# THE ANTIBACTERIAL RESISTANCE: A NEW THREAT

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## SUMMARY

The current trend of antibacterial resistance has been reviewed. In spite of the continuous development in modern medicine in terms of diagnosis and treatment, the rate of emergence of resistance strains of microbes which are untreatable by any known antibiotics is very alarming. Consequently, there is a serious threat to the lives and health of people. The basis and factors that promote antimicrobial resistance are highlighted and various strategies were suggested to successfully contain the antibiotic resistance. It was apparent that a pharmaceutical strategy that entails rational use of antibacterial agents and preservation of microbial communities is of great value in reversing the resistance.

## INTRODUCTION

The discovery and use of antimicrobial agents and immunization procedures against infectious disease have contributed immensely to the average life span and health of humans in developed countries. However, evolution of antibiotic resistance gave birth to killer plagues and flesh - eating bacteria. For instance, the antibiotic resistance strains of staphylococcus and streptococcus are putting the lives and health of people at risk.

Recently in America, in three geographically separate patients, an often deadly bacterium, *Staphylococcus* aureus, responded poorly to a once reliable antidote - the antibiotic vancomycin (1). Fortunately, in those patients, the staph microbe remained susceptible to other drugs and was eradicated. In Nigeria (2,3,4) and most of Africa (5) resistant to vancomycin is yet to be recorded against Gram - positive bacteria. However, vancomycin resistance enterococci (6-9) and reduced susceptibility to vancomycin by *Staph aureus* (10-15) have been reported in the US, Europe and Japan.

Worldwide, many strains of *S. aureus* are already resistant to all antibiotics except vancomycin. Emergence of forms lacking sensitivity to vancomycin signifies that variants untreatable by every known antibiotic are on the way. *S. aureus*, a major cause of hospital acquired infections, has thus moved one step closer to becoming an unstoppable killer.

The looming threat of incurable *S. aureus* is just the latest twist in an international public health nightmare.

Antibiotics became widely available in the 1940's and have been hailed as miracle drugs, magic bullets able to eliminate bacteria without doing much harm to the cells of treated individuals (16). Antimicrobial agents (antibiotics and related medicinal products) have transformed our ability to treat many infectious diseases that were previously killers. They are also used in agriculture to stimulate growth in livestock and to reduce incidence of disease caused by crowded, factory-farm conditions.

However, the misuse, over-prescription and abuse of antibiotics have allowed resistant strains of bacteria to develop and once again threaten health and life. Diseases that were virtually eliminated with the introduction of antibiotics are mutating, gaining strength and resisting treatment. We have come almost full circle!

A "post antimicrobial era" has been feared to be an era whereby available drugs may no longer be effective against bacterial pathogens (16, 17, 18).

Today, many deaths have been attributed to antibiotic resistant streptococcus pneumonia. Even with early diagnosis and every treatment option available to modern medicine, physicians, pharmacists, nurses and their patients are helpless.

Bacterial resistance to commonly used antimicrobial agents in Nigeria was reported as far back as the 1970s and tetracycline, cotrimoxazole, chloramphenicol, streptomycin

and erythromycin were implicated in self-medication (19,20).

It is glaring that now is the time to review the usage of antibiotics in each health institution over time and formulate policies that may preserve the effectiveness of antimicrobial chemotherapy and protect the health and life of people.

The objective of the current study is to review the basis of microbial resistance and proffer strategies to reduce its emergence and spread.

## THE BASIS OF MICROBIAL RESISTANCE OF ANTIBIOTICS

Most of the microorganisms that produce antibiotics are resistant to the action of their own antibiotic. However the organisms are affected by other antibiotics and their antibiotic and may be effective against closely related strains. Generally speaking how or why bacteria are resistant to their own antibiotics is unknown, but it may be worth pondering or studying if we are to understand the cellular and molecular basis of resistance.

## INHERENT (NATURAL) RESISTANCE

Bacteria may be inherently resistant to an antibiotic. For example, streptomycetes has some gene that is responsible for resistance to its own antibiotic, or a Gram-negative bacterium has an outer membrane that establishes a permeability barrier against the antibiotic, or it lacks the target or reaction that is hit by the antibiotic (21) Some bacteria may have multidrug afflux systems such as *AcrE in E. coli, MexB in P. aerogenous* or presence of a drug inactivation enzyme such as AmpC cephalosporinase in klebsiella (22).

## ACQUIRED RESISTANCE

Bacterial populations, previously sensitive to antibiotics can become resistant through changes in the bacterial genome. Two genetic processes in bacteria (23) are responsible for acquired resistance:

### (i) Mutation and selection (vertical evolution)

This is strictly a matter of Darwinian evolution driven by principles of natural selection. A spontaneous mutation in the bacterial chromosome imparts resistance to a member of the bacterial population. In a selective environment of the antibiotic, the wild type (non-mutants) is killed and the resistant mutant is allowed to grow and flourish. The mutation rate for most bacterial genes is approximately 10-8(21). This implies that if a bacterial population doubles, there is likely to be a mutant present for any given gene. Examples are target site modification, reduced permeability or uptake, metabolic by-pass and depression of multidrug efflux systems.

### (ii) Exchange of genes between strains and species (horizontal evolution)

Frequently, bacteria will gain a defense against an antibiotic by taking up resistant genes from other bacterial cells in the vicinity. Indeed the exchange of genes is so pervasive that the entire bacterial world can be thought of as one huge multicellular organism in which the cells interchange their genes with ease. These resistant genes usually are carried on plasmids, a tiny loops of DNA that can help bacteria survive various hazards in the environment. They may also occur on the bacterial chromosome. One bacterium will pass resistant traits to others by giving them a useful plasmid.

However, viruses that occasional extract a gene from one bacterial cell and inject it into a different one (24) can also transfer resistant genes. In addition, after a bacterium dies and releases its contents into the environment another will take up a liberated gene for itself. The mechanisms also involve drug inactivation, efflux system, target site modification and metabolic by-pass. The possibility of passive acquisition of antibiotics resistant organisms from one patient to another has been reported to be higher in developing countries where the standard of environmental hygiene is very low (25).

The combined effects of fast growth rates, high concentrations of cells, genetic processes of mutation and selection, and the ability to exchange genes, account for the extraordinary rates of adaptation and evolution that can be observed in the bacteria. For these reasons bacterial adaptation (resistance) to the antibiotic environment seems to take place very rapidly in evolutionary time.

### FACTORS THAT PROMOTE ANTIBIOTIC RESISTANCE

Although many factors can influence antibiotic resistance, the two main factors are the prevalence of resistance genes and the extent of antibiotic use. If the collective bacterial flora in a community has no genes conferring resistance to a given antibiotic, the antibiotic will successfully eliminate infection caused by any of the bacterial species in the collection. On the other hand, if the flora posses resistance gene and the community uses the drug persistently, bacteria able to defy eradication by the compound will emerge and multiply.

### IRRATIONAL PRESCRIPTION AND USE OF ANTIBIOTICS

There is generally an unjustified faith in the "healing power" of antimicrobials. Physicians out of sympathy or pressure by patient expectations of treatment may prescribe antibiotics even in the absence of appropriate indications. Many physicians agree to misguided patients who demand antibiotic to treat colds and other viral infections that cannot be cured by the drugs. Researchers at the Center for Disease Control and Prevention have estimated that some 50 million of the 150 million outpatient prescriptions for antibiotics in the US every year are unnecessary (1).

In Nigeria, antimicrobials can easily be purchased in pharmacies and markets without prescription. Patients often comply poorly with the prescription, they forget or interrupt their treatment prematurely or may be unable to afford a full course, thereby creating an ideal environment for microbes to adapt rather than be killed.

Further, low quality antibiotics (fake, counterfeit or expired) are still sold and used for self-medication or prophylaxis.

It is common knowledge that when an antibiotic attacks a group of bacteria, cells that are highly susceptible to the drug will die. But cells that have some resistance from the start, or that acquired it later may survive, especially if too little drug is given to overwhelm the cells that are present. Those cells, facing reduced competition from susceptible bacteria will then proliferate. When the drug attacks disease-causing bacteria, they also affect benign bacteria in their path thus eliminating drug-susceptible benign bacteria that could otherwise limit the expansion of pathogens. They simultaneously encourage the growth of resistant benign bacteria thereby increasing the reservoir of resistance traits in the bacterial population.

For example, the widespread use of cephalosporin antibiotic has promoted the proliferation of the once benign intestinal bacterium *E. faecalis*, which is naturally resistant to those drugs. In most people the immune system is able to check the growth of even multidrug-resistant *E. faecalis*, so that it does not produce illness. But in hospitalized patients with compromised immunity, the enterococcus can spread to the heart valves and other organs and establish deadly systemic disease (1). The benign effect has also enabled multidrug-resistant strains of Acinetobacter and Xanthomonas to emerge and become agents of potentially fatal blood-borne infections in hospitalized patients (26).

### ANTIBIOTICS MISUSE/ABUSE

If administered correctly, perhaps only half of the antibiotics consumed every year in Nigeria would have been appropriate to cure bacterial infection. In Nigeria, there is easy access to all classes of antimirobials as they can be readily bought from pharmacies, drug stores, street hawkers and in the open markets (26, 27). This unrestricted (over-the-counter) accessibility to antimicrobial agents enhances the selection and spread of resistant bacteria (28, 29, 30).

### SELF MEDICATION

In the industrialized world, most antibiotics are available only by prescription, but this restriction does not ensure proper use. People often fail to finish the full course of treatment. Patients then stockpile the left over doses and medicate themselves, or their family and friends in less than therapeutic amounts. In both circumstances, the improper dosing will fail to eliminate the disease agent completely and will furthermore encourage growth of the most resistant

strains, which may later produce hard-to-treat disorders.

In a developing nation like Nigeria the use of antibiotics is grossly out of control. Many antibiotics are available over the counter and when resistance becomes a clinical problem, there may not be any substitute because there is no access to new generation antibiotics, which are of course very expensive.

## FAKING AND ADULTERATION

The usually high cost of antibiotics renders them unaffordable to the majority of the developing world population. This leadS to the proliferation of cheaper, but substandard or fake drugs. Continuous use of such suboptimal doses of antibiotics usually results in development of drug resistance.

## VETERINARY AND AGRICULTURAL MISUSE

Antibiotics are also used in treating or preventing infection or mixed with feed to promote the growth of livestock. However, the amounts used to promote growth are too small to combat infection and may be used for weeks or months at a time. No one is entirely sure how the drugs support growth. However, the long term exposure to low doses selects increasing numbers of resistant bacteria in the treated animals which may then pass the microbe to caretakers and, more broadly, to people who prepare and consume undercooked meat. Imported frozen foods or meat have been speculated to harbour some resistant strains of *Staphylococcus aureus*. Similarly, in mechanized agriculture especially in developed worlds, antibiotics are applied as aerosols to acres of fruit trees, for controlling or preventing bacterial infections. High concentrations may kill all bacteria on the trees at the time of spraying, but lingering antibiotic residues can encourage the growth of resistant bacteria that later colonize the fruit during processing and shipping of imported fruits. The amount of resistant bacteria people acquired from food is apparently not trivial.

## CONTAINMENT OF ANTIMICROBIAL RESISTANCE: A PHARMACEUTICAL STRATEGY

Antimicrobial resistance is not an infectious disease, like smallpox or poliomyelitis that we can eradicate. It is a natural response of microbes to exposure to antimicrobial agents. Therefore the approach has to be one of containment, aiming to reduce the rate of emergence and spread of resistance. It is important to recognize that bacteria are a natural and needed part of life. Bacteria, which are microscopic, single-cell entities, abound on inanimate surfaces and on parts of the body including the skin, mucous membrane and the lining of the intestinal tract. In fact they often protect us from disease because they compete with and thus limit the proliferation of pathogenic bacteria. It should also be realized that although antibiotics are needed to control bacterial infections, they could have broad, undesirable effects on microbial ecology. That is, they can produce long lasting change in the kinds and proportions of bacteria such as a mix of antibiotic-resistant and antibiotic-susceptible types. Antimicrobials should therefore be used only when they are truly needed and they should not be administered for viral infections, over which they are not effective.

It is important to determine the magnitude and trends of resistance and to define the relative importance of different contributing factors such as therapeutic, behavioural, economic, social and health system factors, and veterinary and agricultural misuse. Based on this understanding, it should be possible to develop effective methods to contain antimirobial resistance in Nigeria in particular and the world over in general.

## RATIONAL PRESCRIPTION AND USE OF ANTIMICROBIALS

It is obvious that there is an urgent need for a policy by the government, to enforce rational prescription and use of antibiotics, restrict the sales and distribution of antibiotics to registered pharmacies and hospitals as prescription products. When patients receive prescriptions for antibiotics, they should complete the full course of therapy. Physicians, when possible, should try to identify the causative pathogen before beginning therapy so that they can prescribe an antibiotic

targeted specially to that microbe.

### CONFORMING TO WHO POLICIES

Through its antimicrobial resistance monitoring (ARM) activities, WHO assists developing countries, by the provision of training, quality assurance laboratory reagents and computer software (WHONET), to detect and monitor resistance by establishing laboratory-based surveillance networks. WHO also sponsors national policy workshops which aim to improve collaboration between decision makers in developing strategies for monitoring resistance and improving rational use of antimicrobials, including educational programmes for prescribers and users. Other strategies include identifying human medical resistance problems resulting from antimicrobial use in livestock production and improving resistance monitoring in food borne bacteria. It is time for our health ministry to create divisions like Drug Management and Policy whose major responsibility would be to develop and implement strategies for the containment of antimicrobial resistance.

### IMPROVED HYGIENE

Cleanliness people say is next to Godliness; personal and environmental hygiene is very important. The public should wash raw fruit and vegetables thoroughly to clear off both resistant bacteria and possible antibiotic residues. Washing hands after seeing each patient is a major but too often overlooked precaution by health workers.

### INTRODUCTION OF NEW ANTIBIOTICS

New antibiotics could provide more option for treatment. However, because of the technical and regulatory hurdles involved in getting a new product to the market and the structural similarity that exists between the new and the existing antibiotics, researchers should work on strategies that will give new life to existing antibiotics. Levy (1) is already developing a compound to jam a microbial pump that ejects tetracycline from bacteria. When the pump is inactivated, tetracycline can penetrate bacterial cells effectively.

### USE OF NATURAL REMEDIES

Nature offers remedies for several microbial infections, although the mechanisms of their activities have not been elucidated. More scientific investigations should be carried out on natural plants with antimicrobial activity with a view to formulating natural remedies for the resistant microorganisms.

### PUBLIC ENLIGHTENMENT

In order to contain bacterial resistance effectively, there is an urgent need to educate people especially in the rural areas on the implications of antibiotic misuse or abuse. People must realise that they all have a role to play in reversing the looming danger of "absolute bacterial resistance".

### ENVIRONMENTAL MONITORING

Correcting a resistance problem requires both improved management of antibiotic use and restoration of the environmental bacteria susceptible to these drugs. If all reservoirs of susceptible bacteria were eliminated, resistant forms would face no competition for survival and would persist indefinitely.

In the ideal world, public health officials should know the extent of antibiotic resistance in both the infectious and benign bacteria in a community. To treat a specific pathogen, physicians should favour an antibiotic with little or no resistance from any bacteria in the community. And the pharmacist should deliver enough antibiotics to clear the infection completely without destroying all competing susceptible microbes in the body. However, the problem, of course, is that no one knows yet how to determine the "antibiotic threshold" which is a level of antibiotic usage able to correct the infection within a community or hospital without encouraging propagation of resistant strains. Furthermore, most hospitals and communities lack detailed data on the nature of their microbial populations.

### INTERNATIONAL COOPERATION/ALLIANCE

Control of antibiotic resistance on a wider, international scale will require cooperation among countries around the globe and concerted efforts made to educate the

world's populations about drug resistance and the impact of improper antibiotic use. As a step in this direction, various groups are now attempting to track the emergence of resistant bacteria strains. For example, an international organization, the Alliance for the Prudent Use of Antibiotics, in Boston, with Professor Stuart Levy as the president, has been monitoring the worldwide emergence of such strains since 1981. The Nigeria chapter is headed by Professor Adebayo Lamikanra.

## CONCLUSION

The time has come for global society to accept bacteria as normal, generally beneficial component of the world and not try to eliminate them except when they give rise to disease. Reversal of resistance requires a new awareness of the broad consequences of antibiotic use, a perspective that concerns not only the curing of bacterial disease but also the preservation of microbial communities. In that way bacteria susceptible to antibiotics will always be there to outcompete resistant strains.

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