Antimicrobial Drug Resistance, A 'Triad' of Epidemiological Factors.

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ABSTRACT

Over the years, as understanding of the factors associated with antimicrobial drug resistance has progressed, epidemiological study has broadened to include human behaviours, complexity of environment as well as pathogens as a triad of epidemiological factors responsible for the alarming upsurge of antimicrobial drug resistance. The effect on humans and how these challenges can be resolved need immediate attention. Antimicrobial resistance is the reduction in the efficacy of a drug such as antimicrobial drug in curing a microbial mediated infection. The use and misuse of antimicrobial drugs in human medicine and animal husbandry has been implicated as one of the causes of the unabated rise in the number and types of microorganism resistance leading to deaths of millions of people worldwide. Organisms that elicited drug resistant against many antibiotics are numerous and also the drugs(antibiotics) that were once known as 'magic bullets' have become metabolic precursor pools for these microorganisms to thrive, irrespective of their nomenclature as broad spectrum, narrow spectrum, extended spectrum etc and this has increase the morbidity and mortality rate and incurred higher healthcare cost. This review X-rayed the expanding scope of antimicrobial resistance, examined the triads of epidemiological factors in relation to social, economic and disease burdens that promotes the upsurge of resistance to conventional antibiotics and therapeutic failures and proffers useful recommendations that could be helpful in alleviating the problem.

Keywords: *Antimicrobial Resistance, Epidemiological factors, Social Burden, Economic Burdens*.

INTRODUCTION

A drug can be defined as any chemical that can affect living processes and the objective of drug therapy is to provide maximum benefit with minimum harm. Drugs can also be define as substances that are used to treat or prevent diseases. They are used to relieve pains, control mental or physical ailments and diagnose illnesses (http://www.medicinenet.com). Payne (1998) defined drug as any substances other than food that by its chemical or physical nature alters structure or function in the living organism. Drug resistance therefore is the reduction in effectiveness of a drug such as an antimicrobial agent used in curing a disease or condition (h.ttp://www.medicinenet.com). Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to antibiotics [1]. Contrary to popular belief, antibiotic resistance is not a recent phenomenon. Resistance to penicillin was developed by some bacteria as early as 1940, three years before the drug was even approved for public use. The scope of the problem became apparent in the 1980s and 1990s, when scientists and physicians observed treatment failures on a large scale [2].

Antibiotics are products of microorganisms that react with and inhibit the growth of other microorganisms. In some cases, antibiotics have been synthesized by chemists, in which case they are known as chemotherapeutic agents. However, the term antibiotic is better known by lay public. Antibiotics inhibit microbial populations by any of the five major methods. They disrupt cell wall synthesis, interfere with cell membrane function, inhibit protein synthesis, disrupt nucleic acid synthesis and interrupt selected metabolic pathways. Over time, an organism that had once been highly responsive to an antibiotic may become less susceptible, or it may lose sensitivity to the drug entirely. In some cases, resistance to several drugs called multidrug resistance develops. Some drug resistances are developed due to a pre-existing factor in the microorganisms or it may be as a result of some acquired factors. Acquired resistance is of great concern in that it can render currently effective drug useless, thereby creating a clinical crisis and a constant need for new antimicrobial agents[3].

Penicillin resistance for example, results from the production of penicillinase by resistant organism, which can converts penicillin into inactive penicillinoic acid. Resistant strains of *Staphylococcus aureus,* a common but sometimes deadly bacterium was isolated from foot ulcer on a diabetic patient in Detroit, Michigan. Some normally susceptible strains of bacteria may acquire resistance to penicillin because of penicillinase production in genetically adapted varieties of microorganisms. In culture of penicillin-sensitive bacteria, one organism in a hundred million may be a penicillin-resistant mutant. Normally, the

ratio of sensitive to resistant organisms is maintained and no problem develops. When penicillin is present, the sensitive strains do not reproduce whereas the resistant mutants do and eventually dominate the population. This has important clinical implications and is one of the practical reasons why research efforts have been made to develop synthetic penicillin which is resistant to the action of penicillinase [4].

The use and misuse of antimicrobials in human medicine and animal husbandry over the past 70 years has led to a relentless rise in the number and types of microorganism resistance to these medicines, leading to deaths, increased suffering and disability and higher healthcare cost. Controlling the deadliest infectious diseases in the world such as diarrhea diseases, respiratory tract infections and more is difficult today because of the emergence of antimicrobial drug resistance [5]. Resistance has emerged in malaria, tuberculosis and most bacterial infections. Arora (2008) opined that at first, organisms were encountered with low-level resistance to penicillin, and infections caused by these could be treated with larger doses of the antibiotics. Because the low-level resistance was due to mutation which decreases the cell permeability to the antimicrobial agent and if large does are given, then effective concentration of the drug can enter the bacteria cell. In time highly resistant strains emerge which could not be therapeutically controlled [6].

Onyeagba *et.al.,(*2006), reported that there are several reasons why microorganisms may have an inherent resistance to an antibiotic. The organism may lack the structure which the antibiotic inhibits. For instance, some bacteria such as *Mycoplasma* lack typical bacteria cell wall and are naturally resistant to penicillin. The organism may be impermeable to the antibiotic, for instance, most Gram-negative bacteria are impermeable to penicillin G. Some organisms may produce enzymes which alter the antibiotic in an inactive form and render it ineffective. Genetic changes in the microorganism may result to an alteration of the pathway that the antimicrobial agent blocks. For instance, many organisms develop resistance to sulfonamide drugs by the modification of their metabolism to take up preformed folic acid from the environment. Some organisms may be able to pump out an antibiotic entering the cell (efflux)[7].

Nester *et al.,* (2004) observed the alarming trend of increasing antimicrobial resistance and advice everyone to cooperate. On an individual level, physicians as well as the general public must take more responsibility for the appropriate use of these life saving drugs. On a global scale, countries around the world need to make important policy decisions about what is and what is not an appropriate use of these medications [8].

CAUSES OF DRUG RESISTANCE
HUMAN FACTORS

Survey into what is often termed human factors is frequently designed to quantify the relationship and role between the human, antimicrobial appropriated and the targeted causative agents. There is an inevitable negativism about the factors that put each every individual at risks when the information associated with specific antibiotic is disregarded. Human factors include;

Taking of drugs without proper diagnosis and overuse of drugs: It has been estimated that over 50% of the antibiotic prescriptions in hospitals are given without clear evidence of infection or adequate medical indication. Many physicians have administered antibacterial drug to patients with cold, influenza, viral pneumonia and other viral diseases. A recent study showed that over 50% of the patients diagnosed with cold and upper respiratory infections and 66% of those with chest cold (bronchitis) are given antibiotics, even though over 90% of these cases are cause by viruses. Frequently, antibiotics are prescribed without culturing and identifying the pathogen or without determining bacterial sensitivity to the drug. Toxic broad-spectrum antibiotics are sometimes given in place of narrow-spectrum drugs as a substitute for culture and sensitivity testing, with consequent risk of dangerous side effects, opportunistic infections and the selection of drug-resistant mutants [9].

Indiscriminate handling of drug, and over production of antibiotics so as to make money: The sale of antimicrobial drugs is big business. In the United State, millions of pounds of antibiotics valued at billions of dollars are produced annually. Because of the massive quantities of antibiotics being prepared and used, an increasing number of diseases are resisting treatment due to the spread of drug resistant. A good example is *Neisseria gonorrhea,* the causative agent of gonorrhea. Gonorrhea was first treated successfully with sulfonamides in 1936, but by 1942, most strains were resistant and physicians turned to penicillin. Within 16 years a penicillin-resistant strain emerged in Asia. A penicillinase producing *gonococcus* reached the United State in 1976 and is still spreading in this country. Thus penicillin is no longer used to treat gonorrhea[10].

Practices of self medication by people: Drugs are peddled in everywhere in Nigeria with little or no confrontation by the regulatory agency. The most unfortunate things are that the larger percentage of people doing that are, non pharmacist, illiterate that cannot understand what they are recommending to a desperate entity that what to avoid hospital cost where the management are empirical and genuine. They purchase these drugs that are mostly adulterated without proper prescription and self-administered it which eventually will leads to the multiplication of drug resistant strains.

Using of some products as additives: Products such as soap and deodorants often now contain triclosan and other germicides. There is increased evidence that wide spread of triclosan actually favours an increase in antibiotic resistance

Taking of under-dose by patients: The situation is made worse by patients not completing their course of medication. When antibiotic treatment is ended early, drug resistant mutants chances of survival multiplies which could aid the spread of antimicrobial drug resistance.

The use of antibiotics in animal feeds is undoubtedly another factor that increases drug resistance.

The addition of low level of antibiotics to livestock feeds raises the efficiency and rate of weight gain in cattle, pigs and chicken (partially because of infection control in overcrowded animal populations). However, this also increases the number of drug resistant

bacteria in animal intestinal tracts. There is evidence of the spread of bacteria such as *Salmonella* from animals to human populations. Resistance to some antibiotics has been traced to the use of specific farmyard antibiotics. For example, the use of quinolone antibiotic (ciprofloxacin) in swine herbs appears to have promoted ciprofloxacin resistance in pathogenic strains *of Salmonella,* In 2005. the use of fluoroquinolones in United States. Poultry farming was banned in recognition of public health threat[11].

PATHOGENS FACTORS

The use of antibiotics over the last 100 years has led to the development of drug resistant strains of bacteria. These bacterial strains always existed in the microbial population but they never needed to use their resistance mechanisms because they were never confronted with the antibiotic. With widespread antibiotic use, the susceptible bacteria were those with resistance. They quickly multiplied to form populations of drug resistant microorganisms. Examples antimicrobial drug resistance episodes are as follows;

Staphylococci: In 1944 most *Staphylococci* were susceptible to penicillin-G, though a few resistant strains-had been observed. After massive use of penicillin, 65-85% *of Staphylococci* isolated from hospital in 1945. Were -lactamase producers and thus resistant to penicillin-G. The advent of -lactamase penicillin provided a temporary respite, but infections due to penicillin resistant *Staphylococci* are common. Presently, penicillin resistant *Staphylococci* include not only those acquired in hospitals but also 80-90% of those isolated in the communities. These organisms also tend to be resistant to other drugs like tetracycline [12].

Meningococci*:* Until 1962, *Meningococci* were uniformly susceptible to sulfonamides and these drugs were effective for both prophylaxis and therapy. Subsequently, sulfonamide-resistant *Meningococci* spread widely, and the sulfonamides have now lost their usefulness against meningococcal infection. Penicillin remains effective for therapy and rifampicin is employed for prophylaxis. However rifampicin-resistant: *Meningococci* persist in about 1% of individuals who have received rifampicin for prophylaxis[13].

Pneumococci: *Streptococcus pneumoniae* was uniformly susceptible to penicillin-G until 1963 when relatively penicillin-resistant strains were found in South Africa, Japan, Spain and later worldwide. In the United States, 5-10% of *Pneumococci* are resistant to penicillin-G. The penicillin resistance is due to altered penicillin binding proteins. Penicillin resistance in *Pneumococci* tends to be clonal. *Pneumococci* also are frequently resistant to trimethoprim sulfomethazaxole and some times to erythromycin and tetracycline [14].

Salmonella* and *E coli: These come directly from contaminated food. Of the meat that is contaminated with *E coli,* eighty percent of the bacteria are resistant to one or more drugs made. *Salmonella* was first found in humans in the 1970s and in some cases resistant to as many as nine different antibiotics.

Clostridium difficile: This is a nosocomial pathogen that causes diarrhea diseases in hospitals worldwide. Clindamycin-resistant *C. difficile* was reported as the causative agent of large outbreaks of diarrhea in hospital in New York, Arizona, Florida and Massachusetts between 1989 and 1992. Geographically dispersed outbreaks of *C. difficile* strains resistant to fluoroquinolone antibiotics such as ciprofloxacin and levaquin (Levofloxacin) were also reported in North America in 2005[15].

Acinetobacter baumannii: On November 5, 2004, the Centers for Disease Control and Prevention (CDC reported an increasing number *of Acinetobacter baumannii* in bloodstream infections in patients at military, medical facilities in which service members injured in the Iraq/Kuwait region during "Operation Iraq freedom" and in Afghanistan during "Operation Enduring Freedom" were treated. Most of these showed multidrug resistance with few isolates resistant to all drugs tested [16].

ENVIRONMENTAL FACTORS

Health is an extra-ordinary complex amalgam of good fortunes, matching expectations; this is because the factors which lead to inappropriate use of antibiotics in searching for health and eventually lead to antimicrobial resistance are far more complex. Therefore, community attitudes are perhaps the hardest to change because they often conspire against the fundamental rules but engage in rat race to the acceptance of new ideas and believes as preventive rules but with no proves. The following environmental factors include;

Lackadaisical attitudes of regulatory agencies: Due to lack of the modern facilities, underfunding, lack of regular training, the regulatory agencies are grossly incompetent to handle and tackle effectively the evolution of the over-the counters fake drugs and unapproved chemist shops that are everywhere in Nigeria. And since there is no proper verification to ascertain the comparative dosage quantities of these drugs, this could easily support the spread of resistant strains because most of those antibiotics become easily metabolizing nutrient source for the targeted bacteria.

Inordinate drives for profit: There are many criminal manufacturing jungles and hide outs in our environment that are owned by the non pharmacists, the casualties in the school of pharmacy and the likes which are yet undetected because of the geographical terrain of the country and they are pouring well packaged metabolic poison as drugs to the markets which could aid the spread of antimicrobial drug resistance factors.

Non adequate inspection facilities at the port of entrance: Due to the porosity of our port of entrance, non state-of-the art- facilities and sit tight personnel that are refuse to be retired with their archaic method of drug inspections and illegal importation, fake drugs had filtered to everywhere in the country and since their chemical composition, quality and quantity are inadequate, this makes it easy for bacterial with antibiotics degrading enzymes to survive and thereafter results in upsurge and spread of resistant strains of organisms.

Combinations of herbal plant obtained from the local herb sellers with antibiotics: The inherent greediness in potentially economically enslaved black man encourage them to always attempt double barrel approach to the issues of their personal health, because the finances and well equipped community health care centers that are affordable are virtually non existing. In an attempt to get heal quick, some combine un-standardized herbal

concoction with conventional antibiotics which could lead to the development of strange bacteria with transferable genetic features, horizontally or vertically and hence results in the spread of antibiotics resistance.

Government policy: The non sophistication of government policies ranging from non readiness of government to invest more capital on pharmaceutical raw materials and products, over-taxation of the existing productions companies, not putting people into consideration within the limit of their spendable income, non readiness to make information on the danger associated with the abuse of drugs available to the community through their orientation agencies and also in a community where physician wanted exercise their supremacy over the pharmacists instead of working together in harmony and move the system forward in right direction, all these are sure recipe for the upsurge of antimicrobial drug resistance[17].

THE BURDEN OF DRUG RESISTANCE

The emergence and spread of antibiotic or antimicrobial resistance has become a major public health threat worldwide. This has imposed an enormous burden on healthcare systems and on the society in general. The antibiotics that was tagged to be "magic bullet" in 1900s by Paul Ehrlich at the onset of their discoveries are no more magical but has becomes burdens. Some of these burdens include;

Social burden: Resistance to drug has caused sufferings, incapacitation and death. Each year millions of people die as a result of drug resistance. Patients infected with resistant strains are more likely to be sick, spend more time in the hospitals and die of the infection. In the United States, thousands of patients die .every year from infections that lack effective drugs and 60% of hospital infections are caused by drug resistant microbes. For many years, concerned observers reported the gradual development of drug resistance in *Staphylococci, Salmonella* and other *Gonococci.* But during the past decades, the scope of the problem has escalated. It is now a common event to discover microbes that have become resistant to relatively new drugs in a very short time[18].

Economic burden: Drug resistance has imposed an enormous financial burden on both healthcare systems and on society in general, because of direct cost due to prolonged illnesses and treatments in hospitals, indirect cost due to loss of productivity, and societal costs due to morbidity and mortality. This has led to already-scarce healthcare resources being diverted to infection control efforts, and will have long-term implications due to loss of confidence in the medical profession and in the public healthcare delivery system (http//ww\v.euburden.info.com). Billions of dollars are spend in drug resistance. For example, in the United States, estimates of the loss of antibiotic effectiveness in outpatient prescriptions because of drug resistance ranges from 378 million US dollars to 18.6 billion US dollars[19].

CONCLUSION

Drug resistance is considered an important contributor to the burden of infectious diseases. Although there are no current estimates of the magnitude of that burden, there are scores of documented examples of the growing problem presented by drug resistance microbes. The expanding scope of drug resistance among major infectious diseases also carries a substantial economic burden in developing countries, although the full amount has not been assessed. Drugs are essential for human being to withstand attack from microorganisms. Without these drugs microbes would have overpowered us. Because of this, it is important that humans should fight against drug resistance. Jehovah witness magazine tagged; Awake (2009) gave an effective guideline for the safe use of prescribed drugs by stating thus; "follow direction carefully, don't change doses without consulting your doctor, stop taking unprescribed medication on your own, and do not use drugs prescribed for someone else[20]

RECOMMENDATION

The findings of this research review will benefit all if we apply the following recommendations;

- Patient should undergo proper diagnosis before giving any medication.
- Physician's prescription should be strictly followed.
- Efforts by NAFDAC (or any relevant regulatory agencies) to ban substandard drugs should be encouraged by all.
- Government should reduce the abuse of antibiotics through educational programs for health workers to requiring written justification from the physician on all antibiotics prescribed.
- Herbal medication should be encouraged after effective research and approval.
- Government should make a law prohibiting unqualified people from selling and prescribing drugs especially antibiotics.
- Patients must comply with and carefully follow the physician's guidelines. It is important for the patients to take the correct dosage, by the best route, for the appropriate period. This discourages the selection for mutants that can resist low drug levels and ensures elimination of the pathogen.
- The addition of antimicrobial drugs to animal feeds must be curtailed worldwide.
- Administration of two or more drugs together increases the chances that at least one of the drugs will be effective and that a resistant strain of either drug will not be able to persist. The basis for this combined therapy method lies in the unlikelihood of simultaneous resistance to several drugs.
- Vaccine should be used whenever possible to provide alternative protection.
- An unrecommended drug is a suicide pill, people should desist such practices to avoid morbidity, deformity or death.

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