

Bacterial resistance to antibiotics: Update on molecular perspectives

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ABSTRACT

Humanity is plagued by numerous types of infections and diseases caused by microorganisms across the world but the discovery of penicillin in 1928 by Alexander Fleming from fungus and subsequent discoveries of numerous other antibiotics like tetracycline, streptomycin and chloramphenicol etc. has contributed immensely to human health. However, not long after the discovery and public use of antibiotics, the bacterial world maneuvered its metabolic systems to resist antibiotics resulting to the emergence of daring drug resistant bacteria. Amongst several factors, the unrestricted accessibility to and, sometimes unselective use of antibiotics by the general public, huge use of antibiotics in agricultural land and use of fake and adulterated antibiotic in developing countries have been advanced as being responsible for the emergence and development of antibiotic resistant bacteria. Researchers, however, have continued to search for and develop antimicrobials to contain this ugly tide. Some of the recent approaches to combat Multidrug-resistant (MDR) pathogenesis and molecular biological mechanisms are reviewed herein.

Keywords: Bacteria, antibiotic resistance, MDR genes, antimicrobials.

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INTRODUCTION

The scourge of bacterial infections and diseases has continued to haunt humanity worldwide despite the significant efforts made to understand and treat them. Nevertheless, man has also continued to search for means to eradicate or at least manage or control infections and diseases posed by microorganisms such as bacteria. One of such means is the introduction of antibiotics into our health care system in the 1940's (Centers for Disease Control and Prevention, 2013; Gould and Bal, 2013).

However, bacteria possess inherent capacity in their genetic composition to develop resistance to antibiotics as self-defense. Studies have shown that bacteria possess several genes that are able to confer resistance to several classes of antibiotics in nature well before the antibiotic era (Aminov and Mackie, 2007; Kobayashi et al., 2007). Recent studies have shown the re-emergence of bacterial infections and diseases that are resistant to a

wide range of antibiotics (Bush and Macielag, 2010). This trend is really worrisome and several workers have called for urgent attention. Hence in this paper, resistance of bacteria to antibiotics is reviewed with emphasis on updates on molecular innovative approaches.

ANTIBIOTICS AND ANTI-BACTERIAL RESISTANCE

Definitions and discovery

The term 'antibiotic' was coined from the word 'antibiosis' which literally means 'against life'. Antibiotics had always been considered to be organic compounds produced by one microorganism which are toxic to other microorganisms. They were therefore originally, broadly defined as substances, produced by one microorganism, or of biological origin which at low concentrations can

inhibit the growth of, or are lethal to other microorganisms (Schlegel, 2003; Denyer et al., 2004; Russell, 2004). However, the advent of production of antibiotics through synthetic means other than microorganisms or other biological systems seem to have necessitated a modification of its definition.

In pursuance to this apparent necessity, antibiotics has been robustly defined as a chemically heterogeneous group of substances produced by a microorganism, or to a similar substance (produced wholly or partly by chemical synthesis), which in low concentrations kills or inhibits the growth of other microorganisms. Whilst some antibiotics are able to completely kill other bacteria, some are only able to inhibit their growth. Those that kill bacteria are termed bactericidal while those that inhibit bacterial growth are termed bacteriostatic (Walsh, 2003).

Penicillin was the first antibiotic discovered. The exact year of its discovery is somewhat dicey. Whilst some literatures report it as 1928, some others indicate 1929 (Aminov, 2010). The discrepancy stems from the fact that it was discovered in September, 1928 but the discovery was first reported in 1929. Penicillin was discovered by an English Bacteriologist, late Sir Alexander Fleming who accidentally obtained the antibiotic from a soil inhabiting fungus *Penicillium notatum* in 1928, and was able to show by experiments its antibacterial capability against laboratory cultures of numerous disease causing bacteria. Although, the first clinical trials of penicillin were tried on humans in 1940 (Schlegel, 2003), its discovery in 1928 by Fleming heralded the development of antibacterial compounds produced by living organisms.

The discovery and development of the first significant antibiotic "penicillin" in the 1920's, sparked off an unprecedented interest and search for more antibiotics. A few years after penicillin was first clinically tried on human, a new antibiotic, streptomycin was discovered in 1944 by another Microbiologist, Waksman. Streptomycin was also obtained from a soil inhabiting microorganism; in particular a soil bacterium, *Streptomyces griseus*. This new antibiotic has been of tremendous value especially in the treatment of tuberculosis caused by the bacterium *Mycobacterium tuberculosis* (Alimuddin et al., 2013).

So far, about 2000 antibiotics have been discovered and characterized and only a relatively few number of this lot of them are currently used therapeutically (Schlegel, 2003), including those of fungal origin. Most antibiotic drugs were discovered from soil-inhabiting microorganisms which include eubacteria (10% of isolated antibiotics), fungi (20%) and actinomycetes (70%) (Bérdy, 1974; Lechevalier, 1975). Needless to say the search for microorganisms capable of producing compounds as potential source of new antibiotics still goes on unabated among pharmaceutical and clinical microbiologists, and other allied professionals, particularly as the emergence of pathogenic microorganism resistant to antibiotics also remains unabated (Centers for Disease Control and Prevention,

2013; Gould and Bal, 2013).

Antibiotic resistance

The adoption of antibiotics for human health care delivery in the 1940's was greeted by unprecedented jubilation, even though penicillinase enzyme was detected in 1940 in cell extract of *Escherichia coli* and subsequently in *Pseudomonas aeruginosa*, *Salmonella typhi*, *Mycobacterium tuberculosis* and *Klebsiella pneumonia* (Chakraborty, 2016). Man could finally heave a sigh of relief over the dastardly death blows the seemingly invincible and microscopic agents of diseases and infections had inflicted on humanity. But sadly, the much cherished relief over bacterial infections and diseases was far from being a lasting and complete victory.

Just over fifty years after antibiotics were discovered and used in human health care delivery system, world leaders in general and health practitioners in particular, were back on their feet to tackle a seeming resurgence of a battle that was thought to have been won. Quietly and steadily bacteria had developed resistance to the existing antibiotics and man was faced with issues of resistant bacteria. Self-medication and overuse of antibiotics amongst other factors have often been considered to contribute to the emergence of bacteria resistant to antibiotics (Talaro and Chess, 2008; Procópio et al., 2012).

A given strain of bacteria is said to be resistant to an antibiotic when the bacterium is able to resist the effects of the antibiotics after being exposed to it; that is, the bacteria are neither killed nor their growth stopped. When bacteria become resistant, they tend to survive even when exposed to the antibiotic and continue to multiply in the body, potentially causing more harm and spreading to other people or animals (Centers for Disease Control and Prevention, 2013).

The development of resistance, for this reason, is acclaimed in many quarters as solely the result of the indiscriminate use of antibiotics (Goossens, 2009; Talaro and Chess 2008), but bacterial drug resistance in itself is an adaptive response wherein bacteria begin to tolerate an amount of antibiotic that would ordinarily inhibit it. Being able to resist an antibiotic is both an inherent and acquired characteristics of microorganisms. Inherent antibiotic resistance is best explained by the fact that bacteria must of course be resistant to their own product. Bacteria with this type of resistance (inherent) form only a small group in the population (Levin and Rozen, 2006). The major form of antibiotic resistance is the acquired type, and they constitute man's nightmare. Bacteria with acquired resistance are those that were once sensitive to a given antibiotic but develop resistance over time through acquisition of resistant factors from the environment. For instance in the past, *Staphylococcal* strains were effectively controlled by the use benzyl

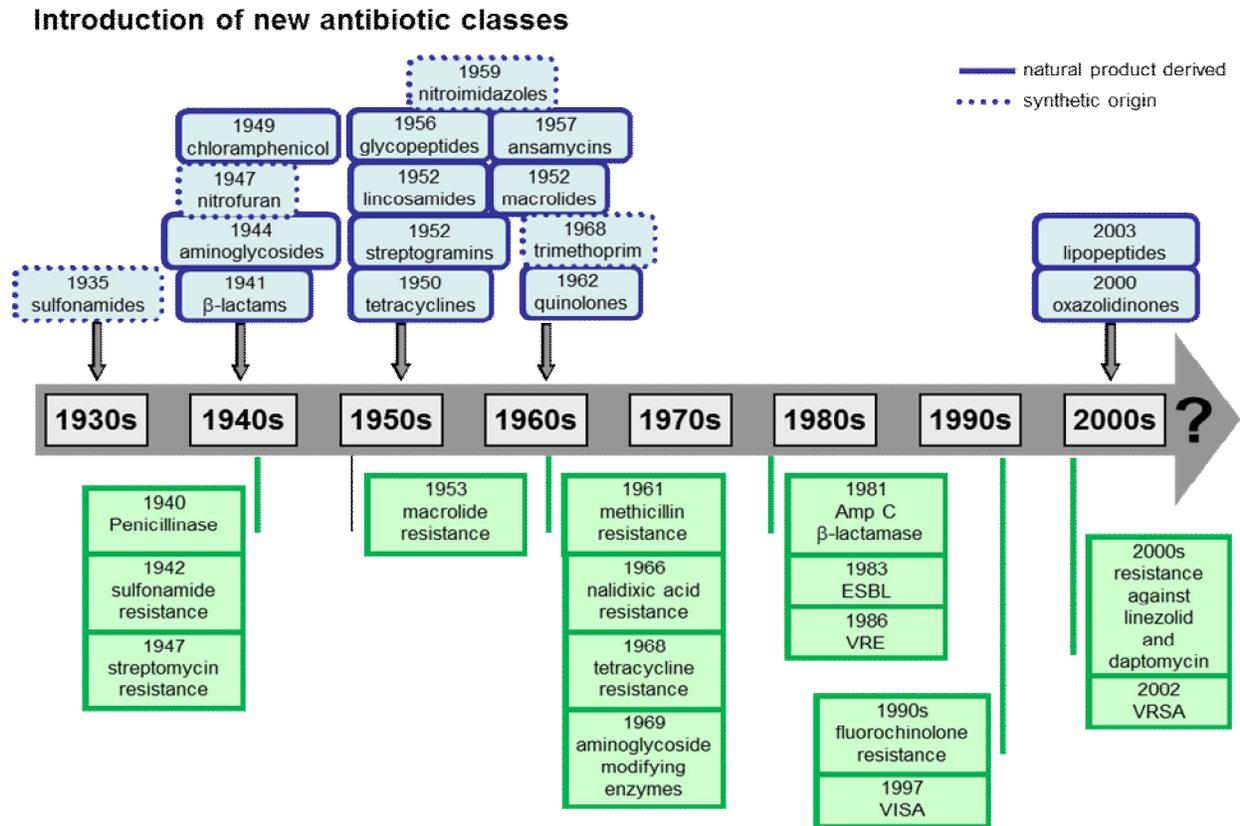


Figure 1. Timeline for antibiotic resistance (Centers for Disease Control and Prevention, 2013).

penicillin because of their susceptibility to the antibiotic penicillin but some strains which are now resistant to the drug have since emerged (Franklin, 2003). (Figure 1)

Bacterial resistance to antibiotics had been known and has been in existence long before penicillin was approved for public use (Wright, 2005). However, the enormity of the challenge of bacterial resistance to antibiotics was exacerbated in the 1950s and 1990s following numerous antibiotics treatment failures.

Bacterial resistance to antibiotics has been variously reported to include two main forms of mechanisms: (i) the efflux pump mechanisms; and (ii) modification to or disruption of an individual gene (Liu and Pop, 2009; Fajardo et al., 2009). However, some studies have revealed in details several mechanisms through which bacteria become resistant to antibiotics (Aleksun and Levy, 2007; Villa et al., 2007; Spratt, 1994; McDermott et al., 2003; Magnet and Blanchard, 2005; Wright, 2005). These include:

- i) Efflux pumps that eliminate the drug from the cell.
- ii) Modifications of the cellular target of the antibiotic which hinders binding of the antibiotic.
- iii) Production of enzymes that are able to digest the antibiotic.
- iv) Activation of an alternate pathway that bypasses drug

action.

v) Down-regulation or elimination of transmembrane porins through which drugs enter the cell. This occurs particularly for Gram-negative bacteria.

vi) Over production of the target enzyme. (Figure 2)

Antibiotic resistant genes and the mechanisms for resistance

The increase in incidences of treatment failures no doubt could be attributed to increase in acquisition of antibiotics resistant factors amongst bacteria. Simply put, bacteria acquire resistance through one or both of two ways:

- i) Spontaneous mutation in critical chromosomal genes (Martinez and Baquero, 2000).
- ii) Acquisition of entire new genes or sets of genes through transfer from another species (Tenover, 2006).

Literature is awash with studies that substantiate the natural occurrence of drug resistance encoding genes residing in plasmids of bacteria. The occurrence of such plasmids is not in response to any stimulus from the environment but they do occur in bacteria long before the latter is exposed to that drug. However, such plasmid

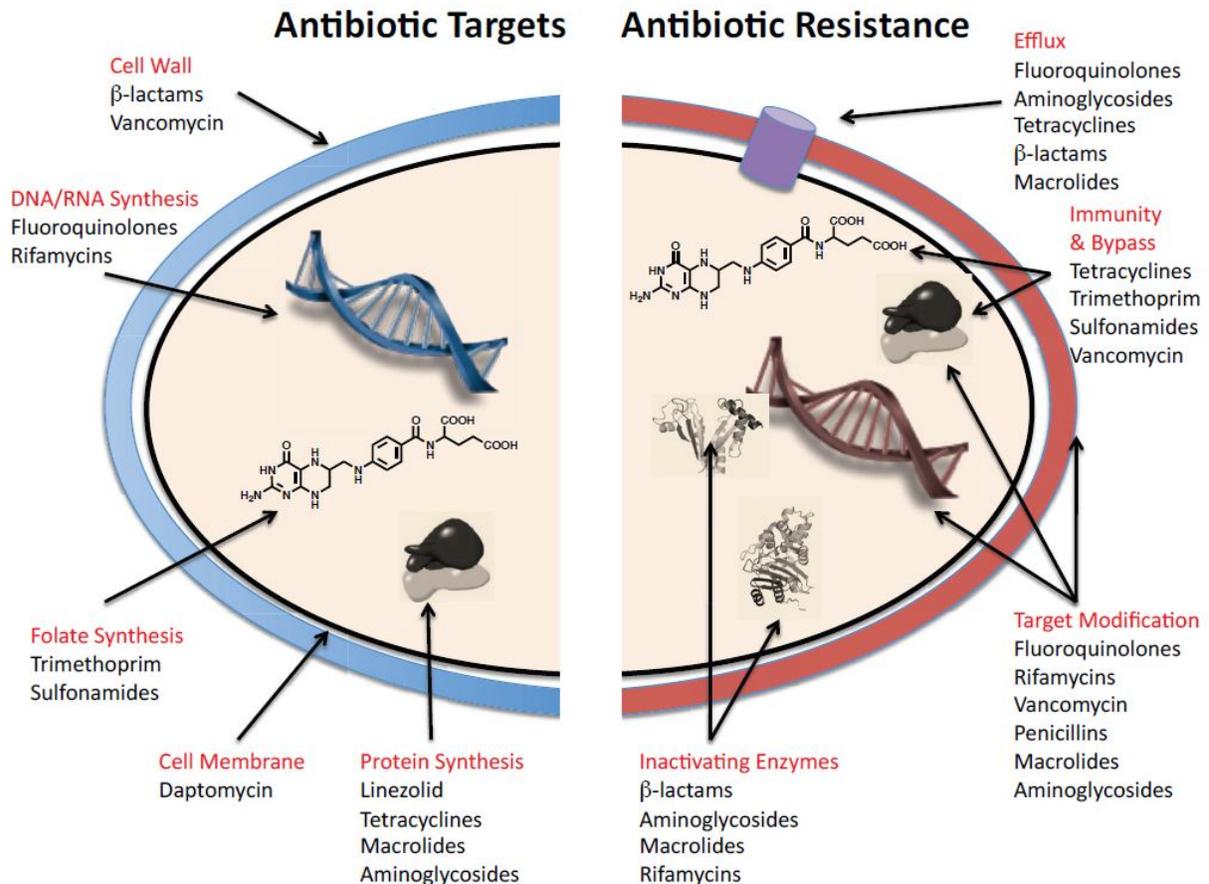


Figure 2. Antibiotic target sites and mechanism of resistance (Wright, 2005).

genes are usually expressed when bacteria are challenged by the drug, conferring resistance and adaptive capability on such bacterial species or strains (Tenover, 2006). Also, many bacteria maintain transposons (transposons are sometimes called jumping genes because they are able to move from one location in a genome to another). Transposons occurring within bacterial plasmids are sometimes duplicated and inserted into another plasmid or from a plasmid to the chromosome. When this happens, such transposons would replicate and be inherited by all subsequent progeny just like any other genetic material. This is obviously one of the mechanisms that facilitates the widespread occurrence and spread of drug resistance among bacteria (Byarugaba, 2004).

A case in point was the discovery of a frightening occurrence of bacterial dysentery which seemed to defy treatment in Japanese hospitals in the 1950s. Bacterial dysentery is caused by bacteria of the genus *Shigella*. This bacterium had been known to be sensitive to a wide array of antibiotics which were used to control the disease at the time. However, sometimes in the 1950s, *Shigella* isolated from patients with dysentery in Japan were found to be concurrently resistant to many of these

drugs, including penicillin, tetracycline, sulfanilamide, streptomycin, and chloramphenicol. This observation was worrisome, and called for further research. Follow up studies showed that this multiple drug resistance phenotype was inherited as a single genetic entity, and could be transmitted to, and confer resistance on other *Shigella* strains and related bacterial species, hitherto sensitive to the aforementioned antibiotics. The vector carrying these resistance capabilities from one cell to another were shown to be a self-replicating element. Amongst others, genes for antibiotic resistance are contained in self-replicating mobile genetic elements, collectively called 'Resistance (R) Factors' which include plasmids, transposons, and integrons (Harbottle et al., 2006; van Hoek et al., 2011). Bacteria usually transmit these Resistance (R) factors by means of conjugation, transduction and transformation of other bacterial strains or species.

Several studies have shown that genes conferring antibiotic resistance on bacteria abound virtually everywhere, in soil, excreta, chicken guts, Arctic snow, rivers, ocean etc (Garmendia et al., 2012; Nesme et al., 2014). Although, the soil harbors the most diversity of antibiotic resistant encoding genes than other bacterial

Table 1: Major classification of antibiotics and MDR genes developed in bacteria.

Name	Class	Source organism	Target	Resistant gene
Benzyl Penicillin	Penicillins	<i>Penicillium notatum</i>	Bacterial cell wall peptidoglycan synthesis	Beta-lactamase (<i>bla</i> genes)
Cefotaxime	Cephalosporins		same	<i>bla</i> CTX-M
Imipenem	Carbapenems		Same	<i>bla</i> KPC, <i>bla</i> NDM1, <i>bla</i> OXA-48

van Hoek et al. (2011).

Table 2. Localization of MDR genes in plasmids of superbugs.

Name of plasmids	Size in bp	Bacteria from which isolated	Accession number	MDR Genes found	Reference(s)
KP1	95kb	<i>Klebsiella pneumoniae</i>	CP009116	Aph, <i>bla</i> TEM, <i>aac</i> 3', <i>aad</i> , <i>arr</i> , <i>bla</i> NDM1	van Duin et al. (2014), Chakraborty (2016)
pKP12226	94kb	<i>Klebsiella pneumoniae</i>	KP453775.	<i>sul</i> 1, <i>aad</i> A4, <i>mph</i> (A), <i>mrx</i> , <i>mph</i> (R), <i>bla</i> CTX-M-15	Shin and Ko (2015)
pUUH239.2	221kb	<i>Klebsiella pneumoniae</i>	NC_016966	(<i>bla</i> (CTX-M-15), <i>bla</i> (TEM-1) and <i>bla</i> (OXA-1, <i>aac</i> (6)-1b-cr, <i>aad</i> A2, <i>tet</i> (A), <i>tet</i> (R), (<i>dhfr</i> XII), <i>sul</i> 1	Sandegren et al. (2012)

habitats, it is evident that antibiotic resistance is a normal part of bacterial ecology and had existed long before the discovery of bacteria and antibiotics (Baquero et al., 2009). Therefore the issue of the indiscriminate use of antibiotics only heightened the emergence of antibiotic resistant bacteria (Roca et al., 2015; Finley et al., 2013; Heuer et al., 2009). Several works directed at studying antibiotic resistant genes within and without clinical settings are continually carried out by scientists and allied professionals. Most of such studies have often led to the discovery of several gene sequences with antibiotic capabilities across different environments (Nesme et al., 2014). (Table 1)

Thousands of MDR genes which are often detected in bacterial conjugative plasmids and sometime also found in MDR islands of bacterial chromosomes of *Escherichia coli* and *Acinetobacter baumannii* and *Vibrio cholera* have been sequenced. Multidrug-resistant (MDR) genes could be mainly divided into three groups: (a) Beta-lactamase genes (*bla*); (b) drug modifying genes (*aac*, *aad*, *aph*; amino glycosides acetyl transferases, Phospho transferases and adenyl transferases) and (c) drug efflux genes (*acr*AB, *env*CD, *mex*AB/CD/XY, *tet*, *mcr*, *nor*A) and others (Chakraborty, 2016). (Table 2)

The constant discovery of resistant genes by different workers, in turn, led to the need to compile, maintain and constantly update a database of all known genes relating to antibiotics. This was by no means a simple feat to accomplish in the past. However, the advancement and fall in cost of carrying out molecular biological techniques and procedures, particularly next-generation DNA sequencing has greatly facilitated the compilation of a

broad and comprehensive antibiotic resistance gene database. For example, culture-independent metagenomic surveys and whole-genome sequencing (WGS) are being increasingly used to examine new antibiotic-resistant isolates, and findings from these works are continually added to the pool of known genes and their distribution within and outside clinical settings (Sekiguchi et al., 2007; Gandhi et al., 2006).

Several databases have been compiled to provide information on the numerous antibiotic resistant genes found or studied. Some of these include InnateDB for innate immunity interactions and pathways (Vila et al., 2007), the Lahey clinic database on Ser β -lactamases, the Repository of Antibiotic resistance Cassettes (Courvalin, 2006), the Antibiotic Resistance Genes Database (ARDB) (Liu and Pop, 2009) and the Antibiotic Resistance Genes Online (ARGO) (Scaria et al., 2005).

The Antibiotic Resistance Genes Database (ARDB) for example is quite robust and versatile as it seeks to unify most of the publicly available information on antibiotic resistance. In this database, each gene and resistance type is annotated with information unique to the gene, such as resistance profile, mechanism of action, ontology etc. In addition, the database is linked to other sequence and protein databases. This versatility provides for sequence similarity searches and preliminary characterization of common mutations that confer antibiotic resistance (Liu and Pop, 2009). The ARDB has been considered a veritable compilation of antibiotic resistance factors that would enhance the identification of resistance genes of newly sequenced genes, genomes, or metagenomes. As at 2009, ARDB had resistance

information for 13,293 genes, 377 types, 257 antibiotics, 632 genomes, 933 species and 124 genera (Liu and Pop, 2009). Some important antibiotic resistance genes in Antibiotic Resistance Genes Database (ARDB) are Aac, Aph and ANT genes responsible for Aminoglycoside resistance, beta-lactam Classes A-D genes responsible for Beta Lactamase resistance, ATP-binding transporters responsible for Macrolide-Lincosamide-Streptogramin B (MLS_B) Resistance, Tetracycline efflux resistance gene responsible for tetracycline resistance and Vancomycin type A-G operon genes responsible for Vancomycin resistance (Liu and Pop, 2009).

Notwithstanding the significant developmental roles of these databases in the various specialized disciplines of Applied Microbiology, some workers were not satisfied, insisting that the compilations of antibiotic resistant genes were too narrow in scope. McArthur and his league of associates (2013), in particular, reiterated that the databases were not regularly updated, and were not designed to effectively, robustly integrate molecular information from genes and their products (antibiotics). As a result of these setbacks, McArthur and his Associates (2013) worked assiduously to compile the famous Comprehensive Antibiotic Research Database (CARD). It would be noteworthy to state that Liu and Pop (2009) that authored and designed ARDB corroborated some of the claims of McArthur and his associates. Specifically, Liu and Pop (2009) indicated that the last update of their database was done as far back as 2009. Furthermore, they truthfully alluded to the fact that the CARD is more inclusive and regularly updated.

The CARD is therefore undoubtedly more robust in application than previous databases; it seeks to harmonize different molecular and sequence data. With CARD database putative antibiotic resistance genes in new unannotated genome sequences could quite easily be identified. This unique platform takes into cognizance antibiotic resistance concerns in health care, agriculture, and the environment, and serves as a bridge linking these different strata of sectors in our society (Liu and Pop, 2009).

Challenges of antibiotic resistance

Infectious diseases due to bacteria are still very much worrisome, responsible for 700,000 deaths annually worldwide, especially among children and the elderly. The rising incidences of Antibiotic resistance (ABR) and the emergence of multidrug-resistance bacteria portend very grave danger in our public health sector (Epps et al., 2013; Nasir et al., 2015). A recent report from the World Health Organization made it very clear that the world is gradually heading for a "post-antibiotic era" if no action is taken to stem the tide of antibiotic resistance. For many years the scientific community, and in particular the medical researchers/practitioners have repeatedly

warned the global society at large on the growing emergence of antibiotic resistance amongst various diseases and infectious agents. Their objective was to warn the human race about the downward depletion of its armory of effective antibiotics, noting the need for concrete, proactive and urgent steps to stem down the momentum of the rather increasing threats from the microbial world. To put in clear perspective, antibiotic resistance was responsible for 2 million illnesses and 23,000 deaths in the USA alone within a year (Centers for Disease Control and Prevention, 2013). As a matter of urgency, WHO has reportedly suggested the imminent outbreak of many epidemics of bacterial diseases like cholera, pox and pneumonia by the year 2050. Moreso, as MDR bacterial spores are contaminated in global air and water, an antibiotic dark age seems inevitable if urgent steps are not taking to carefully study the MDR-genes for new drug development (Chakraborty, 2015; Fosberg et al., 2012; O'Neil, 2014).

The situation of bacterial resistance to antibiotics in Africa and Nigeria in particular is even more worrisome. According to the World Health Organization, bacterial infections accounted for as much as 45% of deaths witnessed at the turn of the century in Africa and South-East Asia (World Health Organization, 2001).

The case of the African region is further exacerbated by scarcity of accurate and reliable data on antibiotic resistance (ABR) (Habib et al., 2003; Nasir et al., 2015; Ndiokubwayo et al., 2013). In view of this dearth of adequate information, Nasir et al. (2015) recently conducted a review of relevant published articles using extensive literature search to ascertain the level of emergence and spread of ABR in Nigeria, with a view to articulate the challenges and proffer possible solutions to ABR surveillance. Sadly, their findings showed that surveillance for ABR in pulmonary tuberculosis was the only system in good function in Nigeria; regrettably, most hospitals have poor ABR systems for other bacteria. Whilst this setback could be linked to multifactorial reasons, this obvious dearth of accurate and reliable data on antibiotic resistance (ABR) further compounds the implementation of possible remedial measures since the magnitude of the problem is largely unquantified (Ndiokubwayo et al., 2013).

This notwithstanding, literature is replete with findings of a few pockets of research undertaken over the years, and most of the results are quite alarmingly frightful. For example Habib et al. (2003) undertook a retrospective study of 438 patients with microbial pathogens from urinary and respiratory tracts in northern Nigeria. Results showed that as much as >50% of *Escherichia coli*, *Klebsiella* species, *Proteus* species and Pneumococci isolated were resistant to Cotrimoxazole, Tetracycline and Ampicillin. Bacterial resistance to antibiotics has indeed compounded Africa's disease burden to respiratory infections, sexually transmitted diseases and diarrheal diseases (Okeke et al., 2007; Okonko et al.,

2009a).

Antibiotic resistance seems to cut across several bacterial species and classes of antibiotics. For example resistance to penicillins, cephalosporins, aminoglycosides and tetracyclines have been noted with bacterial species belonging to the genus *Staphylococcus*. Similarly, Beta-lactamase resistance has increased significantly among bacterial infections caused by *Neisseria*, *Haemophilus*, *Enterobacteriaceae* and *Pseudomonas* species in Africa (Neu, 1984; Okonko et al., 2009b).

A relatively recent study further revealed that bacteria resistant to antibiotics were found in chicken meat, river water and water used for irrigation (Appiah, 2015), showing that bacterial resistance to antibiotic could be transferred to human through these routes. Several reports have identified Brazil, China and India as hotspots of increasing antibiotic use in livestock intensified while nations like Nigeria is said to be future hotspot (Appiah, 2015; O' Neil, 2014). The need to double our efforts at stemming the tide of bacterial antibiotic resistance is indeed very urgent, as available therapeutic options for antibiotic-resistant organisms are diminishing at very alarming rate. Bacterial pathogens are increasingly acquiring multidrug-resistant (MDR) capability (Moland et al., 2006; Lewis et al., 2007; Chikere et al., 2008; Okonko et al., 2009a). Very worrisome is the projected fact that as from 2050 the yearly number of deaths accruable to antibiotic resistance could be as high as 4.15 million in Africa and 4.73 million in Asia, if their prospective governments do not take proactive steps to tackle the issue (O' Neil, 2014).

Antibiotic resistant bacterial infections are emerging at an alarming rate, seemingly catching up with the pace of discovery and use of new drugs. This is quite frustrating for players in the industry; investment in developing drugs seems to be unrewarding, and not profitable. The pharmaceutical industry seems to find itself in a dilemma because, like investors in any other industry whose goal is to make profit, they simply do not want to develop new antibiotics that will become ineffective sooner than expected (Projan, 2003).

Alarmed by this obvious threat of antibiotic resistance some Federal agencies in the USA were summoned to a meeting to discuss and recommend practical ways to deal with the threat (Nutt, 2014). Characteristic of responsive governments, recommendations to tackle the issue were distilled to form part of the nation's strategy with a 5 year plan contained in a 78-page report. In particular, specific goals were spelt out to reduce the overall incidence of *Clostridium difficile* as well as the number of methicillin-resistant *Staphylococcus aureus* (MRSA) infections by 50 percent by the year 2020. The report proposed practical steps to both track resistant germs and to develop novel antibiotics to treat bacterial infections. Furthermore, the US government has proposed co-funding for the manufacture of new drugs as a way to encourage the pharmaceutical industries.

Also, the use of antibiotics in the cultivation and rearing of farm animals and also allowing their use to prevent disease on the same animals are being restricted. To this effect, some researchers are working assiduously to replace antibiotic amended growth promoter feeds with enzyme amended ones to reduce the emergence of antibiotic resistance bacteria in poultry farming (Cowieson, 2005; Ofongo-Abule et al., 2016).

Search and development of new antibiotics

The world is no doubt faced with a global crisis of new emerging infections which are rapidly developing resistance to existing antibiotics. There has to be a concerted effort by all and sundry to stem this ugly trend bedeviling the world's health sector. And recently mcr-1 gene that confers resistance to colistin was also spreading in plasmids. One vital sector positioned to play pivotal role, and has always been in the forefront of checkmating this heinous monster of bacterial resistance to antibiotics is science and technology.

The development and eventual introduction of new promising antibiotics into human health care delivery system is both tedious and slow owing to the sensitivity of the process and the need for caution and meticulousness. For example, the fluoroquinolones as a class of antibiotics was introduced in 1962. These mitigate against DNA gyrase and topoisomerase IV enzymes during DNA replication within bacterial cells (Hooper, 2001) and are effective against both gram-negative and gram-positive bacteria. Although they play an important role in treatment of serious bacterial infections, fluoroquinolones are sometimes not considered to be the best of options because of their numerous toxic side effects (Soni, 2012), and because like other broad-spectrum antibiotics, they encourage the spread of multidrug-resistant bacterial strains (FDA, 2016). However, about 40 years after the introduction of fluoroquinolones another class, the oxazolidinone were introduced in 2000 (Walsh, 2003). Oxazolidinones are a group of synthetic antibiotics which are active against a large spectrum of Gram-positive bacteria, including methicillin- and vancomycin-resistant staphylococci, vancomycin-resistant enterococci, penicillin-resistant pneumococci and anaerobes. They inhibit protein synthesis by binding at the P site at the ribosomal 50S subunit, and only very rare cases of resistance development have been reported (Bozdogan and Appelbaum, 2004).

The span of years it takes to introduce a drug undermines the rigorous and torturous process scientists subject newly discovered antibiotics before getting approval for public use in our health care delivery system.

In recent times bioactive natural products have been attracting a considerable amount of attention as potential agents of intervention in the search of new and effective

antibiotics. This is because they are replete in all environments. A study by Koehn and Carter (2005) revealed that a new set of new classes of bioactive natural products are isolated whenever biological microenvironments are assessed. For instance, the Abyssomicin C that is able to inhibit folate synthesis in methicillin-resistant *Staphylococcus aureus* is produced by a rare *Antinomycete verrucosispota* found in a sediment sample of the Japanese sea (Bister et al., 2004). Some relatively recent studies also show that several plant extracts are active against bacteria including MDR ones (Noumedem et al., 2013; Sahoo et al., 2011).

Characterization of microorganisms and their products have taken a new turn with the advent of molecular biology. There has been considerable development of techniques for characterizing diversity, in particular at the molecular level for both culturable and non-culturable microorganisms (Etebu, 2013; Etebu and Pondei, 2013; Rondon et al., 2000; Theron and Cloete, 2000). The application of molecular approaches in microbial systematics is centered on the availability of genomic data, which stems from the rapid development of DNA sequencing techniques. Molecular approaches, especially those employing the Polymerase Chain Reaction (PCR) methods have revolutionized molecular biology and diagnostics. They provide the most sensitive means for characterizing and classifying microorganisms as well as for their direct detection in environmental samples (Etebu, 2013; Etebu and Pondei, 2013; Lee and Taylor, 1992; Mullis, 1987). Analysis of Ribosomal RNA (rRNA) genes has greatly enhanced phylogenetic studies of organisms including fungi and bacteria through DNA based molecular approaches.

In recent times, researches in Massachusetts Institute of Technology have developed new and novel ways to fight drug-resistant bacteria like methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*. Molecular approaches were employed to turn off gene(s) responsible for antibiotic resistance within the bacterial genome. Also, the researchers have successfully developed antimicrobials termed RNA-guided nucleases (RGNS) whose spectrum of activity is chosen by design. These RNA-guided nucleases (RGNS) are designed to target specific DNA sequences, and are introduced into infectious bacteria via bacteriophage vectors. Although whether or not these approaches have been approved for application in health care delivery is yet to be ascertained, scientific reports show that undesirable genes including antibiotic resistance and virulence determinants in Carbapenem-resistant Enterobacteriaceae and Enterohemorrhagic *Escherichia coli* have been tackled effectively during scientific experiments. In addition, RGNS is able to modulate complex bacterial population by mounting pressure at the DNA level to selectively reduce the prevalence of undesirable genes, while minimizing off target effects and enabling programmable remodeling of microbiota (Citorik et al., 2014).

CONCLUSION AND RECOMMENDATIONS

Man's search for a cure of many bacterial adversaries led to the discovery of antibiotics in the 1940 to 60s. These discoveries tremendously helped humanity to partially win the many battles against bacteria; saved a lot of lives and extended man's life expectancy. However, the unrestricted accessibility to, and sometimes indiscriminate use of antibiotics by the general public, low profit returns by large pharmaceutical industries and use of fake and adulterated antibiotic in developing countries significantly contributes to the emergence of antibiotic resistant bacteria.

The following recommendations are herein proffered in view of antibiotic resistance becoming a global threat, particularly in developing countries:

1. Governments should initiate surveillance programmes' to monitor anti-microbial resistance among bacteria recovered from food animals, humans and retail meats.
2. There should be a continuous public awareness programmed concerning the rising resistant bacteria.
3. Patients should be advised only to take antibiotics exactly as directed by their doctors
4. There should be an initiation on the part of the government to do more research and develop our native medicinal plant products.

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