ORIGINAL ARTICLE

The Role of Drug Resistance in Emergence and Re-emergence of Diseases

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ABSTRACT

Background: Today, the problem of emerging infectious diseases have overshadowed many of the health beliefs and attracted the attention of the scientific societies, and interestingly, many of the scientists believe that not only the emergence of contagious diseases is not merely a new phenomenon, but also it has happened several times and thus had a huge role in the history of the health developments. The increased antibacterial resistance today have made the problem of infectious diseases even more complicated, so that the infections caused by microorganisms resistant to antibiotics have become the most important preoccupation of the physicians.

Aim: The purpose of this study is to express the role of drug resistance in emergence and re-emergence of diseases.

Methods: This study is conducted with retrospective method while reviewing the previous studies in this field referring to scientific websites: Ovid, Blackwell Synergy, Pub Med, Elsevier, Science and Google Scholar, with relative key words.

Findings: Emergence of infectious diseases and re-emergence of some others is not a new phenomenon; as the ecosystem is changing constantly and thereby changes large and small environments, in which humans and their associated microbes live, and they themselves engage in this trend. The factors that cause emergence and re-emergence of infectious diseases are quite various; however, the influence of humans on the ecosystem is of key importance. The microbial factors that comprise over 60% of the biomass are an important part of the internal and external environment of the human body, and in other words, have surrounded the human body from inside and outside. This is while, based on current information, only 0.5% of the 2-3 billion existing microbial species are identified.

Conclusion: The issue of emergence and re-emergence is the subject of the past, present and future medicine history and is the continued problem of public health and therefore should be considered with utmost seriousness by policymakers of the educational and research affairs and also attended by the professors and researchers of the universities of medical sciences in the country, including Medical and veterinary and even agricultural schools.

Keywords: Drug Resistance, Emergence, Ecosystem, Re-emergence.

INTRODUCTION

The history of infectious medicine is full of interactions between humans and microorganisms. The emergence of new infectious disease is considered as an important aspect of the world economy[1,2,3]. There was the time that invasion of microorganisms caused millions of humans to die and then, sometimes hope has come to eradicate such diseases with the discovery of antibiotics and vaccines. In another time, all that has been done went out of the window due to inappropriate management of antibiotics consumption, and then again, new microorganisms have come to the life of human beings due to behaviors and lifestyles and medical technologies. The increased antibacterial resistance today have made the problem of infectious diseases even more complicated so that the infections caused by microorganisms resistant to antibiotics have become the most important preoccupation of the physicians. Development of antibacterial resistance is one of the good examples in this regard. According to the estimations of WHO, 45% of all deaths and 63% of the childhood deaths are still caused by infectious factors and generally Acute Respiratory Infections (ARI), Diarrheal Diseases, Measles, Malaria, AIDS, and Tuberculosis are important causes of death in all countries of the world. The emergence of infectious diseases and re-emergence of some others, however, is not a new phenomenon; as the ecosystem is changing constantly and thereby changes large and small environments, in which humans and their associated microbes live, and they themselves engage in this trend. Sometimes the environment becomes ideal for the growth of the pathogen agent and thereby an unexpected increase in the disease activity or emergence of infection is observed, and or the microbe acquires pathogenic agents and thus lead to the emergence of new disease and re-emergence of the old infectious diseases. The factors causing emergence and re-emergence of the infectious diseases are various and diverse, however, the influence of humans on the ecosystem is of key importance. Penicillin supply followed by the discovery of

Streptomycin significantly reduced diseases, and deaths caused by infectious diseases, unfortunately,however, upon the emergence of drug resistance in bacteria, parasites, viruses and fungal, the effect of advancement in the discovery of miraculous drugs for controlling diseases become inverse. Many of the other pathogens including the causative agents of Malaria, Tuberculosis, Gonorrhea, AIDS, and *Salmonell*a are now resistant to standard treatments. Many of the important drugs that are used for treating common infections have become limited, more expensive and inaccessible in some regions. For instance, we are losing our capability to treat infections caused by *Staphylococcus Aureus*. This bacteria cause wound infection and various abscesses in the skin, lung, bone, brain, and heart and even lead to death.

In 1928 that Fleming discovered penicillin, many of the bacteria used to be sensitive to that, however, by 1943 companies started to mass-produce it and in four years bacteria started to resist against it. The first microbe that became resistant was *Staphylococcus Aureus*. Then in 1967, another kind of penicillin-resistant pneumonia developed from *Streptococcus pneumoniaeoniae* was observed in a remote village in Papua New Guinea. At the same time, the US military personnel stationed in Southeast Asia contracted with Penicillin-resistant Gonorrhea. When those soldiers were coming back home, they brought this new strain with themselves to America and thereby physicians had to find a new drug to treat that.

In 1983,*Enterococcus faecium* intestinal infections acquired in hospitals were added to the list of penicillin-resistant bacteria. The antibiotic resistance is expanding rapidly. For instance, between 1979 to 1987 only 0.2% of the Pneumococcal strains were penicillin-resistant. Unfortunately today, 0.6% of the Pneumococcal strains are penicillin-resistant. Based on the report of the New England magazine on April 28, 1994, researchers found bacteria in the samples provided by the patients that were resistant to all common accessible antibiotic drugs. Drug-resistant infections increase the risk of death, are often associated with prolonged hospitalization period, and sometimes with side effects and necessarily a part of a body limb is removed by surgery such as lung and or a damaged heart valve should be replaced. Upon utilization of antibiotics in small dosages for increasing the growth of animals and considering the residuals of the same substances in human food and by applying compressive effects on human bacteria, resistance emerged in them as well which could surprise the medical community. In 1983, for instance, 18 people in 14 of the Western states of America were poisoned by multi-drug resistant *Salmonell*a due to the consumption of stakes produced from the beef of cows fed by antibiotics.

Problem Statement: Emergence and spread of antibiotic-resistant microbes have become a major concern within the past decade and increase of such resistant species is ongoing. The main part of resistant concerns medical and healthcare departments. Although some patients clearly need antibiotic treatment, however, many imagine that antibiotics are the response to disease when they are sick. They even put pressure on physicians to prescribe antibiotics. The other issue is that patients often discontinue their medications early as soon as they have signs of recovery which actually stimulates resistant bacteria for more growth. Infection returns after a few weeks and then, different drugs should be applied for treatment. The share of antimicrobial agents utilized in animal care is also considerable, not only in terms of increased resistant in animal pathogens , but also is important in terms of transferring bacteria from animal to human. Perhaps antibiotics are the only totally useful and important case of medical advancements of the modern world, however, their effective application is extremely threatened by bacterial resistance which includes numerous resistances among common pathogens and pathogenic agents and thereby, many medical organizations pay a special attention to this issue as the huge, expensive and growing threat of the public health. Growing bacterial resistance not only is derived from the unnecessary prescription of clinical uses by humans , but also massive use of antimicrobials in veterinary which cause the transfer of such pathogens from animals to humans as well plays a significant role. It is estimated that about sixteen million pounds of antimicrobials are spent , of which 80% of their use in agriculture is for therapeutic uses , such as accelerating animal growth, or as insecticides or prophylactic uses are involved in causing resistance, while they have a commercial license, they are often used without veterinary supervision. On the other hand, harmless bacteria might be the source of antibiotic-resistant genes and humans acquire such bacteria when they consume meat products prepared from these animals, and eventually, those resistant genes are transferred to bacteria, which are pathogenic. For instance, application of Sarafloxacin for optimal growth in poultry in the United States caused the emergence of resistance of *Salmonell*a to Fluoroquinolones. Also the application of Avoparcin which is a Glycopeptide anti-microbial causing the emergence of VRSA (Vancomycin Resistant *Staphylococcus Aureus*) and VRE (Vancomycin Resistant Enterococci) could be named[4]. A major part of the antibiotics that are used in animal feed is of the same group as the antibiotics that are used for treating human infections, and include Tetracyclines, Sulfonamides, Penicillins, Macrolides, Fluoroquinolones, Cephalosporins, Aminoglycosides, Chloramphenicol and Streptomycin. Resistant bacteria can be transferred to humans either through the food chain or through contact with animals. *Campylobacter* is frequently found in the intestines of chickens and poultry and humans are contracted with them eating semi-raw chicken meat or through contacting them. In 1989, *Campylobacter*ia were susceptible to Fluoroquinolones. In 1995, (that FDA approved the application of Fluoroquinolones for poultry), Fluoroquinolone-resistant *Campylobacter*ia emerged soon. Antibiotic resistance, therefore, can be a food safety issue as well, and reducing the unnecessary use of antibiotics as supplements for animal feed, would reduce the pressure on microorganisms that form resistant bacteria. Chart 1 displays the emerging trend of resistance in *Salmonella typhimurium* in animals and humans.

Bacterial Resistance Mechanisms

1. Mutation: Takes place through a spontaneous change in DNA of the bacteria. Mutation accidentally takes

place in all organisms. Antibiotic resistance is one of the changes that occur due to accidental mutation[5].

2. Transformation: Takes place when a bacteria receives some of the DNA components of the chromosome of another bacteria.
3. Plasmid Exchange: Antibiotic resistance is located in a small fraction of the DNA of the bacteria, called Plasmid. These plasmids can be accidentally exchanged between bacteria (usually through contact)[6].

The resistance in bacteria can be generally defined in two categories of intrinsic and acquired:

- Intrinsic Resistance (Natural): A bacteria can be intrinsically resistant to an antibiotic. For instance,*Streptomyces* have genes that are responsible for resistance to the antibiotic derived from it (Streptomycin) or the Gram Negative bacteria has an external membrane thatstabilizes the impenetrability against antibiotics[7].
- Acquired Resistance: bacteria can become resistant to antibiotics. For instance, the bacterial population that was previously susceptible to antibiotics become resistant. This type of resistance is derived from changes in the genome of the bacteria. Acquired resistance takes place through two genetic trends in the bacteria, Selective Mutation (sometimes called Vertical Evolution) and Gene Exchange between samples and strains (sometimes called Horizontal Evolution)[8].

Methods for Developing Bacterial Resistance

1. Changing the target molecule; For instance, if the antibiotic attacks a certain enzyme in the bacteria, then the bacteria can perform the same function using a different enzyme and adapt itself[9].
2. Making the antibiotic inactive or ineffective by an enzymatic method[10].
3. Bypassing the drug through creating alternative ways inside the bacteria.
4. Preventing the drug from penetrating the bacteria.
5. Pumping and removing the drug as soon as it enters the bacteria[10,11].

Medical Problem of Drug-Resistant Bacteria: It is obvious that if a bacterial pathogen can form or acquire an antibacterial resistance state, then that substance will be ineffective for treating infections caused by the same bacteria. Therefore right after a pathogen form resistance, then we should find new antibiotics in order to replace the empty place of the old ones. Also, natural penicillins are becoming ineffective against *Staphylococcus* and thus should be replaced by other antibiotics. Tetracyclines are extensively used and have been inappropriately consumed for decades and now they have lost their value and effect for treating many infections. This is while they used to be an interesting drug in the past years. Not only is there a problem regarding finding new antibiotics to fight against old diseases (as resistant types of the bacteria have emerged) but also the other parallel problem is to find new antibiotics for fighting against newly emerged diseases. Many of the bacterial diseases have been discovered within the two past decades; such as Legionnaires 'disease, Lyme Disease, Toxic Shock Syndrome. We are,however, only able to examine the patterns of antibiotic susceptibility and resistance among new pathogens. This is while these pathogens have an extensive pattern and it is apparent that we will soon need new antibiotics to replace the current effective antibiotics against such bacteria. Infectious diseases are still constant threats to all human communities irrespective of age, race, lifestyle, ethical background and the economic status of the community[1]. Basically, drug resistance is observed in any region and country based on the performance of physicians and patients and even pharmacists, which might be different with other regions. All common bacteria in the community and hospital resistant bacteria have the potential to acquire resistance. The most common resistance of pathogens causing diseases in the community are , namely, *Streptococcus pneumoniaeoniae* against Penicillins, *Haemophilus influenzae* and *Moraxella catarrhalis* against ampicillin, *Streptococcus pyogenes* to macrolides, *Neisseria gonorrhoeae* to ciprofloxacin, S*. aureus* and Methicillin, E. *coli* to ampicillin and trimethoprim, Fluoroquinolones *Salmonella*, *Campylobacter* to ciprofloxacin, Metronidazole *Helicobacter Pylori* and *Mycobacterium tuberculosis* to isoniazid and rifampin[12]. Among hospital resistant pathogens, *StaphylococcusAureus* to methicillin and even Vancomycin and Gram-negative bacilli, and especially *Pseudomonas aeruginosa* resistant to one or more antibiotics (ESBL), and *Enterococcus faecium* to ampicillin and vancomycincomprise the issues and problems of most of the treatment centers. The resistance of Zoonotic bacteria based on veterinary policies could cause medical problems upon transferring diseases to human and thereby to cause more complicated decision making for starting antibiotic prescription. Among them, the resistance of *Salmonella* and Listeria Monocytogenes, *Campylobacter jejuni* and Enterohaemorrhagic*Escherichia coli* could be named, which such resistance varies in different countries based on the volume of used antibiotics, whether for therapeutic purposes or for economic purposes and for feeding livestock and poultry, and thereby human diseases would be influenced by such variations[13]. Furthermore, there are bacteria that cause diseases in animals and humans could be infected accidentally and while contacting them, which among them Aeromonas and Vibrios could be named.

Viruses could as well acquire drug resistance or their selective drug resistance during the time, which among them, namely, is the resistance of HIV to Antiretrovirals (14) and the resistance of Herpesviruses to Acyclovir (15). The trend of resistance is increasing even among Funguses that cause serious and severe diseases in humans. Emergency and development of antibiotic-resistant bacteria within the past decade has become a major concern and such increase continues. Some cases of such common bacteria are addressed in the following.

Penicillin-Resistant*Streptococcus pneumoniae*onia (RPSP): RPSP has been rare within the past decade in the US; however, it is currently increasing in many regions. CDC has reported the regions in which the prevalence of Penicillin Pneumococcus Resistance was over 30%. This rate is even much more in other countries, especially in Spain, Hungary, Australia, South Africa,and Jerusalem. Over 90% of *Streptococcus pneumoniae*onia family are penicillin resistant to Spain[16,17]. The resistance of

*Streptococcus pneumoniae*onia family to penicillin in some countries of the world is displayed in Chart 2[18]. The main causes of resistance are assumed to be Selective pressure applied by antibiotics, using widespread agents, and improper prescription of antibiotics.

In order to investigate the resistance to penicillin, laboratories need to utilize 1-µg oxacillin disk or to conduct Minimum Inhibitory Concentration (MIC) test. If the *Streptococcus pneumoniae*onia is reported to be resistant toconductingthesetests, then further tests against widespreadCephalosporins, vancomycin or other antibiotics are recommended. Penicillin is the selective drug for penicillin-susceptible *Streptococcus pneumoniae*. The third generation Cephalosporins (ceftriaxone, cefotaxime or oxime rigidity) with high dosages of penicillin are recommended for penicillin-resistant cases, which varies based on infection site and penicillin resistance level (19). In 1996, about 9-20% of the *Streptococcus pneumoniae* species were resistant to widespread Cephalosporins. Molecular epidemiological studies have indicated antibiotic-resistant clones (methicillin) in various places of the world. Resistance to penicillin and cephalosporin among *Streptococcus pneumoniae* family takes place due to the change of the tendency to the antibiotic bonding of penicillin-binding proteins. It is apparent that such changes of bonding tendencies are the results of genetic recombination with Streptococcus similar to Viridians. The third generation Cephalosporins are still, in many cases, effective for treatment of PRSP infections, however, prevalence of increased resistance to cephalosporin is probable incase of treatment failure. In patients with pneumonia or bacterial pneumonia, penicillin can be used against penicillin-susceptible strains and possibly even medium-resistant strains (MIC 0.1-1µg/ml). As long as the results of susceptibility tests are accessible, high dosages of the third generation cephalosporin and vancomycin can be used for patients with meningitis. Even when this diet is used, some authors recommend a new LP within 24-48 hours after the start of treatment for confirmation of treatment response. In cases with high resistance (MIC 0.1-1µg/ml), however, vancomycin is the selective drug due to the synergistic effect with ceftriaxone[20,21,22]. If the organism is susceptible, then a quinolone, clindamycin or imipenem might be used. A combination of vancomycin with Cephalosporins or rifampin is used in regions in which there is resistance to Cephalosporins, and alternative agents such as meropenem and fluoroquinolones are under study for this purpose.

The most logical measure concerning the increasing antibiotic resistance among Pneumococcus is prevention by vaccination. Recent information on the results of the use of conjugate pneumococcal vaccines has been very encouraging[23]. The licensing of the conjugated pneumococcal vaccine in February 2000 in the United States may be the end of the PRSP problem. The vaccine contains a limited number of pneumococcal serotypes and will have limited effects as new serotypes from remote regions will rapidly replace the vaccine species. Pneumococcal vaccine is recommended for all people over the age of 65 years and over the age of two, who are prone to pneumococcal infections (such as anatomical anesthetics or functional cells, HIV infection, chemotherapy and immunosuppressive drugs). Logical and appropriate use of antibiotics can reduce the selective pressure on drug resistance of the organism and even prevent the emergence of resistant strains.

Methicillin Resistant *StaphylococcusAureus* (MRSA): Methicillin-resistant*Staphylococcus* was recognized in 1961 almost a little after the introduction of methicillin. By late 1990, 35% of the isolated clinical samples of *StaphylococcusAureus* in the United States and England (Chart 3) were methicillin resistant (25). In 1993, 60% of the isolated samples were methicillin resistant and now, MRSA has become a global problem. Although it is apparent that this organism is mostly able to spread in hospital settings, however, its spread is not exclusively limited to hospitals. In a study in Australia, 40% of the healthy native community was carrying MRSA. As the use of widespread antibiotics continued, MRSA has become the common species of *StaphylococcusAureus* necessitates the use of glycopeptides for the routine treatment of all staphylococcal infections. Methicillin resistance indicates resistance to all beta-lactam antibiotics including Penicillins, Cephalosporins, carbapenems and a combination of beta-lactam antibiotics and β-lactamase inhibitors[26].

In order to treat infections caused by MRSA, intravenous therapy with Vancomycin is selective. A combination of vancomycin + aminoglycoside, rifampin or trimethoprim-sulfamethoxazole is prescribed for deeper infections such as endocarditis or osteomyelitis, based on the organism susceptibility[27]. A patient with methicillin-susceptible infection is treated with Penicillins resistance penicillins such as tefillin or oxacillin, however, for patients with penicillin allergy, the first generation cephalosporin (such as cefazolin) is used. If the patient is allergic to ß-lactam agents, then the selective drugs are vancomycin, clindamycin or macrolides (such as erythromycin)[28,29]. MRSA is the major hospital pathogen in third level hospitals and long-term residences and even general hospitals. The rapid diagnosis of MRSA and the application of protection standards and follow-up monitoring and prospective studies are key components of a successful control program. Protective isolation, for instance, a single room and mask for individuals who are in close contact with the patient, wearing gloves when contacting the patient or contaminated material (secretions), and wearing scrubs if there is a risk for clothing to get wet and contaminated and particularly precise hand washing is the most effective method for limiting intra-hospital delivery. Treatment of MRSA transmitted nasal transport in hospital patients and staff during epidemics is recommended as well (30). Mupirocin is a topical antibiotic with antibacterial effects against *Staphylococcus* and MRSA. Administration of internal calcium mupirocin had good results in the removal of nasal cartilage MRSA, which has reduced the prevalence of epidemics in certain clinical conditions, such as neonatal sections, hemodialysis, cardiothoracic surgery, and infectious intramuscular *Staphylococcus*[31]. For patients who are known to be MRSA carriers, the standard isolation precautions should be followed as soon as they are admitted to the health center unless appropriate screening tests prove them MRSA-free. Since 1996, a number of MRSA isolates with vancomycin tolerance (Vancomycin-

resistant *Staphylococcus Aureus*) (VISA) or Glycopeptide-intermediate *Staphylococcus Aureus* (GISA) have been identified and their susceptibility to vancomycin has been reduced. The resistance mechanism of VISA strains is not completely clear,however, the results in a phenotype with cell wall thickening have been associated with continuous or alternating vancomycin use[32]. New agents including Quinupristin/dalfopristin, linosolid and other experimental agents that have been shown to be effective against VISA, MRSA, PRSA, and vancomycin-resistant enterococci (VRE) are recently available.

Vancomycin-Resistant Enterococci (VRE): Enterococcal infections occur with low incidence and include infections of the wound and soft tissues, meningitis, neonatal sepsis, and pneumonia (very rare). Most of the isolated clinical specimens of Enterococci are due to *Enterococcus faecalis*, which accounts for 80-90% of all isolated organisms in clinical specimens. *Enterococcus faecium* (E*. faecium*), which is mostly resistant to antibiotics, is responsible for 5-10% of infections in most establishments[33]. Other strains that are sometimes isolated include E. hirae, E. raffinosus, E. gallinarum, E. casseliflavus, E.avium, E.duran[34]. The most important problem with enterococci is its relative and absolute resistance to antibiotics. Since both intrinsic and acquired resistance occur, susceptibility tests are essential for guidance.

VRE stands for vancomycin-resistant enterococci (Chart 4)[35]. Vancomycin inhibits the synthesis of the bacterial cell wall but performs it one-step ahead of beta-lactams.

Vancomycin is a large molecule that prevents cell wall synthesis by delaying the synthesis of new walls. Resistance to vancomycin occurs when organisms synthesize pre-corsairs that have a lower tendency to vancomycin. This resistance is dependent on the plasmid. Plasmids design enzyme mechanisms for changing the pathway of peptide and glycan biosynthesis and transfer resistance through the injection of genetic material into susceptible enterococcus[24-36]. The most common form of VRE is *Enterococcus faecium*, which is intrinsically resistant to tobramycin, thereby gentamicin aminoglycoside is a choice for combining with bactericidal agents; on the other hand, and many VREs have a high resistance to all aminoglycosides and even gentamicin. Such resistance is due to the production of enzymes that modify and deactivate the phosphorylation and acetylation of the aminoglycoside molecule. This resistance is caused by both plasmid and genetic material on the bacterial chromosome[37]. Some gentamicin-resistant species remain relatively susceptible to streptomycin, which is useful in treating some patients. Infection caused by VRE is common in patients hospitalized in a hospital. The disease spectrum includes asymptomatic colonization, catheter-related infections, and severe clinical infections. The lack of effective treatment factors presents these infections as untreatable with medical treatments. Risk factors for VRE include colonization of Gastrointestinal VRE, old age, severe underlying disease, immunosuppression, ICU hospitalization, surgery (especially the digestive system, cardiovascular and transplantation), intravascular devices, and contact with third-generation Cephalosporins and vancomycin[38].

The following items should be considered for the purpose of reducing infections caused by VRE: Training: Hospital staff needs to be trained about the severity of infection; disease spread methods,and protective strategies.

Early diagnosis and reporting by Clinical Microbiology Laboratory: Conducting periodic surveillance culture feces or rectal swabs) of patients in the hospital departments where VRE is a major issue in order to identify VRE carriers. Also,a periodic test of Enterococcal susceptibility tests should be conducted from all samples and in hospital units before resistance spread in an establishment.

Prevention and control of the spread of disease: Hospitals should observe absolute contact isolation (similar to what is performed for MRSA) including hospitalization of patients with VRE infection in isolated rooms or along with other patients with VRE infection, wearing gloves when entering the patient's room, and using non-proprietary devices (such as a stethoscope, thermometer) for each patient or cohort patients, installation of information signs on doors to inform and apply preventive methods[39].

Preventing overuse of vancomycin: Because previous consumption of vancomycin may be a risk factor for colonization and infection with VRE, inappropriate use of vancomycin should be reduced. In spite of the availability of limited effective antimicrobial agents, few patients died because of this organism, which is probably due to low bacterial virulence. Patients with bacteremia caused by catheter-dependent VRE may respond to systemic therapy by removing the catheter. Postoperative infections soft tissues and abscesses are improved with debridement of surgery and drainage without the use of specific agents. U.T.I caused by VRE improve itself or respond to oral treatments, such as nitrofurantoin, amoxicillin or fluoroquinolones while removing catheter might be also necessary. The use of antibiotic agents to which microorganisms are susceptible should be considered as well[40], although monotherapy with fluoroquinolone, novobiocin or tetracycline is often associated with rapid spread of resistance. Quinupristin/dalfopristin (cisapride) have been used as treatment protocols and are under investigation[41].

Multi-drug Resistant Tuberculosis: Despite the fact that tuberculosis has been thought to have existed since thousands of years ago, and one-third of the world have been already infected with *Mycobacterium tuberculosis*, however, its resistant strains are considered as emerging organisms[42,43]. Multi-drug-resistant tuberculosis (MDR-TB) has become a public health problem in the past decade and has been inflamed with HIV infection epidemy[44]. Genetic basis for resistance to anti-tuberculosis drugs is unknown; however, the underlying mechanism seems to be the result of mutation rather than the acquisition of new genetic elements[45]. MDR-TB is thought to be created as a result of inadequate treatment that allows the emergence and replication of resistant bacteria[46,47]. In the absence of an effective vaccine against tuberculosis, public health practices in controlling MDR and ensuring drug use in cases of drug-susceptible tuberculosis are the most important issues in controlling tuberculosis.

Chart 1: the emergence trend of resistance of *Salmonella typhimurium* to Quinolones in animals and humans.

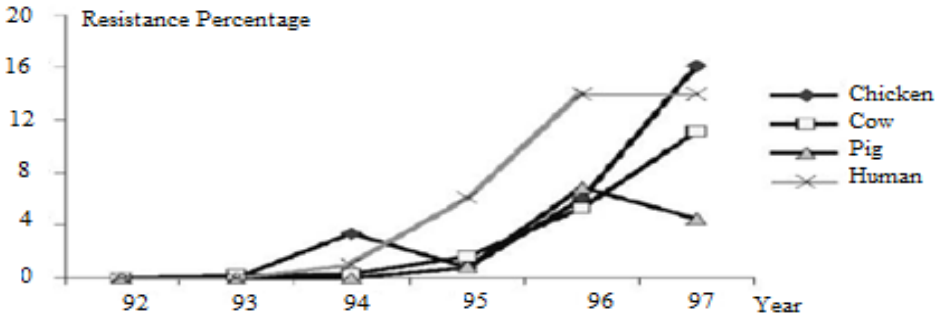


Chart 2: Emergence of penicillin-resistance among pneumococcus in different countries (the 1990s).

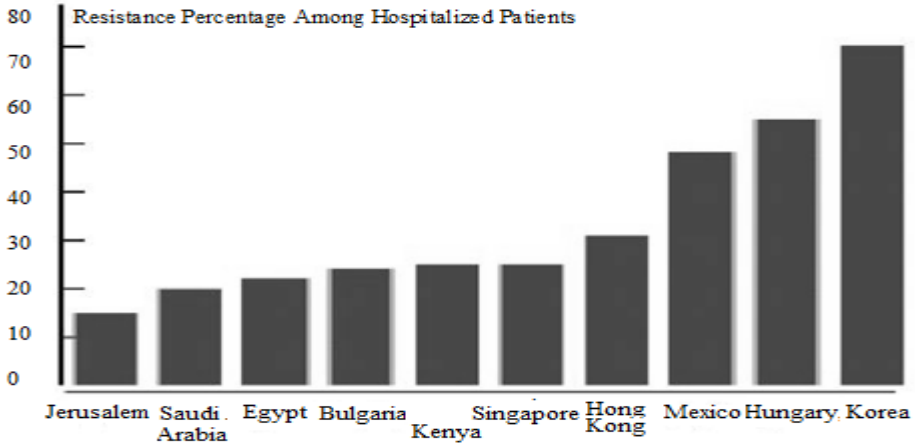


Chart 3: The trend of resistance emergence to methicillin among *Staphylococcus* in England.

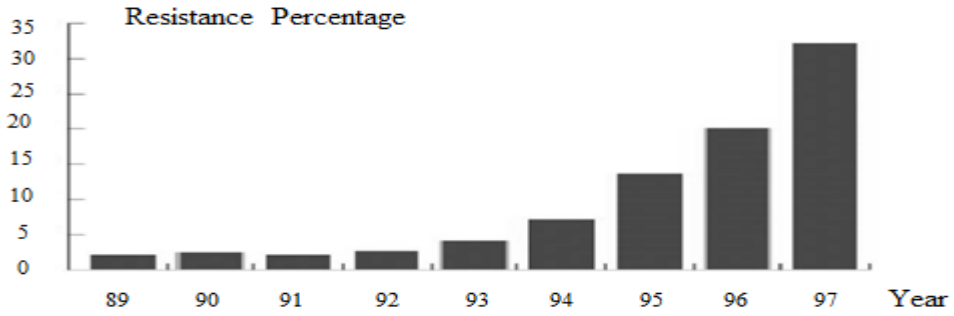
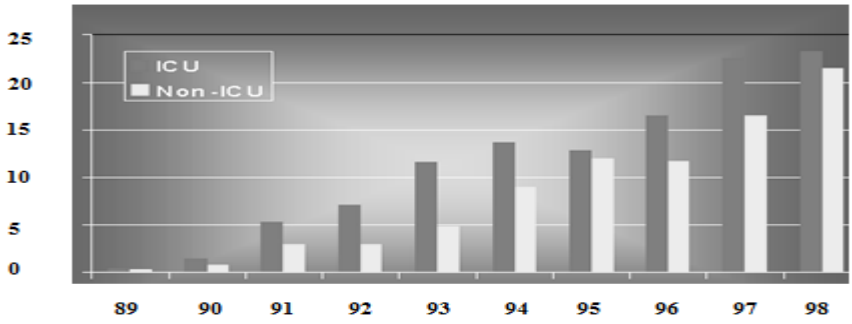


Chart 4: The trend of emergence of vancomycin-resistant enterococci



DISCUSSION AND CONCLUSION

Considering the instrumental abuse of microorganisms with bioterroristic goals and interventions that are carried out by uncommitted scientists in their genome, therefore epidemics that have bioterroristic aspect, while addressing the above-mentioned problem, the susceptibility of the above bacteria to different antibiotics should be measured and then necessary medical treatment will be recommended by selecting an appropriate antibiotic. Establishing and improving monitoring systems for controlling infections caused by drug resistance and the information collected from these systems can provide early knowledge about changes in resistance patterns, drug guidance and vaccine production, which then prevention and control methods will be eased, and the grounds of interventional evaluation is prepared. the establishment and improvement of monitoring systems to determine the risk factors that lead to drug resistance, including the use of antimicrobial drugs in humans, agriculture,and the environment, can assist to evaluate the trend of optimal drug use.

Research: Studying the molecular fields of antimicrobial resistance, and epidemiologic agents associated with the emergence and spread, launching and evaluating new laboratory tests to improve the authenticity and accuracy of detecting anti-microbial resistance in different clinical conditions. Identifying the measure and evaluating appropriate strategies for controlling infection in different conditions to prevent the transmission of resistant infections can lead to a clear future in this regard. In addition, the evaluation of educational and behavioral methods for improving the optimal use of antimicrobial drugs, such as changing the prescribing behaviors in educational and therapeuticstaff, optimal use of drugs and evaluation of vaccine use in preventing resistant infections can be valuable.

Prevention and Control: Implementing public health programs reduces the emergence and development of drug-resistant microorganisms. Such programs include: Infection control strategies in different conditions, behavioral and educational interventions to change the trend of drug prescription among therapeutic staff, behavioral and educational interventions for patients concerning inappropriate use of drugs and compliance with instructions for use, health education programs to promote the use of new vaccines for infectious diseases, providing feedback on antimicrobial resistance information for health authorities to implement and evaluate interventional programs.

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