

## Emergence of Enterobacteriaceae producing extended-spectrum $\beta$ -lactamases (ESBLs) in the community

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**Enterobacteriaceae, especially *Klebsiella* spp. producing extended-spectrum  $\beta$ -lactamases (ESBLs) such as SHV and TEM types, have been established since the 1980s as a major cause of hospital-acquired infections. Appropriate infection control practices have largely prevented the dissemination of these bacteria within many hospitals, although outbreaks have been reported. However, during the late 1990s and 2000s, Enterobacteriaceae (mostly *Escherichia coli*) producing novel ESBLs, the CTX-M enzymes, have been identified predominantly from the community as a cause of urinary tract infections. Resistance to other classes of antibiotics, especially the fluoroquinolones, is often associated with ESBL-producing organisms. Many clinical laboratories are still not aware of the importance of screening for ESBL-producing Enterobacteriaceae originating from the community. A heightened awareness of these organisms by clinicians and enhanced testing by laboratories, including molecular surveillance studies, is required to reduce treatment failures, to limit their introduction into hospitals and to prevent the spread of these emerging pathogens within the community.**

Keywords: antibiotic-resistant organisms, ESBL-producing Enterobacteriaceae, community-onset infection

### Introduction

$\beta$ -Lactam agents such as penicillins, cephalosporins, monobactams and carbapenems, are among the most frequently prescribed antibiotics worldwide. In Gram-negative pathogens,  $\beta$ -lactamases remain the most important contributing factor to  $\beta$ -lactam resistance, and their increasing prevalence, as well as their alarming evolution seem to be directly linked to the clinical use of novel sub-classes of  $\beta$ -lactams.<sup>1</sup>  $\beta$ -Lactamases are bacterial enzymes that inactivate  $\beta$ -lactam antibiotics by hydrolysis, which result in ineffective compounds.<sup>2</sup> At least 400 different types of  $\beta$ -lactamases, originating from clinical isolates, have been described and a web site has been created to monitor the latest developments among the newer types of  $\beta$ -lactamases (web site at <http://www.lahey.org/studies/webt.htm>).<sup>3</sup>

Several excellent reviews have recently been published describing the microbiology, characteristics, structure, epidemiology and treatment options of organisms producing newer types of  $\beta$ -lactamases.<sup>2-8</sup> This report does not aim to be comprehensive, but rather to illustrate that extended-spectrum  $\beta$ -lactamase-(ESBL)

producing bacteria are emerging pathogens in the community, and that clinical laboratories play a critical role for their detection and control.

### Extended-spectrum $\beta$ -lactamases (ESBLs)

ESBLs were first described in 1983, and have the ability to hydrolyse oxyimino-cephalosporins, and monobactams, but not cephamycins or carbapenems.<sup>4</sup> Although ESBLs have been described in a range of Enterobacteriaceae and Pseudomonadaceae from different parts of the world, they are most often identified in *Klebsiella pneumoniae* and *Escherichia coli*. These enzymes belong to the Ambler class A and D  $\beta$ -lactamases.<sup>9</sup> The activity of Class A enzymes is inhibited *in vitro* by  $\beta$ -lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam but those belonging to class D are not. The majority of ESBLs identified in clinical isolates to date, have been SHV or TEM types, which have evolved from narrow-spectrum  $\beta$ -lactamases such as TEM-1, -2 and SHV-1.<sup>4</sup> The CTX-M enzymes have originated from *Kluyvera* spp., and recently gained prominence in Enterobacteriaceae with

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## Review

reports from Europe, Africa, Asia, South America and North America.<sup>10</sup> Other rare types of ESBLs include the GES/IBC, VEB and PER  $\beta$ -lactamases.<sup>11–13</sup> The VEB enzymes are widely distributed in Enterobacteriaceae from South East Asia<sup>11</sup> and *Acinetobacter* spp. from France,<sup>14</sup> whereas the GES/IBC ESBLs are reported from hospital pathogens in countries such as South Africa and France.<sup>13</sup> PER-1  $\beta$ -lactamase has been identified in nosocomial isolates of *Pseudomonas aeruginosa* and *Acinetobacter* spp. from Turkey.<sup>13</sup>

Organisms producing ESBLs are clinically relevant and remain an important cause for failure of therapy with cephalosporins.<sup>2,4</sup> Indeed, the failure of cephalosporin therapy in an infection where the pathogen was reported to be susceptible to the drug in routine susceptibility testing has often been the first indicator that the infecting strain produced an ESBL. ESBLs are often encoded by genes located on large plasmids and these also carry genes for resistance to other antimicrobial agents such as aminoglycosides, trimethoprim, sulphonamides, tetracyclines and chloramphenicol.<sup>15</sup> In addition, recent studies have demonstrated co-transfer of the *qnr* determinant on ESBL-producing plasmids conferring resistance to nalidixic acid with reduced susceptibility to fluoroquinolones.<sup>16,17</sup> Thus, very broad antibiotic resistance extending to multiple antibiotic classes is now a frequent characteristic of ESBL-producing enterobacterial isolates.<sup>4</sup>

The majority of ESBL-producing organisms have been reported from hospitalized patients admitted to intensive care units (ICUs), but infections can occur in almost any area of the hospital,<sup>6</sup> as well as in long-term care facilities<sup>18</sup> and nursing homes.<sup>19</sup>

### CTX-M $\beta$ -lactamases

The CTX-M  $\beta$ -lactamases, now exceeding just over 40 different types, can be divided into five clusters based on their amino acid identities:<sup>10</sup> the CTX-M-1 group including CTX-M-1, -3, -10, -12, -15, -28, -30 and FEC-1; the CTX-M-2 group including CTX-M-2, -4, -5, -6, -7, -20 and Toho-1; the CTX-M-8 group including CTX-M-8; the CTX-M-9 group including CTX-M-9, -13, -14 (also named CTX-M-18), -16, -17, -19, -21, -24, -27 and

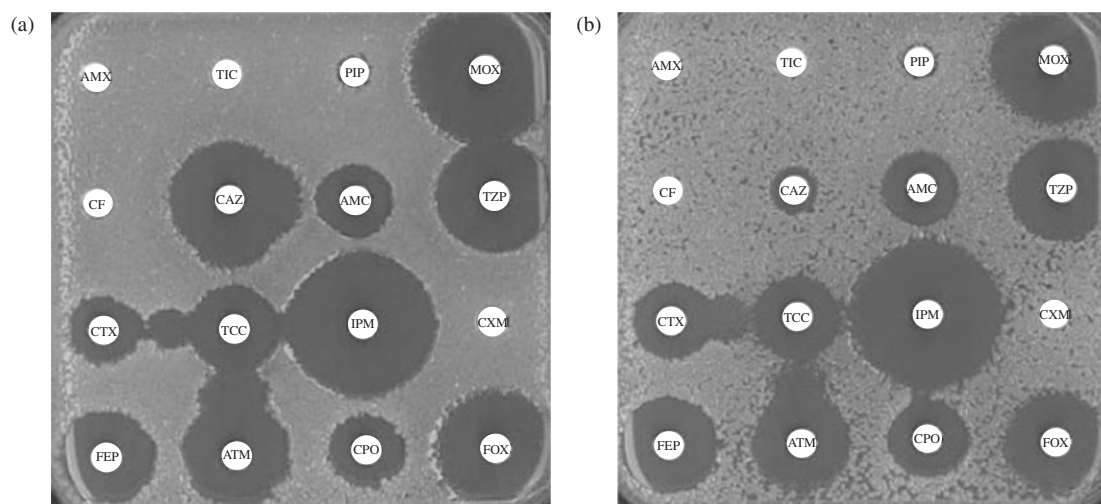
Toho-2; and the CTX-M-25 group with CTX-M-25 and CTX-M-26.  $\beta$ -Lactamases of the CTX-M-2 group are structurally related to the naturally produced  $\beta$ -lactamase of *Kluyvera ascorbata*,<sup>20</sup> CTX-M-8 is related to  $\beta$ -lactamase of *Kluyvera georgiana*,<sup>21</sup> and CTX-M-1 group enzymes are related to the  $\beta$ -lactamases of *Kluyvera cryocrescens*<sup>22</sup> although an enzyme identical to CTX-M-3 was isolated from a strain of *K. ascorbata*.<sup>23</sup> The CTX-M-9 group is related to enzymes from *Kluyvera* spp. isolated in Guyana, which were identical with CTX-M-14.<sup>24</sup>

The first CTX-M variant (previously named MEN-1) was reported in 1991 from France<sup>25</sup> and CTX-M-10 was found retrospectively to be present in community isolates of *E. coli*, *K. pneumoniae* and *Citrobacter freundii* recovered as far back as 1991 from outpatients in Spain.<sup>26</sup> These types of  $\beta$ -lactamases, which recently appeared increasingly in the hospital setting, are often present in *E. coli* and typical community-acquired organisms such as *Salmonella*.<sup>27</sup> The CTX-M enzymes usually have greater activity against cefotaxime than ceftazidime but some of them, such as CTX-M-15 and -19, also hydrolyse ceftazidime efficiently,<sup>28,29</sup> which may complicate their phenotypic recognition (Figure 1).

### Laboratory detection of organisms producing ESBLs

Many clinical laboratories may not be fully aware of the importance of organisms producing ESBLs and how best to detect them.<sup>30</sup> The consequences have been several treatment failures in patients who received inappropriate antibiotics and outbreaks of multidrug-resistant, Gram-negative pathogens, which have required expensive control efforts.<sup>15,31</sup>

The Clinical and Laboratory Standards Institute (CLSI; formerly known as the National Committee for Clinical Laboratory Standards) has published guidelines for ESBL detection in Enterobacteriaceae specifically for *E. coli*, *Klebsiella* spp. and *Proteus* spp.<sup>32</sup> In the UK, the Health Protection Agency (HPA) has also prepared guidelines.<sup>33</sup> These guidelines include an initial screening with either 8 mg/L (CLSI) or 1 mg/L (HPA) of cefpodoxime, 1 mg/L each of cefotaxime, ceftazidime, ceftriaxone, or aztreonam,



**Figure 1.** Antibiograms of two isogenic *Klebsiella pneumoniae* isolates expressing either the CTX-M-14 (also named CTX-M-18) ESBL (a) or its point mutant CTX-M-19 (b) that hydrolyses ceftazidime at a high level. AMX, amoxicillin; TIC, ticarcillin; PIP, piperacillin; MOX, moxalactam; CF, cefalothin; CAZ, ceftazidime; AMC, co-amoxiclav; TZP, piperacillin/tazobactam; CTX, cefotaxime; TCC, ticarcillin/clavulanic acid; IPM, imipenem; CXM, cefuroxime; FEP, cefepime; ATM, aztreonam; CPD, cefpodoxime; FOX, cefoxitin.

followed by confirmatory tests using both cefotaxime and ceftazidime in combination with clavulanate, or the Etest ESBL strips. Automated systems that use similar detection principles have proved to be popular in clinical laboratories, especially those in North America. Clinical laboratories from several countries, especially in Europe, have taken a more pro-active approach to the detection of ESBL-producing organisms. First-line screening tests in these countries are based on double disc synergy testing, combination discs and microdilution tests (with isolates grown in broth containing 1 mg/L of extended-spectrum cephalosporins). Second-line, confirmatory tests require determination of MIC by broth dilution of extended-spectrum cephalosporins with and without clavulanic acid or Etest ESBL confirmation tests.

The on-going detection of organisms producing ESBLs in clinical microbiology laboratories remains a contentious issue and compliance varies widely. Proficiency-testing studies performed by the World Health Organization and Centers for Disease Control have raised concerns about the current ability of many clinical laboratories to detect organisms producing ESBLs.<sup>34–38</sup> In proficiency testing of laboratories outside the United States only 2 of 129 laboratories specifically identified a highly resistant ESBL-producing *K. pneumoniae* isolate.<sup>38</sup> A study recently published showed that only 8% of clinical laboratories from rural hospitals in the USA routinely screened for ESBL-producing organisms.<sup>35</sup> Furthermore, a practice exists among some clinical laboratories to use ceftazidime as the initial screening drug and ceftazidime with clavulanate as the confirmation test.<sup>39,40</sup> A study addressing the laboratory diagnosis of CTX-M-producers indicated that only 20% of 119 isolates producing these enzymes were reported as ESBL-positive when ceftazidime with clavulanate was the only confirmation test.<sup>41</sup>

### Emergence of ESBL-producing organisms in the community setting

Recent data indicate that infections caused by ESBL-producing organisms may be an emerging problem in outpatient settings in various parts of the world. These include several case reports, as well as larger studies from, for example, Canada, France, Israel, Spain, Italy and the UK (Table 1).

Possible community-acquisition of an ESBL-producing isolate was first reported in 1998 from Ireland when a nalidixic acid-resistant *E. coli* producing an ESBL was isolated from the urine of an elderly patient; the type of enzyme was not specified. The patient did not have a recent history of hospitalization, but had received multiple courses of antibiotics.<sup>42</sup>

A laboratory study published in 2001 from the northern part of Israel analysing susceptibility patterns of 8338 bacteria isolated from community urines found that 1.25% of the Gram-negative uropathogens were ESBL producers.<sup>43</sup> The same investigators determined that the risk factors associated with urinary tract infections (UTIs) caused by ESBL-producing bacteria were infections due to *Klebsiella* spp., previous hospitalization, previous antibiotic treatment, male gender over the age of 60 years and diabetes mellitus.<sup>44</sup> The fact that previous hospitalization was a significant risk factor indicated that these infections were most probably community-onset rather than community-acquired disease. A Spanish study from 2002 isolated *E. coli* producing CTX-M-14  $\beta$ -lactamases from the urines of seven patients with UTIs who had never been admitted to a hospital.<sup>45</sup> Genetic analysis showed that the *bla*<sub>CTX-M-14</sub> gene was associated with insertion sequence

*ISEcpl*, which has been shown to be responsible for mobilization and high-level expression of the  $\beta$ -lactamase gene.<sup>46</sup>

Arpin *et al.*<sup>47</sup> conducted a survey for ESBL-producing Enterobacteriaceae among eight private laboratories in the Aquitaine region of France. They identified 39 isolates (including *E. coli*, *K. pneumoniae* and *Proteus mirabilis*) that produced various types of ESBLs (TEM-3, -19, SHV-4 and CTX-M-1) from 38 patients, including 33 residents from nursing homes and five ambulatory patients. The ambulatory patients visited hospitals regularly and corresponded to nosocomial acquisitions whereas the other infections were acquired within various nursing homes. In another French region, Lescure *et al.*<sup>48</sup> noticed that the rate of multiresistant bacteria among patients visiting outpatient clinics had increased during the 1999–2000 period and seven patients were considered to be carriers of ESBL-producing organisms.

A well-designed, case-controlled study determined the epidemiology and clinical features of infections caused by ESBL-producing *E. coli* in 49 non-hospitalized patients (excluding those from nursing homes) in the southern part of Spain.<sup>49</sup> The majority (76%) of patients presented with UTIs, and the risk factors identified were: diabetes mellitus, previous fluoroquinolone use, recurrent UTIs and previous hospital admission (with odds ratio of 5.5, 7.6, 4.5 and 18.2, respectively). The majority of ESBLs (64%) were characterized as CTX-M-9 enzymes.

A different approach was undertaken by Pitout *et al.*<sup>50</sup> who performed a population-based laboratory surveillance of hospital and community sites to define the epidemiology of ESBL-producing *E. coli* infections from 157 patients in a large centralized Canadian region during 2000–2002. The incidence was 5.5/100 000 population/year. Seventy-one percent of the patients had community-onset disease and patients  $\geq 65$  years of age and females had significantly higher rates of infection. The majority of ESBL-producers (70%) were positive for *bla*<sub>CTX-M</sub> genes from the CTX-M-1 and CTX-M-9 groups. Ciprofloxacin resistance was independently associated with the presence of CTX-M  $\beta$ -lactamases and these strains commonly caused community-onset UTIs.

Two studies describing the spread of community-acquired bacteria producing CTX-M  $\beta$ -lactamases have recently appeared from the UK.<sup>51,52</sup> In one, ESBL-producing Enterobacteriaceae were detected from the faecal flora of community and hospital-based patients from York.<sup>51</sup> The authors identified eight ESBL-producing *E. coli* and one ESBL-producing *Salmonella* spp. among 565 faecal specimens from community patients. The  $\beta$ -lactamases identified were CTX-M-9 (present inside a *sull*-type integron that included the Orf513 recombinase), -14 and -15 (associated with mobile element *ISEcpl*) and SHV-12. The second study from the UK was undertaken by Woodford *et al.*<sup>52</sup> who investigated 291 CTX-M-producing *E. coli* from 42 centres that were submitted to the HPA's Antibiotic Resistance Monitoring and Reference Laboratory in London. The community isolates (24% of the 291) were mainly from urines and produced CTX-M-15 associated with the mobile element *ISEcpl* or CTX-M-9. The authors indicated that CTX-M-producing *E. coli* isolates had become widely scattered throughout the UK, and that one epidemic clone producing CTX-M-15 was particularly of concern, since that strain was identified in 110 samples from six different centres. It is noteworthy that most of the CTX-M-15-producing strains were multiresistant to fluoroquinolones, trimethoprim, tetracycline and aminoglycosides.

An interesting description was reported by Prats *et al.*<sup>53</sup> who examined an acute gastroenteritis outbreak involving >100 people

Table 1. Community-onset disease caused by bacteria producing extended-spectrum  $\beta$ -lactamases (ESBLs)

Country and year of study	Type of study	Type of infections	Patients (No)	Risk factors	Organisms	ESBL (mobile element)	Reference
Ireland, 1998	susceptibility reviews	UTIs	1, elderly female	previous antibiotics; repeated UTIs	<i>E. coli</i>	ND	42
Saudi Arabia, 2000	susceptibility reviews	NS	NS	NS	<i>K. pneumoniae</i>	ND	64
France, 2000	susceptibility reviews	UTIs	NS	NS	<i>E. coli</i>	ND	65
Poland, 2001	susceptibility reviews	UTIs	NS	complicated UTIs	<i>E. coli</i>	ND	66
Spain, 2001	susceptibility reviews	UTIs	NS	NS	<i>E. coli</i>	ND	67
Israel, 2001	susceptibility reviews	UTIs	NS	NS	<i>E. coli</i>	ND	43
USA, 2002	susceptibility reviews	UTIs	8, elderly	ambulatory	<i>E. coli</i>	ND	68
Singapore, 2002	case report	bacteraemia	1, female	previous antibiotics	<i>E. coli</i>	ND	69
Israel, 2002	retrospective case series	bacteraemia	6, elderly	previous antibiotics, nursing homes, ambulatory; urine catheters	<i>E. coli, K. pneumoniae, Enterobacter</i> spp.	ND	70
Spain, 2002	molecular surveillance	UTIs	7, NS	NS	<i>E. coli</i>	CTX-M-14 (ISEcpI)	45
Turkey, 2003	susceptibility reviews	UTIs	NS	NS	<i>E. coli</i>	ND	71
Korea, 2003	description of resistance mechanism	gastro enteritis	2, infants	NS	<i>Salmonella</i> spp.	TEM-52	72
Brazil, 2003	susceptibility reviews	soft issue infections	10, NS	diabetes mellitus; previous antibiotics	<i>K. pneumoniae, E. coli</i>	ND	73
Spain, 2003	investigation of gastro enteritis outbreak	gastro enteritis	9, NS	none; <i>Salmonella</i>	<i>E. coli</i>	CTX-M-9	53
France, 2003	susceptibility reviews	NS	38, elderly	gastro enteritis nursing homes; ambulatory	<i>K. pneumoniae, E. coli, Enterobacter</i> spp.	TEM-3, TEM-19, SHV-4, CTX-M-1	47
Israel, 2004	retrospective case series	UTIs	128, elderly	infections due to <i>Klebsiella</i> spp. hospitalization, antibiotic treatment, males >60 years, diabetes mellitus	<i>Proteus</i> spp.	ND	44
Spain, 2004	case controlled	UTIs; bacteraemia	49, elderly	diabetes mellitus fluoroquinolone use recurrent UTIs hospitalization older males	<i>E. coli</i>	CTX-M-9, TEM-like, SHV-like	49
Canada, 2004	population-based surveillance	UTIs; bacteraemia	111, elderly	older females isolate with <i>bla<sub>CTX-M</sub></i>	<i>E. coli</i>	CTX-M-14, CTX-M-1-like	50
Greece, 2004	retrospective case series	UTIs	14, adults, children	NS	<i>E. coli</i>	CTX-M-1, CTX-M-3	56
UK, 2004	molecular surveillance	none, faecal specimens	-	-	<i>E. coli, Salmonella</i> spp.	CTX-M-9 (In60), CTX-M-14, CTXM-15 (ISEcpI)	51
UK, 2004	molecular surveillance	UTIs	NS	NS	<i>E. coli</i>	CTX-M-9, CTX-M-15 (ISEcpI)	52
Spain, 2004	molecular surveillance	none, faecal specimens	-	-	<i>E. coli</i>	CTX-M-2, -9, -10, -14, TEM-4 and SHV-12	26
Canada, 2004	description of resistance mechanism	UTIs	4, elderly	hospitalization	<i>Citrobacter freundii</i>	CTX-M-30 (ISEcpI)	74
Kuwait, 2004	susceptibility reviews	UTIs	NS	NS	<i>E. coli</i>	ND	75
France, 2004	case report	gastro enteritis	2, child, adult	NS	<i>Shigella sonnei, Salmonella</i> spp.	CTX-M-15	63

NS, not stated; ND, not detected.

at a summer camp in Girona, Spain, during June 2002. *E. coli* producing CTX-M-9 was identified from the stools of 11 patients, with the same clone present in seven people. They also demonstrated the spread of similar plasmids between different clones, indicating that both clonal and plasmid outbreaks occurred simultaneously. The dissemination of these ESBL-positive *E. coli* strains was linked to common source exposure such as food or water although the cultures of food items were negative for *E. coli*.

When studying the prevalence of ESBL production in *Shigella* from South Korea during 1991 to 2002, Kim *et al.*<sup>54</sup> noticed a great variety of  $\beta$ -lactamases produced by 20 isolates, including TEM-15, -17, -19, -20, -52 and CTX-M-14. The authors speculated that these acquisitions were related to interspecies spread between medical facilities and the community.

Recently, the change in prevalence of faecal carriage of ESBL-producing Enterobacteriaceae between 1991 and 2003 has been evaluated in non-outbreak situations in Spain.<sup>26</sup> The authors showed that the rates of ESBL-positive isolates increased significantly in both hospitalized patients and outpatients from 0.3% and 0.7% in 1991 to 11.8% and 5.5% in 2003, respectively. TEM-4 and CTX-M-10 were identified from outpatients in 1991 whereas CTX-M-9 and SHV-12 were present in 2003, underlining that a switch occurred in the community that was also observed in the hospital settings. They identified CTX-M-type enzymes in more than 60% of the ESBL producers.

Brigante *et al.*<sup>55</sup> from Italy reported more evidence of the emergence of CTX-M  $\beta$ -lactamases. They compared ESBL-producing *E. coli* recovered from inpatients and outpatients between 1999 and 2003 at their medical centre. In 1999, a single isolate produced a CTX-M enzyme compared with 26 positive isolates identified in 2003.

### Multidrug resistance and molecular epidemiology of ESBL-producing Enterobacteriaceae from the community

Recent surveys from Canada,<sup>50</sup> Italy,<sup>55</sup> Spain<sup>49</sup> Greece<sup>56</sup> and the UK<sup>52</sup> have illustrated an alarming trend of associated resistance to other classes of antimicrobial agents among ESBL-producing organisms isolated from community sites. These surveys show that ESBL-producing *E. coli*, especially those producing CTX-M-types, exhibited co-resistance to trimethoprim-sulfamethoxazole, tetracycline, gentamicin and ciprofloxacin (as many as 66% of isolates were resistant to ciprofloxacin in Canada).<sup>50</sup> The Canadian study also showed that strains producing CTX-M enzymes were significantly more resistant to ciprofloxacin than strains negative for *bla*<sub>CTX-M</sub> genes.

A study conducted by Valverde *et al.*<sup>26</sup> from Spain, indicated that CTX-M-positive strains were often more resistant to different classes of antibiotics than were bacteria producing other types of ESBLs. Strains producing CTX-M-9 or -14 were more resistant to tetracycline and ciprofloxacin than those producing TEM-4 or SHV-12.

The *bla*<sub>CTX-M</sub> genes are often found in association with genetic structures such as *sull*-type integrons and this might explain the multidrug nature of organisms producing these enzymes. This structure is genetically linked to class 1 integrons known to integrate antibiotic resistance gene cassettes responsible for resistance to  $\beta$ -lactams, aminoglycosides, chloramphenicol sulphonamides, and to a lesser extent rifampicin.<sup>10</sup>

Limited data are available regarding the molecular epidemiology of CTX-M-producing bacteria from the community. Pitout *et al.* described a PCR assay involving the use of four sets of primers to amplify group-specific CTX-M  $\beta$ -lactamase genes and used this technique to track CTX-M-producing *E. coli* in the community from Canada. The suggestion of a possible clonal outbreak among these strains<sup>41</sup> resulted in a follow-up study using PFGE, which revealed two closely related restriction patterns among 67 (77%) CTX-M-14 producers that were responsible for a community-wide clonal outbreak of UTIs during 2000 and 2001.<sup>57</sup> However, studies from Spain and the UK, also using PFGE, showed that most *E. coli* producing CTX-M enzymes from the community were not clonally related.<sup>49,52</sup> However, the UK study did suggest some evidence of genetic relatedness among strains producing CTX-M-15.<sup>52</sup>

### Main problem is the dissemination of CTX-M-type $\beta$ -lactamases

The recognition of CTX-M  $\beta$ -lactamases as the predominant type of ESBL among community strains is a cause of concern in many countries such as Canada, UK, Italy, Greece and Spain (Table 1). It is evident that the epidemiology of organisms producing CTX-M enzymes is very different from those that produce TEM- and SHV-derived ESBLs. CTX-M enzymes are not limited to nosocomial infections caused by *Klebsiella* spp., and their potential for spread beyond the hospital environment serves to exacerbate public health concerns. *E. coli* producing CTX-M  $\beta$ -lactamases seem to be true community ESBL-producers and the current emergence and spread of these bacteria is intriguing but worrying.

The association of CTX-M  $\beta$ -lactamase-encoding genes with mobile elements such as *ISEcp1*, could explain the ease with which these enzymes are spreading among bacteria in the community setting. Several investigations have illustrated that animals might represent a possible source for the dissemination of ESBL-encoding genes to humans. The evidence of CTX-M-producing isolates in cattle,<sup>58</sup> poultry,<sup>27</sup> and dogs and cats<sup>59</sup> is worrying since food-producing animals and domestic pets might act as a reservoir for the acquisition of resistant organisms. Shiraki *et al.*<sup>58</sup> hypothesized that production of CTX-M-2 enzyme emerged initially from cattle, with subsequent transmission to humans. However, we are unaware of detailed molecular epidemiological comparisons of CTX-M-producing strains from animals and humans.

The importance of CTX-M-producing *E. coli* as a possible source in nosocomial settings was supported by a study from Canada when two closely related clones (CTXM14A and CTXM14AR) of *E. coli* producing CTX-M-14 were responsible for an outbreak among community patients during 2000 and 2001.<sup>57</sup> CTXM14AR was a derivative of CTXM14A that emerged in hospitals after isolates producing CTXM-14 were earlier introduced from the community.

### Conclusions

Baquero recently speculated about the evolution within the genetic make up of ESBL-producing Enterobacteriaceae involving new emerging pathogens (mostly *E. coli*), novel ESBL-encoding genes (mostly those encoding CTX-M enzymes) and mobile elements such as *ISEcp1* or *sull*-type integrons.<sup>60</sup> This review

indicates that ESBL-producing bacteria, especially *E. coli* producing CTX-M types, from community sources, have become widely prevalent in certain areas of the world and that they are most probably imported into the hospital setting. These strains may be the source of infections in hospitalized individuals, and may be different from the SHV- and TEM-ESBL-producers identified in ICUs and long-term facilities during the 1990s with greater propensity for community spread. Limiting the introduction of ESBL-producing organisms into the hospital setting might prove difficult since routine rectal screening of patients admitted from the community may prove to be impractical.

The clinical laboratory acts as an early warning system, alerting the medical community to new resistance mechanisms present in clinically important bacteria. The detection of ESBL-producing organisms in laboratories is a critical requirement for appropriate management of patients, infection prevention and control efforts, as well for tracking these organisms in surveillance systems. Many laboratories have difficulty in detecting ESBL-mediated resistance because of cost-cutting practices, while others are unaware of the relevant CLSI or HPA guidelines.<sup>30</sup> Most clinical laboratories do not routinely screen or detect ESBL production in bacteria isolated from community-onset infections.<sup>35,40</sup> It is possible that these organisms, especially those with CTX-M  $\beta$ -lactamases, may be prevalent in bacterial populations from the community but have not been identified. All clinical laboratories should rule out ESBL-producing organisms and we recommend that Enterobacteriaceae especially *E. coli*, isolated from community sources should routinely be screened for ESBL production. This might prove to be impractical in various countries, but some large laboratories are capable of performing this on a routine basis. An appropriate approach for initially screening organisms for the presence of CTX-Ms is to use cefpodoxime followed by disc tests using either cefpodoxime with clavulanate, or both cefotaxime with clavulanate and ceftazidime with clavulanate.<sup>41</sup> The continuing failure to do so may result in major adverse consequences such as treatment failure in patients who received inappropriate antibiotics or the uncontrolled spread of ESBL-producing bacteria in the community setting.

A more accurate evaluation of the origin of CTX-M acquisition is needed<sup>61</sup> as well as detailed studies of the distribution of the *Kluyvera* spp. which are the probable environmental reservoir of the resistance genes. Additional studies to define further the risk factors associated with community-onset infections caused by ESBL-producing bacteria should be undertaken to identify those patients who should receive an effective empirical treatment, such as a carbapenem.

Surprisingly, we are now facing a situation for ESBL-producing enterobacterial isolates that mirrors the epidemiology of methicillin-resistance in *Staphylococcus aureus*.<sup>62</sup> In both cases, the resistance mechanisms were first reported in nosocomial pathogens, but this has been followed by the appearance of different clones in the community.

In summary, because of the significant public health implications including the treatment of community-acquired UTIs, the spread of organisms producing ESBLs (especially CTX-Ms) in the community merits close monitoring with enhanced efforts for surveillance. The spread of CTX-M enzymes has already occurred in typical community-acquired pathogens such as *Salmonella* and *Shigella* spp.<sup>54,63</sup> which adds a degree of difficulty for controlling their spread, since most of these species are shared between humans and animals. CTX-M-producing *E. coli* is an

emerging pathogen in the community setting that is not being recognized by the medical community at large.

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