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Review Article

Antimicrobial resistance (AMR)–A public health concern

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Abstract

Antimicrobial resistance (AMR) is a global threat with huge impact on public health. Hence the need for urgent and deliberate efforts to halt the unchecked global spread of this menace especially in developing countries. This review is aimed at discouraging the abuse, overuse and misuse of antibiotics and encouraging novel protocols in the treatment of antibiotic resistant infections. In Nigeria, antibiotics are being used incorrectly as prophylaxis by women and men after sex and also as contraceptives by women after sex, in treatment of infections of viral origin and most times in farm animals as prophylaxis and metaphylaxis which causes resistance. The mechanism of resistance could be through altering the site of action of drugs, inhibiting the uptake of drugs into the organism, changes in the metabolic pathway of the organism or modification of therapeutic agent structure to inactivate these drugs or through bile induced resistance. The cumulative effect of this resistance results in longer hospital stays, increased cost of treatment, increased side effects from the use of multiple and more powerful medications, increase illness from untreatable infections and ultimately death. There is a need to source for long term solutions to curb the spread of antimicrobial resistance. Death from antimicrobial resistance is globally estimated to be more than 700,00 per year, therefore all efforts must be channeled to curbing the spread of antimicrobial resistance (AMR), through reduction in the use of antibiotics, encouraging development of novel antimicrobial agents, encouraging research that will foster the use of probiotics and bacteriophages in treatment of microbial infection.

1. Introduction

Antimicrobial resistance (AMR) has continued to be an ignored global menace and the number of deaths, especially in the developing world keeps increasing. Currently, death from failure of treatments due to AMR is estimated to be more than 700,000 per year worldwide [1] The songs of victory heard in the early 1940's when antibiotic like penicillin was discovered is gradually fading away, the once 'wonder molecules' (antibiotics) are gradually losing the battle against infectious agents through resistance [2]. With increased use of antimicrobial agents world over, the spread of antimicrobial resistance (AMR) and the spectrum of different mechanisms of resistance is increased. In a global scale, antibiotics consumption has been estimated at more than 70 billion doses per annum [3]. The danger of antimicrobial resistance has been on for several decades and the need to effectively treat the increasing range of infections caused by bacteria, parasites, viruses and fungi is being threatened, with a resultant reduction in the efficacy of antimicrobial agents [4]. Centres for Disease Control and Prevention (CDC) in the United States reported that each year, there are at least 2 million illnesses due to resistance to medications

recommended for treatment of bacterial or fungal agents. And in each year more than 23,000 people die when these drugs fail to work [5].

Antimicrobial resistance can be defined as the ability of an organism to continue to multiply or remain viable in the presence of antimicrobial agents that would ordinarily destroy or inhibit them, this ability could be temporary or permanent and can be transmitted to their progeny [2]. Usually, antibiotic dosing is designed to eliminate pathogen populations. However, when these medications are not taken for the total course prescribed, the infective pathogens can adapt at low dose antibiotics concentration, and ultimately produce progeny with complete resistance to the antibiotic used irrespective of the dosage [6]. With increasing Antibiotic resistance, it's becoming difficult to treat infections with the available antimicrobial drugs [7].

New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases, resulting in prolonged illness, increase hospital cost, disability, and death [7, 8].

Africa and South East Asia have been identified in 2014 WHO report as regions without recognised surveillance systems for AMR [3]. This gross lack of quality data often leads to inadequate treatment guidelines for local situations [8]. Another problem is the chasm in public health considering the varying resistance mechanisms and the occurrence of multidrug-resistant bacteria that can merely be identified through systematic screening in quality assured microbiology laboratories [9,10]. If antimicrobial resistance must be tackled in Africa, Nigeria being the most populous country in Africa must be in the driver's seat. In recent times, overuse of antibiotics has been massive, world over antibiotics have been used across all ecosystems in humans, animals, agriculture and aquaculture which is an established link to antimicrobial resistance [2]. Most Nigerians live below $1.50 per day, Poverty is the bane of the common man and has remained a major factor to the worsening health crisis coupled with poor access to basic health services which has led to gross underutilization of health facilities [11]. Antibiotics have been recklessly sold in the open market by people with no idea of how these medications work, by Patent and proprietary medicine vendors (PPMV), unregistered Pharmacies and unregistered clinics operated by profit driven businessmen. This has resulted in the misuse and abuse of these drugs by the public without proper guidance on the proper use of these medications [11]. Physicians and other healthcare workers cannot be exempted and have equally contributed to AMR through antimicrobial overuse occasioned by both omission and commission [12]. The general believes among healthcare workers that a patient expects an antimicrobial might be the major reason behind antimicrobial over-prescription particularly in the outpatient setting [13]. The fate of the public in the public health sector is gradually eroding, due to gross drug shortages and almost zero accessibility to medicine [11]. Private healthcare options have become the solace for the common man as access points to medicines. The public believe in the public health sectors have been sacrificed in the alter of bad governance. It is therefore imperative for the government to adequately equip the public health sectors and improve access to services.

Strong connections of rich businessmen in the distribution channel of drugs coupled with apathy of regulating bodies to monitor and enforce distribution of standard medications has led to the sales of fake drugs including antibiotics with sub therapeutic doses of the active pharmaceutical ingredients (API). This evil has also greatly contributed to the emergence of AMR. Again, the poor enforcement of regulations with regard to the sales of prescription only medicines (POMs) over the counter (OTC), has increasingly made it difficult to control overuse of antimicrobials in general. There is gain to ensure implementation of quality-monitoring and regulation of distribution and sales of drugs while clinicians (in both public & private health sectors), pharmacists and PPMVs are being engaged on the importance of the rational use of antimicrobials. The solution to this menace is to strongly encourage alliance internationally among researchers and policymakers to curb the spread of antimicrobial resistance [12]. Implementation of antimicrobial conservation (AC) programme, tracking of patience to encourage adherence, proper diagnosis before commencement of anti-infective agents and preventing infection transmission are some of the key steps recommended by CDC and other health care professionals to effectively manage antimicrobial resistance crisis [14].

2. Results and discussion

3.1 Mechanisms of antimicrobial Resistance

In a bid to survive, bacteria have evolved with intrinsic mechanisms that enable them to survive in harsh environmental conditions. This intrinsic ability to strive (grow and reproduce) in the presence of antibacterial agent is expressed through two major pathways; i) mutation which relates to mechanism of action of the metabolite or drug ii) transmission of resistant plasmid from one organism to another [15].

3.2 Resistance due to Mutation

Anti-infective agent inhibits or kill bacterial cells through different mechanisms of actions organisms through mutation evade these therapeutic agents by either altering the site of action of drugs, inhibiting the uptake of drug into the organism, changes in the metabolic pathway of the organism or modification of therapeutic agent structure to inactivate these drugs [16] or through bile induced resistance.

Alteration in the target site of antibiotics – the mode of action of some antibiotics is by specific binding to target sites in the bacterial cell. Selective toxicity is what comes to mind when choosing an antimicrobial agent, the drug of choice must be able to differentiate between the target microorganism and the mammalian cell. Any modification in this site of action will confer resistance to these bacterial cells, a typical example is the alteration or genetic modification of P12 protein on the 30's ribosomes of bacterial cell resulting in resistance to streptomycin, modification of L22 protein of 50's ribosome or the enzymatic methylation of the 23rRNA on the 50's ribosomes of bacterial cells can also result in resistance of the bacterial cells to macrolides, chloramphenicol and other antibiotics that act by inhibiting protein synthesis [16, 17]. A loss or modification of penicillin binding proteins (PBP) to PBP2a protein can confer resistance on organisms like *Streptococus pneumonia* and enterococci against Beta lactams (penicillin and cephalosporins) [15,18,19]. Glycopeptides like Vancomycin act on bacterial cell walls by specifically binding to the peptidoglycan precursor D-alanyl-alanine, a modification in this amino acid to D-alanyl-lactate will results in resistance of organisms like *Eterococcus faecium* and *Enterococcus faecalis* strains to the antimicrobial agent [15]. The bactericidal activity of fluoroquinolones is through inhibition of the DNA gyrase enzyme and topoisomerase iv, once a modification occurs on the gene coding for these two enzymes the quinolone antibiotics will fail [16,15].

Inhibition of uptake of antibiotic into an organism or decreased concentration of antimicrobial agent into the bacterial (Efflux Mechanism): Before most antimicrobial agent acts on a bacterial cell; they must be uptake or transport of these antimicrobials through transport channels called porins located in the outer membrane of a bacterial cell and subsequent accumulation in the cell membrane. Bacteria have over the years developed mechanisms to inhibit this transport of hydrophilic molecules through this transport systems by either altering the level of expression of porins, impairing their function or changing the type of porin expressed [15]. A typical example is a shift in the expression of the porin OMPK35 to OMPK36 in *Klebsiella Pneumoniae* resulting in decrease uptake of beta lactam antibiotics and a subsequent decrease in sensitivity of the organisms to the lactam antibiotics [20]. Also, a genetic alteration in porin mediated transport gene OprD found on the outer membrane of Pseudomonas aeruginosa results in decreased expression of this porin or total loss in its expression, leading to reduced or inhibition of uptake and resistance to antibiotics like carbapenems [15, 21]. Microorganisms have also developed mechanism to expel or extrude antimicrobial agents with the help of Adenosine Triphosphate (ATP) dependant pump. A total of 6 major efflux pump super families have been studied which includes: drug metabolite transporter (DMT) superfamily, major facilitator superfamily (MFS), ATP- binding cassette superfamily (ABC), resistance - nodulation division (RND) superfamily, Multidrug toxic compound extrusion (MATE) and Small multidrug resistance (SMDR) superfamily [22-24].

Resistance through change in the bacterial metabolic pathway: Some antibiotics act on bacterial cells by inhibiting the metabolic pathway of these organisms, a typical example is the action of sulfonamide and trimethoprim which act at different sites of the metabolic acid synthesis pathway. Sulfonamides compete with Para- amino benzoic acid, a natural substrate of the enzyme dihydrofolate synthase required for the synthesis of folic acid while the trimethoprim synergistically acts at the later stage of the enzyme blocking the reduction of dihydrofolate to tetrahydrofolate which is the active form of the folic

acid [16, 25]. Resistance develops when mutational changes occur at the promoter region of the DNA coding for the production of dihydrofolate synthase and dihydrofolate reductase leading to the over production of these enzyme, overwhelming the ability of the drug to compete [16]. Resistance can also result from alteration in the gene coding for the two enzymes resulting in decreased sensitivity of the anti-infective sulfonimine and trimethoprim to the enzymes.

Inactivation of therapeutic agents by modification of its structure: One of the ways microorganisms thrive to survive in the presence of antimicrobial agents is by alteration of the structure of the therapeutic agent, for example, the hydroxyl (-OH) and amino(-NH2) group of 2-deoxystreptamine nucleus or the sugar moieties of aminoglycosides are modified by the enzyme amino glycoside modifying enzyme, these modification is either by acetylation (by acetyltransferase enzyme), Phosphorylation (phosphotransferase) or Adenylation (adenyl transferase enzyme) [26]. Chloramphenicol antibiotic can also be inactivated by the enzyme chloramphenicol acetyltransferase (CAT), this enzyme acetylates the hydroxyl group in the antibiotic molecule, hence inhibit its binding to the acetyl transfer centre of the 50's ribosomes subunit [27].

Bile induced resistance: Research has shown that when enteric bacterial cells are exposed to bile acid salt sodium deoxycholate, it can alter structurally the second layer of the cell envelope and the peptidoglycan (PG), this structural rearrangement of the PG can lead to resistance of the bacterial cell to the detergent properties of bile acid and other toxic metabolites [28]. Research has also shown that organisms with induced resistance to bile acid became resistant to ceftazidime and tetracyclines (doxycycline, minocycline and tetracycline), the organism exposed to bile acid had an increased resistance to ceftazidime which was more than 25 time the resistance of the parent cells [29].

3.3 Plasmid mediated antibiotic resistance transfer.

Bacteria have been in existence since antiquity and over the years, have developed mechanisms to survive in harsh environmental conditions. The organisms that develop resistance to antibiotics can through exchange or transfer of genetic material share this gene with other organisms not necessarily phylogenetically related to the donor of the resistance gene [30]. Antibiotic resistance gene (ARG) can be encoded in plasmid a mobile genetic element (MGE) that mediate the transmission of resistance by bacteria cells [30, 31]. Plasmids is a scaffold for drug or multidrug resistance gene transfer. The proliferation of antibiotic resistance is usually through horizontal gene transfer (HGT), here antibiotic resistance plasmids promote their own transfer from one bacterium to another through splicing, transformation and transduction. Plasmids are small circular genetic elements that replicate independently of the chromosomes [30]. These plasmids usually carry genes that enable the host organism adapt to its environment. With the increased use of antibiotics in clinical settings and agriculture, antibiotics leak into the environment and the presence of low concentrations of antibiotics in the vast ecosystem results in development of antibiotic resistance and can be encoded into the bacterial gene [32].

3.4 Causes of antimicrobial resistance

The major cause of antibiotic resistance in Nigeria is misuse; this is largely attributed to lack of enforcement of regulations, uncontrolled redistribution channels and unchecked access to antibiotics [33]. The poor presence of antimicrobial stewardship teams and over-prescription of antibiotics in hospitals are also notable causes of AMR [34, 35]. Antibiotics are sold over the counter, in public buses and open markets resulting in antibiotic abuse and misuse leading to resistance. In Nigeria, ampicillin and cloxacillin (ampiclox) is been abused by young girls as contraceptives after sex [36]. Antibiotics are also abused by both men and women, usually ampiclox 500mg start, is taken after unprotected sex in Nigeria for prevention of infection. The increasing prevalence of antibiotic resistance in microorganisms can be linked to these unguided practices [37]. Overuse of antibiotics has also greatly increased antimicrobial resistance [37]. Reports have shown that an average of 80-90% of anti-infectives are prescribed in primary care for oral use, with half of the recommended antibiotics used in the treatment of upper respiratory tract infections [38]. Antibacterials have continually been self-recommended/ recommended inappropriately in Nigeria for cold and catarrh, allergic reactions, mensural cramps and in

treatment of viral and fungal infections [39]. Antibiotics are taken in Nigeria as prophylaxis with the false hope of boosting immunity, after mensuration to 'flush' the system and sometimes while treating malaria without any clinical need for the antibiotics [40]. Antibiotics are massively used in agriculture as prophylaxis and metaphylaxis in farm animals, this practice is known to favour the emergence of microbial resistance [41].

3.5 Public health impact of antimicrobial resistance.

According to WHO, AMR ranks as one of the top ten global public health threats facing humanity [42]. AMR is dangerously rising to a higher level in every part of the world. New mechanisms of resistance are emerging and spreading globally. The use of antibiotics in treating common infections is becoming harder, infections such as pneumonia, tuberculosis, gonorrhoea, blood poisoning and food borne diseases can no longer be treated with ease. [43]

AMR is a public health concern around the world. The number of bacteria that are resisting antimicrobial agents is rising. The danger of the AMR is that treatable illnesses (like pneumonia, tuberculosis and minor infections) could become incurable. This in turn would put a greater economic burden on families and on the healthcare-system of countries globally [42].

Antimicrobial resistance results in a reduced ability to treat infections and illnesses in people, animals and plants. This will automatically lead to problems like;

Increased human illness from untreatable infections, suffering and death,

Increased cost and length of treatments,

Increased side effects from the use of multiple and more powerful medications.

With Increased risks of spreading resistant microorganisms to others, patients act as a reservoir of infection for a longer period thus posing risk to members of the community and health workers [42].

One of the most important objectives of public health aides or professionals is to stop emergence of new resistance mechanisms which might make the latest generation of antibiotics virtually ineffective. Definite policies and guidelines for appropriate use of antimicrobials, should be introduced and strictly adhered to in all diseases of public health importance like enteric fever, diarrhoea disease, respiratory infections etc just as it found in specific national health programmes such as tuberculosis, AIDS and malaria [44]. Effective public health measures like hygiene and sanitation, improving immunisation coverage, rapid outbreak response and other holistic systems of being in wellness will reduce reliance on antimicrobials and in turn will break the chain of transmission of resistant strains of microorganisms. There is a need to develop serious strategy, develop infrastructure and take urgent calculated and coordinated steps to tackle this menace in public health system [45].

Measures to curb antimicrobial resistance and spread of resistant bacterial several explanations have been given for the inability of humans to curtail the increased antimicrobial resistance which includes complex interaction between doctors, patients and parents over the use of the antimicrobial agents. Although there are needs for a better understanding of the factors that are involved in the emergence and sread of the antimicrobial resistance, actions on how to curb antimicrobial resistance and spread has to continue till we get the expected results.

Monitoring of bacterial resistance is a key component to understanding how serious the problem is. The existing networks for resistance surveillance need to be coordinated and the results made available to help the prescribers to choose appropriate antibiotics for use [46]. At the moment, the Long-term solution to this menace is to focused on how to prevent the emergence of resistance and the spread of the resistant organisms from one person to another. Four (4) typical ways of fighting the development and spread of resistance. Reduction in the use of antimicrobial agents will reduce the selection of resistant bacteria.

Major efforts have to be targeted on diagnosis and treatment of respiratory tract infections which account for 80% of antibiotics used in community. Sales of antibiotics over the counter should be stopped [47]. The need to know the patterns of prescription of antibacterial agents in different infections to identify when clinical practice needs to be improved is key. [48] There is a need for a multifaceted approach to reduce antimicrobial consumption which includes education of the doctors; recommendations for good clinical diagnosis and treatment; and follow up on compliance and guidelines. Public education on the knowledge about the risks and benefits of antimicrobial therapies are also important. Restriction policies of requirement for written prescription duly

signed by qualified prescribers to get antibiotics in both hospital settings and community outlets (Pharmacy) will be added advantage to curb indiscriminate use of antibiotics. Integrated strategies have reduced antibiotics use or curtailed antimicrobial resistance [49].

Hygienic measures are another way to tackle resistance to antimicrobial agents. Improving hygiene and sanitation measures to prevent the spread of resistant bacteria. Some years ago, hygiene and sanitation were the most important ways of preventing the spread of transmissible diseases. Environmental conditions such as crowding and poor sanitation also contribute in the spread and circulation of resistant microorganisms. Improved basic hygiene and sanitation will reduce drastically the spread of resistant organisms [50] In hospitals effective prevention of cross infection and development of strict antimicrobial policies should be in the hands of experts [51]. There are needs for an infection control team with infectious disease specialists, clinical microbiologists, infection control nurses and others. Standard hand hygiene in hospital will also improve hygiene and by extension reduces spread of resistance to the antimicrobial drugs.

Understanding the bacterial flora, the evolution of resistance and mechanism of the transmissibility of resistant bacteria is another way of reducing antimicrobial resistance through research. With a good research, pharmaceutical companies should be considered sourcing for a new antibiotic and should also debunk the idea that research for new antimicrobial are of "low profit" and the speculation that resistance will eventually develop on every new antimicrobial agent.

The increase in resistance to our antimicrobial agents and reluctance of pharmaceutical companies to research more antimicrobial agents has necessitated the exploration of alternative therapies for traditional antimicrobial agents. An alternative agent which can regulate the virulence of microbes as well as inhibit their growth. There are some alternative therapies to the use of antibiotics at different levels of research and development. Example includes:

Probiotics- these are considered to be able to destroy pathogenic microorganisms through the production of metabolites with antimicrobial activity. Metabolites such as bacteriocins and organic acids, improve the gastrointestinal microbial environment enhancing adherence of the probiotics to the intestinal mucosa thereby preventing the attachment of pathogens and also competing with pathogens for nutrients and stimulating the intestinal immune responses. Commonly used probiotics include, bacillus, Lactobacillus, Lactococcus, yeast, Aspergillus etc. [52].

Bacteriophage- are bacterial viruses with the capacity to invade bacterial cells and induce lysis of the bacteria. (Lytic cycle). Bacteriophage also serve as alternative treatment option for bacterial infection [53]. Suggestions have been given by different authors that bacteriophage therapy should serve as alternate therapy to conventional antibiotics [54]. Most importantly now that there is averseness in the development of new antibiotics by pharmaceutical companies, there is a need for aggressive exploration of the possibility of phage therapy as alternative therapy for traditional antimicrobial agents.

3. Conclusions

Antimicrobial resistance is a threat to life. Urgent steps must be geared towards curtailing the spread of resistant bacteria and development of novel antibiotics to treat these superbugs must be encouraged. Sanctions must be placed on the indiscriminate use of antibiotics in both humans and animals. Antibiotic stewardship programs must be implemented and public enlightenment campaign championed to discourage the indiscriminate use of antibiotics.

Abbreviations

AMR- Antimicrobial Resistance
API- Active pharmaceutical ingredients
ARG-Antibiotic resistance gene
MGE - Mobile genetic element
HGT- horizontal gene transfer
ARG-Antibiotic resistance gene

Authors' contributions

Conceived and design the study, S.A.A. and O.L.A. Drafted, revised and approved the manuscript, S.A.A. and O.L.A.

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Conflicts of interest

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