International Journal of Medical Microbiology 303 (2013) 305–317

Contents lists available at SciVerse ScienceDirect

International Journal of Medical Microbiology

journal homepage: www.elsevier.com/locate/ijmm

Mini review

CTX-M-type β-lactamases: A successful story of antibiotic resistance

Marco Maria D'Andrea[a], Fabio Arena[a], Lucia Pallecchi[a], Gian Maria Rossolini[a,b,c,*]

[a] Department of Medical Biotechnologies, University of Siena, 53100 Siena, Italy
[b] Department of Experimental and Clinical Medicine, University of Florence, Italy
[c] Clinical Microbiology and Virology Unit, Department of Laboratory Medicine, Careggi University Hospital, 50139 Florence, Italy

ARTICLE INFO

Keywords:
Antibiotic resistance
Gram-negative pathogens
Extended-spectrum β-lactamases
CTX-M
Epidemiology
Clinical impact

ABSTRACT

Production of extended-spectrum β-lactamases (ESBLs) is the principal mechanism of resistance to oxyimino-cephalosporins evolved by members of the family *Enterobacteriaceae*. Among the several ESBLs emerged among clinical pathogens, the CTX-M-type enzymes have proved the most successful in terms of promiscuity and diffusion in different epidemiological settings, where they have largely replaced and outnumbered other types of ESBLs. Originated by the capture and mobilization of chromosomal β-lactamase genes of strains of *Kluyvera* species, the bla_{CTX-M} genes have become associated with a variety of mobile genetic elements that have mediated rapid and efficient inter-replicon and cell-to-cell dissemination involving highly successful enterobacterial lineages (*e.g. Escherichia coli* ST131 and ST405, or *Klebsiella pneumoniae* CC11 and ST147) to yield high-risk multiresistant clones that have spread on a global scale. The CTX-Mβ-lactamase lineage exhibits a striking plasticity, with a large number of allelic variants belonging in several sublineages, which can be associated with functional heterogeneity of clinical relevance. This review article provides an update on CTX-M-type ESBLs, with focus on structural and functional diversity, epidemiology and clinical significance.

Introduction

The introduction of expanded-spectrum cephalosporins in clinical practice, in the early 1980s, represented a major breakthrough for the treatment of infections caused by *Enterobacteriaceae* and other Gram-negative pathogens. At the same time, the massive use of expanded-spectrum cephalosporins generated a selective pressure that was followed by the rapid emergence of new β-lactamases that were able to degrade and confer resistance to these compounds, named extended-spectrum β-lactamases (ESBLs).

Two major strategies of ESBL evolution have been exploited by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella enterica* and other members of the family *Enterobacteriaceae*: (i) the selection of mutants with expanded substrate specificity from the plasmid-mediated TEM- and SHV-type β-lactamases, that were already prevalent among *Enterobacteriaceae* since the 1970s; and (ii) the capture of novelβ-lactamase genes from the environmental metagenome, encoding enzymes that are naturally endowed with ESBL activity. Among the latter enzymes, the CTX-M type β-lactamases have proved by far the most successful in disseminating in the clinical setting and have overall become the most prevalent ESBLs worldwide.

A number of review articles on CTX-M-type β-lactamases have been published in recent years (Bonnet, 2004; Walther-Rasmussen and Hoiby, 2004; Canton and Coque, 2006; Rossolini et al., 2008; Naseer and Sundsfjord, 2011; Canton et al., 2012; Zhao and Hu, 2013). However, the epidemiology of CTX-M-type ESBLs is evolving rapidly, together with knowledge of their structural and functional properties, and clinical significance. The objective of this paper is to provide a concise update on CTX-M-type β-lactamases, with focus on aspects related with structural and functional diversity, epidemiology and clinical significance.

Diversity and origin of CTX-M-type β-lactamases

The CTX-M-type β-lactamases belong in a quite heterogeneous lineage of molecular class A active site-serine β-lactamases, which includes at least six sublineages or groups (CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, CTX-M-25 and KLUC, named after the archetypal enzymes of each group) that differ from each other by ≥10% amino acid residues (Fig. 1). Each group, in turn, includes a number of minor allelic variants which differ from each other by one or few amino acid substitutions (≤5% amino acid residues) (Fig. 1 and Table 1). Moreover, there are at least four CTX-M variants that exhibit a hybrid structure, namely CTX-M-45 (formerly Toho-2) which is a hybrid of CTX-M-14 with a protein of unknown origin,

* Corresponding author at: Department of Medical Biotechnologies, University of Siena, Policlinico Santa Maria alle Scotte, Viale Bracci, 53100 Siena, Italy.
Tel.: +39 0577 233455; fax: +39 0577 233870.
E-mail address: gianmaria.rossolini@unisi.it (G.M. Rossolini).

1438-4221/$ – see front matter © 2013 Elsevier GmbH. All rights reserved.
http://dx.doi.org/10.1016/j.ijmm.2013.02.008

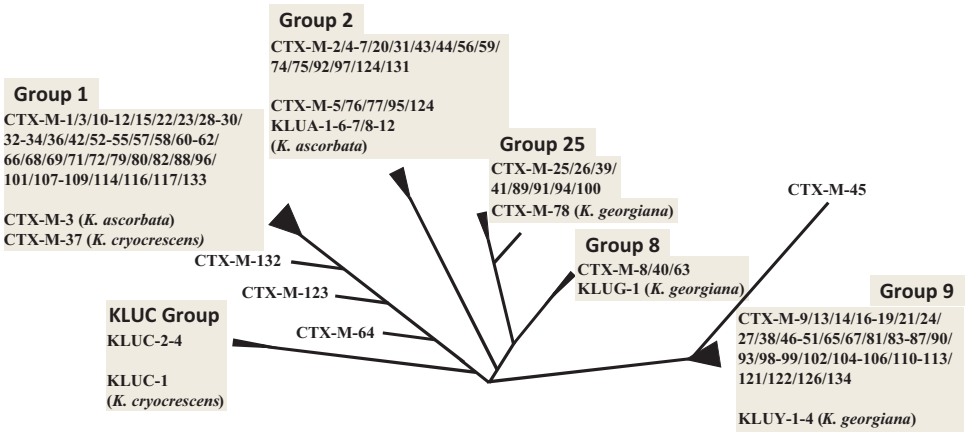

Fig. 1. Tree diagram showing the similarity among enzymes of the CTX-M lineage and clustering of members of different CTX-M groups. The tree was constructed with the TREEVIEW program (Page, 1996) on the basis of amino acid sequence alignment of available sequences of CTX-M enzymes and cognate proteins from *Kluyvera* spp. available at the Lahey Clinic Website (http://www.lahey.org/Studies/) or through the RED-DB database (http://www.fibim.unisi.it/REDDB/). Members of the major groups, along with the putative precursors from *Kluyvera* spp. are shaded in gray. The filled triangles at the end of some branches indicate the presence of minor allelic variants within the corresponding group (triangle sizes reflect the number of variants). CTX-M-18 is identical to CTX-M-14; CTX-M-57 is identical to CTX-M-55; CTX-M-133 is identical to CTX-M-3; CTX-M-44 corresponds to Toho-1; CTX-M-45 corresponds to Toho-2; UOE-1 corresponds to CTX-M-15; UOE-2 and Toho-3 correspond to CTX-M-14.

and CTX-M-64, CTX-M-123 and CTX-M-132 which are hybrids of CTX-M-15 with different segments of CTX-M-14 (Fig. 1). The majority of variants are found within the CTX-M groups 1 and 9 (Fig. 1 and Table 1), suggesting a higher plasticity for these groups. However, this could also reflect the overall higher prevalence of members of these groups (Canton et al., 2012; Zhao and Hu, 2013) that could have allowed a broader opportunity to evolve.

Unlike many acquired β-lactamases for which the original sources remains unknown, the source of bla_{CTX-M} genes has been identified in some species of genus *Kluyvera*, a member of the family *Enterobacteriaceae* that is rarely associated with human infections (Sarria et al., 2001). In fact, close homologs of acquired bla_{CTX-M} genes have been detected in the chromosome of strains of *Kluyvera cryocrescens* (genes encoding CTX-M variants of the CTX-M-1 and KLUC groups) (Decousser et al., 2001; Rodriguez, GenBank entry FN813246.1), *Kluyvera ascorbata* (genes encoding CTX-M variants of groups 1 and 2) (Humeniuk et al., 2002; Rodriguez et al., 2004), and *Kluyvera georgiana* (genes encoding CTX-M variants of groups 8, 9 and 25) (Poirel et al., 2002; Olson et al., 2005; Rodriguez et al., 2010) (Fig. 1).

Each CTX-M group is likely derived from one or more different *Kluyvera* strains, and the existence of several groups of transferable bla_{CTX-M} genes is consistent with a history of multiple gene capture events. Minor allelic variants within each group could reflect either different gene capture events or post-capture protein microevolution occurred in secondary hosts and likely influenced by the selective pressure encountered in clinical and veterinary settings. Finally, the CTX-M enzymes with hybrid structure are apparently derived from recombination events between genes of different groups or of different sources. In fact, co-existence of multiple CTX-M variants in the same host has been reported (Morosini et al., 2010; Sun et al., 2010) and could favor the emergence of such hybrid enzymes. The occurrence of at least three hybrids between CTX-M-15 and CTX-M-14 (*i.e.* CTX-M-64, CTX-M-123 and CTX-M-132) could depend on the high prevalence of these variants (Canton et al., 2012; Zhao and Hu, 2013).

Capture and dissemination mechanisms of bla_{CTX-M} genes

Acquired bla_{CTX-M} genes found in clinical isolates of *Enterobacteriaceae* are generally carried by conjugative plasmids (Carattoli, 2009, 2011; Zhao and Hu, 2013), although in some strains (mostly of *Proteus mirabilis* but occasionally also of other species) they were found integrated into the chromosome (Coque et al., 2008; Navon-Venezia et al., 2008; Fabre et al., 2009; Coelho et al., 2010; Song et al., 2011; Mahrouki et al., 2012).

Analysis of the genetic environment of acquired bla_{CTX-M} genes has revealed heterogeneous contexts. In most cases, acquired bla_{CTX-M} genes are associated with either IS*Ecp1* or IS*CR1*, two different insertion sequences (ISs) that are able to mobilize flanking DNA segments (Toleman et al., 2006; Poirel et al., 2005). These ISs were apparently involved in the capture of bla_{CTX-M} genes from the chromosome of *Kluyvera* spp. and in their transposition to plasmids, which for IS*Ecp1* was also demonstrated in an elegant experimental model (Lartigue et al., 2006). Acquired bla_{CTX-M} genes are usually flanked by additional regions derived from the chromosome of *Kluyvera* spp., the sizes of which may vary and can be a hallmark of different mobilization events (Canton et al., 2012). The ISs involved in the capture and mobilization of bla_{CTX-M} genes also provide strong promoters for high-level expression (Poirel et al., 2003; Di Conza et al., 2005), which is typical of the acquired genes (but not of the precursor genes found in the *Kluyvera* genomic context) and necessary to confer clinical resistance to the bacterial host. IS*Ecp1* was found associated with members of all CTX-M groups (Hopkins et al., 2006; Petrella et al., 2008; Zhao and Hu, 2013), being apparently the most relevant player in the capture and mobilization of bla_{CTX-M} genes. The extent of spacer sequences between IS*Ecp1* and the downstream bla_{CTX-M} gene can influence the level of gene expression and resistance (Ma et al., 2011). IS*CR1* was found associated with members of the CTX-M-2 and CTX-M-9 groups (Canton et al., 2012). Occasionally, also different genetic contexts have been reported: $bla_{CTX-M-8}$ was found associated with IS*10* (GenBank accession no. AF189721), while $bla_{CTX-M-10}$ was found associated with phage-related sequences (Oliver et al., 2001), suggesting the potential involvement of additional genetic elements in mobilization of these ESBL genes. Association of IS*Ecp1*-bla_{CTX-M} modules with additional ISs, such as IS*26*, has also been reported (Cullik et al., 2010; Zhao and Hu, 2013) and could further contribute to mobilization of bla_{CTX-M} genes and plasticity of the cognate genetic elements.

In fact, mobilization of bla_{CTX-M} genes has been very successful, leading to a rapid dispersal of these genes among virtually all major plasmid incompatibility groups circulating in *Enterobacteriaceae* (Carattoli, 2009, 2011; Partridge et al., 2011; Harada et al., 2012; Ho et al., 2012; Nakano et al., 2012; Zhao and Hu, 2013), of which some have played a major role in CTX-M dissemination through

Table 1
Polymorphisms in allelic variants of the five major CTX-M groups. Numbering of amino-acids is according to the first representative of each group (sequential numbering, upper row) or to the standard numbering scheme for class A beta-lactamases (ABL numbering, lower row). Dots indicate identical amino acids. Sequence references can be found in the Lahey Clinic Website (http://www.lahey.org/Studies/).

Group 1																														
Sequential numbering	16	23	27	31	39	42	60	70	77	80	92	98	109	117	122	126	143	161	167	170	177	237	241	242	264	272	277	278	279	289
ABL numbering	12	19	23	27	35	38	57	67	74	77	89	95	106	114	119	123	140	158	164	167	174	235	239	240	263	271	276	277	278	288
CTX-M-1	T	S	Y	A	E	R	Q	A	V	V	N	V	N	D	L	S	S	E	R	P	P	K	G	D	T	K	R	D	V	N
CTX-M-3/133	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-10	.	.	.	V	.	Q	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-11	.	.	.	.	G	.	.	.	.	A	.	.	.	N	P	.	A	.	.	.	.	.	.	.	.	.	.	H	.	-
CTX-M-12	A	.	.	.	.	.	.	.	.	A	S	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	I	D
CTX-M-15	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	D
CTX-M-22	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-23	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	A	.	.	T	.	.	.	.	.	.	.	.	.	.
CTX-M-28	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	.
CTX-M-29	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	.
CTX-M-30	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-32	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.
CTX-M-33	.	.	.	.	.	.	.	.	.	A	.	.	S	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	D
CTX-M-34	.	.	.	V	.	Q	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	C	.	.	.	.	.	.	D
CTX-M-36	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-37	.	.	H	.	.	Q	.	.	.	A	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-42	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	T	.	.	.	.	.	.	.	.	.	D
CTX-M-52	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	A	.	.	S	.	.	.	.	.	.	.	.	.	D
CTX-M-53	.	.	.	V	.	Q	.	.	.	.	.	.	.	N	.	.	A	.	.	.	.	.	.	G	I	.	.	.	.	D
CTX-M-54	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	Q	.	.	.	.	.	.	.	.	.	D
CTX-M-55/57	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	D
CTX-M-58	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.
CTX-M-60	A	.	.	.	.	.	.	.	.	.	S	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	I	D
CTX-M-61	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-62	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	S	.	.	.	.	.	.	.	.	.	D
CTX-M-66	.	N	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-68	.	.	H	V	.	.	.	.	.	A	.	.	.	N	.	.	A	D	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-69	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	N	.	.	.	.
CTX-M-71	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	C	G	.	.	.	.	.	D
CTX-M-72	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	G	.	.	.	.	.	.	.	.	.	.	D
CTX-M-79	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	.
CTX-M-80	.	.	.	V	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	D
CTX-M-82	.	.	.	.	.	.	.	P	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	D
CTX-M-88	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	H	.	.	D
CTX-M-96	A	.	.	.	.	.	.	.	.	A	S	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	I	D
CTX-M-101	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	I	A	.	.	.	.	.	.	G	.	.	.	.	.	D
CTX-M-107	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	.	R	.	G	.	.	.	.	.	-
CTX-M-108	.	.	.	.	.	.	.	.	.	A	.	A	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	-
CTX-M-109	.	.	.	.	.	.	R	.	.	A	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	K
CTX-M-114	.	.	.	.	.	.	.	.	A	.	.	.	.	N	.	.	A	.	.	.	.	.	.	G	.	.	.	.	.	D
CTX-M-116	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-117	.	.	.	.	.	.	.	.	.	A	.	.	.	N	.	.	A	.	.	.	Q	.	.	G	.	.	.	.	.	D

Table 1 (*continued*)

Group 2

Sequential numbering	7	18	30	38	52	64	83	92	101	102	124	128	162	170	174	208	225	228	231	233	242	251	255	275	279	289
ABL numbering	4	14	26	34	48	61	80	89	98	99	121	125	159	167	171	205	222	225	228	230	240	249	253	274	278	288
CTX-M-2	R	P	A	E	L	R	V	H	K	K	E	A	T	P	T	A	R	L	S	V	D	V	E	S	I	H
CTX-M-4	.	.	.	.	Q	V	.	.	R	A	.	G	.	.	S	.	.	M	.	G	.	.	.	.	.	.
CTX-M-5	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	A	.	V	.
CTX-M-6	.	.	.	.	.	L	.	.	.	A	.	G	.	.	S	.	.	.	C	.	.	.	.	.	V	.
CTX-M-7	.	.	.	.	.	V	.	.	R	A	Q	G	.	.	S	.	.	.	.	G	.	.	.	.	V	.
CTX-M-20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	.
CTX-M-31	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-43	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	R	.	.
CTX-M-44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.
CTX-M-56	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	N	.	.
CTX-M-59	.	.	.	.	.	.	.	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-74	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-75	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-76	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	V	.
CTX-M-77	.	.	T	K	.	.	.	.	.	.	.	.	.	.	.	.	Q	.	.	.	.	I	.	.	V	R
CTX-M-92	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.
CTX-M-95	.	.	T	.	.	.	L	.	.	.	.	.	.	.	.	.	Q	.	.	.	.	.	.	.	V	.
CTX-M-97	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-124	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	I	.	.	V	.
CTX-M-131	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.

Group 8

Sequential numbering	92	112	161	195	275
ABL numbering	89	109	158	192	274
CTX-M-8	K	T	N	N	S
CTX-M-40	N	A	D	H	.
CTX-M-63	N	A	D	H	N

Group 25

Sequential numbering	10	27	33	80	92	102	106	122	126	149	157	192	212	225	242	269
ABL numbering	6	23	29	77	89	99	103	119	123	146	154	189	209	222	240	268
CTX-M-25	M	C	V	V	G	P	I	F	S	D	T	A	M	Q	G	S
CTX-M-26	.	.	.	A	.	.	.	.	.	.	.	.	.	R	D	.
CTX-M-39	.	.	.	A	.	.	.	.	.	.	.	.	.	.	D	.
CTX-M-41	.	.	.	A	.	.	V	.	I	.	.	.	.	.	.	.
CTX-M-78	I	Y	I	A	D	S	.	L	.	G	V	T	T	.	D	P
CTX-M-91	.	.	.	.	.	.	.	.	.	.	.	S	.	.	D	.
CTX-M-94	.	.	.	A	.	.	.	L	.	.	.	.	.	.	.	.
CTX-M-100	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.

Table 1 (*continued*)

Group 9

Sequential numbering	6	13	14	16	26	31	33	46	51	56	60	80	85	86	101	109	111	112	114	122	126	135	148	157	170	172	208	212	223	234	237	242	275	277	289	291
ABL numbering	2	9	10	12	22	27	29	42	47	52	57	77	82	83	98	106	108	109	111	119	123	132	145	154	167	169	205	209	220	231	235	240	274	276	288	290
CTX-M-9	V	A	A	C	L	S	V	G	A	A	Q	A	K	Q	K	N	I	A	K	L	S	N	P	A	P	L	A	T	S	A	K	D	S	R	E	L
CTX-M-13	M	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-14/18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.
CTX-M-17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	K	.
CTX-M-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	V	.	.	.	.	.	.
CTX-M-21	.	G	G	G	F	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	R	.	.	.
CTX-M-27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	G	.	.	.	.
CTX-M-38	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	V	.	.	.	.	.	.
CTX-M-46	.	.	.	.	.	N	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-47	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-48	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-49	.	.	.	.	.	.	.	R	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-50	.	.	.	.	.	.	.	.	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-51	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CTX-M-65	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	R	.	.	.
CTX-M-67	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-81	.	.	.	.	.	.	.	.	.	.	.	.	E	.	Q	.	.	.	.	.	.	H	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-83	.	.	.	.	.	.	.	.	.	.	H	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-84	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.	V	.	.	.	.	.	.
CTX-M-85	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-86	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-87	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	L	.	.	.	.	V	.	.	.	.	.	.
CTX-M-90	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-93	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	.	.	.	V	.	G	.	.	.	.
CTX-M-98	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	G	.	.	.	.
CTX-M-99	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	V	.	.	R	.	.	.
CTX-M-102	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	V	.	G	.	.	.	.
CTX-M-104	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	N	.	.	.
CTX-M-105	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	V	.	G	.	.	.	.
CTX-M-106[a]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	R	.	.	H	.	-
CTX-M-110[b]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	N
CTX-M-111	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-112	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-113	.	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	.	.	.	.
CTX-M-121	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	V	.	G	.	.	.	.
CTX-M-122	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	S	.	.	.	.	.	V	.	.	R	.	.	.
CTX-M-126	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	V	.	.	.	.	.	.
CTX-M-134	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	S	.	.	.	.

[a] The available sequence of CTX-M-106 is partial (the last amino acid is not reported).

[b] The last amino acid (an L) of CTX-M-110, which is 292 amino acid-long, is not shown in the table.

Table 2
MICs of expanded-spectrum cephalosporins for *E. coli* strains producing some CTX-M variants. Data are from Novais et al. (2008) (for CTX-M-1 and CTX-M-3 variants), Delmas et al. (2006) (for CTX-M-9 variants), Djamdjian et al. (2011) (for CTX-M-27 variant), and Kimura et al. (2007) (for CTX-M-2 variant).

Enzyme	MIC (mg/L)		
	Cefotaxime	Cefepime	Ceftazidime
CTX-M-1 group			
CTX-M-3	256	32	1
CTX-M-15 (CTX-M-3/D240G)	128	1	2
CTX-M-62 (CTX-M-3/P167S)	1	0.50	32
CTX-M-3/A77V[a]	128	1.5	1
CTX-M-55/57 (CTX-M-3/A77V + D240G)	>256	4	2
CTX-M-52 (CTX-M-3/A77V + P167S)	4	0.25	32
CTX-M-3/N106S[a]	3	1.5	0.50
CTX-M-3/N106S + P167S[a]	3	1.5	32
CTX-M-33 (CTX-M-3/N106S + D240G)	>256	8	2
CTX-M-1	>256	128	4
CTX-M-32 (CTX-M-1/D240G)	256	4	2
CTX-M-1/P167S[a]	16	4	256
CTX-M-58 (CTX-M-1/P167T)	16	4	256
CTX-M-9 group			
CTX-M-9	16	2	1
CTX-M-16 (CTX-M-9/D240G)	16	2	8
CTX-M-9/P167S[a]	0.5	0.12	8
CTX-M-9/P167S + N106S[a]	0.5	0.12	8
CTX-M-9/L169Q[a]	0.5	0.06	8
CTX-M-27	32	0.50	1.5
CTX-M-93 (CTX-M-27/L169Q)	1	0.12	8
CTX-M-2 group			
CTX-M-2	8	ND	1
CTX-M-2/P167S[a]	2	ND	32

[a] Laboratory mutant.

plasmid epidemics. Typical examples are the pandemic dissemination of CTX-M-15 favored by IncFII plasmids (Coque et al., 2008; Partridge et al., 2011), the dissemination of CTX-M-3 in Poland and other Easter European countries contributed by IncN plasmids (Baraniak et al., 2002), the dissemination of CTX-M-65 in China through F33:A-:B-type plasmids (He et al., 2013), and the dissemination of CTX-M-14 plasmids in Spain and United Kingdom through IncK plasmids (Valverde et al., 2009; Cottell et al., 2011; Dhanji et al., 2012; Stokes et al., 2012).

On the other hand, the association of CTX-M-encoding plasmids with highly successful virulent clonal lineages of *E. coli* and *K. pneumonia* has generated a number of the so-called "high-risk" multiresistant and virulent clones (Woodford et al., 2011) that have further contributed to the rapid and global dissemination of CTX-M-type ESBLs. The most paradigmatic examples are represented by the pandemic *E. coli* ST131 clone (phylogenetic group B2), which has greatly contributed to the global dissemination of CTX-M-15 (Rogers et al., 2011), and by *E. coli* clones of clonal complexes STC405 and STC38 (phylogenetic group D) which have been associated with the dispersal of both CTX-M-15 and CTX-M-9 group enzymes (mainly CTX-M-9 and CTX-M-14), respectively (Naseer and Sundsfjord, 2011). In addition, *E. coli* ST10 (phylogenetic group A), which is a typical member of the human gut microbiota but also responsible for intestinal and exta-intestinal infections, was recently associated with dissemination of various CTX-M groups (CTX-M-1, CTX-M-2 and CTX-M-9 groups) (Oteo et al., 2009a; Valverde et al., 2009; Okeke et al., 2010; Fam et al., 2011; Bartoloni et al., 2012; Ben Sallem et al., 2012; Peirano et al., 2012; Reuland et al., 2012; Izdebski et al., 2013). With *K. pneumoniae*, strains of CC11 have been associated with dissemination of CTX-M-15 and CTX-M-14 in various settings (Damjanova et al., 2008; Oteo et al., 2009b; Ko et al., 2010; Lee et al., 2011).

Acquired CTX-M-type β-lactamases have emerged and mostly been reported in *Enterobacteriaceae*. *E. coli* and *K. pneumoniae* are the most common hosts, but CTX-M-type enzymes have also been detected in many other enterobacterial species including *Salmonella enterica*, *Shigella* spp., *Klebsiella oxytoca*, *Enterobacter* spp., *Pantoea agglomerans*, *Citrobacter* spp., *Serratia marcescens*, *P. mirabilis*, *Morganella morganii* and *Providencia* spp. (Zhao and Hu, 2013).

Acquired CTX-M-type ESBLs have been occasionally reported also in non-enterobacterial species including *Pseudomonas aeruginosa* (mostly CTX-M-2 or variants thereof, in Latin America) (Celenza et al., 2006; Picao et al., 2009; Ingold et al., 2011; Polotto et al., 2012), *Acinetobacter* spp. (mostly CTX-M-15, in different regions) (Nagano et al., 2004; Shakil and Khan, 2010; Potron et al., 2011; Manageiro et al., 2012), *Vibrio cholerae* (CTX-M-2, in Latin America) (Petroni et al., 2002), *Vibrio fluvialis* (CTX-M-3, in India) (Chowdhury et al., 2011), *Aeromonas* spp. (CTX-M-3 and CTX-M-15) (Ye et al., 2010; Gomez-Garces et al., 2011), and *Stenotrophomonas maltophilia* (CTX-M-1 in an isolate from a cystic fibrosis patient in the Netherlands) (al Naiemi et al., 2006). Altogether, these findings underscore the possibility of transmission of bla_{CTX-M} genes to non-*Enterobacteriaceae*. However, most cases were sporadic with no significant trends to cross-transmission and spreading, suggesting that non-*Enterobacteriaceae* are poorly conducive to dissemination of bla_{CTX-M} genes.

Functional properties of CTX-M-type β-lactamases and contribution to β-lactam resistance

The CTX-M-type β-lactamases derive their name from the potent cefotaximase activity, which is a functional hallmark of these enzymes. This feature depends on a peculiar electrostatic environment and flexibility of the catalytic pocket, in combination with other structural elements (*e.g.* the conserved Arg276 residue, which acts as a mobile electrostatic arm tracking cefotaxime toward the binding site), that allow an efficient recognition and hydrolysis of the bulky cefotaxime molecule with catalytic efficiencies that are comparable to those for penicillins and narrow-spectrum cephalosporins (Ibuka et al., 2003; Bonnet, 2004; Chen et al., 2005, 2007; Delmas et al., 2010).

Concerning other expanded-spectrum cephalosporins, cefepime is an overall good substrate while the bulkier ceftazidime molecule is poorly recognized and behaves as a poor substrate (Bonnet, 2004). However, the emergence of CTX-M-type variants with increased ceftazidimase activity, likely selected by the use of ceftazidime in clinical practice, has been observed. These variants carry specific amino acid substitutions that improve recognition of ceftadizime, of which the most common are D240G and P167S/T. The D240G substitution would be responsible for an increased mobility of the B3 β-strand and flexibility of the catalytic pocket, allowing a better accommodation for the bulkier ceftazidime molecule (Chen et al., 2005; Delmas et al., 2008), while P167S, located in the Ω loop, would influence the mode of interaction of β-lactams with the binding site (Kimura et al., 2004). The role of these changes has also been confirmed by *in vitro* evolution and site-directed mutagenesis studies with enzymes of various CTX-M groups (Delmas et al., 2006; Kimura et al., 2007; Novais et al., 2008). In these variants, the increase in catalytic efficiency toward ceftazidime is usually sufficient to increase the ceftazidime MIC of the bacterial host above the clinical breakpoint for resistance. The above amino acid substitutions leading to increased ceftazidimase activity, however, may be associated with a trade-off in activity for cefotaxime and/or cefepime, while a combination of the two substitutions was shown to be overall detrimental to the enzyme activity (Table 2). On the other hand, a combination of D240G with L169Q (another substitution in the Ω loop region) was shown to be detrimental to cefotaximase activity but to further enhance ceftazidimase activity in a CTX-M-9-like background (Djamdjian et al., 2011) (Table 2). The antagonistic pleiotropic effect of the D240G and P167S substitutions can be partially suppressed by additional amino acid substitutions, such as A77V and N106S, which in some cases can restore higher-level cefotaxime resistance in the P167S and D240G variants, respectively (Table 2).

The CTX-M-type enzymes are susceptible to conventional β-lactamase inhibitors (*e.g.* clavulanate and tazobactam), and also to the new non β-lactam-derived β-lactamase inhibitor avibactam (Livermore et al., 2008; Lagace-Wiens et al., 2011). Thus far, natural inhibitor-resistant variants of CTX-M-type enzymes have not been reported. However, *in vitro* evolution studies with representatives of various CTX-M groups have shown that evolution of resistance to conventional inhibitors is possible following at least three types of amino acid substitutions (S130G, K234R, S237G), with S130G being the most frequently recovered and providing the highest level of resistance. However, these changes (and especially S130G) were associated with a notable reduction of activity against cephalosporins, and this antagonistic pleiotropy could explain the delayed emergence of similar mutants in the clinical setting (Ripoll et al., 2011). Random mutagenesis experiments with CTX-M-1 have revealed additional amino acid substitutions (V103D and V260L) associated with an inhibitor-resistant phenotype, that were similarly associated with antagonistic pleiotropy for cephalosporin hydrolysis (Perez-Llarena et al., 2011).

Carbapenems are overall stable to CTX-M-type enzymes. However, overexpression of some CTX-Ms (*e.g.* CTX-M-15) in combination with decreased outer membrane permeability can be responsible for decreased susceptibility or resistance to carbapenems in *K. pneumonia* and other enterobacterial species (Elliott et al., 2006; Doumith et al., 2009; Girlich et al., 2009; Leavitt et al., 2009; Bennett et al., 2010; Adler et al., 2013).

CTX-M-producers may exhibit different resistance phenotypes. Resistance to cefotaxime reversible by inhibitors along with susceptibility to ceftazidime in an isolate of *E. coli* or *K. pneumoniae* is highly suggestive (although not specific) for production of a CTX-M-type ESBL. On the other hand, CTX-M production cannot be excluded in case of resistance to ceftazidime and/or resistance to inhibitors, given the occurrence of CTX-M variants with increased ceftazidimase activity and the possibility of production of additional β-lactamases (*e.g.* OXA-1 or carbapenemases) by the same strain (Livermore, 2012). In fact, co-production of CTX-M-type ESBLs with various carbapenemases including VIM-1 (Miro et al., 2010), KPC-2 (Chen et al., 2011), OXA-48 (Cuzon et al., 2011; Pitart et al., 2011) and NDM-1 (Poirel et al., 2011) has been reported as bacterial strategy to enhance antibiotic resistance.

Epidemiology of CTX-M-producers and clinical impact

Since the first sporadic reports in the late 1980s from Japan, Europe and South America (Matsumoto et al., 1988; Bauernfeind et al., 1990, 1992), the CTX-M-type ESBLs have experienced a global diffusion, outnumbering and partially replacing the TEM- and SHV-type ESBLs, and becoming overall the most prevalent type of ESBL. For a comprehensive picture of the penetration and globalization of CTX-M-type enzymes occurred during the past two decades the reader may refer to the recent review article by Canton et al. (2012). Indeed, diffusion of CTX-M-type ESBLs has been very efficient and not limited to health-care settings, but has also involved the community, livestock and companion animals (Ewers et al., 2012), wildlife (Guenther et al., 2011), and river waters (Chen et al., 2010; Dhanji et al., 2011; Chouchani et al., 2012; Tacao et al., 2012).

Although CTX-M-type ESBLs have been detected in several Gram-negative pathogens, the major clinical burden is due to CTX-M-producing *E. coli* and *K. pneumoniae* (the latter mostly in nosocomial settings) (Pitout and Laupland, 2008; Oteo et al., 2010).

CTX-M-producers have been reported as the most prevalent ESBL producers in community-onset urinary tract infections (UTI) in several settings (see for instance Pitout et al., 2004; Rodriguez-Bano et al., 2004; Woodford et al., 2007; Smet et al., 2010; Doi et al., 2012). The high-risk *E. coli* clone ST131 producing CTX-M-15, particularly, has emerged as a serious cause of community-onset multidrug resistant UTI worldwide (Rogers et al., 2011), and these infections seem to occur, more than in the past, among patients without discernible heath care-associated risk factors (Doi et al., 2012). The explanation of this success is still unclear, being possibly related with enhanced fitness for colonization and transmission, and for further steps involved in pathogenesis (Johnson et al., 2012; Vimont et al., 2012). The fact that the resistance profile of CTX-M-producing ST131 *E. coli* isolates often extends to fluoroquinolones and trimethoprim-sulphamethoxazole (Rogers et al., 2011) (which are the most popular oral treatments for community-onset UTI) has important clinical implications: under these circumstances the oral options remain fosfomycin and nitrofurantoin, that retain efficacy against a high percentage of isolates (Prakash et al., 2009).

CTX-M-producing *E. coli* are also an important cause of community-onset bloodstream infections (BSI), that are often secondary to an UTI (Rodriguez-Bano et al., 2006; Pitout and Laupland, 2008). A higher propensity for urinary sepsis above other sites of infection by ST131 *vs.* non-ST131 ESBL-producing *E. coli* has been reported (Pitout et al., 2009) and has obvious implications for the choice of empirical antibiotic therapy, which may be critical in preventing progression to bacteremia. Studies on BSI caused by CTX-M-producers have revealed mortality rates around 20–30%, with common risk factors including diabetes, recent history of urinary tract infections/renal diseases, and recent use of antibiotics (mostly fluoroquinolones) (Table 3). Concerning treatment issues, better survival rates are consistently associated with carbapenem use (Rodriguez-Bano et al., 2006; Chaubey et al., 2010; Park et al., 2012), while outcome in patients treated with beta-lactam/beta-lactamase inhibitor combinations or cephalosporins are less consistent and often conflicting (Bin et al., 2006; Rodriguez-Bano et al., 2006; Chaubey et al., 2010). This issue has earned more

Table 3
Selection of studies reporting risk factors and outcomes of BSI caused by *E. coli* producing ESBLs, mostly of CTX-M-type.

Study design[a]	Country	No. of cases	Risk factors	Mortality	Year	References
HCA and CA BSI (70% CTX-M-type)	Spain	43	Diabetes, malignancy, urinary tract catheter, recent antibiotic exposure	20% (14-day)	2001–2005	Rodriguez-Bano et al. (2006)
BSI (69% CTX-M type)	Taiwan	60	Chronic renal failure, ICU stay	22% (14-day)	2005–2007	Wu et al. (2011)
HCA and CA BSI (90% CTX-M type)	Canada	72	Diabetes, malignancy, renal disease	22% (case fatality rate)	2006–2007	Chaubey et al. (2010)
BSI in patients with hematologic malignancies (84% CTX-M type)	Mexico	100	Diabetes, recent antibiotic exposure	34% (60-day)	2004–2009	Cornejo-Juarez et al. (2012)
HCA and CA BSI (72% CTX-M type)	USA	300	Diabetes, urinary catheter, recent hospitalization or antibiotic exposure	11% (28-day)[b]	2008–2010	Park et al. (2012)
HCA and CA BSI by ST-131*E. coli* (72% CTX-M type)	Taiwan	36	Urinary tract infections, fluoroquinolone exposure	22% (14-day) 25% (28-day)	2005–2010	Chung et al. (2012)

[a] HCA, health care-associated; CA, community-associated.
[b] Mortality data were available for 144 patients.

relevance since 2010, when both Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have given indications for reporting susceptibility data of ESBL-producing *Enterobacteriaceae* according to MIC values, regardless of ESBL production. In fact, a significant proportion of CTX-M-producing isolates are now categorized as susceptible to ceftazidime and cefepime (Wang et al., 2011; Williamson et al., 2012).

Colonization of the gastrointestinal tract represents a key factor in the clinical impact and epidemiology of CTX-M-producing enterobacteria. Indeed, most cases of infections caused by CTX-M-producers are preceded by colonization of the gut (Ben-Ami et al., 2006), and carriers are the main source of CTX-M-producers in health-care settings as well as an important vehicle for dissemination in the community (Canton and Coque, 2006) and for global dissemination *via* international travelers (van der Bij and Pitout, 2012).

Since the beginning of the CTX-M pandemic, a number of studies have been performed on the prevalence of fecal carriage of CTX-M-producing enterobacteria among healthy individuals in the community. Although heterogeneous by inclusion criteria and microbiological procedures, those studies overall revealed the presence of an important communitary reservoir of CTX-M-producing enterobacteria. The most recent studies report proportions of fecal carriage of CTX-M-producers ranging from 5 to 12% in the population of various geographical settings (Europe, Asia, America), with remarkably higher rates in some areas (Table 4). Evolution of the prevalence of fecal carriage of CTX-M-producing enterobacteria in the same community settings has also been investigated in a few cases. A 10-fold increase in the rate of healthy carriers of ESBL-producing *E. coli* has recently been reported among individuals attending a check-up center in France over a 5-year period (0.6% in 2006 *vs.* 6% in 2011), which was found to be mainly contributed by the emergence of CTX-M-type determinants (0% in 2006 *vs.* 5.2% in 2011) (Nicolas-Chanoine et al., 2012). A remarkable and relentless increasing trend in the fecal carriage of CTX-M-producers was also observed, over the last two decades, in healthy children living in small urban areas of Bolivia (0% in 1992 *vs.* 0.1% in 2002 *vs.* 1.6% in 2005 *vs.* 12% in 2011) (Pallecchi et al., 2004, 2007; Bartoloni et al., 2012). In the latter setting, a radical change in the dominant CTX-M groups was also observed, with CTX-M-2 group, responsible for the emergence and early dissemination of CTX-M-type ESBLs in the studied area, being largely replaced by CTX-M-1 and CTX-M-9 groups. A similar epidemiological evolution has recently been observed also in clinical isolates of *Enterobacteriaceae* from various South American countries where, although CTX-M-2 group remains endemic, the emergence of new CTX-M groups (mainly CTX-M-1 and CTX-M-9) has been documented (Cergole-Novella et al., 2010; Garcia-Fulgueiras et al., 2011; Peirano et al., 2011; Ruiz et al., 2011; Tollentino et al., 2011; Redondo et al., 2012; Sennati et al., 2012). Altogether, these findings emphasize the importance of the community reservoir in the evolution dynamics of CTX-M-producing pathogens.

Some studies have investigated the dissemination of CTX-M-producers within households, demonstrating overall high transmission rates (Rodriguez-Bano et al., 2008; Valverde et al., 2008; Lo et al., 2010; Tande et al., 2010; Hilty et al., 2012). In particular, being a relative or household member of a patient with a urinary tract infection caused by an ESBL-producer (of CTX-M- or SHV-type) was found to be associated with an increased risk of being a carrier, while person-to-person transmission or acquisition from a common source (possibly related with the food chain) might contribute to intra-familiar dissemination of ESBL determinants (Rodriguez-Bano et al., 2008).

The importance of the food chain for the dissemination of CTX-M-producing *Enterobacteriaceae* among the general population has been demonstrated by the detection of the same CTX-M-producing strains in diners and food-handlers (Lavilla et al., 2008). The recent report of a large food-borne nosocomial outbreak due to a CTX-M-15-producing *Klebsiella pneumoniae* (Calbo et al., 2011) further emphasizes the importance of the food chain in dissemination of similar pathogens and of establishing food control programs to detect their presence.

Diagnostic issues

Diagnosis of CTX-M-producers may be relevant to molecular epidemiology and infection control. While CTX-M production can be suspected in ESBL producers that exhibit certain resistance profiles (see above), molecular analysis is needed to confirm the presence of a CTX-M-type determinant. Diversity of $bla_{\text{CTX-M}}$ genes complicates molecular detection, and various strategies have been proposed, based on multiplex PCR (Woodford et al., 2006; Naas et al., 2007; Pitout et al., 2007; Dallenne et al., 2010) or on diagnostic microarrays (Batchelor et al., 2008; Endimiani et al., 2010; Naas et al., 2010). Unambiguous confirmation of the allelic variant or identification of a new variant requires sequencing of the entire coding sequence.

Table 4
Selection of studies on the prevalence of healthy carriers of CTX-M-producing *Enterobacteriaceae* in community settings.

Country (location)	Year	Studied individuals	Species	Prevalence of carriers	CTX-M groups, relative rates [variants]				References
					1	2	8	9	
France	2011	Attending a free check-up visit ($n = 345$)	*E. coli*	5.2%	74% [1,15]	5% [2]		21% [14]	Nicolas-Chanoine et al. (2012)
Spain	2003	Volunteers ($n = 108$)	*Enterobacteriaceae*	1.9%		50% [2-like]		50% [14]	Valverde et al. (2004)
Spain	2007	Volunteers ($n = 105$)	*E. coli*	5.7%	50% [1,32]		17% [8]	33% [14]	Vinue et al. (2009)
Switzerland	2010	Staff of meat-processing companies ($n = 586$)	*Enterobacteriaceae*	5.6%	73% [1,15]	6% [2]		21% [14]	Geser et al. (2012)
Bolivia	2011	Children ($n = 482$)	*E. coli*	12%	42% [3,15]	4% [2]	12% [8]	42% [14,65]	Bartoloni et al. (2012)
French Guyana	2006	Volunteers ($n = 163$)	*E. coli*	7%		92% [2]	8% [8]		Woerther et al. (2010)
Japan	2009–2010	Volunteers ($n = 218$)	*Enterobacteriaceae*	6%	15% [3,15]	31% [2]	15% [8]	39% [14]	Luvsansharav et al. (2011)
Thailand	2010	Volunteers ($n = 417$)	*Enterobacteriaceae*	66%	39%		1%	60%	Luvsansharav et al. (2012)
Thailand	2008	Volunteers ($n = 160$)	*Enterobacteriaceae*	51%	11%	ND	ND	87%	Sasaki et al. (2010)
Lebanon	2003	University students ($n = 382$)	*Enterobacteriaceae*	1.8%	100% [15]				Moubareck et al. (2005)
Tunisia	2009–2010	Volunteers ($n = 150$)	*E. coli*	6.6%	100% [1]				Ben Sallem et al. (2012)
Senegal	NR[a]	Children ($n = 20$)	*E. coli*	10%	100% [15]				Ruppe et al. (2009)
Cameroon	2009	University students ($n = 150$)	*Enterobacteriaceae*	6.7%	100% [15]				Lonchel et al. (2012)

[a] Not reported.

Conclusions

The rapid and extensive dissemination of CTX-M-type ESBLs in clinical and veterinary settings, but also among commensal bacteria of humans and animals and in the environment, is one of the most successful histories of microbial drug resistance observed in the antibiotic era. This success likely depend on the combination of various factors including efficient capture and dispersal of $bla_{CTX\text{-}M}$ gene by mobile genetic elements, association of these elements with highly successful bacterial clones, low fitness cost imposed by CTX-M production, high selective pressure generated by the massive use of expanded-spectrum cephalosporins and fluoroquinolones (which can co-select CTX-M-producing strains that are often resistant also to these drugs) in clinical and veterinary settings. Indeed, the CTX-M pandemic has provided a major contribution to the rapid increase of resistance to expanded-spectrum cephalosporins among *Enterobacetriaceae* worldwide, which has been in turn a major driver for carbapenem usage and, consequently, for the recent emergence of carbapenem resistance among *Enterobacteriaceae*. As such, CTX-M-type β-lactamases should be regarded as a major target for surveillance, infection control and fundamental investigation in the field of microbial drug resistance.

Acknowledgements

Research on antibiotic resistance mechanisms in the Laboratories of the Authors has been funded by Grants from the European Commission (TROCAR contractHEALTH-F3-2008-223031; TEMPOtest-QC contract HEALTH-2009-241742; EvoTAR contract LSHM-2011-282004), and from the Italian Ministry of University and Research (PRIN 2009, protocol no. 200929YFMK_004).

References

Adler, M., Anjum, M., Andersson, D.I., Sandegren, L., 2013. Influence of acquired β-lactamases on the evolution of spontaneous carbapenem resistance in *Escherichia coli*. J. Antimicrob. Chemother. 68, 51–59.

al Naiemi, N., Duim, B., Bart, A., 2006. A CTX-M extended-spectrum β-lactamase in *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. J. Med. Microbiol. 55, 1607–1608.

Baraniak, A., Fiett, J., Sulikowska, A., Hryniewicz, W., Gniadkowski, M., 2002. Countrywide spread of CTX-M-3 extended-spectrum β-lactamase-producing microorganisms of the family *Enterobacteriaceae* in Poland. Antimicrob. Agents Chemother. 46, 151–159.

Bartoloni, A., Pallecchi, L., Riccobono, E., Mantella, A., Di Magnelli, D., Maggio, T., Villagran, A.L., Lara, Y., Saavedra, C., Strohmeyer, M., Bartalesi, F., Trigoso, C., Rossolini, G.M., 2012. Relentless increase of resistance to fluoroquinolones and expanded-spectrum cephalosporins in *Escherichia coli*: 20 years of surveillance in resource-limited settings from Latin America. Clin. Microbiol. Infect., http://dx.doi.org/10.1111/j.1469-0691.2012.03807.x.

Batchelor, M., Hopkins, K.L., Liebana, E., Slickers, P., Ehricht, R., Mafura, M., Aarestrup, F., Mevius, D., Clifton-Hadley, F.A., Woodward, M.J., Davies, R.H., Threlfall, E.J., Anjum, M.F., 2008. Development of a miniaturised microarray-based assay for the rapid identification of antimicrobial resistance genes in Gram-negative bacteria. Int. J. Antimicrob. Agents 31, 440–451.

Bauernfeind, A., Grimm, H., Schweighart, S., 1990. A new plasmidic cefotaximase in a clinical isolate of *Escherichia coli*. Infection 18, 294–298.

Bauernfeind, A., Casellas, J.M., Goldberg, M., Holley, M., Jungwirth, R., Mangold, P., Rohnisch, T., Schweighart, S., Wilhelm, R., 1992. A new plasmidic cefotaximase from patients infected with *Salmonella typhimurium*. Infection 20, 158–163.

Ben-Ami, R., Schwaber, M.J., Navon-Venezia, S., Schwartz, D., Giladi, M., Chmelnitsky, I., Leavitt, A., Carmeli, Y., 2006. Influx of extended-spectrum β-lactamase-producing enterobacteriaceae into the hospital. Clin. Infect. Dis. 42, 925–934.

Ben Sallem, R., Ben Slama, K., Estepa, V., Jouini, A., Gharsa, H., Klibi, N., Saenz, Y., Ruiz-Larrea, F., Boudabous, A., Torres, C., 2012. Prevalence and characterisation of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* isolates in healthy volunteers in Tunisia. Eur. J. Clin. Microbiol. Infect. Dis. 31, 1511–1516.

Bennett, J.W., Mende, K., Herrera, M.L., Yu, X., Lewis, J.S., Wickes, B.L., Jorgensen, J.H., Murray, C.K., 2010. Mechanisms of carbapenem resistance among a collection of *Enterobacteriaceae* clinical isolates in a Texas city. Diagn. Microbiol. Infect. Dis. 66, 445–448.

Bin, C., Hui, W., Renyuan, Z., Yongzhong, N., Xiuli, X., Yingchun, X., Yuanjue, Z., Minjun, C., 2006. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamase-producing *Escherichia coli*. Diagn. Microbiol. Infect. Dis. 56, 351–357.

Bonnet, R., 2004. Growing group of extended-spectrum β-lactamases: the CTX-M enzymes. Antimicrob. Agents Chemother. 48, 1–14.

Calbo, E., Freixas, N., Xercavins, M., Riera, M., Nicolas, C., Monistrol, O., Sole Mdel, M., Sala, M.R., Vila, J., Garau, J., 2011. Foodborne nosocomial outbreak of SHV1 and CTX-M-15-producing *Klebsiella pneumoniae*: epidemiology and control. Clin. Infect. Dis. 52, 743–749.

Canton, R., Coque, T.M., 2006. The CTX-M β-lactamase pandemic. Curr. Opin. Microbiol. 9, 466–475.

Canton, R., Gonzalez-Alba, J.M., Galan, J.C., 2012. CTX-M enzymes: origin and diffusion. Front. Microbiol. 3, 110.

Carattoli, A., 2009. Resistance plasmid families in *Enterobacteriaceae*. Antimicrob. Agents Chemother. 53, 2227–2238.

Carattoli, A., 2011. Plasmids in Gram negatives: molecular typing of resistance plasmids. Int. J. Med. Microbiol. 301, 654–658.

Celenza, G., Pellegrini, C., Caccamo, M., Segatore, B., Amicosante, G., Perilli, M., 2006. Spread of bla_{CTX-M}-type and bla_{PER-2} β-lactamase genes in clinical isolates from Bolivian hospitals. J. Antimicrob. Chemother. 57, 975–978.

Cergole-Novella, M.C., Guth, B.E., Castanheira, M., Carmo, M.S., Pignatari, A.C., 2010. First description of $bla_{CTX-M-14}$- and $bla_{CTX-M-15}$-producing *Escherichia coli* isolates in Brazil. Microb. Drug Resist. 16, 177–184.

Chaubey, V.P., Pitout, J.D., Dalton, B., Ross, T., Church, D.L., Gregson, D.B., Laupland, K.B., 2010. Clinical outcome of empiric antimicrobial therapy of bacteremia due to extended-spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*. BMC Res. Notes 3, 116.

Chen, H., Shu, W., Chang, X., Chen, J.A., Guo, Y., Tan, Y., 2010. The profile of antibiotics resistance and integrons of extended-spectrum β-lactamase producing thermotolerant coliforms isolated from the Yangtze River basin in Chongqing. Environ. Pollut. 158, 2459–2464.

Chen, S., Hu, F., Xu, X., Liu, Y., Wu, W., Zhu, D., Wang, H., 2011. High prevalence of KPC-2-type carbapenemase coupled with CTX-M-type extended-spectrum β-lactamases in carbapenem-resistant *Klebsiella pneumoniae* in a teaching hospital in China. Antimicrob. Agents Chemother. 55, 2493–2494.

Chen, Y., Delmas, J., Sirot, J., Shoichet, B., Bonnet, R., 2005. Atomic resolution structures of CTX-M β-lactamases: extended spectrum activities from increased mobility and decreased stability. J. Mol. Biol. 348, 349–362.

Chen, Y., Bonnet, R., Shoichet, B.K., 2007. The acylation mechanism of CTX-M β-lactamase at 0.88 Å resolution. J. Am. Chem. Soc. 129, 5378–5380.

Chouchani, C., Marrakchi, R., Henriques, I., Correia, A., 2012. Occurrence of IMP-8, IMP-10, and IMP-13 metallo-β-lactamases located on class 1 integrons and other extended-spectrum β-lactamases in bacterial isolates from Tunisian rivers. Scand. J. Infect. Dis., Sep 19 [Epub ahead of print].

Chowdhury, G., Pazhani, G.P., Nair, G.B., Ghosh, A., Ramamurthy, T., 2011. Transferable plasmid-mediated quinolone resistance in association with extended-spectrum β-lactamases and fluoroquinolone-acetylating aminoglycoside-6′-N-acetyltransferase in clinical isolates of *Vibrio fluvialis*. Int. J. Antimicrob. Agents 38, 169–173.

Chung, H.C., Lai, C.H., Lin, J.N., Huang, C.K., Liang, S.H., Chen, W.F., Shih, Y.C., Lin, H.H., Wang, J.L., 2012. Bacteremia caused by extended-spectrum-β-lactamase-producing *Escherichia coli* sequence type ST131 and non-ST131 clones: comparison of demographic data, clinical features, and mortality. Antimicrob. Agents Chemother. 56, 618–622.

Coelho, A., Gonzalez-Lopez, J.J., Miro, E., Alonso-Tarres, C., Mirelis, B., Larrosa, M.N., Bartolome, R.M., Andreu, A., Navarro, F., Johnson, J.R., Prats, G., 2010. Characterisation of the CTX-M-15-encoding gene in *Klebsiella pneumoniae* strains from the Barcelona metropolitan area: plasmid diversity and chromosomal integration. Int. J. Antimicrob. Agents 36, 73–78.

Coque, T.M., Novais, A., Carattoli, A., Poirel, L., Pitout, J., Peixe, L., Baquero, F., Canton, R., Nordmann, P., 2008. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum β-lactamase CTX-M-15. Emerg. Infect. Dis. 14, 195–200.

Cornejo-Juarez, P., Perez-Jimenez, C., Silva-Sanchez, J., Velazquez-Acosta, C., Gonzalez-Lara, F., Reyna-Flores, F., Sanchez-Perez, A., Volkow-Fernandez, P., 2012. Molecular analysis and risk factors for *Escherichia coli* producing extended-spectrum β-lactamase bloodstream infection in hematological malignancies. PLoS One 7, e35780.

Cottell, J.L., Webber, M.A., Coldham, N.G., Taylor, D.L., Cerdeno-Tarraga, A.M., Hauser, H., Thomson, N.R., Woodward, M.J., Piddock, L.J., 2011. Complete sequence and molecular epidemiology of IncK epidemic plasmid encoding $bla_{CTX-M-14}$. Emerg. Infect. Dis. 17, 645–652.

Cullik, A., Pfeifer, Y., Prager, R., von Baum, H., Witte, W., 2010. A novel IS*26* structure surrounds bla_{CTX-M} genes in different plasmids from German clinical *Escherichia coli* isolates. J. Med. Microbiol. 59, 580–587.

Cuzon, G., Ouanich, J., Gondret, R., Naas, T., Nordmann, P., 2011. Outbreak of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in France. Antimicrob. Agents Chemother. 55, 2420–2423.

Dallenne, C., Da Costa, A., Decre, D., Favier, C., Arlet, G., 2010. Development of a set of multiplex PCR assays for the detection of genes encoding important β-lactamases in *Enterobacteriaceae*. J. Antimicrob. Chemother. 65, 490–495.

Damjanova, I., Toth, A., Paszti, J., Hajbel-Vekony, G., Jakab, M., Berta, J., Milch, H., Fuzi, M., 2008. Expansion and countrywide dissemination of ST11, ST15 and ST147 ciprofloxacin-resistant CTX-M-15-type β-lactamase-producing Klebsiella pneumoniae epidemic clones in Hungary in 2005 – the new 'MRSAs'? J. Antimicrob. Chemother. 62, 978–985.

Decousser, J.W., Poirel, L., Nordmann, P., 2001. Characterization of a chromosomally encoded extended-spectrum class A β-lactamase from *Kluyvera cryocrescens*. Antimicrob. Agents Chemother. 45, 3595–3598.

Delmas, J., Robin, F., Carvalho, F., Mongaret, C., Bonnet, R., 2006. Prediction of the evolution of ceftazidime resistance in extended-spectrum β-lactamase CTX-M-9. Antimicrob. Agents Chemother. 50, 731–738.

Delmas, J., Chen, Y., Prati, F., Robin, F., Shoichet, B.K., Bonnet, R., 2008. Structure and dynamics of CTX-M enzymes reveal insights into substrate accommodation by extended-spectrum β-lactamases. J. Mol. Biol. 375, 192–201.

Delmas, J., Leyssene, D., Dubois, D., Birck, C., Vazeille, E., Robin, F., Bonnet, R., 2010. Structural insights into substrate recognition and product expulsion in CTX-M enzymes. J. Mol. Biol. 400, 108–120.

Dhanji, H., Murphy, N.M., Akhigbe, C., Doumith, M., Hope, R., Livermore, D.M., Woodford, N., 2011. Isolation of fluoroquinolone-resistant O25b:H4-ST131 *Escherichia coli* with CTX-M-14 extended-spectrum β-lactamase from UK river water. J. Antimicrob. Chemother. 66, 512–516.

Dhanji, H., Khan, P., Cottell, J.L., Piddock, L.J., Zhang, J., Livermore, D.M., Woodford, N., 2012. Dissemination of pCT-like IncK plasmids harboring CTX-M-14 extended-spectrum β-lactamase among clinical *Escherichia coli* isolates in the United Kingdom. Antimicrob. Agents Chemother. 56, 3376–3377.

Di Conza, J.A., Gutkind, G.O., Mollerach, M.E., Ayala, J.A., 2005. Transcriptional analysis of the $bla_{CTX-M-2}$ gene in *Salmonella enterica* serovar Infantis. Antimicrob. Agents Chemother. 49, 3014–3017.

Djamdjian, L., Naas, T., Tande, D., Cuzon, G., Hanrotel-Saliou, C., Nordmann, P., 2011. CTX-M-93, a CTX-M variant lacking penicillin hydrolytic activity. Antimicrob. Agents Chemother. 55, 1861–1866.

Doi, Y., Park, Y.S., Rivera, J.I., Adams-Haduch, J.M., Hingwe, A., Sordillo, E.M., Lewis, J.S., Howard, W.J., Johnson, L.E., Polsky, B., Jorgensen, J.H., Richter, S.S., Shutt, K.A., Paterson, D.L., 2012. Community-Associated Extended-Spectrum β-Lactamase-Producing *Escherichia coli* Infection in the United States. Clin. Infect. Dis., Dec 27 [Epub ahead of print].

Doumith, M., Ellington, M.J., Livermore, D.M., Woodford, N., 2009. Molecular mechanisms disrupting porin expression in ertapenem-resistant *Klebsiella* and *Enterobacter* spp. clinical isolates from the UK. J. Antimicrob. Chemother. 63, 659–667.

Elliott, E., Brink, A.J., van Greune, J., Els, Z., Woodford, N., Turton, J., Warner, M., Livermore, D.M., 2006. In vivo development of ertapenem resistance in a patient with pneumonia caused by *Klebsiella pneumoniae* with an extended-spectrum β-lactamase. Clin. Infect. Dis. 42, e95–e98.

Endimiani, A., Hujer, A.M., Hujer, K.M., Gatta, J.A., Schriver, A.C., Jacobs, M.R., Rice, L.B., Bonomo, R.A., 2010. Evaluation of a commercial microarray system for detection of SHV-, TEM-, CTX-M-, and KPC-type β-lactamase genes in Gram-negative isolates. J. Clin. Microbiol. 48, 2618–2622.

Ewers, C., Bethe, A., Semmler, T., Guenther, S., Wieler, L.H., 2012. Extended-spectrum β-lactamase-producing and AmpC-producing *Escherichia coli* from livestock and companion animals, and their putative impact on public health: a global perspective. Clin. Microbiol. Infect. 18, 646–655.

Fabre, L., Delaune, A., Espie, E., Nygard, K., Pardos, M., Polomack, L., Guesnier, F., Galimand, M., Lassen, J., Weill, F.X., 2009. Chromosomal integration of the extended-spectrum β-lactamase gene $bla_{CTX-M-15}$ in *Salmonella enterica* serotype Concord isolates from internationally adopted children. Antimicrob. Agents Chemother. 53, 1808–1816.

Fam, N., Leflon-Guibout, V., Fouad, S., Aboul-Fadl, L., Marcon, E., Desouky, D., El-Defrawy, I., Abou-Aitta, A., Klena, J., Nicolas-Chanoine, M.H., 2011. CTX-M-15-producing *Escherichia coli* clinical isolates in Cairo (Egypt), including isolates of clonal complex ST10 and clones ST131, ST73, and ST405 in both community and hospital settings. Microb. Drug Resist. 17, 67–73.

Garcia-Fulgueiras, V., Bado, I., Mota, M.I., Robino, L., Cordeiro, N.F., Varela, A., Algorta, G., Gutkind, G., Ayala, J.A., Vignoli, R., 2011. Extended-spectrum β-lactamases and plasmid-mediated quinolone resistance in enterobacterial clinical isolates in the paediatric hospital of Uruguay. J. Antimicrob. Chemother. 66, 1725–1729.

Geser, N., Stephan, R., Korczak, B.M., Beutin, L., Hachler, H., 2012. Molecular identification of extended-spectrum-β-lactamase genes from *Enterobacteriaceae* isolated from healthy human carriers in Switzerland. Antimicrob. Agents Chemother. 56, 1609–1612.

Girlich, D., Poirel, L., Nordmann, P., 2009. CTX-M expression and selection of ertapenem resistance in *Klebsiella pneumoniae* and *Escherichia coli*. Antimicrob. Agents Chemother. 53, 832–834.

Gomez-Garces, J.L., Saez, D., Almagro, M., Fernandez-Romero, S., Merino, F., Campos, J., Oteo, J., 2011. Osteomyelitis associated to CTX-M-15-producing *Aeromonas hydrophila*: first description in the literature. Diagn. Microbiol. Infect. Dis. 70, 420–422.

Guenther, S., Ewers, C., Wieler, L.H., 2011. Extended-spectrum β-lactamases producing *E. coli* in wildlife, yet another form of environmental pollution? Front. Microbiol. 2, 246.

Harada, S., Ishii, Y., Saga, T., Kouyama, Y., Tateda, K., Yamaguchi, K., 2012. Chromosomal integration and location on IncT plasmids of the $bla_{CTX-M-2}$ gene in *Proteus mirabilis* clinical isolates. Antimicrob. Agents Chemother. 56, 1093–1096.

He, L., Partridge, S.R., Yang, X., Hou, J., Deng, Y., Yao, Q., Zeng, Z., Chen, Z., Liu, J.H., 2013. Complete nucleotide sequence of pHN7A8, an F33:A-:B-type epidemic plasmid carrying $bla_{CTX-M-65}$, *fosA3* and *rmtB* from China. J. Antimicrob. Chemother. 68, 46–50.

Hilty, M., Betsch, B.Y., Bogli-Stuber, K., Heiniger, N., Stadler, M., Kuffer, M., Kronenberg, A., Rohrer, C., Aebi, S., Endimiani, A., Droz, S., Muhlemann, K., 2012. Transmission dynamics of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in the tertiary care hospital and the household setting. Clin. Infect. Dis. 55, 967–975.

Ho, P.L., Lo, W.U., Yeung, M.K., Li, Z., Chan, J., Chow, K.H., Yam, W.C., Tong, A.H., Bao, J.Y., Lin, C.H., Lok, S., Chiu, S.S., 2012. Dissemination of pHK01-like

incompatibility group IncFII plasmids encoding CTX-M-14 in *Escherichia coli* from human and animal sources. Vet. Microbiol. 158, 172–179.
Hopkins, K.L., Deheer-Graham, A., Threlfall, E.J., Batchelor, M.J., Liebana, E., 2006. Novel plasmid-mediated CTX-M-8 subgroup extended-spectrum β-lactamase (CTX-M-40) isolated in the UK. Int. J. Antimicrob. Agents 27, 572–575.
Humeniuk, C., Arlet, G., Gautier, V., Grimont, P., Labia, R., Philippon, A., 2002. β-Lactamases of *Kluyvera ascorbata*, probable progenitors of some plasmid-encoded CTX-M types. Antimicrob. Agents Chemother. 46, 3045–3049.
Ibuka, A.S., Ishii, Y., Galleni, M., Ishiguro, M., Yamaguchi, K., Frere, J.M., Matsuzawa, H., Sakai, H., 2003. Crystal structure of extended-spectrum β-lactamase Toho-1: insights into the molecular mechanism for catalytic reaction and substrate specificity expansion. Biochemistry 42, 10634–10643.
Ingold, A.J., Castro, M., Nabon, A., Borthagaray, G., Marquez, C., 2011. VIM-2 metallo-β-lactamase gene detection in a class 1 integron associated to $bla_{CTX-M-2}$ in a *Pseudomonas aeruginosa* clinical isolate in Uruguay: first communication. Rev. Argent. Microbiol. 43, 198–202.
Izdebski, R., Baraniak, A., Fiett, J., Adler, A., Kazma, M., Salomon, J., Lawrence, C., Rossini, A., Salvia, A., Vidal Samso, J., Fierro, J., Paul, M., Lerman, Y., Malhotra-Kumar, S., Lammens, C., Goossens, H., Hryniewicz, W., Brun-Buisson, C., Carmeli, Y., Gniadkowski, M., 2013. Clonal structure, extended-spectrum β-lactamases, and acquired AmpC-type cephalosporinases of *Escherichia* coli populations colonizing patients in rehabilitation centers in four countries. Antimicrob. Agents Chemother. 57, 309–316.
Johnson, J.R., Porter, S.B., Zhanel, G., Kuskowski, M.A., Denamur, E., 2012. Virulence of *Escherichia coli* clinical isolates in a murine sepsis model in relation to sequence type ST131 status, fluoroquinolone resistance, and virulence genotype. Infect. Immun. 80, 1554–1562.
Kimura, S., Ishiguro, M., Ishii, Y., Alba, J., Yamaguchi, K., 2004. Role of a mutation at position 167 of CTX-M-19 in ceftazidime hydrolysis. Antimicrob. Agents Chemother. 48, 1454–1460.
Kimura, S., Ishii, Y., Tateda, K., Yamaguchi, K., 2007. Predictive analysis of ceftazidime hydrolysis in CTX-M-type β-lactamase family members with a mutational substitution at position 167. Int. J. Antimicrob. Agents 29, 326–331.
Ko, K.S., Lee, J.Y., Baek, J.Y., Suh, J.Y., Lee, M.Y., Choi, J.Y., Yeom, J.S., Kim, Y.S., Jung, S.I., Shin, S.Y., Heo, S.T., Kwon, K.T., Son, J.S., Kim, S.W., Chang, H.H., Ki, H.K., Chung, D.R., Peck, K.R., Song, J.H., 2010. Predominance of an ST11 extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* clone causing bacteraemia and urinary tract infections in Korea. J. Med. Microbiol. 59, 822–828.
Lagace-Wiens, P.R., Tailor, F., Simner, P., DeCorby, M., Karlowsky, J.A., Walkty, A., Hoban, D.J., Zhanel, G.G., 2011. Activity of NXL104 in combination with β-lactams against genetically characterized *Escherichia coli* and *Klebsiella pneumoniae* isolates producing class A extended-spectrum β-lactamases and class C β-lactamases. Antimicrob. Agents Chemother. 55, 2434–2437.
Lartigue, M.F., Poirel, L., Aubert, D., Nordmann, P., 2006. In vitro analysis of IS*Ecp1B*-mediated mobilization of naturally occurring β-lactamase gene bla_{CTX-M} of *Kluyvera ascorbata*. Antimicrob. Agents Chemother. 50, 1282–1286.
Lavilla, S., Gonzalez-Lopez, J.J., Sabate, M., Garcia-Fernandez, A., Larrosa, M.N., Bartolome, R.M., Carattoli, A., Prats, G., 2008. Prevalence of *qnr* genes among extended-spectrum β-lactamase-producing enterobacterial isolates in Barcelona, Spain. J. Antimicrob. Chemother. 61, 291–295.
Leavitt, A., Chmelnitsky, I., Colodner, R., Ofek, I., Carmeli, Y., Navon-Venezia, S., 2009. Ertapenem resistance among extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* isolates. J. Clin. Microbiol. 47, 969–974.
Lee, M.Y., Ko, K.S., Kang, C.I., Chung, D.R., Peck, K.R., Song, J.H., 2011. High prevalence of CTX-M-15-producing *Klebsiella pneumoniae* isolates in Asian countries: diverse clones and clonal dissemination. Int. J. Antimicrob. Agents 38, 160–163.
Livermore, D.M., Mushtaq, S., Warner, M., Miossec, C., Woodford, N., 2008. NXL104 combinations versus *Enterobacteriaceae* with CTX-M extended-spectrum β-lactamases and carbapenemases. J. Antimicrob. Chemother. 62, 1053–1056.
Livermore, D.M., 2012. Current epidemiology and growing resistance of gram-negative pathogens. Korean J. Intern. Med. 27, 128–142.
Lo, W.U., Ho, P.L., Chow, K.H., Lai, E.L., Yeung, F., Chiu, S.S., 2010. Fecal carriage of CTXM type extended-spectrum β-lactamase-producing organisms by children and their household contacts. J. Infect. 60, 286–292.
Lonchel, C.M., Meex, C., Gangoue-Pieboji, J., Boreux, R., Assoumou, M.C., Melin, P., De Mol, P., 2012. Proportion of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in community setting in Ngaoundere, Cameroon. BMC Infect. Dis. 12, 53.
Luvsansharav, U.O., Hirai, I., Niki, M., Nakata, A., Yoshinaga, A., Moriyama, T., Yamamoto, Y., 2011. Prevalence of fecal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* among healthy adult people in Japan. J. Infect. Chemother. 17, 722–725.
Luvsansharav, U.O., Hirai, I., Nakata, A., Imura, K., Yamauchi, K., Niki, M., Komalamisra, C., Kusolsuk, T., Yamamoto, Y., 2012. Prevalence of and risk factors associated with faecal carriage of CTX-M β-lactamase-producing *Enterobacteriaceae* in rural Thai communities. J. Antimicrob. Chemother. 67, 1769–1774.
Ma, L., Siu, L.K., Lu, P.L., 2011. Effect of spacer sequences between bla_{CTX-M} and IS*Ecp1* on bla_{CTX-M} expression. J. Med. Microbiol. 60, 1787–1792.
Mahrouki, S., Belhadj, O., Chihi, H., Mohamed, B.M., Celenza, G., Amicosante, G., Perilli, M., 2012. Chromosomal $bla_{CTX-M-15}$ associated with IS*Ecp1* in *Proteus mirabilis* and *Morganella morganii* isolated at the Military Hospital of Tunis, Tunisia. J. Med. Microbiol. 61, 1286–1289.
Manageiro, V., Jones-Dias, D., Ferreira, E., Louro, D., Canica, M., 2012. Genetic diversity and clonal evolution of carbapenem-resistant *Acinetobacter baumannii* isolates from Portugal and the dissemination of ST118. Int. J. Antimicrob. Agents 40, 398–403.
Matsumoto, Y., Ikeda, F., Kamimura, T., Yokota, Y., Mine, Y., 1988. Novel plasmid-mediated β-lactamase from *Escherichia coli* that inactivates oxyimino-cephalosporins. Antimicrob. Agents Chemother. 32, 1243–1246.
Miro, E., Segura, C., Navarro, F., Sorli, L., Coll, P., Horcajada, J.P., Alvarez-Lerma, F., Salvado, M., 2010. Spread of plasmids containing the bla_{VIM-1} and bla_{CTX-M} genes and the *qnr* determinant in *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* isolates. J. Antimicrob. Chemother. 65, 661–665.
Morosini, M.I., Valverde, A., Garcia-Castillo, M., Nordmann, P., Canton, R., 2010. Persistent isolation of *Salmonella* Concord harbouring CTX-M-15, SHV-12 and QnrA1 in an asymptomatic adopted Ethiopian child in Spain also colonized with CTX-M-14- and QnrB-producing Enterobacteriaceae. J. Antimicrob. Chemother. 65, 1545–1546.
Moubareck, C., Daoud, Z., Hakime, N.I., Hamze, M., Mangeney, N., Matta, H., Mokhbat, J.E., Rohban, R., Sarkis, D.K., Doucet-Populaire, F., 2005. Countrywide spread of community- and hospital-acquired extended-spectrum β-lactamase CTX-M-15-producing *Enterobacteriaceae* in Lebanon. J. Clin. Microbiol. 43, 3309–3313.
Naas, T., Oxacelay, C., Nordmann, P., 2007. Identification of CTX-M-type extended-spectrum-β-lactamase genes using real-time PCR and pyrosequencing. Antimicrob. Agents Chemother. 51, 223–230.
Naas, T., Cuzon, G., Truong, H., Bernabeu, S., Nordmann, P., 2010. Evaluation of a DNA microarray, the check-points ESBL/KPC array, for rapid detection of TEM, SHV, and CTX-M extended-spectrum β-lactamases and KPC carbapenemases. Antimicrob. Agents Chemother. 54, 3086–3092.
Nagano, N., Nagano, Y., Cordevant, C., Shibata, N., Arakawa, Y., 2004. Nosocomial transmission of CTX-M-2 β-lactamase-producing *Acinetobacter baumannii* in a neurosurgery ward. J. Clin. Microbiol. 42, 3978–3984.
Nakano, R., Nakano, A., Abe, M., Inoue, M., Okamoto, R., 2012. Regional outbreak of CTX-M-2 β-lactamase-producing *Proteus mirabilis* in Japan. J. Med. Microbiol. 61, 1727–1735.
Naseer, U., Sundsfjord, A., 2011. The CTX-M conundrum: dissemination of plasmids and *Escherichia coli* clones. Microb. Drug Resist. 17, 83–97.
Navon-Venezia, S., Chmelnitsky, I., Leavitt, A., Carmeli, Y., 2008. Dissemination of the CTX-M-25 family β-lactamases among *Klebsiella pneumoniae*, *Escherichia coli* and *Enterobacter cloacae* and identification of the novel enzyme CTX-M-41 in *Proteus mirabilis* in Israel. J. Antimicrob. Chemother. 62, 289–295.
Nicolas-Chanoine, M.H., Gruson, C., Bialek-Davenet, S., Bertrand, X., Thomas-Jean, F., Bert, F., Moyat, M., Meiller, E., Marcon, E., Danchin, N., Noussair, L., Moreau, R., Leflon-Guibout, V., 2012. 10-Fold increase (2006-11) in the rate of healthy subjects with extended-spectrum β-lactamase-producing *Escherichia coli* faecal carriage in a Parisian check-up centre. J. Antimicrob. Chemother., Nov 9 [Epub ahead of print].
Novais, A., Canton, R., Coque, T.M., Moya, A., Baquero, F., Galan, J.C., 2008. Mutational events in cefotaximase extended-spectrum β-lactamases of the CTX-M-1 cluster involved in ceftazidime resistance. Antimicrob. Agents Chemother. 52, 2377–2382.
Okeke, I.N., Wallace-Gadsden, F., Simons, H.R., Matthews, N., Labar, A.S., Hwang, J., Wain, J., 2010. Multi-locus sequence typing of enteroaggregative *Escherichia coli* isolates from Nigerian children uncovers multiple lineages. PLoS One 5, e14093.
Oliver, A., Perez-Diaz, J.C., Coque, T.M., Baquero, F., Canton, R., 2001. Nucleotide sequence and characterization of a novel cefotaxime-hydrolyzing β-lactamase (CTX-M-10) isolated in Spain. Antimicrob. Agents Chemother. 45, 616–620.
Olson, A.B., Silverman, M., Boyd, D.A., McGeer, A., Willey, B.M., Pong-Porter, V., Daneman, N., Mulvey, M.R., 2005. Identification of a progenitor of the CTX-M-9 group of extended-spectrum β-lactamases from *Kluyvera georgiana* isolated in Guyana. Antimicrob. Agents Chemother. 49, 2112–2115.
Oteo, J., Diestra, K., Juan, C., Bautista, V., Novais, A., Perez-Vazquez, M., Moya, B., Miro, E., Coque, T.M., Oliver, A., Canton, R., Navarro, F., Campos, J., 2009a. Extended-spectrum β-lactamase-producing *Escherichia coli* in Spain belong to a large variety of multilocus sequence typing types, including ST10 complex/A, ST23 complex/A and ST131/B2. Int. J. Antimicrob. Agents 34, 173–176.
Oteo, J., Cuevas, O., Lopez-Rodriguez, I., Banderas-Florido, A., Vindel, A., Perez-Vazquez, M., Bautista, V., Arroyo, M., Garcia-Caballero, J., Marin-Casanova, P., Gonzalez-Sanz, R., Fuentes-Gomez, V., Ona-Compan, S., Garcia-Cobos, S., Campos, J., 2009b. Emergence of CTX-M-15-producing *Klebsiella pneumoniae* of multilocus sequence types 1, 11, 14, 17, 20, 35 and 36 as pathogens and colonizers in newborns and adults. J. Antimicrob. Chemother. 64, 524–528.
Oteo, J., Perez-Vazquez, M., Campos, J., 2010. Extended-spectrum β-lactamase producing *Escherichia coli*: changing epidemiology and clinical impact. Curr. Opin. Infect. Dis. 23, 320–326.
Page, R.D., 1996. TreeView: an application to display phylogenetic trees on personal computers. Comput. Appl. Biosci. 12, 357–358.
Pallecchi, L., Malossi, M., Mantella, A., Gotuzzo, E., Trigoso, C., Bartoloni, A., Paradisi, F., Kronvall, G., Rossolini, G.M., 2004. Detection of CTX-M-type β-lactamase genes in fecal *Escherichia coli* isolates from healthy children in Bolivia and Peru. Antimicrob. Agents Chemother. 48, 4556–4561.
Pallecchi, L., Bartoloni, A., Fiorelli, C., Mantella, A., Di Maggio, T., Gamboa, H., Gotuzzo, E., Kronvall, G., Paradisi, F., Rossolini, G.M., 2007. Rapid dissemination and diversity of CTX-M extended-spectrum β-lactamase genes in commensal *Escherichia coli* isolates from healthy children from low-resource settings in Latin America. Antimicrob. Agents Chemother. 51, 2720–2725.
Park, S.Y., Kang, C.I., Joo, E.J., Ha, Y.E., Wi, Y.M., Chung, D.R., Peck, K.R., Lee, N.Y., Song, J.H., 2012. Risk factors for multidrug resistance in nosocomial bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. Microb. Drug Resist. 18, 518–524.

Partridge, S.R., Ellem, J.A., Tetu, S.G., Zong, Z., Paulsen, I.T., Iredell, J.R., 2011. Complete sequence of pJIE143, a pir-type plasmid carrying IS*Ecp1*-$bla_{CTX-M-15}$ from an *Escherichia coli* ST131 isolate. Antimicrob. Agents Chemother. 55, 5933–5935.

Peirano, G., Asensi, M.D., Pitondo-Silva, A., Pitout, J.D., 2011. Molecular characteristics of extended-spectrum β-lactamase-producing *Escherichia coli* from Rio de Janeiro, Brazil. Clin. Microbiol. Infect. 17, 1039–1043.

Peirano, G., van der Bij, A.K., Gregson, D.B., Pitout, J.D., 2012. Molecular epidemiology over an 11-year period (2000 to 2010) of extended-spectrum β-lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. J. Clin. Microbiol. 50, 294–299.

Perez-Llarena, F.J., Kerff, F., Abian, O., Mallo, S., Fernandez, M.C., Galleni, M., Sancho, J., Bou, G., 2011. Distant and new mutations in CTX-M-1 β-lactamase affect cefotaxime hydrolysis. Antimicrob. Agents Chemother. 55, 4361–4368.

Petrella, S., Ziental-Gelus, N., Mayer, C., Renard, M., Jarlier, V., Sougakoff, W., 2008. Genetic and structural insights into the dissemination potential of the extremely broad-spectrum class A β-lactamase KPC-2 identified in an *Escherichia coli* strain and an *Enterobacter cloacae* strain isolated from the same patient in France. Antimicrob. Agents Chemother. 52, 3725–3736.

Petroni, A., Corso, A., Melano, R., Cacace, M.L., Bru, A.M., Rossi, A., Galas, M., 2002. Plasmidic extended-spectrum β-lactamases in *Vibrio cholerae* O1 El Tor isolates in Argentina. Antimicrob. Agents Chemother. 46, 1462–1468.

Picao, R.C., Poirel, L., Gales, A.C., Nordmann, P., 2009. Further identification of CTX-M-2 extended-spectrum β-lactamase in *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. 53, 2225–2226.

Pitart, C., Sole, M., Roca, I., Fabrega, A., Vila, J., Marco, F., 2011. First outbreak of a plasmid-mediated carbapenem-hydrolyzing OXA-48 β-lactamase in *Klebsiella pneumoniae* in Spain. Antimicrob. Agents Chemother. 55, 4398–4401.

Pitout, J.D., Hossain, A., Hanson, N.D., 2004. Phenotypic and molecular detection of CTX-M-beta-lactamases produced by *Escherichia coli* and *Klebsiella* spp. J. Clin. Microbiol. 42, 5715–5721.

Pitout, J.D., Hamilton, N., Church, D.L., Nordmann, P., Poirel, L., 2007. Development and clinical validation of a molecular diagnostic assay to detect CTX-M-type β-lactamases in *Enterobacteriaceae*. Clin. Microbiol. Infect. 13, 291–297.

Pitout, J.D., Laupland, K.B., 2008. Extended-spectrum β-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. Lancet Infect. Dis. 8, 159–166.

Pitout, J.D., Gregson, D.B., Campbell, L., Laupland, K.B., 2009. Molecular characteristics of extended-spectrum-β-lactamase-producing *Escherichia coli* isolates causing bacteremia in the Calgary Health Region from 2000 to 2007: emergence of clone ST131 as a cause of community-acquired infections. Antimicrob. Agents Chemother. 53, 2846–2851.

Poirel, L., Kampfer, P., Nordmann, P., 2002. Chromosome-encoded Ambler class A β-lactamase of *Kluyvera georgiana*, a probable progenitor of a subgroup of CTX-M extended-spectrum β-lactamases. Antimicrob. Agents Chemother. 46, 4038–4040.

Poirel, L., Decousser, J.W., Nordmann, P., 2003. Insertion sequence IS*Ecp1B* is involved in expression and mobilization of a bla_{CTX-M} β-lactamase gene. Antimicrob. Agents Chemother. 47, 2938–2945.

Poirel, L., Lartigue, M.F., Decousser, J.W., Nordmann, P., 2005. IS*Ecp1B*-mediated transposition of bla_{CTX-M} in *Escherichia coli*. Antimicrob. Agents Chemother. 49, 447–450.

Poirel, L., Revathi, G., Bernabeu, S., Nordmann, P., 2011. Detection of NDM-1-producing *Klebsiella pneumoniae* in Kenya. Antimicrob. Agents Chemother. 55, 934–936.

Polotto, M., Casella, T., de Lucca Oliveira, M.G., Rubio, F.G., Nogueira, M.L., de Almeida, M.T., Nogueira, M.C., 2012. Detection of *P. aeruginosa* harboring $bla_{CTX-M-2}$, bla_{GES-1} and bla_{GES-5}, bla_{IMP-1} and bla_{SPM-1} causing infections in Brazilian tertiary-care hospital. BMC Infect. Dis. 12, 176.

Potron, A., Munoz-Price, L.S., Nordmann, P., Cleary, T., Poirel, L., 2011. Genetic features of CTX-M-15-producing *Acinetobacter baumannii* from Haiti. Antimicrob. Agents Chemother. 55, 5946–5948.

Prakash, V., Lewis, J.S., Herrera, M.L., Wickes, B.L., Jorgensen, J.H., 2009. Oral and parenteral therapeutic options for outpatient urinary infections caused by *Enterobacteriaceae* producing CTX-M extended-spectrum β-lactamases. Antimicrob. Agents Chemother. 53, 1278–1280.

Redondo, C., Chalbaud, A., Alonso, G., 2012. Frequency and diversity of CTX-M enzymes among extended-spectrum β-lactamase-producing *Enterobacteriaceae* isolates from Caracas, Venezuela. Microb. Drug Resist., Oct 15 [Epub ahead of print].

Reuland, E.A., Overdevest, I.T., al Naiemi, N., Kalpoe, J.S., Rijnsburger, M.C., Raadsen, S.A., Ligtenberg-Burgman, I., van der Zwaluw, K.W., Heck, M., Savelkoul, P.H., Kluytmans, J.A., Vandenbroucke-Grauls, C.M., 2012. High prevalence of ESBL-producing *Enterobacteriaceae* carriage in Dutch community patients with gastrointestinal complaints. Clin. Microbiol. Infect., http://dx.doi.org/10.1111/j.1469-0691.2012.03947.x.

Ripoll, A., Baquero, F., Novais, A., Rodriguez-Dominguez, M.J., Turrientes, M.C., Canton, R., Galan, J.C., 2011. In vitro selection of variants resistant to β-lactams plus beta-lactamase inhibitors in CTX-M beta-lactamases: predicting the in vivo scenario? Antimicrob. Agents Chemother. 55, 4530–4536.

Rodriguez-Bano, J., Navarro, M.D., Romero, L., Martinez-Martinez, L., Muniain, M.A., Perea, E.J., Perez-Cano, R., Pascual, A., 2004. Epidemiology and clinical features of infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* in nonhospitalized patients. J. Clin. Microbiol. 42, 1089–1094.

Rodriguez-Bano, J., Navarro, M.D., Romero, L., Muniain, M.A., de Cueto, M., Rios, M.J., Hernandez, J.R., Pascual, A., 2006. Bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli* in the CTX-M era: a new clinical challenge. Clin. Infect. Dis. 43, 1407–1414.

Rodriguez-Bano, J., Lopez-Cerero, L., Navarro, M.D., Diaz de, Alba, P., Pascual, A., 2008. Faecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli*: prevalence, risk factors and molecular epidemiology. J. Antimicrob. Chemother. 62, 1142–1149.

Rodriguez, M.M., Power, P., Radice, M., Vay, C., Famiglietti, A., Galleni, M., Ayala, J.A., Gutkind, G., 2004. Chromosome-encoded CTX-M-3 from *Kluyvera ascorbata*: a possible origin of plasmid-borne CTX-M-1-derived cefotaximases. Antimicrob. Agents Chemother. 48, 4895–4897.

Rodriguez, M.M., Power, P., Sader, H., Galleni, M., Gutkind, G., 2010. Novel chromosome-encoded CTX-M-78 β-lactamase from a *Kluyvera georgiana* clinical isolate as a putative origin of CTX-M-25 subgroup. Antimicrob. Agents Chemother. 54, 3070–3071.

Rogers, B.A., Sidjabat, H.E., Paterson, D.L., 2011. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. J. Antimicrob. Chemother. 66, 1–14.

Rossolini, G.M., D'Andrea, M.M., Mugnaioli, C., 2008. The spread of CTX-M-type extended-spectrum β-lactamases. Clin. Microbiol. Infect. 14 (Suppl. 1), 33–41.

Ruiz, S.J., Montealegre, M.C., Ruiz-Garbajosa, P., Correa, A., Briceno, D.F., Martinez, E., Rosso, F., Munoz, M., Quinn, J.P., Canton, R., Villegas, M.V., 2011. First characterization of CTX-M-15-producing *Escherichia coli* ST131 and ST405 clones causing community-onset infections in South America. J. Clin. Microbiol. 49, 1993–1996.

Ruppe, E., Woerther, P.L., Diop, A., Sene, A.M., Da Costa, A., Arlet, G., Andremont, A., Rouveix, B., 2009. Carriage of CTX-M-15-producing *Escherichia coli* isolates among children living in a remote village in Senegal. Antimicrob. Agents Chemother. 53, 3135–3137.

Sarria, J.C., Vidal, A.M., Kimbrough III, R.C., 2001. Infections caused by *Kluyvera* species in humans. Clin. Infect. Dis. 33, E69–E74.

Sasaki, T., Hirai, I., Niki, M., Nakamura, T., Komalamisra, C., Maipanich, W., Kusolsuk, T., Sa-Nguankiat, S., Pubampen, S., Yamamoto, Y., 2010. High prevalence of CTX-M β-lactamase-producing *Enterobacteriaceae* in stool specimens obtained from healthy individuals in Thailand. J. Antimicrob. Chemother. 65, 666–668.

Sennati, S., Santella, G., Di Conza, J., Pallecchi, L., Pino, M., Ghiglione, B., Rossolini, G.M., Radice, M., Gutkind, G., 2012. Changing epidemiology of extended-spectrum β-lactamases in Argentina: emergence of CTX-M-15. Antimicrob. Agents Chemother. 56, 6003–6005.

Shakil, S., Khan, A.U., 2010. Detection of CTX-M-15-producing and carbapenem-resistant *Acinetobacter baumannii* strains from urine from an Indian hospital. J. Chemother. 22, 324–327.

Smet, A., Martel, A., Persoons, D., Dewulf, J., Heyndrickx, M., Claeys, G., Lontie, M., Van Meensel, B., Herman, L., Haesebrouck, F., Butaye, P., 2010. Characterization of extended-spectrum β-lactamases produced by *Escherichia coli* isolated from hospitalized and nonhospitalized patients: emergence of CTX-M-15-producing strains causing urinary tract infections. Microb. Drug Resist. 16, 129–134.

Song, W., Kim, J., Bae, I.K., Jeong, S.H., Seo, Y.H., Shin, J.H., Jang, S.J., Uh, Y., Shin, J.H., Lee, M.K., Lee, K., 2011. Chromosome-encoded AmpC and CTX-M extended-spectrum β-lactamases in clinical isolates of *Proteus mirabilis* from Korea. Antimicrob. Agents Chemother. 55, 1414–1419.

Stokes, M.O., Cottell, J.L., Piddock, L.J., Wu, G., Wootton, M., Mevius, D.J., Randall, L.P., Teale, C.J., Fielder, M.D., Coldham, N.G., 2012. Detection and characterization of pCT-like plasmid vectors for $bla_{CTX-M-14}$ in *Escherichia coli* isolates from humans, turkeys and cattle in England and Wales. J. Antimicrob. Chemother. 67, 1639–1644.

Sun, Y., Zeng, Z., Chen, S., Ma, J., He, L., Liu, Y., Deng, Y., Lei, T., Zhao, J., Liu, J.H., 2010. High prevalence of bla_{CTX-M} extended-spectrum β-lactamase genes in *Escherichia coli* isolates from pets and emergence of CTX-M-64 in China. Clin. Microbiol. Infect. 16, 1475–1481.

Tacao, M., Correia, A., Henriques, I., 2012. Resistance to broad-spectrum antibiotics in aquatic systems: anthropogenic activities modulate the dissemination of bla_{CTX-M}-like genes. Appl. Environ. Microbiol. 78, 4134–4140.

Tande, D., Boisrame-Gastrin, S., Munck, M.R., Hery-Arnaud, G., Gouriou, S., Jallot, N., Nordmann, P., Naas, T., 2010. Intrafamilial transmission of extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Salmonella enterica* Babelsberg among the families of internationally adopted children. J. Antimicrob. Chemother. 65, 859–865.

Toleman, M.A., Bennett, P.M., Walsh, T.R., 2006. IS *CR* elements: novel gene-capturing systems of the 21st century? Microbiol. Mol. Biol. Rev. 70, 296–316.

Tollentino, F.M., Polotto, M., Nogueira, M.L., Lincopan, N., Neves, P., Mamizuka, E.M., Remeli, G.A., de Almeida, M.T., Rubio, F.G., Nogueira, M.C., 2011. High prevalence of bla_{CTX-M} extended spectrum β-lactamase genes in *Klebsiella pneumoniae* isolates from a tertiary care hospital: first report of bla_{SHV-12}, bla_{SHV-31}, bla_{SHV-38}, and $bla_{CTX-M-15}$ in Brazil. Microb. Drug Resist. 17, 7–16.

Valverde, A., Coque, T.M., Sanchez-Moreno, M.P., Rollan, A., Baquero, F., Canton, R., 2004. Dramatic increase in prevalence of fecal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* during nonoutbreak situations in Spain. J. Clin. Microbiol. 42, 4769–4775.

Valverde, A., Grill, F., Coque, T.M., Pintado, V., Baquero, F., Canton, R., Cobo, J., 2008. High rate of intestinal colonization with extended-spectrum-beta-lactamase-producing organisms in household contacts of infected community patients. J. Clin. Microbiol. 46, 2796–2799.

Valverde, A., Canton, R., Garcillan-Barcia, M.P., Novais, A., Galan, J.C., Alvarado, A., de la Cruz, F., Baquero, F., Coque, T.M., 2009. Spread of $bla_{CTX-M-14}$ is driven mainly by IncK plasmids disseminated among *Escherichia coli* phylogroups A, B1, and D in Spain. Antimicrob. Agents Chemother. 53, 5204–5212.

van der Bij, A.K., Pitout, J.D., 2012. The role of international travel in the worldwide spread of multiresistant *Enterobacteriaceae*. J. Antimicrob. Chemother. 67, 2090–2100.

Vimont, S., Boyd, A., Bleibtreu, A., Bens, M., Goujon, J.M., Garry, L., Clermont, O., Denamur, E., Arlet, G., Vandewalle, A., 2012. The CTX-M-15-producing *Escherichia coli* clone O25b: H4-ST131 has high intestine colonization and urinary tract infection abilities. PLoS One 7, e46547.

Vinue, L., Saenz, Y., Martinez, S., Somalo, S., Moreno, M.A., Torres, C., Zarazaga, M., 2009. Prevalence and diversity of extended-spectrum β-lactamases in faecal *Escherichia coli* isolates from healthy humans in Spain. Clin. Microbiol. Infect. 15, 954–957.

Walther-Rasmussen, J., Hoiby, N., 2004. Cefotaximases (CTX-M-ases), an expanding family of extended-spectrum β-lactamases. Can. J. Microbiol. 50, 137–165.

Wang, P., Hu, F., Xiong, Z., Ye, X., Zhu, D., Wang, Y.F., Wang, M., 2011. Susceptibility of extended-spectrum-β-lactamase-producing *Enterobacteriaceae* according to the new CLSI breakpoints. J. Clin. Microbiol. 49, 3127–3131.

Williamson, D.A., Roberts, S.A., Smith, M., Heffernan, H., Tiong, A., Pope, C., Freeman, J.T., 2012. High rates of susceptibility to ceftazidime among globally prevalent CTX-M-producing *Escherichia coli*: potential clinical implications of the revised CLSI interpretive criteria. Eur. J. Clin. Microbiol. Infect. Dis. 31, 821–824.

Woerther, P.L., Angebault, C., Lescat, M., Ruppe, E., Skurnik, D., Mniai, A.E., Clermont, O., Jacquier, H., Costa, A.D., Renard, M., Bettinger, R.M., Epelboin, L., Dupont, C., Guillemot, D., Rousset, F., Arlet, G., Denamur, E., Djossou, F., Andremont, A., 2010. Emergence and dissemination of extended-spectrum β-lactamase-producing *Escherichia coli* in the community: lessons from the study of a remote and controlled population. J. Infect. Dis. 202, 515–523.

Woodford, N., Fagan, E.J., Ellington, M.J., 2006. Multiplex PCR for rapid detection of genes encoding CTX-M extended-spectrum β-lactamases. J. Antimicrob. Chemother. 57, 154–155.

Woodford, N., Kaufmann, M.E., Karisik, E., Hartley, J.W., 2007. Molecular epidemiology of multiresistant *Escherichia coli* isolates from community-onset urinary tract infections in Cornwall, England. J. Antimicrob. Chemother. 59, 106–109.

Woodford, N., Turton, J.F., Livermore, D.M., 2011. Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. FEMS Microbiol. Rev. 35, 736–755.

Wu, U.I., Wang, J.L., Chen, W.C., Chang, S.C., Chen, Y.C., 2011. Risk factors and outcomes of *Escherichia coli* bacteremia caused by strains that produce CTX-M or non-CTX-M extended-spectrum-β-lactamases. Eur. J. Clin. Microbiol. Infect. Dis. 30, 33–39.

Ye, Y., Xu, X.H., Li, J.B., 2010. Emergence of CTX-M-3, TEM-1 and a new plasmid-mediated MOX-4 AmpC in a multiresistant *Aeromonas caviae* isolate from a patient with pneumonia. J. Med. Microbiol. 59, 843–847.

Zhao, W.H., Hu, Z.Q., 2013. Epidemiology and genetics of CTX-M extended-spectrum β-lactamases in Gram-negative bacteria. Crit. Rev. Microbiol. 39, 79–101.