Antimicrobial Resistance: The Great Hurdle

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Abstract—This review study designed to investigate the main factors that contributed in the antimicrobial resistance. Antimicrobial resistance is an inevitable, undeniable and may not be a preventable phenomenon. It will continue to emerge and spread as a public health problem as long as we use and misuse antimicrobial agents. Factors implicated in antimicrobial resistance would not be easily enumerated. However, veterinary medicine, human hospitals, patients themselves and the community’s economical and cultural status are considered the major contributors in the antimicrobial resistance issue. Bacteria are remarkably adaptive and evolve and acquire new traits of antimicrobial resistance mechanisms through chromosomal mutations or from external sources through horizontal gene transfer due to its genome plasticity. However, mortalities and economical costs associated with antimicrobial resistant bacteria has no limitations and strategies made to hamper antibiotic resistance had no positive progress, and in some cases totally failed. Therefore, novel approaches to deal with antimicrobial resistance are highly required. The aim of this study was to illustrate the major factors that contributed in the antibiotics resistance and to investigate the cost attributed to antibiotic resistance. Furthermore the report aimed to demonstrate some conventional solutions that may obstacle antibiotic resistance.

Index terms: Antibiotic resistance; Veterinary medicine, Human hospitals, patients, Economic status, Cultural status

I. INTRODUCTION

When discovered, antimicrobials were considered as the miracle that let man get rid of his phobias from infectious diseases. But their popularity has rapidly led to overuse and, consequently, their effectiveness was gradually lost [1]. In the last five decades, there were excessive uses of antibiotics worldwide not only in humans' hospitals and communities for prevention and treatment of human infectious diseases, but also in the animal farms for many purposes such as prophylaxis, therapeutics and growth promotion [1].

The excessive and inappropriate use of antibiotics whether in human hospital or in animal farms in one way or another gave rise to the emergence of antibiotics resistant bacteria [2, 3]. In addition, many other factors played a significant role in the dissemination of antimicrobial resistance; all are considered as major driving forces for antimicrobial resistance. These factors include patient’s knowledge towards antimicrobials and socioeconomical and cultural status of the community. The more antibiotics are used, the more likelihood that bacteria develop a mechanisms to resist them [4]. Accordingly, most of the significant bacterial infections, if not all, are becoming resistant to at least one or two antibiotics due to the profligate use of the most common classes of antibiotics such as penicillin, tetracycline, macrolides, glycopeptides and fluoroquinolones [5]. When Antibiotic resistance occurs the consequences are so severe for people who have common infections that once were easily treatable with antibiotics. When antibiotics fail to work, the consequences are dire and may be reflected in long-lasting illnesses, more extended hospitalization, more expensive and toxic medications, greater opportunity for the spread of the infection to others, and finally, the risk of complications and death may increase. The aim of this review was an attempt to enumerate the major factors that implicated in antimicrobial resistance.

Multidrug resistance (MDR)

Hitherto, antimicrobial resistance is considered a medical crisis particularly the emergence of resistance to multiple antimicrobial agents in pathogenic bacteria. This leads to the emergence of
multi drug resistant bacteria (MDR). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [6, 7]. Many different definitions for multidrug-resistant (MDR) are being used in the medical literature to characterize the different patterns of resistance found in healthcare-associated antimicrobial resistant bacteria. For instance, extensively drug-resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and pandrug resistant (PDR) bacteria was defined as non-susceptibility to all agents in all antimicrobial categories [6, 7]. However, most commonly the emergence of MDR is clearly related to the quantity of antibiotics and the way they were used [8, 9]. MDR may also be related to acquisition of different antibiotics resistance traits or a single trait in the same DNA molecule, such as multi drugs efflux pumps, that extrudes many antibiotics and many promote export of numerous dyes, detergents, inhibitors, disinfectants and organic solvents [10, 11]. Presently MDR infections that are prevalent all over hospitals and communities are responsible for the observation that patients are succumbed to death due to the unreliable efficiency of available drugs. The infected patients may receive several, sometimes six to seven different drugs, for the treatment [12]. For example, a multidrug resistant Staphylococcus aureus (MRSA) strains that possess a new virulence toxin (Panton-Valentine leukocidin) have emerged in communities of industrialized countries [13, 14]. The so called ‘community-acquired MRSA’ is resistant to the β-lactam antibiotics, requiring physicians to commence alternative therapies when MRSA is suspected. Children were found to be succumbed to community acquired MRSA infection because the disease had become too far advanced by the time that another effective therapy was initiated [15]. Furthermore, it is noteworthy that M. tuberculosis, particularly in some endemic areas, bears resistance to as many as eight drugs, making some individuals with tuberculosis incurable [16, 17]. Generally, multidrug resistance occurred through the sequential use of multiple different kinds of antibiotics. The first antibiotic would select a single resistance gene, and eventually, bacteria resistant to the first antibiotic will continue to develop resistance to others as long as they were introduced into the environment. Thus MDR becomes like a snowball rolling downhill, becoming bigger and stronger and not losing what it had acquired before.

Animals’ Farms and the Emergence of Antibiotics Resistance

There are clear scientific evidences on the link between the use of antibiotics in food producing animals and the emergence and selection of antibiotics resistance in pathogenic bacteria that infect human [1]. Some antimicrobial drugs in the farms are given in ways that promote and initiate antibiotic resistance. For instance, when given in a sub-therapeutic doses, mass treatment and long-term administration as applied for antimicrobial growth promoters, or by using drugs added to food and water for prophylaxis [18]. In these manners intestinal commensal as well as pathogenic bacteria will become reservoirs for the resistance genes that may disseminate their resistance determinants to human pathogens through the food chain or through direct contact or via environmental routes. In Europe, there is a strong evidence that resistance to vancomycin by Enterococci (VRE) is developed in animals that were fed an antibiotic for growth promotion purposes called avoparcin, a vancomycin analogue [19]. The strains of VRE remains on the carcasses of animals after slaughter. VRE was then found on foods that were sold at the retail level [19]. Also In the former German Democratic Republic, nourseothricin replaced oxytetracycline in animal feed in 1983 and was used exclusively in animals. When the use was stopped in 1990, streptomycin resistance had spread from the faecal flora of nourseothricin fed pigs to Escherichia coli in the gut flora of the farm workers, their families and healthy community members [20]. In case of the foodborne pathogens, Salmonella and Campylobacter, the use of antimicrobial drugs in the animal food select for antimicrobial resistant bacteria that are then transmitted to human through the food chain. For instance, in case of nontyphoidal Salmonella serotypes, the bacteria have been transmitted to human in food chain or through direct contact with animals [3]. Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of Salmonella serotypes with reduced susceptiblity to fluoroquinolones in humans has become a cause for particular concern [3]. This phenomenon has been observed in countries such as
France, Germany, Ireland, the Netherlands, Russia Federation, Spain and the United Kingdom [3]. Further, in the United States, fluoroquinolone resistance was not described in the foodborne pathogens Campylobacter until it was licensed for veterinary use in 1995 [21]. It is noteworthy that, in Australia, fluoroquinolones are not approved for use in food production animals and as a consequence Australia appears to be one of the few, if not the only, country in the world where there is no a major problem with fluoroquinolone-resistant Salmonella and Campylobacter [22].

Antimicrobial resistance arising in food animals could involve not just overt pathogens but relatively nonpathogenic microbes such as Escherichia coli, Enterococci, or Bacteroides species [23]. These organisms could become reservoirs of antimicrobial resistance elements that can colonize humans via the food chain or environment. The resistance elements could be transferred to ordinary pathogens or to other commensal bacteria that sometimes cause human disease, such as Klebsiella and Enterobacter species. Because these commensal species are not associated with food animals, the sources of these resistances may be difficult to ascertain. Antibiotics also can reach the circuit of human life through the dusting of fruit trees for disease prophylaxis [24] and the application of antibiotic-laden animal manure on croplands [25, 26]. These varied applications are all added to the continued selection of resistant bacteria. As a consequence to the excessive and inappropriate use of antibiotics in animals' farms, a good environment for the emergence and dissemination of antibiotics resistance determinants among pathogenic and non-pathogenic bacteria can be created. Therefore, the result is the emergence of antibiotics resistant strains that were before responding to the current available antibiotics. These will consequently be transferred to humans through the food chain.

**Human’s Hospitals and the Emergence of Antibiotics Resistant Bacteria**

It does not make sense for us to focus heavily in the source of the antibiotic resistance in the animal farms. In fact, what is coming from human hospitals and the physicians' offices and clinics is greater than that of the farms. In fact, various forms of antimicrobial resistance are now pervading all communities and health care settings including the home care environment due to the inappropriate use of antibiotics [27]. There is a close link between the development of antibiotic resistance and the use of antibiotic agents in the hospital [28], and strategies to control resistance have until recently been limited, primarily to hospitals [29]. About 70% of hospital isolates of Staphylococcus aureus are now resistant to all beta-lactam antibiotics, which had been the first line of treatment [30, 31]. The major reason is that antibiotics are being inappropriately used in human hospitals, added to the inaccurate prescription of the suitable therapy. Because treatment is usually begins before the antimicrobial susceptibilities of the pathogen are known, the initial choice of antimicrobial agent is made empirically [32—34]. This leads to a poorer response, and can be considered as the first clue for initiation of antibiotic resistance. Moreover the use of sub-therapeutic doses creates a situation where highly resistant strains can be selected sequentially and this is a condition that prevails in many cases when antibiotics are used without proper prescription or in patient non-compliance.

Hospitals are a critical component of the antibiotic resistance problem worldwide. The combination of highly susceptible patients, intensive and prolonged antimicrobial use and cross-infection have resulted in nosocomial infections with highly resistant bacteria pathogens [35]. Moreover, failure to implement simple infection control practices such as hand washing and changing gloves before and after contact with patients is a common cause of infection spread in hospitals throughout the world [35]. Another fatal mistake contributing to the problem of the antibiotics resistance in the hospitals is the rapid shift to stronger, newer and broad spectrum antibiotics, aiming for quick elimination of the infection, instead of prescribing narrow spectrum antibiotics. In addition to their broad-spectrum activity, quinolones, amoxicillin–clavulanate, and second- and third-generation cephalosporins are widely used for empirical treatment of severe or complicated infections. Sometimes they are directed for the treatment of otherwise resistant organisms [36—40]. Broad-spectrum antibiotics are also being extensively used for conditions that often require no antibiotic treatment at all such as diseases with predominantly viral causes such as common cold, unspecified upper respiratory tract infections, and acute bronchitis [41].
This rapid shift may select for antimicrobial resistant strains that were once susceptible to narrow spectrum antibiotics. Moreover, clinical misuse of antibiotics may be more common among private practitioners than among public health personnel [42]. Private practitioners charge higher fees and the demand for antibiotics seen in private patients is higher, and more drugs are available in private clinics than in public hospitals [43, 44].

**Contribution of Patients in Antibiotic Resistance**

Among patients themselves, there is a lack of knowledge about differential diagnosis of infectious diseases and antimicrobial therapy [45]. Sometimes patients in the industrialized country pressure their doctors and demand antibiotics for only that they are not feeling well or are slightly pyretic [46]. In addition some patients with bacterial infections cannot afford to complete a full regimen of antibiotics and discontinue the therapy after the symptoms are alleviated but before the treatment is completed. Sometimes patients may share the medicines of the other patients due to symptoms similarity between the diseases. They may also exaggerate their symptoms in order to have an antibiotics prescription. Some of them may save a part of the antibiotic course for future use [47]. In some countries, antibiotics are available over-the-counter and it can be purchased directly from the pharmacy as commodities without doctor’s consultation [48, 49]. These kinds of self-medication with antimicrobial agents have been found to be inadequately dosed [50] or may not contain adequate amounts of active ingredients, especially if they are counterfeited drugs [45]. For example Okey et al (2007) stated that, for self medication in one report, a total of 4,128 patients visited the pharmacies for antibiotic agents within three months period of data collection [51]. Out of this number, 1,742 (42.2%) came with a prescription from qualified medical personnel and 2,386 (57.8%) came without prescription [51]. Moreover many developing countries allow the dispensation of antibiotics without a prescription; this can lead to self-medication and dispensation of drugs by untrained people [52]. For instance, in a survey from the Rajbari district of Bangladesh, 100,000 doses of antibiotics had been dispensed without a prescription in one month [53]. In another study, 92% of medications dispensed by pharmacies were dispensed without a prescription [54]. Also, a survey of drugstores showed that 66% of antibiotic purchases were made without a prescription [55]. This provides the worst scenario for emergence of antibiotics resistance [56]. With the morbidity and mortality associated with resistant bacteria, particularly *Streptococcus pneumonia*, physicians need to educate patients not only on preventative measures (such as immunoprophylaxis), but also on avoidance of antibiotic misuse unless there is strong evidence for bacterial infection [57].

**Socio-economic and Socio-cultural Factors Contribution to Antimicrobial Resistance**

The possible influences of socio-economic and socio-cultural factors upon the development and spread of antibiotic resistance and determinants have been addressed [58]. In general, the lack of resources and bad cultural behaviors hampered the implementation of most strategies against spread and distribution of antibiotic resistance. In many developing countries poverty is considered as the major driving force for selection of antimicrobial resistance [59]. The patients in these countries may suffer poverty and lack money which renders them unable to seek physician consultation. They directed themselves to self medication and buy the least expensive medication under the assumption that they were all bioequivalent [59]. Further, such patients may truncate the course of therapy because of their inability to pay for the full course of medication [42, 55, 59]. Such inappropriate use of antibiotics for inadequate periods of time can exert strong selective pressures on bacterial populations and can contribute to antibiotic resistance [52].
### Table 1: Some common antibiotics resistant bacteria

<table>
<thead>
<tr>
<th>Bacterium/species</th>
<th>Disease</th>
<th>Resisted antibiotics</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Bacteraemia, Pneumonia, Wounds infections, Toxic shock syndrome</td>
<td>Chloramphenicol, Rifampin, Methicillin, Ciprofloxacin, Clindamycin, Erythromycin, Beta-lactams, Tetracycline, Trimethoprim.</td>
<td>[32, 76, 100, 128]</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Meningitis, Pneumonia, Otitis media</td>
<td>Aminoglycosides, Penicillin, Chloramphenicol, Erythromycin, Trimethoprim- Sulfamethoxazole.</td>
<td>[95, 128]</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Tuberculosis</td>
<td>Aminoglycosides, Ethambutol, Rifampin Isoniazid, Pyrazinamide.</td>
<td>[16, 69, 128]</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
<td>Epiglottitis, Meningitis, Otitis media, Sinusitis</td>
<td>Beta-lactams, Chloramphenicol, Tetracycline, Trimethoprim.</td>
<td>[128]</td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
<td>Pneumonia, Blood infections, Urinary tract infection, Surgical wound infections, Diarrhea.</td>
<td>Aminoglycosides, Beta-lactams, Chloramphenicol, Trimethoprim, Cephalosporins and carbapenems</td>
<td>[107, 108, 128, 129, 130]</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Bacteremia, Urinary tract infection, Surgical wound infections</td>
<td>Aminoglycosides, Beta-lactams, Erythromycin, Vancomycin</td>
<td>[76, 128]</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Gonorrhea</td>
<td>Beta-lactams, Penicillin, Spectinomycin, Tetracycline</td>
<td>[128, 139]</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Blood infection, Pneumonia, Urinary tract infections</td>
<td>Aminoglycosides, Polymixins, Quinolones, Carbapenems</td>
<td>[131, 130]</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>Pneumonia, Urinary tract infection</td>
<td>Carbapenems</td>
<td>[132, 138]</td>
</tr>
<tr>
<td><em>Campylobacter spp</em></td>
<td>Gastroentritis, Diarrhea</td>
<td>Fluoroquinolones, Macrolides</td>
<td>[99, 133, 134, 140]</td>
</tr>
<tr>
<td><em>Salmonella enterica</em></td>
<td>Enteric fever, Diarrhea</td>
<td>Ampicillin, Chloramphenicol, Co-trimoxazole, Ofloxacin, Ciprofloxacin (trimethoprim-sulfamethoxazole),</td>
<td>[75, 135, 136, 137]</td>
</tr>
</tbody>
</table>
On the other hand, socio-cultural behaviors have its clear impact on the emergence of antibiotics resistance and its genes. For example the unorthodox female college students are increasingly using the over-counter medicines during their menstrual period to prevent the perceived risk of infection and to treat the menstrual symptoms such as cramps and bloating [60]. The choice of antimicrobials varies between ampicillin, ampicillin-cloxacillin combinations, metronidazole or tetracycline, depending on socioeconomic ranking and other physiological conditions such as menstrual flow rate, color and general appearance of flow and onset of cramps [60]. Here, the prescription of the antimicrobial drugs by the untrained personnel may contribute greatly into the selection process of resistant bacteria.

**Economical Cost of Antibiotics Resistance**

Resistance to antimicrobial drugs is an important health concern, as well as economic problem [61]. The economic cost associated with antibiotic resistant is attributed to the long period of treatment, long lasting stay in hospital and consequently absenteeism from work. This is in addition to the obvious fact that, drugs used for treatment are expensive, particularly when multiple courses of antibiotics are required. Further, an increased rate of mortality is expected as compared to that associated with antibiotic susceptible bacteria [62]. Several studies have investigated the difference in mortality between patients with infection caused by methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin susceptible *Staphylococcus aureus* (MSSA) [63—65]. For instance, it was estimated that the death rates for MRSA were 21% against 8% for MSSA, and the economic cost increased to 22% as associated with MRSA [63]. The national costs of antimicrobial resistance for the United States have been estimated $30 billion for the resistant MRSA compared to $100 million for susceptible MRSA annually [64]. In 1992 the Office of Technology Assessment of Congress has estimated the minimal hospital cost associated with nosocomial infections caused by antibiotic-resistant bacteria to be $1.3 billion per year [65]. In a study by Einarsson et al (1998), the treatment of pneumonia caused by penicillin non susceptible *Streptococcus pneumoniae*, costed more than the treatment of pneumonia caused by susceptible strains [66]. Despite that the disease is milder; the reported higher costs was due to the longer hospital stay (26.8 vs 11.5 days) and the medicines expenses ($736 vs $213) [66]. Furthermore, in a study in patients undergoing surgery, the cost of infections due to resistant Gram negative bacilli was compared to infections due to nonresistant strains [67]. In this study a difference in the median hospital cost was estimated as $51,000 and the difference in the median cost for antibiotics was more than $1,800 per case [67]. Moreover, one report stated that tuberculosis has doubled the cost of standard treatment from $13,000 to $30,000 [68]. Rajbhandary et al (2004) stated that treatment of multidrug resistant tuberculosis (MDR-TB) which is considered as a serious public-health threat in the U.S. has increased from $12,000 for a non-MDR-TB patient as compared to $180,000 in multidrug-resistant strain [69].

**Why Should we Pay Attention to Antimicrobial Resistance?**

Now almost about two third a century from the greatest discovery of the magic bullets (antibiotics), the bacteria is persistently developing new mechanisms and strategies to combat the effectiveness of antimicrobials and adapting to new environments [97]. Resistant bacterial strains have emerged and distributed all over the hospitals and health care units worldwide because of genetic plasticity of the microorganisms, heavy selective pressures of antimicrobial use and the mobility of the world population [97]. We have now reached an unacceptable situation and the warning of antimicrobial resistance should not be ignored. Some hospital strains of invasive Gram-negative enteric bacteria and *Enterococci* are not susceptible to any available drug. Resistant bacteria, particularly *Staphylococci, Enterococci, Klebsiella pneumoniae, and Pseudomonas spp* are becoming a common inhabitant in healthcare institutions [70—73]. Multiple drug-resistant tubercle bacilli have appeared and spread rapidly in patients with the acquired immunodeficiency syndrome (AIDS) [16]. Drug-resistant *Shigella and Salmonella* species are widespread in Asia and in Central and South America [74, 75]. Resistant bacteria may also spread and impose themselves as infection-control problems, not only within healthcare institutions, but in communities as well. Clinically important bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) [71, 76] and extended-spectrum β-lactamase (ESBL) – producing *E. coli* [77, 78] are increasingly observed in the community. What makes the problem of antimicrobial resistant bacteria rise on the top is its...
association with human lives and the economical cost it causes. Recent estimates of the relationship between antimicrobial resistant pathogens and health care costs suggest that patients in the United States infected with antimicrobial resistant organisms incur average costs ranging from $6000 to $30,000[79]. Moreover, mortality, morbidity and length of hospitalization all increased as the antimicrobial resistance continued to develop in Staphylococci, Enterococci, and Gram-negative bacilli [79]. It is noteworthy that in the developing countries there are more than 14 million humans die each year due to bacterial infectious diseases that is estimated to mount up to 46 % of all death cases [80]. Finally, resistance to antimicrobial agents has contributed to recent increases in infectious disease mortality worldwide and is considered a public health problem of deep concern. Despite the fact that antimicrobial resistance is inevitable and may not be totally preventable, rigorously following the righteous protocols and programmes that may aid in reducing the prevalence of antibiotics-resistant bacteria will reduce the fears and havoc caused by these resistant bacteria.

How can we Control the Spread of Antibiotic Resistance Dilemma

Overwhelming evidence exists that antimicrobial resistance is worsening all over the world, without clear available interventions and solutions. Therefore, greater efforts must be paid to prevent and hamper the spread of antibiotic resistance in human hospitals, communities and within animal and agriculture facilities.

IN THE VETERINARY FIELD:

Stop Antibiotic Usage for Growth Promotion

In the context of antimicrobial use in the animal farms as growth promoter, for instance, in Denmark, they banned the use of antimicrobials as growth promoter in animals’ food. The result of this decision is a remarkable collapse in the overall uses of antimicrobials from 206 000 kg in 1994 to 94 000 kg in 2000; an over 50%, where the use of avoparcin, bacitracin, spiramycin, tylosin and virginiamycin for growth promotion was abandoned [1]. In addition to that, the ban has also had a marked effect on resistance rates in Enterococci in the faecal flora of man and animals [1, 81—85]. Also it is noteworthy that the Australia’s policy of prohibiting fluoroquinolones for growth promotion in animal feed resulted in a low level of fluoroquinolones resistant Campylobacter jejuni [86]. In contrast, in the United States, the approval of fluoroquinolones use in animals feed followed by of an increasing level during the period 1994-1996 of fluoroquinolone
resistance in human [86]. According to a recent study, removal of growth promoters reduced broiler chicken feed efficiency by less than 1% without affecting other measures of production efficiency [87]. There was some increase in the rate of necrotic enteritis infections while mortalities did not change and there was no loss in kilogram of broilers produced per square meter [87].

**Veterinary Drugs Prescription**

It is of a vital importance to produce guidelines for veterinarians and other responsible persons in animal medicine field on the correct prescription and use of antimicrobials in animal therapy, taking into attention the indication, dosing intervals, duration and exposure to the drug. Furthermore, drugs that can be used in human medicine or can have co-selection with human drugs should be avoided such as penicillin, macrolides and fluoroquinolones. It is imperative that all who are involved in the authorization, manufacture, sale and supply, prescription and use of antimicrobials in food-producing animals act legally, responsibly and with the utmost care in order to limit the spread of resistant microorganisms among animals so as to protect the health of consumers.

**Education of Farmers**

Investigation of knowledge and practices among farmers regarding antibiotic use and resistance is of great importance. For instance, a report from 81 farms in Sudan demonstrated that farmers are believed to misuse antibiotics in animal farming [88]. This may leads to daily exposure to resistant bacteria and antibiotic residues. Farmers misused antibiotics due to their ignorance of the importance of optimal use of antibiotics and the potential health hazards and the economical waste associated with antibiotic misuse. Moreover the report demonstrated that 52% of farmers were uneducated or had studied for <6 years and only 30% of the farmers had heard of antibiotic resistance [88]. Thus a significant association between low education, poor knowledge of farmers on antibiotic use, antibiotic resistance and zoonotic infections was prominent. Therefore farmers should be educated about the antimicrobial resistance problem. How to deal with their animals health by not combining the diseased animals with the healthier ones, using the drugs prudently and in a proper concentrations, consulting a veterinarian rather than relying on their own experience in diagnosing the diseases which may lead to inappropriate antimicrobial use. Farms owners should be educated about how to improve the hygiene and preventive measurements and the follow-up vaccination programmes. The educational resources and programmes should be in simplified ways taking into account farmers’ languages and the use of videos, laminated posters and flowcharts and educational seminars. This is in addition to encouraging veterinarians to reduce their consultation fees [89]. Dealing with all these aspect may help ensuring antimicrobial effectiveness in animals farms.

**HUMAN HOSPITALS**

**Better Prescriptions**

Over the past decade, several agencies and governmental reports have focused on the excess use of antibiotics and some of them brought antibiotics resistance problem into the political arena [90 — 93]. These reports differed in emphasis, but all run after particular purposes such as reducing antibiotic use, improved antibiotic selection and prescription regimens, prevention of cross-infection and new antibiotic development [94]. In particular, most of these reports stressed on the need to reduce community prescribing, which accounts for more than 80% of all antibiotic use that much of it pointlessly directed against viral respiratory infections [90]. In fact there are many observations supported that through reducing antibiotic use, a reduction in antibiotic resistance in the community will be the consequence [94]. For instance, Streptococcus pyogenes resistant to macrolides in Finland, had obviously scored reduction in the resistance prevalence in the clinical strains from 19% to 8.5% [95], penicillin-resistant pneumococci (S. pneumoniae) in Iceland also declined to 14% [4] and banning of avoparcin, vancomycin analogue, as a growth promoter in Denmark resulted in the drop of Enterococcus faecium resistance to vancomycin from 41% in 1996 to 8% in 1998 [96]. As a consequence, in order to effectively avoid antimicrobial resistance, clinicians must actively give up prescribing antibiotics for viral diseases and they should not respond to their patient demand for prescribing. Moreover, in order to provide adequate therapy, clinicians must take into account the spectrum of the antibiotic they prescribe, especially in the empirical antibiotics therapy. Ideally, initially is to use as narrow spectrum an antibiotic as possible; otherwise the severity of the infection, particularly those associated with mortality, may drive the empirical prescription of broad spectrum antibiotic. If culture and sensitivity testing yields the cause, the antibiotic can be changed when the results are known. This practice is termed stream lining [97].

**Hands Hygiene and other Sanitary Interventions**

A major gap in hospital hygiene is the failure of hospital personnel to practice adequate hand hygiene.
In fact, in most surveys of hand washing adherences in various patient-care settings, personnel have practiced appropriate hand hygiene in only 25% to 50% of opportunities [29]. In October 2002, the Centers for Disease Control and Prevention (CDC), released new guidelines for hand hygiene in health care settings [98]. Generally, this includes washing hand with water and antimicrobial or non antimicrobial soap. Important hygienic approaches also include cleaning hands with antisepsics before and after contact with patients and the use of alcohol based hand rub containing an emollient for routinely decontaminating hands [99]. Encouragement of the use of disposable examination gloves during contacts with patients and their environments and the worn of these disposable examination gloves for all contacts even with intact skin or the environment of at-risk patients is recommended. In addition to that, gowns always should be worn as part of contact precautions for all patient and environmental contact with patients known to be colonized by antibiotic-resistant pathogens such as MRSA and VRE. Masks should be worn as part of isolation precautions when entering the room of a patient colonized or infected with antibiotic-resistant pathogens [99]. Materials used for routine examination of patients such as thermometers, stethoscopes, tourniquets should be cleaned and disinfected before and after patient’s examination to pervade transfer of antimicrobial resistance pathogens [99].

Partitioning and Categorization of the Patients
Patients diagnosed with potentially serious resistant bacterial infections such as methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococci* should be isolated in special units. Evidence of reduction of MRSA by measures that included an isolation ward, nurse cohorting, or other interventions is clear in Australian hospitals policy where patients colonized with MRSA are isolated in special units, a process that has led to the lowest levels of MRSA and MDR *Staphylococci* among all Australian hospitals [100, 101].

Abbreviated Courses of Antimicrobial Therapy
The more the use of the same antimicrobial agent for longer treatment, the more the increasing risk of colonization or infection with antimicrobial resistant bacteria. Guillemet et al (1998) reported that the use of antibiotics for more than 7 days increases the risk of infection in children with penicillin-resistant *Streptococcus pneumoniae* by more than 3-fold [50]. Also Singh et al (2000) examined the effect of a 3-days course of ciprofloxacin as compared to standard antibiotic treatment for 10 to 12 days in the intensive care unit patients with pulmonary infiltrates [102]. They observed no differences in the mortalities but a lower length of stay in the short duration group. In contrast, antimicrobial resistance and super infection rates were higher in the group receiving standard treatment. The Infectious Diseases Society of America (IDSA) and American Thoracic Society updated their joint guidelines for treating community-acquired pneumonia (CAP) [98]. The updated guidelines recommended 5 days of antibiotic treatment for patients with CAP who are stable while for the febrile 48 to 72 hours of treatment is proposed [53]. More studies are needed to identify drug concentrations, dosages, and schedules for suppression of mutations that lead to antimicrobial resistance in bacteria [97].

Cycling of antibiotics
Cycling or rotation of antibiotics is considered a new intervention in prescribing antibiotics that may affect the prevalence of resistance in hospitals [103]. For instance, replacement of amikacin for gentamicin and tobramycin as the aminoglycoside of choice was associated with a decline in the prevalence of aminoglycoside-resistant Gram-negative bacilli [104]. The higher serum levels of amikacin and the infrequent appearance in the hospital environment of amikacin-modifying enzymes that can confer amikacin resistance in Gram-negative bacilli were the underpinnings of the success of this strategy [29]. Also switching from prescribing cephalosporins to prescribing a combination of penicillins and β-lactamase inhibitors have been associated with reduced colonization and infection with vancomycin-resistant *Enterococci* [105], *Clostridium difficile* [106] and cephalosporinase-producing *Enterobacteriaceae* [107]. However despite of its advantage to affect antimicrobial resistance prevalence, cyclic use of antibiotics can create new problems since it may selectively lead to the emergence of resistance to unrelated classes of drugs caused by genetic linkage of resistance mechanisms [103, 108].

Education of the Patients
Changing the attitude and behavioral situation of the patient towards the prudent use of antimicrobial agents is considered a major factor in reducing the risk of antimicrobial resistance. Patients should be aware enough and not pressurize their doctors to prescribe drugs, especially in cases that do not require antimicrobial prescription such as viral diseases (colds, most coughs, many types of sore throat, and influenza-flu). Furthermore patients should be instructed to complete the full regimen of the prescribed antibiotics even though the disease symptoms are alleviated and they must not skip doses as antibiotics are most effective when they are taken
regularly. Patients must be strongly advised against taking antibiotics that were prescribed for other persons and never take the leftover medicines because taking the wrong medicine can delay getting the appropriate treatment and may allow the condition to get worse. In addition to that, patients should be educated not to keep any drugs for future use and any drug excess and remnants should be immediately discarded away. Further, patients should be taught about the risk of having drugs without prescriptions and flee from what is called self medication, evade buying from the venders in the streets, because these drugs maybe inadequately dosed or may not contain adequate amounts of active ingredients, especially if they are counterfeit drugs. The CDC, the Alliance for Prudent Use of Antibiotics (APUA) and other groups have published educational brochures for the public and for health care providers [97]. The CDC educational programmes included the Get Smart program which focused on outpatients [109]. This is in addition to the 12-steps Campaign to Prevent Antimicrobial Resistance in Healthcare Settings [15].

Development of Diagnostic Tools
Development of laboratories rapid diagnostics tools, particularly those important for bacterial identification, susceptibility testing and disc diffusion or minimal inhibitory concentration test for drugs, would aid in the accurate initial therapeutic selection. Diagnostic tools can provide an immediate result that confirms or rules out viral infection. Hence, this will play an important role in reducing inappropriate use of antibiotics.

Development of New Antimicrobial Agents
The development of new therapeutic agents is becoming an urgent issue, especially with the current advances in the molecular biology techniques such as genomics and bioinformatics. The novel therapeutics agents should not only be a successful breakthrough but should also be able to evade the current bacterial resistance mechanisms that form the major obstacle in selecting the new agents. Further, it has to target new bacterial genes products as well. Also the new products should have broad spectrum antimicrobial activity, little or no toxicity and have minimal side effects in humans. Many large pharmaceutical companies with renowned histories in producing antimicrobial agents eliminated their antimicrobial discovery groups entirely, mainly, due to prohibitive costs of developing and testing new drugs in addition to drug trials and the brief patent life. However and fortunately the development of new and novel antimicrobial agents has been left to relatively small pharmaceutical and biotechnologies companies whose sales and profits strategies are more in line with those of conventional strategies [110 - 112].

Surveillances
Information on the emergence and prevalence of antimicrobial resistant organisms and the use of antimicrobial drugs, whether in human hospitals or animal farms, is a paramount to help experts to analyze and interpret trends and identify strategies to prevent and control antimicrobial resistance. National, regional, state and local surveillance systems of drug susceptibility are needed to communicate the current status of resistance in a location, facilitating more appropriate choices of treatment. In this regard the Alliance for the Prudent Use of Antibiotics has established its Global Advisory on Antibiotic Resistance Data project GAARD to synthesize, evaluate and report the surveillance data from five large global surveillance systems. The GAARD project [113] is a global public-private partnership involving the world’s largest independent surveillance systems tracking antimicrobial resistance.

Vaccinations
Encouragement and development of alternative novel means in lieu of antimicrobial therapy of bacterial pathogens such as vaccination, undoubtedly, can diminish bacterial diseases and reduce the demand for antimicrobial therapy. Recently, conjugative vaccines have been introduced against *Haemophilus influenzae* serotype b [114], *Neisseria meningitides* [115] and *Streptococcus pneumonia* [116]. The use of novel molecular biology techniques such as bioinformatics which may predict genome sequences will add a step forward to discover new genes products and their location in the bacterial cell surface [117, 118]. This approach has led to the identification of new vaccine candidates against *Streptococcus pneumonia* [119, 120], *Neisseria meningitides* [121, 122] and *Mycobacterium tuberculosis* [123]. Optimal administration of all available vaccines to children and adults offers protection against infection and infectious complications and reduces the need for antibiotics [97]. It is noteworthy that vaccines development and delivery is a little problematic since it substitutes the commensal flora with the pathogenic bacteria in the immunocompromised patients. This may results in the destruction of the natural defenses against recognized pathogens [12].

ALTERNATIVE INTERVENTIONS
Bacteriophage therapy
Bacteriophages (phages) are viruses that target and infect bacterial cells. They were discovered before the era of antimicrobial chemotherapy as bacterial
killers. However their practice was abruptly stopped when synthetic antibiotics were introduced after World War II. Recently, the spread of antimicrobial resistance worldwide, with no clearly available solution, has triggered the scholars to re-introduce bacteriophages as therapeutics agents for bacterial diseases. In a successful experiment, bacteriophage was reported to rescue mice infected with a vancomycin-resistant Enterococcus faecium bacteremia [57]. Bacteriophage therapy is a potentially useful approach in infection control, especially that their exponential growth and natural mutational ability make bacteriophages great candidates for thwarting bacterial resistance. Nevertheless, they should be introduced in the early stages of development and must be tested and evaluated, like antibiotic drugs, in rigorously controlled experiments.

Probiotics
Another alternative intervention may be of a paramount significance such as the use of probiotics that revive susceptible bacteria. Probiotics are live, nonpathogenic bacteria or yeasts that colonize a host. They referred to “friendly bacteria” and they have profound beneficial effect on health and inhibiting the growth of pathogenic resistant bacteria. They can replace the resistant bacteria in areas where severe reduction in susceptible bacteria occurs. For instance, the commercial product “Preempt” contains a group of bacterial strains from adult hens, which compete and prevent colonization of Salmonella gallinarum in chickens [124]. In another study, pretreatment with Lactobacillus- and Bifidobacterium containing-yoghurt can improve the efficacy of quadruple therapy in eradicating residual Helicobacter pylori infection after failed triple therapy [125]. In addition to that, probiotic lactobacilli inhibited the urogenital pathogen growth and adhesion, and colonized the vagina following oral intake in patients infected with urogenital pathogens [126]. Probiotics can be easily obtained in regular yoghurt, kefir, cottage cheeses, preserved vegetables and powdered drink mixes. Although probiotics can outweigh the revival, competition and domination of the susceptible bacterial strains in a particular environment, some complications of specific probiotics have been reported in immunocompromised or severely ill patients [127].

CONCLUSION
Despite that the war against bacteria began since the thirties of last century with the discovery of penicillin and, later, streptomycin, a complete defeat of bacterial infections has never been achieved. Since their application for treatment the bacteria developed mechanisms that eroded the effectiveness of these antibiotics. By the time and stealthily, bacteria dominating the battle area and become resistant even to the newly synthesized therapeutics agents such as fluoroquinolones, vancomycin and carbapenems, which are often the drugs of last resort. Not only to this extend, but also new virulent bacterial strains are emerged in hospitals and community such as MRSA, VRE and MDR- tuberculosis with the least or no susceptibility to the current available antimicrobials. To re-war these pathogens, we need to change our knowledge about antimicrobial usage and direct it towards new technologies that can track the clonal nature of these pathogens. Moreover, we need to double our effort by intensifying research for new effective therapeutic agents and preserve that at our hand. Efforts should also be directed towards the commensal flora, because they are considered as our allies in reverting resistant bacteria and out-compete with them. Finally prudent and careful use of antimicrobial agents should be the frontrunner line of defense against antimicrobial resistance, otherwise the proportion of expectations will increase to the extent that there will be no other antimicrobial agent that can effectively acts against these pathogens. This indicates the shift to a new era of new mysterious therapeutics agents we do not know what dangers they may hide for us.

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