ABSTRACT

Antibiotic resistance is an emerging threat worldwide, endangering the treatment of serious diseases. Widespread resistance to beta-lactam antibiotics among Gram-negative bacteria (GNB) is a serious threat to the currently used antibacterial therapy. Extended-spectrum beta-lactamases (ESBLs) are a group of enzymes capable of hydrolyzing extended-spectrum cephalosporins and are inhibited by clavulanic acid. These enzymes are a major cause of hospital-acquired infections and community-acquired infections caused by E. coli (Escherichia coli). E. coli forms a part of normal intestinal flora and is an important reservoir of the antibiotic-resistant genes for ESBLs. These resistant antibiotic genes can be easily spread among GNB as these are carried on plasmids. Fecal carriers of ESBL-producing E. coli in hospitalized patients and in community can be a reservoir for person-to-person transmission strengthening their dissemination. Over the last few decades, there had been a considerable increase in the emergence and spread of ESBL-producing bacteria favoring the predominance of antibiotic-resistant bacteria which results in morbidity, mortality, and increased hospital expenditure. The gastrointestinal tract plays an important role in development of antibiotic-resistant microorganisms and harboring the microorganisms as commensal. Antibiotic consumption may lead to alteration in the genome of the microorganisms leading to emergence of resistant microorganisms. The resistant microorganisms may then spread into the environment through faces aiding dissemination of the resistant genes.

Keywords: Morbidity, Mortality, Extended-spectrum beta-lactamases, Escherichia coli.
lactam hydrolyzing enzymes called as beta-lactamases and Gram-positive bacteria have conferred resistance by producing an altered PBPs which is insensitive to beta-lactams [14].

**AN INSIGHT INTO THE HISTORY OF ESBLs**

The beginning of antibiotic era with the discovery of penicillin by Alexander Fleming in the year 1928 is marked by the consecutive development of antimicrobial resistance among different pathogens. Alexander Fleming in 1928 observed the growth of a mould of the genus *Penicillium* inhibiting the growth of bacteria in close vicinity of the mould. He identified that the mould produces an antibacterial substance called penicillin [15]. Even before the introduction of penicillin for the therapeutic use, a bacterial enzyme penicillinase was discovered by Abraham and Chain in 1940. Only after few years of introduction of penicillin for clinical use, penicillin-resistant beta-lactamases were reported in various Gram-positive and GNB. These beta-lactamases were thought to break down the beta-lactam ring of the antibiotic resulting in ineffective antibiotic [12]. The first plasmid-mediated beta-lactamase in GNB was tennomera (TEM)-1 which was described in the early 1960s.

To counter the effect of beta-lactamases, broad-spectrum cephalosporin was introduced and they remained the first line of treatment for over 20 years. However, soon after the availability of these antibiotics, enzymes resistant to broad-spectrum cephalosporins emerged known as ESBLs. In 1983, the first report of bacteria producing ESBLs was published. TEM was named so as it was first found in *E. coli* isolated from the blood of a patient named Temoneira from Greece [5]. In these 20 years, many new antibiotics were developed to treat infections to resist the action of beta-lactamases. However, with the discovery of each new antibiotic, a new class of beta-lactamases has emerged such as the use of broad-spectrum cephalosporins has lead the development of broad-spectrum beta-lactamases (TEM-1, SHV-1) which have emerged as a result of single nucleotide mutation in the TEM or SHV beta-lactamases. Widespread use of third-generation cephalosporins and aztreonam is believed to be the predominant cause of mutations in the earlier discovered broad-spectrum beta-lactamases (TEM, SHV) and has led to the development of ESBLs. The term ESBL was first used by Philippon, so that they can be differentiated from the broad-spectrum beta-lactamases [16]. By the end of 20th century, many studies have been published studying the recovery of ESBLs from various clinical isolates and in different parts of the world [17]. Some of the studies have also proposed the use of inhibitors of beta-lactamases such as tazobactam for treating infections caused by ESBL-producing bacteria [12].

**ESBL-PRODUCING *E. COlI* IN THE GUT: A SERIOUS THREAT**

Human gastrointestinal tract (GIT) harbors a large number of bacteria, and *E. coli* forms one of the largest groups, so there is an important role played by the gut in the acquisition and transmission of resistant pathogens [9]. *E. coli* is a GNB belonging to the family *Enterobacteriaceae* and colonizes the GIT of the human forming the most abundant facultative anaerobe of the human intestinal microflora. Although *E. coli* is found as a commensal microorganism in the intestine of human, there are variants of *E. coli* that are pathogenic as well. Pathogenic strains can be classified as intestinal pathogens causing diarrhea and extraintestinal pathogens causing a variety of other infections including urinary tract infections, meningitis, and septicaemia [10]. *E. coli* presents as gut normal microflora may carry antibiotic-resistant genes on plasmids. Pathogenic diarrhea causing strains of *E. coli* can acquire resistant genes from the commensal *E. coli* in the intestine. Due to the augmented use of antibiotics, the sensitive strains of *E. coli* are killed allowing a more resistant ESBL-producing *E. coli* to survive and grow rapidly to increase in number. These resistant bacteria may then spread to the other person through environment contaminated with faces of these persons [19]. Poor hand hygiene and close contact with the cattle harboring the resistant *E. coli* can be an important contributing factors for the spread of ESBL-producing *E. coli* from a common source or from person to person [20].

**CLASSIFICATION OF BETALACTAMS AND TYPES OF ESBL**

More than 200 types of ESBLs are known till now. There are different schemes for the classification of beta-lactam. The two major classification schemes followed for classifying beta-lactam into different categories are the Ambler molecular classification and the Bush-Jacoby-Medeiros functional classification [21]. Ambler classification scheme divides beta-lactamases into Class A, Class B, Class C, and Class D enzymes on the basis of protein sequence (amino acid similarity). In the Ambler classification scheme, beta-lactamases of Classes A, C, and D are serine beta-lactamases. In contrast, the Class B enzymes are MBL with the exception of OXA-type enzymes (which are Class D enzymes). The ESBLs are of molecular Class A [13]. 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 and SHV-1. The Bush-Jacoby-Medeiros classification scheme also called as functional classification scheme classifies beta-lactamase based on substrate and inhibitor profile. According to this scheme, ESBL belongs to the “2be” group or 2d Group (OXA type ESBL). The 2be designation shows that these enzymes are derived from Group 2b beta-lactamases (for example, TEM-1, TEM-2, and SHV-1): the “e” of 2be denotes that the beta-lactamases have an extended spectrum. The ESBLs derived from TEM-1, TEM-2, or SHV-1 differ from their progenitors by as few as one amino acid. This has resulted in a profound change in the enzymatic activity of the ESBLs so that they can now hydrolyze the third-generation cephalosporins or aztreonam, hence the extension of spectrum compared to the parent enzymes [21]. Table 1 shows the Bush Jacoby functional classification and Amber molecular classification of ESBL along with their characteristics.

**EPIDEMIOLOGY OF ESBL-PRODUCING *E. COlI***

Antimicrobial resistance is rapidly spreading across the globe and entails a significant threat to public health. Antibiotic resistance increases the morbidity, mortality, and costs of treating infectious diseases [22,23]. The gut plays a vital role in the development of antibiotic resistance, and the emergence of resistant microorganisms in the gut may be related to ingestion- or antibiotic-induced alterations in microorganisms. The resistant organisms then contaminate the environment. Asymptomatic fecal carriage of ESBL-producing bacteria had been reported from several countries and continents with wide differences in carriage rates between geographic areas. Over the years, prevalence of ESBL-producing *E. coli* has increased enormously. Various studies have documented the prevalence and susceptibility of ESBL-producing *E. coli*, and each one had reported quite different ESBL rates. As mentioned earlier also, ESBL were first described in 1983 from Germany and England. Various surveys conducted across the region had demonstrated the geographical variation. In a survey of laboratories in the Netherlands, <1% of *E. coli* and *K. pneumoniae* strains possessed ESBL [24]. While in another study conducted in France and Italy, cefazidime resistance was observed in as many as 40% of strains of *K. pneumoniae* [25]. The first ESBL-producing organisms were first reported in the US in 1988 [26].

A study conducted in Vietnam observed a prevalence of 87.4% of GNB from various clinical specimens out of a total 350 isolates. Of these GNB isolates, 88.9% were *Enterobacteriaceae*, of which 14.7% were ESBL-positive [27]. A study conducted by Ko et al., at South Korea, documented 22.4% of *K. pneumoniae* isolates and 10.2% of *E. coli* isolates as ESBL producers [28]. In a study from India, the percentage of ESBL-positive isolates was found to be elevated, with 23.1% of isolates being ESBL-positive [29]. Of the isolates from India, 48.4% of isolates were *E. coli* and 51.6% were *K. pneumoniae* [30]. ESBL prevalence of 30-60% of from intensive care units in Brazil, Colombia, and Venezuela had been reported [31-34]. Moreover, several studies had been conducted to test the prevalence fecal carriage of ESBL-producing GNB as these carriers can form important reservoirs for the transmission of hospital-acquired infection (HAI) and community-acquired infections caused by these bacteria. In a study conducted at South Africa by Mahomed and Mahomed out of
isolates were obtained from 97 stool samples. The isolates were tested for their susceptibility to third-generation cephalosporins, besides ceftazidime, cefotaxime, and ertapenem. The study included STEB-producing Enterobacteriaceae isolates from 127 stools. The isolates were confirmed as ESBL-positive by performing antibiotic susceptibility testing on Mueller-Hinton agar using a 0.5 McFarland standard inoculum. Screening method for detection of ESBL production is based on measuring the zone of inhibition. E. coli isolates may be regarded as positive for screening test for ESBL production under the following conditions as shown in Table 2.

### BROTH MICRODILUTION METHOD

Broth microdilution test can be performed with Mueller-Hinton broth to determine the minimum inhibitory concentration. A positive test for ESBL-producing E. coli isolates is indicated by a MIC ≥8 µg/ml for cefpodoxime, MIC ≥2 µg/ml for cefazidime, aztreonam, cefotaxime, or ceftiraxone.

### SELECTIVE MEDIUM FOR DETECTION OF ESBL-PRODUCING E. COLI

Screening can also be made by the use of selective medium such as chrom ID ESBL agar, Brilliance ESBL agar, and HiCrome ESBL agar. ESBL-producing E. coli isolates produce blue-violate colonies on chrom ID ESBL agar and pink to burgundy colonies on Brilliance ESBL agar and either pink or purple colonies on HiCrome ESBL agar.

The isolates showing positive screening are then tested further by confirmatory methods for ESBL detection as positive screening does not necessarily rule out the production of ESBL.

### PHENOTYPIC CONFIRMATORY METHODS FOR THE DETECTION OF ESBL PRODUCTION

#### Double disc synergy test

Standardized inoculums of the test isolate are swabbed on the surface of a Mueller-Hintonagar plate. A combination disc, such as cefazidime and clavulanic acid (30/10 mcg), piperacillin and tazobactam disc (100/10 mcg), were placed at the center surface of the plate. Disc containing 30 mcg of cefazidime, ceftoxime, ceftriaxone, and 10 mcg of cefpodoxime was placed at a distance of 1.8 cm away from the central disc.

An extension in the zone of inhibition around the peripheral disc toward the centrally placed cefazidime/clavulanic acid disc indicated ESBL production. An advantage of this method is that the method is relatively simple.

#### Combined disc test (inhibitor potentiated disc test)

Cephalexin disc (30 mcg), ceftriaxone (30 mcg) and cefpodoxime (30 mcg) with or without clavulanic acid, 10 mcg, was placed on the Mueller-Hinton agar inoculated with the test organism. An increase in the inhibition zone diameter of ≥5 mm in cephalosporins, as shown in Table 2, is indicative of ESBL production.

### PHENOTYPIC METHODS FOR THE DETECTION OF ESBL PRODUCTION IN E. COLI ISOLATES

Phenotypic detection of ESBL-producing E. coli isoslates in clinical laboratory can be done by performing various screening and confirmatory tests according to the guidelines lead by clinical laboratory standard institute [41].

### Screening methods for ESBL producers

Susceptibility of positive E. coli to third-generation cephalosporins is detected by performing antibiotic susceptibility test on Mueller-Hinton agar using a 0.5 McFarland standard inoculum. Screening method for detection of ESBL production is based on measuring the zone of inhibition. E. coli isolates may be regarded as positive for screening test for ESBL production under the following conditions as shown in Table 2.
Table 3: Worldwide distribution of ESBL-producing Enterobacteriaceae

| Study group   | Year of study | Study area | Clinical isolates | ESBL prevalence (%) | Risk factors                  |
|--------------|---------------|------------|-------------------|---------------------|------------------------------|
| Blom et al [41] | 2016          | Sweden     | E. coli           | 10                  | Foreign travel               |
| Asir et al [42] | 2015          | India      | E. coli           | 21                  | Invasive devices such as urinary catheters |
| Mohamed and Mohamed [34] | 2014          | South Africa | E. coli and K. pneumoniae | 4.7                  | Contaminated food and water |
| Shaky et al [43] | 2013          | India      | E. coli           | 9                   | Higher socioeconomic status  |
| Reuland et al [35] | 2012          | Netherlands | Enterobacteriaceae | 10.1                | Foreign travel               |
| Wickramasinghe et al [44] | 2012          | UK         | E. coli           | 11.3                | Foreign travel               |
| Woerther et al [37] | 2011          | Niger      | E. coli           | 31                  | Transmission from hospitals  |
| Peirano et al [45] | 2011          | Canada     | E. coli           | 14                  | Foreign travel               |
| Herrin et al [46] | 2011          | Madagascar | Enterobacteriaceae | 10.1                | Hospital acquisition         |

disc combined with clavulanic acid, compared to cephalosporins alone, indicated ESBL production.

Risk factors for acquisition of ESBL

The prevalence of ESBLs among clinical isolates varies between countries and from institution to institution. Several studies have already revealed various risk factors associated with colonization and infection with ESBL-producing organisms. In prolonged hospital stay, patients on medical devices such as urinary catheters, and central venous lines have been associated with infections by these organisms. Further, surgical procedures and indiscriminate use of antibiotics are added risk factors for the acquisition of ESBL-producing organisms. Presence of highly resistant pathogens in hospital sewage may result in transmission of resistant bacteria from environment to human.

Table 3 also describes various studies conducted across the world in different years to study the prevalence and the associated risk factors of ESBL-producing E. coli and other GNB.

CONCLUSIONS

Colonization with multidrug-resistant isolates, including ESBL-producing isolates, is one of the significant risk factors for infection. Therefore, importance of detection of carriers of antimicrobial-resistant bacteria in hospitalized patients as well as in community is of utmost value. Antibiotic selection pressure in hospital may be the contributing factor for the presence of large number of carriers harboring resistant bacteria. By minimizing selective pressure through judicious use of antibiotics, we may well be able to maintain antimicrobial susceptibility patterns at a level and we can tackle with. It was observed that healthy individuals also carried the commensal ESBL-producing E. coli in their gut in a high percentage. The occurrence of these ESBL-positive E. coli strains as colonizers in the community indicates a reservoir outside the hospitals that should be taken seriously regarding implementation of screening and hygiene precautions for prevention of infections with these drug-resistant bacteria.

Strict adherence to patient hygiene and infection control practices may be enforced to curtail hospital acquired infections. Rational use of antibiotics would substantially decrease pressure on the gut microbiota and thereby limit acquisition of resistant genes among these microorganisms. There is a need to have stringent local and national research and surveillance efforts to monitor resistance pattern of commensal E. coli.

REFERENCES

1. Ventola CL. The antibiotic resistance crisis: Part 1: Causes and threats. Pharm Ther 2015;40(4):277-83.
2. Rolain JM, Cantor R, Cornaglia G. Emergence of antibiotic resistance: Need for a new paradigm. Clin Microbiol Infect 2012;18:615-6.
3. Shaikh S, Fatima J, Shakil S, Rizvi SM, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi J Biol Sci 2015;22(1):90-101.
4. Kong KF, Schnepf L, Mathee K. Beta-lactam antibiotics: From antibiosis to resistance and bacteriology. APMIS Actapathol Microbiol Et Immunol Scand 2010;118(1):1-36.
5. Paterson DL, Bonomo RA. Extended-spectrum β-lactamasas: A clinical update. Clin Microbiol Rev 2005;18(4):567-84.
6. Vaidya VK. Horizontal transfer of antimicrobial resistance by extended-spectrum β-lactamase-producing Enterobacteriaceae. J Lab Phys 2011;3(1):37-42.
7. Lagace-Wiens PR, Nichol KA, Nicolle LE, Decorby MR, McCracken M, Alfa MJ et al. ESBL genotypes in fluoroquinolone-resistant and fluoroquinolone-susceptible ESBL-producing Escherichia coli urinary isolates in Manitoba. Can J Infect Dis Med Microbiol 2007;18(2):133-7.
8. Philippin A, Labia R, Jacoby G. Extended-spectrum beta-lactamases. Antimicrob Agents Chemother 1989;33:1131-6.
9. Huddleston JR. Horizontal gene transfer in the human gastrointestinal tract: Potential spread of antibiotic resistance genes. Infect Drug Resist 2014;7:167-76.
10. Levy SB, Marshall B. Antibacterial resistance worldwide: Causes, challenges and responses. Nat Med 2004;10:5123-9.
11. Murray B. New aspects of antimicrobial resistance and the resulting therapeutic dilemmas. J Infect Dis 1991;163:1185.
12. Drawz SM, Bonomo RA. Three decades of β-lactamase inhibitors. Clin Microbiol Rev 2010;23(1):160-211.
13. Spratt BG. Properties of the penicillin-binding proteins of Escherichia coli K12. Eur J Biochem 1977;72(2):341-52.
14. Chambers HF. Penicillin-binding protein-mediated resistance in pneumococci and staphylococci. J Infect Dis 1999;179 Suppl 2:S535-9.
15. Aminov RI. A brief history of the antibiotic era: Lessons learned and challenges for the future. Front Microbiol 2010;1:134.
16. Bradford PA. Extended-spectrum β-lactamases in the 21st century: Characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001;14(4):933-51.
17. Rawat D, Nair D. Extended-spectrum β-lactamases in gram negative bacteria. J Glob Infect Dis 2010;2(3):263-74.
18. Katouli M. Population structure of gut Escherichia coli and its role in development of extra-intestinal infections. Iran J Microbiol 2010;2(2):59-72.
19. Carlet J. The gut is the epicentre of antibiotic resistance. Antimicrob Resist Infect Control 2012;1(1):39.
20. Brolund A. Overview of ESBL-producing Enterobacteriaceae from a Nordic perspective. Infect Ecol Epidemiol 2014;4. DOI: 10.3402/iee.v4.24555.
21. Busk J, Jacoby GA. Updated functional classification of β-lactamases. Antimicrob Agents Chemother 2010;54(3):960-76.
22. Rice LB. The clinical consequences of antimicrobial resistance. Curr Opin Microbiol 2009;12(5):476-81.
23. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 2010;74(3):473-33.
24. Stobberingh EE, Arends J, Hoogkamp-Korstanje JA, Goessens WH, Visser MR. Occurrence of extended-spectrum beta lactamases in Dutch hospitals. Infection 1999;27:348-54.
25. Branger C, Lesimple AL, Bruneu B, Berry P, Lambert-Zechovsky N. A long-term investigation of the clonal dissemination of Klebsiella pneumoniae isolates producing extended-spectrum beta lactamases in a university hospital. J Med Microbiol 1998;47:201-9.
26. Jacoby GA. Extended-spectrum β-lactamases and other enzymes providing resistance to oximino β-lactams. Infect Dis Clin N Am 1997;11:875-87.
27. Jones SL, Nguyen VK, Nguyen TM, Athan E. Prevalence of ESBL in
multiresistant gram-negative organisms in a surgical hospital in Ho Chi Minh city, Vietnam. Trop Med Int Health 2006;11:1725-30.
28. Ko KS, Lee MY, Song JH, Lee H, Jung DS, Jung SI, et al. Prevalence and characterization of extended-spectrum beta-lactamase producing Enterobacteriaceae isolated in Korean hospitals. Diagn Microbiol Infect Dis 2008;61:453-9.
29. Varaiya AY, Dogra JD, Kalkarni MH, Bhalekar PN. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumonia in diabetic foot infections. Indian J Pathol Microbiol 2008;51:370-2.
30. Mendes C, Hsiung A, Kiffer C, Oplustil V, Sinto S, Sampaio J, et al. Evaluation of the in vitro activity of 9 antimicrobials against bacterial strains isolated from patients in intensive care units in Brazil. MYSTIC antimicrobial surveillance program. Braz J Infect Dis 2000;4:236-44.
31. Otman J, Cavassin ED, Perugini ME, Vidotto MC. An outbreak of extended-spectrum beta-lactamase-producing Klebsiella species in a neonatal intensive care unit in Brazil. Infect Control Hosp Epidemiol 2002;23:8-9.
32. Pfäffer MA, Jones RN, Doern GV. Multicenter evaluation of the antimicrobial activity for six broad-spectrum beta-lactams in Venezuela: Comparison of data from 1997 and 1998 using the etest method. Venezuelan antimicrobial resistance study group. Diagn Microbiol Infect Dis 1999;35:153-8.
33. Pfäffer MA, Jones RN, Doern GV, Salazar JC. Multicenter evaluation of antimicrobial resistance to six broad-spectrum beta-lactams in Colombia: Comparison of data from 1997 and 1998 using the Etest method. The Colombian antimicrobial resistance study group. Diagn Microbiol Infect Dis 1999;35:235-41.
34. Mahomed S, Mahomed Y. Faecal carriage of extended spectrum beta-lactamase producing Escherichia coli and Klebsiella pneumoniae in children from the community of Kwadedangendale, KwaZulu-Natal, South Africa. Int J Infect Control 2014;11:3.
35. Reuland EA, Overdevest IT, Al-Naiemi N, Kalpoe JS, Rijnsburger MC, Raadsen SA, et al. High prevalence of ESBL-producing Enterobacteriaceae carriage in Dutch community patients with gastrointestinal complaints. Clin Microbiol Infect 2013;19(6):542-9.
36. Ruppe E, Woerther PL, Diop A, Sene AM, da Costa A, Arlet G, et al. Carriage of CTX-M-15-producing Escherichia coli isolates among children living in a remote village in Senegal. Antimicrob Agents Chemother 2009;53:3135-7.
37. Woerther PL, Angebault C, Jacquier H, Hugede HC, Janssens AC, Sayadi S, et al. Massive increase, spread, and exchange of extended spectrum beta-lactamase-encoding genes among intestinal Enterobacteriaceae in hospitalized children with severe acute malnutrition in Niger. Clin Infect Dis 2011;53:677-85.
38. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
39. Sanidhya R, Priya RL, Selvam E. Antibiotic susceptibility pattern and ESBL prevalence in Escherichia coli isolates from pus samples in a tertiary care hospital. Int J Pharm Pharm Sci 2015;7(3):263-4.
40. Muraleetharan M, Vishwanathan T. Epidemiological studies on varying extended spectrum beta-lactamase-producing uropathogenic bacteria. Int J Pharm Pharm Sci 2014;6(11):57-60.
41. Blom A, Ahl J, Månsson F, Resman F, Tham J. The prevalence of ESBL-producing Enterobacteriaceae in a nursing home setting compared with elderly living at home: A cross-sectional comparison. BMC Infect Dis 2016;16:111.
42. Asir J, Nair S, Devi S, Prashanth K, Saranathan R, Kanungo R. Simultaneous gut colonisation and infection by ESBL-producing Escherichia coli in hospitalised patients. Acad Manage J 2015;8(6):200-7.
43. Shaker P, Barrett P, Diwan V, Marothi Y, Shah H, Chhari N, et al. Antibiotic resistance among Escherichia coli isolates from stool samples of children aged 3 to 14 years from Ujjain, India. BMC Infect Dis 2013;13:477.
44. Wickramasinghe NH, Xu L, Eustace A, Shabir S, Saluja T, Hawkey PM, et al. High community faecal carriage rates of CTX-M ESBL-producing Escherichia coli in a specific population group in Birmingham, UK. J Antimicrob Chemother 2012;67(5):1108-13.
45. Peirano G, Laupland KB, Gregson DB, Pitout JD. Colonization of returning travelers with CTX-M-producing Escherichia coli. J Travel Med 2011;18:299-303.
46. Herindrainy P, Randrianirina F, Ratovoson R, Hariniana ER, Buisson Y, Genel N, et al. Rectal carriage of extended-spectrum beta-lactamase-producing gram-negative bacilli in community settings in Madagascar. PLoS One 2011;6(7):e22738.