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A Review on the Occurrence, Effects and Control Measures of Antimicrobial Resistance in Livestock & its Human Health Impacts

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Abstract: Veterinary medical agents are generally used in veterinary medicine for different purpose: therapeutic treatment of active infection or prophylactic medication to prevent or to minimize the incidence of infection, production enhancement (growth promotion), control of reproduction, pre-slaughter control of stress and improvement of feed efficiency with antibiotic drugs and hormones. However, antimicrobial resistance has become an increasingly important public and animal health problem because of the imprudent use of antimicrobial drugs and failure to ensure proper diagnosis and adherence to treatment. Bacteria will continue to develop resistance to currently available antibacterial drugs by either new mutations or the exchange of genetic information. In many health care facilities around the world, bacterial pathogens that express multiple resistance mechanisms are becoming the norm, complicating treatment and increasing both human and animal morbidity and financial costs. Prudent use of antibacterial drugs: using the appropriate drugs at the appropriate dosage and for appropriate duration is one important means of reducing the selective pressure that helps the emergency of resistant organisms, and strict attention to infection control guidelines to contain the spread of resistant organisms.
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1. Introduction

Antimicrobial agents have been used in livestock and poultry since the early 1950s to treat infections and improve growth and feed efficiency. After the discovery of penicillin by Fleming in 1929, the Sulphonamides, the first class of antimicrobial was launched in 1937 followed in 1944 by streptomycin, the first amino glycoside. Since then, several other classes of antibiotics have followed: chloramphenicol, tetracycline, macrolide, vancomycin, methicillin, cephalosporin, quinolones, lipopeptides and glycopeptides (Giguere, 2006).

The use of Antimicrobial agents in food animals that have a human analog increases the likely hood that bacterial pathogens that have food animals reservoirs will develop cross resistance to antimicrobial agents used in human medicine. Antimicrobial resistance is defined as the ability of microbial organisms to grow or survive in the presence of antimicrobial at concentration that is usually sufficient to inhibit or kill microorganisms of the same species. Microorganisms may be tolerant or inherently resistant to particular antimicrobials or they may acquire resistance to antimicrobials to which they are normally sensitive. The World health organization, following series of consultation in 1997, 1999 and 2000, has recommended that, unless a risk based evaluation demonstrates their safety, the use of antimicrobial agents in food animals for growth promotion that belong to classes of antimicrobial agent used in human should be terminated (WHO, 2000). The increase in AMR has narrowed the potential uses of antibiotics for the treatment of infection in humans and animals (Angulo *et al.,* 2004). The presence of AMR bacteria in primary animal production represents a high risk for humans since AMR bacteria of animal origin can be transmitted from animals to humans through the food supply (food borne pathogens), water or direct contact with animals (Funck *et al.,* 2006).

In farms, factors that can influence bacterial resistance vary depending on herd or flock health status, farm management and environment (Acar and Molen, 2006). These practice include over prescription of broad spectrum drugs by veterinarians instead of narrow spectrum drugs, feeding of low dose of antibiotics for growth promotion (Prescott, 2008) and use of none approved drugs or drugs used in extra level manner are believed to contribute to the development of anti microbial resistance (Sharma *et al.,* 2005). Although wide spread use of antimicrobials in the primary sector has benefits for producers, it also contributes to the increasing emergence of AMR bacteria (Aerstrup and Pires, 2009). The mechanism of resistance to antimicrobials is due to enzymatic modification, efflux pump, and altered target sites and by pass of synthetic pathway (Rice and Bonomo, 1996).

Studies in Ethiopia showed high percentage of antimicrobial usage. According to 2002 National pharmaceutical sector assessment, antimicrobial was prescribed for 58% of patients. Antibiotics use in treatment of non bloody, watery diarrhea and non pneumonia acute respiratory infection showed significant deviation from standard Treatment Guide lines (SGT), (WHO, 2002). A study in different part of the country also suggest similar finding: antimicrobial were prescribed for 63.84% of patients in Harari region health facilities (Mennasie,2004); 60% health centers and 65% health stations of north west Ethiopia (Desta *et al.,*1997) and 25.6% in Jimma university hospital in south west Ethiopia (Wubeante, 2005). Increasing awareness of the problem of antibiotic resistance in the community and the threat that resistant bacteria may pose is a key first step in addressing this problem. A strategy to limit antimicrobial resistance are based on four basic principles, which are containment of resistant species, infection prevention, infection eradication, and optimizing antibiotic utilization (Raymond *et al.,* 2002).

Therefore, the objectives of this paper are:

- To review on the mechanisms of antimicrobial resistance development.
- To issue basic highlights about problems associated with antimicrobial resistance.
- To outline the occurrence, effect and control of antimicrobial resistance in animals.

2. Antimicrobials

The terms antimicrobial and antibiotic are often used interchangeably. In technical terms, ‘’ antimicrobial ‘’refers to any substance (including synthetic compounds) and substances of microbial origin (such as penicillin) that are active against the microbes. Antimicrobial agents interfere with specific bacterial processes needed for growth or division of cells. Compounds that inhibit bacterial growth are termed bacteriostatic while those that kill the bacteria are termed bactericidal. Antimicrobials are commonly used to treat infectious disease in animals, humans, and plants and these substances may be naturally occurring, semi-synthetic or synthetic. Chemical modification of the structure of antibiotics leads to the development of the compounds with an altered spectrum of activities (Giguere, 2006).

2.1 The Use of Antimicrobials

Antimicrobials are not only used to treat human illness but have also been used in livestock and poultry for more than half a century to control, treat diseases and, low dose in animal feed to promote growth and improve production of animal products (manna *et al.,* 2006). Veterinary medicinal agents are generally used in veterinary medicine for different purposes: therapeutic treatment of active infection or prophylactic medication to prevent or to minimize the incidence of infection and production enhancement (growth promotion), control of reproduction, pre-slaughter control of stress and improvement of feed efficiency with antibiotic drug and hormone (NRC, 1999).

2.1.1Treatment of active infections

The majority of antibiotic use in hospitals or in veterinary clinics is for treatment of active infections. According to their chemical structure, the most commonly used antimicrobials for treatment of food producing animals can be grouped into five major classes such as the β–lactams (e.g. penicillin and cephalosporin), tetracycline (e.g. oxy tetracycline, doxycycline and chlortetracycline), aminoglycosides (e.g. streptomycin, neomycin and gentamycin), macrolides (e.g. erythromycin) and sulphonamides (e.g. sulfamethazine) (Mitchell *et al.,*1998).

2.1.2. Prophylaxis

In large surgical cases half of all antimicrobial are used to prevent possible infections (prophylaxis) (Kernodle and Kaiser, 1990). The timing of administration of antimicrobial for prophylaxis proved that antimicrobial can prevent infections when administered two hours prior to surgery. They also suggested that antimicrobials given at times other than in the two hours before surgery are not effective in preventing infections. Moreover, appropriate use would reduce antibiotic use and help control antibiotic resistance (Evance *et al.,* 2008).

2.1.3 Growth promoter

Antimicrobial growth promoters (AGPs) are antimicrobial added to the feed of food animals to enhance their growth rate and production performance. AGPs reduce normal intestinal flora and harmful gut bacteria. The effect on growth may be due to a combination of both fewer normal intestinal flora and

fewer harmful bacteria. In Denmark, as well as in other countries, only a few glycopeptides have been used; for humans, vancomycin and (to a lesser extent) teicoplanin have been used, and for animals avoparcin has been used exclusively as a feed additive for growth promotion. The resulting concentration in the gastrointestinal tract of the animal is sufficient to inhibit the susceptible bacteria and markedly affect the composition of the bacterial gut flora (Junsen, 2007).

3. Mechanisms Of Antimicrobial Resistance

Antimicrobial resistance is defined as the ability of a micro organism to grow or survive in the presence of an antimicrobial at concentration that is usually sufficient to inhibit or kill micro-organisms of the same species. Micro-organism may be tolerant, or inherently resistant to particular antimicrobials, or they may acquire resistance to an antimicrobial to which they are normally sensitive. Bacteria can resist antibiotics as a result of chromosomal mutation or by exchange of genetic material, which carry resistance genes, through transformation, transduction or conjugation by plasmids (Opal *et al.,* 2000). For the majority of antimicrobials, AMR is the result of the acquisition of extra chromosomal resistance genes. The use of antibiotics should have created a catastrophic situation or microbial population but the genetic flexibility allowed bacteria to survive and multiply under the antibiotic pressure, the mechanism of resistance to antimicrobial agents can be due to??? (Rice and Bonomo,2006).

3.1 Enzymatic Modification

β lactamase is the most studied group of enzymes responsible for this mechanism of resistance. Example, **β** lactam antibiotic **(**penicillin and cephalosporin) can be inactivated by the enzyme known as **β** lactamase; they opened the four membered **β** lactam rings found in penicillin, cephalosporin and monobactam, neuclophilic attack on **β** lactam amide bond by the hydroxyl group of series residue located at active site of enzyme. Any acyl enzyme intermediate characterize by an ester bond between the enzyme and cephalosporin is produced. This ester bond then efficiently hydrolyzed by water liberating active **β** lactamase and inactivate **β** lactam antibiotic. Most **β** lactamase act to some degree against both penicillin and cephalosporin. The solution for **β** lactamase induced resistance is the use of **β** lactamase inhibiters such as clavulanic acids, sulbactam and tazobactam. Clavulanic acid contains **β** lactam ring which covalently bind to the enzyme at or near the active site (Rang *et al.,* 1999).

The other major groups of antibiotic modifying enzymes are the three classes of aminoglycoside modifying enzyme such as phosphotranspherase (PT), aminoglycosides acetyltranferase (AAT) and adenyltransferase (ANT). The enzymes are located in cytoplasm and only inactivate drug as it enters the cell. They are frequently plasmid mediated wide spread among gram negative and gram positive (Bertrand and Eday, 2004)

3.2 Efflux Pump

An efflux Pump, which consists of cytoplasmic and pericytoplasmic protein components, can be produced by gram negative organisms. This efflux pump can efficiently transport some beta lactam antimicrobial from the periplasm back across the outer membrane, for example extrusion of nafcillin by salmonella typhimurium (Katzung and Range, 1999). Active transport (Efflux pump) has been described for the removal of some antibiotic such as, tetracycline, macrolides, and quinolones. β lactam antibiotic gain intracellular access to gram negative via a water filled hallow membrane protein known as porine. Imipenem is carbapenem antibiotic and some imipenem is taken up in to cell. Similar mechanisms involving other porine is seen in low level of fluoroquinolones and aminoglycoside resistance gram negative bacteria. Increased efflux via emergence dependent membrane transport pump is common mechanism for resistance to tetracycline in gram negative bacteria (Levine *et al.,* 2003).

3.3 Altered Target Site

All antibiotic have molecular target which they interfere with to inhibit growth or kill bacteria, when structural change occur in that target molecule to resist the action of antibiotic they will be resistant. Some organisms produce penicillin binding protein (PBPs) that have low affinity for binding beta lactam antimicrobial and are only inhibited at relatively higher drug concentrations; methicillin resistant in staphylococcus and penicillin resistance in pneumococci are example of this mechanism (Katzung, 2001). Enterococcus species are inherently resistant to cephalosporin because the enzyme (PBPs) which responsible for synthesis of major structural component of the cell wall (peptidoglycans) have low binding affinity for them and are therefore not inhibited by them. Streptococcus pneumonia if fully susceptible to penicillin but by the process of transformation cells can take up DNA from others species of streptococci that have PBPs with low affinity for penicillin. Alteration in PBPs prevent beta lactam drugs from binding to them, similarly change in ribosomal RNA, the target for the macrolides prevent this drug from interfering with ribosomal function (Nakajim,1999).

3.4 By Pass Of Synthetic Path Way

Bacteria can continue to produce a target which inhibited by the antibiotic, but if they produce in alternative target which is not inhibited the cell continue to grow in the presence of antibiotic by

effectively "by passing" the effect of antibiotic. The transferable mechanism of resistance to vancomycin seen in vancomycin resitance enerococcus (VRE) species encoded by the vancomycin gene complex is an interesting variant of bypass mechanism (Wilson *et al.,* 2005).

4. Antimicrobial Resistant Tests

Antimicrobial resistant test is a laboratory technique which is usually employed for the detection and quantification of antimicrobial resistance. Its primary objectives are to predict the in vivo success or failure of antibiotic therapy. Test are performed In vitro and measure the growth response of an isolated organism to a particular drug and the test result should be used to guide antibiotic choice and it should be combined with clinical information and experience when selecting the most appropriate antibiotics. Some of the laboratory detection techniques are discussed as follows (Jacobs *et al.,* 2003).

4.1 Traditional Susceptibility Test

Traditional susceptibility test measure a property of organisms such as its ability to grow in the presence of a certain concentration of antibiotic. Information about antibiotic resistance/susceptibility is developed by testing the bacteria isolated from the infection against six to twelve different antimicrobial or more if necessary. Four methods that are currently used to determine the antibiotic susceptibility or resistance of bacteria: 1) Disk diffusion test, 2) Broth dilution test, 3) Agar dilution test, 4) Agar gradient methods (Jorgensen, 1995).

4.1.1Disk diffusion tests

Disk diffusion test measure the size of a clear area of no bacteria growth around a sterile paper disk containing antibiotic. The size of this area called the" zone of inhibition, ''can be measured and reported directly, or the measurement can be compared to criteria established by the National Committee for critical laboratory standards (NCCLS) to classify the bacteria as susceptible, intermediate or resistant (Jorgensen,1995).

Even though these tests are well standardized for certain bacteria based on the costs of equipment and a supply, the disk diffusion method is the least costly. It can also be the most informative under most conditions because the size of the zone of inhibition provide raw data that have not been subjected to interpretation, and zone of inhibition information is more quantitative than broth dilution tests that are sometimes based on only one or two dilutions (Brien, 2004)

4.1.2 Broth dilution test

Dilution tests measure the concentration of antibiotic that is necessary to prevent the growth of bacteria. In broth dilution test (BDT), known amounts of bacteria are deposited in to small test tube containing 1 to 2 milliliters of sterile nutrient growth medium ("broth") containing different concentration of antibiotic. The lowest concentration of antibiotic that prevents growth of the bacteria defined the minimum Inhibitory concentration (MIC) while the MIC provides information about the concentration that will inhibit the growth of a bacterium (IMPACT, 2006).

Imperative guidelines provided by NCCLS publications help clinical microbiologists and physicians interpret MICs as clinical categories of S, I, and R. A disadvantage of this method is the large number of test tubes and racks and large volumes of media that are required to test a single bacteria culture. The BDT is currently the most popular antibiotic sensitivity test in the U.S. To hold down costs and reduce the space need for incubation of test cultures, many laboratories do not use the entire series of dilutions. Instead, based on NCCLS interpretive criteria, only two to three dilution of each antibiotic are used. One of the dilution set to match the "break point "that defines the division between the resistant and intermediate response; another dilution matches the concentration that defines the breaking point between the intermediate and susceptible responses. The true break point might be somewhat different from the guide lines, and this fact can cause errors in classifying the bacteria as resistant or susceptible (Abe and Wada. 2003).

4.1.3Agar dilution test

Agar dilution test are similar to the broth dilution tests in that they measure the MIC. In these tests, a small volume of a bacterial suspension usually 1-2 micro liters is transferred to each of a series of agar plates containing known concentration of antimicrobial. Multi long devices are used to transfer approximately 100 colonies at one time (Rippin *et al.,* 2004).

4.1.4Agar gradient methods

Two commercial methods, the Etest1 and the spiral gradient endpoint system, use antibiotic concentration gradients on agar plates. Both tests establish MICs that compare closely with those determined in the disk diffusion or broth dilution tests, and both are useful for testing anaerobic and other hard to grow bacteria. These tests may have a special advantage for resistance surveillance because they have a continuous concentration gradient and are able to show subtle change in susceptibility, and the wide concentration gradients of these tests cover the MIC range of susceptibility of a wide variety of pathogens and allow both low-level and high level resistance to be detected. The Etest® (BioMérieux) is a commercial version of this technique. In the procedure, a strip impregnated with an increasing concentration gradient

of the antimicrobial agent from one end to the other is deposited on the agar surface, previously inoculated with the microorganism tested. The E test is reportedly easy to use in most laboratory setting and requires no complicated procedures (Heiter and Bourbeau, 2003)

4.2Antibiotiic Resistance Gene Test

These are tests which directly measure the presence of a bacterial gene. The new gene tests bring with them a new set of considerations' bacterium might contain a gene of resistance, but not "express "it under the conditions of the traditional diagnostic tests, or a resistance gene may have undergone a mutation that does not affect its function but that makes its presence undetectable, or the genes of dead bacteria may be detected with DNA tests. For example, samples from a patient who is being successfully treated with ant-TB drugs often test positive in DNA tests, but negative in culture-based tests that rely on growing the organism. These are problems that must be considered in designing new genetic tests and using them in clinical practice (Heiter and Bourbear, 2003).

One huge advantage of tests that measure the presence of a bacterial gene is that they are quick; many tests take only a few hours or less. Another advantage is that they generally have much higher sensitive is very useful. The development of faster and more susceptible genetically based tests for bacteria started in the early 1980s, but most are still not available for routine use. Nevertheless, some of these tests such as those that are able to diagnose tuberculosis in a few hours instead of a week represent a significant technological advancement that has improved clinical practice (Jacobs *et al.,* 2003).

4.2.1 DNA Probe Assays

Single Stranded fragments of DNA or RNA that are complementary to a target DNA or RNA sequence will form a double stranded molecule known as a "stable hybrid", under a certain reaction conditions. Diagnostic fragments, or probes, which will bind to target DNAs or RNAs, are labeled with enzymes or dyes so that the binding of the probe to the target can be detected. These are organisms that for the most part are difficult or slow to cultivate and identify in the laboratory (Heiter and Bourbeau, 2003).

One important disadvantage of probe-based methods to date has been their low sensitivity compared to culture based methods. One promising methods probe-based test that does have adequate sensitivity is a rapid direct DNA, probe- test form Gen-Probe that can identify Group A Streptococcus directly from throat swabs. However, Heiter and Bourbeau conclude that because this test requires two hours, the test will not be useful for point-of-care testing in a professional offices or emergency room clinics Rippin *et al.,* 2004).

4.2.2 Target amplification methods

One of the most promising approaches for increasing the sensitivity of probe-based DNA test is to amplify the target DNA sequence through such methods as Polymerase chain reaction (PCR), which can rapidly generate millions of copies of bacterial or resistance gene DNA or RNA sequences. Species specific PCR detection assay have been developed for at least 50 different bacterial pathogens, and specific sequences are available from a much larger number of species, for which PCR primers can be designed. In general, these tests are designed to produce results in a few hours. After the nucleic acid is isolated and amplified by a technique such as PCR, the nucleic acid can be sequenced to identify the organism (Abe and Wada, 2003).

4.3 Enzymatic Tests

Enzymatic Tests can directly measure the presence of an enzyme that confers antibiotic resistance, such as beta-lactamases that inactivate penicillin and other β-lactam antimicrobial and the enzyme that inactivates chloramphenicol. The detection of the ß-lactamase requires only a few minutes, but it is limited to only a few bacterial species. Moreover, it does not detect penicillin resistant caused by other mechanisms, such as the production of modified penicillin binding proteins. The test for the chloramphenicol inactivating enzyme requires one to two hours can be used detect the most common form of chloramphenicol resistance, but it has decreasing utility because of the declining use of this antibiotic (Stratton and Cooksay, 2000).

5. The Human Health Impact Of Antimicrobial Resistance In Animal Populations

Antibiotic usage in veterinary practice may impact human health because animals can serve as mediators, reservoirs and disseminators of resistant strains and/or AMR genes. Consequently, imprudent use of antimicrobials in animals may unnecessarily result in increased in human morbidity, increased human mortality, reduced efficacy of related antibiotics used for human for human medicine, increased health care costs, increased potential for carriage and dissemination of pathogens with in human populations and facilitated emergency of resistant human pathogens (Hendrikson *et al.,* 2004).

5.1 Increased Human Morbidly and Mortality

Higher case fatality rates are seen for patients infected with AMR organisms compared with those infected with antibiotic sensitivity organisms (Homberg *et al.,* 2004). The patients infected with strains resistant to ampicillin, chloramphenicol, streptomycin, sulfonamide and tetracycline were 4.8% more likely to die within 2 years. Furthermore, they established that quinolone resistance in this organism

was associated with a mortality rate 10.3 times higher than the general population (Helms *et al.,* 2002).

5.2 Reduced Efficacy to Related Antibiotics Used in Human Medicine

Antimicrobial resistance due to particular antibiotic used in food animals may result in reduced efficacy of most or all members of that same antibiotic class, some of which may be extremely important for human medicine. This occurs because of the similarity of the antibiotic's related structural components, which causes cross recognition and cross resistance for all or most of the antibiotics within the same antibiotic class. An example is the emergence and spread of vancomycin resistant enerococci (VRE) in hospitals following the extensive use of avoparcin in animals, a glycopeptides antimicrobial agent that is structurally similar to vancomycin (Mac Donald *et a*l., 2001).

5.4 Increased Human Health Care Costs

An increased human health care cost is another important consequence of antimicrobial resistance. Increased costs may be due to the need for addition antibiotic treatments, longer hospitalization, more diagnostic tests, higher professionals' costs and more pain management. With the increase in incidence and prevalence of AMR in the last few years, the current actual cost is now likely to be much higher. In 1998, the institute of medicine estimated the annual cost of infections caused by antibiotic resistant bacteria to be US$ 4 to 5 million (Mac Growan, 2001).

5.5 Increased Carriage and Dissemination

Because of their survival advantage, resistant bacteria may remain viable for long periods in the environment and in animal reservoirs where they can eventually be transmitted to humans. Acquisition of resistant bacteria from farm animals has been shown to occur either via ingestion of foods of animal origin or via direct contact with infected animals (Heinderikson *et al.,* 2004). In last few years, animals have been implicated in the maintenance, spread and transmissions of some type of MRSA among humans. Studies identified both livestock and companion animals as a potential source of MRSA for humans, and close contact with these animals was identified as a risk factor for their carriage in people. MRSA has been found in human closely associated with carrier animals; among pet owner (lee, 2003), veterinarians and veterinary personnel (Anderson *et al.,* 2008).

5.6 Facilitated Emergence of Resistance in Human Pathogens

Using mathematical models, Smith (Smith *et al.,* 2002) demonstrated that the use of animal agricultural antibiotics can hasten the appearance of AMR bacteria in humans, with the greatest impact occurring soon after the first emergence of resistance. Although it is true that such change and adaptation can occur independently of antimicrobial use in animals, the existence of resistance gene in animal population can expedite the process by contributing a pool of resistant gene and resistant bacteria in the environment and reservoir hosts (Davies, 2004).

6. Controlling Antibiotic Resistance

Decreasing the amount of antibiotic prescribed might limit the development of resistance. The smarter approach to resistance prevention would be to identify and target effective ways to control antibiotic use. Guidelines that spell out when not to use antimicrobial are as important as those that specify when and how to use them. Strategies to limit antimicrobial resistance are based on four basic principles, which are containment of resistance species, infection prevention, infection eradication, and optimizing antibiotic utilization (Raymond *et al.,* 2002).

6.1Prudent use of Antimicrobial

Optimizing antibiotic utilization is an important and promising means of limiting the spread of antibiotic resistance. As antibiotic utilization is a rampant and prior antibiotic administration is an important risk factor for development of antibiotic resistance infections, the most basic goal of antibiotic stewardship is the appropriate utilization of antibiotic. Prudent use means optimizing the efficiency of antimicrobial drug use while minimizing the development and spread of resistance that many antimicrobial are over used or used inappropriately. Surveillance system to track the emergency and spread of disease causing bacteria are essential new technologies that quickly and accurately identify bacteria will improve use of antimicrobial (Kunin, 1995).

6.2 Accurate Rapid Diagnosis

Swift identification and treatment; the sooner the infectious organism is detected and correctly identified, the higher the chance that it will not become drug resistance since it will have less time to mutate. Treatment should be limited to bacterial infections using antimicrobial directed against the causative agent, given in optimal dosage, dosage intervals and length of treatment with step taken to ensure maximum patient concordance with the treatment regimen, and only when the benefit of the treatment outweighs the individuals and global risk (Cookson, 2000).

6.3 Encouragement of New Drug and Vaccine Development

Vaccine can be designed to fight resistant and non-resistant pathogens alike. Merck, for example, is developing vaccine against *staphylococcus aureus* that may protect against MRSA infection. On the other hand, by specifically targeting the mechanisms of resistance; it may be possible to develop vaccines against antibiotic resistant bacteria pathogens, thereby

supplanting populations of resistant bacteria with susceptible, treatable bacteria. Vaccines prevent infections and reduce the need for antimicrobial. Effective vaccines against bacteria will reduce the use of antimicrobial (CDC, 2006).

6.4 Drug Combination

Combination therapy is an approach in which more than one antibiotic is administered simultaneously for a given infection. Oftentimes, combinational treatment is tantamount to mono therapy because a pathogen is not susceptible to one or more of the drugs, or one of the drugs does not penetrate the site of the infection. In tuberculosis, the aim of combination treatment is to decrease the risk of resistance of mutation. The concomitant use of two or more active agent vastly improves cure rate by preventing the development of resistance antimicrobial. Synergistic combinations of antimicrobial agent have been shown to be better than single agent therapy in relatively few infections (Wilson *et al.,* 1995).

6.5 Proper Prescription of Antimicrobials

For most drugs, increasing dose and shortening the treatment period apparently are less effective in selecting for resistance than the usual dose the regimen. Encourage the development and the use of guidelines and treatment algorithms to foster appropriate use of antimicrobials, and empower formulary managers to limit antimicrobial use to the prescription of an appropriate range of selected antimicrobials. Supervision, audit and support of diagnostic, prescribing and dispensing practices to promote appropriate use of antimicrobials is important (WHO, 2001).

6.6 Regulate use of antimicrobial food producing animals

On the farm, the use of antimicrobial should be improved and more extensively controlled. Europe has banned the use of growth promoters, but this is only a part of needed improvements in veterinary medicine, including promotion and implementation of prudent use of antimicrobial, quality of animal housing, biosecurity, and vaccinations global effort is essential. It is entirely likely the managing antibiotic usage should be a necessary a part any program to contain resistance, but there is still not a great deal of data to support the possible actions (Levy, 2003).

7. Conclusion And Recommendations

A wide spread availability and use of antimicrobial have severe negative implications on global health care: among these drugs resistance is the most important one. The primary economic implication of resistance on the diminishing efficiency of antibiotic treatment includes the need to rely on more expensive drugs that may be practically unaffordable for most primary health care problems. Besides, drugs resistance causes high mortality and morbidity in humans and animals. In other terms, it is an international pandemic that compromises the treatment of all infectious diseases. The reasons behind the establishment and spread of resistance are complex, mostly multi-factorial. Responsible actions taken to ensure appropriate use where necessary and disposal of antimicrobial, in concert with containment policies, will impact on animal and human health benefits. Such actions to be taken at the local, national and international levels imply considerable efforts on the human animal and the financial sides. Based on the above facts the following recommendations are forwarded:

- ✓ Restricted unlimited usage of antimicrobial drugs in agriculture that has impact on public health has paramount importance.
- ✓ The government and non-governmental organization should impose control over illegal usage and importation of drugs.
- ✓ It is far better to adopt appropriate diagnosis of antimicrobial resistance in animals so as to establish prudent use of antimicrobials.
- ✓ The risk for human health arising from the selection of antimicrobial-resistant pathogenic bacteria as a result of the sub- therapeutic use of antimicrobial in animal husbandry calls for careful scientific evaluation.
- ✓ Adopting appropriate surveillance of antimicrobial resistance is by far the best crucial as it is fundamental to undertaking trends in resistance, to developing treatment guidelines accurately and to assessing the effectiveness of intervention appropriately.
- ✓ Creating awareness on the public health hazard and economic impact of antimicrobial resistance in animals is decisive.

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