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A Review on Antibiotic Resistance: An Old Solution but a New Problem

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ABSTRACT

Antibiotics are chemical agents that prevent bacterial growth by stopping the bacterial cell from dividing (bacteriostatic) or with the aid of killing them (bactericidal). So antibiotics are an integral part of drug treatments used to make sure human and animal health. However, the widespread use, misuse and overuse of antibiotics in human and animal has raised the concern about the development of resistant bacteria that own a capacity danger to animals and humans. Antibiotic-resistant microorganisms have been defined as 'nightmare microorganisms' that 'pose a catastrophic risk' to people in every country in the world. Therefore, the need for educating patients and the public is vital to combat the antimicrobial resistance (AMR) conflict. This paper intends to study on AMR and further to recommend its control measures.

Abbreviations: AMR, Antimicrobial resistance; MDR, Multidrug-resistant; AGPs, Antibiotic growth promoters; WHO, World health organization; ABR, Antibacterial resistance; FTT, Fecal transplant therapy; UK, United Kingdom; NDM-1, New Delhi Metallo-β-lactamase; *S, Staphylococcus; E, Escherichia*; R&D, Research and development.

1. INTRODUCTION

Antibiotics are the 'wonder drugs' to combat microbes. For decades, multiple varieties of antibiotics have not only been used for therapeutic purposes but practiced prophylactically across other industries such as agriculture and animal husbandry [1]. Penicillin was the first natural antibiotic to be discovered accidentally by Alexander Fleming in 1928 when the *Penicillium* fungus contaminated a culture plate in his laboratory, however, penicillin was not developed for use until the late 1930s [2]. AMR within a wide range of infectious agents is a growing public health threat of broad concern to countries and multiple sectors [3]. Increasingly, governments around the world are beginning to pay attention to a problem so serious that it threatens the achievements of modern medicine. A post-antibiotic era, in which common infections and minor injuries can kill far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century [4]. AMR threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi. This report examines, for the first time, the current status of surveillance and information on AMR, in particular, antibacterial resistance (ABR), at the country level worldwide [5]. AMR results in reduced efficacy of antibacterial, antiparasitic, antiviral and antifungal drugs, making the treatment of patients difficult, costly, or even impossible. The impact on particularly vulnerable patients is most obvious, resulting in prolonged illness and increased mortality [6].

2. USE of ANTIBIOTICS

Studies have shown that resistance to antibiotics is directly linked to their usage. It would, therefore, be important to briefly review the patterns of antibiotic use [7]. In 2010, India recorded a staggering 12.9 billion units of antibiotic consumption, which was the highest among all the countries [8]. Also, an increased consumption rate of carbapenems, lincosamides, glycopeptides, linezolid, and daptomycin has been reported in one study [9]. The reasons leading to such situations are multiple, as explained hereunder:

1. Easy access to medicines over-the-counter in medical stores (chemist/pharmacy outlets)

2. Self-medication through hearsay or information gathered from the internet or upon the advice of the shopkeeper

3. Non-availability and non-utilization of the laboratory service for cultures and antibiotic susceptibility testing

4. The varying approach of treating doctors- owing to the anxiety of missing a bacterial infection or covering for secondary bacterial infection, lack of up to date knowledge on the current revised guidelines and algorithms for antibiotic usage

5. Empirical but incorrect use of antibiotics, simultaneous use of more than a single antibiotic when not necessary, not de-escalating when possible, inefficiency in the review of the response to antibiotics

6. Regulatory issues- Lack of strict implementation of policies (such as schedule H_1) and control by the regulatory authorities

7. Varied perceptions such as perceived demand and expectations among key stakeholders and ethical challenges among healthcare professionals

8. Unethical commercial practices to promote the sale of antibiotics in large quantities

9. Use of antibiotics by other non-medical and informal healthcare providers [10].

Not only misuse and overuse, but underuse due to is lack of access common in India. Lack of access to good quality, affordable antibiotics leads to significant mortality (especially in children), and hence, there is an urgent need to maximize access and limit excess antibiotic use. Besides the healthcare sector, antibiotics are also used in livestock such as in animal husbandry, fisheries, and agricultural sectors for therapeutic purposes as well as growth promotion. Environmental pollution using pharmaceutical waste, waste from livestock, and hospitals is another dimension contributing to the crisis of antibiotic resistance [11].

3. ORIGIN of ANTIBIOTIC RESISTANCE

Antibiotic resistance was reported to occur when a drug loses its ability to inhibit bacterial growth effectively [12]. Bacteria become 'resistant' and continue to multiply in the presence of therapeutic levels of the antibiotics. Bacteria, when replicates even in the presence of the antibiotics, are called resistant bacteria [13]. Antibiotics are usually effective against them, but when the microbes become less sensitive or resistant, it requires a higher than the normal concentration of the same drug to affect. The emergence of AMR was observed shortly after the introduction of new antimicrobial compounds. Antibiotic resistance can occur as a natural selection process where nature empowers all bacteria with some degree of low-level resistance [14]. For example, one study confirmed that sulfamethoxazole and trimethoprim, ampicillin and tetracycline that were commonly used in yesteryears, but now have no longer role in treating non-cholera diarrhea disease in Thailand. At the same time, another study conducted in Bangladesh showed the effectiveness of the same drugs in treating them effectively. Resistance was documented even before the beginning of the usage of antibiotics in fighting the infection [15]. Non-judicial use of antibiotics is responsible for making microbes resistant. Since the introduction of sulfonamides in 1937, the development in the 1930s, which reveals the same mechanism of resistance that still operates even now, more than 80 years later. Within 6 years of the production of the aminoglycosides, aminoglycoside-resistant strains of *Staphylococcus aureus* were developed. Introduced in 1961, Methicillin was the first of the semisynthetic penicillinase-resistant, penicillin to target strains of penicillinase-producing *S. aureus* [16]. However, resistance to methicillin was reported soon after its initiation. Further, although fluoroquinolones were introduced for the treatment of Gram-negative bacterial diseases in the 1980s, fluoroquinolones resistance later revealed that these drugs were also used to treat Gram-positive infections. Quinolone resistance emerged as stepwise attainment of chromosomal mutations, particularly among the methicillin-resistant strains (Figure 1) [17]. Most recently, the clinical isolates of Vancomycin-resistant *S. aureus* were found in 2002, after 44 years of Vancomycin introduction to the market. Antibiotics used in agriculture are often the same or similar to antibiotic compounds used clinically, this over usage could also invite drug resistance. The food chain can be considered the main route of transmission of antibiotic-resistant bacteria between animal and human populations [18]. In some developed countries, animals receive antibiotics in their food, water, or parenterally which may be responsible for carrying microbe resistance to that specific antibiotic. For example, the use of antibiotics in cattle feed as growth promoters increase antibiotic resistance. Recent evidence suggests that poultry or pork might be a possible source of quinolone-resistant *Escherichia coli* in the rural villages in Barcelona, where one-fourth of children were found to be fecal carriers of these organisms. However, these kids were never exposed to quinolones [19].

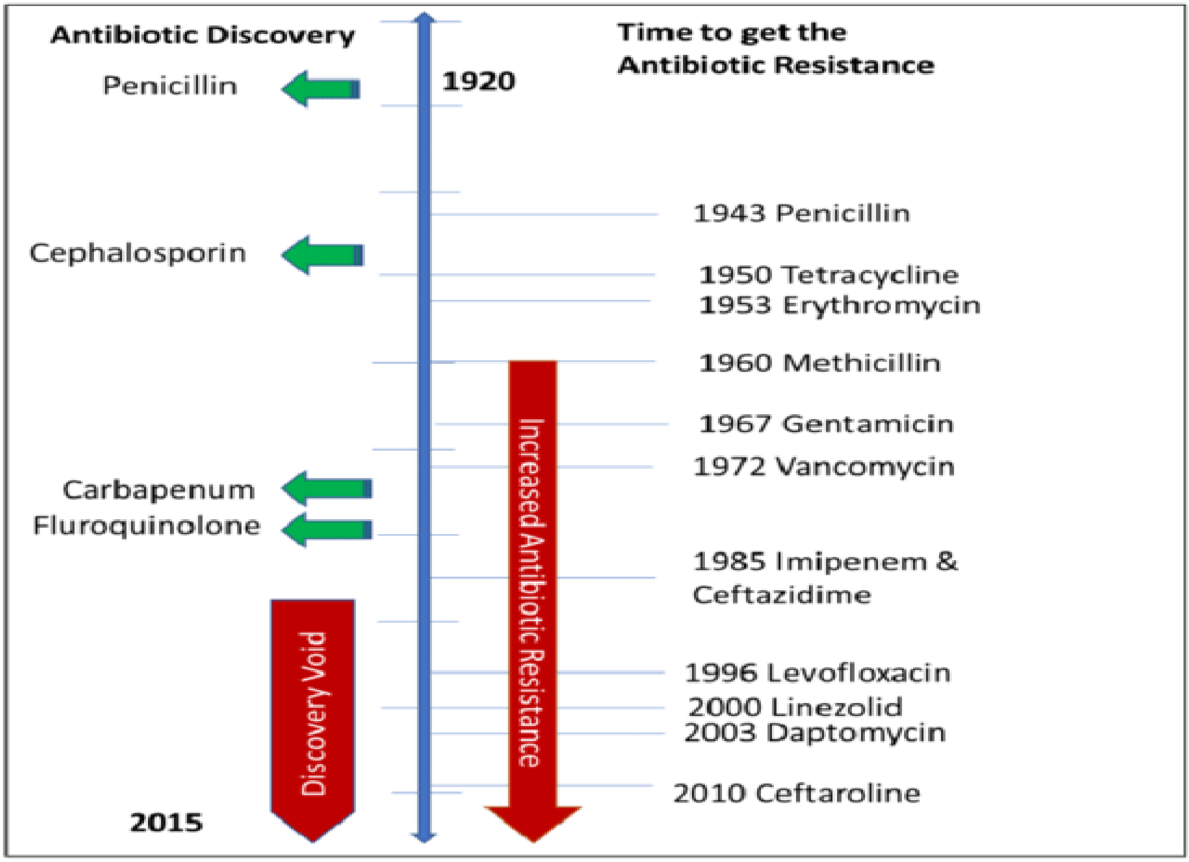
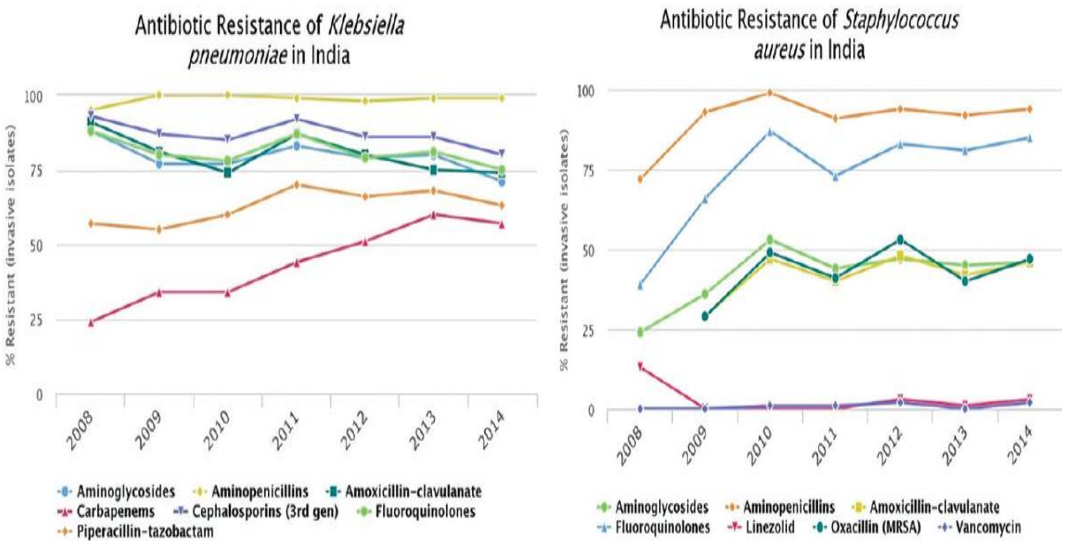


Figure No. 1: Graphical representation of the onset of antibiotic resistance versus time to get antibiotic resistance. (History of antibiotic discovery (green arrow) and time of first reported year of antibiotic resistance (right side). The red arrow (lower direction) indicates the discovery void and increased antibiotic resistance. The blue line indicates the time flow).

4. ANTIBIOTIC RESISTANCE in INDIA

India carries one of the largest burdens of drug-resistant pathogens worldwide, including the highest burden of multidrug-resistant tuberculosis, alarmingly high resistance among Gram-negative and Gram-positive bacteria (Figure 2) even to newer antimicrobials such as carbapenems and faropenem since its introduction in 2010 [20]. Regional studies report high AMR among pathogens such as *Salmonella typhi*, *Shigella*, *Pseudomonas* and *Acinetobacter*. Annually, more than 50 thousand newborns baby is estimated to die from sepsis due to pathogens resistant to first-line antibiotics [21]. While exact population burden estimates are not available, neonates and elderly are thought to be worse affected. 2 million deaths are projected to occur in India due to AMR by the year 2050. It is no surprise that the emergence of enzyme New Delhi Metallo-β-lactamase (NDM-1), named after the national capital of India, in 2008 rapidly spread to other countries [22]. The present article reviews the progress in addressing AMR in India after 10 years of the emergence of NDM-1. Infectious diseases remain a leading cause of mortality in India. Bacterial sepsis, acute respiratory illness, and acute diarrheal diseases are leading killers of children under 5 years of age. India is one of the largest consumers of antibiotics worldwide and antibiotic sales continue to increase rapidly. Despite the decline in communicable diseases, antibiotic use continues to increase (Figure 3) [23].



(A) **(B)**

Figure No. 2: (A) Resistance patterns of *Klebsiella pneumonia* (B) *Staphylococcus. aureus* isolates in India (Figure generated by the Center for Disease Dynamics using blood and cerebrospinal fluid isolates from inpatients collected by a private laboratory network in India with 5700 collection centers nationwide).

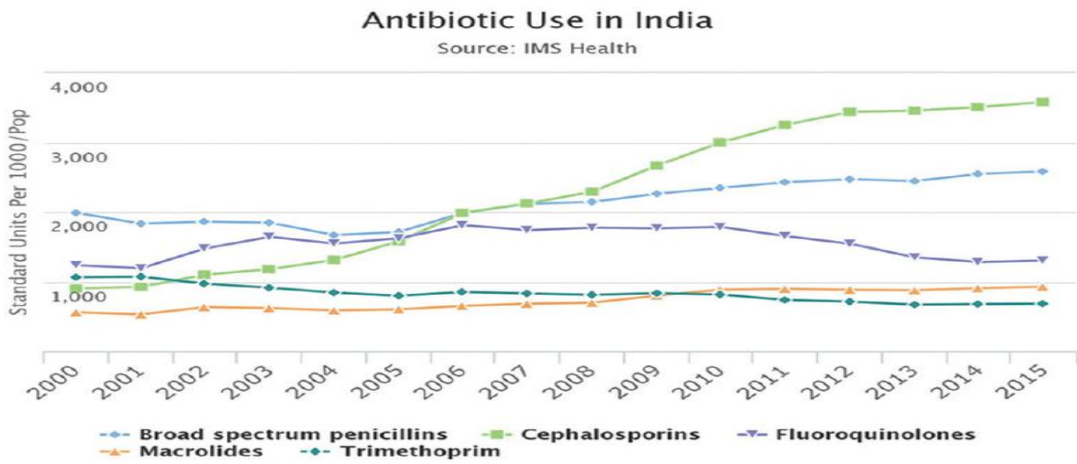


Figure No. 3: Use data from the Center for disease dynamics aggregated from two antibiotic consumption databases.

The high burden of AMR in India is driven by multiple factors. Antibiotic over-prescription is driven by a poor understanding of its dangers and contribution to AMR on the part of the provider as well as patients who lack knowledge regarding appropriate antibiotic use. Also, pharmacists who are often the first point of care, dispense antibiotics without a physician prescription, offer alternative antibiotics even when patients present with a prescription [24]. Within the hospital's lack of monitoring of antibiotic use is one of the major factors driving the spread of resistance. Health system factors are also at fault. Physicians routinely receive compensation from pharmaceutical companies in exchange for antibiotic prescriptions. Alarming rates of resistance have been reported in animal isolates of human pathogens, but the evidence is insufficient to make national estimates. Available data indicate to rising rates of AMR, across multiple pathogens of clinical importance, in the country. In 2008, about 29% of isolates of *S. aureus* were methicillin-resistant, and by 2014, this had risen to 47%. In contrast, in countries with effective antibiotic stewardship and/or infection prevention and control programs, the proportion of methicillin-resistant *S. aureus* isolates have been decreasing [25].

5. GLOBAL BURDEN of ANTIBIOTIC RESISTANCE

In the 1960s, a rapid increase in MDR *Salmonella* was noted in the United Kingdom. The UK published a 'Swann Report' which reported that the chief cause for the development of resistance to infections was the use of antibiotic growth promoters (AGPs). It highlighted the ban of antibiotics for growth promotion, particularly those which were meant for human therapy. However, usage of antibiotics such as avoparcin, bacitracin, virginiamycin, bambermycin, and tylosin continued as narrow-spectrum substitutes which had less impact on the wide range of gut flora [26]. The most astonishing fact observed was that there existed a structural relationship between these antimicrobials and the ones intended for clinical use in humans. Hence, the use of one antibiotic produced cross-resistance with the other. An example of cross-resistance was observable with avoparcin and vancomycin (therapeutic drug in humans) which led to the development of vancomycin-resistant *enterococci*. Ribotyping methods revealed that there was a resemblance between the patterns obtained from farms and sewage with that of *Enterococci* obtained in the hospital. Although the United States does not permit the use of gentamycin for growth promotion, it was most frequently used in broiler production for preventing early mortality in poultry animals. The danger of carrying gentamicin-resistant *E. coli* was 32 times more in pupils who worked in poultry compared to non-poultry workers; 50% of workers in poultry were colonized with gentamicin-resistant *E. coli*, whereas it was just 3% in the general population. In China, samples obtained from gentamicin-resistant urinary tract infections and fecal *E. coli* isolates from humans and animal food disclosed that 84.1% of human samples and 75.5% of animal samples had aaaC2 gene responsible for resistance to gentamicin [27]. Clenbuterol, a beta-agonist, is used to produce meat comprising of more protein and less fat. Bio-resistant bacteria (*S. xylosus*) have been found in the air in broiler farms. This airborne transmission may pose a risk of the easy spread of epidemic diseases, a danger to public health. Currently, colistin is considered to be the last resort against MDR pathogenic bacteria, particularly the ones resistant to carbapenems. Excessive utilization of colistin in farm animals in China has led to the development of resistance in *E. coli* through the colistin-resistance MCR-1 gene. China has, therefore, banned colistin usage as an AGP and released a mandate to control its use in the therapy of animals. Recently, even India has banned the manufacture, sale, and use of colistin in food-producing animals in the year 2019 under the Drugs and Cosmetics Act, 1940 [28,29].

6. THE ECONOMIC CONSIDERATIONS

India spends only 4.7% of its total Gross Domestic Product on health, with government share only one-fourth (1.15%) of it, makes the task massive. One study found the median cost of treatment of a resistant bacterial infection to be more than a year wages of a rural worker. Poor public health infrastructure, a high burden of disease, and unregulated sales of antibiotics have contributed to a rapid rise in resistant infections in India [30]. This has a huge socio-economic impact due to deaths and increased costs due to prolonged stay in hospital, additional and repeated laboratory investigations, and loss of work for treating resistant bacterial infections. There are no proper documented estimates on the economic impacts of AMR in India. It can be assumed that due to the high incidence of malaria, tuberculosis, and HIV in India and lack of regulations on the use of antibiotics in humans and the production of food-producing animals, the impacts of AMR on the Indian economy could be huge [31].

7. CONTROL STRATEGIES OF ANTIBIOTIC RESISTANCE

The problem of AMR is aggravated by the fact that most world pharmaceutical companies consider research for new antimicrobials as being of 'low profit' and some speculate that resistance will eventually develop for new antimicrobials anyway. Consequently, they prefer to invest in the development of drugs for chronic diseases (diabetes, hypertension) as well as those used to improve lifestyle (e.g., Sildenafil, Vardenafil, Tadalafil, etc.) [32]. Therefore, the long-term solution should be focused on methods to prevent the emergence of resistance or the spread of resistant organisms from one person to another person (Table 1) [33-35].

Table No. 1: Strategies to contain and minimize the development of AMR.

S. No.	Control strategies	Contribution
1	Hygiene & sanitation	Improving basic hygiene and sanitation will reduce the spread of resistant organisms.
2	Vaccination	Vaccination may reduce the severity of the disease, provide protection against the shedding of pathogens and even raise the threshold load of pathogens required for infection.
3	Alternative therapies	The reluctance of pharmaceutical companies to invest in research and development (R&D) of novel antimicrobial agents necessitate the exploration of alternative therapies such as bacteriophage, probiotics and Quorum Sensing inhibitors.
4	Education	Health care providers, dispensers and patients need to be educated on how the use and misuse of antimicrobial may contribute to the development of resistance.
5	Infection prevention & control	Proper hospital infection control may prevent the spread of nosocomial pathogens and resistant microbes that may have easily been disseminated to the community if these measures were not in place.

7.1. Hygiene sanitation: Apart from the irrational use of antimicrobials, unique environmental conditions such as crowding and poor sanitation also contribute to the circulation and spread of resistant microorganisms. Transmission of resistant pathogens is facilitated by person to person contact, through contaminated water, food or by vectors. Improving basic hygiene and sanitation will reduce the spread of resistant organisms. Improving infection prevention and control in hospitals will reduce the nosocomial spread of bacteria with acquired resistance such as *S. aureus* amongst others [36].

7.2. Vaccination: While antimicrobials are used for treatment, vaccines are a primary mode of prevention of infectious diseases. Prior vaccination may reduce the severity of the disease, provide protection against the shedding of pathogens and even raise the threshold load of pathogens required for infection. Also, indirect population protection of some vaccines as a result of herd immunity in unvaccinated individuals represents the additional advantage of vaccination. In most regions of the world, several diseases such as smallpox, measles, mumps rubella, diphtheria, hepatitis A, pertussis, and polio have been prevented by vaccination. However, even with the most effective vaccine, the need for antimicrobials or alternative treatment options will still in some cases be solicited [37]. For example, in the case of genetic drift, escape mutants and serotype or strain replacement diseases, vaccination may fail to confer full protection from disease. For bacterial infections, the introduction of conjugate vaccines, for example, *S. pneumonia* has reduced the outbreak of respiratory infections in children in developing countries [38,39].

7.3. Alternative therapies: The increase in microbial resistance to traditional antimicrobials and the reluctance of pharmaceutical companies to invest in R&D of novel antimicrobial agents necessitate the exploration of alternative therapies [40]. The future focus of medical therapeutics and research is to look beyond antibiotics, and search for alternatives which can regulate the microbial virulence as well as growth inhibition. There are currently a couple of other alternatives approaches at different levels of R&D (Table 2) [41-45].

Table No. 2

A	The use of bacteriophage is emerging as an alternative treatment option for bacterial infections. Many authors have suggested that bacteriophage therapy is a necessary alternative to conventional antibiotics. Bacteriophages are bacterial viruses with the capacity to invade bacterial cells and induce lysis of the bacteria (lytic cycle). In the present era of MDR bacteria and reluctance in the development of new antibiotics by pharmaceutical companies, the need to aggressively explore the possibility of phage therapy is unprecedented.
B	Quorum Sensing inhibitors represent an important antimicrobial target that may prevent, suppress, and/or treat infectious diseases. The mechanistic details (including auto-inducers) of Quorum Sensing are different between Gram-negative and Gram-positive bacteria. Gram-negative bacteria utilize *N*-acyl L-homoserine lactones, which are homoserine lactone rings with an additional fatty acid side chain while Gram-positive bacteria use oligopeptides. While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors or quorum quenchers simply attenuate bacterial virulence. A large body of work on Quorum Sensing has been carried out in deadly pathogens like *Pseudomonas aeruginosa*, *S. aureus*, *Vibrio fischeri*, *Vibrio harveyi*, *E. coli*, and *Vibrio cholera,* etc. A number of these studies have succeeded in exploiting the bacterial Quorum Sensing system as a potential target for the treatment of bacterial infections. The inhibition of the Quorum Sensing system is believed to be advantageous over conventional antibiotics because only the communication mechanism between the bacteria is disrupted without killing the individual cells. Hence, this strategy should generate lower selective pressure and reduce the rate at which AMR develops during the treatment.
C	Probiotics, otherwise referred to as fecal transplant therapy (FTT) is a treatment option that has been employed for decades, albeit with mixed results. FTT is the act of using fecal material from pathogen-free healthy donors to repopulate the microbiota of a recipient. Probiotics are considered to be able to destroy pathogenic microorganisms by producing antimicrobial compounds such as bacteriocins and organic acids, improve the gastrointestinal microbial environment by adherence to intestinal mucosa thereby preventing attachment of pathogens and competing with pathogens for nutrients, stimulate the intestinal immune responses and improve the digestion and absorption of nutrients. The commonly used probiotics include *Bacillus*, *Lactobacillus*, *Lactococcus*, *Streptococcus*, *Enterococcus*, *Pediococcus*, *Bifidobacterium*, *Bacteroides*, *Pseudomonas*, yeast, *Aspergillus*, and *Trichoderma*, etc. This treatment option is an old practice, used many years ago, especially in China and had been successfully used to treat *Clostridium difficile* infections as well as other enteric diseases. Taken together, the application of these alternative therapies is not limited to developing countries and most are still under development or at different stages of clinical trial and their routine availability will require governmental approval and subvention in developing countries.

8. SUMMARY

AMR is at an all-time high in all parts of the world. Despite measures taken using some member states of WHO, antibiotic use in humans, animals, and agriculture is increasing. The high economic burden within the healthcare sector has come to be a burning difficulty, due to extended health facility remains isolation wards, stringent contamination control measures, and treatment failures. The public health leaders should set up a pan surveillance gadget coordinated at national and international levels, ongoing analysis and a mandatory reporting system for antibiotic resistance. Both domestic and international guidelines want to be conventional and adhered to stop the overuse and misuse of antibiotics.

Conflict of interest

The authors have declared that no conflicts of interest exist.

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