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Review Article

NEW FRONTIERS IN PHARMACEUTICAL MICROBIOLOGY AND BIOTECHNOLOGY: ADDRESSING THE GLOBAL BURDEN OF INFECTIOUS DISEASES

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ABSTRACT

Infectious diseases have persisted as an intractable challenge to human civilization, bringing along enormous health and economic burdens to the world's population. This problem cuts across all the regions of the world and various income strata. Periodic analyses of the problem conducted by organisations, such as the World Health Organisation, and the Institute of Health Metrics and Evaluation, portray the low-to-medium income countries (LMICs), mostly Caribbean countries, South Asia and Sub-Saharan Africa, as bearing the heaviest measure of the burden, compared to the developed countries. Characterisations, such as "infectious diseases of poverty (IDoPs)" are associated with these regions where high rates of morbidity and mortality are recorded as the result of inadequate healthcare facilities, including therapeutic and prophylactic tools. These inadequacies have resulted in widespread misuse of antibiotics in the treatment of bacterial and, unnecessarily, viral infections, with the consequential global explosion of antimicrobial resistance (AMR). However, there is growing understanding of the mechanisms of microbial resistance to antibiotics. And "battle of wits" is ongoing between the continually mutative microbes and the unrelenting bio-experts. This review highlights some recorded health and economic challenges that are attributed to microbial infections and antimicrobial resistance. It equally provides some insight into the scientific advancements being made at the global stage in the battle to eradicate the double scourges of infectious diseases and AMR.

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INTRODUCTION

Pharmaceutical microbiology is the study of discovery, production and evaluation of antimicrobial agents, the procedures for therapy of microbial infections as well as preservation of pharmaceutical products against microbial degradation. Impacts of microbial infections, whether considered on a global, regional or national scale, appear in three broad modes. The first impact arises from spread of infectious diseases among humans, animals, birds and plants. For humans, this manifests in the associated bouts of morbidity or mortality. The second aspect of microbial challenges is antimicrobial resistance (AMR) by microorganisms, which has placed an enormous burden on antimicrobial chemotherapy globally. Thirdly, certain microorganisms can contaminate pharmaceutical, food and cosmetic products, leading to instability and decline of quality. In this report, the socio-economic and health impacts of microbial infections will be presented. The account will also illustrate the burden of antimicrobial resistance on the therapeutics of microbial infections. Advances in pharmaceutical microbiology and biotechnology towards combating microbial infections and antimicrobial resistance will be discussed, illustrating some breakthroughs in global efforts at counterbalancing the various aspects of microbial burden.

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DEMOGRAPHIC BURDEN OF MICROBIAL INFECTIONS

At various eras, there have been attempts to monitor and quantify the burden of diseases, including microbial infections, at national levels. The metrics used in estimating burden of disease are mortality rates, morbidity patterns, life expectancy and economic losses [1]. But in 1996, the Institute of Health Metrics and Evaluation developed and used "Disability-adjusted life years (DALY)" in a Global Burden of Disease (GBD) study [2]. Simply put, DALY is a time-based measure that is interpreted as the number of productive years lost as a result of disability that may be caused by infectious diseases or other non-infectious morbidities [3]. It encompasses years of life lost (YLL) and years lost due to disability (YLD). Thus, DALY = YLL + YLD [3]. The use of DALY as a universally accepted standard metric for the burden of diseases has, however, remained a subject of debate among researchers [4 – 6]. Irrespective of the metrics adopted, microbial diseases have remained the leading causes of morbidity and mortality globally [7].

In a 2019 GBD analysis of global mortality caused by infectious diseases, it was found that an estimated 13.7 million deaths were caused by bacterial pathogens [8]. Among the bacteria investigated in that study, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were responsible for 54.9% of the deaths. In a similar study carried out concurrently within the Chinese sub-continent, an estimated 1.3 million deaths were attributed to bacterial pathogens, and this accounted for 12.1% of total deaths in China, 2019 [9]. In the case of China, *E. coli*, *Strep. pneumoniae*, *S. aureus*, Enterobacter spp. and *Acinetobacter baumanii* were the five leading pathogens [9].

There are significant geographical variations in death rates caused by infectious pathogens. In the low-to-medium-income countries (LMICs), such as the Caribbean countries, South Asia and Sub-Saharan Africa, the infectious diseases of poverty (IDoPs) are of major concern, because of the high rates of morbidity and mortality, as well as high costs of healthcare [10]. IDoPs cut across bacterial, fungal, plasmodial and viral infections, and they include the three most important ones (HIV/AIDS, tuberculosis and malaria), the twenty neglected tropical diseases, and other emerging or re-emerging infectious diseases, such as Ebola virus disease (EVD), avian influenza, and COVID-19 [11 – 13]. Wherever they occurred, these diseases were associated with high rates of morbidity and mortality. For example, the EVD was prevalent in West Africa between 2013 and 2016, and caused more than 28,000 human infections and over 11,300 deaths [14]. According to the WHO, from 1976, when EVD was identified in the Democratic Republic of Congo, until 2020, approximately 33,600 human infections, including over 14,700 deaths, occurred in the DRC alone [15]. Over the past decades, several other viral diseases, such as Lassa fever [16], Crimean-Congo haemorrhagic fever [17], Marburg fever [18] and Rift-valley fever [19] have produced high rates of morbidity and mortality in the East-African sub-continent. During these periods, various types of highly infectious respiratory pathogens, the beta-coronaviruses, broke out in Asia. The first severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in 2003 [20], while SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was reported in China, 2019 [21] and later became a global pandemic. Emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) was recorded in 2012 [22]. HIV and AIDS are still globally widespread. To date, the disease is believed to have claimed an estimated 42.3 million lives globally [23]. In 2023, the number of people living with HIV in Nigeria was estimated at two million, with approximately 50,000 AIDS-related deaths [24]. According to the global AIDS update, however, in 2024, Sub-Saharan Africa recorded the highest reduction in the number of new cases as compared to other parts of the world [25].

ECONOMIC BURDEN OF MICROBIAL INFECTIONS

Besides the costs in human lives and losses of productive years, infectious diseases place heavy economic burdens on individuals, families and nations. The average per capita out-of-pocket expenditure on healthcare-associated infections (HAI) in 2022 was US$2.76 in Nigeria, while the total economic cost of HAI was US$4.5 million or 0.94% of the Gross Domestic Product for that year [26]. In addition to the cumulative burden on national economies, isolated microbial diseases also take huge tolls on the economic productivity and incomes of households [27]. A study in 14 countries of Sub-Saharan Africa revealed a huge financial burden incurred for tackling infectious diseases in the sub-region [28]. With over 4.8 million infections and an estimated 500,000 deaths, the economic losses added up to US$13 billion [28]. This situation was attributed to inadequate availability of clean water, sanitation and hygiene (WASH) facilities, especially in rural areas of Sub-Saharan African countries [29].

In developed, high-income countries, microbial infections may not be directly associated with inadequacies of WASH facilities [30] but are, nonetheless, high with enormous economic burdens [31]. For example, in the USA, central-line-associated bloodstream infections (CLABSIs), ventilator-associated pneumonia (VAP), surgical site infections, *Clostridium difficile* infections, and catheter-associated urinary tract infections (CAUTIs) have collectively contributed to an annual medical cost of US$9.8 billion [32]. Similar hospital-acquired infections in Brazil were said to cost an estimated amount of US$68.8 million to 13 selected ICUs [33]. A retrospective case study conducted in a Chinese hospital indicated that the rate of nosocomial infections was 2.66% with a 9-month hospitalization cost of US$8,220 in each instance [34].

ANTIMICROBIAL RESISTANCE IN THE GLOBAL MICROBIAL CHALLENGE

The major challenge to antimicrobial chemotherapy is microbial development of resistance to various antimicrobial agents, especially antibiotics and antiviral agents [35, 36]. Antimicrobial resistance (AMR) has become a global threat to human existence in the 21st century [37]. It is estimated that, by 2050, AMR will account for 10 million human deaths globally per annum [38]. Both national governments and non-governmental organizations have become more aware of this existential threat and enough concerns are being expressed in various quarters [39, 40]. For example, the World Health Organization (WHO) has declared AMR as one of the global health threats confronting 21st century humanity [41]. Apart from morbidity and mortality impacts, AMR poses significant economic burdens. The World Bank estimates that AMR could raise healthcare costs to US$1 trillion by 2025, and US$3.4 trillion gross domestic product losses per year by 2030 [42]. The third of the United Nations Sustainable Development Goals is to ensure healthy lives and promote well-being for all, but it is feared that unless AMR is eradicated, the SDG No. 3 will not be realised on target [43].

In Sub-Saharan Africa, the picture is no less scary. A recent commentary by Dr. Abiodun Egwuenu, a Field Epidemiologist and Antimicrobial Resistance Programme Manager with the Nigerian Centre for Disease Control (NCDC), who is a lead writer for Nigerian Health Watch, reveals that Sub-Saharan Africa has the highest death rates attributed to antimicrobial-resistant infections [44]. According to the report, as high as 255,000 such deaths were recorded in 2022; and that accounted for 27 deaths for every 100,000 persons in Western Sub-Saharan Africa. In a 2017 publication, jointly produced by three Federal Ministries in Nigeria (Agriculture; Environment; and Health), the burden of antimicrobial resistance in Nigeria is elaborately documented [45]. The report indicates that multidrug resistance is prevalent among a wide range of bacteria, which include MDR-*Mycobacterium tuberculosis*, resistant strains of enteric pathogens (*E. coli*, Shigella, non-typhoidal Salmonella spp, *Vibro cholerae*, *Salmonella* Typhi, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, as well as multidrug-resistant UTIs in Nigeria. There are obvious consequences of antimicrobial resistance, as illustrated in Figure 1.

CAUSES OF ANTIMICROBIAL RESISTANCE

Between 1929 (when penicillin was discovered) and 1960, there was a rapid boom in the development of antimicrobials leading to the emergence of different structural classes of antibiotics. The following two decades were, however, a period of apparent stagnation in the licensing of new antibiotics. That led to over-dependence on the existing antimicrobials, and gradually microbial resistance to the antibiotics started to emerge [46]. Despite appropriate measures that have been recommended to curtail the spread of antimicrobial-resistant organisms, some socioeconomic factors seem to contribute in the exacerbation of this global threat. Compared to people living in high-income countries, persons in the low- and medium-income countries are more at risk of the dangers of AMR [47]. Regions with little or no access to clean water, sanitation, and genuine antimicrobials, are more prone to the incidence of AMR. In such countries, inadequacies of healthcare facilities, competent personnel, basic diagnostic testing, and rational prescribing, can lead to widespread misuse of antibiotics [48], with resultant increases in cases of AMR. Other factors that are associated with spread of resistant bacteria are: the rampant misuse of antimicrobials/antibiotics in veterinary healthcare, agriculture, environment, livestock, pets, and among humans [49].

ANTIBIOTIC RESISTANCE GENE PROFILES

Despite the socio-economic factors [50] that contribute to the spread of AMR, microorganisms respond to exposures to antimicrobials at the gene level [51]. Through microbial genetic adaptations, antimicrobial resistance can be developed by the following mechanisms: reduced membrane permeability, increased efflux pump, modification of target enzymes, enzymatic degradation of antibiotics, and biofilm formation [52]. Details of these mechanisms are available in microbiology literature [53]. With the help of high-throughput polymerase chain reactions (PCR) and metagenomics, more than one hundred antimicrobial genes, or their mutants, that are responsible for microbial resistance to all classes of antibiotics, including the so-called last-line, next generation antibiotics, such as colistimethate and tigecycline, have been identified [54 – 57]. With persistence of the problem of AMR, there will always be an unending search for new antimicrobial agents, and the goal is to develop novel chemical entities that will act by modes to which bacterial resistance does not exist. We look forward to that ideal era.

COMBATING ANTIMICROBIAL RESISTANCE

The aim, in this article, is to review the efforts that have been made towards finding solutions to the global microbial challenges and, by extension, AMR. What readily comes to mind are the conventional strategies that we teach in undergraduate classes [58]. These methods include:

- Improved personal and environmental hygiene.
- Vaccination programmes.
- Reduced dependence on antibiotic therapy.
- Surveillance for new cases of AMR in humans and animals.
- Proper diagnoses to isolate resistant infections.
- Rational prescribing of antibiotics.
- Controlled use of antimicrobials in veterinary care, agriculture and the environment.
- Withdrawal of ineffective antibiotics from circulation.
- Prevention of bacterial biofilm formation and destruction of pre-formed biofilms.
- Development of new antibiotics, diagnostics and vaccines that can curb the devastating impacts of AMR.

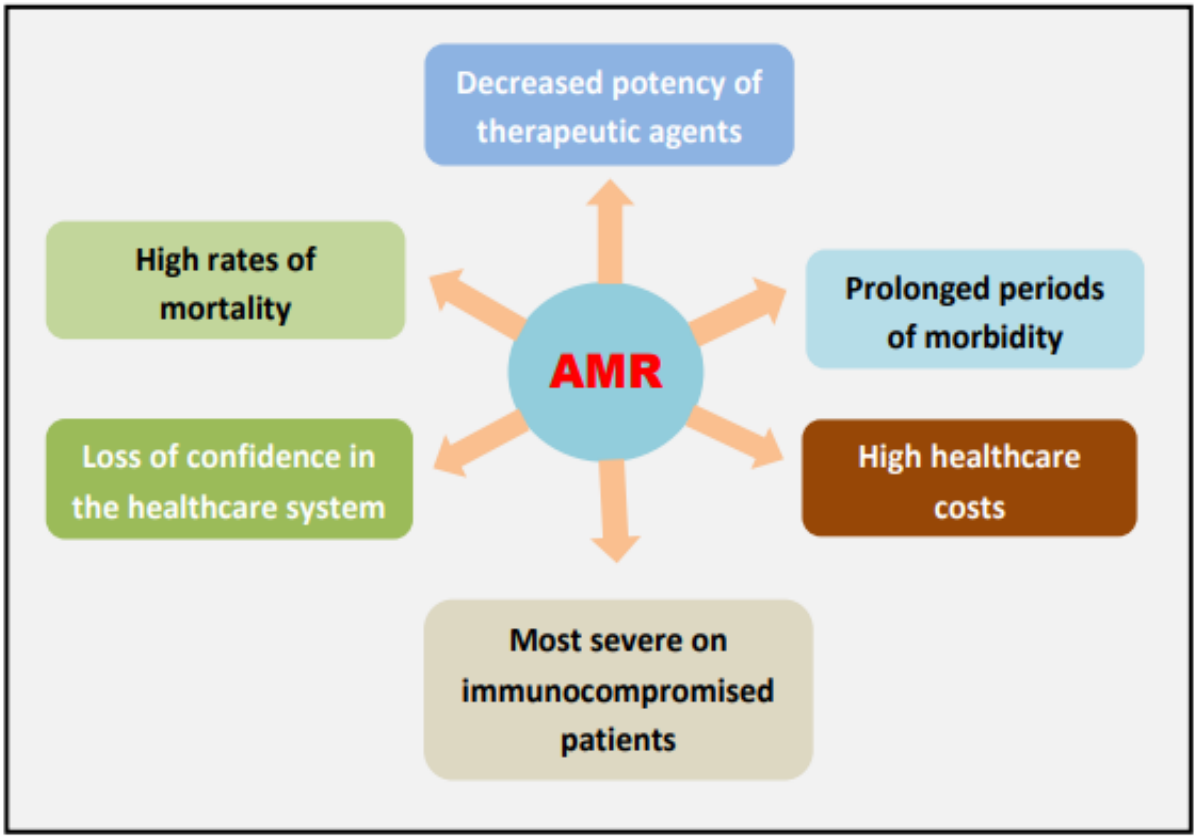

Figure 1: Summary of the impacts of antimicrobial resistance (AMR).

These measures can be effective if they are judiciously and resolutely implemented at the global scale.

ADVANCES IN ANTIMICROBIAL INNOVATIONS

Besides the conventional methods outlined above, there is a wide range of recent advancements in the global efforts at controlling AMR. Advances in pharmaceutical microbiology entail the evolution of techniques, including biotechnological processes, for eliminating AMR, to guarantee optimal therapeutic outcomes in the management of infectious diseases, and contributing to global health security [36]. In different parts of the world, biomedical experts are constantly engaged in high-throughput screening of antimicrobial chemotypes [59]. From these efforts, various antibiotic and non-antibiotic strategies, aimed at combating antimicrobial resistance, have evolved.

(a) Antimicrobial peptides (AMPs)

In recent years, the design and syntheses of antimicrobial peptides have stimulated enormous interest because of their capacities to reduce antimicrobial resistance. A number of peptides with antimicrobial capacities have emerged as powerful alternatives to traditional antibiotics, and they have proved to be effective against multidrug-resistant microbes [60]. Antimicrobial peptides are designed to act by, at least, two mechanisms, the membrane action and non-membrane action, as shown in Figure 2. Among the rapidly developing AMPs is cecropin, which is the first animal AMP to be developed [61]. Others include a series of antimicrobial peptides developed from human peptides, which are capable of destroying MDR pathogens by blocking biofilm formation or eliminating pre-existing biofilms [62]. FOTyr-AMP is a synthetic combination of nitric oxide and an AMP, which has superior antimicrobial action over that of cephalosporin C [63]. A proline-rich AMP was found to kill bacteria rapidly and reduce preformed bacterial biofilms by more than 50% [64].

Despite the high prospects of peptide antimicrobial drugs, only polymixin B is yet licensed for therapeutic use [65]. Others are still at various levels of development or clinical trial [66]. The major problem associated with the antimicrobial peptides is their susceptibility to protease enzyme degradation [67]. Moreover, the extraction of natural peptides is complicated, and chemical synthesis is expensive [68]. These impediments tend to discourage industrial-scale production of AMPs [69].

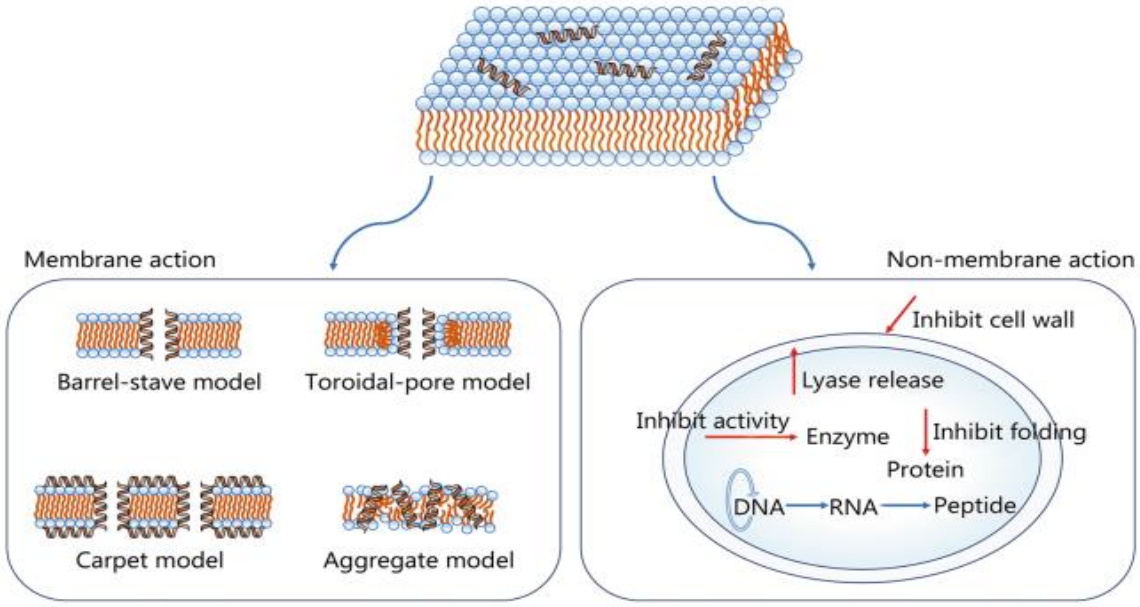

Figure 2: Mechanisms of antimicrobial action by antimicrobial peptides. The direct bactericidal mechanism of AMPs is performed through interacting with negatively charged membranes, resulting in increased membrane permeability, cell lysis, or release of intracellular contents, which ultimately leads to cell death. There are four main models of membrane action, namely barrel-stave model, toroidal-pore model, carpet model and aggregate model. Another antibacterial mechanism is one in which AMPs penetrate the cytoplasm and interfere with intracellular processes, such as inhibition of DNA, RNA and protein syntheses, protein folding, enzyme activity and cell wall synthesis, as well as promoting the release of lyase enzymes to destroy cell structures. (Adapted from Zhan *et al.* [60])

(b) Synergistic antibacterial adjuvants

One of the mechanisms in antimicrobial resistance is the development of bacterial enzymes that can inactivate susceptible antibiotics. A well-known example of such enzymes is the β-lactamase, which can inactivate β-lactam antibiotics. Inhibitors of β-lactamase are used as adjuvants to potentiate the β-lactam antibiotics [70]. Clavulanic acid is the most popular β-lactamase inhibitor in clinical use. It penetrates the cell wall of most bacteria more effectively than other β-lactamase inhibitors [71]. Amoxicillin-clavulanic acid combination, which was introduced clinically in 1981, is still of high therapeutic value to date. Clavulanic acid-ticarcillin combination is also commercially available. Other commercially available combinations are: sulbactam-ampicillin [72] and tazobactam-piperacillin [73]. Auranofin is an antirheumatic drug, but it is capable of potentiating carbepenems against β-lactamase-producing *Escherichia coli* [74].

(c) Efflux pump inhibitor adjuvants

Apart from the enzyme inhibitors, efflux pump inhibitors can also be used as adjuvants to antibiotics in the fight against antimicrobial resistance. In the last two decades, tremendous efforts have been made to identify effective efflux pump inhibitors [75]. In the process, a multidrug efflux pump gene, NorA, was discovered, and this is responsible for antimicrobial resistance in MRSA [76]. However, Brawley and colleagues [77] have identified an antigen-binding fragment (F_{ab}), which is capable of inhibiting NorA, thus enhancing the actions of antibiotics against MRSA. Similarly, Felicetti *et al*. [78] have produced a series of methoxy-2-phenylquinoline derivatives that have shown good inhibitory activities against NorA, thus reducing resistance of *Staphylococcus aureus* against ciprofloxacin. Further studies by Grimsey *et al*. [79] have demonstrated that the antipsychotic drugs, chlorpromazine and amitriptyline, are potent inhibitors of AcrB, the multidrug efflux pump gene in *E. coli* and *Salmonella* Typhimurium. Therefore, used as adjuvants, these compounds can potentiate the actions of antibiotics against multidrug-resistant bacteria.

(d) Photodynamic antimicrobial chemotherapy (PACT)

This is another novel approach in the fight against bacterial resistance to antibiotics. It is an oxidative destruction mechanism based on the synergistic actions of three components: a photosensitive material, light and oxygen [80]. Using this antimicrobial strategy, an electric field stimulates

the electroluminescent and photosensitive materials to generate reactive oxygen species (ROS) [81]. With the aid of a penetrating laser machine, the ROS is focused on the infected part of the body to exert antibacterial actions against drug-resistant bacteria. PACT has the advantage of being non-invasive; it is useful for localized infection treatment, suitable for wound healing, exhibits as high as 99.9% antibacterial effect, and has near-zero occurrence of bacterial resistance [82].

(e) Metallic nanomedicines used against AMR

Studies have shown that metallic nanomaterials containing silver, zinc, gold, copper or iron can be used for the treatment of bacterial infections [83]. In addition, nanomaterials of ZnO or CuO have been shown to exhibit synergistic effects when combined with conventional antibiotics [84], thus enhancing antibacterial actions and reducing bacterial resistance. There is abundance of literature showing that, used singly or in combination with other antimicrobial agents, metallic nanomaterials can significantly enhance antibacterial outcomes, through various mechanisms, such as, disruption of cytoplasmic membrane potential [85], interference with bacterial enzyme action [86], and prevention of biofilm formation or destruction of pre-formed biofilms [87].

(f) Non-metallic nanocarriers used against AMR

Some non-metallic nanocarriers also have promise for highly effective antibacterial therapy (HEAT). These include:

***Lipid-based nanocarriers (liposomes and nanostructured lipid carriers)*:** These have attracted a lot of attention as versatile delivery systems for antimicrobial agents [88].

Exosomes: Exosomes are intracellular membrane-bound vesicles that play crucial roles in intercellular communications. They have been used as effective agents for delivering drugs, including antibiotics, to receptor sites [89].

Polymeric nanocarriers: A variety of natural or synthetic biodegradable and biocompatible polymers can be used in constructing nanocarriers [90, 91]. The polymers include, poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), sodium glycolate, and chitosan [92]. Incorporating antimicrobial agents into polymeric nanocarriers has been effective in overcoming antimicrobial resistance [93]. Some workers have adopted the strategy of polymer blends in developing polymeric nanocarriers of antibiotics [94]. Several other versions and modifications of polymeric nanocarriers of antimicrobial compounds are available for the combat against AMR [95].

Micelles: The amphiphilic nanostructure of micelles provides an appropriate environment for encapsulation and solubilisation of antimicrobial agents [96]. Some nano-sized micelles have been found to enhance the antimicrobial activity of antibiotics, thereby, in specific cases, eliminating multidrug-resistant organisms [97]. The capacity of micelles to penetrate biofilms and deliver antimicrobial agents inside the microbial cells presents an intriguing mechanism for combating AMR [98, 99].

Nanofibres: Nanofibres can be produced from solutions of natural polymers (such as gelatin or chitosan) [100], synthetic polymers (such as poly (lactic acid)), poly (oxyethylene oxide) [101], or polymer combinations [102]. When subjected to the influence of electric charges, in an electrospinning technique [103], the polymer in solution is turned into filaments or thread-like structures of nanometre size range [102]. During the formation process, antibiotics can be incorporated into the nanofibre scaffold, and that can enhance controlled drug release [104]. Nanofibres have a wide range of applications in drug delivery technology, and have successfully been employed in bone tissue repair efforts [105]. Moreover, the efficiency of nanofibre drug carrier systems, in the control of MDR pathogens, has gained appreciable attention [106].

Dendrimers: The term, “dendrimer” is derived from a Greek word, *dendrima*, which means, “tree”. As drug delivery systems, dendrimers are three-dimensional nanopolymeric structures that mimic the appearance of a tree, with well-defined branches (Figure 3) [107]. Various polymers can be used to construct dendrimers. These include polyamidoamine (PAMAM), polylysine (PLL), polypropylene imine (PPI), polyglycerol (PG), polyester and polysilane [108]. Production of amphiphilic dendrimers [109] or phosphorus dendrimers [110] has also been demonstrated. Because of their unique structures, dendrimers can entrap large amounts of drugs within their interior cavities, or covalently attach them to functional groups on the “branches” [111]. In the fight against MDR pathogens, dendrimers have been explored as carriers for antibiotics [112], or directly for their intrinsic antibacterial properties [113]. Studies have shown that activities of antibiotics delivered in dendrimers were significantly potentiated [114, 115].

Mesoporous nanomaterials: Mesoporous nanomaterials that have been experimented on in the fight against AMR include metal oxides, polymers and silica [116]. These materials are used to produce nanoparticles that have well-structured pores in the mesoporous size range (2 – 50 nm). Mesoporous silica nanoparticles (MSNs) are known to exhibit high capacity for drug entrapment, providing controlled drug release [117, 118]. In a study reported by Dereje *et al.* [119], MSNs were used as nanocarriers for squaraine dye (a photosensitizer with antimicrobial properties), and it was demonstrated that the loaded nanosystem exhibited more remarkable antibacterial activities against *Staphylococcus aureus* and *Escherichia coli*, as compared to the plain dye. MSNs have effectively been used as valuable carriers of antibiotics to treat bacterial infections by which the system minimizes the burden of antimicrobial resistance [120]. Several other organic materials (proteins, enzymes and peptides) that possess the capacity to block the various

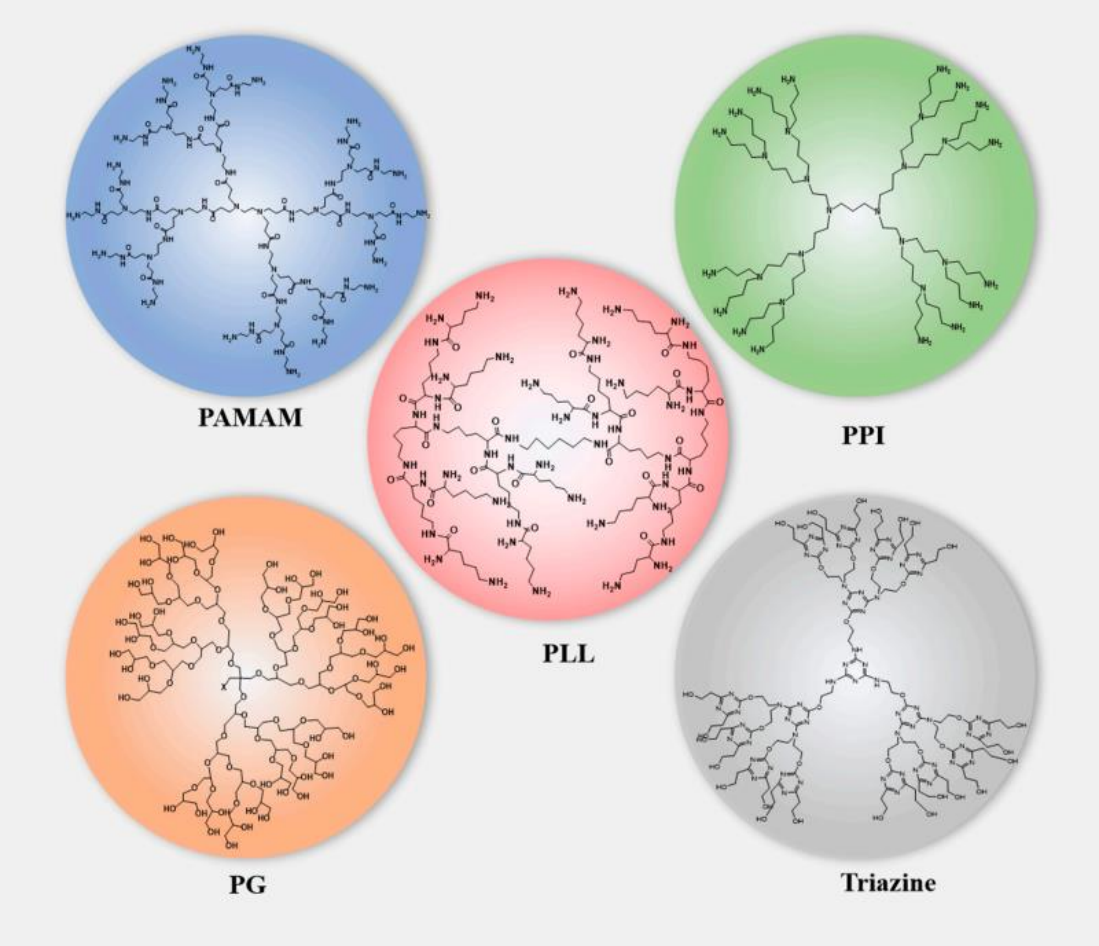

Figure: 3. Structures of dendrimers used as drug delivery systems. (Adapted from An *et al*. [107])

mechanisms of antimicrobial resistance have been employed to produce organically modified multifunctional MSNs [121]. In this way, multifunctional MSNs have been used to enhance the permeation of antibiotics through bacterial cell wall [122] and destruction of bacterial biofilms [123], all being useful strategies to mitigate AMR.

(g) Biotechnological approaches to combating AMR

Biotechnology has played, and will continue to play, significant roles in the fight against AMR. Consequently, several biotechnological approaches have been used to develop novel antibiotics, such as peptidomimetics [124, 125] and antimicrobial peptides [126, 127]. Some of these techniques include:

Gene mining: The science of genomics has opened doors to antibiotic discovery. Genomic mining makes use of bioinformatics tools to identify potential antibiotic-producing genes, leading to the discovery of novel, stable antibiotics [128] from biosynthetic gene clusters (BGCs) [128, 129]. For example, new antibiotics discovered in glycopeptide BGCs were found to be stable against vancomycin-resistance genes and, so, sustained their lethal activities against multidrug-resistant isolates of *S. aureus* [130]. Similarly, three highly potent lipopeptide antibiotics were identified from BGCs of *Streptomyces* species [131]. Genes encoding resistance to the antibiotics were not located in the lipopeptide BGCs, and that means the antibiotics may be robustly stable in the fight against AMR.

Antibiotic-antibody conjugates: Another aspect of the biotechnologically driven battle against AMR is the use of antibiotic-antibody conjugates (AACs). This approach has stimulated considerable interest among researchers as they seek to improve the efficacy of antibiotics against multidrug-resistant pathogens [132]. It is an innovative technology that relies on the exceptional specificity of monoclonal antibodies (mAbs) to bind target antigens, and this can be used to deliver potent antibiotics directly to bacterial cells [133]. In a typical case, it was recorded that a single dose of anti-*S. aureus* antibodies, conjugated to vancomycin, eradicated intracellular methicillin-resistant *S. aureus* within 24 hours [134], which was substantially better than the standard twice daily dosage of vancomycin.

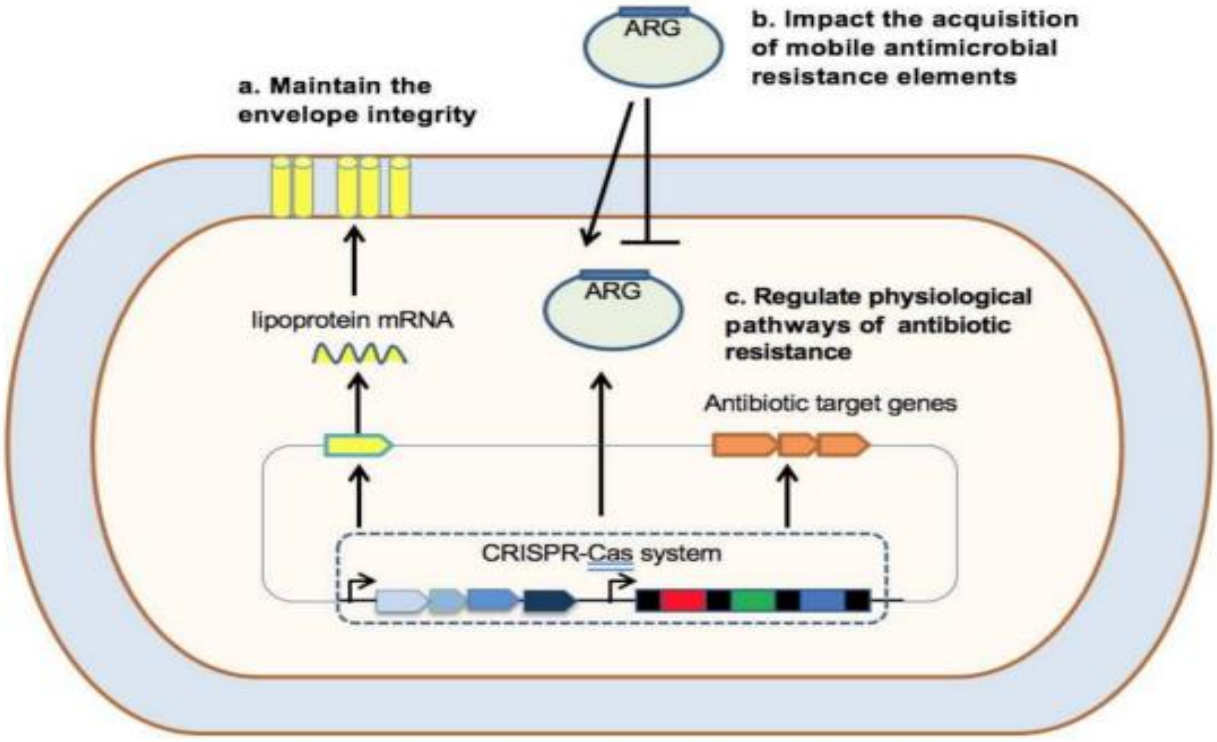

Figure 4: Various ways by which the CRISPR-Cas system impacts antibiotic resistance in bacteria. (a) The CRISPR-Cas system can maintain envelope integrity by regulating envelope lipoprotein expression to enhance antibiotic resistance. (b) The CRISPR-Cas system can prevent the acquisition of mobile antimicrobial resistance elements to stop antibiotic resistance. (c) The CRISPR-Cas system can regulate the physiological pathway involved in the antimicrobial resistance of bacteria. ARG stands for antimicrobial resistance gene. (Adapted from Kang *et al.* [136])

CRISPR-Cas system: Clustered Regularly Interspaced Short Palindromic Repeats-Cas system is currently regarded as the most inventive biotechnology, not only in gene editing but also, in the control of AMR [135, 136]. Several research works have consolidated the CRISPR-Cas-based strategies for preventing the spread of MDR pathogens [137 – 139]. The various ways by which the CRISPR-Cas system can modulate AMR are illustrated in Figure 4. This technology has also been employed in the eradication of some infectious viruses [140], and these are areas that are worth investing research efforts in.

Phage therapy: This approach has been explored as an alternative to traditional antibiotics in the combat against AMR [141]. Phage therapy involves the delivery of lytic phages to patients suffering from bacterial infections so as to eradicate the pathogenic organisms [142]. The high point in successful deployment of phage therapy is reduction in the use of antibiotics [143]. This can potentially limit the emergence of new resistant pathogens. Phage therapy also offers the prospect of eliminating suberbugs [143]. Although phages are effective against antibiotic-resistant bacteria, the pathogens can acquire a variety of defence mechanisms to survive phage attacks [144]. This has led to the deployment of bacteriophage cocktails used alone [145] or in combination with antibiotics [146] in the combat against AMR.

Manipulation of the human microbiome: The human microbiome normally plays important roles in maintaining good health and combating microbial infections [147]. Manipulating the human microbiome with probiotics and prebiotics can help in controlling the spread of antibiotic-resistant pathogens [148]. With the application of biotechnology, strains of probiotics can be tailored to out-compete resistant bacteria and prevent the establishment and persistence of MDR infections [149, 150].

(h) Vaccines against AMR

The effectiveness of vaccines in reducing AMR has been under-emphasized. This is, probably, due to the indirect roles vaccines play in this specific area. By preventing life-threatening diseases caused by bacterial or viral pathogens, effective vaccination can lead to reduction in widespread misuse of antibiotics, which consequently lowers AMR [151]. Successful population-based vaccination programmes are known to provide indirect protection to unvaccinated persons

through herd immunity [152]. In this way, the spread of resistant infectious diseases can be controlled, and unnecessary use of antibiotics can be eliminated [153]. Particular attention has been given to these possibilities, and successes have been recorded from global efforts aimed at using bacterial vaccines to reduce antimicrobial resistance [154, 155]. One of the ways that misuse of antibiotics can lead to AMR, is in using antibiotics to treat viral infections [156]. This practice is rampant among the naïve antibiotic users. To reduce this aspect of antibiotic misuse and prevent AMR, it is essential to prevent viral infections. Effective vaccinations against various viral infections will, not only prevent the spread of viral diseases but, also reduce the tendency for antibiotic use in treating viral diseases [157]. This shows that viral vaccines can play an important indirect role in reducing AMR.

(i) Application of artificial intelligence in the control of AMR

Due to the advances in biomedical technology and increasing availability of biological data (including omics data), artificial intelligence (AI) has been recognised as a powerful tool in analysing these large volumes of data. In this way, AI has proved useful in the fight against diseases, especially microbial infections [158] and drug discovery [159]. AI has considerably impacted the discovery of antimicrobial agents, specifically the highly active antimicrobial peptides [160, 161]. AI has also played increasingly important roles in other aspects of the fight against AMR [162] including diagnosis of bacterial infections and treatment [163] as well as phage therapy [164]. The AI-driven approach to antibiotic discovery has additionally led to the identification of compounds that are active against metabolically dominant bacteria, which are traditionally resistant to conventional antibiotics [165]. Considering its varied potentials, AI offers much optimism in the concerted fight against MDR pathogens.

CONCLUSION

Infectious diseases, caused by microbial pathogens, remain a global health challenge despite enormous resources invested by world health agencies, governments and researchers at annihilating the scourge. Despite the global scope of the problem, the negative impacts are felt mostly in sub-Saharan Africa and other LMICs. Microbial diseases negatively impact economies of the affected countries, hampering socio-economic growth and general productivity. Large populations in the LMICs lack access to clean water and sanitation. This has been attributed to widespread poverty and lack of economic capacity to access quality healthcare, with resultant high rates of death annually. Efforts by the World Health Organization and other global humanitarian bodies have yielded considerable results, but the situation appears to demand continuous, endless interventions in the supply of antibiotics, vaccines and other medical devices.

The burden is exacerbated by the potentials of microbial pathogens to continuously evolve resistance mechanisms against the various antimicrobial agents. Nonetheless, there have been endless efforts, in the scientific research community, aimed at bringing an end to the menace of infectious diseases. Advances in research and development have been made in understanding the dynamics of cellular systems, molecular biology, genomics, proteomics, diseases, vaccines, novel antibiotics, gene editing, nanoscience, and especially phage therapy. With the enormity of biological data being generated from these efforts, artificial intelligence has come handy in the areas of data analysis, antibiotics discovery, high-throughput diagnoses, and various aspects of biotechnology.

Given the seemingly endless threat of infectious diseases, concerted global consciousness is required to escalate these efforts and leverage on the advancements in pharmaceutical microbiology and biotechnology. This demands for continued surveillance to ensure early detection of novel threats; coordinated global response to outbreaks; enhancement of public health infrastructure; expansion of laboratory capacities for rapid diagnoses of emerging pathogens; massive investments in research; development of cutting-edge diagnostics, vaccines and therapeutics; as well as promotion of the One Health approaches that recognise the interconnectedness of human, animal and environmental health [166, 167].

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AUTHORS' CONTRIBUTIONS

CFK developed the manuscript; VCO conceptualized the theme, provided supervision and review.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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