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Review Article

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The emergence of extended-spectrum β-lactamases and carbapenemases from none human sources: The challenges and opportunities

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Abstract

The widespread of extended-spectrum β-lactamases and Carbapenemases from none human is rapidly increasing worldwide. Their presence in all ecosphere manifesting the spotlight of the global public health threat that significantly challenging modern medicine even to the recent one-health system approach. Overuse and misuse of antibiotics are the main triggering factors for antimicrobial selective pressure and clonal dissemination of resistance genes both in human and animal sources. Several none human sources are acting as the main reservoir of various microbial resistance genes leading to create a relentless epidemiological picture in the future. The irrational use of antibiotics in animal's veterinary medicine reinforce the dissemination of extended-spectrum β-lactamase and carbapenemases especially among Gram-negative bacteria from food-producing animals, birds, lakes, rivers, livestock, animal husbandry, industries, sewages and hospital wastewater to clinical and community settings. Indeed, antimicrobial resistance genes harboured by the bacterial strains are capable of transmitting into clinical and community settings. The global dissemination of the multi-drug resistant extended-spectrum β-lactamases and carbapenemases-synthesizing organism across all ecosystems is limiting the appropriate choice of antimicrobial agents to treat infection judiciously. Lack of public awareness to antimicrobials, poor sanitary conditions, and poor infection prevention measures combined with poor antimicrobial stewardship creates an ubiquitous spread of antimicrobial-resistance genes across the entire ecosystem. The direct or indirect contact of human with contaminated animal products such as urines and faeces that have been contaminated with pathogenic bacteria hastens the horizontal gene transfer of resistance genes across all the community of the bacteria. As a result, a systematic and careful investigation of the potential resistance gene pools reservoirs to address the current emergence of β-lactamases hydrolyzing organisms through integrated, intensive, holistic and scientific rigours activities are widely in need. Besides, understanding of the complex human, animal and wider environment interplay has found the frontline strategy to mitigate antimicrobial resistance burdensome in human and animal settings.

Keywords: antimicrobial resistance, none human sources, β-lactamases, carbapenemases, challenges, debre tabor, Ethiopia

Abbreviations: AMR, antimicrobial resistance; ARG, antimicrobial-resistance genes; CP, carbapenemase; CPP, carbapenemase producing pathogens; ESBLs, extended-spectrum β-lactamases; ESKAPE, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp;* GNB, gram-negative bacilli; HGT, horizontal gen transfer

Introduction

The rise in antibiotic-resistant organisms followed by the lack of new drug development has remained the global public health problem. The emergence of antimicrobial drug resistance especially among *Enterobacteriaceae* remained quite problematic in both human and veterinary medicine. Antimicrobial resistance is a complex phenomenon due to the triangular interplay of the host, pathogen and antimicrobial agents or wider environments which subsequently leaves the global health community under a limed choice of antimicrobial agents.[1,2] Despite the discovery of antibiotics was the milestone in the history of human medicine to tackle infectious diseases; the evolution of acquired antimicrobial resistance in clinical and community settings grossly underpins the current modern medicine and demands a call for combating the spread of antimicrobial-resistance genes.[3] Nowadays, many microorganisms especially pathogens such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) (ESKAPE) has shown a significant therapeutic paradigm shifts both in human and none human origins. These pathogens chiefly characterized by a paradigm of pathogenesis and antimicrobial resistance mechanisms that have considered the emerging public health threat globally. The Gram-negative bacilli (GNB) group withstand resistance to a broad range of antimicrobial agents because carbapenems are antimicrobial of the last resort for GNB but not for *Staphylococcus aureus* and *Enterococcus faecium*. [4] Antimicrobial resistance attributed to the emergence of extended-spectrum β-lactamases (ESBLs) and carbapenemases-producing pathogens (CPP) like in the family of *Enterobacteriaceae* has dramatically escalated the clinical, socio-economic situations of human beings. This growing public health threat significantly overlooked therapeutic options particularly in the developing world because of the lack of advanced diagnostic facilities and poorer antimicrobial stewardship programs to mitigate the spread of resistance genes.[2,5]

ESBLs are a member of enzymes synthesized by some bacteria capable of hydrolyzing broad-spectrum β-lactam antibiotics like cephalosporins, penicillins and monobactams. This is the most prototypical for rapid dissemination of resistance genes in the hospital environment. Similarly, CPP have several groups of enzymes mainly detected in the GNB such as *E.coli*, *P. aeruginosa*, *Acinetobacter baumannii* that enhance to confer resistance to carbapenems. Both ESBLs and CPP are responsible for a wide range of diseases such as bloodstream, pneumonia, wound, urinary tract in many clinical settings. However, the degree of severity may vary as a result; multidrug-resistant ESBL and CPP strains cause significant mortality and morbidity rather then their counterparts due to difficulties to eradicate them mainly in immunodeficient patients.[1,5,6] The evolution of ESBLs and CPP like in *Enterobacteriaceae* from none human sources such as animals, hospital wastewater has become a great concern to the public health sector. The ubiquitous nature of microbes and the ability to interact with the natural environment and animals in their niches pose serious health problems. This is because several none human sources are the natural reservoirs to carry resistance genes and disseminate into human beings via cross-transmission. Not surprisingly, an environmental object like Computer keyboards have been reported as a source of infections unveiling they could be contaminated and serve as a fomite in the hospital setting.[7,8] No matter how ESBLs and CPPs from none human sources such food, birds, animals and hospital wastewater are dramatically emerging as a reservoir of antibiotic-resistance genes; a potential source of any novel resistance genes and transmission modality to humans is underestimated. As a result, the clinical correlation to any increasing direct or indirect clinical and economic impacts has been remained obscured for years. Due to the lack of robust regulatory policy in human and veterinary medicine, antimicrobial resistance due to miss/overuse of antimicrobial agents is the major health problem that enhances easily dissemination of resistance genes from none human sources to human settings. None human sources provide a selective environment to multidrug-resistant pathogens such as ESBLs and CPP that subsequently, pose serious health problems.[6–8] Despite awareness in the burdens of inappropriate use and dissemination of antimicrobial agents in clinical medicine, the potential source of resistance genes (pool of resistance genes) that favour the evolution of ESBLs/CPP from none human sources are overlooked in many developing countries like our country Ethiopia. The lack of advanced diagnostic tools, multidisciplinary research approaches such one health system approach to unlock the potential squeals arise from none human source is underestimated. Therefore, this review article aims to discuss the evolution of both ESBLs and CPP that are detected from none human sources and their link to public health impacts. Besides, It exploits the current challenges and intensify the opportunities and substantially scale-up toward public health significance of pathogens isolated from none human sources to any clinical correlations in our set up. To best of our knowledge, only few documented data is available in Ethiopia concerning the emergence of ESBLs and CPP from none human sources such as animals, animals' food products, wastewater samples discharged from health facilities, abattoirs and downstream rivers.[9,10] Hence, the review article will provides a strategy to combat the rapid emergence of antimicrobial resistances, hasten to establish active surveillance and public awareness of the global public health the emergency where modern medicine is severely facing.[11]

Main text

Characteristics of extended-spectrum β-lactamases and carbapenemases

In modern medicine, extended-spectrum β- lactams and carbapenems resistance due to the diverse group of enzymes has remained a worrisome issue to adhere to judicious treatment of infectious diseases. This is the most important aspect of clinical medicine. Because the β- lactamase enzymes hydrolyze the β-lactam, a ring of the drug and subsequently decrease its clinical efficacy. Carbapenem degrading beta-lactamases are the most powerful enzymes that allow the bacteria such as *Enterobacteriaceae* to confer resistance to a wide range of antimicrobial agents. Hence, the multidrug resistance due to ESBLs and carbapenemases(CP) in many GNB has nowadays reached an alarming rate both an alarming rate both in human and in veterinary medicine [9, 10]. The plasmid-mediated enzymes synthesis that inactivates β-lactam ring has shown resistance to the classical broad-spectrum β-lactams. Nowadays, ESBL is a diverse group that embodies TEM, SHV, CTX-M, OXA, and PER β-lactamase families (Table1). These most important emerging traits are observed among the GNB. On the other hand, Carbapenemases owing to the Ambler classes A, B, and D or Bush groups 2f, 3, and 2d are the β-lactamases members that hydrolyze carbapenems such as imipenem, ertapenem, meropenem, and doripenem. These are the last resort of antimicrobial agent to treat infections. However, antimicrobial resistance to these groups of agents has attained a great concern of the global health community.[2,9–11] The increasing evolution of the plasmid-mediated production of inactivating enzymes in various strains of bacteria is responsible to cause both healthcare-associated and community-acquired infections. The public health consequence is unpleasant especially when the disease is belonging to ESBL, AmpC and CPP. The decrease in the clinical efficacy of β- lactam drugs and carbapenems leaves the patient under a limited choice of antimicrobial plausibly combination therapy. Very often, isolates from none human origin are quite difficult to distinguish from the clinical isolates that finally subtle to deliver a distinctive therapeutic approach.[5,9]

Table 1 Characteristics of ESBLs, AmpC and carbapenemase enzymes

Enzyme	Ambler classification	Examples	Spectrum of resistance	Inhibitors
ESBLs	Class A	TEM (other than parent enzymes TEM-1, 2 and 13), SHV (other than parent enzyme SHV-1), CTX-M	Penicillins Cephalosporins Monobactams	Clavulanic acid Tazobactam Sulbactam
AmpC	Class C	CMY, FOX, ACT, MOX, ACC, DHA	Penicillins Cephalosporins Cephamycins Monobactams	Cloxacillin Boronic acid

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Table Continued...

Enzyme	Ambler classification	Examples	Spectrum of resistance	Inhibitors
Carbapenemases				
Metallo β-lactamases (MBL	Class B	NDM, VIM, IMP	Penicillins Cephalosporins Cephamycins Carbapenems	EDTA and other metal chelators
KPC type	Class A	KPC	Penicillins Cephalosporins Cephamycins Carbapenems	Clavulanic acid (weak inhibition), Tazobactam, Boronic acid
OXA type	Class D	OXA-48	Penicillins Carbapenems	NaCl

Source: Adapted from Bush et al.[12]

Mechanisms of antimicrobial resistance

Antimicrobial resistance (AMR) has become the global public health problem in its many aspects. Inappropriate antimicrobial use like as the misuse and abuse in human and veterinary medicine has remained the leading cause to pose a significant public health threat in many countries of the world.[2,10] No matter how antimicrobial agents have still played a significant role in reducing the spread of infectious diseases since their discovery, measurable mortality and morbidity rate both in humans and veterinary medicine remained high. The post-antibiotic era, which is accompanied by AMR, creates a conducive vicinity to microorganisms to gain resistance gene that throws human to a few lists of drugs.[11] Not surprisingly, microbes undergo distinctive metabolic mechanisms, possess a diverse group of enzymes and specialized cellular compartments as such observed between the Gram-positive and negative bacterial to adapt to any environmental fluctuating conditions including the different physio-chemical properties. Unless and otherwise, they will jeopardize their survival. In most cases, none human sources greatly strengthen antimicrobial selective pressure mainly due to the complex interactions of the pathogens with their environment throughout genetic exchanges with gene pool of environment resistant microorganisms. This is the major step for the microbe to acquire resistance genes via its genomic plasticity so that it protects and cope up itself from an attack of the host immunity including antimicrobial aggressive actions.[12] Beta-lactam drugs are the most widely used antimicrobial agents to treat infections in veterinary and human medicines. However, resistance to the beta-lactams mainly mediated by different microbial strategies such as active efflux pumps of the drug, altered drug's receptor sites, modification of the channel proteins, enzymatic hydrolysis of the drug so that the drug is no longer active to reach into the site of infections. Many bacterial isolates particularly the *Enterobacteriaceae* are producing the newer β-lactamases era such as extended-spectrum β lactamases, carbapenemases and the plasmid-mediated AmpC β-lactamases. This newer era enhances pathogenic strains to confer resistance to the regimen administrated to treat infections. This is mainly due to its ability to amplify selective pressure so that it renders them resistant and continue carrying resistance genetic traits to the community.[2,5,10,11]

Basically, the resistance ability of a microbe can be intrinsic or acquired. The innate/inborn resistance of the microbe that attributes to features like physiology and anatomy is not the centre of concern for an emerging aspect of antimicrobial agents. This is because the microbe is intrinsically resistant due to the presence of inherent traits that render antimicrobial nasty consequences. Unlike this, the most encountering phenomenon in clinical, community and none human settings are acquiring resistance. This belongs the pathogen's ability to undergo genetic changes (vertical or horizontal gene transfer), plasmid-mediated mutation via its mobile genetic elements so that secured its drug-susceptible progeny from an attack of host immunity and antimicrobials deleterious effects. That is why none human sources are acting as a potential reservoir of drug-resistance genes.[7,12,13]

Nowadays, bacteria within the family *Enterobacteriaceae* such *Enterobacter spp*., *Klebsiella spp*., *Escherichia coli*, *Proteus spp*., *Serratia marcescens*, *Citrobacter spp*. and other GNB including *Pseudomonas aeruginosa* and *Acinetobacter* spp. are the important pathogens that have been spreading easily to humans with mechanisms like hand carriage, contaminated food or food-derived products. In addition, environmental source, particularly from hospital wastewater, is a common phenomenon.[10] This gradual interaction of clinical pathogens with none human sources allows acquiring resistance genes; finally confers resistance to antibiotics through plasmids, transposons, and subsequently amplify resistance genes. So new strategies to deescalate an abrupt of antimicrobial resistance especially to those, which declare the emergence ESBL, and CP from none human sources are demanding a great public health concern to combat globally. Many evolutionary origins of resistance are indicating that many bacteria harboured AMR genes long before the antibiotic era and evolved dozens of defence mechanisms even against synthetic compounds.[11]

Several studies concerning the evolution of resistance genes unveiled that expression of AMR genes in the natural ecosystems can serve as a defence mechanism against including their toxins and self-preservation strategies in antimicrobial-producing bacteria. Many resistance genes and determinants from these bacteria can be transferred to other bacterial species. Principally, β-lactamase encoded environmental bacteria could be involved in the synthesis of structural components instead of providing resistance to β-lactam antimicrobials and carbapenems. This is because of none human sources such as environmental soil, water, food and animals have found to carry a pool of resistance genes, which can act as a potential reservoir of resistance genes for human pathogens.[12,13,]

Epidemiology of ESBL and carbapenemases from none human sources

AMR is a fundamentally important global public health problem that has remained the leading consequence to escalate clinical and socio-economic aspects of human beings worldwide. In this case, not only ESBLs but also, CP have evolved as a global threat to human health. The isolates disseminated in the hospital and community settings. The distinction between the clinical isolates and isolates from none human source like that from the environments (soil, water), animals (domestic and wild), foods, wastewater, vegetables and other sources is very difficult due to a poor diagnostic approach in many countries of the world.[10,11] The increased prevalence of ESBL and CP from none human sources is considering the main burden for the treatment of infections in humans and animals medicine. The evolving ESBL producers such as CTX-M-1, TEM-52 are the most common types in poultry. *Enterobacteriaceae* such as *E. coli* and *Salmonella spp*. that carry the resistance genes to encode ESBL detected in poultry.[12] ESBL and CPP are emerging globally in humans and animals settings. The daily interaction of human beings with animals, environmental, food and water opens the chance of contracting the multidrug resistance-ESBL and CP strains which are remained the burning concern of none human sources as a potential reservoir of ESBLs, AmpCs and CP encoding genes for humans. Prevalence significantly affects human health in several dimensions. The spread of ESBLs or CPP from poultry to humans as foodborne diseases and via the environment leads to a major hazard for public health. Complications with multi-drug resistant ESBL bacteria isolated from none human sources are quite difficult to treat and diagnose which eventually resulted in deleterious health impacts.[13,14] The diverse occurrence of ESBL and CP among several none human sources including in water, soil, and animal's fecal indeed rises a piece of evidence that speculates animals origins constitute a potent reservoir of resistance genes that encode ESBL and CP particularly among the GNB. This is mainly due to the lack of robust regulatory policies that maintain the rational usage of antimicrobials over any misuse of antibiotics in human and veterinary medicine. That is why the direct and indirect consequence of none human sources remained worrisome to human being due to their high potential contribution to the spread of drug-resistant bacteria across all ecosystems. Furthermore, carbapenems antimicrobials are still lacking a license for veterinary medicine globally. Unless and otherwise the animals being treated should be banned from entering the food production which intern reverse the deleterious impacts.[15,16]

Sources of ESBL and Carbapenemases among none human sources

The growing concern of ESBL and CP has been reported in bacteria isolated from non-human sources like as *Salmonella enterica sub spp. enterica*. In this regard. It is very difficult to conclude the exact origin of the strains especially in areas where the resources are highly limited. The precise origins of the genes encoding for ESBL and CP producing organisms from none human sources remain undefined. Nevertheless, they have all escaped from environmental bacteria; human is severely affected due to the lack of advanced diagnostic facilities including low-trained human resources and inadequate data availability especially in developing countries that may lead into the poor clinical correlation.[1] The lack of local epidemiological data concerning the ESBL and/or CPP prevalence and their pattern of drug resistance is even a bottleneck in developing countries. However, exceptions including OXA-48 family of enzymes occur naturally in *Shewanella* spp. that originates from lake sediments and OXA-23 carbapenemase, which is entirely restricted to *Acinetobacter baumannii* that originates from the environment. Detection of carbapenemase resistance genes from none human sources by molecular techniques such as polymerase chain reaction, proteomics and metagenomics approaches has limited clinical value due to the host species origin is not defined rigorously. Disregard of ample findings of CP from none human sources such as hospital influent, their clinical relevance to human is overlooked.[10–12] The prevalence of ESBL and CPP is common in poultry production mainly due to its complexity in the food and agricultural industry. The global increase in population and high demand for poultry food consumption such as meat and eggs, different countries engaged in trading despite transported in a vulnerable system that can easily be hacked by multi-drug resistant organisms. Once the organisms are got introduced into the complex system of the food chain, they will become a global public health threat.[13] The main CP including KPC and OXA-48 (non-Metallo-carbapenemases) in addition to IMP, NDM and VIM (Metallo-carbapenemases) cumulatively responsible for a wide range of clinical concerns. However, their existence in food production animals or companion animals has underestimated. This significant uncertainty greatly affects modern medicine in many ways.[14] Easy transmission of pathogenic isolates from none human sources as reported *K.pneumoniae* strain with OXA-48 carbapenemase in dogs indicated that poor hand hygiene is an important reservoir for spreading of OXA-48 carbapenemase in many veterinary clinics (Table 2).[9,13–41] Foods contaminated with *Salmonella* and *E.coli* isolates are capable of harbouring VIM-1 carbapenemase. Furthermore, the role of wild birds, swine, sewage, effluent and lakes are the most important natural reservoir for ESBL and CP encoding genes in many countries of the world.[15]

Table 2 Summary of ESBL and carbapenemases from none human sources

Bacterial species	Animal sources	Year of isolation	Country	Gene types	References
Salmonella enterica	Pig/poultry	2011	Germany	blaVIM-1	[13]
E. coli	Pig/poultry	2011-2013	Germany	blaVIM-1	[14]
Salmonella enterica	Cat	Unknown	Australia	blaIMP-4	[15]
E. coli	Dog/cat	2008-2009	USA	blaNDM-1	[16]
E. coli	Pig	2014-2015	China	blaNDM-1	[17]
E. coli	Dog	2014-2015	Algeria	blaNDM-5	[18]
K. pneumoniae	Cow	2015	China	blaNDM-5	[19]
E. coli	Poultry	2015	China	blaNDM-5	[20]
E. coli	Cow	2015	India	blaNDM-5	[21]
E. coli/K. pneumoniae	Dog	2013	Germany	blaOXA-48	[22]
E. coli	Dog/cat	2009-2013	USA	blaOXA-48	[23]
E. coli	Dog	2015	France	blaOXA-48	[24]
E. coli	Chicken	2013	Lebanon	blaOXA-48	[25]
E.coli	Poultry	2016	Algeria	CTX-M 1, SHV-12	[26]

Table Continued...

Bacterial species	**Animal sources**	**Year of isolation**	**Country**	**Gene types**	**References**
E.coli/K. pneumoniae	Swine	2017	Algeria	CTX-M-15	[27]
E.coli	Poultry	2018	Tunisia	CMY-2	[28]
A. baumannii	Fish	2016	Algeria	OXA-23	[29]
E. coli	Poultry	2017	Egypt	CTX-M-14	[30]
E. coli	Cattle	2016	Egypt	mcr-1	[31]
E. coli	Poultry	2018	Lebanon	CTX-M	[32]
A. baumannii	Cattle	2016	Lebanon	OXA-23	[33]
E. coli	Poultry	2014	Palestine	CTX-M	[34]
E. coli	Poultry	2015	Turkey	CMY-2	[35]
E. coli	Swine	2017	Italy	OXA-181	[36]
K. oxytoca	Cat	2014	Italy	CTX-M-9	[37]
E. coli	Poultry	2012	Spain	CTX-M, SHV	[38]
K. pneumoniae	Dog	2016	Spain	VIM-1	[39]
A. baumannii	Dog	2016	France	OXA-23	[40]
K. pneumoniae	Sheep	2013	France	CTX-M-15	[41]
E.coli/K. pneumoniae	wastewater	2019	Ethiopia	Not done	[9]

The use and introduction of antimicrobials agents have been long in history since their discovery both in human medicine and in veterinary medicine. They have been playing a crucial role in reducing significant mortality and mortality rates despite the rapid cross-dissemination of resistance remained a public health threat. Abundant contemporary data concerning the spread of ESBL and CP resistance genes particularly with Gram-negative bacilli (GNB) isolated from none human sources such as food-producing animals, environmental sources and birds are increasing. Due to the practice of misuse of antibiotics in many countries of the world, the active surveillance system, antibiotics monitoring, prevention and control to mitigate the global emergence of ESBL and CP is eagerly demanding global cooperation with an emphasis on intensive research activates and advanced diagnostic facilities. The widespread of the drug-resistant ESBL and CP encoded genes in almost all ecosystems settings accelerate a rapid hammering of developing countries like Ethiopia where resources are severely limited.[19,39] In fact, antimicrobial resistance the major scientific challenges of the 21st century to tackle with One-health approach. The need for an interdisciplinary approach to remain flexible with the alarming increase prevalence rate of ESBL/AmpC and CP has gotten less attention especially for the international traders engaged in food animals and animal products transportation. The condition with carbapenemases in animals is quite different from human. Because many countries of the world are unlicensed for carbapenems leading to the very restricted use of carbapenems in veterinary clinics. As a result, this favours a selective situation for great circulation of none human sources strains in human and eventually a major hazard for humans by creating a fresh and menace epidemiological pictures in the future.[29,39,40]

Mechanisms of ESBL and Carbapenemase disseminations

The global emergence of multiple-drug resistant microbes has been studied extensively. However, no course is still certain to reverse the situations, which leave behind many scientists with their concern of the future menaces. The microbial complex interactions within their ecosystem, microbial de-novo mutation to pace the deleterious impacts of antimicrobial agents, thereby acquisition of resistance genes pools from their natural environment allow responding effectively for any stresses and fluctuating conditions. The existence of plenty of reservoirs for resistance genes in the natural environment has a paramount significance for none clinical microbes to trigger antimicrobial selective pressure in their cellular community due to natural antimicrobials exist in animal, human, hospital waste water.[39,40] Environmental pollution like global warming involves the spread of resistance genes. Worldwide distributions of ESBL and CP with varying degree of prevalence in the community and hospitals are responsible for causing a wide range of infections such as bloodstream infections, urinary tract infections and pulmonary infections. An ease distribution from the natural environments and the like none human sources to humans has considered a serious global health threat. Despite encouraging efforts in ESBL and CPP *Enterobacteriaceae* for a centre and focus for a dozen of studies, guidelines, infection prevention and control; the alarming increase of the global prevalence with significant rates of morbidity and mortality in both human and animal medicine still posing a great mental strain even for the recent one-health approach.[1,2,7,29] It is plausible that resistance genes encoding for ESBL and CP bacterial isolates such as the GNB can be transferred to other interspecies and genetically distant ones. Beta-lactamase enzymes encoded by plasmids in any environmental bacteria are likely involved in the biosynthesis of peptidoglycans rather than in providing resistance to β-lactam and carbapenem drugs. In addition, environmental entities like soil, sewage, hospital wastewater, and hospital effluent and rivers water have shown carrying of a pool of resistance genes that can serve as a reservoir of resistance genes for human clinical pathogens.[41,42] Several environmental changes such as anthropogenic activities, use of antimicrobials, rising human population, urbanization, lack of treatment of sewage and poorer disposal of animal waste trigger the rapid emergence of resistant bacteria populations. The transfer of resistance genes among humans, animals and the environment is the most common in a low socio-economic setting population. In this area there is frequent contact between human settlements, food-producing animals and the environmental entities the greatly enhance over dozens of bacterial population to acquire the new reservoir resistance.[19,35,43] Spread of resistance genes from animal to human is the common phenomena in many ways. This likely embodied both local and global mechanisms of the spread between pathogenic and non-pathogenic bacteria. Transmission of resistance genes is typically made from livestock to humans through food consumption, direct contact with animals and their waste in the environment. In addition to this, fomites can also play an important contribution in the local and global spread of resistant bacteria. Farm-to-farm dissemination of multidrug-resistant bacteria has been demonstrated from farm equipment like machinery. Food animals can be an immense reservoir of resistance genes unless the use of antibiotics in agriculture and food production has been restricted to mitigate the public health impacts.[39]

Overuse and misuse of antibiotics considered the major driving factors in promoting antibiotic resistance pathogens in clinical settings on one way and antimicrobial abuse such as prescription of antibiotics without the infection to a particular bacterial on the other way are the major concern of the public health sector to combat antibiotics jointly. Lack of public awareness of antibiotics severely hammered the socio-economic of developing countries in many dimensions.[2,40] Resistance gens recruitment from the environmental gene pool for drug-resistant ESBL and CP producing functions either conferring resistance to antibiotics via genes that have recruited by pathogenic bacteria or the environmental bacteria harbour has an unexplored pool of genes to its community. Over a period, these antimicrobial-resistance genes (ARG) have the potential to pass to the next bacterial communities. The horizontal genes transfer (HGT) is the most common process that promotes a pathogenic bacterium to acquire ARG from the environmental gene pool. This is made by conjugation, transformation, and transduction despite other mobile genetic elements are engaged. From the three processes of HGT to acquire ARG, Conjugation that occurs by direct contact between two bacteria or through plasmids is the most common. A mobile genetic element like transposons can also participate in carrying of antibiotic-resistance genes from the environmental gene pool (Figure 1).[2,41–43] Antimicrobial resistance is likely to develop in environmental bacteria, thereby creating animal and human health problem if the bacteria contaminate water, food crops or animal feed. This is a conducive opportunity for bacterial to introduce into the human and animal gut. Water is a stronger instrumental factor to the spread of ARG and the bacteria itself either on its natural flow far away or through anthropogenic activities including irrigation (Figure 2). That is why water is considered a major route for transmission of pathogenic bacteria from several none human sources to humans. Concerns are higher in an area where water quality, facility, sanitation and access is very limited. Hence, it is reasonable to consider that emergence of ESBL and CPP strains chiefly due to human linked factors including irrational antibiotic prescription with poor regulations, the lack of antimicrobial stewardship programs aimed to mitigate infections outbreak among clinical settings combined with the use of antibiotics for promotion of animal growth and production in the agricultural sector Figure 2.[43,44]

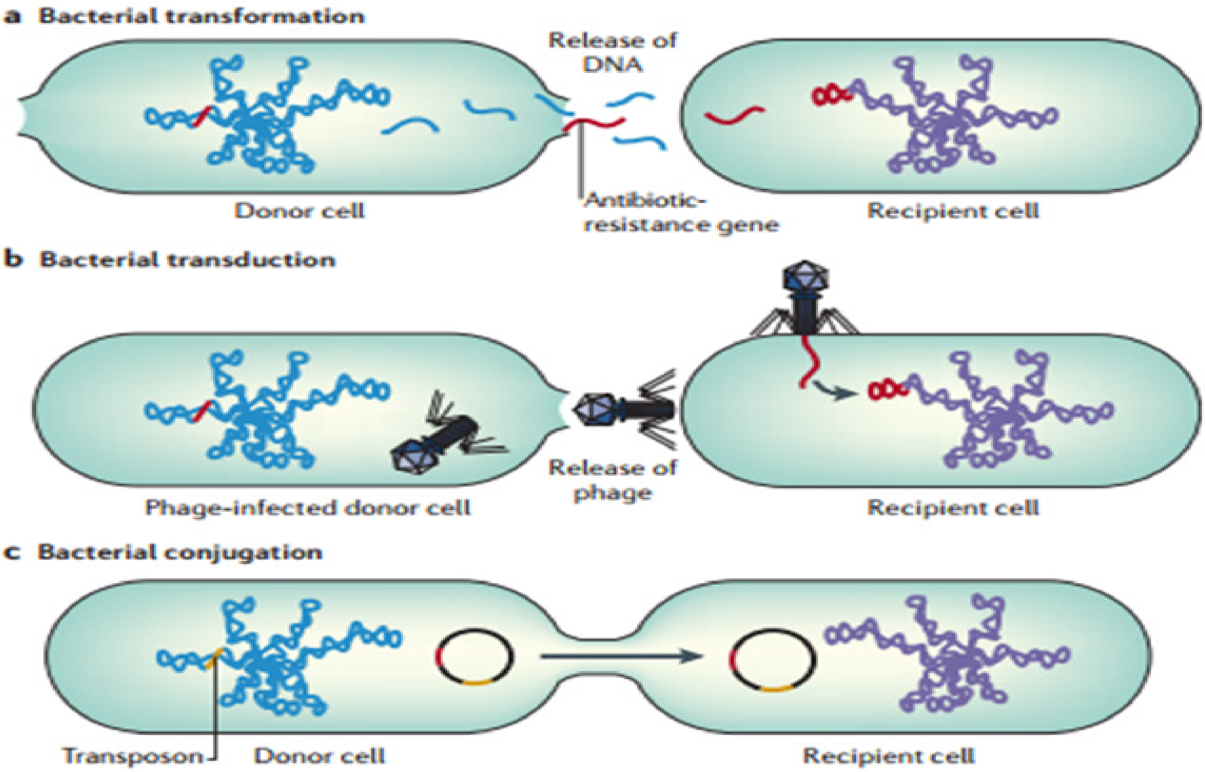

Figure 1 Horizontal gene transfer between bacteria; Adopted from Furuya & Lowy[42]

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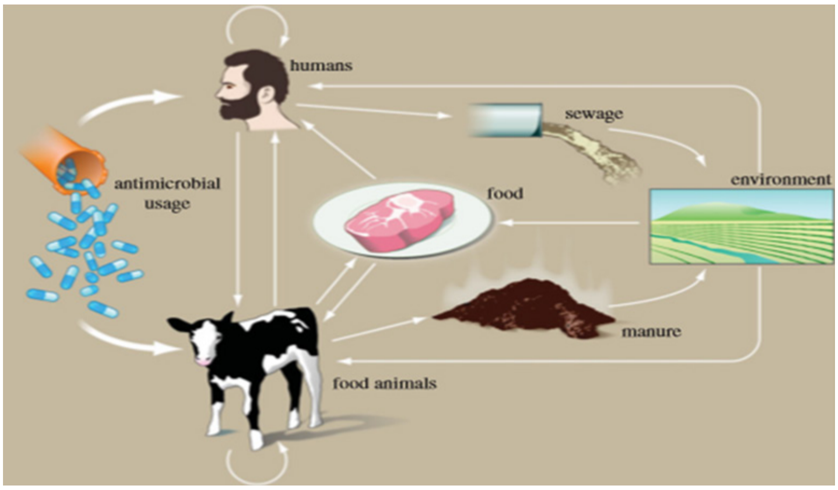

Figure 2 Routes of transmission of antimicrobial resistance between farm animals, the wider environment and humans; Adopted from Woolhouse ME & Ward MJ[45]

The main challenges and opportunities

The globally relentless increase in the magnitude of antimicrobial resistance in human medicine and veterinary medicine has considered a new phenomenon confronting global public health. Pathogenic strains especially evolve from none human sources have found frontline problems to the one- health approach. The intensive distribution and public health demand of antimicrobials in human medicine are analogous to the desire for antimicrobials in livestock production (animal husbandry), industries, agriculture setting. No matter of the venerable groups, exposure from none human sources to human mainly mediated due to the direct contact with resistant bacteria in livestock and associated derived food products. Animal waste products like urine and faeces that are freely exposed to the natural environment promotes creating favourable resistome to any resistance genes pools.[41,43,44]

Challenges of ESBL and CP from none human sources

Infections due to ESBL and CP producing organisms

ESBL and CPP principally *E. coli* and *K. pneumoniae* may cause serious infections including bloodstream, pneumonia, wound, urinary tract infections in healthcare-associated and community settings. Infections due to ESBL and CP producing microorganisms are responsible for significant mortality and morbidity. The clinical complications are substantially higher when human contract this multidrug resistant ESBL/CP producers from none human sources due to the presence of environmental resistome.[2,5]

The risk factors that contribute to the spread of ARG

The risk factors associated with infection and colonization with ESBLs or CPs in many clinical settings are due to the existence of naturally occurring several resistance gene reservoirs for ESBL, and CP such in human faecal carriers, animal foods, and livestock, human direct contact with domestic and wild animals and sewage. Clonal dissemination of none human sources ESBL/CPP *Enterobacteriaceae* in hospitals is causing by great outbreaks. Antimicrobial resistance is a multifactorial health problem. Overuse and misuse of antimicrobial agents is the principal factor for the global dissemination of antimicrobials. Socialization such as household and childcare facilities are the potent reservoirs for the pathogenic bacteria to harbour in many ways. The practice of antimicrobials agents in animal and food production like the complex food-processing chains hastens the discharge of drug-resistant organisms into the hospitals, nursing homes and long-term care facilities. This is the most important facilitating factor for a pathogen to acquire foreign genetic resistance elements via HGT to maintain its survival.[27,35,39,43]

ESBL/CP is a growing public health threat globally

Antimicrobial resistance has become an international health problem both in human and animal medicine. It is menacing the current approach of modern medicine that is dramatically underpinning in many aspects. Drug resistance is not only confined to Gram-negative pathogens but also common among the Gram-positive causing different infections in the hospital and the community levels. Antimicrobial resistance duet to "ESKAPE" pathogens such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* species should be given much emphasize due to their public health concern.[46–48]

Responsible for significant economic and healthcare-associated costs

A menace in AMR resulting in increasing costs in many dimensions including the veterinary clinics and human health systems. Nosocomial infections principally bloodstream infections or patient illness due to the consumption of food contaminated by ESBL/CPP are responsible to huge hospital costs. In this regard, healthcare-associated costs are substantially higher chiefly due to prolonged hospital stays and the use of expensive drugs to recover their illness. Furthermore, dozens of drug-associated adverse side effects that leave the patients to several economic costs are observed during the post-antibiotic era.[12,22,46–48]

Research gaps related to none human dimensions of AMR

Many none human sources like the natural environment have a significant role in dissemination and emergence of drug-resistant pathogens through antibiotic selective pressure. It is insufficient knowledge regarding the sources of antibiotics and resistant bacteria, evolutionary processes in the environment, exposure, routes to humans and possible intervention to any barriers. Therefore, an intensive surveillance and research activity to fill any gaps in knowledge that led

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to the public awareness creation concerning the emergence and spread of antimicrobial-resistance genes from genes pools in the natural environment are eagerly demanding issue in its many aspects. This is a collective approach that needs to address ESBL/CP evolutions among none human sources thereby improving the overall human and animal health.[5,49,50]

Therapeutics challenges of ESBL, AmpC and CP organisms

In the contemporary scenario, only a few choices of antimicrobials drugs are commercially available to treat infections particularly to carbapenem-resistant GNB in many areas of the world. The different categories of "carbapenemases" carbapenem-hydrolyzing β-lactamases have remained the main therapeutic challenges of the 21st century. An increase in the ESBL/CP resistance genes, particularly among GNB, is accompanied by increased patient morbidity and mortality rates worldwide.[2,3,48]

Opportunities to combat/reduce ESBL and CP from none human sources

I. **The strategic plan of one health approach:** This one health approach is an emerging element of modern medicine to address both humans and animals influences in a very systematic way the so-called the concept of human-environmental systems or social-ecological system. This collaborative approach is playing a milestone in food chain productions, livestock, agriculture, environment, food-producing animals, food safety and hospitals to combat AMR.[2,48]

II. **The AMR active surveillance and monitoring program:** Many countries of the world are working jointly and closely with different health sectors and institutions to overcome the emergence of AMR and associated risk factors. Many promising national and international reaction to AMR is reported. On its ground, ESBL/CP antimicrobial resistance disregard of its origin demands a cross-sectional approach that involves various health professionals, holistic and integrated strategic approach mainly based on the one health concept to get ride-off the current health menaces. In addition, a collaboration of policy-makers and health authorities is in need to alleviate the clinical and economic loses.[40,41,48]

III. **Intensive research activities:** Whenever possible, breakthrough research works to mitigate the current public health burdensome due to ESBL/CPP from none human sources should be intensively done. The spread of ESBL and carbapenemase-producing organisms like *Enterobacteriaceae* among different none human sources are becoming highly worrisome. A scientific rigour based research activities to reverse the burden of antibiotic-resistance genes in the environment greatly demanding so that judicious treatment will be maintained in human and veterinary medicine. Research activities will help in Managing resistance in farm animals, food-processing chains. Active surveillance is also playing a role in reducing antimicrobial usage in veterinary medicine.[2,45] ESBL, AmpC and CPP *Enterobacteriaceae* from various none human sources has been found a threat for humans. Intensive research activity is in need due to an emerging public health problem particularly with acquired CPP that are evolving from the food-producing animal, environment, companion animals and wildlife. As a result, the new research finding will support pharmacists, veterinarians and the clinical physicians to regulate the rational use of a specific antimicrobial agent, to implement effective drug traceability protocols, to design effective antimicrobial agents and to motivate a wider drug surveillance program.[44,46,51,52]

Conclusion

The evolution of ESBL and CP from none human sources is rapidly growing globally. The existence disregard of their origins is troublesome. Acquired carbapenemases from animals, food products and environmental sources have been reported in many countries of the world. The presence of antimicrobial-resistance genes that confers ESBL/CPP mainly due to encoded genes pool in the natural environment enhances clinical pathogenic ESBL/CP strains to sustain their existence and any hijacking influence of antimicrobial agents. The presence of ESBL/CP resistance encoding genes among non-lactose fermenters *Enterobacteriaceae* from various none human sources such as animal husbandry, agriculture, food processing industries, companion animals and domestic or wildlife bird is the common phenomenon worldwide. Gradually, the direct or indirect contact of human with environmental sources opens the new gate for contracting of drug-resistant pathogens. The clinical correlation is still underestimated mainly in the developing world due to multiple factors. Consequently, intensive, integrated, strategic, and holistic and breakthrough research activities are eagerly demanding to resolve once and for the last time to the globally rising public health threat. Unless and otherwise, the future is not too far to suffer from the pan-drug resistant pathogens.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

All the available data and material used in this study is presented in the main paper.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

TK was the primary researcher, conceived, designed the study, participated, drafted and finalized the manuscript for publication. LW assisted, reviewed the initial and final drafts of the manuscript. All authors read and approved the final manuscript for publication.

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