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Antibiotic Resistance: Challenges and Prospect for Therapy in Developing Countries

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Authors' contributions

This work was carried out in collaboration between all authors. Author MYT designed the study, managed the literature searches and prepared the first draft of the manuscript. Authors OI and FOI thoroughly reviewed the scientific contents and made desired corrections in the final draft of the manuscript. All the authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The hope raised by the discovery of antibiotics has been marred by the emergence of antibiotic resistance. The major reason for this is the inappropriate use of antibiotics due to a lack of uniform policy and disregard to hospital infection control practices. Bacterial infections increase the morbidity and mortality, increase the cost of treatment, and prolong hospital stay adding to the economical burden on the nation. The problem is further compounded by the lack of education and "over the counter" availability of antibiotics in developing countries where no one really has a good idea of the extent of antibiotic resistance, because it hasn't been monitored in a coordinated fashion and there is no good national system to test for antibiotic resistance. This menace can be managed by a lot of concerted efforts with only a few prescribed in this review study.

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1. INTRODUCTION

Antibiotics are given to human for protective treatment of infectious diseases and about 90% of antibiotics are used outside the hospitals environment and the remainder in the hospitals. Antibiotics are not only used in excess but also inappropriately and this accounts for 20% to 50% of all antibiotics used [1,2]. Other studies have shown that most bacteria that cause infections are resistant to at least one of the antimicrobial agents most commonly used for treatment in the hospitals while others are resistant to all approved antibiotics and can only be treated with drugs that is under test or that is potentially toxic [1,3]. Resistance is defined as the inability of normal dosage and concentration of antimicrobial agent to inhibit the growth of bacteria. Similarly, multiple drug resistance is defined as the resistance to two or more classes of antibiotics [4,5]. Cross resistance is define as resistance to an antibiotic to which the organism has not been exposed to due to acquisition of resistance to another antibiotic [4,6]. As reported previously, resistance to multiple drugs was first detected among enteric bacteria—namely, *Escherichia coli*, *Shigella* and *Salmonella* spp which posed severe clinical problems and cost lives, particularly in developing countries. However, the resistance problem was perceived by those in the developed countries, as inquisitiveness of little health concern confined to gastrointestinal organisms in distant countries. This attitude changed in the 1970s when *Haemophilus influenzae* and *Neisseria gonorrhoeae*, emerged with resistance to ampicillin and, in the case of *Haemophilus*, with resistance to chloramphenicol and tetracycline as well [4,7]. The rate of occurrence of resistance increases in many different bacteria which are gingered by increasing antimicrobial use especially in developing countries where antimicrobials were readily available without written order by a physician. The spread of the resistance was aided by poor sanitation conditions while access to new potent but more expensive antibiotics was prevented by small proportion of healthcare budgets [8]. The severity of and difficulty in treating multi-drug resistant (MDR) strains enhance the use of several, sometimes six to seven different, drugs [9].

Antibiotic resistance among bacteria constitute a nuisance throughout the world. It is said that gradual change of bacteria towards resistance to antimicrobial drugs, including multidrug resistance, is unavoidable because it represents a particular aspect of the general evolution of bacteria that is unstoppable [10]. Antibiotic resistance is no longer a problem of the developing countries alone. Even after all the progress made in medicine and the availability of a large number of antibiotics today, a person can die in a developed country also due to infection with resistant bacteria [11,12].

2. OVERVIEW OF MECHANISM OF ANTIBIOTIC RESISTANCE

Drug resistance is mobile; transfer of resistance genes among bacteria may occur by means of mobile genetic elements such as bacteriophages, plasmids, naked DNA or transposons. These genes are usually made to act against a particular class or type of antibiotic, although several genes, each carrying a single drug resistance characteristic, can accumulate in the same organism. In the absence of plasmids and transposons, resistance can also be mediated in bacteria through sequential mutations in chromosomes [4,8,13,14].

There are two (2) basic mechanisms by which organisms develop resistance to antimicrobial agents [12]. These are genetic and biological mechanisms.

2.1 Biological Mechanism of Antibiotic Resistance

Resistance can only develop if a gene is able to express itself and produce a tangible biological effect resulting in the loss of activity of the antibiotic (Table 1) [12]. These biological mechanisms are described below;

2.1.1 Reduced drug accumulation

This is achieved by decreasing the rate of inflow of drug into the cell and/or increasing active effluence of the drug across the cell surface (porins) [15]. Most Gram-negative bacteria outer membrane act as permeability barrier against entry of antibiotics e.g. penicillin. The efflux pumps, located in the cell membrane are one method of protection that many bacteria use against the influx of antibiotics [16]. The offensive antibiotic is pumped out of the cells that possess these pumps before antibiotic can cause harm to the cellular machinery.

2.1.2 Alteration of drug target site

This occurs in different dimension. For example, beta-lactam antibiotics (eg penicillin) disrupt cell wall synthesis by binding to the active site of penicillin binding protein (PBP) and irreversibly inhibit the final cross-linking (transpeptidation) of the nascent peptidoglycan layer. However, beta-lactam resistant bacteria possess altered penicillin binding proteins; as such the beta-lactam cannot bind as effectively to these altered PBPs. Hence, the beta-lactams are less effective at disrupting cell wall synthesis [17]. Similarly, in bacteria that are susceptible to vancomycin, vancomycin prevents transverse connection of peptidoglycan by binding to D-ala-D-ala dipeptide to the muramyl peptide. However, organisms that acquire vancomycin resistance does so by changing D-ala-D-ala to D–ala–D–lactate, which does not bind to vancomycin [18]. Also, the possession of ribosomal protection protein by some microbes protects ribosome by binding them and changing their confirmation. The change in the ribosome shape prevent antibiotic from binding and interfering with protein synthesis [16].

2.1.3 Enzymatic inactivation

Some bacteria produce enzymes that are capable of inactivating, degrade, or modify the antimicrobial agent [12].

Resistance to beta–lactam antibiotics occur due to the production of the enzyme β-lactamase or the penicillinase which hydrolyzed or break open the β-lactam ring of the antibiotic, rendering the antibiotic ineffective. This mechanism can be chromosomal or plasmid mediated [17].

2.1.4 Alteration of metabolic pathway

In bacteria that are susceptible to sulphonamides, Para-amino benzoic acid (PABA) is an important precursor metabolite for the synthesis of folic acid and nucleic acid. However, bacteria that are resistant to sulphonamides do not require PABA. Instead, like mammalian cell, they turn to utilizing preformed folic acid [19].

2.1.5 Loss of enzyme in drug activation

This is a new mechanism of antibiotic resistance. In this case, the antibiotic itself is an inactive form of the drug (prodrug), which has no effect against the bacteria. Rather, the prodrug is activated by bacterial enzymes into the most active form which has deleterious effect on the organisms. For example, Metronidazole is a prodrug which when activated by bacterial enzyme (nitroreductase) forms reactive species that damage the bacterial DNA. Thus resistance to this antibiotic can result from mutations in this enzyme or acquisition of a new enzyme to replace the sensitive one [18].

2.2 Genetic Mechanism

In this case resistance to antibiotic can be natural (intrinsic) or acquired. Natural form of antibiotic resistance is caused by spontaneous gene mutation in the lack of selective pressure due to the presence of antibiotics (Table 2).

Natural resistance is the inherent ability of a bacterial species to withstand the activity of a particular antimicrobial agent through its natural occurring genes found on the host chromosomes which allow tolerance of a particular drug or antimicrobial class. Such natural insensitivity can be due to: Lack of affinity of the drug for the bacterial target, inaccessibility of the drug into the bacterial cell, extrusion of the drug by chromosomally encoded active exporters, innate production of enzymes that inactivate the drug [4,20].

Acquired mechanisms involved transfer of antimicrobial genes from one bacterium to another bacterium (Table 2). The genes that carry the resistant determinants are usually located on plasmids, bacteriophages, transposons, and other mobile genetic material. Resistance genes can also be located as gene cassette within integrons [21]. The most common mechanisms in which the resistant determinants are transferred are conjugation, transformation and transduction (Fig. 1). Conjugation is accomplished via plasmids and conjugative transposons, transduction via bactriophages, while transformation occur through incorporation into the chromosome of chromosomal DNA, plasmids, and other DNAs from dying organisms [4]. Although transfer of resistant gene among bacteria within the same genus is common, this process is also not uncommon between bacteria of different genera, including transfer between distant organisms as Gram-positive and Gram-negative bacteria. Plasmids contain genes that are essential for the initiation and control of replication. Some plasmids also contain genes that ensure stable inheritance, such as conjugal transfer. Plasmid may also carry genes that provide resistance to naturally occurring antibiotics in a competitive environmental niche. More than one plasmid can exist within a single

bacterium, where their genes add to the total genetics of the organism. Transposons are mobile genetic elements that can exist on plasmids or integrate into other transposons or the host's chromosome. Integrons have been recognised as naturally occurring gene expression elements Integrons contain collections of genes cassettes that are responsible for the recruitment and assembly of antibiotic resistance genes in clusters. Resistance genes that emerge on a plasmid, located within a transposons or an integrons, may be transferred to other strains and species, enabling it to penetrate into niches not accessible to its original host strain [4,21-23].

Table 1. Mode of action and Biological mechanisms of resistance to some class of antibiotics

Class of antibiotic	Mechanism of action	Mechanism of resistance	Specific means of achieving resistance
Aminoglyosides e.g. gentamicin,	Inhibition of protein synthesis by binding to the 30s ribosomal subunit	Modification of enzymes	Modifying enzymes alter various sites on the aminoglycosides such that the ability of this drug to bind the ribosome and halt protein synthesis is greatly diminished or lost entirely.
		Reduced uptake	The number of character in porin channel is changed or altered such that aminoglycosides uptake is diminished.
Quinolones e.g. ciprofloxacin,	Bind to DNA gyrase and inhibit supercoiling	Reduced uptake	Alterations in the outer membrane diminishes uptake of drug and/or activation of an "efflux" pump that removes quinolones before intracellular concentration is sufficient for inhibiting DNA metabolism.
		Altered target	Changes in DNA gyrase subunits decrease the ability of quinolones to bind this enzyme and interfere with DNA processes
Beta-lactams e.g. ceftazidime	Inhibiting bacterial cell wall synthesis and binding to penicillin-binding protein (PBPs)	Enzymatic destruction	Destruction of beta-lactam rings by beta-lactamase enzymes inhibits the ability of antibiotic to bind to PBP (Penicillin-binding protein), and interfere with cell wall synthesis.
		Altered target	This is achieved by mutational changes in original PBPs or acquisition of different PBPs which will lead to inability of the antibiotic to bind to the PBP and inhibit cell wall synthesis
		Reduced uptake	Beta-lactam antibiotics usually cross the outer membrane to reach the PBP of Gram-negative bacteria. Decreased or a change in the number or character of these channels can reduce beta-lactam uptake.
Glycopeptides e.g. vancomycin	Preventing cross-linking of peptidoglycan	Altered target	Alteration in the molecular structure of cell wall precursor components decreases binding of vancomycin so that cell wall synthesis is able to continue.

Table 2. Genetic mechanisms of antibiotic resistance

Resistance through	Mechanisms/Genetic elements involved
Mutation	Caused by exogenous agents, DNA polymerase errors, deletions, insertions and duplications.
Horizontal genes transfer	Transformation, transduction or conjugation. Many of the resistance genes are carried on plasmids, transposons or integrons which Facilitates acquisition and dissemination of these genes

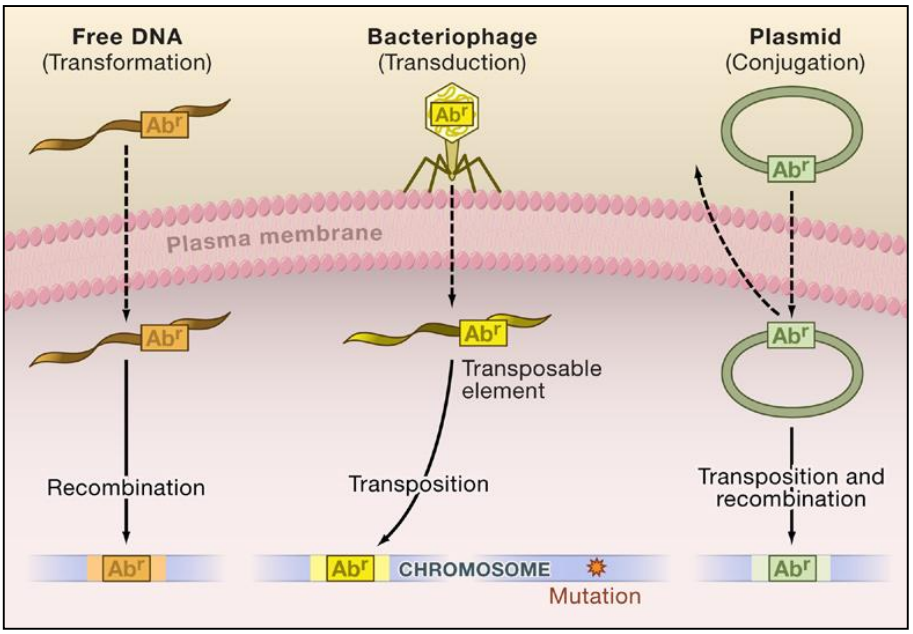

Fig. 1. Acquisition of antibiotic resistance: Adopted from [22]

Bacteria can become antibiotic resistant (Abr) by mutation of the target gene in the chromosome. They can acquire foreign genetic material by incorporating free DNA segments into their chromosome (transformation). Genes are also transferred following infection by bacteriophage (transduction) and through plasmids and conjugative transposons during conjugation. The general term transposable element has been used to designate

3. CHALLENGES OF ANTIBIOTIC RESISTANCE

The erosion of effective antimicrobial agents continues as we witness the increased rate of occurrence of resistance to all drugs—in particular, the fluoroquinolones, vancomycin and carbapenems, which are often the drugs of last resort. Considering the inflow of relative few/absence of new antimicrobials to the market and with new imminent danger arising from resistant Gram-negative bacteria, however, the number of drug options leaves us perilously close to none or only a single effective agent for some life-threatening infections [4].

Several studies have shown that Hundreds of β-lactam-degrading enzymes from bacterial strains are rapidly undermining the effectiveness of penicillins and late-generation cephalosporin agents. The increase in bacterial enzymes which are active against carbapenems and most other β-lactams is disturbing and frightening [4,24]. It was also reported that treating infections caused by some strains of *Pseudomonas aeruginosa* was abortive to all available antibiotics which consequently led to use of relatively toxic antibiotic, colistin, which served as desperate remedy. Moreover, variant types of highly virulent methicillin resistant *Staphylococcus aureus* (MRSA) in communities constitute a public health threat to day-to-day activities especially among populations at risk. Remarkably, organisms such as enterococci, *Escherichia coli*, *P. aeruginosa, Acinetobacter baumanii* and pneumococci, that were once regarded as harmless organisms have become emerging pathogens [4,25,26]. When infections become resistant to first choice or first line antimicrobials, alternative treatment option need to be sought, which are nearly always expensive in many developing countries. Consequently, some diseases can no longer be treated in areas where resistance to first-line drugs is common. The end result is that patient infected with such drug resistant organisms are likely to have ineffective treatment, longer stay in hospitals, need of treatment with broad spectrum antibiotics that are more toxic and more expensive [1,27]. In a study to determine the cost of antibiotic resistance, one study has observed that infections caused by antibiotic-resistant organisms double presumably the costs of therapy as compared with drug-susceptible infections. This cost according to them would translate into millions of dollars associated with infections caused by antibiotic resistant organisms [4]. One will wonder what will be the

cost implication and consequences in developing countries!

In developing countries, little or no priority is given to antibiotic resistance. This is reflected in the lack of will and legislations to bar factors that promote the abuse of antibiotic in both community and hospital settings. Moreover, funds are scarcely release to spur scientist into research that will translate into discovery of novel antibiotics with multiple mode of actions or strategies that will truncate the spread of antibiotic resistance. Thus, in these countries, no one really has a good idea of the extent and damage caused by antibiotic resistance because it hasn't been monitor; where it is done, not in concerted or coordinated manner. It is possible also that few or some hospitals might monitor its own resistance but there is no good national framework to test or monitor antibiotic resistance in most, if not all developing countries. If this trend is allowed to continue uncheck, sooner than expected, the resurgence of 'pre-antibiotic era' will set in and therapy for common bacterial infections will be unreached.

Faced with such a challenge, there is need to develop alternative approaches in addition to the search for new antimicrobial compounds. Such approaches might include strategies that target resistance mechanisms coupled with antibiotics [28].

4. FACTORS RESPONSIBLE FOR IN-CREASING ANTIBIOTIC RESISTANCE

The increase in antibiotic resistance in both hospital and community settings are generally influenced by variable factors which are briefly summarized below;

4.1 Irrational/Misuse and Suboptimal Usage of Antibiotics

This may occur in different forms; either through unjustifiable written order by trained medical personnel, or through recommendation and prescription by unskilled personnel who are less informed of the harmful consequences of using antibiotics irrationally [4,29]. Inappropriate administration or intake of antibiotic that may occur due to short course therapy, at suboptimal dosage with low level potency or for the wrong diagnosis always enhances the likelihood of bacterial resistance to these drugs [1,3]. Hospital doctors often prescribe antibiotics excessively and inappropriately, as shown in many studies. Lack of adequate and enough training in infectious diseases and antibiotic treatment, insufficient use of microbiological information, need for self reassurance and fear of litigation are the factors that are prompting the prescription and use of broad spectrum drugs [1,30]. Suboptimal doses of antibiotics may favour the selection of multi drug resistant organisms [31].

4.2 Degraded Antibiotics

The active ingredients of most antibiotics are adversely affected by excessive temperature conditions. This temperature limits can either be in the form of temperatures above 25^{o}C or relatively high humidity. These conditions are prevalent in tropical countries where transportation, distributions and storage of antibiotics are poorly controlled and antibiotics may be degraded [29]. It was also observed that most handlers of antibiotics in most developing countries are untrained. Consequently, antibiotics are often seen hawked on the streets either in plastics baskets or show case cabinet under harsh temperature conditions. Those that are sold in stores and shops are not provided with cooling systems that will regulate or lower the room temperature, as such, these antibiotics are degraded before been sold to consumers. To support this claim, a study of eight batches of tetracycline capsules in Nigeria, reported that all the batches of tetracycline obtained from sources other than the manufacturers are actively degraded and do not contained active drug levels within the formulary limits [29,32].

4.3 Faked Drugs

Faked drugs are drugs which possessed little or no active ingredients displayed on its label, or it is a product for which excipients have been replaced by ingredients of less quality and less expensive mostly at the time of manufacture, with deleterious effect on the consumer. A study has shown that most instances of fake drugs reported to World Health Organisation or to Interpol from 28 countries in the past 33 years were produced in developing countries [29,33,34].

4.4 Lack of Uniform Surveillance of Antibiotic Resistance

In developing countries, relatively little is known about the burden and consequences of antibiotic resistance. This is because there is no strategy put in place to monitor the level and pattern of

drug resistance in health care settings. Uniform surveillance is needed to monitor the spread of resistance, and thus understand the scale of the problem, in order to provide crucial data for the development of containment strategies.

4.5 Monotherapy

Monotherapy is the process of using a single method or treatment such as drug therapy to tackle and attempt to treat a condition or disorder. Use of monotherapy as opposed to combination therapy favours selection of resistance in certain infections [35,36]. In 2007, WHO member states adopted world health Assembly resolution which calls for a progressive removal of oral artemisinin-based monotherapies from market. According to them, the continued use of oral artemisinin-based monotherapies is considered to be a major contributing factor to the development of resistance to artemisinin derivatives [37]. Use of monotherapy as opposed to combination therapy favours selection of resistance in certain infections [38,35].

4.6 Use of Antibiotics in Agriculture and Veterinary

The widespread use of antibiotics in developing countries to treat infections and promote growth in livestock help to intensified farming more especially in the area of meat production for human consumption. Although the use of antimicrobial agents is of great benefit in livestock production, however, it posed a public health concern as some of the newly emerging resistant bacteria in animals are transmitted to humans via food of animal origin or through direct contact with farm animals. Moreover, consumers of meat containing leftover of antibiotics may be directly exposed to these drugs. It was also reported that bacterial population in the gut of the animals intended for human consumption may developed resistance if exposed to suboptimal concentration of antibiotics. Consequently, treating diseases caused by these resistant bacteria in humans with available antibiotics will be counterproductive and expensive [37,39]. Also, the emergence of vancomycin-resistant enterococci (VRE) is a good example of resistant bacteria in animals that humans are susceptible to [36]. A report has shown that the use of antimicrobials in agriculture is responsible for the development of resistance in these bacteria [37]. The use of antibiotics directly on fruits and vegetables and indirectly through the application of sewage sludge in farm land resulted in the emergence of antibiotics resistant bacteria on these farm products [40], which serve as potential vehicle for the transmission of antibiotic resistant organisms.

4.7 Hospital Infections

Inadequate hospital control practices, disregard to standard precautions and economic shortfalls favour the emergence and spread of hospital associated infections [19,39] which help to promote resistance to antibiotics.

4.8 Environmental Factors

Freshwater sources have been reported in different part of the world to harbour antibiotic resistant organisms which are a reflection of antibiotic used and burden in the environment [41]. Contaminations from chemical fertilizers used in the fields, from animal feeds or crops, waste products from humans and treated animals and production of antibiotics from soil organisms favour selection of resistant organism in nature and may serve as an avenue through which resistant organisms are transferred into rivers and other water bodies that could be useful for drinking and other domestic purposes [40]. All these factors contribute to the natural reservoirs of resistance genes which may provide a source of transferable genes [39]

5. FACTORS THAT PROMOTES THE ABUSE OF ANTIBIOTICS WHICH FAVOUR SELECTION FOR RESISTANT BACTERIA

The misuse of antibiotics by both trained and unskilled health practitioners and lay persons, in addition to poor drug quality and unhygienic conditions have been identified as the major cause of antibiotic resistance [29]. The predisposing factors responsible for such abuse of antibiotics are as follows;

5.1 Ignorance and Poverty

It is often said that ‘poverty’ or ‘ignorance’ is a disease. Poverty and ignorance are two factors that interplay and play an important role in the misuse of antibiotic in most developing countries which in turn provide an enabling ground for the development of antibiotic resistance. Inability to buy a complete regimen, or to take a complete regimen of antibiotics coupled with inability to reach to qualified doctors due to either poverty or

ignorance for rational prescriptions of antibiotics [39] contribute immensely to irrational therapy which in turn favour the development of antibiotic resistance.

5.2 Prescribers' Perception Factor

The pattern and mode of prescription of antibiotics varies from one location to the other and from one physician to another. While some prescriptions might be accurate and rational, others may be irrational and may take the form of incorrect dosage or inappropriate prescription. It was reported in Tanzania, that over 90% of antibiotics were prescribed with incorrect dosage [42] and in India most prescriptions did not have detail description of dose [43]. Also, in China and Ghana, it was reported that antibiotics were prescribed for viral respiratory tract infections which constitute inappropriate prescription or therapy [44,45]. Providers often prescribed antibiotics unnecessarily due to some prevalent factors, which range from; lack of empiric education on antibiotics, which may lead to uncertainty about the diagnosis and correct drug(s) to prescribe, fear of poor patient outcome, earning a living through selling medicines [37], etc.

5.3 Patients Demands Factor

Factors related to patient's perspective contribute majorly to misuse of antibiotics. This is reflected in patient's perspective on the use of expensive antibiotics. It was reported that many patients that are well able prefer to purchase new antibiotics not minding its cost than older antibiotics which are less expensive. This is because of their perception that newer agents are more potent than older agents. This perception consequently, increases unnecessary money spent on health care and encourages selection of resistance to these newer agents as well as to older agents in their class [1]. Even if prescribers are certain of their diagnosis, they are still greatly influenced by patients' demands. In Tanzania for example, it was reported that most health workers admitted to prescribing inappropriate drugs demanded by socially influential patients, to avoid being labelled "difficult" [46]. However, the extent to which prescribers are swayed by their patients is obscure and probably varies according to the experience and confidence of the prescriber. There is some evidence that patients demand is not actually what influences prescribers during the consultation process, but rather it was noted that it is prescriber's perception of patient demand that influences their prescription [37,47].

5.4 Scarcity of Well Trained Health Personnel

It is noteworthy to know that well trained health personnel are rare and insufficient and cannot serve the entire populations, especially in rural areas. Where they are available, most of them have almost no access to objective and empirical health information about diagnosis [29] and drugs. Thus, most people in developing countries are left with little or no choice of consulting unskilled health practitioners.

5.5 Self Medication

A report from previous study revealed that 50% - 80% of Bangladesh patients infected with *Shigella* spp. agreed that they had taken at least an antibiotic prior to hospital visit. According to them, the number of patients who self-medicate was probably higher, because patients are often reluctant to admit having taken antibiotics before visiting hospital [29,48]. Yah et al. [49] revealed that 145 (20.1%) of their study population self-prescribed, while 56 (7.7%) and 397 (54.9%) used prescriptions from friends or relatives and drug retailers respectively.

5.6 Poor Patient's Compliance

Poor patients compliance to antibiotics might be in different forms which include; interruption of treatment when they begin to feel better to where patient forgets to take medication or may be unable to afford the treatment [37,50] which may lead to antibiotic abuse and consequently increases the burden of antibiotic resistance. Yah et al. [49] in their study on penicillin usage and ampicillin resistance revealed that 63.3% of patients undergo incomplete regimen. This according to them, it was because many antibiotics were expensive, consequently, extremely poor patients purchased incomplete dose of antibiotics whenever possible and stop treatment when symptoms disappear allowing the pathogen at sub-lethal stage, thereby encouraging fast emerging resistant pathogens. Non - compliance with antibiotic therapy was also reported by Pechere et al. [51].

5.7 Accessibility to Drug Outlets

In most developing countries, unofficial drug outlets and stores are readily more available and accessible than government designated centres.

Thus, people are encouraged to buy drugs from unofficial distributors because drugs are often not available in government hospitals and designated centres [29]. Previous studies have shown also that because unofficial sources offer the option of purchasing antibiotics in small quantities comparable to government hospitals [52], many indigent patients patronised unofficial source more readily.

5.8 Commercial Promotion by Pharmaceuticals

Previous studies have shown that advertisement of antimicrobials by pharmaceutical companies influences physicians' prescribing behaviour and use patterns. The effect of these advertisements is to promote the use of antibiotics that should be kept in reserve as first line choices and also promote the use of antibiotics for infections and conditions that will probably resolve on its own without taken any action. Both situations represent irrational use of antibiotics and evidently have the potential to lead to increased resistance. Secondly, these pharmaceutical companies promote the advertisement of new, most potent and expensive antibiotics; drugs that can generate large sum of money for the companies, if sales volumes are large. For example, it was reported that in Philippines between 1994 and 1995, advertisement by pharmaceuticals companies recommends the use of lincomycin for tonsillitis/pharyngitis and clindamycin in upper respiratory tract infections which is improper because the most likely cause of any of these conditions is a viral infection where antibiotics are of less important. Once again, antibiotics are being advertised for conditions that do not require them. The inherent attachment to pharmaceutical advertisement is because in many cases in developing countries doctors lack sources of objective information about antibiotics. These doctors are entirely dependent on advertisement materials from companies, with all of the biases that this material entails [37,53].

6. FACTORS INFLUENCING THE DISSEMINATION OF RESISTANT ORGANISMS

6.1 Overcrowding and Unhygienic Conditions

Due to endemicity of antibiotic-resistant faecal organisms in developing countries, visitors coming to such countries passively acquired antibiotic resistant commensal organisms even if they are not exposed to antibiotics at any given time. This suggests that that they encounter a reservoir of antibiotic resistant strains during travel and point to the fact that apparently healthy individuals in developing countries carry potentially pathogenic antibiotic resistant organisms asymptomatically. Several factors are responsible for that, which includes; migration to urban centres, overcrowding and improper sewage disposal which promote the spread and exchange of antibiotic resistant organisms between people and the exchange of resistant genes among bacteria, thereby increasing the prevalence of resistant strains [29,54]. A study in Nigeria shows that unhygienic conditions among other factors are responsible for the presence and transmission of antibiotic resistant organisms via sachet water [41].

Another study in Nigeria revealed that resistant *E. coli* isolates from persons in an urban metropolis were significantly more likely to be resistant to some antibiotics than isolates from residents of nearby smaller towns and villages. The study further revealed that strains isolated from these urban centres were more likely to show resistance too many antibiotics in comparable to isolates from rural areas. Consequently, as urban migration continues unabated, overcrowding increases in urban centres while hygiene and sanitation declines, the likelihood of spread of antibiotic resistant organisms and commensal pathogens may also be on the increase [29,55].

6.2 Insufficient Hospital Infection Control Practices

In developing countries, many hospitals possessed elementary Infection control practices which are often affected by traditional norms and insufficient funds [29]. Consequently, hospital associated pathogens and resistant organisms may be spread to the outside community. Hence, the spread of these resistant organisms may be accelerated due to some factors such as; improper disposal of hospital waste, non-compliance with hand washing by health practitioners and visitors. A study revealed that untreated hospital waste in Uganda was often dumped into public sewers or thrown into rubbish heaps ravaged by scavengers [56].

6.3 Economic and Political Factors

Several studies have shown that most carefully design plan targeted against antibiotic resistance

in developing countries are halted due to limited resources and probably lack of political will. Data from the World Bank showed that developing countries spent significantly less per person on health when compared to industrialized countries that spent more. Consequently, drug supply to health centres in developing countries is inadequate or at best erratic [29,57] and quality health care delivery is shallow and poor.

It is sad to note that armed conflict which hampered developmental programs and health care delivery and services especially in rural areas is mostly rampart in developing countries, which conditions promotes rapid spread of resistant pathogens. More so, countries not at war are faced with corruption and mismanagement of funds which create large populations living in abject poverty and high risk for infection due to poor sanitary condition. Consequently, most patients cannot afford quality medical care even if treatment is subsidized. Thus, patients with infectious diseases, unable to afford medical treatment may infect others [58].

7. CONTROL/PREVENTION OF ANTIBIOTIC RESISTANCE

There are several steps that need to be taken to stop the accelerated increase in antibiotic resistance and to enable the efficacy of antibiotics in the future.

7.1 Rational Use of Antibiotics

The rational or appropriate use of antibiotics can be defined as the administration of the most suitable (empiric) antibiotic agent, at the right time, with the right dose and for the right duration [59,60]. Reaching this goal is obviously not simple. A multidisciplinary approach is needed to improve the quality of antibiotic prescribing, with education and implementation of practice guidelines as key interventions [61-63].

7.2 Surveillance and Infection Control

Preventing the spread of resistant bacteria, especially in health-care institutions, is a key element in controlling antibiotic resistance. Surveillance is needed mainly for patients transferred from locations with high resistance rates and for multi-drug resistant bacteria, with strict adherence to infection control guidelines [64].

7.3 Antibiotic Cycling and Scheduled Antibiotic Changes

Antibiotic cycling has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance [65]. Niederman, [66] stated that in theory, a class of antibiotic or specific antibiotic is withdrawn from use for a defined period and is reintroduced at a later time in an attempt to limit bacterial resistance. Studies have shown that this protocol can potentially restore the effectiveness of antibiotic because bacterial resistance to the withdrawn antibiotics might have reduced [67]. Some studies have, however, tracked a decline in resistance frequencies when an antibiotic is removed [68]. A significant countrywide reversal of macrolide resistance in *Streptococcus pyogenes* resulted from a Finnish nationwide campaign to reduce macrolide usage resulted to resistance declined in two years [67]. Nonetheless, it was observed generally that low level resistance continue unabated and reintroduction of the antimicrobial will re-select resistant strains despite months or even years of non use [4].

7.4 Use of Narrow Spectrum and Older Antibiotics

Another approach to combat resistance is to continue using older agents as first line choices, in preference to newer, more potent drugs, in an effort to preserve the activity of the new drugs. Thus the newer agents are reserved for infections caused by mutated multiresistant strains [69]. Several investigations revealed that some infections such as urinary tract infections (UTI), community acquired pneumonia, can usually be successfully treated with narrow-spectrum antibiotic agents especially if the infections are not life-threatening [70].

7.5 Rapid Diagnostic Methods

In diverse clinical settings, antibiotics are initiated in sick children when a bacterial infection cannot be ruled out, leading to antibiotic overuse [71]. Common examples are pneumonia, neonatal fever, febrile neutropenia and immunocompetent children with upper respiratory tract infections that are most often viral; while only a minority of the patients suffering from these medical conditions is affected by bacterial infections, antibiotics are generally administered indiscriminately, as there is no reliable means of diagnosing those with bacterial infections. Rapid,

highly sensitive and specific diagnostic tests that will accurately identify the causative pathogens or distinguish between bacterial and viral infections will reduce antibiotic overuse [72].

8. PROSPECT FOR ANTIBIOTIC THERAPY

Studies have shown that there are many and various strategies to combat antibiotic resistance. However, this study highlights and reviews only three of such strategies which are; antimicrobial weaponry from natural products, synthetic chemical compounds turned into antibiotics, and phages.

8.1 Antimicrobial Peptides (AMPs)

Antimicrobial peptides (AMPs) are said to provide important defence mechanisms in various organisms which includes humans, birds, fish, insects and plants [19,73-75]. Their nature allows them to bind and enter into organism's membrane bilayer to form pores by various mechanisms [76-78]. More so, several studies suggest that AMPs exhibit multidirectional mode of action against microbial strains which includes; inhibiting cell wall synthesis [79], inhibit nucleic acid synthesis [80-83], inhibit enzymatic activity [84,85], or impede protein synthesis [80-83] and lots more [19]. These features distinguish some AMPs as refreshingly new and most needed class of antibiotics. Thus, AMPs can be employed to perfect conventional antibiotic therapy [86-88]. Interestingly, some studies over the years have shown that AMPs have been widely used against infections caused by antibiotic-resistant bacteria and also have the potentials to be use as alternative antibiotics [89,90].

The successful use of AMPs in clinical trial as prescribed by previous studies is narrowed by a lot of factors and challenges which includes; costs of synthesis, screening and manufacturing, susceptibility to proteolysis, local toxicity and lots more [91]. Despites the drawback notwithstanding, the unique nature of AMPs, couple with their multiple and broad- spectrum activities with potential low levels of induced resistance, seem to represent a promising, unique future strategy to overcome increasing antibiotic-resistant pathogens [19]. However, it is interesting to know that the misuse and inappropriate use of AMPs in future may lead to more resistant forms of microorganisms that produce deadly infections [19] if appropriate care and strategies were not put in place.

8.2 Phage Therapy

Bacteriophages are viruses that infect bacteria. They possessed the potential to specifically attack and kill only host bacterial cells at the end of infection process [92]. Phage therapy is aimed at using specific bactriophage to fight against undesirable bacteria such as those associated with infectious diseases [93]. In the 1930s, phage has been used to treat various bacterial infections but with the discovery and coming of antibiotics, research into the therapeutic applications of phage was marred [19]. In the opinion of this review, the advantages possessed by phages in combating undesirable specific bacteria over the use of chemical antibiotics are the properties exploited in phage therapy. These properties are highlighted thus; it has been observed that the mechanisms of resistance to antimicrobials as exhibited by most bacteria spp are more prone on chemical antibiotics comparable to phage. Hence, phage can be used to treat antibiotic resistant organisms. The organisms being infected by phages are usually unable to regain their viability; this property shows that phages are bactericidal in nature. This is in contrast to some antibiotics which are bacteriostatic. Phages can increase in number over the course of treatment which consequently removed the need of repeated doses as in the case of antibiotics that are metabolised and excreted. Phages due to their specificity tend to only minimally disrupt normal flora which is a side effect in antibiotic ingestion. They have low inherent toxicities, seem to be capable of disrupting bacterial biofilms and are equally effective against antibiotic-sensitive and antibiotic-resistant bacteria [19,93,94]. It was also reported that engineered bacteriophages reduce the number of antibiotic-resistant bacteria that comes from an antibiotic-treated population and act as a robust adjuvant for other bactericidal antibiotics [95,96]. The use of phage therapy to treat bacterial infections that failed to respond to conventional antibiotics is currently being used only in Russia and Georgia [97,98].

8.3 Phytochemicals from Plants

Plants have traditionally provided a source of hope for novel drug compounds, as plant herbal mixtures have made large contributions to human health and well-being [99]. Owing to their popular use as remedies for many infectious diseases, searches for substances with antimicrobial activity in plants are frequent [100,101]. Plants are rich in a wide variety of

secondary metabolites (phytochemicals) such as tannins, terpenoids, alkaloids, and flavonoids, which have been found *in vitro* to have antimicrobial properties [102-104].

Phytochemicals are the secondary metabolites usually found in plants and perform specific functional roles. In most cases, phytochemicals help to defend plant against intrusion by microorganisms, insects and herbivores. It is interesting to note that in the ancient times, phytochemicals, in the form of plants, were the only weapon used to fight against infections caused by microorganisms. In recent times they are still indispensable as they constitute the central components of today's pharmaceuticals. With the incidence of multidrug-resistant pathogens and the menace they constitute to therapy, researchers are focusing on plants derivatives as possible solutions [19]. Production of efflux pump inhibitors by plant would be one way to ensure delivery of the antimicrobial compounds into bacterial cells. This hypothesis has been supported by the findings of Stermitz et al. [105], who observed that *Berberis* plants which produce the antimicrobial compound, berberine, also make the MDR inhibitors 5-methoxyhydnocarpin D (5-MHC-D) and pheophorbide A. The MDR inhibitors facilitated the penetration of berberine into a model Gram-positive bacterium, *S. aureus*. In testing their hypothesis, Tegos *et al*. [106], showed that two MDR inhibitors (INF271 and MC207110) dramatically increased the effectiveness of thirteen putative plant antimicrobial compounds against Gram-negative and Gram-positive bacteria including isolates known to express efflux pumps. In the nearby future, it is proposed that Phytochemicals isolated from nature and then synthesized chemically are likely to provide the most potent antimicrobial drugs [19] that will curtail the menace cause by multi-drug resistant organism.

9. CONCLUSION

Antibiotic resistance is no longer a problem of the developing countries alone. Even after all the advances in therapeutics and availability of a large number of antibiotics today, a person can die in a developed country also due to infection with resistant bacteria. The concern raise by the continue increase in antibiotic resistance has undoubtedly cause urgent changes in the existing antibiotics at the same time the production of novel antibiotics [19]. Appropriate antimicrobial use is an integral component of any programme to slow down the appearance and dissemination of antimicrobial resistant microorganisms in the health care setting and community settings. The role of antibiotics in the treatment of infectious diseases cannot be overemphasized in the present and also in the future. The problems of few new antimicrobials produced by pharmaceuticals and the increasing number of multidrug resistance reported worldwide mean that we must redouble our efforts to preserve the agents at hand, while increasing effort to the search for new therapeutics [4].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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