171), FII(Yp)	Romania	2013	Km	MF042355
pNDM-TJ11	bla_{NDM-1}	FIB(pNDM-Mar), HI1B(pNDM-MAR)	NA	NA	Ko	MG845200
(A105R1B5)	bla_{NDM-1}	X3	South Africa	NA	Km	32
p3-NDM	bla_{NDM-1}	X3	China	2013	Ko	KY913899 (119)
pK516_NDM5	bla_{NDM-5}	X3	China	2016	Ko	CP022351 (244)
pK518_NDM5	bla_{NDM-5}	X3	China	2017	Km	CP023188
pKlox-45574cz	bla_{NDM-5}	X3	NA	NA	Ko	MG833406
pFDL-VIM	bla_{VIM-1}	A/C	Italy	2019	Ko	MN783744 (397)
pSE15-SA01028	bla_{VIM-1}	HI2	Spain	2016–2017	Ko	CP026661 (96)
pKp1050-3	bla_{VIM-1}	L	Spain	2016–2017	Ko	CP023419 (96)
pKOX105(K9534)	bla_{VIM-1}	N (ST7)	Spain	2016–2017	Ko	NC_014208 (96)
pKOX105	bla_{VIM-1}	N (ST7)	Italy	2008	Ko	HM126016 (319)
(E912)	bla_{VIM-1}	W	Greece	2007	Ko	398
—	bla_{VIM-4}	A/C	Italy	2013	Ko	121
—	bla_{OXA-48}	L	Tunisia	2013–2016	Ko	104
—	bla_{OXA-48}	L	Morocco	2010	Ko	120
p211DT2019_2	bla_{OXA-48}	L	NA	2019	Km	JACYGO010000003
pA6sk3_4	bla_{OXA-48}	L	NA	2019	Km	JACYGP010000006
—	bla_{OXA-48}	L	NA	NA	Ko	MK249860
pKp_Goe_414-5	bla_{OXA-48}	L	Spain	2016–2017	Ko	CP018342 (96)
pKp_Goe_588-2	bla_{OXA-48}	L	Spain	2016–2017	Ko	CP018694 (96)
pKPoxa-48N1	bla_{OXA-48}	L	Germany	2012	Ko	NC_021488 (331)

[a]NA, not available.
[b]Names in parentheses are host strains of unnamed plasmids. —, unnamed.
[c]The sequence type of IncN plasmids is shown in parentheses. ua, novel, unassigned ST in the pMLST scheme (https://cge.cbs.dtu.dk/services/pMLST/) for IncN plasmids.
[d]Kg, *K. grimontii*; Km, *K. michiganensis*; Ko, *K. oxytoca*.

These bla_{KPC-2}-carrying plasmids belong to various replicon types, including IncF, IncHI, IncN, IncP, IncW, and IncX. Among the plasmids, IncN appears to be particularly common and could be further assigned to plasmid sequence types using the plasmid multilocus sequence typing (pMLST) scheme (https://cge.cbs.dtu.dk/services/pMLST/). In particular, 9 ST15 IncN bla_{KPC-2}-carrying plasmids were identified in Germany in 2014 or 2017, but unfortunately, no epidemiological information is available for these plasmids to determine whether there was an outbreak due to plasmid-mediated carbapenem resistance. Four ST6 IncN bla_{KPC-2}-carrying plasmids were found in the United States in 1997 and 2015 (Table 9), while the remaining four IncN plasmids were reported in the United States in 2015 (190), Germany in 2016 (302), or Spain in 2013 (390), but their sequences are not available to determine the STs. A variety of IncF bla_{KPC-2}-carrying plasmids have also been seen in the complex (34, 244, 313), but it appears that no particular IncF plasmids dominate (Table 9). Other bla_{KPC-2}-carrying plasmids belong to IncHI1, IncP6 (96, 119, 390), IncW (156), or IncX3 (390). There were four bla_{KPC-3}-carrying plasmids of either IncF or IncN in the United States in 2009 (190), Spain in 2016 to 2017 (96), and Switzerland in 2017 (166). bla_{GES-5} was found on two IncQ plasmids, one of which (pJF707; accession no. KX946994) has also been found to be widespread across other species and genera of the *Enterobacteriaceae* in multiple hospitals in the United Kingdom (391).

Thirty-three plasmids carrying class B MBL genes in the *K. oxytoca* complex have been reported in the literature or have been deposited in NCBI (Table 9). In the complex, most bla_{NDM}-carrying plasmids belong to IncX3 (32, 119, 244, 303), which is well known to mediate the inter- and intraspecies transfer of bla_{NDM} genes in the *Enterobacteriaceae* (392). bla_{NDM}-carrying plasmids of IncA/C (96, 296, 326), IncF (244, 323, 393), or IncHI have also been reported in the complex. bla_{IMP}-carrying plasmids in the complex belong to IncF, IncHI, IncL/M (394), IncN (119, 124, 395, 396), and IncR (124, 396), with IncN plasmids being relatively common and generally also containing an additional IncR replicon. bla_{VIM}-carrying plasmids belong to IncA/C (121, 397), IncHI (96), IncL (96), IncN (96, 319), and IncW (398).

A total of 8 bla_{OXA-48}-carrying plasmids have been found in the complex (Table 9), all of which belong to IncL/M and were isolated in Europe (Germany and Spain) (96, 331) and North Africa (Morocco and Tunisia) (104, 120). No plasmid MLST scheme is available for IncL/M plasmids at present, and further analysis of

these IncL/M bla_{OXA-48}-carrying plasmids is warranted to investigate whether there is one or several common plasmids mediating the dissemination of bla_{OXA-48} across different geographic locations.

Plasmids Carrying *mcr* or Virulence Genes in the Complex

Among *mcr* genes identified in the complex, six plasmids, all of which carried *mcr-9*, have been found in the *K. oxytoca* complex and belong to either IncFIB(K) or IncHI (337, 338) (GenBank accession no. CP011596, CP011617, and CP017930), while an *mcr-1*-carrying plasmid has been identified in the complex but its plasmid replicon type is unknown (336). As for virulence, genes encoding tilivalline and tilimycin associated with AAHC are chromosomally located in the *K. oxytoca* complex.

CONCLUDING REMARKS

The *K. oxytoca* complex comprises 6 known species—*K. oxytoca*, *K. michiganensis*, *K. grimontii*, *K. huaxiensis*, *K. pasteurii*, *and K. spallanzanii*—and three new unnamed species. These species are closely related and are difficult, if not impossible, to differentiate on the basis of phenotypic characteristics. Precise species identification relies on genome sequencing and analysis. bla_{OXY} is characteristic of and omnipresent in the *K. oxytoca* complex. The gene can be assigned to 12 genotypes, i.e., bla_{OXY-1} to bla_{OXY-12}, the carriage of which corresponds to species designation within the complex. The *K. oxytoca* complex is part of the human commensal microflora in the skin, mouth, gut, and respiratory system and is also an important pathogen causing AAHC and a number of other infections, but it is much less prevalent than *K. pneumoniae*. Two cytotoxins, tilivalline and tilimycin, cause the pathological changes of AAHC. The *K. oxytoca* complex has also been responsible for many outbreaks of health care-associated infections worldwide, many of which likely stem from water sources, such as sinks and humidifiers. The clonal background of *K. oxytoca* clinical isolates remains poorly understood, but isolates of clonal complex 2 appear to be widely distributed and have been associated with carbapenem resistance and outbreaks. In the worldwide bacterial collection of SENTRY, the rates of nonsusceptibility of the 5,724 clinical isolates of the *K. oxytoca* complex to carbapenems, ceftriaxone, ciprofloxacin, colistin, and tigecycline were 1.8%, 12.5%, 7.1%, 0.8%, and 0.1%, respectively. The rates of nonsusceptibility to carbapenems and cephalosporins have increased during the past 7 years. In addition to the intrinsic bla_{OXY}, a number of genes encoding β-lactamases with various hydrolysis spectra, including the carbapenemases GES-5, GIM, IMP, KPC, NDM, OXA-48, and VIM and ESBLs such as a few CTX-M variants and several TEM and SHV variants, have been found in the complex. bla_{KPC-2} appears to be the most common carbapenemase gene and is mainly seen on IncN or IncF plasmids. The likelihood of being well adapted to health care environments, the flexibility to acquire antimicrobial resistance, and the presence of diverse virulence genes may help the *K. oxytoca* complex to become a major threat to human health. If not carefully monitored, it could easily go on to impose much greater challenges for therapy and infection control in the future, akin to those currently presented by *K. pneumoniae*.

There are a number of notable research gaps in our knowledge of the *K. oxytoca* complex. First, the three novel species of the *K. oxytoca* complex defined here by genome-based analysis warrant further investigation using phenotypic methods to establish their species status and to propose appropriate species names under the current code for prokaryotes (25). Second, the clinical significance of each species of the *K. oxytoca* complex, including the colonization incidence in patients, their prevalence as pathogens in various infections, and the disease spectrum, manifestation, severity, and prognosis, remains largely unknown. In other words, whether precise species identification within the *K. oxytoca* complex has implications for patient treatment and prognosis prediction as well as epidemiological surveillance and infection control is yet to be elucidated. Unless such clinical significance of each species has been demonstrated, we believe that the precise species identification within the *K. oxytoca* complex is required for research purposes but may not be necessary for routine clinical practice at present. Third, virulence factors crucial to the *K. oxytoca* complex causing infections other than AAHC are largely not understood. Fourth, the ability of the *K. oxytoca* complex to survive and persist in health care environments, in particular water-containing ones such as

sinks, needs to be fully characterized. Fifth, more surveillance of the antimicrobial susceptibility of the *K. oxytoca* complex clinical isolates in international or regional collections is required, in particular isolates from Africa, Asia, and South America, to provide a comprehensive view of the current status and changing trend of antimicrobial resistance. Sixth, the population structure and global epidemiology of the *K. oxytoca* complex isolates are understudied. Whether there are certain high-risk clones of the *K. oxytoca* complex mediating resistance to key antimicrobial agents, particularly carbapenems, across different geographic locations remains to be determined. Seventh, more studies of plasmids in the complex are needed to explore whether there are particular plasmids mediating the wide dissemination of important antimicrobial resistance genes, such as bla_{KPC-2}.

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We declare no conflict of interest.

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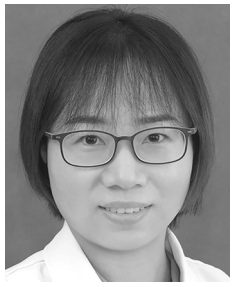
Jing Yang is a specialist in critical care medicine. She obtained her M.B.B.S. and Ph.D. from West China School of Medicine, Sichuan University (Chengdu, China). She received research training as a visiting fellow in the Department of Genetic Medicine, Weill Cornell Medical College (New York, USA) from 2013 to 2015. She completed her residency in critical care medicine and has been an intensivist at West China Hospital. Her research interests have been focused on the management of critically ill patients with serious infections, especially those caused by multidrug-resistant microorganisms. She started her postdoctoral training in Center of Infectious Disease in 2019 and is currently working on understanding the relationship between human gut microbiota and colonization/infection of carbapenem-resistant Gram-negative bacteria.



Haiyan Long is a physician and a postdoctoral fellow at West China Hospital, Sichuan University. She obtained her doctoral and master degrees from Sichuan University and her M.B.B.S. from Hebei Medical University, China. She received a Chinese government scholarship from the China Scholarship Council to study at the University of Birmingham, UK, as a joint Ph.D. student for one year. Her Ph.D. thesis was about the molecular epidemiology and dissemination mechanisms of carbapenem-resistant *Escherichia coli*, and she is currently interested in antiplasmid treatment and plasmid curing.

Ya Hu obtained her medical doctor's degree from Sichuan University in 2020 and her M.B.B.S. from Sichuan University in 2016. She was funded by China Scholarship Council in 2018 and proceeded with one year of training in the field of bioinformatics from the University of Birmingham. She has been working at the Center of Infectious Diseases, West China Hospital, Sichuan University, as a physician since September 2020. She has also been working as a postdoctoral fellow since November 2020, and her research interests are antimicrobial resistance mechanisms and drug resistance plasmids in *Enterobacteriaceae*.

Yu Feng has been working at Center of Infectious Diseases, West China Hospital of Sichuan University, as a research assistant since 2014, received four-year training in the fields of microbiology, genetics, and biochemistry from the University of Adelaide, Australia, and was awarded the Honours Degree of Bachelor of Science with First Class Honours at the end of 2013. As a researcher in the hospital, he is interested in dealing with clinical isolates, especially multidrug-resistant strains of the family *Enterobacteriaceae*, focusing on epidemiology status and resistance mechanisms. In addition, he has gained valuable and practical knowledge of bioinformatics from a variety of training programs as well as long-term working experience and is currently responsible for *in silico* works of the laboratory.

Alan McNally is Director of the Institute of Microbiology and Infection in the College of Medical and Dental Sciences at University of Birmingham. Dr. McNally studied for a B.Sc. in molecular microbiology at University of Glasgow before moving to University of Edinburgh to undertake a Ph.D. in virulence gene regulation. Postdoctoral positions at University of Bristol and then the Veterinary Laboratories Agency in Surrey, UK, followed, working on subjects including bacterial pathogenesis and avian influenza virus molecular epidemiology. This led to an academic position at Nottingham Trent University, first as a senior lecturer and then reader, where he developed his research expertise in microbial genomics and evolution. Dr. McNally moved to University of Birmingham in 2016 and was promoted to Director of the Institute of Microbiology in 2018. He now combines his background in classical microbiology with his expertise in genomics gained over the last 12 years to study the evolution of antimicrobial resistance.

Zhiyong Zong is a specialist in infectious diseases. He is Head of the Infection Control Department, Director of Center for Pathogen Research, and a professor at West China Hospital, Sichuan University (Chengdu, China). He obtained his medical M.B.B.S. degree from West China University for Medical Sciences (Chengdu, China) and completed his medical training at West China Hospital. He obtained his Ph.D. from the University of Sydney (Sydney, Australia). He received the Newtown Advanced Fellowship from the Royal Society (UK) and was an International Ambassador of the Society for Hospital Epidemiology of America (SHEA). His main research interests are the epidemiology and mechanisms of antimicrobial resistance in the *Enterobacteriaceae* and the prevention and control of multidrug-resistant organisms.