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**REVIEW ON ANTIBIOTIC RESISTANCE AND ITS MECHANISM OF
DEVELOPMENT**

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REVIEW ON ANTIBIOTIC RESISTANCE AND ITS MECHANISM OF DEVELOPMENT

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Abstract

Purpose: Antibiotics are chemical agents that prevent bacterial growth by stopping the bacterial cell from dividing (bacteriostatic) or by killing them (bactericidal). So antibiotics are the integral part of medicines used to insure human and animal health. However, the wide spread use, misuse and overuse of antibiotics in human and animal has raised the concern about the development of resistant bacteria that possess a potential danger to animals and humans. Antibiotic resistant microorganisms have been described as “nightmare bacteria” that “pose a catastrophic threat” to people in every country in the world. So, the aim of this seminar paper is to review on antibiotics resistance and further to recommend on its control measures.

Methods: The use of antibiotics in sub therapeutic doses, non-laboratory oriented therapy and poor storage are some of the factors that engender antibiotic resistance. As there are many different mechanisms in which antibiotics can kill or inhibit the growth and multiplication of bacteria, there are also different mechanisms of resistance in which bacteria developed against antibiotics. The use of antibiotics as growth promoters in food animal producers is significant cause for antibiotic resistance in animals. Even today zoonosis of the resistant strains is able to occur and become a risk to human health. There are guidelines in both human and Veterinary Medicine for rational use of antibiotics. Several new initiatives such as vaccines, bacteriocins, competitive exclusions, bacteriophages and others are being put in place to halt and control the alarming trend of resistance to antibiotics. But, there are still some indications on the misuse of antibiotics by health care providers, unskilled practitioners and drug consumers. Thus, awareness creation should be conducted on rational use of antibiotics in veterinary and medical practice to mitigate the occurrence of antibiotic resistance.

Key words: *Antibiotics, Mechanisms, Resistance*

1. INTRODUCTION

Antibiotics are mainly used both in human and veterinary medicine to insure human and animal health worldwide. Beside medical therapy, antibiotics have also been used to improve aquaculture and agricultural production. However, the emergence of resistant bacteria to commonly used effective antibiotics, resulted in the need for stronger drugs and more costly therapy. New forms of antibiotic resistance can even easily crossing with remarkable speed across international boundaries and spread between continents. World health leaders have

described antibiotic resistant microorganisms as “nightmare bacteria” that “pose a catastrophic threat” to people in every country in the world [1].

Some studies on bacterial resistance have shown that there is a huge diversity of resistance mechanisms, in which the distribution and interaction is mostly complex and unknown. However, there are varieties of biochemical and physiological mechanisms that are responsible for the development of antibiotic resistance. The mechanism of resistance may be evolution of either genetically inherent or the result of the microorganism being exposed to antibiotics. Most of the antibiotic resistance has emerged as a result of mutation or through transfer of genetic material between microorganisms. Several of various recent studies revealed that almost 400 different bacteria have demonstrated about 20,000 possible resistant genes [2].

The resistances that evolve within bacteria that affect animals have the potential to affect humans. Zoonosis of the resistant strains is able to occur, posing a risk to human health. People who are employed at farms or food animal production facilities are at a higher risk of infection with a resistant strain of bacteria [3].

Antibiotic resistant infections occur too often and with increasing frequency, interfering with the effective treatment of people and animals. Antibiotic resistance has increased due to the introduction of antibiotics into an environment. In general practice, there are concerns about some common infections which are becoming difficult to treat an illness with antibiotic resistant bacteria which may take longer to resolve [4]. To preserve the effectiveness of antibiotics, it is critical to examine the uses of these drugs, in both humans and animals. Several new initiatives are being put in place to halt the alarming trend of resistance to antibiotics and to deal with the ever-increasing number of infections caused by resistant bacteria [5].

Emergence of antibiotics resistance could be result of the use and misuse of antibiotics both in humans and animals. As a result it may leads to increased mortality, morbidity, costs of treatment, and loss of production in animals. Even though, there were various indications on the misuse of antibiotics by health care providers, unskilled practitioners and drug consumers, there is still inadequate awareness as well as surveillance on the control and prevention of antibiotic resistance in general and in veterinary practice in particular. Therefore, the objectives of this seminar paper are:

- ❖ To review on antibiotic resistance, its mechanisms of development and impacts
- ❖ Further to recommend on its control measures

2. ANTIBIOTIC RESISTANCE AND ITS MECHANISM OF DEVELOPMENT

2.1. Antibiotics

2.1.1. Definition

Antibiotics are chemical agents that prevent bacterial growth by stopping the bacterial cell from dividing (bacteriostatic) or by killing them (bactericidal). The terms antibiotic and antimicrobial are often used interchangeably but are not synonymous. Antibiotics are substances of microbial origin (such as penicillin) while “antimicrobial” refers to any substance including synthetic compounds which destroys microbes [6].

Antibiotics are used to treat and or prevent disease in human and animals. The reductions in death afforded by effective antibiotics for bacterial infections of all types, ranging from simple skin infections to infections of the bloodstream, lung, abdomen, as well as brain, so enormous that the lives of both human and animals are saved due to treatment by using antibiotics [7].

2.1.2. Mechanism of action of antibiotics

In order to appreciate the mechanisms of resistance, it is important to understand how antimicrobial agents act. One of the most common mechanisms of action is targeting the cell wall, which is present in bacteria (prokaryotic cells) but absent in humans (eukaryotic cells). Thus, antimicrobial agents act selectively on vital microbial functions with minimal effects or without affecting host functions. Different classes of antibiotics possess specific modes of action by which they inhibit the growth or kill bacteria [8].

Table 1: A list of antimicrobial agents and their modes of action

Antimicrobial agents	Group	Mode of action
Ampicillin , Augmentin Amoxicillin	Penicillins	Inhibitor of cell wall synthesis
Ceftriaxone	Cephalosporins	Inhibitor of cell wall synthesis
Chloramphenicol	Chloramphenicol	Inhibitor of protein synthesis
Erythromycin Azithromycin	Macrolides	Inhibitor of protein synthesis
Gentamycin, streptomycin	Aminoglycosides	Inhibitor of protein synthesis
Oxytetracycline	Tetracyclines	
Nalidixicacid Ciprofloxacin	Quinolones	Inhibitors of DNA synthesis
Sulfamethazine Trimethopim	Sulfonamides	Competitive inhibitors of folic acid synthesis

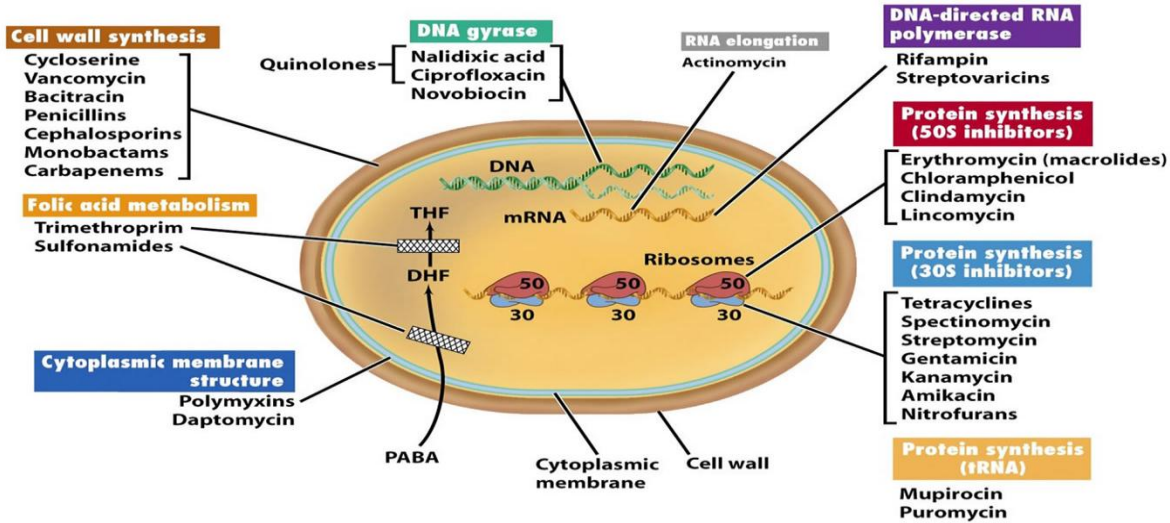


Figure 20-14 Brock Biology of Microorganisms 11/e
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Figure 1: Mechanism of action of antibiotics (Source:[http:// www.text book of Brook biology of microorganisms org.com](http://www.textbookofbiology.com)).

2.2. Antibiotic Resistance

Antibiotic resistance is the ability of a bacterium or other microorganisms to survive and reproduce in the presence of antibiotic doses that were previously thought effective against them [9]. The origin of antibiotic resistance genes are unclear; however, studies using clinical isolates collected before the introduction of antibiotics demonstrated susceptibility, although, conjugative plasmids were present [10].

Normally, most cells in a naive, susceptible bacterial population which can cause an infection are susceptible to particular antibiotic upon exposure. However, there is always a minute sub-population of resistant bacterial cells that will be able to multiply at higher concentrations in insufficient antibiotic concentration which kill the subpopulation so that micro-organisms survives in the environment [11]. Resistance is often associated with reduced bacterial fitness, and it has been proposed that a reduction in antibiotic use will pose selective pressure to acquire resistance would benefit the fitter susceptible bacteria, enabling them to outcompete resistant strains over time [12].

Antibiotic resistant bacteria are a growing public health emergency since infections from resistant bacteria are more hard and costly to treat. For instance, since the 1990s, some strains of Salmonella became resistant to a range of antibiotics. Resistance is supposed to be occurred from the use of antibiotics in human and animals' husbandry. The major problem in the clinical practice today is the emergence of multiple-drug resistance, which is resistance to several types of antimicrobial agent [13].

Resistance to an antibiotic may be an inherent property of the infecting organism or it may be acquired. Acquired resistance may result from mutation or from transfer of an extra chromosomal genetic material followed by selection of resistant organisms during therapy [14]. There is a range of mechanisms by which an organism can acquire resistance, the simplest being genetic mutation. Resistant mutants will have a strong survival advantage in the face of antibiotic exposures, giving rise to the total usage of antibacterial agents in a population and the increased proportion of isolates that exhibit resistance to those agents [15].

2.2.1. Factors that engender antibiotic resistance

The use of antibiotics at recommended dosage levels to treat confirmed bacterial infections is a type of exposure for which the benefit far outweighs the risk of selecting resistant strains [16]. Unfortunately, much of the antibiotic therapy is not laboratory oriented or even laboratory extrapolated. This coupled with the high proportion of life-threatening infections that require immediate treatment. So the prescribed antibiotic should be with first-line drugs such as ampicillin, ampiclox, cotrimoxazole, chloramphenicol, erythromycin, gentamicin, penicillin, tetracycline and metronidazole [17, 18].

The treatment of infected people in many parts of Africa is further challenged by the fact that prohibitive cost of newer second-line antimicrobials like amoxicillin-clavulanate, cefuroxime, ceftriaxone, ofloxacin, ciprofloxacin, azithromycin, amikacin and others, when available, places them out of the reach for the majority of patients. Since there is no broad enough selection profile of the second-line drugs, there is usually no cost effective customization of empiric antibiotic therapy [19].

Other challenges include the use of sub-therapeutic doses (mainly by improper prescription or patient non-compliance) which creates a situation whereby highly resistant strains are selected sequentially; and the supply of poor quality (substandard) drugs of which neither the prescriber nor the patient is aware that provides sub-inhibitory selective pressure to kill bacteria. Other problems include man-made conditions (warm, moist and unhygienic environments) which are not only conducive to the spread of pathogens but also good for the resistant organisms that carry resistant genes e.g. resistance in clinical *E. coli*, *salmonella* or *shigellaenteritis*[20].

The other factor is the poor storage which leads to drug degradation by heat and/or humidity during the course of distribution. In addition, overcrowding and lack of resources for effective infection control in many healthcare facilities fuelling hospital epidemics of resistant organisms such as methicillin resistant staphylococci, multiple resistant rods, vancomycin resistant strains and others [21].

2.2.2. Mechanism of antibiotic resistance

As there are many different ways in which antibiotics can kill or inhibit the growth and multiplication of microorganisms, there are also many mechanisms of resistance that microorganisms innately possess or have developed over time through exposure of antibiotics. It is possible that through one mechanism, an organism can become resistant to many different classes of antibiotics, especially if the modes of action are similar. Sometimes resistance can be shared between individual bacteria through the production of “resistance plasmids,” the pieces of DNA capable of being transferred from one cell to another [22].

Resistance genes transferred between organisms via these mobile genetic elements (MGEs) is the most common and clinically more important in multi-drug resistance (MDR) of Gram-negative bacteria than resistance arises through mutation. There is ample evidence that MGEs are able to transfer resistance mechanisms between genera; for example, MGEs of *enterococci* being transferred to *Staphylococcus aureus*[15].

A microorganism is resistant if it exhibits “significantly reduced susceptibility” when compared with that of the “original isolate” or a group of sensitive strains (Chapman, 1998). Resistance can result from mutations in housekeeping structural or regulatory genes, or alternatively, horizontal acquisition of foreign genetic information [14].

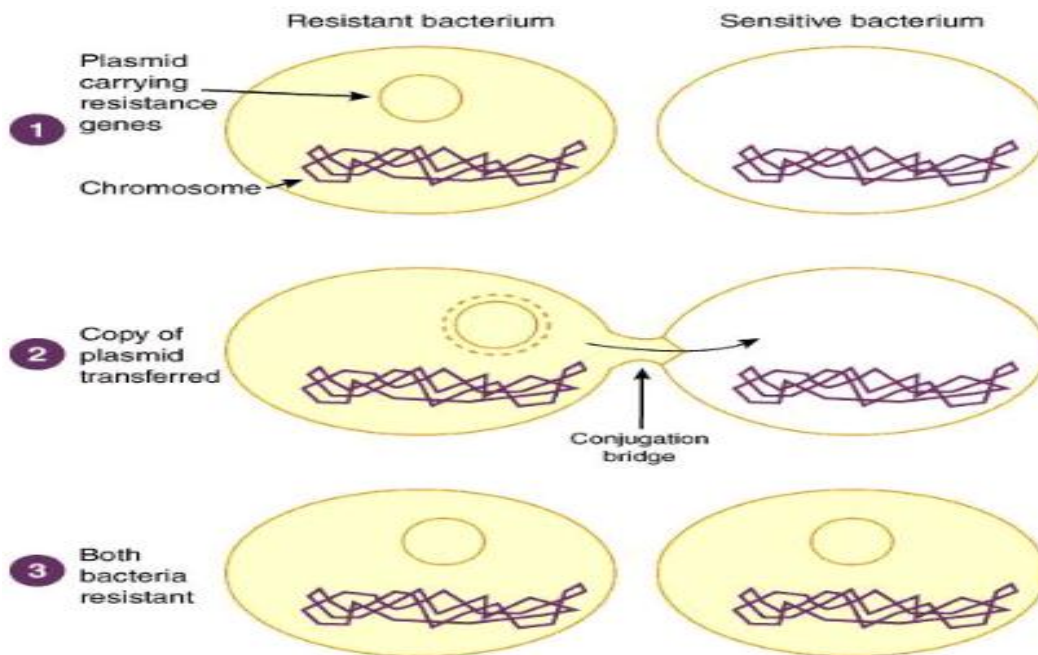


Figure2: Horizontal gene transfer: resistance gene being transferred from one bacterium to another. **Source:**[23].

Resistance can be described in two ways: intrinsic or natural whereby microorganisms naturally do not possess target sites for the drugs and therefore the drug does not affect them (e.g. *Mycoplasma* species resistant to penicillins) or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into the microbial cell in order to affect their action (e.g. many *enterobacteriaceae*). The other is acquired resistance whereby a naturally susceptible microorganism acquires ways of not being affected by the drug [24].

Antibiotic inactivation: On some occasions cell may gain resistance to antibiotics is by making an enzyme that renders the drug inactive, or that decreases the functionality of the antibiotics. The best example is beta lactamases which has capable of breaking the beta-lactam rings of beta lactam antibiotics such as penicillin. In such manner, the breakage of the beta-lactam ring stops the antibiotic from being able to attach to the peptidoglycan precursors. But it will be less likely that penicillin or other similar drugs will be able to disrupt the integrity of the cell wall, as long as the organism produces beta lactamases [25]. This method of resistance can be transferred from one bacterium to another through the production of the R-plasmids, and is common in strains of methicillin resistant *Staphylococcus aureus* (MRSA)[26].

Reduced membrane permeability: Another common way of interfering with antibiotics is through the prevention of entrance of the drug into the cell. Gram negative bacteria have an outer cell membrane, and drugs must pass through the cell pores, which are channels that span the outer membrane and allow the entry and exit of materials into or out of the cell. In order to enter the cell or interact with the cell wall, the drugs must be able to pass through the pores [27].

A gene mutation can result in altered pores, usually by changing the electrical charge or the physical structure which can make it more difficult for antibiotics to enter the cell. The antibiotic is still functionally active, but it will fail to reach its target site. A microorganism can develop resistance to multiple drug classes at once in this manner. But some gram negative bacteria are innately resistant to large drugs like vancomycin, which is too large to pass through the pores even before a mutation occurs [28].

Modification of target site: Many antibiotics act by binding to a target molecular component of the microorganism. A microorganism can decrease the effectiveness of a drug if the target molecule changes slightly in its structure so that antibiotic may no longer be able to bind to the target molecule. For example, tetracyclines block the transfer RNA access site by binding to it. In turn slight changes in the access site may result in microbial resistance to tetracyclines[10].

Efflux or transport of antibiotic: Another mechanism by which microorganisms can become resistant to antibiotics is by utilizing an efflux pump. An efflux pump is a biological pump that can force the antibiotic out of the cell, so that it cannot reach or stay in contact with its target. This method of antimicrobial resistance may often create resistance to more than one class of antibiotics, especially the macrolides, tetracyclines, and fluoroquinolones because these antibiotics inhibit different aspects of protein and DNA biosynthesis and therefore must be intracellular to exert their effect [27].

The genetic alterations in bacteria cause resistance to antibiotics in one or more of four principle ways, as shown in Figure 3; the target molecules are structurally altered to prevent antibiotic binding; reduce membrane permeability (antibiotics are excluded from cell entry); antibiotics are inactivated through enzymatic degradation; or they are pumped out the cell by efflux pump [50].

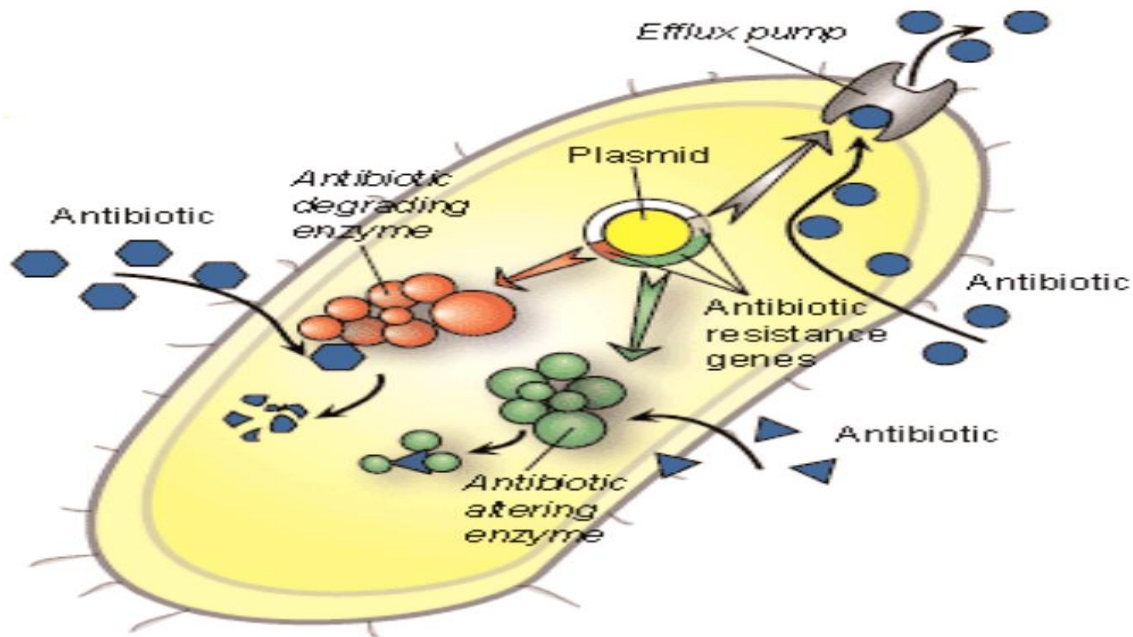


Figure 3: Resistance mechanism of bacteria.

Source: (Adopted from [http:// www.chembio.uoguelph.ca](http://www.chembio.uoguelph.ca)), accessed on April 21, 2017.

2.2.3. Multiple antibiotic resistances

R-plasmids possess regions with the resistance genes and resistance to a number of different antibiotics that can be mediated by the same R-factor and is known as multiple antibiotic resistances [29]. The prevalence of multiple drug resistance bacteria itself is a serious problem, but transfer of multiple drug resistance to other members of the family *Enterobacteriaceae*, particularly *E. coli*, *Salmonella* and *Shigella* makes it even greater concern to clinicians in curbing infections in medical and veterinary practice [30, 31].

An example of MDR pathogen is *vancomycin* resistant *Enterococcus* (VRE), which can cause infection in many parts of the body. Researcher Jane Siegel found that VRE “was associated with increased mortality, length of hospital stay, admission to the intensive care unit, surgical procedures, and costs when VRE patients were compared with a matched hospital population” [32].

Another example of MDR pathogen is MRSA. *Staphylococcus aureus* is a common bacterium that causes the urinary tract, wound, skin infections, and other complications. It is also one of the most common nosocomial infections, and one in twenty health care workers are colonized with MRSA and has a higher rate of causing symptomatic or fatal infections than methicillin susceptible *S. aureus*[33].

2.2.4. Antibiotic resistance in animals

Antibiotic usage in Veterinary Medicine and food animal production in developed countries has reached high levels [3]. In addition to treating diseases, food animal producers now had a new means of promoting growth of their livestock [34]. The success of antibiotics in the treatment and prevention of disease within companion pets and food animals has helped to control the spread of infectious diseases and improve the quality of life for many animals. However, the creation, and subsequent overuse of a wide variety of antibiotics since the past century has led to the development of antibiotic resistant strains of bacteria [35].

Most concern about antibiotic resistance in animal isolates of bacteria is directed towards the enteric bacteria, *E. coli*, *salmonella*, *thermophilic campylobacters* and *enterococci* [33]. Resistance to other antibiotics was detected as new agents were introduced for therapeutic and growth-promoting purposes [36]. Feeding oxytetracycline to recently-weaned pigs was found to be the risk factor for rapid increase in the incidence of tetracycline resistance, which was widely distributed among all strains of *E. coli* present, rather than being restricted to a few selected clones [37].

Recently, feeding low doses of ampicillin to chickens was shown to select for high levels of resistance to that antibiotic. In herds and flocks treated with tetracycline, amino glycoside and sulphonamide, widespread resistance is seen. Resistance is generally less prevalent in salmonella, but that resistance to tetracyclines, sulphonamides and streptomycin is quite wide spread [38].

2.2.5. Economic significance of antibiotic resistance

The detrimental health effects produced by antibiotic resistance go hand in hand with a negative impact on the budget of health systems and, more broadly, on the economy. From the micro-level to the macro-level, antimicrobial resistant micro-organisms (ARMs) have a direct negative impact on many actors and economic dimensions. First, by requiring more intensive therapies, antibiotic resistance increases health expenditures. Second, patients and their families may undergo additional non-healthcare related expenditures (e.g. travel time) or suffer from income loss due to ill-health. At the societal level, antibiotic resistance negatively impact labor market outcomes due to absence from work which, down the line, negatively affect the broader economic performances of countries [39].

The main drivers underlying the additional expenditure are: More intensive medical procedures as, for example, an increased likelihood of Undergoing surgery among patients infected with resistant organisms. Surgery may range from debridement of infected tissue to amputation [40]; Excess length of stay or treatment until the infection is eradicated. This entails additional medical and nurse care (and, consequently, time) as well as use of other additional hospital resources. Changes in physicians' prescribing habits that may start prescribing second-line antibiotics even to patients with first-line antibiotic susceptible infections, if the prevalence of ARMs is perceived as increased [41].

2.2.6. Public health significance of antibiotic resistance

Transmission of antibiotic resistant bacteria to man: Many antibiotics that are used in animal feed are also used to treat diseases in man. Such use of antibiotics in feed raised the concern among public health authorities and consumers because such level use of the drug may cause occurrence of bacterial resistance in the gastrointestinal tract (GIT) of these animals. Such resistance can also transfer to bacterial inhabitants of the GIT through food chain [42].

The feeding of low levels of antibiotics such as tetracycline and penicillin in poultry, swine and calves to promote growth has resulted in a great increase in the reservoir of resistant bacteria. These resistant bacteria from animals may reach the human population. This is well established with Salmonella infections. Antibiotic resistant bacteria spread from animals to human indirectly via food (e.g. by contamination of carcasses during slaughter), or less commonly by direct contact (farmers, abattoir workers) [43].

2.2.6. Control of antibiotic resistances

Responsible use: Guidelines exist for responsible (proper, appropriate, prudent, or judicious) use of antibiotics in veterinary and human medicine, and are similar in the medical and agricultural sectors [44]. Veterinary and animal producer organizations in many countries have developed and implemented responsible use of guidelines. These address use in various species, including poultry, swine, dairy and beef cattle, and sheep. International organizations, such as the OIE, WHO, also have developed principles or codes of practice to contain antibiotic resistance. The WHO published global principles for the containment of antimicrobial resistance in animals intended for food [45].

The OIE issued five documents concerning antibiotic resistance, including guidelines for the responsible and prudent use of antimicrobial agents in Veterinary Medicine. The other four documents deal with risk analysis methodology, monitoring of use quantities, surveillance programs, and laboratory methodologies [46]. Most of the recommendations of the various guidelines can be summarized in three objectives: emphasize actions to prevent disease, thereby eliminating the need for therapeutic use of antibiotics; if a disease occurs in or threatens animals, consider methods other than antibiotic use to mitigate or prevent the effects of the disease; and if antibiotics are necessary to prevent, control or treat a disease, first consider the use of antibiotics that are less important to human or veterinary medicine [47].

Alternative practice: Herd, flock, and other health management programs overseen by veterinary or other professionals attempt to minimize infectious disease outbreaks by using non-antibiotic interventions early in the life of the animals. The rationale is to promote healthy animals that do not become ill and are, thus, unlikely to be treated with an antibiotic agent. Several current approaches are available. These non-antibiotic approaches have led to a need to establish performance standards for regulatory and commercial purposes [38].

Preventing infectious diseases in animals: Focus should be given to the continuous implementation of appropriate measures for disease prevention, to decrease the need for antibiotics. To minimize infection in food animal production and decrease the amount of antibiotics used, efforts should aim to improve animal health, thereby eliminating or reducing the need for antibiotics for treatment or prophylaxis. This can be achieved by improving hygiene, biosecurity and health management on farms and preventing disease through the use of vaccines and other measures such as probiotics (beneficial bacteria found in various foods), prebiotics

(non-digestible foods that help probiotic bacteria grow and flourish) or competitive exclusion products (intestinal bacterial flora that limit the colonization of some bacterial pathogens) [48].

Vaccines have been a key component of disease prevention for many years because they have many favorable attributes such as low cost, ease of administration, efficacy, multiple agent efficacy (viruses, bacteria, mycoplasma, and parasites), and safety (worker, animal, environmental, lack of food residue). Adjuvants are sometimes included with vaccines to enhance the immune response. Various delivery systems or routes of administration (for example muscle injection or, aerosol, topical, or oral (mucosal) are used to administer the vaccine into the animal [49].

Future research in veterinary vaccine adjuvants will focus on particle delivery to antigen presenting cells and immune stimulatory adjuvants to affect a higher and longer lasting state of immune response [50]. New oral delivery systems, such as plant-based vaccines, are being developed that offer ease of administration, production, and other benefits, although the regulatory acceptance of these products remains to be clarified [51].

Bacteriophages have been used successfully to prevent and treat bacterial diseases in humans and animals in Russia, but have failed to gain acceptance in Western countries owing to the focus on antibiotic use [52]. Anti-infective, bacteriophages have several attractive attributes including specificity because, bacteriophage is directed toward a single kind of bacterium (limited host range), but its lethality, projected low cost, and no residues in the food product is rewarding. However, questions surrounding the safety of using recombinant therapies, environmental containment, and phage resistance remain unresolved [53].

The other way is through use of Competitive exclusion in which direct-fed microbial products containing live microorganisms (known as probiotics) or products containing enzymes as the active ingredient are currently marketed in many countries. Probiotics, which contain one or more types of microorganisms and are administered orally, are currently approved for use in food animals in Europe and other countries, but as for the use of antibiotics for growth promotion, their mode of action is not fully understood. Probiotic bacteria could affect normal gut microflora by competitive exclusion of pathogenic bacteria, production of antibacterial products or enzymes that act on gut bacteria, or production of other metabolites that affect gut commensals [48].

Bacteriocins have also been investigated for their potential use in the control of certain zoonotic pathogens in the avian intestinal tract because they are pore-forming antibacterial proteins produced by microorganisms. One bacteriocin, nisin, has been approved for use in several food products [54].

3. ANTIBIOTIC RESISTANCE IN ETHIOPIA

Emergence of antibiotics resistance is a result of the use, overuse and misuse of antibiotics both in human and animals' health practices. In Ethiopia, there were indications on the misuse of antibiotics by health care providers, unskilled practitioners and drug consumers. These coupled with rapid spread of resistant bacteria and inadequate surveillance contributed to the problem. Studies on antibacterial resistance and on bacterial infections have shown that emerging antibacterial resistance threatens the management of bacterial infections. However, the prevention and containment has received far too little attention. The consequences of this

phenomenon include increased mortality, morbidity, costs of treatment, and loss of production in animals [55].

In Ethiopia the control of drugs from the government authorities and information on the rational use of drugs pertaining to veterinary drug is very limited. In addition there is lack of awareness and preparedness among the controlling authorities and producers in dealing with the risk of indiscriminate use of antibiotics to the livestock and to the consumers. Even no formal control mechanisms exist to protect the consumers against the consumption of meat and milk products containing harmful drug residues in the country [56].

The most health workers do not adhere to the rational antimicrobial prescription guidelines. The diagnosis of a disease is generally presumptive; drug sensitivity tests are not carried out and the selection of drugs is primarily based on their availability rather than their efficacy. In addition, a few antimicrobials were commonly prescribed and factors that could help reduce the rates of emergence of resistant pathogens were not considered by most respondents. Moreover, verbal prescription is the major form of prescription and the prescription papers used in some clinics does not contain all the relevant information. In a study on the antimicrobial resistance features of salmonella isolates of dairy cattle in Addis Ababa, almost all isolates (20/21) were multi drug resistant [57].

The irrational use of drugs is a major problem in present day clinical practices as it could result in toxicities and treatment failures in patients and in the emergence of drug resistant pathogens. Whilst drug resistant bacteria were traditionally acquired in hospitals due to high antimicrobial use and disease transmission rate, community acquired drug resistant bacteria are becoming increasingly common [58]. Resistance may escalate to the point at which the efficacy of drugs will no more be predictable and infections once treatable could become untreatable [59].

In addition, the most common problems for the increasing of antibiotic resistance, in Ethiopian situation, are weak storage capacity of pharmaceuticals, long stock-outs of essential drugs in public health facilities, widespread over the counter (OTC) availability of antimicrobials, poor dispensing, drug quality concerns, especially in rural areas, unregistered drugs and drug sellers in rural areas, low patient knowledge about drugs dispensed to them and weak monitoring and lack of antibiotic policy and evaluations [60].

4. CONCLUSION AND RECOMMENDATIONS

Antibiotics are extensively used both on human and animal health practices in developed and developing countries of the world mainly for treatment and control of various diseases. However the use, misuse and overuse of these medicines contributed favorable conditions for the emergence, occurrence and development of antibiotic resistant bacteria. Similarly, the other factor which contributes for includes: Sub-therapeutic doses, non-laboratory oriented antibiotic therapy, use of ineffective drugs and poor storage of drugs. These all can result infections with much more difficult to treat. Even though there are guidelines in both human and veterinary medicine for responsible use of antibiotics, vaccination, competitive exclusions and others for rational use and the control of antibiotic resistance, there are still some indications on the misuse of antibiotics by health care providers, unskilled practitioners and drug consumers. These all coupled with rapid spread of resistant bacteria consequently, may lead to increased mortality,

morbidity, costs of treatment, and loss of production in animals. Even though the effect of antibiotic resistance is magnificent, there is still inadequate surveillance and far little attention on rational use of drugs to minimize antibiotic resistance. So based on the above conclusion the following recommendations are forwarded:

- Awareness creation should be conducted on rational use of drugs for the community and other stake holders.
- Antibiotic treatment should be provided after isolation, identification and conduction of drug sensitivity test.
- Use of antibiotics as growth promoters should be prohibited.
- Narrow spectrum antibiotics should be the first choice when antibiotic therapy is justified.
- Research needs to be developed on the best ways to mitigate the development of antibiotic resistance.

LIST OF ABBREVIATIONS

AMR	Antimicrobial Resistance
ARM	Antimicrobial Resistance Micro-organisms
CDC	Centers for Disease Control and prevention
DACA	Drug Administration and Control Authority of Ethiopia
DNA	Deoxyribo-Nucleic Acid
E. Coli	Escherichia Coli
FMOH	Federal Ministry of Health
GIT	Gastrointestinal tract
JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
MDR	Multi-Drug Resistance
MGE	Mobile Genetic Elements
MRSA	Methicillin Resistant Staphylococcus aureus
MSH	Management Sciences for Health
PABA	Para-Amino Benzoic Acid
OIE	Office of International des Epizootics
OTC	Over The Counter
RNA	Ribo-Nucleic Acid
VRE	Vancomycin Resistant <i>Enterococcus</i>
WHO	World Health Organization

Declarations

The authors declared that this our original work and effort.

Competing interest

The author declared that the manuscript has no competing interest

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