Extended Spectrum Beta-lactamases: Definition, Classification and Epidemiology

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Abstract
Extended spectrum beta-lactamases (ESBLs) are defined as enzymes produced by certain bacteria that are able to hydrolyze extended spectrum cephalosporin. They are therefore effective against beta-lactam antibiotics such as ceftazidime, ceftriaxone, cefotaxime and oxyimino-monobactam. The objective of the current review is to provide a better understanding of ESBL and the epidemiology of ESBL producing organisms which are among those responsible for antibiotic resistant strains. Globally, ESBLs are considered to be problematic, particularly in hospitalized patients. There is an increasing frequency of ESBL in different parts of the world. The high risk patients are those contaminated with ESBL producer strains as it renders treatment to be ineffective in these patients. Thus, there an immediate needs to identify EBSL and formulate strategic policy initiatives to reduce their prevalence.

Introduction
Extended spectrum beta-lactamases (ESBLs) are defined as enzymes produced by certain bacteria that are able to hydrolyze extended spectrum cephalosporin. They are therefore effective against beta-lactam antibiotics like ceftazidime, ceftriaxone, cefotaxime and oxyimino-monobactam (Bradford, 2001; Paterson and Bonomo, 2005). Carbapenems and cephamycine are effective against ESBL producer strains. Generally, ESBLs are inhibited by clavulanic acid and tazobactam. ESBLs are found in Gram-negative bacteria, especially in enterobacteriacea and *Pseudomonas aeruginosa* (Bradford, 2001; Nordmann and Guibert, 1998). The most important beta-lactamase that is prevalent is TEM-1. It is estimated that more than 90% of ampicillin resistance among *E.coli* is related to the presence of TEM-1 (Livermore, 1995). TEM-1 is able to hydrolyze penicillin and first generation cephalosporins. The first derivative of TEM-1 is TEM-2, with a single replacement of amino acids (Du Bois et al., 1995). The difference between beta-lactamase enzymes is the substitution of amino acids that produces different phenotype of enzymes. Another prevalent type of beta- lactamases is SHV-1, which was described initially in *K. pneumoniae.* It is estimated that SHV-1 is responsible for plasmid mediated ampicillin resistance in bacteria which harbors it. The replacement of amino acids causes the change in enzyme structures and its activities (Bradford, 2001). The substitutions are more common among TEM, SHV and OXA enzymes in defined amino acids positions. The combination of altered amino acids produces different phenotypes of beta-lactamase enzymes with varying ability to hydrolyze 3rd generation cephalosporin and increases the level of resistance to beta-lactamase inhibitors (Winokur et al., 2000). It is observed that the use of different oxamino –beta –lactam antibiotics as well as 1st generation cephalosporin and penicillin have caused changes in ESBLs (Blazquez et al., 2000). As the use of beta- lactams antibiotics was excessive, the ESBLs producer strains were selected. These strains produce different phenotypes and effect changes in porins such as Omp (Shakib et al., 2012) to develop resistance to cephamycins and other antimicrobials (Bradford et al., 1994). The plasmids are responsible for ESBL production and also contain other genes that show resistance to aminoglycoside and cotrimoxazole (Villa et al., 2000). Studies revealed that Quinolone resistance is more prevalent in strains that produce ESBL although, the mechanism of co-resistance is not clear (Paterson et al., 2000). ESBLs are currently very important in the medical field. This is because they are able to make the strains resistant to cephalosporins, the workhorse hospital antibiotics applied for many illnesses as first line antibiotics. Any delay in identification and failure to treat the severe infections caused by ESBL producers would result in increasing morbidity and mortality. As ESBL producer strains often show multidrug resistance, such as resistance to amino glycosides and fluoroquinolones, the therapeutic options associated with these strains are limited. It is thus obvious that there is an increasing prevalence of ESBLs producers and the ESBLs producer strains are causing higher levels of morbidity, mortality, and health care-associated costs.

The objective of the current review is to obtain a better understanding of ESBL and the epidemiology of ESBL producer organisms which are also responsible for antibiotic resistance strains.

Classification of beta-lactamases
There is a different scheme for classification of beta-lactamases, the most famous was developed by Bush, Jacoby and Medeiros (Bush et al., 1995). This scheme is

Table 1. Classification of beta-lactamases

Ambler Class	Bush Group	Characteristics of beta-lactamases	Number of enzymes
C	1	Often chromosomal enzymes in gram-negatives but some are Plasmid-coded. Not inhibited by clavulanic acid.	51
A	2a	Staphylococcal and enterococcal penicillinases	23
	2b	Broad spectrum betalactamases including TEM-1 and SHV-1, mainly occurring in gram-negatives	16
	2be	Extended spectrum betalactamases (ESBL)	200
	2br	Inhibitor-resistant TEM (IRT) betalactamases	24
	2c	Carbenicillin-hydrolysing enzymes	19
	2d	Cloxacillin (oxacillin) hydrolysing enzymes	31
	2e	Cephalosporinases inhibited by clavulanic acid	20
	2f	Carbapenem-hydrolysing enzyme inhibited by clavulanic acid	4
B	3	Metallo-enzymes that hydrolyse carbapenems and other betalactams except monobactams. Not inhibited by clavulanic acid	24
D	4	Miscellaneous enzymes that do not fit into other groups	9

based on the molecular structure and earlier schemes. According to the Bush, Jacoby and Medeiros scheme, beta-lactamases are divided into four groups as shown in Table 1. The first scheme, introduced by Ambler (Ambler et al., 1991), which is also widely used, is shown in table 1 as well.

Group I (Ambler Class C) beta-lactamases (also known as AmpC enzymes).
This group is resistant to beta- lactamase inhibitors like clavolunate and mostly is found on chromosomes (Minami et al., 1980). In this class, the enzyme is inducible. Thus any exposure of bacteria to beta-lactame antibiotics leads to an increase in enzyme production. As beta-lactam antibiotics are different, they are able to stimulate different levels of beta-lactamase production. The enzymes in group I are found in the Enterobacteriacea family as well as *P. aeruginosa*. Studies have also shown the shift of enzymes

from chromosome to plasmid in some strains such as *E.coli* and *Klebsiella* spp (Sanders and Sanders, 1992). The Group I producer beta-lactamases are resistant to beta lactam/beta-lactamase inhibitor combinations, penicillins, cephamycins, as well as 1st, 2nd and 3rd generation cephalosporins. They are sensitive to cefepime and carbapenems (Sanders et al., 1996).

Group 2 (Ambler Class A) enzymes
As the enzymes classified into group 2 are harbored by plasmid, they could easily be transmitted into different bacterial cells, causing rapid resistance to such enzymes. The beta-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam inhibit the original group 2 enzymes. The main group 2 enzymes are TEM and SHV. TEM-1 was first identified in 1965 in the Enterobacteriacea family. Then it spread to bacteria such as *Haemophilus, Neisseria,* and *Vibrio* spp. SHV-1 was discovered in 1979

and is commonly found in *Klebsiella spp* and *E. coli* (De Champs et al., 1991). Group 2 enzymes could hydrolyze ampicillin and 1 st, 2 nd and 3rd generation cephalosporins as well as monobactams (the extended spectrum betalactamases or ESBLs) and they are resistant to beta-lactamase (Livermore, 1995).

Group 3 (Ambler Class B) enzymes
These are metallo-enzymes capable of destroying carbapenems (Burn-Buisson et al., 1987).These enzymes are frequently found in *P. aeruginosa*, *Bacteroides fragilis* and *Stenotrophomonas maltophilia*.

Group 4 beta-lactamases
Group 4 beta-lactamases contains those unusual penicillinases not inhibited by clavulanic acid. Four of these enzymes exhibit high rates of hydrolysis with carbenicillin and/or cloxacillin. Several exhibit unusual behavior with respect to metal ion involvement. Whether these enzymes represent another molecular class of beta-lactamase is not known.

Types of ESBLs
The types of ESBLs that are important are as follows:

TEM - beta - lactamases
The TEM-type ESBL are derivatives from TEM-1 and TEM-2 (Figure 1). TEM-3 was first discovered in *K. pneumoniae* in France in 1984. Initially it was known as CTX-1, because of its activity against cefotaxime (Burn-Buisson et al., 1987).Now it is called TEM-3, which is different from TEM-2, which is a replacement of two amino acids (Sougakoff et al., 1987). The numbers of TEM type beta-lactamases currently exceed 100. All of them, with the exception of TEM-1 and TEM-2, are ESBLs. The most common TEM type ESBL is found in *E.coli* and *K.pneumoniae.* However, they could appear in the other Gram-negative bacteria (Livermore, 1995) and also in different genera of *Enterobacteriaceae* (*Enterobacter aerogenes, Enterobacter cloacae, Morganella morganii, Proteus mirabilis* and *Salmonella* spp) (Morosini et al., 1995; Marchandin et al., 1999). In *Non-Enterobacteriaceae*, they are in *P. aeruginosa* (Nordmann and Guibert, 1998).

SHV - beta - lactamases
The SHV is more prevalent than the other types of ESBLs in clinical isolates of bacteria (Jacoby, 1997). Unlike the TEM-type beta-lactamases, fewer SHV type beta-
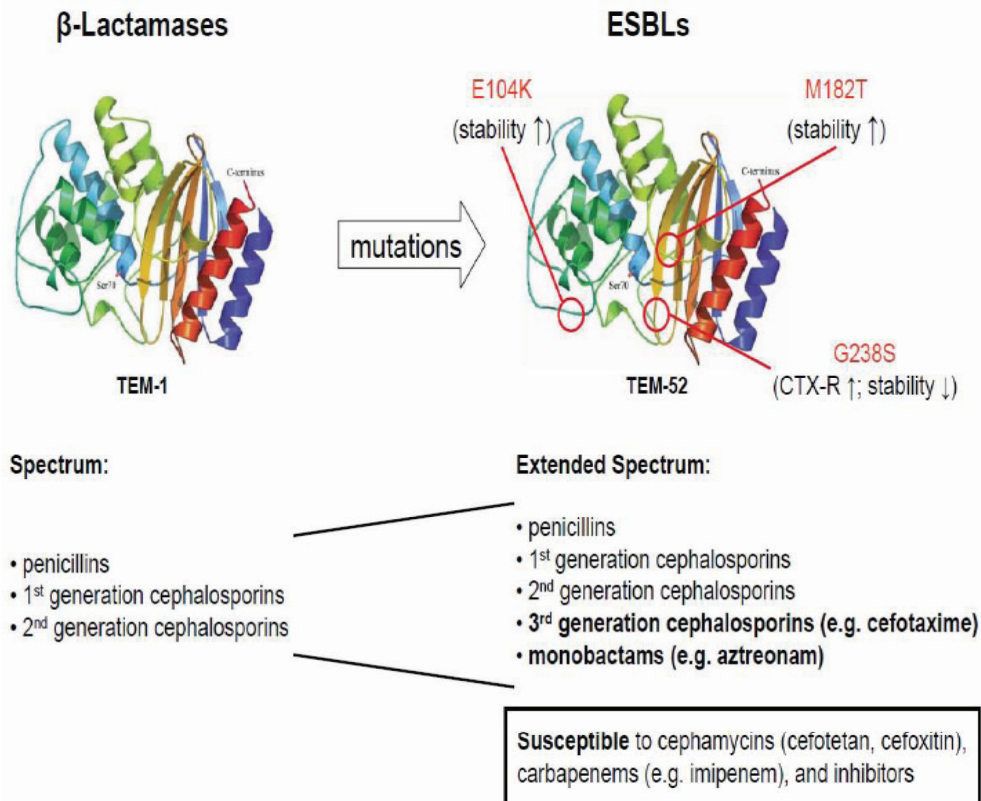
Figure 1. Amino acid substitution of TEM-1 and make new TEM-52.

lactamase are derived from SHV-1. Most strains have SHV on their plasmid through the replacement of serine to glycine at position 238. In addition, some strains change lysine to glutamate at position 240. The serine residue at position 238 is essential for hydrolyzing ceftazidime and the lysine residue is critical for hydrolyzing cefotaxime. More than 100 SHV varieties are known worldwide currently. SHV-type of ESBLs are found in a wide range of *Enterobacteriaceae* (Harrif-Heraud et al., 1997) *P.aeruginosa* and *Acinetobacter* spp (Huang et al., 2004; Poirel et al., 2004).

CTX - M beta - lactamases
CTX-M was first described by Tzouvelekis in 2000 (Tzouvelekis et al., 2000). The term CTX-M beta-lactamase denotes its ability to cefotaxime (Bonnet, 2004). CTX-M is able to hydrolyze cephalothin better than benzyl-penicillin and cefotaxime better than ceftazidime. On the other hand, though the MIC analysis of bacteria for resistance to ceftazidime was carried out, some of the CTX-M- type beta-lactamases showed resistance to this drug (Poirel et al., 2002). Further, the resistance to Aztreonam was having been identified to be variable. CTX-M-type beta-lactamases are able to hydrolyze cefipime (Tzouvelekis et al., 2000). They inhibit better with beta-lactamase inhibitor tazobactam than sulbactam and clavulanate (Bush et al., 1993). Unlike TEM and SHV enzymes, there is no point mutation in CTX-M and it is believed that CTX-M was first identified from the chromosome Kluyvera *spp* following its transforming to plasmid (Radice et al., 2002). Thus far, 128 types of CTX-M have been reported and are classified into five classes as follows: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9 and CTX-M-25. They are found in different *Enterobacteriaceae,* including *Salmonella spp* (Bradford et al., 1998).

Epidemiology of ESBLs
The epidemiology of ESBL in different parts of the world is different (Figures 2, 3). Some of the epidemiology studies are as follows:
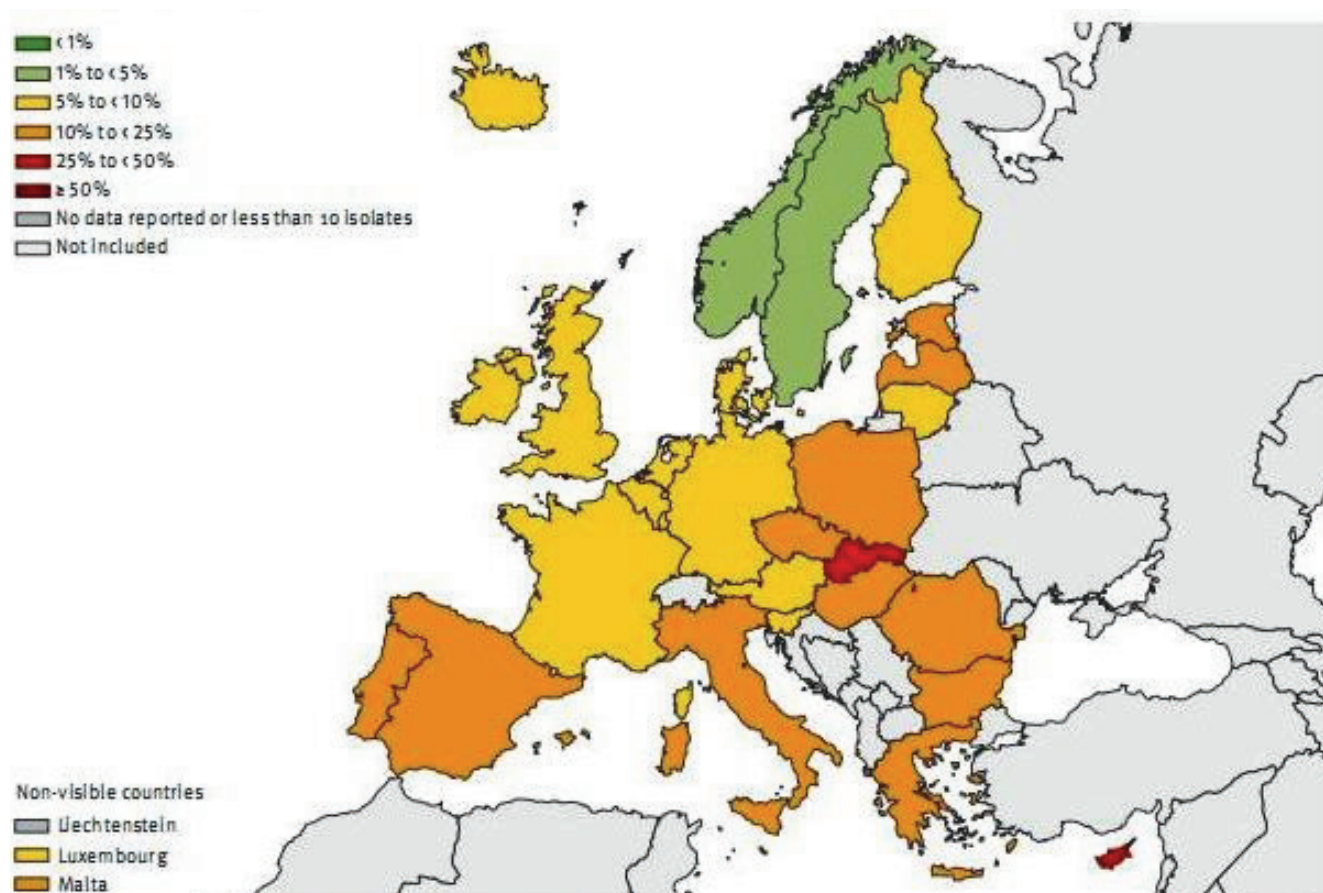
Figure 2. *E. coli*: percentage (%) of invasive isolates resistant to third-generation cephalosporins, EU/EEA, 2011.
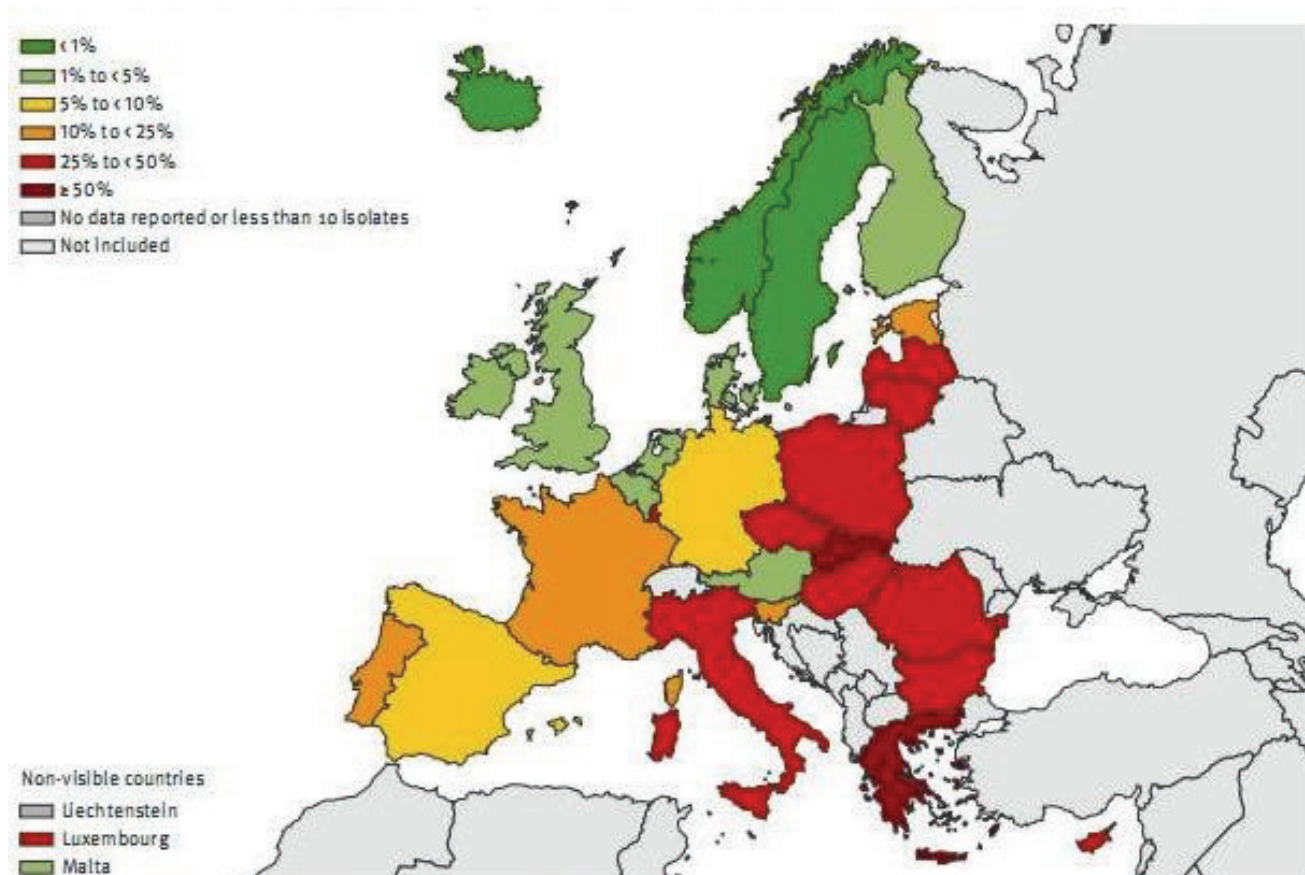
Figure 3. *K. pneumoniae*: percentage (%) of invasive isolates resistant to third-generation cephalosporins, EU/EEA, 2011.

Europe
The first report of ESBL producer strains was from Europe, specifically Germany (Knothe et al., 1983) and England (Du Bois et al., 1995). Subsequently, the vast majority of ESBL positive strains were found in France (Philippon et al., 1989). The first occurrence of ESBL in France was in 1986, where of 54 patients from three intensive care units (ICUs) were found positive for ESBL (Burn-Buisson et al., 1987). In the decade of the 1990s, about 25 to 35% of nosocomial infections by *K. pneumoniae* isolates in France were found positive for ESBL (Marty and Jarlier, 1998). In recent times, the frequency of ESBL among Enterobacteriaceae in France was under 1%, while there were an increasing prevalence of CTX-M (Galas et al., 2008). The studies also showed that the prevalence of ESBL producer strains in 2005 was much lower than in previous years, for instance *P. mirabilis* (3.7% decreasing to 1.3%), *Enterobacter aerogenes* (53.5% decreasing to 21.4%) and *K. pneumoniae* (9.4% decreasing to 3.71%). However, there was an increase in *E. coli* ESBL producer from 0.2% to 2% (Arpin et al., 2007). According to a national surveillance report, there was an increase in ESBL producer strains in northern European countries such as Denmark, Norway and Sweden. The studies also showed prevalence of ESBL positive strains in Spain and Portugal.

Further increasing prevalence of CTX-M among patients with urinary tract infections (Oteo et al., 2006; Machado et al., 2007) were observed. In the last ten years, Italy also showed an increase in ESBL positive strains (Luzzaro et al., 2006). The frequency of the occurrence of ESBL positive strains was more than 10% in Eastern Europe countries such as Hungary, Poland, Romania, Russia and Turkey. In all the mentioned countries, *K. pneumoniae* was found to be dominant ESBL positive (Damjanova et al., 2007; Korten et al., 2007; Markovska et al., 2008). The enzymes mostly responsible for ESBL production in Eastern Europe countries are: CTX-M-3, SHV-2 and SHV-5. It is evident that there is an increasing prevalence of CTX-M-15 and it constitutes the epidemiology of ESBL in all the European countries (Oteo et al., 2006). According to EARSS data for 2011 concerning only invasive isolates (Casellas and Goldberg, 1989), the resistance to third-generation cephalosporins in *E. coli* isolates at that time varied from 3% in Sweden to 36 % in Cyprus, and showed a clear north- to-south gradient, with the highest percentages of resistance reported from southern Europe and lower percentages reported by countries in northern Europe. Between 2008 and 2011, the percentages of *E. coli* isolates resistant to third-generation cephalosporins significantly increased in 18 of 28 reporting countries. No

country showed a decreasing trend during this period (Figure 2). The corresponding rates for *K. pneumoniae* ranged from the 2% noted in Sweden to the incredibly high levels of 81% in Bulgaria. Trend analyses for the period 2008 to 2011 showed significantly increasing trends for 10 of 25 reporting countries, while none of the countries showed a decreasing trend. The percentages of third-generation cephalosporin-resistant isolates reported as ESBL- positive ranged between 65% and 100% (Figure 3) (EARSS, 2011).

South and Central America
SHV-2 and SHV-5 were first reported to harbor *K. pneumoniae* during the period 1988 to 1989 in Chile and Argentina (EARSS, 2011). The studies revealed that ESBLs positive were identified in 30 to 60% of *Klebsiella spp* in Brazil, Colombia, and Venezuela (Mendes et al., 2000). The prevalence of ESBL producer *E. coli* and *Klebsiella* in Latin America showed an increase in 2008 compared to the previous years. Generally, 26% of *E. coli* and 35% of *K. pneumoniae* in Latin American were ESBL producers in 2008. In 2003, 10% of *E. coli* and 14% of *K. pneumoniae* were positive for ESBL production, while in 2004, it was 10% of *E. coli* and 18% of *K. pneumoniae* (Rossi et al., 2006).

North America
The first ESBL positive reported in 1988 in the United States, was *K. pneumoniae* with TEM-10 (Jacoby et al., 1988). This was followed by TEM-12 and TEM -26 (Bush, 2008). In 2001, it was reported that 5.6% of strains were ESBL positive in the United States (Winokur et al., 2001). In 2009, a survey on *E. coli* reported that 9% of *E. coli* were ESBL producers (Bhusal et al., 2011). Further, there were also reports of outbreaks of SHV type ESBLs . Sanchez *et al.* (Sanchez et al., 2010) investigated data obtained from The Surveillance Network (TSN) concerning in vitro antimicrobial resistance in US outpatients between 2000 and 2010, and their results showed that resistance to ceftriaxone rose from 0.2% to 2.3% and resistance to cefuroxime increased from 1.5% to 5%, but the bacterial isolates in focus were not tested for ESBLs.

Africa
There have been some studies which showed a high prevalence of ESBL producing *K. pneumoniae* in South Africa (Cotton et al.,2000). A survey conducted during a one year period, between 1998 to 1999, in a South African hospital indicated that 36.1% of *K. pneumoniae* were ESBL producers (Bell et al., 2002).

　　Unfortunately, few investigations have been conducted in sub-Saharan Africa, and they have provided very little data (Aibinu et al., 2003; Kariuki et al., 2007). The first study of ESBLs in Tanzania was performed in 2001–2002 and analyzed blood isolates from neonates, and it was found that 25% of the *E. coli* and 17% of the *K. pneumoniae* produced ESBLs, mainly the CTX-M-15 and TEM-63 types (Blomberg et al., 2005). In a more recent investigation conducted at a tertiary hospital in Mwanza, Tanzania, the overall prevalence of ESBLs in all Gram-negative bacteria (377 clinical isolates) was 29%. The ESBL prevalence was 64% in *K. pneumoniae* but 24% in *E.*

coli (Kariuki et al., 2007). Dramatic figures were also obtained in a small study at an orphanage in Mali, where 63% of the adults and 100% of the children were found to carry ESBL-producing Enterobacteriaceae that showed extensive co-resistance to other antibiotics (Tande et al., 2009). Furthermore, in Madagascar, Herindrainy *et al.* (Herindrainy et al., 2011) observed that 10% of non-hospitalized patients carried ESBLs, in the majority of the cases CTX-M-15, and these investigators also found that poverty was a significant risk factor for carriage.

Middle East
The studies in the Middle East revealed a higher prevalence of ESBL than in others parts of the world. A survey on *E. coli* ESBL producers in Egypt, conducted during the period 1999 to 2000, indicated that , 38% of the *E. coli* tested positive for ESBLs. In another study in Iran, undertaken between 2007 and 2008, 45% of the *K. pneumoniae* isolated from urinary tract infections were found to be ESBL producers (Ghafourian et al., 2012). In the same study, it was detected that, 59.2% of *K. pneumoniae* of the clinical isolates from respiratory tract infections tested positive for ESBL production (Ghafourian et al., 2011). In Iran, a one year study on *E. coli* collected from urinary tract infections showed that25% of the isolates were ESBL producers (Pakzad et al., 2011). In 2007 in a study in K. pneumonia demonstrated different range of ESBL production in different cities (Mohebi et al., 2012). In Saudi Arabia, about 26% of *K. pneumniae* isolated in 2008 produced ESBLs. In most of the isolates SHV-12, CTX-M-15 and TEM-1 were responsible for resistance to 3rd generation cephalosporin (Tawfik et al., 2011). ESBLs were also detected in some North African countries (AitMhand et al., 2002). Moubareck and colleagues (Moubareck et al., 2005) analysed faecal samples in Lebanon in 2003 and noted that ESBL carriage differed somewhat between patients (16%), healthcare workers (3%), and healthy subjects (2%), and also that there was a predominance of the CTX-M-15 enzyme (83%). Other researchers in Lebanon (Khanfar et al., 2009) observed that the proportion of ESBL-producing isolates was significantly larger among inpatients (15.4%) than in outpatients (4.5%). Moreover, data collected over three years in Kuwait showed that the levels of ESBLs were lower in community 25 isolates of *K. pneumoniae* (17%) and *E. coli* (12%) than in the corresponding hospital isolates (28% and 26%, respectively) (Al Benwan et al., 2010).

Australia
The first report of an ESBL positive strain in Australia was found in *Klebsiella spp* (gentamicin resistance) in a study done between 1986 and 1988 (Mulgrave, 1990). They later found that SHV was responsible for ESBL production in *Klebsiella spp* (Mulgrave and Attwood, 1993). In the last decade, ESBL positive strains were also identified in all the regions in Australia. It is estimated that 5% of isolates in Australia are positive for ESBL production (Bell et al., 2002).

Asia
The first isolates of *K. pneumoniae* harboring SHV-2 were reported from China in 1988 (Rossi et al., 2006). Recently,

the study of ESBLs in Asia showed a high prevalence among clinical strains. In 2001, the first CTX-M positive strains were reported in New Delhi (Karim et al., 2001). Some studies on limited isolates collected between 1998 and 1999, showed that 30.7% of *K. pneumoniae* and 24.5% of *E.coli* isolates were ESBL producers (Bell et al., 2002). In China, between 1997-1999, 27% of *E. coli* and *K. pneumonia* were identified to be ESBL producers (Du et al., 2002). It is estimated that 5 to 8% of *E. coli* isolates from Korea, Japan, Malaysia, and Singapore were positive for ESBL while it was 12 to 24% in Thailand, Taiwan, the Philippines, and Indonesia. However, the *K. pneumoniae* ESBL producers were less than 5% (Lewis et al., 1999) while in other Asian countries it was between 20 to 50%. There are variations between different hospitals. It has been reported that 1/4 of all the *K. pneumoniae* collected from various hospitals in Japan between 1998 to 1999 tested positive for ESBL production (Bell et al., 2002). The predilection of ESBLs for *K. pneumoniae* has never been clearly explained. It should be noted that the parent enzyme of TEM-type ESBLs, that is TEM-1, is widespread in many other species. Almost all the non-ESBL-producing *K. pneumoniae* isolates have chromosomally mediated SHV-1 beta-lactamases (Babini and Livermore, 2000). As early as the mid 1990s, it was noted that 25% of the *Enterobacteriaceae* in Thailand were producing ESBLs, mainly different SHV enzymes (Hawkey, 2008). Luvsansharav *et al.* (Luvsansharav et al., 2012) analyzed stool samples from healthy volunteers in Thailand in 2009, and the results showed that 30–50% of these subjects in three different regions were ESBL carriers (CTX-M types). The first report of CTX-M-producing *Enterobacteriaceae* in New Delhi was published in 2001 (Karim et al., 2001). Later, in 2006, Ensor et al. (Ensor et al., 2006) found that 66% of third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae* from three medical centers in India harbored the CTX-M-15 type of ESBL, which was also the only CTX-M enzyme found, and an investigation of 10 other centers in that country showed that rates of ESBL-producing *Enterobacteriaceae* reached 70% (Mathai et al, 2002). In other recent studies, Sankar *et al.* (Sankar et al., 2012) observed ESBL rates of 46% and 50% in out- and inpatients, respectively, and Nasa and co-workers (Nasa et al., 2012) detected ESBL production in almost 80% of clinical isolates. Investigations from India and Pakistan shows an alarming and rapid increase in the prevalence of *Enterobacteriaceae* with NDM-1 with prevalence rate from 6.9% in a hospital in Varanasi, India, to 18.5% in Rawalpindi, Pakistan (Nordmann et al., 2011) and perhaps the spread of these enzyme could be even more rapid than the spread of the CTX-M enzymes.

Risk Factors for Colonization and Infection with ESBL Producers
Many surveys were undertaken to design case control for identification of risk factors for colonization and infection with ESBL producer strains (Ariffin et al., 2000). An analysis of the findings of these surveys reveal a plethora of conflicting results, especially in terms of the differences in the investigated population, case study, controls, and sample sizes (Paterson, 2002). Nevertheless, some generalizations could be made. The high-risk patients

contaminated with ESBL are those who have severe illnesses and prolonged hospitalization. The median length of hospitalization prior to collection of positive strain for ESBL production range between 11 to 67 days. Use of large quantities of antibiotics is also a risk factor for ESBL production (Ariffin et al., 2000). Furthermore, a strong correlation was evident between using ceftazidime and the frequency of ceftazidime-resistant strains in the wards of the same hospital. In a survey of 15 hospitals, an association was detected between cephalosporin and aztreonam usage as well as an isolation rate of ESBL positive strains. Using different classes of antibiotics also resulted in infections due to ESBL positive strains. These include quinolones, cotrimoxazol, aminoglycosides, and metronidazole. However, no association was noted between use of beta-lactam/beta-lactamase inhibitor combinations, penicillins, or carbapenems and the presence of ESBL positive strains. Transmission of such bacteria usually occurs via the faecal- oral route, either directly or indirectly through hand contact with healthcare workers, and it is facilitated by overcrowding. Historically, *K. pneumoniae* and treatment in ICUs are associated with many of the risk factors, which include various medical devices such as central and arterial access lines, and nasogastric and endotracheal tubes. Other risk factors mentioned in the literature are prolonged hospital stays, living in nursing homes or long-term care facilities, underlying medical conditions, recent surgery, haemodialysis, and also prior use of antibiotics, particularly quinolones and third-generation cephalosporins, but also co-trimoxazole, aminoglycoside, and metronidazole (Lytsy et al., 2008; Pitout and Laupland, 2008). However, the positive predictive value of these risk factors is low (Ruppe et al., 2012). Plasmids encoding quinolone-resistant ESBLs and other ESBLs in general have been identified around the world, and the association between the use of quinolones and development of ESBLs is often referred to as "collateral damage" that is an adverse ecological effect of antibiotics (Paterson et al., 2000; Robicsek et al., 2006). Compared to *E. coli,* it is often assumed that *Klebsiella* is more successful in disseminating, and the latter bacteria are now the most abundant. In a study by Harris *et al.* (Harris et al., 2007), it seemed that, despite a larger reservoir of *E. coli* at ICU admission, there was more extensive transmission of *K. pneumoniae.* Over the past few years the researchers (Tham et al., 2010) have found evidence that international travel to highly endemic areas (i.e., Asia, the Middle East, and Africa) represents one of the most important risk factors for ESBL carriage especially in the community.

Conclusion
ESBLs are known to cause problems in patients who are especially hospitalized. There have been reports of an increasing prevalence of ESBLs in different regions of the world. The high risk patients are known to be those who are contaminated with ESBL producer strains as this renders treatments to be ineffective on them. Thus there is an urgent need for immediate identification and appropriate policy directions to reduce the prevalence of ESBLs. In dealing with the infected patient, priority must be given to

appropriate and effective antimicrobials, good hand hygiene, and avoiding unnecessary procedures, including central venous catheters. On an institutional level, screening and isolating all such infected patients with appropriate infection control practices, restricting use of broad spectrum cephalosporins across the hospital (implementing a stricter antimicrobial policy) and investigating environmental contamination are important. here is no doubt that ESBL-producing infections are of grave concern to the medical world. They are associated with an increased morbidity and mortality and can be difficult and time consuming to identify. Coupled with the fact that prevalence rates are rising globally, including in nonhospital settings, and the dire lack of effectiveness antimicrobial therapy, the future is tremendously concerning. Urgent work is required to develop quicker, cost-effective, and reliable diagnostic tools as well as new effective therapies.

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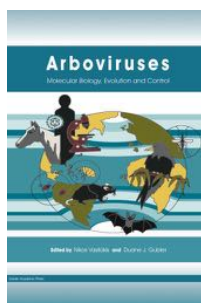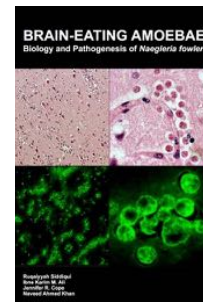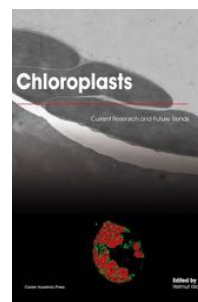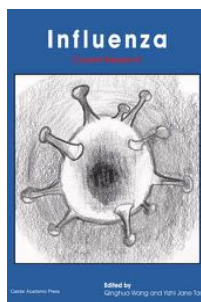
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