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Review on antimicrobial agent and antimicrobial resistance

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Abstract
The introduction of antimicrobial agents was a breakthrough health intervention that helped save millions of lives around the world and that provided a sense of control on the part of clinicians over host–pathogen interactions. Yet despite the concrete advances in prevention and treatment of infectious diseases, there has been a parallel surge in resistance to antimicrobials that is seriously compromising the gains made over the past century. Acknowledging the underlying mechanisms such as inappropriate use of antibiotics in humans and the agricultural applications of antibiotics for growth promotion and prophylaxis is a first and essential step to contain global antimicrobial resistance. However, it is also critical to consider in parallel the broad social, economic and political drivers and ethical significance of antimicrobial promotion in developing countries. Moreover, these socio-ethical factors constitute tangible targets against which public policy interventions can be developed to remedy growing concerns over the spread of antimicrobial resistance.

Keywords: antimicrobial agent, pathogen, public

1. Introduction
Antimicrobials are used to treat infections by different disease-causing microorganisms, including bacteria, viruses, parasites and fungi. In the vast majority of cases where antimicrobials are used, the microorganisms have found a way to evade or resist the antimicrobial agent. Resistance occurs wherever antimicrobials are used in the community, on the farm, and in healthcare. The introduction of penicillin, in the early 1940s, was perceived as marking the end of infectious diseases [3]. However, the emergence of resistant strains was reported just a few years after its use. Since then, resistant clones to various classes of antibiotics have been found to spread worldwide [76]. In some areas, more than 90% resistance has been reported to commonly used antibiotics such as penicillin, ampicillin, co-trimoxazole and gentamicin [82]. The overuse of antibiotics in human and animals has contributed to the emergence of resistant clones [13]. It is a fact that the availability of antimicrobials and their proper use have reduced morbidity and mortality due to infectious [2].
In developed countries, the use of antibiotics is strictly controlled, which is not the case in developing countries. The treatment of bacterial infections in developing countries like Africa is largely empirical and in most instances, there are no laboratory results to guide therapy. Moreover, there are no data on common bacterial isolates and their susceptibility patterns from larger surveillance studies aimed at developing tools for therapeutic guidance. Developing countries bear 95% of the global infectious diseases burden and rely on empirical antimicrobial treatment to counteract these diseases [52]. This has resulted in many infectious diseases, once easily curable, to become untreatable [108]. Methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and multi-resistant *Mycobacterium tuberculosis,* to name only a few of the many antimicrobial resistant microbes, pose serious ongoing challenges to biomedicine and public health. While substantial progress has been made in discerning the underlying biological, genetic and environmental causes of the emergence of antimicrobial resistance, there has been much less attention to important social factors such as socio-economic disparities and the impact of drug development and delivery strategies (in both developed and developing countries). The inappropriate use of antibiotics and the underlying mechanisms of antimicrobial resistance have broad social and ethical significance that transcends individual patients or specific communities who suffer from treatment failures [86].

Hence, the main objective of this seminar paper is to provide an insight on the general implication of drug resistance bacteria in developing countries related to the prevention of animal diseases.

2. Historical development of antimicrobial agent and antimicrobial resistance

Antimicrobial resistance is defined as a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics, leading to survival despite exposure to antimicrobials [61]. The modern era of antibiotics started with the discovery of penicillin by Sir Alexander Fleming in 1928 [101]; [90]. Since then, antibiotics have transformed modern medicine and saved millions of lives [48]. Penicillin was successful in controlling bacterial infections among World War II soldiers [101]. However, shortly thereafter, penicillin resistance became a substantial clinical problem, so that, by the 1950s, many of the advances of the prior decade were threatened [103]. In response, new beta-lactam antibiotics were discovered, developed, and deployed, restoring confidence. However, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified during that same decade, in the United Kingdom in 1962 and in the United States in 1968 [101].

The development of a resistant microorganism and its subsequent transmission in the human or animal population is often a multi-factorial and multi-step process. One major factor in the increasing problem of resistance in human pathogens is the overuse and injudicious use of antimicrobials in the hospital and community environments. There is also concern that antimicrobial use in food animals can lead to the selection of antimicrobial resistant zoonotic enteric pathogens which may then be transferred to people by the consumption of contaminated food or by direct animal contact. Though instances of resistance transfer, either direct or indirect, from animals to humans have been described, [110] the true magnitude of the medical impact from antimicrobial resistant bacteria originating from food animals or companion animals (pets and horses), is mostly unknown. Another concern is resistant bacteria excreted in the feces of animals who have received antimicrobials, which contributes to the reservoir of resistant bacteria in the environment [66]. Antimicrobials are used in plant agriculture and in aquaculture to destroy and prevent fungal and bacterial pests. This use may also contribute to the environmental reservoir of resistant microbes. In addition, the contribution of companion animals, i.e., pets and horses, to resistance in humans is unknown [85].

There are many other factors which contribute to the rising incidence of resistance in human pathogens. These factors include liberal availability of antimicrobials in some countries and societal factors such as the increasing number of immune-compromised individuals, unnecessary antimicrobial use caused by patient demands for antimicrobial treatment of viral infections, the changing population age structure, and an increase in institutional care environments such as day care centers, nursing homes and hospitals. In these environments large numbers of susceptible persons in close contact, and with high incidence of antibiotic use, promote transmission of resistant microbes and factors. Similarly in animal agriculture, the current trend in developed countries toward more concentrated livestock production, with fewer farms and more animals per farm, places large numbers of susceptible animals in close physical contact. In addition, increasing international travel and trade allows resistant organisms to quickly disseminate globally [71].

2.2 Drug Resistant Organisms

2.2.1 Drug Résistance Bacteria

Staphylococcus aureus (informally known as "Staph aureus" or a "Staph infection") is one of the major resistant pathogens. Found on the mucous membranes and the human and animals skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was one of the earlier bacteria in which penicillin resistance was found in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin due to significant kidney toxicity. Methicillin-resistant Staphylococcus aureus (MRSA) was first detected in Britain in 1961, and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of sepsis in the UK in 1999, up from 4% in 1991. Half of all *S. aureus* infections in the U.S. are resistant to penicillin, methicillin, tetracycline and erythromycin [21].

Streptococcus pyogenes (Group A Streptococcus: GAS) infections can usually be treated with many different antibiotics. Early treatment may reduce the risk of death from invasive group A streptococcal disease. However, even the best medical care does not prevent death in every case. For those with very severe illness, supportive care in an intensive-care unit may be needed. For persons with necrotizing fasciitis, surgery often is needed to remove damaged tissue. Strains of *S. pyogenes* resistant to macrolide antibiotics have emerged; however, all strains remain uniformly susceptible to penicillin [6].

Resistance of Streptococcus pneumoniae to penicillin and other beta-lactams is increasing worldwide. S. pneumoniae is responsible for pneumonia, bacteremia, otitis media, meningitis, sinusitis, peritonitis and arthritis [6].

Pseudomonas aeruginosa is a highly prevalent opportunistic pathogen. One of the most worrisome characteristics of *P. aeruginosa* is its low antibiotic susceptibility, which is attributable to a concerted action of multidrug efflux pumps with chromosomally encoded antibiotic resistance genes (e.g., mexAB-oprM, mexXY) and the low permeability of the bacterial cellular envelopes (Poole,2004.) Clostridium difficile is a nosocomial pathogen that causes diarrheal disease in hospitals worldwide [43]; [78] *C. difficile* colitis is most strongly associated with fluoroquinolones, cephalosporins, carbapenems, and clindamycin [15]; [44]. Some research suggests the overuse of antibiotics in the raising of livestock is contributing to outbreaks of bacterial infections such as *C. difficile* [88].

Antibiotics, especially those with a broad activity spectrum (such as clindamycin) disrupt normal intestinal flora. This can lead to an overgrowth of *C. difficile*, which flourishes under these conditions. Pseudomembranous colitis can follow, creating generalized inflammation of the colon and the development of "pseudomembrane", a viscous collection of inflammatory cells, fibrin, and necrotic cells [99].

Infection with Escherichia coli and Salmonella can result from the consumption of contaminated food and water. Both of these bacteria are well known for causing nosocomial (hospital-linked) infections, and often, these strains found in hospitals are antibiotic resistant due to adaptations to wide spread antibiotic use [33].

Klebsiella pneumonia carbapenemase (KPC)-producing bacteria are a group of emerging highly drug-resistant Gram-negative bacilli causing infections associated with significant

morbidity and mortality whose incidence is rapidly increasing in a variety of clinical settings around the world. *Klebsiella pneumoniae* includes numerous mechanisms for antibiotic resistance, many of which are located on highly mobile genetic elements [58]. Carbapenem antibiotics are generally not effective against KPC-producing organisms [10].

Tuberculosis is increasing across the globe, especially in developing countries, over the past few years. TB resistant to antibiotics is called MDR TB (Multidrug Resistant TB). Globally, MDR TB causes 150,000 deaths annually. The rise of the HIV/AIDS epidemic has contributed to this [72].

TB was considered one of the most prevalent diseases, and did not have a cure until the discovery of Streptomycin by Selman Waksman in 1943 [55]. However, the bacteria soon developed resistance. Since then, drugs such as isoniazid and rifampin have been used. M. tuberculosis develops resistance to drugs by spontaneous mutations in its genomes. Resistance to one drug is common, and this is why treatment is usually done with more than one drug. Extensively Drug-Resistant TB (XDR TB) is TB that is also resistant to the second line of drugs [46].

Neisseria gonorrhoeae is a sexually transmitted pathogen that can cause pelvic pain, pain on urination, penile and vaginal discharge, as well as systemic symptoms. The bacteria was first identified in 1879. In the 1940s effective treatment with penicillin became available, but by the 1970s resistant strains predominated [70].

The extensive antimicrobial use has been precipitated by the high prevalence of infectious diseases in certain developing countries. It is interesting to note that many antimicrobials (e.g. penicillin) have become victims of their initial success (i.e. efficacy) they were widely overused and not always with a sound rational indication of their prescription. It is now estimated that 50% of antimicrobial prescriptions are associated with inappropriate use, either because of unnecessary length of treatment, wrong choice of prescription or dosage regimen, or use in persons without a discernible sign of infection [11]. The different types of drug resistance mechanisms used by various bacterial species are mentioned as follows:

2.3.1 Mutational alteration of the target protein

Man-made compounds, such as fluoroquinolones, are unlikely to become inactivated by the enzymatic mechanisms described below. However, bacteria can still become resistant through mutations that make the target protein less susceptible to the agent. Fluorquinolone resistance is mainly (but not exclusively) due to mutations in the target enzymes, DNA topoisomerases [56].

Another example of resistance attributable to target modification is that conferred by the erm gene, which is usually plasmid coded and produces the methylation of adenine at position 2058 of the 50S rRNA, causing resistance to macrolides (erythromycin and many others), lincosamide, and streptogramin of group B, the MLS phenotype [111]. Sulfa drugs (synthetic competitors of p-aminobenzoic acids that inhibit dihydropteroate synthetase and trimethoprim, a synthetic inhibitor of dihydrofolate reductase) have been used in combination. They select for drug-resistant mutants of the respective enzymes. In this case, the high-level production of drug-resistant target enzymes from plasmids can make the bacteria resistant, and the resistant genes have spread widely on plasmids [59].

2.3.2 Enzymatic Inactivation of the drug

This is a common resistance mechanism for antibiotics of natural origin, such as aminoglycosides (kanamycin, tobramycin, and amikacin), which are inactivated by enzymatic phosphorylation by aminoglycoside phosphoryl transferase (APH), acetylation by aminoglycoside acetyltransferase (AAC), or adenylation (by aminoglycoside adenyltransferase or nucleotidyltransferase), and β-lactams (penicillins, cephalosporins, and carbapenems such as imipenem), which are inactivated by enzymatic hydrolysis by β-lactamases, usually in the periplasm. Genes coding for these inactivating enzymes can easily produce resistance as additional genetic components on plasmids [56].

2.3.3 Acquisition of genes for less susceptible target proteins from other species

Sequencing of the genes coding for the targets of penicillin, DD-transpeptidase or penicillin-binding proteins (PBPs), revealed that penicillin resistance among Streptococcus pneumoniae was due to the production of mosaic proteins, parts of which came from other organisms. We note that *S. pneumoniae* is an organism capable of natural transformation and may import foreign DNA. Interestingly, a similar mechanism of penicillin resistance was also found in another organism capable of natural transformation [114].

An extreme case of this scenario is the generation of MRSA. MRSA strains contain a new methicillin-resistant PBP, called PBP-2A or 2′, whose expression is often induced by methicillin and other β-lactams. The gene for this new PBP is located in a large (30–60-kb) segment of DNA, which apparently came from an organism other than *S. aureus* [35] and also contains other antibiotic resistance genes. *S. aureus* is not naturally transformable, and it is unclear how this horizontal transfer of a large DNA segment occurred [64].

2.3.4 Bypassing of the target

Vancomycin, a fermentation product from streptomycetes, has an unusual mode of action. Instead of inhibiting an enzyme, it binds to a substrate, the lipid-linked disaccharide-pentapeptide, a precursor of cell wall peptidoglycan. Because of this mechanism, many assumed that it would be impossible to generate resistance against vancomycin. However, vancomycin resistance is now prevalent among enterococci, normal inhabitants of our intestinal tract. Because enterococci are naturally resistant to β-lactams, aminoglycosides, macrolides, and tetracycline, these vancomycin-resistant strains of enterococci become prevalent in a hospital environment, colonize the patients, and cause infections that are difficult to treat. Study of the resistance mechanism showed that the end of the pentapeptide, d-Ala-d-Ala, where vancomycin binds, was replaced in the resistant strain by an ester structure, d-Ala-d-lactic acid, which is not bound by vancomycin. Production of this altered structure requires the participation of several imported genes [26].

2.3.5 Preventing drug access to targets

The multidrug efflux systems contribute significantly to the increased resistance to multiple antibiotics in bacteria. A major challenge in developing efficacious antibiotics against drug-resistant pathogens is to identify compounds that can counteract the efflux functions. The wealth of bacterial genomics information available suggests the presence of a variety of efflux systems in bacteria. Even a single bacterium may possess multiple efflux transporters of different families, with the overlapping substrate spectra. Accumulating

evidence has indicated that the MexXY multidrug efflux system is a primary determinant of aminoglycoside resistance in Pseudomonas aeruginosa [81].

As a summary the picture bellow shows the various mechanisms by bacteria develops resistance to the major antimicrobials.

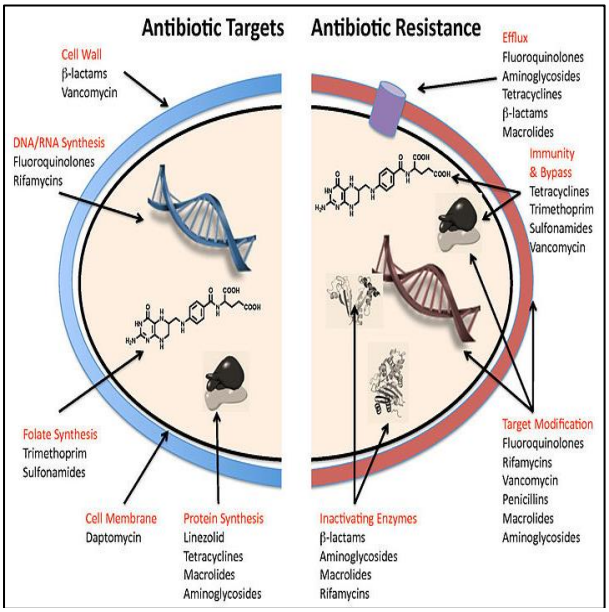

Fig 1: mechanisms of drug resistance development

3. Use of antibiotics in food animal industry and development of antimicrobial resistance

In commercial food animal production, large quantities of antimicrobials are used to treat and prevent diseases and to promote animal growth [94]. In the latter case, antimicrobials are added to feed or drinking water at subtherapeutic levels. The Union of Concerned Scientists (UCS) reported that 11,200 metric tons of antimicrobials were used annually in the swine, poultry, and cattle industries for nontherapeutic purposes alone [79].

Antibiotic Resistant Bacteria – A Continuous Challenge in the New Millennium 470 antibiotics produced annually are used in food-animal production at therapeutic and sub therapeutic (for prophylaxis and growth promotion) levels [14]; [106]. Antimicrobials of almost all classes have been used in animal production. Some classes are primarily used for disease treatment or prevention, such as quinolones, lincosamides, and aminoglycosides, while others are used for both growth promotion and disease treatment/prevention, such as penicillins, macrolides, polypeptides, streptogramins, and tetracyclines. A survey by the American Health Institute (AHI, 2001) showed that among the antimicrobials used also in human medicine, tetracyclines leads the usage with an assumption of 3,239 tons per year followed by a combination of macrolides, lincosamides, polypeptides, streptogramins, and cephalosporins with an annual usage of 1,937 tons [31]. Such usage of antimicrobials creates selective pressure for development of AMR. Most of the bacteria carried by individual animals are within the intestinal tract, reaching a density of 1011 bacteria/g fecal content. In mammalian animals, bacteria account for about 50% of the feces. Most of the intestinal bacteria are commensally bacteria belonging to several hundred species [9]. Because antimicrobials were fed to animals for extended periods of time (weeks or months), intestinal bacteria are under persistent selective pressure to develop resistance to the antimicrobials used. As a result, AMR develops primarily in the intestinal tract and feces become the single largest reservoir of AMR arising from food animal production [31]. It is although the majority of AMR present in animal manure is carried by commensal bacteria, the resistance genes can be transferred to bacteria pathogenic to animals and/or humans [22]; [112].

Figure 2 illustrates the dissemination of AMR to broad environments through vertical gene transfer (VGT) and horizontal gene transfer (HGT).

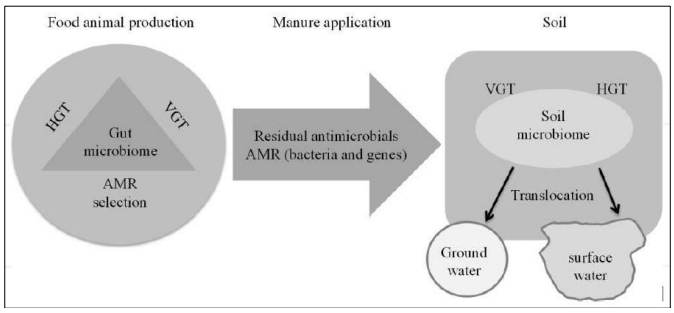

Fig 2: Conceptualized view showing the possible fates of antimicrobial resistance (AMR) and residual antimicrobials after land application of animal manure (modified based on [31]).

The severity of AMR is also reflected by the wide occurrence of AMR to many drugs important to both animals and humans. Resistance has been seen to almost all kinds of veterinary antibiotics, including aminoglycoside, sulfadiazine, ampicillin, erythromycin, chloramphenicol, streptomycin, sulphonamide and tetracycline [54]; [74]. Additionally, AMR is distributed in many bacterial species. For example, resistance to tetracycline has been found in 26 different bacterial genera and in 60 species from swine manure. Furthermore, with the wider use of antibiotics, multiple drug resistance often develops [37]; [73]. There has been a rapid emergence of multiple drug resistance concomitant with widespread use of antimicrobials in both human medicine and animal husbandry in the past 10 to 15 years [53]; [57].

4. Status of drug resistance pathogen in developing countries

In developing countries the self-medication of antimicrobials is a common practice, since these medications can often be purchased without a prescription and their sales are poorly regulated by local governments [41]. In the face of these realities, drug promotion activities could lead to a greater coercive influence on consumers, whether they be healthy persons taking antibiotics for unjustified (e.g. fear of disease) reasons or patients with infectious diseases. Taken together, we suggest that the adverse downstream consequences of aggressive drug promotion can be more deleterious in a developing world context. This also means that the ethical standards and stringency by which drug promotion practices are evaluated need to be different (i.e. higher ethical standards and lower ethical thresholds) in the case of developing world populations that are vulnerable in terms of both economic access to antimicrobials and access to information and educational resources to objectively interpret the drug promotion material provided by drug manufacturers [36].

5. The growing challenges of antibacterial drug resistance in Ethiopia

Similar to other developing countries, infectious diseases are a major cause of morbidity and mortality in Ethiopia. The Department of Disease Prevention and Control of the

Ethiopian Federal Ministry of Health reports that the common diseases caused by bacteria include diarrhoeal diseases, TB, sexually transmitted infections and meningococcal meningitis [47].

Mycobacterium tuberculosis: In Ethiopia, there have been reports on drug resistance in M. tuberculosis, mainly from the capital city Addis Ababa. An earlier study conducted in Addis Ababa in 1984 on anti-TB drug resistance among new TB patients showed a drug resistance rate of 15% for isoniazid (INH), 5% for streptomycin (SM) and 5% for both INH and SM. There was no rifampicin (RIF) resistance reported and hence no multidrug-resistant (MDR)-TB (resistant to at least INH and RIF) [65].

Methicillin-resistant Staphylococcus aureus (MRSA) study from south-western Ethiopia showed that 8.3% of *S. aureus* and 10.3% of coagulase-negative staphylococci were methicillin-resistant. Of the S. aureus isolates, 90.3% and 91.7% were resistant to penicillin and ampicillin, respectively [42]. The resistance rates of S. aureus and Staphylococcus saprophyticus to ampicillin were 89.0% and 92.3%, respectively. The same group of bacterial isolates showed resistance to trimethoprim/ sulfamethoxazole (SXT) at rates of 82.3% and 89.0%, whilst for tetracycline the rates were 85.9% and 92.7%, respectively [49]. Overall multiple drug resistance was 93.1%, whilst 2.5% of the isolates were resistant to one antibiotic and 4.4% were sensitive to all antibiotics tested. In the last decade, the rate of MDR isolates from urinary tract infection patients increased from 68% to 93.1% in Amhara Region [105]; [19].

Gram-negative bacteria diarrhoeal diseases impose a heavy burden on developing countries, accounting for 1.5 billion cases of illness a year in children under-5. The burden of diarrhoeal disease is highest in deprived areas where there is poor sanitation, inadequate hygiene and unsafe drinking water. In certain developing countries, epidemics of diarrhoeal diseases such as cholera and dysentery affect both adults and children [4] study from eastern Ethiopia reported that isolates of Salmonella and Shigella were resistant to six commonly used antibiotics (ampicillin, amoxicillin, tetracycline, gentamicin, chloramphenicol and norfloxacin). In total, 28 Salmonella (11.5%) and 17 Shigella (6.7%) were isolated from 244 stool samples. The resistance rate of Salmonella isolates was 100% to ampicillin and amoxicillin, 71.4% to tetracycline, 62.3% to chloramphenicol and 7.1% to norfloxacin. The resistance rate of Shigella isolates was 100% to ampicillin and amoxicillin, 70.6% to tetracycline, 29.4% to chloramphenicol and 5.9% to norfloxacin [5].

Salmonella clinical isolates were usually susceptible to most of the drugs tested in Addis Ababa three decades ago. However, >80% of the isolates displayed resistance to ampicillin, amoxicillin, chloramphenicol and SXT in the same area by the year 2011 [18]. Moreover, resistance Escherichia coli isolates derived from a wide variety of clinical materials are found to be resistant to many of the commonly used antibiotics such as ampicillin [45] and most studies showed that 74% of them are resistant to two or more antibiotics. Reports from different clinical samples showed that >80% of Klebsiella spp. isolates were resistant to SXT [7]. Therefore, increasing resistance to antibiotics will drastically limit treatment options. In reports from 2012, wound and blood culture from surgically operated patients and urine cultures from pregnant women and diabetics patients showed that all isolates were resistant to the antibiotics that are commonly used in the country ates as high as 100% for ampicillin and amoxicillin have been reported in other parts of Ethiopia [114].

6. The possible mitigating strategies

6.1. Appropriate antibiotic prescribing

Since the resistance to the first commercial antimicrobial agent (penicillin) was identified in 1948 [12], almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use [25]. As antibiotic-resistant pathogens are observed almost concurrently with the use of new antibiotics in hospital [66], one can easily suppose that wherever antibiotics are used, antibiotic resistance will inevitably follow. Unfortunately, although antibiotic resistance has increased, the development of novel antimicrobial agents has dramatically declined over the past 30 years. Therefore, to prevent the return of the pre-antibiotic era, one must use existing antibiotics more judiciously [104].

6.2. Antimicrobial stewardship programs

Many institutions conduct Antimicrobial Stewardship Programs (ASPs) to optimize antimicrobial therapy, reduce treatment-related cost and improve clinical outcomes and safety, and reduce or stabilize antimicrobial resistance [87]. The formal guidelines for ASPs were developed in 2007 by the Infection Diseases Society of America (IDSA) and the Society of Healthcare Epidemiology of America (SHEA) [36]. Typically, ASPs are executed by multidisciplinary antimicrobial utilization teams comprising physicians, pharmacists, microbiologists, epidemiologists and infectious disease specialists, with adequate experience in their respective fields. Many studies demonstrated that ASPs have the potential to restrict the emergence and spread of resistance [38]. ASPs have demonstrated a link between antimicrobial use and the emergence of resistance. The following are some examples in this regard: fluoroquinolone use and MRSA [75]; vancomycin use and vancomycin-resistant enterococci [50]; cephalosporin use and cephalosporin-resistant Enterobacteriaceae [23]; and carbapenem use and carbapenem-resistant Acinetobacter, Pseudomonas, and Enterobacteriaceae [97], [98].

6.3. Education

Space their everyday treatment decisions [26]. It is noteworthy that almost any clinician can prescribe antibiotics without any regulation or certification, whereas only specialists in oncology can prescribe and administer anti-cancer drugs [87]. To optimize antimicrobial prescribing, the prescribers should have appropriate knowledge of general medicine, microbial virulence, immunological and genetic host factors, PK and PD properties of drugs, and basic knowledge of epidemiology [1]. Prescribers of antibiotics such as physicians and pharmacists encounter dual, somewhat contradictory responsibilities. On the one hand, they want to provide optimal therapy for their patients and this responsibility tends to promote an overuse of antibiotics. On the other hand, they have a responsibility to future patients and to public health in sustaining the efficiency of antibiotics and minimizing antibiotic resistance, but this responsibility is sometimes ignored. There have been reports that about 50% of the antibiotic prescriptions, both in the community and in hospitals, can be considered inappropriate (inadequate dosing and wrong duration) [36]. As most of the antimicrobial agents are used in primary care [51], education on antibiotic prescribing in primary care is important [113].

6.4. Hygiene and disinfection

MDR pathogens often cause hospital-acquired infections, which require more expensive antibiotics and further hospitalization. Although the main source of MDR pathogens

is thought to be the endogenous flora of patients, healthcare workers are also considered an important source [27]; [102]. Therefore, appropriate hospital disinfection and personal hygiene of healthcare workers are required to prevent hospital-acquired infections. The Centers of Disease Control and Prevention (CDC) and the SHEA offered guidelines for preventing nosocomial transmission of MDR bacteria in hospitals [84]. Transmission of healthcare-associated pathogens through the hands of healthcare workers is particularly the most common cause for spreading [100]. Contamination of the hands of healthcare workers could result either directly from contact with patients or indirectly from touching contaminated environmental surfaces [109]; [63]. Several studies have demonstrated that an increase in hand washing compliance significantly decreases nosocomial infections by MRSA in intensive care units (ICUs) [89]. The World Health Organization (WHO) and the CDC presented hand hygiene guidelines in healthcare [91].

7. Control of drug resistance in animals

To prevent the emergence and transfer of antibiotic resistance in food animals, new methods to manage infectious diseases in animal husbandry are required. For example, optimal use of existing vaccines can be a viable alternative. Improving hygiene [20], using enzymes, probiotics, prebiotics, and acids to improve health [24]; [28] and utilizing bacteriocins, antimicrobial peptides, and bacteriophages as substitutes for antibiotics might be good methods to promote growth in food animals and decrease infectious diseases in them [11]; [62]. Further, it is worthwhile to formulate internationally acceptable standard protocols about the use of antibiotics in animal husbandry and about surveillance programs to monitor global emergence of MDR bacteria [94].

8. Conclusion and Recommendation

Infectious diseases are an important contributor to the mortality and morbidity rates in developing countries. The development and promotion of antimicrobial drugs can thus be perceived as an essential tool in the fight against epidemics. Unfortunately, history has shown that shortly after the introduction of new antimicrobials, there is an emergence of resistance in pathogens, worsening the occurrence of infectious diseases through the spread of resistant pathogen strains in the population. This resistant pathogen phenomenon complicates enormously the task of national and international public health organizations. Physicians may thus reasonably feel unequipped when facing infectious disease occurrence and resistance. In developing countries, the sparse resources available for and allocated to continuous education for health-care professionals necessarily limit the capacity of these professionals to critically judge pharmaceutical drug promotion material.

- The problems occurred as a result of drug resistant bacteria have an ultimate negative impact in both intensive and smallholder animal production in most of the developing countries, so great consideration during drug prescription, administration and follow-up should have to taken.

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