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An Overview on the Rise of Antimicrobial Resistance and Its Potential Threat in the Control of Diseases in Developing Countries

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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. 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. 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 immunosuppressed 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 animals, frequent and overdose use of antibiotics as a growth promoters is the dominant cause of antimicrobial resistance. The impact of drug resistance has been causing a severe effect in the control and prevention of diseases in both human beings and livestock. 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: Antibiotics, Antimicrobial resistance, Developing countries, Human, Livestock

1. INTRODUCTION

Antimicrobials are used to treat infections that can be caused by different microorganisms, including bacteria, viruses, parasites and fungi. In the vast majority of cases where antimicrobials are used, the microorganisms find a way to evade or resist the antimicrobial agent. Resistance occurs wherever antimicrobials are used in the community, on a farm, and in healthcare centers. The introduction of penicillin, in the early 1940s, was perceived as marking the end of infectious diseases (Abraham and Chain, 1940). However, the emergences of resistant strains were reported just a few years after its use. Since then, resistant clones to various classes of antibiotics have been found to spread worldwide (Manges *et al*., 2001). In some areas, more than 90% resistance has been reported to commonly used antibiotics such as penicillin, ampicillin, co-trimoxazole and gentamicin (Mshana *et al.,* 2009).

The overuse of antibiotics in human and animals has contributed to the emergence of resistant clones (Aarestrup and Wegener, 1999; Barton and Wilkins, 2001). It is a fact that the availability of antimicrobials and their proper use have reduced morbidity and mortality due to infectious disease. 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 (Hart and Kariuk, 1998). This has resulted in many infectious diseases, once easily curable, to become untreatable (Vlieghe, 2008; WHO, 2011).

Methicillin resistant *S. aureus*, Penicillin resistant *Streptococcus pneumoniae* and multi-resistant *Mycobacterium tuberculosis are among the* few antimicrobial-resistant microbes that 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 antimicrobial 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 (oliver *et al.,* 2010).

Hence, the objective of this seminar paper is:

- To provide an insight on the general implication of drug resistant bacteria in developing countries related to control of infectious diseases.

2. DRUG RESISTANT MICROORGANISMS

2.1. Drug resistant 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 antimicrobial 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 antimicrobial 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 (Bozdogan *et al*., 2003).

Streptococcus pyogenes (Group A Streptococcus: GAS) infections can usually be treated with, many different antimicrobials. 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 antimicrobial have emerged; however, all strains remain uniformly susceptible to penicillin (Albrich *et al*., 2004). 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 (Albrich *et al*., 2004).

Pseudomonas aeruginosa is a highly prevalent opportunistic pathogen. One of the most worrisome characteristics of *P. aeruginosa* is its low antimicrobial susceptibility, which is attributable to a concerted action of multidrug efflux pumps with chromosomally encoded antimicrobial resistance genes and the low permeability of the bacterial cellular envelopes (Poole, 2004). *Clostridium difficile* is a nosocomial pathogen that causes diarrheal disease in hospitals worldwide (Gerding *et al*., 1995; McDonald, 2005). *C. difficile* colitis is most strongly associated with Fluoroquinolones, Cephalosporins, Carbapenems, and Clindamycin (Gifford and Kirkland, 2006; Baxter *et al*., 2008).

Some research suggests the overuse of antimicrobial in the raising of livestock is contributing to outbreaks of bacterial infections such as *C. difficile*. Antimicrobials, 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 "pseudo membrane", a viscous collection of inflammatory cells, fibrin, and necrotic cells. 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 (Davies and Davies, 2010).

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 antimicrobial resistance, many of which are located on highly mobile genetic elements (Hudson *et al*., 2014). Carbapenem antimicrobials are generally not effective against KPC-producing organisms (Arnold *et al.,* 2011).

Tuberculosis is increasing across the globe, especially in developing countries, over the past few years. TB resistant to antibiotics is called Multidrug Resistant TB (MDR TB). Globally, MDR TB causes 150,000 deaths annually (Edward *et al*., 2013). The rise of the HIV/AIDS epidemic has contributed to this (LoBue, 2009).

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 (Herzog, 1998). 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 (LoBue, 2009; Gao *et al*., 2010).

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 were first identified in 1879 (Ligon and Lee, 2005). In the 1940s effective treatment with Penicillin became available, but by the 1970s resistant

strains predominated.

2.2. Mechanisms of antimicrobial resistance

The emergence of resistance in microbes can be precipitated most obviously by overuse of antimicrobials. Inappropriate antimicrobial use can easily develop as a downstream consequence of excessive drug promotion activities invulnerable global populations who maybe devoid of in formation channels to make informed decisions on benefits and risks of antimicrobials .Hence, it is not surprising that the use and prescription of antimicrobials, which escalated significantly until the mid-1990s, was immediately followed by an increase in antimicrobial resistance worldwide (McCaig *et al*.,1998).

The different types of drug resistance mechanisms used by various bacterial species are mentioned as follows:

2.2.1. 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 (Hooper, 2000).

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 50_S rRNA, causing resistance to macrolides (Erythromycin and many others), Lincosamide, and Streptogramin (Weisblum, 1995). Sulfa drugs (synthetic competitors of p-aminobenzoic acids that inhibit dihydropteroatesynthetase and trimethoprim, a synthetic inhibitor of dihydrofolatereductase) 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 (Huovinen *et al*., 1995).

2.2.2 . 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 byaminoglycosidephosphoryltransferase (APH), acetylation by Aminoglycoside acetyltransferase (AAC), or adenylation (by aminoglycoside adenyltransferase or nucleotidyl transferase), 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 (Hooper, 2000).

2.2.3. 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. 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* 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 (Kuroda *et al*., 2001; De-Lencastre *et al*., 2007).

2.2.4. Bypassing of the target

VanA-type resistance, which is a high level of resistance to Vancomycin and Teicoplanin, is mediated by transposon Tn*1546*, which encodes proteins involved in transposition, regulation of resistance expression, synthesis of modified peptidoglycan precursors ending in d-alanine-d-lactate (d-Ala-d-Lac), and elimination of normal precursors ending in d-Ala-d-Ala (Arthur *et al*., 1996). Synthesis of pentadepsipeptide precursors is responsible for diminished binding affinity of glycopeptides for their target. In all the VRSA strains studied, Tn*1546* is plasmid borne (Périchon and Courvalin, 2009; Zhu *et al*., 2010), whether Tn*1546* was transposed from the incoming enterococcal plasmid into a resident plasmid or, in certain instances, the enterococcal plasmid was maintained in the *S. aureus* recipient (Zhu *et al*., 2008). Two strains, VRSA-7 and VRSA-9, are partially dependent on Vancomycin for growth (Meziane-Cherif, 2010). As observed for Vancomycin-dependent enterococci, these isolates possess an impaired chromosomal d-Ala:d-Ala ligase (Ddl), with mutations responsible for 1,000- and 200-fold decreases in enzyme activity, respectively. Growth of these strains is enhanced in the presence of Vancomycin or Teicoplanin in the culture medium, which allows induction of the *vanA* resistance pathway.

2.2.5. 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 multidrug efflux system is a primary determinant of aminoglycoside resistance in *Pseudomonas aeruginosa* (Morita *et al.,* 2012*).*

3. 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 (Gassman, 1999). 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 (WHO, 2011).

At the turn of the century, the World Health Organization estimated that infections accounted for 45% of deaths in Africa and South-East Asia and that these diseases were responsible for 48% of premature deaths worldwide. Bacteria cause a significant proportion of infections in Africa. Unfortunately, in a remarkably short time, resistance to antibiotics has undermined the idealistic hope that bacterial infection would cease to be an important cause of death and disease. Indeed, antibiotic resistance increasingly compromises the outcome of many infections that were, until recently, treatable and remain the most common diseases in Africa resistant tuberculosis (TB) infections are highly prevalent in some African countries (WHO,1998). High resistance rates can often be correlated to the absence of properly implemented control programs such as directly observed treatment, short-course schemes (Mwinga, 2001). In a survey conducted in an area of Cameroon that lacks a fully functional TB control program, multi-drug resistance TB was observed in 27.6% of the patients with a previous history of treatment (Kuaban *et al*., 2000).

TB is a pertinent case in point because it is highly prevalent in many African and other developing countries (Dye *et al*., 2002) but many other bacterial infections are severely compromised by resistance. These include diseases caused by to Gram-negative enteric rods, respiratory infections, bacterial meningitis, sexually transmitted diseases as well as hospital acquired infections. Due to the widespread distribution of Penicillinase-producing Neisseria gonorrhea, Penicillin or Ampicillin can no longer be employed in the empiric management of gonorrhea (Van Dyck *et al*., 2000; Bakare *et al.,* 2000). The prevalence of gonococcal resistance to affordable alternatives - such as Tetracyclines, Thiamphenicol and Spectinomycin - continues to rise and resistance to Fluoroquinolones has emerged (Van Dyck *et al*., 2000).

4. 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 diarrheal diseases, TB, sexually transmitted infections and meningococcal meningitis (Goredema *et al*., 2006).

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), 5% for Streptomycin (SM) and 5% for both Isoniazid and Streptomycin. There was no Rifampicin (RIF) resistance reported and hence no multidrug-resistant (MDR)-TB (resistant to at least isoniazid and RIF) (Lemma *et al*., 19 84).

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 (Gebre-Sealsssie, 2007). 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 (Hagos and Gedif, 2009). 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 (Tessema *at al*., 2007; Biadglegne and Abera, 2009).

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 (Acar and Ro stel, 2001). 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) (Reda *et al*., 2001). 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 (Reda *et al*., 2011).

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 (Beyene *et al*., 2011). 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 (Gizachew *et al*., 2013) 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 (Alemu *et al*., 2012; Yismaw *et al*., 2012). 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 (Reda *et al.,* 2011).

5. THE POSSIBLE MITIGATING STRATEGIES

5.1. Appropriate antibiotic prescribing

Since the resistance to the first commercial antimicrobial agent (penicillin) was identified in 1948 (Barber and Rozwadowska, 1948), almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use (Cantas *et al*., 2013). As antibiotic-resistant pathogens are observed almost concurrently with the use of new antibiotics in hospital (Levys, 1998), 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 (Spellberg *et al*., 2004). Therefore, to prevent the return of the pre-antibiotic era, one must use existing antibiotics more judiciously.

5.2. Antimicrobial stewardship programs

Many institutions conduct Antimicrobial Stewardship Programs (ASPs) to optimize antimicrobial therapy, reduce treatment-related cost, improve clinical outcomes and safety, and reduce or stabilize antimicrobial resistance (Owens, 2008). 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) (Dellit *et al*, 2007). 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 (Drew, 2009). 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 (Madaras *et al*., 2006); Vancomycin use and Vancomycin-resistant enterococci (Harbarth *et al*., 2002); Cephalosporin use and Cephalosporin-resistant Enterobacteriaceae (Calil, 2001); and Carbapenem use and Carbapenem-resistant Acinetobacter, Pseudomonas, and Enterobacteriaceae (Go *et al*., 1994; Rahal *et al.,* 2002).

5.3. Education

Much of the success of ASPs depends on educating the clinicians, especially on making their everyday treatment decisions (Canton and Bryan, 2012). 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 (Owens, 2008). 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. 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) (Dellit *et al*., 2007; Pulcini *et al*., 2007). As most of the antimicrobial agents are used in primary care (Harnden *et al*., 2007; Wise, 2004), education on antimicrobial prescribing in primary care

is important.

5.4. 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 (Caron and Mousa, 2010; Siegele *et al*., 2007). 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 (Muto *et al*., 2003; Siegel *et al*., 2007). Transmission of healthcare-associated pathogens through the hands of healthcare workers is particularly the most common cause for spreading (Sax *et al*., 2009). Contamination of the hands of healthcare workers could result either directly from contact with patients or indirectly from touching contaminated environmental surfaces (Weber *et al*., 2010; Kramer *et al*., 2006). Several studies have demonstrated that an increase in hand washing compliance significantly decreases nosocomial infections by MRSA in intensive care units (ICUs) (Peacock *et al*., 1980; Pittet *et al*., 2000). WHO and the CDC presented hand hygiene guidelines in health care (Pittet *et al*., 2009).

6. CONTROL OF DRUG RESISTANCE IN LIVESTOCK

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 (Potter *et al*., 2008). Improving hygiene (Boklund *et al.,* 2004), using enzymes, probiotics, prebiotics, and acids to improve health (Callaway *et al*., 2008; Castanon, 2007) 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 (Atterbury, 2000; Joerger, 2003). 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.

7. CONCLUSION AND RECOMMENDATIONS

The problems occurred as a result of drug résistance bacteria have an ultimate negative impact in human and smallholder animal production in most of the developing countries. Avoiding of using antibiotics as a growth promoting factors in livestock, atrict regulation on prescription of antimicrobials by health care providers and carrying out advanced researches to innovate novel antibacterial agents are recommended as means of alleviating problems related o antimicrobial reistance.

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