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Impact of Antibiotics on Human Health and Environment

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Abstract

Antibiotics can be categorized as one of the major discoveries of the last century that has changed the course of treatment of various diseases. The boons of antibiotics are a large array, nevertheless, the banes are so too. The increased use of antibiotics and their residues have caused significant increase in the number of pathogens with multi-drug resistance genes in past few years. These have also caused an irreversible damage to the environment and human health. In this brief review we aim to summarize the severity of impact caused by antibiotic pollution on human health and also the environment.

Key Words: antibiotics, pollution, multi drug resistance bacteria

INTRODUCTION

Discovery of antibiotics (means anti-life, derived from Greek word ἀντι anti, "against" and βίος bios, "life") and its use to treat bacterial infections has been a deep-rooted cornerstone for the modern medicine world. In 192, Alexander Flemming discovered penicillin by chance and since then it is considered to be one of the most significant discoveries of the 20th century [1]. Penicillin was capable of inhibiting the cell wall synthesis in bacteria and ceasing infectious pathogens such as Staphylococcus aureus [2]. From 1940s to 1970s, the pharmaceutical industry swayed heavily with discovery pf antibiotics and this led to large scale production of more than 160 new antibiotics and semi-synthetic derivates which played a key role in treatment of infectious diseases [3]. Regardless of the ability of these wonder drugs in lowering the mortality and morbidity caused by common infections, the bacteria were capable to show resistance to these under laboratory conditions followed by clinical [4-6]. Irrespective of this, the widespread **overuse and misuse** of antibiotics continued and lead to evolution of microbial pathogens with resistance to antibiotics, today known as antimicrobial resistance (AR). In the present scenario, antibiotic resistant microbes are seen as one of the most critical public health crises. AR is accountable for over 7 million deaths annually and is expected that it would be around 10 million by 2050 [7, 8]. The BRIC countries i.e., Brazil, Russia, India, and China have very acute situation of AR, with the Defined Daily Dose (DDD) being 1000/individuals/day from

2010-2015. A 13% increase in DDD has been observed in India, and 89% for China [9-11]. AR has affects more than 2 million people in the USA/year and 30,000 deaths have been reported in the European Union [12]. These impose a significant financial burden on the world economies and the rate of antibiotic discovery has also greatly reduced over the past few decades causing antibiotic crisis [13, 14]. The crisis however has not affected the use of antibiotics and it has ruthlessly increased in the past decade and due to extrapolation of antibiotic use in medicine like in cancer treatment, organ transplant, surgeries, etc. [15] and in more segments of commercial interests such as in livestock's [16]. The usage of antibiotics is seeing up rise in aquaculture as well [17]. Due to their increased use these human-made pharmaceutical offspring are now found in sewage, wastewater treatment plants, aquatic bodies, etc. They are known to be one of the major pollutants of terrestrial, marine, and freshwater ecosystems in the current scenario [18].

Applications of antibiotics

Antibiotics are commonly used in treatment of diseases (human and animals) [19, 20], animal husbandry [21], beekeeping [22], fish farming and other forms of aquaculture [23], ethanol production [24, 25], horticulture [26, 27], antifouling paints [28, 29], and food preservation [30]. (Figure 1)

Impact of antibiotics on human health

Many antibiotics were developed in the years between 1940 and 1980, including fluoroquinolones (e.g., ciprofloxacin), aminoglycosides (e.g., tobramycin), β-lactams (e.g., penicillin, cephalosporin, and carbapenem), polymyxins (e.g., colistin), tetracyclines, macrolides (e.g., erythromycin), and glycopeptides (e.g., vancomycin) [31]. In between 2015-2018 only three new antibiotics were developed [32-34].

The microbes make about 70% of the total biomass on our biosphere and participate and contribute towards the environmental sustenance. They have been here for millions of years and owing to their shorter life span cycles they are capable of rapidly adapting to the environment by generating stable genetic variations. Antibiotic resistance arises when a bacterial cell grows to adapt in the presence of the antibiotic/s. This compliance guarantees their survival and causes threat to human and animal health [7, 35]. AR is a naturally occurring process via genetic variations [36]. The overuse of antibiotics today has however accelerated this process [37, 38] and these AR resistant microbes (ARB) are ubiquitously present in the air, water and soil. They can spread from one person to another or can be contracted from animal [39]. AR is spread by exchange of AR genes (ARG) (present on plasmids) and can also get transferred between distantly related bacteria.

The use of antibiotics in agriculture and animal husbandry: the humans and animals feeding upon these products can get exposed to the ARBs. Such contaminated food items cause numerous gastrointestinal diseases like campylobacteriosis and salmonellosis. A risk assessment model estimated the risk Campylobacter jejuni infection that arose from the resistance developed against fluoroquinolone, given to cattle. Within one year of use of fluroquinolone on cattle, 12 infection cases that year and followed by 44 cases and one death was reported after 10 years [40]. Another study reported of illness caused due to use of fluoroquinolone, annually in the US [41]. Vigorous use of antibiotics for human and animal health issues has resulted in serious health related problems along with environmental problems. The use of increased concentrations of antibiotics has led to the bioavailability of subsequent residues in the wastewater causing the evolution of ARBs. The bacteria present in the wastewater tackle these residues from various antibiotics and develop resistance or even multi drug resistance (MDR). The residues of antibiotics from animal-based food are an additional major concern for human health. The ingestion of these residues can lead to different disorders such as direct toxicity, allergic reactions, carcinogenic effects (e.g.: sulfamethazine, 4-dedimethyl amino-4-oxo-tetracycline and furazolidone), mutagenicity, nephropathy (e.g.: gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (e.g.: chloramphenicol), allergy (e.g.: penicillin), and destruction of useful microbiota present in the gastrointestinal tract, especially children, elderly, pregnant and immune compromised [42, 43].

The presence of these residues is so prolonged that MDR develops even at sub-inhibitory concentrations of the respective antibiotic. These changes in the genetic makeup contribute towards the development of AR Genes (ARGs). The waste generated from hospitals and pharmaceuticals dealing with the production of antibiotics are majorly responsible for MDR. The water treated at wastewater plants is eventually used up by the agricultural sector thus contaminating the ground water and soil [44, 45]. Another source of contamination of soil and water is the faecal and urinal excretion by living beings under the effect of treatment by antibiotics. The microorganisms present in this municipal waste also develop MDR and is one of hotspots for bearing ARBs and ARGs. For example, it is a major source for development of ARGs in Enterobacteriaceae and which can be horizontally transferred to the new bacterial population arising there [46-48]. Some data suggest that MDR bacteria are more profoundly found in the effluent than the affluent of treated wastewater suggesting that as the antibiotics and residues enter any ecosystem, issues have been expressed concerning the influence of their remnants on the aquatic ecosystem [49, 50].

Owing to their adjustment to the gastrointestinal tract, suitability of various ARBs in soil and water is estimated to be at low point, causing to increased endurance times in the order of weeks to months [51, 52]. The effect that antibiotics had on human health were well documented that led to increase in average life span by about 15 years, in standardized clinical trials and pharmacology reports [52]. Secondary effects seemed to be inevitable but yet it came into light that several side effects include altered susceptibility to infections, impairment of mechanism responsible for absorption of vitamins, medicines and the growth of resistant organisms [53]. One of the most common side effects of antibiotic use was the antibiotic associated diarrhea and in some cases inflammation of the colon (colitis) or a more severe form of colitis called pseudomembranous colitis [54]. These alterations were linked to the harmful effects of antibiotics on human microbiota or microbial flora that mainly includes Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteria [55, 56].

Significant advances have been made to decipher the disorders caused due to use of antibiotics despite the fact that these were supposed to be used as safe medications but their overuse can induce lethal effects [57]. Medications like cephalosporins, quinolones and carbapenems have high chances of causing resistance and hence should be used with precautions.

As per the reports by the Centre for Disease Dynamics, Economics & Policy (CDDEP) the ARBs and associated diseases (ADEs) are prevalent in hospitals because the administration of high doses of intravenous antibiotics and extended treatment periods or drug interactions due to concomitant antibiotic treatment with other therapies [58] and lead to innumerable deaths and if this remains unattended and the misuse of antibiotics continue, the chances of using these drugs will diminish in the future [59]. It has been reported that 50% of hospitalized patients receive antibiotics but 30% of the prescribed drugs are redundant [60]. Kokado et.al. Conducted a survey and showed that most cases of ADEs were gastrointestinal disorders (8.9%), dermatological manifestations, (53.4%) and liver dysfunction (9.7%) and renal irregularities. β-lactams had 51.3% of ADE incidences followed by fluoroquinolones with 17.5% and other antibiotics, including macrolides, sulphonamides, anti-MRSA, and injectable tetracyclines, also have significantly lower ADE rates [61]. In cases of outpatients, ADE were caused by antibiotics prescribed via oral use sulphonamides (23.2%), penicillin (20.8%), and quinolones (15.7%) [62]. Irrespective of the patient status, ADEs can cause damage and dysfunction in human body systems ranging from skin allergies to anaphylactic attacks [57, 63]. Other diseases may include hepatobiliary, renal, cardiac, respiratory, hematological, neurological, and musculoskeletal disorders.

Impact of antibiotics on environment

The residues from antibiotics, ARBs and resistant genes are deemed to be as pollutants of environmental and are held accountable for public health crisis across the globe. The soil and water environment have been considered as crucial basins and reservoirs of antibiotic resistance, and they are more affected by agriculture [64-66]. The disorganized and vicious usage of antibiotics can cause higher concentrations in the environment, known as antibiotic pollution. Resources via which antibiotics can be out into the environment are disparate, including streams of human waste, and veterinarian usage and livestock raising [67]. The primary and major source of antibiotic leakage into waste streams is the antibiotics used for therapeutics for human and used in for growth promotion, prevention of infection in animals. This happens because of the incomplete metabolism and hence the accumulation in water and leading to further accumulation of ARBs and ARGs in water streams [68, 69]. Moreover, antibiotics and associated residues restricted in animal manure can percolate from the heap to surface and groundwater, and also into the soil.

Many sources have characterized ARBs and ARGs in vegetables like lettuce, cabbage, radish, green corn, onion, carrot, and fluted pumpkins grown on manure fertilized soils and irrigated with wastewater [70]. Bonyadian et.al. confirmed the presence of antibiotic-resistant vero-toxigenic E. coli on vegetable samples gathered at random from shops in Iran [71]. However, the direct intake of vegetables (uncooked or raw) by humans might lead to the transfer of ARBs and ARGs causing bacterial infections. A great deal of eutrophication of rivers and sea occurs as these receive discharge from farmlands, where animal manure and sewage sludge is being used as fertilizer and that contains palpable concentrations of ARBs and their resistance elements, along with biologically active metabolites of antibiotics or the parent compounds [72].

Measures of prevention and control of antibiotic use

Antibiotic resistance can be controlled with the following:

1. Enhancing knowledge and understanding of antimicrobial resistance
2. Boosting research and development
3. Lowering the rate of infections
4. Augmenting the use of antibiotics
5. Secure sustainable investments in the field of ARBs and ARGs
6. Non-traditional antimicrobial therapies to minimize the use of conventional antibiotics: like the use of phages, vaccines, bacteriocins, probiotics, etc.
7. Irradiation or ionizing radiation for treatment of wastewater
8. Biological remediation technology
9. Biosensors for the detection of antibiotic residues
10. Electrochemical methods to reduce contamination in milk or water

CONCLUSION

The mass production of antimicrobial substances, their excessive use for medical purposes, particularly in food-producing animals, and the many pathways of their release into the environment have all been linked to a significant increase in the number of pathogens with multi-drug resistance genes in recent years. Such resistance is now posing a severe threat to public health. To combat this tendency and safeguard the efficacy of existing antibiotics, current efforts are centered on restricting antibiotic usage on a wide scale and inappropriately.

Low antibiotic concentrations in the environment have considerable biological effects, and selection pressure can nevertheless promote resistance acquisition. However, thorough understanding of the rates of antibiotic class dispersion and degradation in the environment must be collected. The following are the main concerns: What are the concentrations of different antibiotics in environmental samples, and what values are required for microbial cells to acquire resistance? In particular, new antimicrobial medications are being developed to address diseases caused by resistant microorganisms. Alternative methods for treating resistant organisms are being proposed by research organizations all over the world, and a post-antibiotic golden age defined by the use of biological, biogenic, or bio-based goods and therapies is widely anticipated. Regardless of such efforts, there is an urgent need to protect public health and maintain the efficacy of already used antibiotics. To this end, it is vital to keep the environment free of antibiotic residues and their active metabolites, which are known to be responsible for the accumulation of drug resistance. As a result, efforts should be made to get a better understanding of antibiotic usage patterns in various parts of the world, as well as the evolution of drug resistance at the clinical and environmental levels. Furthermore, interventions and routine monitoring programmes, as well as public education efforts at all levels, including healthcare, community, and individual, should be prioritized.

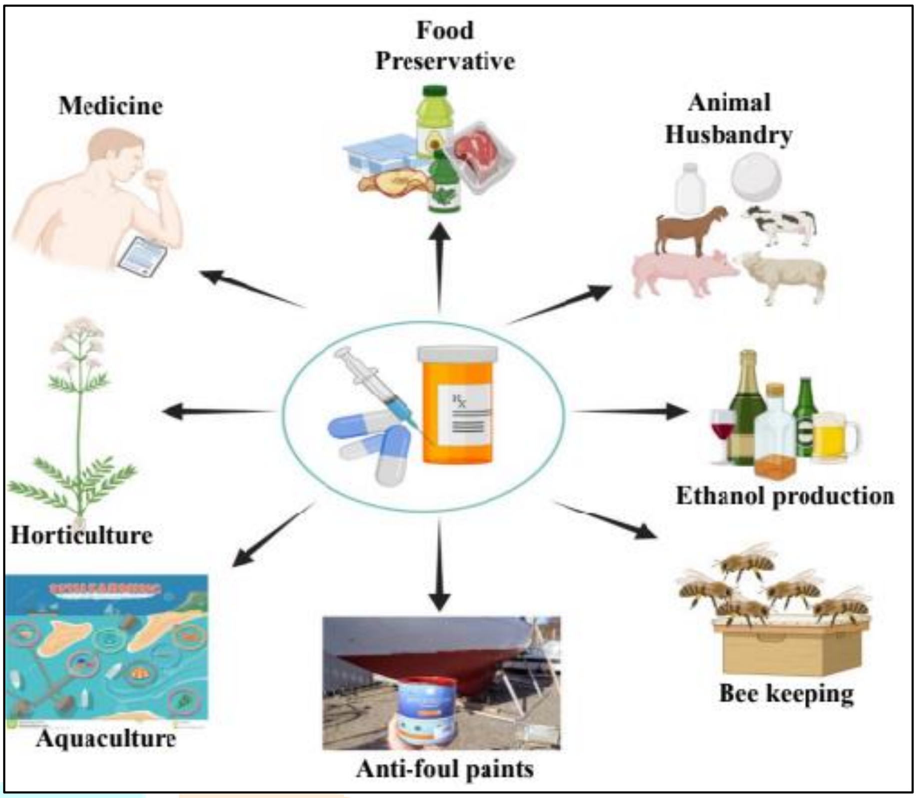

Figure 1. Applications of antibiotics in various fields

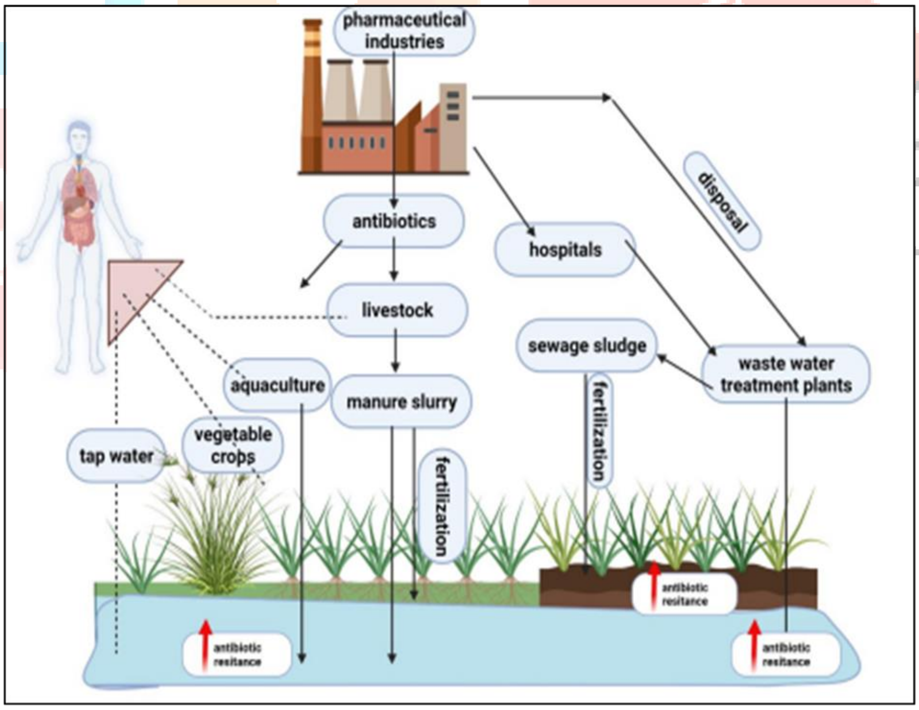

Figure 2. A concise summary of antibiotics and their impact on humans and environment

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