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Microbial Antibiotic Resistance and Heavy Metal Tolerance and their Implications and prospects with Environment

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ABSTRACT

Most natural waterways include microorganisms, which are extensively dispersed across the natural world. Their diversity and abundance can serve as indicators of whether a body of water is suitable for fish, wildlife, or leisure and recreational uses. Hundreds of antimicrobial medicines have been produced for use in humans and animals since the discovery of penicillin in the late 1920s, significantly lowering the morbidity and mortality linked to a variety of infectious illnesses. Approximately half of the over one million tons of antibiotics that have been discharged into the biosphere in the past fifty years are thought to have entered through veterinary and agricultural systems the ongoing exposure of microbial populations to substances chosen for resistance strains, such as antibiotics, chemical compounds, heavy metals, and other agents. Bacteria that have adapted to the presence of heavy metals and evolved effective metal resistance mechanisms live in ecosystems that have been contaminated by dangerous quantities of heavy metals. Based on the degree of pollution, the frequency of plasmids differed from site to site, according to ecological research on the incidence of plasmids in natural populations of freshwater, marine, estuarine, and terrestrial bacteria.

Keywords: *Antibiotic Resistance, Heavy Metal Tolerance, Environment, Bacteria, plants*

INTRODUCTION

Most natural waterways include microorganisms, which are extensively dispersed across the natural world. According to [1-2] their diversity and abundance may be used as a gauge for whether or not a body of water is suitable for fish, animals, or leisure and recreational uses. The earliest recorded account of *Escherich coli* dates back to 1885 and was written by *Theodor Escherich* [2]. He determined that infantile diarrhoea was caused by a bacteria known as bacteria coli commune. In honor of its discoverer, the current name Escherichia coli was adopted and formally approved in 1958. While *E. Coli* was once thought to be a non-pathogenic bacterium in basic genetics and molecular biology research, millions of people worldwide are infected with it every year in both industrialized and developing nations [3].

When the American Public Health Association published the first edition of standard techniques of water analysis in 1905, *B. coli*, which is now known as *Escherichia coli*, was suggested as a useful indication of the bacteriological quality of the water. The coliform group was the primary indication of water contamination for a long time. Nevertheless, techniques were created to limit the counting of those coliforms that are more obviously of faecal origin, therefore the organisms in this category are not restricted to faecal origins. Higher incubation temperatures were required in a modified approach developed by [4-7]. In addition to having all the characteristics of the total coliform group, this indicator group may digest lactose and produce gas in 24 hours at 44.5 0C (APHA, 1998). The use of streptococci as a measure of the hygienic quality of swimming pool water was suggested by [8-9] found that among swimmers at maritime beaches, the enterococcus group of streptococci correlated best with gastrointestinal symptoms. Nowadays, the most commonly used markers of faecal contamination in water are total coliforms, faecal coliforms, and faecal streptococci [8-12] showed that the variety of coliform flora is often great in natural environments, such the intestinal flora, or in contaminated water, with several species and strains of each species present.

According to [13] one of the biggest risks in water is faecal pollution, which comes from the digestive systems of humans or animals. The direct counting of many enteric pathogens in water samples is not appropriate for normal research, although being theoretically feasible. A trustworthy substitute is the use of marker organisms to suggest the potential presence of intestinal infections [14] notes that no surface water exists in the highly developed regions of Europe, particularly in areas with a large tourist density, without sewage contamination. All surface water must be regarded as contagious as harmful microorganisms are constantly excreted by certain members of the community. It is not feasible to analyze every type of bacteria that could potentially cause an infectious disease, such as pathogenic organisms from the intestinal tract like Salmonella, Shigella, Vibrio cholerae, etc., including some enteroviruses, in connection with routine water monitoring. As a result, the typical water analysis process solely looks for "bacterial indicators of pollution." There is a clear correlation between a proven faecal contamination and the potential risk of infection. At the same time, enteric pathogen contamination of water has dramatically grown globally [15]. These patterns highlight how crucial it is to comprehend how bacterial pathogens behave in aquatic settings once they enter the water and are subjected to ambient stimuli [16].

Both in humans and animals, enterobacteria are recognized to be the cause of certain gastrointestinal disorders. Over the past 20 years, there has been a significant shift in the methodology used to understand their pathophysiology. After cholera toxin was identified as a mediator of *diarrhea, enterobacteria* were examined for the existence of enterotoxic compounds. Numerous enterobacterial agents have been demonstrated to create enterotoxins. The enterotoxigenicity and enterotoxins of E. coli attracted significant attention, despite the fact that the majority of enteric bacteria generate enterotoxins [17]. Numerous serotypes of *E. coli* exist, some of which are linked to specific illnesses in humans and animals. Gastroenteritis has been linked to around fourteen antigen types of *E. coli* [18]. A significant portion of the typical gut flora in humans and other animals includes E. coli. From the faeces of healthy people, a wide variety of non-pathogenic *E. Coli* strains from various serotypes may be identified. However, certain strains of *E. Coli* have a higher propensity to cause illness than other main pathogens. The enteric pathogens and the extra intestinal pathogens are the two main groups into which these pathogens have been roughly divided. Enterotoxigenic *Escherichia coli* (ETEC) is the primary cause of diarrhea in humans, especially in young children from developing nations and people from developed nations who travel to these regions (traveler's diarrhoea) [18]. New born animals, namely piglets [19-21] and lambs (Hodgson, 1994), are also susceptible to diarrhoea caused by ETEC. The most common way that humans become infected is via eating contaminated food or drinking water. ETEC populate the small intestine after intake and adhere to its mucosa. The characteristic symptoms of ETEC infections are caused by significant failure of the electrolyte and water transport in enterocytes, rather than any discernible local inflammation or histological alteration in the intestinal mucosa [22]. In third-world nations, *enteropathogenic E. coli* (EPEC) is another significant cause of diarrhoea. Typically spread by tainted food, EPEC attach themselves firmly to the villus tips' epithelial cells and cause what are known as attaching and effacing lesions in the small intestine [23]. Shiga like toxin producing *E. coli* (STEC) can produce a wide variety of symptoms in humans, from simple diarrhoea to more serious illnesses such hemorrhagic colitis and the sometimes fatal hemorrhagic syndrome [24]. Clinical isolates from these species appear to have certain characteristics in common with uropathogenic *E. coli* (UPEC) of human origin. E. coli also commonly causes urinary tract infections in dogs and cats [25]. According to [26] UPEC may be the cause of severe pyelonephritis as well as simple cystitis.

Bacterial virulence genes have evolved to be specific to their hosts so they may perform certain functions throughout an infection. They produced a wide variety of kinds with varying pathogenicity within a species because they may spread not only between members of the same bacterial species but also between other bacterial species. It appears that novel combinations of distinct virulence genes give rise to new pathotypes [27]. Since the mechanism of pathogenicity is directly influenced by virulence factors, their genes make excellent targets for molecular analysis of potential pathogenicity and pathotype typing, which is useful not only for medical diagnosis but also for food and water quality control procedures, safety evaluations, and other processes. Numerous *E. Coli* virulence genes are found on mobile components like plasmids, which means that new pathotypes with novel combinations are always evolving. Furthermore, a great variety of *E. Coli* strains with specific virulence genes that alone do not provide any particular harmful phenotype should be expected. These strains, which are primarily untyped or unanalyzed, may represent a significant ambient genetic reservoir for virulence traits and may play a key role in the emergence of novel diseases [28]. It is particularly interesting in this context to study the transfer of genes encoding virulence and antibiotic resistance within the bacterial flora [29-31]

Antibiotic Resistance among Bacteria

Hundreds of antimicrobial medicines have been produced for use in humans and animals since the discovery of penicillin in the late 1920s, significantly lowering the morbidity and mortality linked to a variety of infectious illnesses [32]. During the past 50 years, more than one million tons of antibiotics have been discharged into the biosphere [33] of these, it is believed that 50% have entered the veterinary and agricultural sectors [34]. Subtherapeutic antibiotic use for enhanced growth and feed efficiency in farm animals is a contentious practice that is widely accepted in contemporary global agriculture. Human usage of antibiotics may be viewed as a massive evolutionary experiment that provides a window into real-time, non-natural selection at work.

Around the world, there has been an almost constant growth in the number of pathogenic and commensal bacterial species, strains, and drugs to which they are resistant [35]. The majority of affluent nations have seen an increase in the use of antimicrobials despite regional variations in the frequency of antibiotic usage [36]. The emergence of bacterial resistance to antimicrobials can be attributed to factors associated to human antibiotic usage, such as patient and practitioner overuse of antibiotics and subpar medication quality in poorer nations [37]. Unfortunately, a basic biological principle was disregarded when these medications—antibiotics and chemotherapeutic agents—were utilized for treatment and other reasons [38-39]. All organisms have mechanisms in place from nature to keep them from becoming extinct, and when drugs attacked bacteria, resistant forms of the bacteria emerged [40]. There are documented cases of bacteria developing resistant to any of the current antibiotics, and the prevalence of organisms resistant to many antibiotics that are not treatable with any of the current antibiotics is startlingly high [41].

An epidemiological approach is necessary, as with any public health issue, because the evolution of resistance in human pathogenic and commensal microorganisms is the consequence of the interplay between antibiotic exposure and the transmission of resistance, both within and between individuals [42]. The selection of resistance in bacteria may be influenced by low and extended exposure to antibiotics, according to epidemiological research and the application of the pharmacodynamic concept [43]. Microorganisms originating from humans and diverse sources have been found to have a higher prevalence of antibiotic resistance in a range of habitats, including rivers, pastures, and sewage [44-45].

The development of metal-tolerant and antibiotic-resistant microorganisms results from exposure to metal-contaminated environments, which leads to the co-incidental co-selection of resistance factors for heavy metals and antibiotics [46-47]. Estuaries and sewage are two examples of metal-contaminated settings from which microorganisms resistant to both antibiotics and metals have been identified [48-49].

Additionally, the usage of antibiotics has led to an extraordinary rise in the prevalence of multiple-resistant clinical bacterial

strains worldwide. Numerous recent review studies [50-51] that addressed different elements of this subject demonstrate the relevance of this mechanism of resistance in clinical settings. The antibiotic resistance of coliform bacteria in treated and untreated drinking water has been brought to the notice of several employees. [52] conducted a thorough assessment of antibiotic resistance in coliform. Following gastroenteritis outbreaks caused by causative agents identified as multiple antibiotic resistant (MAR) organisms, there was a notable influence on the incidence of resistance in India, according to reports (ICMR 1984–85). Coliform strains isolated from the Gomti river, a Ganges tributary that passes through the highly populated, quickly industrializing Indo Gangetic plain, have been studied for the presence of single and MAR strains as well as metal tolerance [53].

From the feces of cattle exposed to antimicrobial drugs and people connected to the animals, multidrug resistant coliform bacteria were recovered [54]. In particular, hemorrhagic colitis (HC) and hemolytic-uremic syndrome (HUS) in humans are known to be mostly caused by *E. Coli* 0157:H7 and 0157: NM [55]. According to estimates from the US Centers for Disease Control and Prevention, *E. Coli* 0157:H7 is responsible for around 73,400 illnesses and 60 fatalities in the US annually [56]. According to recent findings [57-59] *E. coli* is becoming more resistant to antibiotics.

Microbial resistance to heavy metals

Organic materials [60-62] and other agents selected for resistance strains are all continually exposed to microbial populations. Ecosystems poisoned by hazardous levels of heavy metals are home to bacteria that have adapted to their presence and developed efficient metal resistance mechanisms. In polluted environments, there is a generalized bacterial resistance to heavy metals. Metals are a big threat to the ecological system since they injure most living things [63]. Microbes are known to have a diverse range of genetic information that enables them to withstand metallic stress, despite the fact that larger species are easily destroyed by the harmful effects of metals [64]. A resistance mechanism to almost all harmful metals has developed as a result of selective pressure from any environment that contains metals. Organic materials [65] antibiotics [66-69] and other agents selected for resistance strains are all continually exposed to microbial populations. Ecosystems poisoned by hazardous levels of heavy metals are home to bacteria that have adapted to their presence and developed efficient metal resistance mechanisms. In polluted environments, there is a generalized bacterial resistance to heavy metals. Metals pose a severe threat to the ecological system since they affect most living things [70]. Nearly all eubacterial taxa under study have these highly specialized, plasmid-mediated mechanisms [71] microorganisms have been found to be resistant to specific metals through research conducted since the early 1970s. Most of these reports involved aerobic microorganisms, with notable examples including Bacillus sp., Pseudomonas aeroginosa, Escherichia coli, and Staphylococcus sp. [72-75]. There are particular resistance mechanisms for each hazardous heavy metal [76]. Lead is classified as a transition element and is a member of element groups IVa, C, Si, Ge, Sn, and Pb. It is even rarer in seawater than mercury [77]. Its poor solubility contributes to its low biologically accessible concentration. Lead is therefore not very hazardous to microbes. Although the toxicity of lead to humans and animals has long been known, lead has been utilized extensively for 2,500 years, most recently as a gasoline additive [78]. There have been reports of precipitation of lead phosphate within the cells of lead-tolerant bacteria [79] and of their isolation [80-81]. The two major forms of chromium are as the trivalent cation Cr (Ill) and as Cr (VI) in the divalent oxyanion chromate. Under physiological settings, reduction/oxidation processes between the two states are thermodynamically conceivable [80]. It is likely that chromate reduction and chromate outflow work together to provide chromate resistance. Pseudomonas fluorescence strain LB300 was the first bacterium to be proved to be resistant to chromate; it was demonstrated to decrease chromate (Bopp and Ehrlich, 1988). Since then, a wide range of bacteria capable of reducing chromate have been discovered [81]. Then, it was believed that chromate efflux was the primary basis for chromate resistance; however, new findings for Ralstonia sp. CH_{34} indicate that both efflux and reduction mechanisms are involved [82] discovered further instances of plasmidencoded arsenic resistance in *Staphylococcus xylosus*. The most researched example is the arsenic resistance of *E. coli* encoded in a plasmid [83]. Copper reacts with radicals readily; it interacts with molecular oxygen the best. Because of its radical nature, copper is extremely poisonous, and many species are more susceptible to it than *E. coli* [84].

There are two main mechanisms of Cu^{2+} resistance that have been found. Conversely, E. coli uses active efflux to decrease Cu storage [85]. In *E. Coli*, chromosomally encoded functions and plasmid-encoded copper resistance interact substantially [86]. The phenotype of the two copper-resistant bacteria differs, despite the homologous copper resistance determinants being demonstrated in *E. Coli* and *Pseudomonas sp. Pseudomonas* strains turn blue on high copper-containing media due to copper accumulation in the periplasm and outer membrane [87], *E. Coli* remains colourless. Cobalt is mostly present in the Co^{+} form; Co^{+} is of medium toxicity and is quickly collected by the system in the majority of bacterial cells, but Co^{+} is only stable in complex compounds [88]. Gram-negative bacteria's resistance to cobalt is based on trans-envelope efflux, which is facilitated by RND (resistance, nodulation, cell division) transporters. The most common form of free nickel is the cationic Ni^{+} form. The toxicity of nickel and cobalt are similar. In Saccharomyces cerevisiae and bacteria, nickel mostly enters the cell through the CorA system [89]. An ABC transporter and a periplasmic nickel-binding protein provide nickel to *E. Coli* for hydrogenase production. Zinc only exists as Zn^{+}, a divalent cation. Under biological circumstances, the zinc cation cannot undergo redox alterations due to its fully filled d-orbitals. Zinc is as harmful to Escherichia coli as copper, nickel, and cobalt are. Zinc-induced insufficiency might be the basis for zinc toxicity. Zinc efflux in *Escherichia coli* may be caused by the ZntA or ZiaA P-type ATPase [90]. Despite a great deal of research, particularly on the toxicity of cadmium in microorganisms, no clear mechanisms of action have been identified. The kind of bacteria affects how much Cd^{2+} they take up. The magnesium absorption mechanism is the means by which Cd^{2+} is transported in the gram-negative. Manganese has relatively low toxicity. It appears that all bacteria have great specificity and affinity for Mn^{2+} transport systems. According to reports, among all the elements examined in bacteria, mercury is the most dangerous. Mercury has no useful function due to its extreme toxicity. However, because bacteria are likely to encounter hazardous levels of mercury, are widely distributed and provide a major source of mercury resistance determinants.

Surveys of microorganisms possibly helpful for biological monitoring have been inspired by the widespread concern produced by the diffusion of harmful metals into our living environment through industrial emissions and leaching from hazardous wastes [91]. The presence of heavy metals as environmental pollutants appears to be directly associated with bacterial resistance to these elements [92], microbial metal resistance is also fascinating for basic and applied study, especially in the areas of plasmid genetics and the physiology of bacteria in contaminated environments. When studying ecology and microbiology in contaminated settings, metal-resistant bacteria are thought to be a beneficial tool. Examples of such applications include the study of geochemical processes, the use of bioindicators for environmental monitoring in polluted habitats, and environmental gene transfer Frankia is a member of the Actinomycetales order, and its genetic markers are few. The tolerance to heavy metals, antibiotics, and antimetabolites are a few of the most helpful genetic indicators. In addition to being helpful in the creation of cloning vectors, these directly selectable features offer a mechanism for positive selection in genetic research. A cell may try to defend vulnerable cellular components by developing a metal resistance mechanism. Restricting metal entry or changing biological constituents reduces their susceptibility to metals. The kind and quantity of metal absorption systems, the function that each metal serves in regular metabolism, and the pressure exerted on plasmid-based genes are some of the variables that impact an organism's level of resistance.

Epidemiology of infectious drug resistance

One major issue in the treatment of bacterial infections is multi-drug resistance. Numerous recent review papers that cover different parts of this subject attest to the relevance of this mechanism of resistance in clinical settings [93]. The increasing number of pathogenic bacteria that have been discovered and shown resistance to several antibiotics has raised concerns in recent years. Treatment of patients with bacterial infections they acquired in the community or in a hospital is severely hampered by this phenomenon [94].

Actually, the medical significance of infectious medication resistance was the primary motivator for the study's inception. A significant concern in the field of public health is the rising prevalence of antibiotic resistance among clinical bacterial isolates [95]. R-factors cause host bacteria to become comparatively resistant to medicines, making treatments ineffective against bacteria that carry R-factors. Additionally, the majority of R-factors have multiple drug resistance indicators, and the most significant, most potent, and least toxic chemotherapeutic medicines against infections caused by gram-negative bacilli are the pharmaceuticals implicated in such multiple drug resistance. Subsequently investigated an epidemic of infantile diarrhoea in a Tokyo nursery caused by *E. coli* (OSS: K59 [B5]) [96]. During the early stages of the epidemic, only drug-sensitive strains of *E. Coli* (OSS: K59 [B5]) were identified from the patients. Nevertheless, the *E. Coli* strains (055:K59 [B5]) that were recovered from the patients during the middle phase of the outbreak were resistant to a number of medications and these strains most likely possessed R-factors.

Chemotherapeutic chemicals are frequently administered to a large number of animals virtually every day, which makes their usage as feed additives for animals seem to be a major concern. It has been demonstrated that low drug concentrations in the feed cause a selection of R+ bacteria in the animals' intestines, despite the fact that the concentration of the medications provided is far lower than their therapeutic levels. R+ enteric bacteria are present in between 50 and 100 percent of animals administered antibiotics, according to [97]. Based on epidemiological investigations, it has been determined that strains of salmonella originating from domestic animals are responsible for a significant number of human illnesses. It has been observed that an increasing number of Salmonella strains resistant to drugs are emerging from both humans and animals. What's more significant is that most drug-resistant enteric bacteria that are recovered from animals fed antibiotics have R-factors, and non-pathogenic enteric bacteria may transfer these R-factors to human pathogens. The R-factor will be passed from the R+ intestinal bacteria to the R- newcomers if one consumes R+ *E. coli*. Chemotherapeutic medicines promote the R+ bacterial selection and subsequent colonization of the intestinal tract, which increases the likelihood of R-transfers and facilitates such transfer processes.

Because R-factors often replicate in synchronization with host chromosomes, despite the fact that their replication happens independently of one another, the progeny of R+ bacteria are typically R+. The infectious dissemination of R factors to other bacteria is a distinctive characteristic of their heredity. Therefore, R+ bacteria may multiply their cells and distribute their R-factors virally to establish themselves. Chemotherapeutic drugs contribute to the spread of R-factors through both processes of selection.

Numerous drug-resistant forms of Shigella have sharply increased in number in recent years, according to epidemiological research conducted in Japan. According to [98] the incidence of R+ Shigella strains in Japan in 1968 was estimated to be more than 80% of all isolates. Studies conducted in different US districts [99-101] have likewise revealed a prevalence of multiple drug-resistant Shigella strains that ranges from 20 to 25%. A consistent trend toward an increase was seen in all reports that examined yearly variations in the frequency of R+ strains in the United States. It has been determined that the frequency of R strain is on the order of R+ Shigella in studies on pathogenic E. coli [102] When antibiotics are added to cattle and poultry feed, the prevalence of R+ strains is significantly higher. Antibiotic-resistant bacteria were found in the intestines of 50–99% of the animals under study.

The typical gut flora may acquire these factors by ingestion of bacteria harboring R-factors, or R+ bacteria. Consequently, these organisms serve as a reservoir of resistance that they can spread to susceptible bacteria that cause illness, decreasing the effectiveness of antibacterial treatment [104]. When a patient receiving medication treats even a small number of R+ bacteria, these organisms proliferate and spread their resistance to other germs [105]. R-factor is also transmitted through wounds. The resistance of *Pseudomonas aeroginosa* bacteria to *carbenicillin*, the preferred medication for treating illnesses caused by these organisms, has become a significant issue, particularly when treating burn victims. *Enterobacteria* such *E. Coli, Klebsiella aerogens, proteus*, or *Providencia sp*. are typically the donor bacteria. The discovery of R+ bacteria dates back to 1959 in Japan. Their prevalence among S. typhimurium isolates rose from 21% in 1964 to 61% in 1965, after they were identified from patients in Britain shortly after [106]. R-factors create a health risk that goes beyond medication resistance. Pathogens like S. typhi and Shigella sp. may become more pathogenic and infectious as a result of them [107]. Other plasmids, such as

those that spread entero pathogenicity among *E. coli* species, may be carried by bacteria in addition to R-factors. There has been evidence of plasmid recombination, and it is possible for R-factors containing genes that may turn *E. coli* into a disease resistant to drugs to arise and spread quickly.

The most common infections in hospitals nowadays are those brought on by bacteria that may have R-factors. These infections are becoming more common. Approximately one Gram negative bacterium per 100 hospital patients is known to occur annually in many different states in the US, with death rates ranging from 30 to 50 percent. This indicates that gram-negative bacterial infections cause over 100,000 deaths in that nation annually. In the sewage effluent of Bermingham, Alabama, in 1969, 0.5 percent of coliforms (5 x 103 R+ coliforms ml-I) contained R-factors. This number quadrupled a year later (Sturtevant et al., 1971). Four percent of coliforms were found in Pietermaritzburg's sewage discharge in 1972. A hospital in this city in South Africa had waste water that had 129 x 103 R+ coliforms ml-I (or 26% of all coliforms). Of these microbes, 49% possessed transmissible resistance to five different medications.

[108] demonstrated that throughout the maturation pond treatment of traditionally cleansed sewage, the proportion of coliforms carrying R-factors grew from 0.86 to 2.45. This suggests that in some water environments, R+ bacteria could live longer. The ecological network of resistance has been hypothesized to come to an end with the medical effects of antibiotic usage in agricultural and veterinary medicine. These practices contribute to reservoirs of resistance, routes of transmission, and selective pressure. A tragic, but likely uncommon, incidence involves the deaths of two patients in Denmark due to resistant Salmonella typhimurium DT 104 contracted via pork. Aeromonas isolates from 72 hospital effluents and 91 fish hatchery tanks were found to have oxytetracycline resistance plasmids. These plasmids, which are closely related to Inc U plasmids like pASOT and PRASI (from *Aeromonas salmonicida* found in fish forms in Norway and Scotland) and plE420 (from E. coli isolated from a German hospital), showed that 11 and 6 strains, respectively, transferred oxytetracycline plasmids to E. coli J53-1. Similar tetracycline resistance encoding plasmids have been spread between various Aeromonas sp. and E. coli, as well as between the human and aquaculture elements in different geographical locations, PRASI and plE4120 appeared to be identical—both carried the tetracycline resistance transposon Tn1721.

R-plasmid and its transfer

Extrachromosomal DNA components of bacteria called plasmids make up a somewhat stable but necessary gene pool. For the most part, they are not necessary for the host bacterium's proper development and metabolism. Frequently, though, these genetic components include genes for an additional function that enhances the host's ability to withstand harsh conditions or to successfully compete with other microbes of the same or other species. In terms of human medicine, the most well-known plasmids are those that indicate antibiotic resistances. But it's becoming clearer that plasmids also define characteristics that directly increase a range of bacteria' pathogenicity. Genes that give resistance to heavy metals, antibiotics, and other hazardous substances are found in many plasmids. This kind of plasmid is known as an R-plasmid. [109] found that Shigella isolates from Japanese cases of dysentery have R-factors. Through conjugative transfer within a bacterial population, they expand quickly and continue to exist under the influence of selection. As a result, there might be a significant public health issue if an entire population develops resistance to heavy metals and/or antibiotics.

The frequency of plasmids varied from site to site depending on the extent of the pollution, according to ecological studies on the incidence of plasmids in natural populations of terrestrial [110] and fresh water bacteria [111]. The rising spread of multi-resistant bacterial diseases has highlighted the need of studying plasmid transfer in natural contexts [112]. Clinical bacterial isolates frequently include drug resistance plasmids, and as a result, these strains may inherit various antibiotic resistance, which can seriously hamper the prompt and simple treatment of bacterial infections [113] R-plasmids are responsible for 80% of drug resistance in enterobacteriaceae.

Numerous natural settings, including soil, animal intestines and aquatic ecosystems are sites of plasmid transmission. Lederberg and Tatum's 1946 straightforward experiment served as the basis for the concept of bacterial conjugation, which is the direct transfer of genetic material from one cell to another. They did not explicitly demonstrate that gene transfer required physical contact between the cells. The lengthy treatises by [114] discuss a large portion of the early research on bacterial conjugation. [115] provided the first thorough analysis of this topic. Other researchers 115-116] have also examined a variety of R-factors. Interest in infection, drug-resistant plasmids (R-factors), and the bacteria that carry them has increased since it was discovered in 1959 that drug resistance could be passed across members of the Enterobacteriaceae family. It was also noted by Harada and colleagues (1960) that medication resistance might spread between different Enterobacteriaceae taxa. It was also observed that cell-to-cell contact may transfer the R-factor to several additional taxa, including Vibrio, Pasteurella, and Pseudomonas sp. Transferable medication resistance was initially shown in the UK by Datta in 1962 and in Europe by Lebek in 1963.

However, investigations on transferable drug resistance among bacterial isolates of drinking water in India have lately attracted the attention of Indian experts [117]. Research carried out by shown that R-factor plasmid vectors may be used to transmit resistant traits to susceptible recipient species in the gut. Mazodier and Davies studied natural gene transfer across distantly related species (1991). It was shown that plasmid DNA may be transferred from E. coli to other gram-positive bacteria by conjugation as well as the other way around, from enterococci to *E. coli* [118] reported on the transmissibility of antibiotic resistance among different antibiotic-resistant coliforms.

Numerous researchers have documented the transfer of plasmids that give resistance to antibiotics and heavy metals during conjugation [119]. Resistance genes are reasonably stable and easy to deal with, thus many researchers have utilized them as markers to select for trans conjugants [120]. Several reviews [121] examined the conjugation mechanism of F. related plasmids. Recently, a thorough compilation of studies addressing bacterial conjugation was released. A bacterial cell can exhibit a newly acquired characteristic by absorbing free DNA from its surroundings and incorporating it through a process known as genetic transformation. The initial method of bacterial genetic exchange was called bacterial transformation. It was first found in Streptococcus pneumoniae and subsequently shown in *Bacillus subtilis* and *Haemophilus influenzae*.

In 1970. Mandel and Higa discovered that after being exposed to calcium ions, phages P2 and X could transfect *E. coli.* [122] adjusted the procedure and were able to successfully introduce DNA from an antibiotic-resistant plasmid into $CaC1_2$-treated *E. coli* cells (Competent cells). Numerous reviews have been published on *B. subtilis's* natural transformation. The unique method of transmission on plasmid exchange between gut bacteria in vivo has only been the subject of a relatively small number of research [123]. It is well known that E. faecalis cells can transmit the tetracycline-resistant pheromone-inducible plasmid pCF10 very effectively when they are in liquid media *in vitro*. The transfer of this plasmid between isogenic strains of E. faecalis OGI colonizing in the digestive tract of mini pigs treated with streptomycin was examined by [124].

Curing of R-plasmids

Generally speaking, plasmids can be removed from host cells by a procedure called curing. Certain plasmids spontaneously separate and become deleted. The majority, however, are incredibly stable and need to be treated with curing agents or undergo other treatments (such as thymine starvation or elevated growth temperature) in order to increase the frequency of spontaneous segregation [125]. This process prevents plasmid replication while leaving host cell reproduction unaffected. The first report of acriflavin's efficacy in eradicating F-factor in E. coli K-12 was made by [126]. Certain R-plasmids are eliminated by these chemicals, most likely by intercalation into the plasmid DNA, which results in a selective suppression of plasmid DNA replication. [127] demonstrated how dyes like acriflavin and acridine orange may remove R-factors from enteric bacteria. Even the removal of a plasmid may not be sufficient evidence in certain species to establish that a feature is plasmid-encoded, according to [128]. This is a result of plasmids' propensity to integrate into the chromosome of their bacterial host. Acridine dye therapy has been used to cure R-factors in vitro. Acridine orange was also utilized by [129] to treat F' lac caused by E. coli K-12. Agaric orange has been used in concert with other strategies to eradicate the antibiotic-resistant R-plasmid in several bacterial strains [130] to effectively cure resistant plasmids in Gram-positive and Gram-negative bacteria, respectively. Acridine orange was used to cure a chromium-resistant plasmid in pseudomonads, as reported by [131]. Similar to acridines, mitomycin C facilitates the bacterial removal of R-factor. Mitomycin-C was effectively employed by [132] to cure plasmid contained genes that dictate camphor (CAM) oxidation in Pseudomonas putida. It has been demonstrated that mitomycin C introduces alkylating cross-links between the double stranded DNA's two strands [135]. Numerous researchers [133-134] have reported curing R-plasmid using mitomycin C. Mitomycin C (5–20 pg/ml) was shown to be effective in eliminating antibiotic-resistant plasmids, according to [136]. Thus, chromium and other heavy metal-resistant plasmids (Hg^{2+}, Ag^{3+}, Cu^{2+}, Ni^{2+}, CO^{2+}) have been reported to be eliminated by numerous researchers employing mitomycin C as a curing agent. According to [136] *Pseudomonas putida* KT 2441 lost its plasmid-mediated chromium resistance following five rounds of sub culturing on basic nutrient agar.

CONCLUSION

In conclusion, the interrelated issues of microbial antibiotic resistance and heavy metal tolerance pose significant challenges to environmental and public health. These challenges are exacerbated by the increasing prevalence of resistant microbes in various environments, driven by the overuse of antibiotics in healthcare and agriculture, and the widespread pollution of ecosystems with heavy metals from industrial activities. The environmental persistence of these resistant and tolerant microbes not only disrupts natural microbial communities but also poses a risk of transferring resistance traits to pathogenic bacteria, complicating medical treatments and potentially leading to more severe health outbreaks.

Addressing these challenges requires a multifaceted approach. This includes stringent monitoring and regulation of antibiotic and heavy metal usage, increased research to understand the mechanisms behind resistance and tolerance, and the development of new, more effective antimicrobial agents. Public health initiatives focused on educating the public and professionals about the risks and responsible use of antibiotics are crucial. Furthermore, global cooperation is essential, given the boundary-crossing nature of microbial resistance. Innovative remediation techniques to clean up heavy metal pollutants from the environment can help in reducing the selection pressure that fosters the development of tolerance.

The prospects for effectively managing microbial antibiotic resistance and heavy metal tolerance hinge on our ability to integrate scientific research, policy-making, and public awareness. While the challenges are daunting, ongoing advancements in biotechnology, environmental science, and global health policy provide a basis for optimism. By harnessing these advancements and fostering international collaboration, we can work towards mitigating the environmental impacts of these issues and safeguarding public health.

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