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Beta-lactamases and their Global Health Implications–One: Epidemiological Profile, Paradigm of Nigerian Chickens Escherichia coli and Staphylococcus aureus Isolates

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Abstract

Beta-lactamases are enzymes produced by some bacteria, which makes them resistant to β-lactam antibiotics such aspenicillins, cephalosporins, cephamycins and carbapenems. In this article epidemiological profileofβ–lactamases were reviewed, with some observation on Nigerian chickens*Escherichia coli* and S*taphylococcus aureus* isolates. Extended-spectrum β–lactamases produced by enterobacteria and penicillinases/methicillinases produced by Staphylococci constitute the growing classes of plasmid–mediated and chromosomally–mediated β–lactamases that confer resistances to all β–lactam agents and to more than 90% of non–β–lactam antimicrobials. The TEM, SHV, CTX–M and Oxa type β–lactamases are plasmid–mediated enzymes which posses extended–spectrum activity, whereas, penicillinases, methicillinases and AmpC enzymes can both be chromosomally- and plasmid–mediated. The CTX–M, TEM, and AmpC–producing *Escherichia coli* and the methicillinase-producing *Staphylococcus aureus* have been isolated from chickens with increased frequencies worldwide. Recent report of detection from chickens in Nigeria has placed it among the few African Countries where β–lactamases have been detected. Reports of exponential increase in the isolation of β-lactamases in both humans and animals have been documented,with a dramatic increase around the world, of TEM-, SHV-, CTX-M- and OXA-types and methicillinases. The global diversification of these enzymes may pose a greatpublic health challenge.

Keywords: Beta-lactamases; Bacteria; *Escherichia coli*; *Staphylococcus aureus*; Epidemiology

Introduction

β– lactamase–producing bacteria according to Brook [1]can play a role in poly-microbial infections, either by direct pathogenic impact in causing the infection, or by indirect effect through their ability to produce the enzyme β –lactamase.This enzyme was said to hydrolyze both penicillins and extended-spectrum cephalosporins includingaztreonam[2] and even cefepime and imipenem[3]. The β –lactamase enzyme remains the most important method of bacterial defense against β-lactam antibiotics.As reported by Mirzaeeet al., [3], the development and widespread use of oxyimino-cephalosporinshas led to the emergence of extended-spectrum beta–lactamases (ESBLs) in bacteria; and Ma et al., [4]stated that the emergent resistant ESBLs in various bacterial organisms,with some bacteria producing multiple β-lactamases (e.g. blaTEM, blaSHV and blaCTX-M encoded by a single plasmid of one bacterium)is alarming.

The present paper attempted to highlight β-lactamases and their epidemiological profile, with some observation on *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) chicken isolates from Nigeria. There have been frequent reports on the dramatic increase of the prevalence of beta-lactamases from many regions around the world.The highest prevalence reported being extended-spectrum β-lactamasesfrom Asia [5] and Europe [6] and low prevalences from North America and Africa [7].The worldwide spread of these enzymes has partially been attributed to international travelsas suggested by Tängdénet al., [8],and possibly importation of animals or animal products infected withβ-lactamase-producing-organisms. The frequency of isolation of β-lactamase-producing-organisms in food animals and wildlife was reported by Winokuret al., [9], Hornish and Kotarski[10]and Carmen and Myrian[11] with exponential increase over the years.

The Beta-Lactamases

β-lactamases are enzymes produced by some bacteria and are responsible for their resistance to β-lactam antibiotics such as penicillins, cephalosporins, cephamycins and carbapenems[12]. Since the inception of β–lactam antibiotics into clinical use, β–lactamase enzymes have co-evolved with them [13]. The earlier events included increased prevalence of enzymes in bacteria in which they were present but uncommon and spread to pathogens such as *Haemophilusinfluenzae(H. influenzae)* and *Neisseria gonorrhoeae (N. gonorrhoeae)* in which the enzymes were previously lacking [14]. Agents which shared resistance properties to the then common β–lactamases including cephamycins, cephalosporins and the monobactams which were introduced of recent, were countered with a plethora of new β–lactamases including plasmid-mediated ESBLs, AmpC enzymes and carbapenemases by Enterobacteria[7, 14]. Chromosomally-encoded AmpC β–lactamases were also found to confer resistance to the latest β–lactam agents with variable success [3]. In *S. aureus* the enzymesare carried by either the plasmid or chromosome and are constitutively or inductively expressed on exposure to β-lactam antibiotics as explained by Livermore[15]. ESBLs represent an impressive example of the ability of gram negative bacteria to develop new antibiotic resistance mechanisms in the face of the introduction of new antimicrobial agents [16].

Epidemiology

The epidemiology of β–lactamases has evidenced different periods since these enzymes were first reported, and includes epidemics, sporadic cases, polyclonality, and epidemics of associated plasmids which carry the genes responsible for the expression of these enzymes. The distribution of β–lactamase–producing bacteria and that of these enzymes varies greatly among geographical regions (Table 1), especially ESBLs which are mainly found in *E. coli*. According to Rafael et al.,[17] the current spread of virulence genes in microorganisms may probably be due to multi-factorial processes that could include elements and genetic structures associated with the blaBLEE genes;so also the microorganisms producing these enzyme-associated resistance and processes of co-selecton, clonal complexes [18] and virulence mechanism [19].

Despite the global use of β–lactam antibiotics, uneven distribution of the enzymes responsible for resistance to oxyimino–cephalosporins and carbapenemshas been existing [14]. Reports on detection of ESBLs in Africa have been limited to Saharan countries [7] and information from sub-saharan Africa is scarce. In America, Asia and Europe many countries have reported β–lactamases that are even resistant to ceftazidime and carbapenems[7].

The ESBLs mainly occur in *Klebsiellapneumoniae*, *K.oxytoca* and *E. coli*, but have been isolated from Citrobacter, Enterobacter, Proteus,Serratia, Salmonella [20] and other species ofEnterobacteria such as enterobacteriaceae and *Serratiamercescens*[21] and non-enteric bacteria: *Pseudomonas aeruginosa*(*P. aeruginosa*) and *Acinetobacterbaumannii*(*A.baumannii*) [22, 23]. The ESBLs SHV-5, SHV-12, CTX–M-3 and CTX–M-14 have been reported as the most prevalent types in isolates of *K. pneumoniae* and *E. coli*[21], but differ on geographc locations.

Table 1: Epidemiology of beta – lactamases

S/n	ß-lactamase type	Varients	Resistance to	Prevalence		Reference
				Organism	Region	
1	TEM*. TEM – 1, 2, 3, 10,12, 26, 154, etc.	160	Penicillins	Gram-negative *E. coli, N. gonorrhoae, K. pneumonia*	Worldwide	Pitoutet al. [7]
2	SHV(Shigella virulent). SHV – 1, 2, 5, 12 etc.	Over 60	Penicillins	Gram-negative *K. pneumonia, E. coli* etc.	Worldwide	Paterson et al. [24]
3	CTX – M (Cefotaximases). CTX – M – 1, 9, 14, 15, 72, 81 etc.	Over 100	Cefotaxime	Gram negative *Salmonella E. coli* etc.	Worldwide	James et al. [25], Mamlouk et al. [26]
4	Oxacillinases (OXA) OXA – 1, 2, 3, 10, 23, 24, 51, 69, etc. Methicillinases	150	Cloxacillin Penicillin Cephalothin Ceftazidime	Gram –ve/+ve *Pseudomonas aeruginosa Citrobacter Staphylococci*	Europe Asia	Jun et al. [27] Lee [28]
5.	IRT (Inhibitor-Resistant TEM) ß-lactamases	Over 20	Penicillins and extended-spectrum ß-lactam agents	Gram negative *E. coli Klebsiella Citrobacter*	Worldwide	Pfaller and Segreti [29]
6	AmpC ß-lactamases e.g. CMY, MIR, FOX, BIL, GES, IMP. DHA	Over 30	Cephalosporins Cephamycins Oxyimino- ß – lactam agents	Gram negative *Citrobacter Seratia Enterobacter*	Europe (Korea Norway Newzealand Portugal)	Naseeeret al. [30] 2010 Yoonet al. [31] Christopheret al. [32]
7	Carbapenemases e.g. VIM, KPC, IMP	Over 20	Cephamycins Carbapenems Imipenems All ß -lactams	Gram negative *Pseudomonas Klebsiella Acinetobacter*	Worldwide	Pfaller and Segreti [29], Cuzon et al. [33]

*TEM was named after the patient, Temoneira, from whom the ß-lactamase was first isolated

In a study of 1,300 *E. coli* isolates, [9] reported strains which expressed the ESBLs phenotype as follows: Latin America (8.5%), western Pacific (7.95%), Europe (5.3%), USA (3.3%) and Canada (4.2%). In another study in Taiwan (2001–2006), from a sample of 569 isolates, 15.5% out of 182 *E. coli* strains were found to express the ESBLs phenotype [34]. In a large data set of 6,850 *E. coli* isolates from Belgium, collected between 2004 and 2006, 72 isolates were found to over-express their chromosomal cephalosporinases and 11 contained plasmid–mediated cephalosporinases, and among the chromosomal AmpC enzymes 12 expressed extended–spectrum AmpC[35].

In an 8 year survey conducted in Greece, an increasing prevalence of penicillinases was reported: out of a total of 6,089 isolates investigated, 35.7% produced penicillinases, 0.61% produced cephalosporinases and 0.94% expressed ESBLs [36]. Further study conducted in 2007 on 3,004 isolates of gram-negative bacteria in Asia – Pacific region, [37] reports that 42.2% of *E. coli* and 35.8% of *Klebsiella species* expressed the ESBLs phenotype and 79.0% *E. coli*, 64.9% *K. pneumoniae* and 100% *K. oxytoca* in India, and 55.0% in China and 50.8% in Thailand expressing the enzymes.

The ESBLs types TEM–1, TEM–2 and SHV–1 having an extended substrate profile that permits the hydrolysis of all cephalosporins, penicillins and aztreonams are commonly found in *Klebsiellaspp* and *E. coli*[38], and have been found in *Enterobacter*, *Salmonella*, *Proteus* and *Citrobacter sp*.,*Shigelladysenteriae*, *Morganellamorganni*,*Serratiamarcescens*, *P.aeruginosa*, *Burkholderiacepacia* and *Capnocytophagaochracea*[39]. The TEM–type β–lactamases mostly occur in *E. coli* and *K. pneumoniae*, and in other gram–negative bacteria with increasing frequency. Isolation of TEM β–lactamases have been reported in increased frequencies worldwide, with predominant isolates: TEM–10, TEM–12 and TEM–26 from USA [23, 7], TEM–3, TEM–20 and TEM–21 from Tunisia [40], TEM–24, TEM–52, TEM–12, TEM–154, TEM–10 from Portugal [41], TEM – 4 and TEM – 110 in Spain and TEM – 1 from South Africa [7]. The SHV–type β–lactamases occur worldwide [23] and the most common types detected include SHV-1, SHV-2, SHV-5, SHV-11, SHV-12, SHV-26, SHV-26, SHV-89 and SHV-90 in Europe: reported more often from Spain and Portugal [41 - 44]. In USA, SHV-1, SHV-5 and SHV-12 most commonly reported [23], in Asia, SHV–89 from China [45] and SHV–2, SHV–5 and SHV–12 from Turkey [46]. Predominant in Africa were SHV-1, SHV-2 and SHV-12: from Tunisia, Senegal and Egypt [7].

Cefotaximases (CTX–M) –type ESBLs have increasingly been detected globally [26], and have mainly been found in strains of *Salmonella enterica*serovar*typhimurium* and *E. coli*, but have also been described in other species of bacteria. These enzymes have emerged as the most common type of ESBLs worldwide, easily surpassing the incidence of TEM and SHV ESBLs in most locales [25]. Types CTX–M–9 and CTX–M–10, CTX–M–14 and CTX–M–15 were reported of persistent increase in isolates of *K. pneumonia* between 1989 and 2004 in Spain [43].

In parts of South America and Eastern Europe, CTX–M–2, CTX–M–3 and CTX–M–14 were predominant, whilst CTX–M–15 was most detected in *E. coli* from the United Kingdom [47]. Clonal out breaks of CTX-M -15 enzyme have also been reported from Canada, India, Kuwait, France, Switzerland, Portugal and Spain [18], and South Africa [7]. The frequency of detection of CTX–M–14, CTX–M–9, CTX–M–10, CTX–M–1, CTX–M–15 and CTX–M–32 also increased in *E. coli* and other bacterial organisms from Spain between 2000 and 2005 [43]. In Africa, CTX–M–12 in *K. pneumoniae* from Kenya, and CTX–M–15 in *K. pneumonia*e and *E. coli* from Cameroon, Tanzania and Nigeria respectively have been reported [48 - 51]. Other types, CTX–M–14, CTX–M–15 and CTX–M–27 have been detected with increased frequencies in *K. pneumoniae* from Tunisia, Central Africa, Algeria, and Senegal [26]. First detection of CTX–M–47, CTX–M–48, CTX–M–49 and CTX–M–50 enzymes from isolates of *K. pneumoniae* and *E. coli* in these African countries was reported in 2008 [52].

The Oxacillinases (OXA–type β–lactamases) have occurred mainly in *Acinetobacter spp*., but have been found mostly in*Pseudomonsaeruginosa*. The OXA-types (OXA–1, OXA–2 and OXA–10) have widely been reported with some exhibiting resistance against ceftazidime[14, 23]. The detection of OXA–2 and OXA–143 from Spain [27], and OXA–2 and OXA–3 from the UK [53] have been reported. The AmpC type β–lactamases are typically encoded on the chromosome of many Gram-negative bacteria including *Citrobacter*, *Serratia* and *Enterobacter spp*. and *P. aeruginosa*[54]. According to [31] CMY–2 and DHA–1 were the most common plasmid–mediated AmpC β–lactamases in *E. coli* from South Korea. Reports of CMY–2, CMY–7 and DHA–1 in *E. coli* isolates from Norway [30] and CMY–29 and CMY–30 in *E. coli*, Klebsiella, salmonellaand *proteus spp*. from NewZealand[32] were documented. The CMY enzyme was first described in 2006 from a virulent strain of *Enterobacteraerogenes*[55], and the enzyme was said to be carried on a plasmid pYMG–1 and is therefore transmissible to other bacterial strains [56].

Carbapenemases are derivatives of classes A–D β–lactamases; Plasmid–mediated IMP–type carbapenemases were detected in Japan in 1990 in both enteric gram-negative bacteria and *Pseudomonas* and *Acinetobacter sp*. and the enzyme which now has spread to other countries in the Far-East, was reported in Europe, Canada and Brazil in 1997 [29]. First isolation of IMP–1 and the plasmid–mediated MIR–1 was in *E. coli* from China [57]. VIM–type carbapenemases is the second growing family of the AmpC β–lactamases.

They are widely distributed in Europe, South America and the Far-East, as well asthe USA. VIM–1 and VIM–2 were predominantly and frequently detected variants in Europe and the Far-East, whilst VIM–3 and VIM–4 were the minor variants of VIM–1 and VIM–2 respectively [29]. The VIM–enzymes being very rarely found in Enterobacteriaceae, were however isolated from this species in Spain [58]. The *K. pneumomiae*carbapenemases (KPC) was shown to have the ability to be encoded by self-transmissible plasmids. The KPC (KPC–1, KPC–2 and KPC–3) initially detected in Enterobacter from USA, has incidentally became the most important cabarpenemases worldwide [33]. Other plasmid–mediated ESBLs such as PER, VEB, GES and IBC have been described in *P. aeruginosa* and Enterobacteriaceae, but at a limited geographical locations are however not common. However, PER–1 was more common in multi-resistant *Acinetobacterspp* from Korea, Turkey, France and Italy [14]. VEB–1 and VEB–2 were isolated in South-East Asia, and GES–1, GES–2 and IBC–2 were detected in isolates from South Africa, France and Greece [22].

Several studies have reported the isolation of β–lactamase enzymes in humans, but only few animal studies have been documented. However, the frequency of isolation of β–lactamases from animals has been on the increase over the few decades [59 – 61, 11, 44]. The ESBLs was first isolated from humans in 1983 and plasmid–mediated AmpC enzymes in 1988 [38]. Ten years later the first isolation of an ESBL–producing microorganism (SHV–12 β–lactamase – producing *E. coli*) from animals was reported [11]. Since then there has been an alarming increase in the detection of ESBLs, mainly of the CTX–M group in *E. coli* strains in healthy animals destined for human consumption, and to a lesser extent, in pets and even wild animals [11].

Available data depicting ESBLs detected in *E. coli* isolates from animals revealed that 6% TEM Variants (TEM–52), 15% SHV variants (SHV–2 and SHV–12) and 79% CTX–M variants (CTX–M–1, CTX–M–9, CTX–M–14 and CTX–M–15) isolated from Europe; and from Asia, similar percentage of CTX–M–2, CTX–M–3, CTX–M–13, CTX–M–14, and CTX–M–24 were isolated [11]. The most common CTX–M–1 and CTX–M–2 were isolated from isolates of *K. pneumoniae* and *E. coli* in poultry in Brazil, South America [44, 61]. The most predominantly reported ESBLs in *E. coli* from animals are CTX–M–1, CTX–M–14, CTX–M–14 and SHV–12 mainly from birds, CTX–M–1 from swine and CTX–M–2 from cattle [11]. In Europe, ESBLs–producing *E. coli* were detected in 60% of chickens carcasses, 10% of healthy chickens faeces and 5.7% of healthy swine faeces, with TEM–52, SHV–2 and CTX–M–1 being common in chickens, and SHV–12 most common in swine in Portugal [44]; TEM–34, TEM–40, TEM–30 and TEM–51 were more common in swine, and AmpC enzymes more common in chickens in Spain [62]. From broiler farms in Belgium, some *E. coli* isolates producing more than one type of β–lactamases were reported [63]. From analysis of 752 *E. coli* isolates submitted to the *E. coli* reference centre of Pennisylvania State University (the centre provides characterization of *E. coli* isolates submitted from outside sources) between 1976 and 2000, including 68 isolates from humans submitted from 9 US States, 45 from Saudi Arabia, 13 from Argentina, 4 from Canada, 3 from Mexico, 3 from Zambia and 1 from Singapore; 248 isolates from cattle submitted from Michigan, 56 from Iowa, 33 from Pennisylvania, 65 from other US States and 2 from Canada; 51 isolates from turkeys submitted from 13 US States; 49 isolates from chickens submitted from 10 US States, 2 from Canada and 2 from India; 22 isolates from swine submitted from 7 US States, 3 from South Korea, and 1 from India and 74 isolates from non–food animals submitted from 20 US States, 5 from Paraguay, and 2 from Hungary; β–lactamase–resistant strains in O26, O103, O111, O128 and O145 isolates suspected to be AmpC β–lactamases were detected [64]. The authors also observed that the isolates exhibited multiple antibiotics resistant phenotypes. The highest frequencies of resistant phenotypes were in isolates from humans and turkeys. Resistant profiles among isolates from cattle, chickens and swine were similar. The emergence and dissemination of β–lactamase *E. coli* strains of serotypes O126, O103, O111, O128 and O145 may complicate treatment of certain urinary tract infections in humans and animals as well [64].

*Mec*A–mediated ß–lactamase coagulase-negative Staphylococci(CoNS) were reported from healthy horses in Japan [65]. Methicillin-Resistant *Staphylococcus Aureus* (MRSA) possessing the *Mec*A gene renders the whole family of ß–lactam antibiotics including penicillin, methicillin (oxacillin), and even cephalosporins ineffective [66]. MRSA carrying the *Mec*A gene was isolated from chicken meat samples in Korea [67] and non *Mec*A MRSA have been isolated from dogs, cattle and chickens [28, 67] and in horses, cats and other species of animals [60].

Previous study [68], reports 121 (67.6%) of 179 penicillinase - positive *S. aureus* isolates from milk of healthy cows.

Nigerian Isolates of Beta-Lactamases

The occurrence of β–lactamases has been scarcely reported in Nigeria.However, in a recent study of β–lactamase-producing bacteria in Nigeria, Mamzaet al. [69] reported the isolation of β–lactamase strains of *E coli*and *S. aureus*. According to Mamzaet al.[70], out of a total of 1300 tissue samples collected from chickens in Maiduguri, Nigeria, 805 (64.1%) *E. coli* and 660 (52.5%) *S. aureus* wer eisolated, and 10.5%, 10.3% and 12.7% of the *E. coli* isolates from broilers, layers and local chickens respectively, produced β–lactamases.Serotyping of the β–lactamase-producing *E. coli*isolates, authors discovered O26, O1, O2, O78, O86 and O141 from these chickens,which exhibited high multidrug resistance similar to AmpC enzyme producers.

The first isolation of ß–lactamases in animals in Nigeria, from *S. aureus*was also documentedin 2010[70]. The ß–lactamase*S. aureus*exhibited high resistance to penicillin and other non beta-lactam antibiotics. From the study, out of 660 *S. aureus* isolates, 8.8% were positive for ß–lactamase enzyme production,ß–lactamases were isolated from both healthy and diseased chickens. The proportion of ß–lactamases 4.3%, 17.7% and 3.7% of the *S. aureus*isolates were isolated from broilers, layers and local chickens respectively. The ß–lactamases isolated from chickens reported here were however, not characterized or determined by molecular methodsto ascertain the types and genetic identity of the enzymes (a potential limitation in that study), but the study however, did add Nigeria to the growing list of countries where β–lactamases have been isolated from animals.In humans the first report of isolation of ß–lactamase in Nigeria was in *K. pneumoniae*[51], where out of 30 isolates 17 produced CTX–M type ß–lactamases; from which 2 were CTX–M–15 enzymes, making the first report in West Africa of detection of β–lactamases in humans.

Conclusion

The persistence of β–lactamase–producing bacteria in our healthcare centres and the emergence of same in the Veterinary field is a threat to both therapeutic and healthcare services. Although the precise cause and route of β–lactamase-producing strains into the Veterinary field could not be determined, it is clear that β–lactamase-producing bacterial strains do exist, and are being transmitted regardless of the use of ß–lactam antibiotics in this field.The alarming global dissemination of β–lactamases highlights the need for epidemiological monitoring of the organisms producing these enzymes and prudent use of antibiotics.

References

1. Brook, I. (2005): Beta-lactamase-producing bacteria. Reviews in Medical Microbiology, 16: 91 – 99.
2. Bradford, P. A. (2001): Extended-spectrum beta-lactamases in the 21st Century, characterization, epidemiology, and detection of this important resistance threat. Clinical MicrobiologyReviews, 48: 933 – 951.
3. Mirzaee, M., M. R. Pourmand, M. Chitsaz, and S. mansouri (2009). Antibiotic resistance to third generation cephalosporins due to CTX – M – type ESBLs in isolates of Escherichia coli. Iranian Journal of Public Health, 38: 10 – 17.
4. Ma, L., F.-Y. Chang, C.-P. Fung, T.-L. Chen, J.-C. Lin, P.-L. Lu, L.-Y. Huang, J.-C. Chang, and L. K. Siu (2005). Variety of TEM-, SHV-, and CTX-M-type beta- lactamases present in recent clinical isolates of Escherichia coli, Klebsiellapneumoniae, and Enterobacter cloacae from Taiwan. Microbial Drug Resistance, 11, 31–39.
5. Sasaki, T., I. Hirai, M. Niki, T. Nakamura, C. Komalamisra, W. Maipanich, T. Kusolsuk, S. Sa-nguankiat, S. Pubampen, and Y. Yamamoto (2010).High prevalence of CTX-M-beta-lactamase-producing Enterobacteriaceae in stool specimens obtained from healthy individuals in Thailand. Journal of Antimicrobial Chemotherapy, 65, 666–668.
6. Cantón, R., A.Novais, A.Valverde, E.Machado, L. Peixe, F. Baquero, and T.M. Conque (2008). Prevalence and spread ofextended-spectrum beta-lactamase-producing Enterobacteriaceae in Europe.Clinical Microbiology and Infection, 14 (Suppl. 1): 144–153.
7. Pitout, J. D. D., K. S. Thomson, N. D. Hanson, A. F. Ehrhardt, E. S. Moland, and C. C. Sanders (1998). Beta-lactamases responsible for resistance to expanded-spectrum cephalosporins in Klebsiellapneumoniae, Escherichia coli, and Proteus mirabilis isolates recovered in South Africa. Antimicrobial Agents and Chemotherapy, 42: 1350 – 1354.
8. Tängdén, T., O.Cars, A.Melhus, and E. Löwdin (2010). Foreign travel is a major risk factor forcolonization with Escherichia coli producing CTX-M-type extended-spectrumbeta-lactamases: a prospective study with Swedish volunteers. Antimicrobial Agents and Chemotherapy, 54: 3548 – 3564.
9. Winokur, P. L., R. Canton, J. M. Casellas, and N. Legakis (2001). Variations in the prevalence of strains expressing an extended-spectrum beta-lactamase phenotype and characterization of isolates from Eurpoe, the Americas, and the western Pacific region. Clinical Infectious Diseases, 32 Suppl 2: S93 – S103.
10. Hornish, R. E. and S. F. Kotarski (2002). Cephalosporinases in Veterinary Medicine ceftiorfur use in food animals. Current Topics in Medicinal and Chemistry, 2: 717 – 731.
11. Carmen, T., and Z. Myrian (2007). Extended-spectrum beta-lactamase in animals and their importance in transmission to humans EnfermedadesInfecciosasMicrobiologiaClinica 25, suppl 2: 29 – 37.

12. Bush, K., G. A. Jacoby, and A. A. Mederios (1995). A functional classification scheme for beta-lactamases and its correlation with molecular structure.Antimicrobial Agents and Chemotherapy, 39: 1211 – 1233.

13. Medeiros, A. A. (1997). Evolution and dissemination of beta-lactamases accelerated by generations of beta-lactam antibiotics. Clinical Infectious Diseases 24: suppl 1: S19 – S45.

14. Jacoby, G. A. M. D., and L. S. Munoz-Price M. D (2005). Mechanisms of diseases: The new ß-lactamases. New England Journal of Medicine, 352: 380 – 391.

15. Livermore, D. M. (1995). Beta-lactamases in laboratory and clinical resistance. Clinical Microbiology Reviews, 5: 557 – 584.

16. Paterson, D. L. and R. A. Bonomo (2005). Extended-spectrum beta-lactamases: A clininal update. Clinical Microbiology Reviews, 18: 657 – 686.

17. Rafael, C., A. Valverde, A. Novais, F. Baquero, and T. Coque (2007). Evolution and current situation of extended-spectrum beta-lactamases (ESBLs). EnfermedadesInfecciosasMicrobiologiaClinica, 25, suppl 2: 2 – 10.

18. Teresa, C., A. Novais, A. Caratolli, L. Poirel, J. Pitout, L. Peixe, F. Baquero, R. Canton, and P. Nordman (2008). Dissemination of clonally related Escherichia coli strains expressing extended-spectrum beta-lactamase CTX – M – 15.Emeging Infectious Diseases, 14: 196 – 200.

19. Pass, M. A., R. Odedra, and R. M. Batt (2000): Multiplex PCRs for identification of Escherichia coli virulence genes. Journal of clinical Microbiology,38: 2001 – 2004.

20. Thomson, K. S., and E. S. Moland (2000). Version 2000: the new beta-lactamases of gram-negative bacteria at the dawn of the new millennium. Microbes Infections, 2: 1225 – 1235.

21. Yu, W. L., Y. C. Chang, and J. Walther-Rasmunssen (2006). Extended-spectrum beta-lactamases in Taiwan: epidemiology, detection, treatment and infection control. Journal of Microbiology, Immunology and Infection, 39: 264 -267.

22. Weldehagen, G. F., L. Poirel, and P. Nordman (2003). Ambler class A extended–spectrum beta-lactamases in Pseudomonas aeruginosa: novel developments and clinical impact. Antimicrobial Agents and Chemotherapy, 47: 2385 – 2392.

23. Poirel, L., T. Naas, and P. Nordman (2010). Diversity, Epidemiology, and genetics of class D {beta-lactamses}. Antimicrobial Agents and Chemotherapy, 54: 24 – 38.

24. Paterson, D. L., Hujer, K. M., Hujer, A. M. B. Yeiser, M. D. Bonomo, L. B. Rice, R. A. Bonomo and the International Klebsiella study Group (2003). Extended-spectrum beta–lactamases in klebsiellapneumoniae blood stream isolates from seven countries: Dominance and wide spread prevalence of SHV- and CTX – M – type beta-lactamases. Antimicrobial Agents and Chemotherapy,47: 3545 – 3560

25. James, H. J., M. L. McElmeel, L. C. Fulcher, and B. L. Zimmer (2010). Detection of CTX–M type extended-spectrum beta-lactamases by testing with microscan overnight and extended-spectrum beta-lactamase confirmation panels. Journal of Clinical Microbiology, 48: 120 – 123.

26. Mamlouk, K., I. B–B. Boubakar, V. Gautier, S. Vimont, B. Picard, S. B. Redjeb, and G. Arlet (2006). Emrgence and outbreaks of CTX – M beta-lactamase-producing Escherichia coli and Klebsiellapneumoniae strains in a Tunisian Hospital. Journal of Clinical Microbiology, 44: 4049 – 4056.

27. Jun, Y., J. Cheng, S. Zhen, Y. Ying, G. Yu-Feng, L. Jia-bin, and Z. Xue-jun (2009). Characterization of two plasmid-encoded cefotaximase found in clincalEscherichia coli isolates: CTX–M–65 and a novel enzyme, CTX–M–87. Journal of Medical Microbiology, 58: 811 – 815.

28. Lee, J. H. (2006): Occurrence of methicillin-resistant Staphylococcus aureus strains from cattle and chickens, and analyses of their mecA mecR1 and mecI genes. Veterinary Microbiology, 114: 155-159.

29. Pfaller, M.A., and J. Segreti (2006). Overview of the epidemiological profile and laboratory detection of extended-spectrum beta-lactamases. Clinical Infectious Diseases, 42 (Suppl 4): S153 – S163.

30. Naseer, U., B. Halderson, G. S. Simonsen, and A. Sundsfjord (2010). Sporadic occurrence of CMY–2–producing multidrug–resistant Escherichia coli of ST–complexes 38 and 448, and ST 131 in Norway. Clinical Microbiology and Infections, 16: 171 – 178.

31. Yoon, S. P., Y. Sunmi, S. Mi-Run, Y. K. Jin, K. C. Yong, and H. Pai (2009). Risk factors and clinical features of infections caused by plasmid-mediated AmpC beta-lactamase-producing Enterobacteriaceae. International Journal of Antimicrobial Agents 16: Abstract.

32. Christopher, E., E. C. Philip, and M. H. Helen (2009). CMY – 29 and CMY – 30: Two novel plasmid-mediated AmpC {beta}-lactamases. Antimicrobial Agents and Chemotherapy, 4: Abstract.

33. Cuzon, G., T. Naas, and P. Nordmann (2010). KPC carbapenemases: what issue in Clinical Microbiology? PathologieBiologie (Paris), 58: 39 – 45.

34. Liu, C–Y., C–L. Lu, Y–T. Huang, C–H Liao, and P–R Hsueh (2009). In vitro activities of moxifloxacin and tigecycline against bacterial isolates associated with intra-abdominal infections at a medical center in Taiwan, 2001 – 2006. European Journal of Clinical Microbiology and Infectious Diseases, 28: 1437 – 1442.

35. Bogaerts, P., H. Rodrigues-Villalobos, C. Bauraing, A. Deplano, C. Laurent, C. Berlin, M. J. Struelens, and Y. Glupczynski (2010). Molecular characetrization of AmpC-producing Escherichia coli clinical isolates recovered at two Belgian hospitals. Pathological Biology (Paris) 58: 78 – 83.

36. Ioannis, K. N., B. Stavroula, G. Alexandros, and A. S. Demetrios (2009). Analysis of beta–lactam resistance phenotypes of Escherichia coli: An 8–year survey conducted in Greece. Roumanian Archives of Microbiology and Immunology, 67: 10 – 13.

37. Stephen, P.H., Samuel K.B., Daryl J.H., Robert E.B., Po-Ren H. & David L.P. (2009).Emergence of high levels of extended-spectrum-beta-lactamase-producing Gram-negative bacilli in the Asia-Pacific Region: data from the study for monitoring antimicrobial resistance trends (SMART) Program, 2007. Antimicrobial Agents and Chemotherapy, 53, 3280-3284.

38. Kenneth, S.Thomson (2001). Controversies about extended-spectrum and AmpC beta–lactamases. Emerging Infectious Diseases, 7: 333 – 336.

39. Philippon, A., R. Labia, and G. A. Jacoby (1989). Extended-spectrum beta-lactamases. Antimicrobial Agents and Chemotherapy, 33: 1131 – 1136.

40. Ben Hassen, A., G. Fournier, A. Kechrid, C. Fendri, S. Ben Redjeb, and A. Pilippon (1990). Resistance enzymatique au cefotaxime chez cinquante-six souches de Klebsiella spp., Escherichia colietSalmonella spp. dans un hôpitaltunisien (19984-1988). PathologieBiologie(Paris), 38, 464-469.

41. Elisabete, M., M. C. Teresa, C. Rafael, N. Angela, C. S. Joâo, B. Fernando, and P. Luisa (2007). High diversity of extended-spectrum {beta}-lactamases among clinical isolates of Enterobacteriaceae from Portugal. Journal of Antimicrobial Chemotherapy, 60: 1370 – 1374.

42. Luciene, A. R. M., L. Poirel, A. C. T. Nathalia, A. L. C. Danini, and P. Nordman (2009). Predominance of CTX – M – type extended-spectrum beta-lactamase genes among enterobacterial isolates from outpatients in Brazil. Diagnostic Microbiology and Infectious Diseases. 62: 202 – 206.

43. Aránzazu, V., M. C. Teresa, G. M. Lucia, B. Fernando, and C. Rafael (2008). Complex molecular epidemiology of extended–spectrum beta–lactamases in Klebsiellapneumoniae: a long term perspective from a single institution in Madrid. Journal of Antimicrobial Chemotherapy, 61: 64 – 72.

44. Elisabete, M., M. C. Teresa, C. Rafael, C. S. Joâo, and P. Luisa (2008). Antibiotic resistance integrons and extended-spectrum {beta}-lactamases among Enterobacteriaceae isolates recovered from chickens and swine in Portugal. Journal of Antimicrobal Chemotherapy, 62: 296 – 302.

45. Jia-Bin, L., J. Cheng, Q. Wang, Y. Chen, Y. Ye, and X. Zhang (2008). A novel SHV– type beta–lactamase variant (SHV – 89) in clinical isolates in china. Molecular Biology Reports, 36: 1441 – 1148.

46. Hüseyim, T., and I. B. Hakki (2005). Characterization of TEM – and SHV – derived extended-spectrum beta-lactamases in Hospital-based Enterobacteriaceae in Turkey. Japanese Journal of Infectious Diseases, 58: 162 – 167.

47. Woodford, N., M. E. Ward, M. E. Kauffmann, J. Turton, E. J. Fagan, D. James, A. P. Johnson, R. Pike, M. Warner, T. Cheasy, et al (2004). Community and hospitalspread of Escherichia coli producing CTX – M extended-spectrum beta-lactamases in the UK. Journal of Antimicrobial Chemotherapy, 54: 735 – 743.

48. Kariuki, S., J. E. Corkill, G. Revathi, R. Musoke, and C. A. Hart (2001). Molecular characterization of a novel plasmid-encoded cefotaxime (CTX – M – 12) found in clinical Klebsiellapneumoniae isolates from Kenya. Antimicrobial Agents and Chemotherapy, 45: 2141 – 2143.

49. Gangoue-Pleboji, J., V. Miriagou, S. Vourli, E. Tzelepi, P. Ngassam, and L. S. Tzouvelekis (2005). Emergence of CTX–M–15 – producing Eneterobacteria in Cameroon and characterization of $bla_{CTX-M-15}$ carrying element. Antimicrobial AgentsandChemotherapy, 49: 441 – 443.

50. Blomberg, B., R. Juren, K. P. Manji, B-S, Tanim, D. S. Mwakagile, W. K. Urassa, M. Fataki, V. Msangi, M. G. Tellevik, S. Y. Maselle, and N. Langeland (2005). High rate of fatal cases of pediatric septicaemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Daressallam, Tanzania Journal ofClinical Microbiology, 43: 745 – 749.

51. Soge, O. O., A. M. Queenan, K. K. Ojo, B. A. Adeniyi, and M. C. Roberts (2005). CTX – M –15 extended-spectrum beta-lactamases from Nigerian Klebsiellapneumoniae. Journal of Antimicrobial Chemotherapy, 57: 24 – 30.

52. Jun, C., Y. Ying, W. Ying-Ying, l. Hui, l. Xu, and L. Jia-Bin (2008). Phenotypic and molecular characterization of 5 novel CTX–M enzymes carried by Klebsiella pneumonia and Escherichia coli. ActaPharmacologicaSinica, 29: 217 – 225.

53. Livermore, D. M., S. Mustag, Y. Ge, and M. Warner (2009). Activity of cephalosporin CXA–101 (FR 264 205) against Pseudomonas aeruginosa and Burkholderiacepaciagroup strains and isolates. International Journal of Antimicrobial Agents, 34: 402 – 406.

54. Bauernfeind, A., Y. Chong, and S. Schweighart (1989). Extended–spectrum beta–lactamase in Klebsiellapneumoniaeincluding ressitance to cephamycins. Infections17: 316 – 321.

55. Kim, J.Y., H. I. I. Jung, Y. J. An, J. H. Lee, S. J. Kim, S. H. Jeong, K. J. Lee, S. Pann-Ghill, H. S. Lee, S. H. Lee, and C. Sun-Shin (2006): Structural basis for extended substrate spectrum of CMY–10, a plasmid-encoded class C beta-lactamases. Molecular Microbiology 60: 907 – 916.

56. Lee, J.H., H. I Jung,., J. H. Jung, J. S. Park, J. B. Ahn, S. H. Jeong, B. C. Jeong, J. H. Lee, and S. H. Lee(2004): Dissemination of transferable AmpC–type beta-lactamases (CMY–10) in a Korean hospital. Microbial drug Resistance, 10: 224 - 230.

57. Li-rong, C., Z. Hong-wei, C. Jia-chang, Z. Rong, and C. Gong-Xiang (2009). Detection of plasmid-mediated IMP–1 metallo-beta-lactamases and quinolone resistance determinants in an ertapenem-resistant Enterobacter cloacae isolates. Journal of Zhejiang University of Science, B 10: 348 – 354.

58. Cendejas, E., R. Gómez-Gil, P. Gómez-Sánchez, and J. Mingorance (2010). Detection and Characterization of Enterobacteriaceae producing metallo-beta-lactamases in a tertiary –care hospital in Spain. Clinical Microbiology and Infections, 16: 181 - 183.

59. Seguin, J. C., R. D. Walker, J. P. Caron, W. E. Kloos, C. G. George, R. J. Hollis, R. N. Jones, and M. A. Pfaller (1999). Methicillin –Resistant Staphylococcus aureusoutbreaks in a Veterinary Teaching Hospital; Potential human to human transmission. Journal of Clinical Microbiology,37: 1459 – 1463.

60. vanDuijkeren, E., A. T. A. Box, M. E. O. C. Heck, W. J. B. Wannet and A. C. Fluit (2004): methicillin-Resistant Staphylococci isolated from animals. Veterinary Microbiology, 103: 91 – 97.

61. Sueli, A. F., D. L. Paterson, A. C. Ghilardi-Rodrigues, J. M. Adams-Haduch, A–T.Tavechio, and D. Yohei (2009). CTX–M–2–producing Salmonella typhymurium isolated from pediatric patients and poultry in Brazil. Microbial Drug Resistance, 15: 317 – 321.

62. Laura, B., Z. Myrian, S. Yolanda, R. Fernanda, and T. Carmen (2002): Beta–lactamases in ampicillin-resistant Escherichia coli isolates from food, humans and healthy animals. Antimicrobial agents and Chemotherapy 46: 3156-3166.

63. Smet, A., A. Martel, D. Persoon, J. Dewulf, M. Yeyndrickx, B. Catry, L. Herman, E. Haesebrouck, and P. Butaye (2008). Diversity of extended-spectrum beta-lactamases and class C beta-lactamases among cloacalEscherichia coli isolates in Belgian broiler farms. Antimicrobial Agents and Chemotherapy,4: 1238 – 1243.

64. Shroeder, C. M., J. Meng, S. Zhao, C. Debroy, J. Torcolini, C. Zhao, P. F. McDermott, D. G. Wagner, R. D. Walker, and D. G. White (2002). Antimicrobial Resistance of Escherichia coli O26, O103, O111, O128 and O145 from animals and humans. Emerging Infectious Diseases, 8: 1409 – 1414.

65. Yasuda, R., J. Kawano, H. Onda, M. Takagi, A. Shimizu, and T. Anzai (2000). Methicillin-resistant coagulase-negative Staphylococci isolated from healthy horses in Japan. American Journal of Veterinary Research, 61: 1451 – 1455.

66. Friendship, B., and S. Weese (2009). Methicillin Resistant Staphylococcus aureus (MRSA). Advanced Pork Production, 20: 173 – 180.

67. Kwon, N. H., K. T. Park, W. K. Jung, H. Y. Youn, Y. Lee, S. H. Kim, W. Bae, J. Y. Kim, J.Y. Kim, J.M. Kim, S.K. Hong, and Y.H. Park (2006): Characteristics of methicillin–resistant Staphylococcus aureus isolated from chicken meat and hospitalized dogs in Korea and their epidemiological relatedness. Veterinary Microbiology, 117: 304 – 312.

68. Mazura, F. (1990). Determination of beta-lactamase production in strains of Staphylococcus aureus isolated from milk of cows. Veterinary Medicine (proha), 35: 267 – 274.

69. Mamza, S. A., G. O. Egwu, and G. D. Mshelia (2010a). Antibiotic susceptibility patterns of beta-lactamase-producing Escherichia coli and Staphylococcus aureus isolated from chickens in Maiduguri (Arid zone), Nigeria. Veterinarskiarhiv, 80: 283 –297.

70. Mamza, S. A., G. O. Egwu, and G. D. Mshelia (2010b). Beta-lactamase Escherichia coli and Staphylococcus aureus isolated from chickens in Nigeria. Veterinary Italiana, 46:155 – 165.