Introduction

Extended-spectrum $\beta$-lactamases (ESBLs) are the most influential mechanism for cephalosporin resistance in Enterobacteriaceae, particularly in Escherichia coli and Klebsiella pneumoniae. ESBLs confer resistance to penicillins, broad-spectrum cephalosporins with an oxyimino side chain (cefotaxime, ceftriaxone and ceftazidime) and the oxyimino-monobactam aztreonam, but can be inhibited by serine-type $\beta$-lactamase inhibitors as sulbactam, clavulanate and tazobactam (Philippon et al., 1989; Bradford, 2001). SHV-2 is the first ESBL, identified in a clinical isolate of Klebsiella ozaenae in Germany (Kliebe et al., 1985). To date, over 10 families have been documented to be associated with ESBLs, including CTX-M, SHV, TEM, PER, VEB, BES, GES, TLA, SFO and OXA (Paterson and Bonomo, 2005).

CTX-M enzymes, the plasmid-mediated acquired cefotaximases from a distinct phylogenetic lineage, constitute a rapidly growing family of extended-spectrum $\beta$-lactamases (ESBLs) with significant clinical impact. CTX-Ms are found in at least 26 bacterial species, particularly in Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis. At least 109 members in CTX-M family are identified and can be divided into seven clusters based on their phylogeny. CTX-M-15 and CTX-M-14 are the most dominant variants. Chromosome-encoded intrinsic cefotaximases in Kluyvera spp. are proposed to be the progenitors of CTX-Ms, while IS$\text{Ecp1}$, IS$\text{CR1}$ and plasmid are closely associated with their mobilization and dissemination.

Keywords: CTX-M, cefotaximase, extended-spectrum $\beta$-lactamase (ESBL), IS$\text{Ecp1}$, IS$\text{CR1}$, plasmid

Epidemiology of CTX-M ESBLs

Occurrence and bacterial hosts

A plasmid-mediated cefotaximase was identified from a clinical isolate of E. coli in Munich, Germany, and designated CTX-M in reference to its hydrolytic activity and the region where it was found (Bauernfeind et al., 1990). To date, the numbers of CTX-M variants and the recognized organisms harboring the genes have dramatically increased. At least 109 CTX-M variants, CTX-M-1 to CTX-M-124, have been identified (Table 1) and assigned in the Lahey database (Jacoby and Bush, 2012). The amino-acid sequences of CTX-M-14 and...
### Table 1. CTX-M ESBLs and their bacterial hosts.

| CTX-M (alternate name) | Bacterial host | GenBank accession no. | Reference |
|------------------------|----------------|-----------------------|-----------|
| CTX-M-1 (MEN-1)        | *Escherichia coli* | X92506 | Bauernfeind et al., 1996 |
|                        | *Enterobacter cloacae* |       | al Naiemi et al., 2006 |
|                        | *Klebsiella pneumoniae* |       | Komatsu et al., 2001 |
|                        | *Proteus mirabilis* |       | al Naiemi et al., 2006 |
|                        | *Pseudomonas aeruginosa* |       | al Naiemi et al., 2006 |
|                        | *Salmonella enterica* |       | Rodríguez et al., 2009 |
|                        | *Serratia marcescens* |       | Choi et al., 2007 |
|                        | *Stenotrophomonas maltophilia* |      | al Naiemi et al., 2006 |
| CTX-M-2                | *Salmonella enterica* | X92507 | Bauernfeind et al., 1996 |
|                        | *Acinetobacter baumannii* |       | Nagano et al., 2004 |
|                        | *Citrobacter koseri* |       | al Naiemi et al., 2006 |
|                        | *Escherichia coli* |       | Arduino et al., 2003 |
|                        | *Enterobacter cloacae* |       | Arduino et al., 2003 |
|                        | *Klebsiella pneumoniae* |       | Arduino et al., 2003 |
|                        | *Morganella morganii* |       | Power et al., 2005 |
|                        | *Proteus mirabilis* |       | Bonnet et al., 2000 |
|                        | *Providencia stuartii* |       | Minarini et al. 2009 |
|                        | *Pseudomonas aeruginosa* |       | Bonnet et al., 2003 |
|                        | *Serratia marcescens* |       | Bonnet et al., 2003 |
|                        | *Vibrio cholerae* |       | Soler Bistué et al., 2006 |
| CTX-M-3                | *Citrobacter freundii* | Y10278 | Gniadkowski et al., 1998 |
|                        | *Aeromonas caviae* |       | Ye et al., 2010 |
|                        | *Escherichia coli* |       | Yan et al., 2000 |
|                        | *Enterobacter cloacae* |       | De Champs et al., 2000 |
|                        | *Enterobacter aerogenes* |       | Liu et al., 2009 |
|                        | *Klebsiella pneumoniae* |       | Baraniak et al., 2002b |
|                        | *Klebsiella oxytoca* |       | Baraniak et al., 2002b |
|                        | *Morganella morganii* |       | Baraniak et al., 2002b |
|                        | *Proteus mirabilis* |       | Eckert et al., 2006 |
|                        | *Salmonella enterica* |       | Gierczyński et al., 2003 |
|                        | *Serratia marcescens* |       | Baraniak et al., 2002b |
|                        | *Shigella flexneri* |       | Galimand et al., 2005 |
|                        | *Shigella sonnei* |       | Acikgoz et al., 2003 |
| CTX-M-4                | *Salmonella enterica* | Y14156 | Gazouli et al., 1998b |
| CTX-M-5                | *Salmonella enterica* | U95364 | Bradford et al., 1998 |
| CTX-M-6 (renumbered)   | *Salmonella enterica* | AF462635 | Gazouli et al., 1998a |
| CTX-M-7 (renumbered)   | *Salmonella enterica* | AJ005044 | Gazouli et al., 1998a |
| CTX-M-8                | *Citrobacter amalonaticus* | AF188721 | Bonnet et al., 2000 |
|                        | *Enterobacter cloacae* |       | Bonnet et al., 2000 |
|                        | *Enterobacter aerogenes* |       | Bonnet et al., 2000 |
|                        | *Escherichia coli* |       | Minarini et al. 2009 |
| CTX-M-9                | *Escherichia coli* | AF174129 | Sabaté et al., 2000 |
|                        | *Citrobacter freundii* |       | Minarini et al. 2009 |
|                        | *Enterobacter aerogenes* | EF441350 | Chanaowong et al., 2002 |
|                        | *Enterobacter cloacae* |       | Ho et al., 2005b |
|                        | *Enterobacter hormaechei* |       | Chanaowong et al., 2002 |
|                        | *Klebsiella pneumoniae* |       | Alobwede et al., 2003 |
|                        | *Klebsiella oxytoca* |       | García Fernández et al., 2007 |
|                        | *Salmonella enterica* |       | Choi et al., 2007 |
|                        | *Serratia marcescens* |       | |
| CTX-M-10               | *Escherichia coli* | AF255298 | Oliver et al., 2001 |
|                        | *Citrobacter freundii* |       | Valverde et al., 2004 |
|                        | *Enterobacter cloacae* |       | Cantón et al., 2002 |

(Continued)
Table 1. (Continued).

| CTX-M (alternate name) | Bacterial host | GenBank accession no. | Reference |
|------------------------|----------------|-----------------------|-----------|
| CTX-M-11               | Klebsiella pneumoniae | AY005110             | Cantón et al., 2002 |
| CTX-M-12               | Klebsiella pneumoniae | AF305837             | Coque et al., 2002 |
| CTX-M-13               | Klebsiella pneumoniae | AF252623             | Kariuki et al., 2001 |
| CTX-M-14               | Escherichia coli     | DQ058147             | Bae et al., 2006b |
| CTX-M-15 (UOE-1) *     | Escherichia coli     | AY044436             | Song et al., 2011 |
| CTX-M-16 *             | Escherichia coli     | AY029068             | Ho et al., 2005b |
| CTX-M-17               | Klebsiella pneumoniae | AY033516             | Ho et al., 2005a |
| CTX-M-18s              | Klebsiella pneumoniae | AF325133             | Chanawong et al., 2002 |
| CTX-M-19 *             | Klebsiella pneumoniae | AF325134             | Kanamori et al., 2011 |
| CTX-M-20               | Proteus mirabilis    | AY080894             | Kanamori et al., 2011 |
| CTX-M-21               | Escherichia coli     | EU118595             | Kanamori et al., 2011 |
| CTX-M-22               | Klebsiella pneumoniae | DQ350883             | Kanamori et al., 2011 |
| CTX-M-23 *             | Escherichia coli     | AY044436             | Kim et al., 2005 |
| CTX-M-24               | Klebsiella pneumoniae | AY033516             | Song et al., 2011 |
| CTX-M-25               | Proteus mirabilis    | AY080894             | Song et al., 2011 |
| CTX-M-26               | Enterobacter cloacae | EU118595             | Chanawong et al., 2002 |
| CTX-M-27               | Serratia liquefaciens | DQ350883             | Ho et al., 2005b |
| CTX-M-28               | Shigella flexneri    | AY033516             | Ho et al., 2005a |
| CTX-M-29               | Shigella sonnei      | AY033516             | Chanawong et al., 2002 |
| CTX-M-30               | Escherichia coli     | AY033516             | Kanamori et al., 2011 |
| CTX-M-31               | Klebsiella pneumoniae | AF325133             | Kanamori et al., 2011 |
| CTX-M-32               | Proteus mirabilis    | AY080894             | Kanamori et al., 2011 |
| CTX-M-33               | Enterobacter cloacae | EU118595             | Kanamori et al., 2011 |
| CTX-M-34               | Serratia liquefaciens | DQ350883             | Kanamori et al., 2011 |
| CTX-M-35               | Shigella flexneri    | AY033516             | Kanamori et al., 2011 |
| CTX-M-36               | Shigella sonnei      | AY033516             | Kanamori et al., 2011 |
| CTX-M-37               | Escherichia coli     | AY033516             | Chanawong et al., 2002 |
| CTX-M-38               | Klebsiella pneumoniae | AY080894             | Ho et al., 2005b |
| CTX-M-39               | Proteus mirabilis    | AY080894             | Ho et al., 2005a |
| CTX-M-40               | Enterobacter cloacae | EU118595             | Chanawong et al., 2002 |
| CTX-M-41               | Serratia liquefaciens | DQ350883             | Ho et al., 2005b |
| CTX-M-42               | Shigella flexneri    | AY033516             | Ho et al., 2005a |
| CTX-M-43               | Shigella sonnei      | AY033516             | Chanawong et al., 2002 |
| CTX-M-44               | Escherichia coli     | AY033516             | Ho et al., 2005b |
| CTX-M-45               | Klebsiella pneumoniae | AY080894             | Ho et al., 2005a |
| CTX-M-46               | Proteus mirabilis    | AY080894             | Chanawong et al., 2002 |
| CTX-M-47               | Enterobacter cloacae | EU118595             | Chanawong et al., 2002 |
| CTX-M-48               | Serratia liquefaciens | DQ350883             | Chanawong et al., 2002 |
| CTX-M-49               | Shigella flexneri    | AY033516             | Chanawong et al., 2002 |
| CTX-M-50               | Shigella sonnei      | AY033516             | Chanawong et al., 2002 |
| CTX-M-51               | Escherichia coli     | AY033516             | Chanawong et al., 2002 |
| CTX-M-52               | Klebsiella pneumoniae | AY080894             | Chanawong et al., 2002 |
| CTX-M-53               | Proteus mirabilis    | AY080894             | Chanawong et al., 2002 |
| CTX-M-54               | Enterobacter cloacae | EU118595             | Chanawong et al., 2002 |
| CTX-M-55               | Serratia liquefaciens | DQ350883             | Chanawong et al., 2002 |
| CTX-M-56               | Shigella flexneri    | AY033516             | Chanawong et al., 2002 |
| CTX-M-57               | Shigella sonnei      | AY033516             | Chanawong et al., 2002 |
| CTX-M-58               | Escherichia coli     | AY033516             | Chanawong et al., 2002 |
| CTX-M-59               | Klebsiella pneumoniae | AY080894             | Chanawong et al., 2002 |
| CTX-M-60               | Proteus mirabilis    | AY080894             | Chanawong et al., 2002 |
| CTX-M-61               | Enterobacter cloacae | EU118595             | Chanawong et al., 2002 |
| CTX-M-62               | Serratia liquefaciens | DQ350883             | Chanawong et al., 2002 |
| CTX-M-63               | Shigella flexneri    | AY033516             | Chanawong et al., 2002 |
| CTX-M-64               | Shigella sonnei      | AY033516             | Chanawong et al., 2002 |

(Continued)
| CTX-M (alternate name) | Bacterial host | GenBank accession no. | Reference |
|-----------------------|----------------|----------------------|-----------|
| CTX-M-25 *            | *              |                      |           |
| CTX-M-26              | *              |                      |           |
| CTX-M-27 *            | *              |                      |           |
| CTX-M-28              | *              |                      |           |
| CTX-M-29              | *              |                      |           |
| CTX-M-30              | *              |                      |           |
| CTX-M-31              | *              |                      |           |
| CTX-M-32 *            | *              |                      |           |
| CTX-M-33              | *              |                      |           |
| CTX-M-34              | *              |                      |           |
| CTX-M-35 *            | *              |                      |           |
| CTX-M-36              | *              |                      |           |
| CTX-M-37 *            | *              |                      |           |
| CTX-M-38              | *              |                      |           |
| CTX-M-39              | *              |                      |           |
| CTX-M-40 *            | *              |                      |           |
| CTX-M-41              | *              |                      |           |
| CTX-M-42 *            | *              |                      |           |
| CTX-M-43              | *              |                      |           |
| CTX-M-44 (Toho-1)     | *              |                      |           |
| CTX-M-45 (Toho-2)     | *              |                      |           |
| CTX-M-46              | *              |                      |           |
| CTX-M-47              | *              |                      |           |
| CTX-M-48              | *              |                      |           |
| CTX-M-49              | *              |                      |           |
| CTX-M-50              | *              |                      |           |
| CTX-M-51              | *              |                      |           |
| CTX-M-52              | *              |                      |           |
| CTX-M-53 *            | *              |                      |           |

(Continued)
Table 1. (Continued).

| CTX-M (alternate name) | Bacterial host                       | GenBank accession no. | Reference          |
|------------------------|--------------------------------------|-----------------------|--------------------|
| CTX-M-54 *             | Klebsiella pneumoniae                | DQ303459              | Bae et al., 2006a  |
| CTX-M-55 *             | Escherichia coli                     | DQ885477              | Kiratisin et al., 2007 |
|                        | Klebsiella pneumoniae                |                      | Kiratisin et al., 2007 |
|                        | Shigella sonnei                      |                      | Zhang et al., 2011  |
| CTX-M-56               | Escherichia coli                     | EF374097              | Pallecchi et al., 2007 |
| CTX-M-57†              | Salmonella enterica                  | DQ810789              | Hopkins et al., 2008 |
|                        | Shigella sonnei                      | EU086736              |                    |
| CTX-M-58 *             | Escherichia coli                     | EF210159              |                    |
| CTX-M-59               | Klebsiella pneumoniae                | DQ408762              | de Oliveira et al., 2008 |
| CTX-M-60               | Klebsiella pneumoniae                | AM411407              |                    |
| CTX-M-61               | Salmonella enterica                  | EF219142              | Brasme et al., 2007 |
|                        | Klebsiella pneumoniae                |                      | Mendonça et al., 2009 |
| CTX-M-62 *             | Klebsiella pneumoniae                | EF219134              | Zong et al., 2008   |
| CTX-M-63               | Klebsiella pneumoniae                | AB205197              |                    |
|                        | Morganella morganii                  | EU660216              |                    |
|                        | Salmonella enterica                  |                      |                    |
|                        | Enterobacter cloacae                 | GQ300937              |                    |
| CTX-M-64 *             | Shigella sonnei                      | AB284167              | Nagano et al., 2009 |
|                        | Escherichia coli                     |                      | Sun et al., 2010    |
| CTX-M-65               | Escherichia coli                     | EF418608              | Doi et al. 2008     |
|                        | Citrobacter freundii                 | EF394372              |                    |
|                        | Salmonella enterica                  | FJ907380              |                    |
| CTX-M-66               | Proteus mirabilis                    | EF576988              | Wu et al., 2008     |
| CTX-M-67               | Escherichia coli                     | EF581888              | Oteo et al., 2008   |
| CTX-M-68               | Klebsiella pneumoniae                | EU177100              | Heffernan et al., 2009 |
| CTX-M-69               | Escherichia coli                     | EU402393              |                    |
| CTX-M-70†              | Assigned                             |                      |                    |
| CTX-M-71               | Klebsiella pneumoniae                | FJ815436              | Schneider et al., 2009 |
| CTX-M-72               | Klebsiella pneumoniae                | AY847148              | Cheng et al., 2009  |
| CTX-M-73†              | Assigned                             |                      |                    |
| CTX-M-74               | Enterobacter cloacae                 | GQ149243              | Minarini et al., 2009 |
| CTX-M-75               | Providencia stuartii                 | GQ149244              | Minarini et al., 2009 |
| c-CTX-M-76 ¤           | Kluyvera ascorbata                   | AM982520              |                    |
| c-CTX-M-77 ¤           | Kluyvera ascorbata                   | AM982521              |                    |
| c-CTX-M-78 ¤           | Kluyvera georgiana                   | AM982522              | Rodriguez et al., 2010 |
| CTX-M-79               | Escherichia coli                     | EF426798              | Tian et al., 2008   |
| CTX-M-80               | Klebsiella pneumoniae                | EU202673              | Cheng et al., 2010  |
| CTX-M-81               | Klebsiella pneumoniae                | EU136031              | Cheng et al., 2010  |
| CTX-M-82 *             | Escherichia coli                     | DQ256091              | Liu et al., 2009    |
| CTX-M-83               | Salmonella enterica                  | FJ214366              | Cui et al., 2009    |
| CTX-M-84               | Salmonella enterica                  | FJ214367              | Cui et al., 2009    |
| CTX-M-85               | Salmonella enterica                  | FJ214368              | Cui et al., 2009    |
| CTX-M-86               | Salmonella enterica                  | FJ214369              | Cui et al., 2009    |
| CTX-M-87 (renumbered)  | Escherichia coli                     | EU545409              | Yin et al., 2009    |
| CTX-M-88               | Salmonella enterica                  | FJ873739              | Ranjarbar et al., 2010 |
| CTX-M-89               | Proteus mirabilis                    | FJ971899              | McGettigan et al., 2009 |
|                        | Enterobacter cloacae                 | FJ966096              |                    |
| CTX-M-90               | Salmonella enterica                  | FJ907381              |                    |
|                        | Proteus mirabilis                    |                      |                    |
| CTX-M-91               | Proteus mirabilis                    | GQ870432              | Song et al., 2011   |
| CTX-M-92               | Escherichia coli                     | GU127598              | Sepuinee et al., 2010 |
|                        | Klebsiella pneumoniae                |                      | Sepuinee et al., 2010 |
| CTX-M-93 *             | Escherichia coli                     | HQ166709              | Djamdjian et al., 2011 |
| CTX-M-94               | Escherichia coli                     | HM167760              |                    |
| c-CTX-M-95 ¤           | Kluyvera ascorbata                   | FN813245              |                    |
CTX-M-18 and of CTX-M-55 and CTX-M-57 are identical, and CTX-M-118 has been withdrawn. There is no detailed information available for the assigned members CTX-M-70, -73, -74, -75, -76, -77, -78, -95, -98, -99, -100, -103, -106, -107, -108, -109, -112, -113, -114, -115, -116, -117, -118, -119, -120, and -124 so far. In addition, CTX-M-76, -77, -78 and -95 are chromosome-encoded intrinsic cefotaximases in *Kluyvera* spp., and therefore, they are not counted into the CTX-M family. CTX-M-2, -3 and -37 are plasmid-mediated enzymes but also found on chromosomes in *Kluyvera* spp. To clarify the differences, the term c-CTX-M is used for such chromosome-encoded CTX-Ms in this article. Of the studied CTX-Ms, at least 19 variants display the enhanced catalytic efficiencies against ceftazidime (Table 1).

CTX-M enzymes as the most prevalent ESBLs in *E. coli, K. pneumoniae* and *P. mirabilis*

The high prevalence of CTX-M ESBL genes in Enterobacteriaceae, particularly in *E. coli, K. pneumoniae* and *P. mirabilis*, has been documented worldwide (Bonnet, 2004; Cantón and Coque, 2006), while the CTX-Ms are not prominent in *P. aeruginosa* and *A. baumannii* (Zhao and Hu, 2010, 2012).

A study on the resistance of Enterobacteriaceae to third-generation cephalosporin was undertaken in 16 British hospitals over a 12-week period (Potz et al., 2006). Of 19,252 clinical isolates, CTX-M-producing strains accounted for 1.7%, higher than other ESBLs-producing strains (0.6%) and high-level AmpC-producing strains (0.4%). Particularly, of the resistance isolates of *E. coli* (*n* = 574) and *Klebsiella* spp. (*n* = 243), the CTX-M-producing strains accounted for 50.9% and 81.9%, respectively, by contrast with other ESBLs-producing strains (15.3% and 11.1%), high-level AmpC-producing strains (7.1% and 0.8%) and non-β-lactamase-producing strains (26.7% and 3.3%).

A rapid occurrence of CTX-M-producing strains in Enterobacteriaceae was documented by several longitudinal surveillances. Of 20,258 *E. coli* isolates studied in

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**Table 1. (Continued).**

| CTX-M (alternate name) | Bacterial host                  | GenBank accession no. | Reference |
|------------------------|---------------------------------|-----------------------|-----------|
| CTX-M-96 (CTX-M-12a)   | *Klebsiella pneumoniae*         | AJ704396              | Zhang et al., 2011 |
| CTX-M-97               | *Escherichia coli*              | HM776707              |           |
| CTX-M-98               | *Escherichia coli*              | HM755448              |           |
| CTX-M-99               | *Klebsiella pneumoniae*         | HM803271              |           |
| CTX-M-100              | Assigned                        |                       |           |
| CTX-M-101              | *Escherichia coli*              | HQ398214              |           |
| CTX-M-102              | *Escherichia coli*              | HQ398215              |           |
| CTX-M-103              | Assigned                        |                       |           |
| CTX-M-104              | *Escherichia coli*              | HQ833652              |           |
| CTX-M-105              | *Escherichia coli*              | HQ833651              |           |
| CTX-M-106              | *Escherichia coli*              | HQ913565              |           |
| CTX-M-107              | *Shigella flexneri*             | JF274244              |           |
| CTX-M-108              | *Shigella flexneri*             | JF274245              |           |
| CTX-M-109              | *Shigella flexneri*             | JF274248              |           |
| CTX-M-110              | *Shigella sonnei*               | JF274242              |           |
| CTX-M-111              | *Shigella flexneri*             | JF274243              |           |
| CTX-M-112              | *Shigella sonnei*               | JF274246              |           |
| CTX-M-113              | *Shigella flexneri*             | JF274247              |           |
| CTX-M-114              | *Providencia rettgeri*          | GQ351346              |           |
| CTX-M-115              | Assigned                        |                       |           |
| CTX-M-116              | *Proteus mirabilis*             | JF966749              |           |
| CTX-M-117              | *Escherichia coli*              | JN227585              |           |
| CTX-M-118              | Withdrawn                       |                       |           |
| CTX-M-119              | Assigned                        |                       |           |
| CTX-M-120              | Assigned                        |                       |           |
| CTX-M-121              | *Escherichia coli*              | JN790862              |           |
| CTX-M-122              | *Escherichia coli*              | JN790863              |           |
| CTX-M-123              | *Escherichia coli*              | JN790864              |           |
| CTX-M-124              | Assigned                        |                       |           |

*, with enhanced catalytic efficiencies against ceftazidime; †, have been assigned in the Lahey database (Jacoby and Bush 2012); ‡, chromosome-encoded intrinsic cefotaximase identified in *Kluyvera* spp.; §, CTX-M-18 and CTX-M-14, CTX-M-57 and CTX-M-55 are identical in their amino acid sequences.
Italy, the prevalence of ESBL-producing strains increased from 0.2% in 1999 to 1.6% in 2003, of which CTX-M-positive strains increased from 12.5% to 38.2% (Brigante et al., 2005). Of 1574 *P. mirabilis* clinical isolates collected in a Taiwanese hospital during 1999–2005, 44 CTX-M-producing strains were detected at a rate of 0.7% in 1999 and approximately 6% after 2002 (Wu et al., 2008). Of 11,407 *E. coli* isolates from urine samples of outpatients in the USA, 107 CTX-M-producing strains were detected at a rate of 0.07% in 2003 and 1.66% in 2008 (Qi et al., 2010).

CTX-M-producing strains widespread not only in human but also in animals and in environments. Of 240 *E. coli* isolates from health and sick pets during 2007–2008 in China, 97 strains (40.4%) harbored ESBL-encoding genes, of which 96 strains were confirmed to be carriers of *bla<sub>CTX-M</sub>* genes (Sun et al., 2010). Of 16 multi-drug resistant *E. coli* isolates from river water during 2000–2001 in South Korea, 10 strains harbored CTX-M-14 gene (Kim et al., 2008). Of 79 food samples of animal origin in Tunisia, *bla<sub>CTX-M</sub>* genes were identified in 34 food samples. Of 79 food samples of animal origin in Tunisia, 41% (34/83) were ESBL producers (288 isolates) (Damjanova et al., 2008). Of the CTX-M-15 producers derived from three genetically different, CTX-M-15 and CTX-M-14 are the most dominant variants detected worldwide in clinically important pathogens, followed by CTX-M-2, CTX-M-3 and CTX-M-1 (Table 1). Conjugative plasmid-mediated horizontal transfer and clonal spread contributed to the increased prevalence.

Of 171 CTX-M-producing *E. coli* isolates from 11 Canadian medical centers in 2007, the positive rates for CTX-M-15, CTX-M-14, CTX-M-3 and CTX-M-27 were 86.5%, 9.9%, 2.9% and 0.6%, respectively (Peirano et al., 2010). Of 202 CTX-M-producing *K. pneumoniae* isolates from 41 medical centers in Hungary in 2005, 97% were CTX-M-15 producers derived from three genetically distinct clones (Damjanova et al., 2008). Of the CTX-M-producing (288 *E. coli* and 142 *K. pneumoniae* isolates) collected from 6 provinces in China during 1998–2002, CTX-M-14 was predominantly detected in 77.4% and 52.8% of the isolates, respectively, followed by CTX-M-3 (18.4% and 29.6%), CTX-M-24 (5.6% and 14.1%) and CTX-M-15 (0.7% and 1.4%) (Yu et al., 2007). An outbreak of CTX-M-producing *S. enterica* infection occurred in a university hospital in Algeria during 2008–2009, and all of 200 isolates from 138 patients were CTX-M-15 producers, identified to be a single clone (Naas et al., 2011).

Of 44 clinical isolates of CTX-M-producing *P. mirabilis* from a Taiwanese hospital, CTX-M-14 and CTX-M-3 positive strains accounted for 50% and 49.9%, respectively (Wu et al., 2008). Of 71 CTX-M-producing *P. mirabilis* isolates collected from 132 geographically distant hospitals in Japan, however, 100% of the strains carried the *bla<sub>CTX-M-2</sub>*-like genes (Shibata et al., 2006). CTX-M-2 was also predominant in *C. koseri*, accounting for 76.7% of ESBL-producing strains (*n* = 60) collected from 10 areas throughout Japan in a 5-month period between 2009 and 2010 (Kanamori et al., 2011).

**Phylogeny, origin and evolution of CTX-M enzymes**

**Amino-acid identity and phylogeny**

The deduced amino-acid sequences of CTX-Ms comprise 291 residues, with the exceptions of CTX-M-11 (282), CTX-M-107 and -108 (288), CTX-M-45 and -109 (289), CTX-M-40, -63 and -106 (290) and CTX-M-110 (292). Based on the phylogenetic tree of amino-acid sequences, CTX-M enzymes may be divided into seven clusters (Figure 1).

CTX-M-3 cluster includes 42 members, sharing 97.6–99.7% identity in amino-acid sequences. The other clusters are as follows: CTX-M-14 cluster, 38 members, 97.3–99.7% identity; CTX-M-2 cluster, 16 members, 95.2–99.7% identity; CTX-M-25 cluster, 7 members, 98.6–99.7% identity; CTX-M-8 cluster, 3 members, 97.9–99.7% identity; CTX-M-64 cluster, 2 members, 95.9% identity. There is only one member in CTX-M-45 cluster. Among CTX-M variants, CTX-M-4 and CTX-M-45 are most divergent with 91 amino-acid substitutions.

**Variations of amino-acid sequences**

Based on the central positions in phylogenetic tree (Figure 1), CTX-M-2, -3, -8, -14, -25, -45 and -64 are chosen as the representative enzymes in each cluster. The amino-acid sequences of the seven enzymes are aligned, and numbered according to the standard numbering scheme for the class A serine β-lactamases, giving the active site serine residue the Ambler number 70 (Ambler et al., 1991) (Figure 2). The sequences of CTX-M variants are then compared with their representative in each cluster (Table 2). In the CTX-M-3 cluster, for example, a single amino-acid is substituted between CTX-M-3 and CTX-M-15 (22), -22, -42, -54, -62, -66, -72 or -80, while 5 amino-acids are substituted between CTX-M-3 and CTX-M-58.

**Origin of CTX-M family**

In the family Enterobacteriaceae, the genus *Kluyvera* is a relatively new member, which has been isolated from various clinical specimens and regarded as a potentially virulent pathogen (Sarria et al., 2001). Some *Kluyvera* spp. harbor chromosome-encoded intrinsic genes of
Cefotaximases which are closely associated with CTX-Ms (Decousser et al., 2001; Humeniuk et al., 2002; Rodríguez et al., 2004). Generally, *Kluyvera* spp. are susceptible to cefotaxime in despite of the presence of naturally occurring cefotaximases. However, the recombinant clones of *E. coli* with *Kluyvera*-derived cefotaximase genes exhibited a significant increase in resistance to cefotaxime (Decousser et al., 2001; Humeniuk et al., 2002;
Figure 2. Comparison of amino-acid sequences of seven representative enzymes in the CTX-M family. Amino-acids are numbered according to the standard numbering scheme for the class A serine β-lactamases, giving the active site serine residue the Ambler number 70. Dots indicate identical amino-acids compared to CTX-M-2. Deletion mutations are expressed with short lines. The underlined amino-acids, 70SXXK73, 107P, 130SDN132, 143GG144, 166E and 234KXG236, represent the conserved residues in typical class A serine β-lactamases.

Table 2. Amino acid substitutions of CTX-M variants compared to their representative enzymes.

| CTX-M Amino acid substitution | CTX-M Amino acid substitution |
|--------------------------------|--------------------------------|
| CTX-M-2                         | CTX-M-4                         |
| CTX-M-3                         | CTX-M-5                         |
| CTX-M-6                         | CTX-M-7                         |
| CTX-M-8                         | CTX-M-9                         |
| CTX-M-10                        | CTX-M-11                        |
| CTX-M-12                        | CTX-M-13                        |
| CTX-M-14                        | CTX-M-15                        |
| CTX-M-16                        | CTX-M-17                        |
| CTX-M-18                        | CTX-M-19                        |
| CTX-M-20                        | CTX-M-21                        |
| CTX-M-22                        | CTX-M-23                        |
| CTX-M-24                        | CTX-M-25                        |
| CTX-M-26                        | CTX-M-27                        |
| CTX-M-28                        | CTX-M-29                        |
| CTX-M-30                        | CTX-M-31                        |
| CTX-M-32                        | CTX-M-33                        |
| CTX-M-34                        | CTX-M-35                        |
| CTX-M-36                        | CTX-M-37                        |
| CTX-M-38                        | CTX-M-39                        |
| CTX-M-40                        | CTX-M-41                        |
| CTX-M-42                        | CTX-M-43                        |
| CTX-M-44                        | CTX-M-45                        |

(Continued)
Rodríguez et al., 2004), suggesting that a proper genetic platform is necessary for the gene expression. The chromosome-encoded cefotaximases identified in *Kluyvera* spp. include KLUA, KLUG, KLUY, KLUC, c-CTX-M-2, c-CTX-M-3, c-CTX-M-7, c-CTX-M-28, c-CTX-M-79 and c-CTX-M-95. All of them comprise 291 amino-acid residues. An aspartate aminotransferase-encoding gene is found commonly upstream of these chromosomal *bla* genes, which is replaced by IS*ecp1* or IS*cr1* in the plasmid-harbored *bla*_{CTX-M} genes (see the details under next section).

KLIJA-1 to -5 and -8 to -12 (GenBank accession no. AJ272538, AJ251722, AJ427461, AJ427462, AJ427463, AJ427465, AJ427466, AJ427467, AJ427468, AJ427469) are a group of chromosomal cefotaximases identified in *K. ascorbata*, with minor variations (<5%) in their

| Cluster 2 | Cluster 3 |
|----------|-----------|
| CTX-M-75 | P14S      |
| CTX-M-92 | A205T     |
| CTX-M-97 | R3G       |

Table 2. (Continued).  

| Cluster 14 | vs. CTX-M-14 |
|------------|--------------|
| CTX-M-46   | S27N, A47P   |
| CTX-M-47   | G42R         |
| CTX-M-48   | S27N         |
| CTX-M-49   | G42R, A47P   |

| Cluster 25 | vs. CTX-M-25 |
|------------|--------------|
| Cluster 64 | vs. CTX-M-64 |

Critical Reviews in Microbiology
amino-acid sequences (Humeniuk et al., 2002). KLUA-2 shares 100% identity with plasmid-mediated CTX-M-5. CTX-M-2 and CTX-M-3 originally identified on plasmids were also found on the chromosomes of K. ascorbata (Rodríguez et al., 2004; Lartigue et al., 2006). The immediate upstream- and downstream-sequences of bla\textsubscript{KLUA-1} and plasmid-mediated bla genes in CTX-M-2 cluster (bla\textsubscript{CTX-M-2, -4, -5, -6, -7, -44}) share 85 to 100% identities (Di Conza et al., 2002; Humeniuk et al., 2002). The architectures of the flanking regions corresponding to c-CTX-M-3 and plasmid-mediated CTX-M-3 are identical, including a 128 bp immediate upstream region and the first 373 bp of the downstream region of the bla gene (Rodríguez et al., 2004). The c-CTX-M-76, -77 and -95 (AM982520, AM982521, FN813245) identified in K. ascorbata also share high identities with the enzymes in CTX-M-2 cluster.

KLUY-1 to -4 (AY623932, AY623935, AY623934, AY623933) are a group of chromosomal cefotaximases identified in K. Georgiana (Olson et al., 2005). They share high homology with the enzymes in CTX-M-14 cluster. Typically, KLUY-1 exhibits 100% amino-acid identity with CTX-M-14. The upstream- and downstream-sequences of bla\textsubscript{KLUY} and bla\textsubscript{CTX-M-9, -13, -14} also share consistent identity. A 42 bp upstream region of bla\textsubscript{CTX-M-14} is identical to the corresponding region of bla\textsubscript{KLUY} genes. A 347 bp downstream region of bla\textsubscript{CTX-M-9} and bla\textsubscript{CTX-M-13} shares 95.7–98.6% identities with the corresponding region of bla\textsubscript{KLUY} genes (Olson et al., 2005).

KLUG-1 (AF501233) and c-CTX-M-78 (AM982522) are the chromosomal cefotaximases identified in K. Georgiana. KLUG-1 shares 99% amino-acid identity with the plasmid-mediated CTX-M-8 (Poirel et al., 2002b). The c-CTX-M-78 possesses high homology with the known members of CTX-M-25 cluster, sharing 95.2–96.2% identities (Rodríguez et al., 2010).

CTX-M-37 was also found on the chromosome of K. cryocrescens (FN813246), suggesting the c-CTX-M-37 as an origin of CTX-M-3 cluster. KLUC-1 (AY026417) and KLUC-2 (EF057432), with a single amino-acid substitution, are two chromosome-encoded cefotaximases identified in K. cryocrescens (Decousser et al., 2001). KLUC-1 and -2 are diverse from the known CTX-Ms, sharing only 87.6% identity with CTX-M-3. Notably, KLUC-2 was also identified on a plasmid carried by a clinical isolate of E. cloacae, indicating the transfer of bla\textsubscript{KLUC} from chromosome to the plasmid (Petrella et al., 2008). We would like to suggest the plasmid-mediated KLUC-2 as a novel cluster or member of CTX-M family.

CTX-M-64 shows a chimeric sequence of both CTX-M-14 (central portion) and CTX-M-15 (N- and C-terminal moieties), suggesting an origination owing to homologous recombination between the bla\textsubscript{CTX-M-14} and bla\textsubscript{CTX-M-15} genes (Nagano et al., 2009).

Taken together, the origins of the acquired CTX-Ms in various clusters can be traced back to the intrinsic cefotaximase genes harbored by Kluyvera spp., of which the CTX-M-2 cluster appears to be derived from K. ascorbata, the CTX-M-14, CTX-M-8 and CTX-M-25 clusters from K. georgiana, while the CTX-M-3 cluster from both K. ascorbata and K. cryocrescens (Figure 3).

**Genetic platforms of CTX-M enzymes**

**IS\textsubscript{Ecp1}**

Insertion sequences (ISs) are the smallest transposable elements (<2.5 kb) capable of independent transposition in an organism, thereby causing insertion mutations and genome rearrangements (Mahillon and Chandler, 1998). ISs play three basic roles in bacteria: encoding a transposase which makes a genetic element mobile; providing promoters to activate silent genes or enhance expression of downstream determinants; moving IS-mobilized genes among integrons, transposons, plasmids and chromosomes, thereby greatly increasing the opportunity a resistance determinant becomes transferable.

Of the genetic platforms associated with CTX-Ms, IS\textsubscript{Ecp1} is one of the most important elements (Table 3). IS\textsubscript{Ecp1} was first identified on the plasmid pST01 in E. coli strain 79 (AJ242809), hence its name (Stapleton, 1999). IS\textsubscript{Ecp1} is composed of an orf encoding a transposase with 420 amino-acids and two imperfect and inverted
Table 3. Genetic platforms of CTX-M enzymes.

| CTX-M  | Genetic platform | Bacterial host | Reference/GenBank accession no. |
|--------|------------------|----------------|---------------------------------|
| CTX-M-1| ISEcp1-bla<sub>CTX-M-1</sub>-orf477  
ISEcp1- Δ----I526-ISEcp1Δ-bla<sub>CTX-M-1</sub>-orf477∆  
intI1-dfrA7-aadA5-qacE1-sul1-ISCR1-bla<sub>CTX-M-1</sub>-orf3-IS3000-qacE1-sul1-like-orf5  
intI1-dfrA7-aadA5-qacE1-sul1-ORF1-bla<sub>CTX-M-1</sub>-orf3-IS3000-qacE1-sul1-like-orf5  
intI1-dfrA7-aadA5-qacE1-sul1-ORF1-bla<sub>CTX-M-1</sub>-orf3-IS3000-qacE1-sul1-like-orf5  | E. coli  
K. pneumoniae  
E. coli  
E. coli  | Eckert et al., 2006  
Diestra et al., 2009  
Cullik et al., 2010  
Su et al., 2008 |
| CTX-M-2| intI1-aacA4-bla<sub>CTX-M-2</sub>-orfD-qacE1-sul1-ISCR1-bla<sub>CTX-M-2</sub>-orf3-Δ-qacE1-sul1  
intI1-aacA4-bla<sub>CTX-M-2</sub>-orfD-qacE1-sul1-ISCR1-bla<sub>CTX-M-2</sub>-orf3-Δ-qacE1-sul1  
intI1-aacA4-bla<sub>CTX-M-2</sub>-orfD-qacE1-sul1-ORF1-bla<sub>CTX-M-2</sub>-orf3-Δ-qacE1-sul1  
intI1-aacA4-bla<sub>CTX-M-2</sub>-orfD-qacE1-sul1-ORF1-bla<sub>CTX-M-2</sub>-orf3-Δ-qacE1-sul1 | P. mirabilis  
V. cholera  
S. enterica  
K. pneumoniae  | Arduino et al., 2002  
Soler Bistué et al., 2006  
AI311891  
EU780013 |
| CTX-M-3| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-3</sub>-orf3A-qacE1 | K. pneumoniae  | EU622037 |
| CTX-M-4| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-4</sub>-orf3A-qacE1 | K. pneumoniae  | EU622040 |
| CTX-M-5| intI1-dfrA1-aadA2-qacE1-sul1-ORF1-bla<sub>CTX-M-5</sub>-orf3A-qacE1-sul1  
intI1-dfrA1-aadA2-qacE1-sul1-ORF1-bla<sub>CTX-M-5</sub>-orf3A-qacE1-sul1  
intI1-dfrA1-aadA2-qacE1-sul1-ORF1-bla<sub>CTX-M-5</sub>-orf3A-qacE1-sul1  
intI1-dfrA1-aadA2-qacE1-sul1-ORF1-bla<sub>CTX-M-5</sub>-orf3A-qacE1-sul1  | E. coli  
S. enterica  
K. pneumoniae  
K. pneumoniae  | Eckert et al., 2006  
EFS925750  
EFS925751  
EU622039 |
| CTX-M-6| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-6</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-6</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622041 |
| CTX-M-7| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-7</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-7</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622043 |
| CTX-M-8| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-8</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-8</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622044 |
| CTX-M-9| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-9</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-9</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622045 |
| CTX-M-10| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-10</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-10</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622046 |
| CTX-M-11| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-11</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-11</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622047 |
| CTX-M-12| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-12</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-12</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622048 |
| CTX-M-13| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-13</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-13</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622049 |
| CTX-M-14| intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-14</sub>-orf3A-qacE1-sul1  
intI1-aacA1-qacE1-sul1-ORF1-bla<sub>CTX-M-14</sub>-orf3A-qacE1-sul1  | K. pneumoniae  | EU622050 |

(Continued)
Table 3. (Continued).

| CTX-M | Genetic platform | Bacterial host | Reference/GenBank accession no. |
|-------|------------------|----------------|---------------------------------|
| CTX-M-15 | IS{Ecp1–bla}_{CTX-M-15}–orf77 | A. hydrophila | Gómez-Garcés et al., 2011 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3 | E. coli | Eckert et al., 2006 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3 | A. baumannii | JN788267 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Lartigue et al., 2004 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Eckert et al., 2006 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | S. enterica | Fabre et al., 2009 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Eckert et al., 2006 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Brasme et al., 2007 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | AM910790 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | K. pneumoniae | Cao et al., 2002 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | K. pneumoniae | Poirel et al., 2003 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | AJ16344 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | AJ16346 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | S. liquefaciens | HM470254 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Eckert et al., 2006 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | Wu et al., 2008 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | Navon-Venezia et al. 2008 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Munday et al. 2004 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | K. pneumoniae | Navon-Venezia et al. 2008 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | K. pneumoniae | Munday et al. 2004 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | S. enterica | Bouallègue-Godet et al., 2005 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Sun et al., 2010 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Fernández et al., 2007 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Diestra et al., 2009 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Navon-Venezia et al. 2008 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Navon-Venezia et al. 2008 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Hopkins et al., 2006 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | DQ061159 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | S. enterica | Doublet et al., 2009 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | K. pneumoniae | Bae et al., 2006a |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Sun et al., 2010 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | JN777127 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | EU622856 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | K. pneumoniae | Zong et al., 2010 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | S. sonnei | Nagano et al., 2009 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Sun et al., 2010 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | Wu et al., 2008 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. cloacae | Minarini et al. 2009 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. stuartii | Minarini et al. 2009 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | FI169498 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | GU477621 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. cloacae | FJ966096 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | Song et al., 2011 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | Song et al., 2011 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | Djamdjian et al., 2011 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | HM755448 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | HQ398214 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | HQ398215 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | HQ33652 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | HQ33651 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | P. mirabilis | JF966749 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | JN790862 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | JN790863 |
|       | IS{Ecp1–bla}_{CTX-M-15}–orf773–Tn3Δ | E. coli | JN790864 |

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ISecp1 can mobilize the downstream-located bla<sub>CTX-M</sub> gene and provide a promoter for its expression (Karim et al., 2001; Cao et al., 2002; Poirel et al., 2003, 2005; Dhanji et al., 2011b).

Co-existence of ISeep1 and bla<sub>CTX-M</sub> at a high rate in CTX-M-producing E. coli isolates is well documented. ISeep1 was identified upstream of bla<sub>CTX-M</sub> genes in 86.9% of the isolates (93/107) recovered from health and sick pets in China, and no major clonal relatedness was observed (Sun et al., 2010). Similarly, ISeep1 was identified upstream of bla<sub>CTX-M</sub>-14 in 91.4% of the clinical isolates (32/35) in Korea (Kim et al., 2011), and upstream of bla<sub>CTX-M</sub>-1 in 69.2% of the isolates (9/13) from food samples in Tunisia (Ben Slama et al., 2010). In addition, variations of ISeep1 were also observed. ISeep1B, originally identified upstream of a bla<sub>CTX-M</sub>-19 gene cassette (AF458080), differs from ISeep1 by three nucleotide substitutions (Poirel et al., 2003). Of the 174 ISeep1-like and bla<sub>CTX-M</sub>-15 complex from E. coli isolates, the intact ISeep1, truncated ISeep1 with various lengths and a 24 bp remnant of ISeep1 accounted for 62%, 33.3% and 4.6%, respectively (Dhanji et al., 2011b). Notably, ISeep1 was also detected upstream of chromosomal bla<sub>CTX-M</sub>-2 genes in 4 P. mirabilis isolates in Japan (Harada et al., 2012), highlighting the ISeep1-mediated movement of bla<sub>CTX-M</sub> genes between plasmids and chromosomes.

ISeep1-bla<sub>CTX-M</sub>-IS903 (Figure 4A) and ISeep1-bla<sub>CTX-M</sub>-orf477 (Figure 4B) are two major genetic platforms. In some cases, ISeep1-mobilized bla<sub>CTX-M</sub> is inserted in a class 1 integron (Figure 4C). IS903 (V00359) encodes a transposase with 307 amino-acids and was originally found on a kanamycin resistance transposon Tn903 (Oka et al., 1981). IS903 and IS903-like elements, such as IS903C and IS903D, are located downstream of bla<sub>CTX-M</sub>-14 genes (Table 3), including bla<sub>CTX-M</sub>-14-like genes (bla<sub>CTX-M</sub>-14, -16, -17, -18, -24, -27, -65, -69, -93, -98, -102, -104, -105, -121, -122) and bla<sub>CTX-M</sub>-1-like gene (bla<sub>CTX-M</sub>-1). orf477 encodes a protein of 158 amino-acids with unknown function and the orf477 and orf477-like elements were found downstream of plasmid-harbored bla<sub>CTX-M</sub>-3-like genes.

**Figure 4.** Typical genetic platforms of CTX-M enzymes. A & B: the bla<sub>CTX-M</sub> gene cassettes bracketed upstream by ISeep1/ISeep1-like and downstream by IS903/IS903-like (A) or orf477/orf477-like (B); C: bla<sub>CTX-M</sub> genes associated with class 1 integron-ISeep1; D & E: bla<sub>CTX-M</sub> genes associated with class 1 integron-ISCR1 complex. CS, conserved segment; intI, integrase gene; qacEΔ1, quaternary ammonium resistance gene; sulI, sulphonamide resistance gene; 3′-CS2, the second copy of 3′-conserved segment.
The orf57 was also identified downstream of the chromosomal bla\textsubscript{CTX-M-93} in K. ascorbata, of the chromosomal bla\textsubscript{KLTV1}, -2, -3, -4, in K. georgiana, and of the chromosomal bla\textsubscript{CTX-M-37} (FN9813426) in K. cryocrescens (Rodriguez et al., 2004; Olson et al., 2005), footnoting the IS\textsubscript{ECp1}-mediated transfer of bla\textsubscript{CTX-M} genes together with the orf57 from the chromosomes of Kluyvera spp. to plasmids.

**Class 1 integron-IS\textsubscript{CR1} complex**

Integrons are defined as mobile DNA elements that can capture genes by site-specific recombination (Stokes and Hall, 1989). A typical class 1 integron consists of a 5′ conserved segment (5′-CS), a variable region and a 3′ conserved segment (3′-CS). The 5′-CS consists of the gene encoding integrase (intI1), the site adjacent to intI1 for the insertion of captured genes (attI), and a promoter region (Pc). The 3′-CS often consists of a partially deleted qac gene (qacEA1) fused to a sul1 gene, and confers resistance to antiseptics and sulfonamide, respectively. Class 1 integrons play a critical role in acquiring and spreading metallo-β-lactamases (Mazel, 2006; Zhao and Hu, 2011a,b). The role of integrons in CTX-M gene acquisition and dissemination, however, is still unclear. The physical link of some bla\textsubscript{CTX-M} genes with class 1 integron-IS\textsubscript{ECp1} complex (Figure 4C) and class 1 integron-IS\textsubscript{CR1} complex (Figure 4D, 4E) indicates a possible association among the three genetic elements.

IS\textsubscript{CR1} is another important element in the genetic platforms associated with the mobilization and dissemination of CTX-M genes (Rodriguez-Martinez et al. 2006; Toleman et al., 2006). Common region 1 (CR1) was first found as element associated with but distinct from class 1 integrons (Stokes et al., 1993). The CR1 element was renamed IS\textsubscript{CR1} because it possesses the key motifs of IS\textsubscript{91}-like element and accommodates orf513 gene which codes a putative transposase of 513 amino-acids (Toleman et al., 2006). IS\textsubscript{CR1} is particularly important for CTX-M-2 and CTX-M-9 genes (Table 3). In most instance, the IS\textsubscript{CR1}-bla\textsubscript{CTX-M-2} is located between a typical class 1 integron and a fuse type of orfβ3 and qacEA1/sul1 (Table 3, Figure 4D). Notably, the genes harbored by class 1 integrons in their variable regions, such as bla\textsubscript{OXA-23}, aacA4, cmlA and dfr, are also associated with bacterial resistance to β-lactam, aminoglycoside, chloramphenicol and trimethoprim, respectively.

Molecular epidemiological study performed in Argentina during 1993–2000 showed that class 1 integron-IS\textsubscript{CR1} complex was adjacent to bla\textsubscript{CTX-M-2} in all the CTX-M-2 producers (n = 35), including Acinetobacter spp., E. cloacae, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, S. enterica and S. marcescens, while only 1.5% of the bla\textsubscript{CTX-M-2-negative} isolates (n = 65) harbored IS\textsubscript{CR1} (Arduino et al., 2003). These data strongly implicate the association of IS\textsubscript{CR1} with the emergence and dissemination of bla\textsubscript{CTX-M-2} gene. In addition, IS\textsubscript{CR1} is also related to bla\textsubscript{CTX-M-89} (members of CTX-M-2 cluster) and bla\textsubscript{CTX-M-1, -9, -14} (Table 3).

**Other IS and phage-related sequences**

Besides IS\textsubscript{ECp1}, IS903 and IS\textsubscript{CR1} described above, IS1, IS5, IS10, IS26, IS504, IS1294, IS1326, IS3000, IS4321 and IS6100 were also found to be adjacent to bla\textsubscript{CTX-M} genes (Table 3). In some cases, several IS elements co-existed in a gene complex, for example, intI1-dfrA12-orfI-aadA2-qacEΔ1-sul1-IS\textsubscript{CR1}-IS\textsubscript{6100}-IS\textsubscript{ECp1}-bla\textsubscript{CTX-M-14}-IS903D (Ba et al., 2008). Such heterogeneity may be explained by a continuously recombinatorial exchange of gene cassettes, denoting the sophisticated genetic rearrangement strategies that organisms acquire and dispense resistance genes.

A 12.2-kb DNA fragment containing bla\textsubscript{CTX-M-10} gene in plasmid pRYCE21 was cloned from K. pneumoniae, and further detected in other bacterial species including E. coli, E. cloacae and E. gergoviae. Analysis of the sequence showed a phage-related 3.5-kb element immediately upstream of the bla\textsubscript{CTX-M-10} gene cassettes. This phage-related fragment corresponds to four orf, of which orf2, orfβ and orf4 display homology to the genes of conserved phage tail proteins (Oliver et al., 2005). Although there is a limited report on phage-related CTX-M genes, this finding indicates that phages may also function as a tool for bla\textsubscript{CTX-M} associated genetic elements to become transferable.

**Plasmids**

The movement of IS-mobilized genes between chromosomes and plasmids greatly increase the opportunity a resistance determinant becomes transferable. Particularly, conjugative plasmid is one of the most important mechanisms for intra-species, inter-species and inter-genus gene transfers.

Plasmids are usually classified on their incompatibility (Inc), defined as the inability of two plasmids to be propagated stably in the same bacterial strain; thus, only compatible plasmids can be rescued in transconjugants (Novick et al., 1976). At least 29 Inc groups have been recognized among plasmids of enteric bacteria, including IncFI, IncFII, IncFIII, IncFIV, IncFV, IncFVI, IncI, IncII, IncIIC, IncHI1, IncHI2, IncHI3, IncA/C, IncB, IncD, IncJ, IncK, IncLM, IncN, IncO, IncP, IncS, IncT, IncU, IncV, IncW, IncX, IncY and com9 (Novick et al., 1976; Couturier et al., 1988). The IncFI, IncA/C, IncLM, and IncI1 plasmids show the highest occurrence among the typied resistance plasmids (Carattoli, 2009).

Molecular epidemiological studies have revealed a close and significant linkage of bla\textsubscript{CTX-M} genes to plasmids, mainly belonged to IncF, IncI, IncN, IncHI2, IncLM and IncK groups (Table 4). The IncF group (FIA, FIB and FII) is the most prevalent in transmitting bla\textsubscript{CTX-M-1} genes while IncF and IncI1 are closely related to the widespread of bla\textsubscript{CTX-M-1} genes. In addition, the bla\textsubscript{CTX-M-1} gene is dominantly harbored by IncN and IncI1, bla\textsubscript{CTX-M-3} gene by IncLM and IncI1, and bla\textsubscript{CTX-M-9} gene by IncHI2.

Unlike the plasmids with broad host range, such as IncP, IncA/C and IncQ, IncF plasmids are limited by host range to the genera of Enterobacteriaceae (Toukdarian, 2003).
Table 4. Plasmids associated with the spread of CTX-M genes.

| CTX-M gene (No. of isolates) | Inc group (No. of isolates) | Rate* | Resource | Reference |
|-----------------------------|----------------------------|-------|----------|-----------|
| **bla**<sub>CTX-M-1</sub> (119) | N (119) | 100% | *E. coli* from bovine on a dairy farm with high consumption of cephalosporins in Czech Republic, 2008 | Dolejska et al., 2011 |
| **bla**<sub>CTX-M-1</sub> (10) | I1 (10) | 100% | *S. enterica* from poultry and humans in France, 2003–08 | Cloeckaert et al., 2010 |
| **bla**<sub>CTX-M-3</sub> (14) | L/M (13) | 92.9% | Enterobacteriaceae from Bulgaria, Poland and France | Galimand et al., 2005 |
| **bla**<sub>CTX-M-9</sub> (41) | HI2 (24), P1-α (10), FIB (4), HI2, FI (2), I1 (1) | 58.5%, 9.8%, 4.9%, 2.4% | Enterobacteriaceae from a university hospital in Spain, 1996–03 | Novais et al., 2006 |
| **bla**<sub>CTX-M-14</sub> (40) | K (27), I1 (11), HI2 (2) | 67.5%, 27.5%, 2.4% | *E. coli* from patients and healthy volunteers in Spain, 2000–05 | Valverde et al., 2009 |
| **bla**<sub>CTX-M-14</sub> (25) | F (8), I1 (5), E, I1 (3), N (1), Q (1) | 32%, 20%, 12%, 4%, 4% | *E. coli* from 20 hospitals in 15 provinces in China, 2007–08 | Cao et al., 2011 |
| **bla**<sub>CTX-M-14</sub> (23) | FII (13), I1-Iγ (4), FII, I1-Iγ (1), K (1) | 56.5%, 17.4%, 4.3%, 4.3% | *E. coli* from outpatients in Hong Kong, 2002–04 | Ho et al., 2011 |
| **bla**<sub>CTX-M-14</sub> (18) | FII (17), FI (1) | 94.4%, 5.6% | *E. coli* from a hospital in Turkey, 2002–04 | Gonullu et al., 2008 |
| **bla**<sub>CTX-M-14</sub> (36) | FI (36) | 100% | *E. coli* from a university hospital in Germany, 2006–07 | Mshana et al., 2009 |
| **bla**<sub>CTX-M-15</sub> (55) | FIIA (41), A/C (3), FIIA, A/C (4) | 74.5%, 5.5%, 7.3% | *K. pneumoniae* from patients in 9 Asian countries, 2008–09 | Lee et al., 2011 |
| **bla**<sub>CTX-M-15</sub> (11) | N (8), I1 (3) | 72.7%, 27.3% | *E. coli* from different areas in France, 1997–02 | Marcadé et al., 2009 |
| **bla**<sub>CTX-M-15</sub> (15) | F (9), K (2) | 60%, 13.3% | *E. coli* and *K. pneumoniae* from 11 hospitals in Spain, 2004 | Diestra et al., 2009 |
| **bla**<sub>CTX-M-15</sub> (19) | F (12), I1 (1), L/M (1), N (1) | 63.2%, 5.3%, 5.3%, 5.3% | *E. coli* from a survey among 3193 healthy children in Peru & Bolivia, 2005 | Pallecchi et al., 2007 |
| **bla**<sub>CTX-M-15</sub> (13) | K (12) | 92.3% | *E. coli* from faeces of residents in 16 nursing homes in the UK, 2004–06 | Dhanji et al., 2011a |
| **bla**<sub>CTX-M-15</sub> (4) | F (4) | 100% | *E. coli* from a survey among 3193 healthy children in Peru & Bolivia, 2005 | Pallecchi et al., 2007 |
| **bla**<sub>CTX-M-15</sub> (3) | N (3) | 100% | *E. coli* from faeces of residents in 16 nursing homes in the UK, 2004–06 | Dhanji et al., 2011a |

*Rate = (No. in the 2nd column/No. in the 1st column) × 100%.*
Pseudomonas. high prevalence and widespread of the CTX-M genes in new hosts, while the properties of plasmid incompatibility and the secondary chromosomal insertions of CTX-M bilis chromosomes (Song et al., 2011). The genes of bla were also found on the chromosomes of P. mirabilis (Navon-Venezia et al., 2008).

In addition, chromosomal integration of bla gene was reported in E. coli, K. pneumoniae and S. enterica (Coque et al., 2008; Coelho et al., 2010; Fabre et al., 2009). Chromosomal bla was observed in one strain of 30 E. coli isolates collected in Barcelona during 1996–1999 (García et al., 2005).

Conclusion
Plasmid-mediated CTX-M enzymes are the most prevalent ESBLs, particularly in E. coli, K. pneumoniae and P. mirabilis. At least 109 members in CTX-M family are identified and can be divided into seven clusters based on their phylogeny. CTX-M-15 and CTX-M-14 are the most dominant variants in the family, followed by CTX-M-2, CTX-M-3 and CTX-M-1.

The CTX-M genes can be traced back to the chromosome-encoded cefotaximases genes in Kluwyvera spp., strongly indicating that the plasmid-mediated CTX-M enzymes are originally from Kluwyvera. Multiple genetic elements, especially IScep1 and ISCR1, are involved in the mobilization of bla genes from the chromosomes to plasmids. Conjugative plasmids are responsible for the transfer of the bla genes to new hosts, while the properties of plasmid incompatibility and host range are closely associated with the high prevalence and widespread of the CTX-M genes in Enterobacteriaceae, but not in Acinetobacter and Pseudomonas.

Declaration of interest
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