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PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN THE ENVIRONMENT WITH EMPHASIS ON HORIZONTAL TRANSFER OF ANTIBIOTIC RESISTANCE GENES

Abstract: Pharmaceuticals and personal care products (PPCPs) discharged into environment has several adverse impacts. PPCPs are widely utilised for veterinary as well as cosmetic and personal health reasons. These are members of the expanding class of substances known as Contaminants of Emerging Concern (CECs). Antibiotic resistance in the environment and garbage generated by PPCP endanger life. The World Health Organisation (WHO) now recognises antibiotic resistance as a significant global health problem due to the expected increase in mortality caused by it. In the past ten years, mounting data has led experts to believe that the environment has a significant impact on the development of resistance. For human diseases, the external environment serves as a source of resistance genes. It also serves as a major pathway for the spread of resistant bacteria among various habitats and human populations. Large-scale DNA sequencing methods are employed in this thesis to better comprehend the dangers posed by environmental antibiotic resistance. The quantification of the number is an important step in this process. Metagenomic measurement of the number of antibiotic resistance genes in various contexts is a crucial step in this process. However, it's also crucial to put this data into a broader context by integrating things like taxonomic information, antibiotic concentrations, and the genomic locations of found resistance genes.

Keywords: antimicrobial resistance, bacterial resistance, fate of PPCP, pharmaceutically active compounds (PhACs), PPCP flow routes, PPCP flow through food chain, PPCP treatment technologies, waste water treatment plants

Introduction

Contaminants of Emerging Concern (CEC) pose a risk to both human health and the environment. Several common household items are among the main sources of CECs. Based on their source, chemical properties, destiny, and the mechanisms that underlie their effects, CECs can be grouped in a number of different ways.

The main causes of the production of high risk. CECs include bacteria, antibiotic resistant genes, and disinfection by-products (DBPs). Over a few hundred kilo tons are thought to be consumed each year in terms of pharmacologically active substances. Since CECs are an integral component of many things we use every day, it is exceedingly difficult to prevent their proliferation. In addition to the rising use of ECs in daily life and the resulting rise in environmental contamination.

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The negative impacts of biological amplification and bioaccumulation cannot be overlooked, in addition to the expanding use of CECs in daily life and the resulting rise in environmental contamination. There are various ways that CECs toward the environment. The reuse or agricultural use of wastewater sludge could also contribute to the proliferation of CECs. The lack of clear rules and quality standards that address the acceptable levels of CECs is one of the main obstacles to controlling the mobility of CECs. As a result, CECs were not typically studied in the environment, which increases their potential to harm the ecosystem.

There is pressing need for pollution abatement and also there is an even more pressing need to create viable value chains from contaminated substrates (air, water and soil) especially in developing economies. The EU Green Deal and UN Sustainable Development Goals are in way mirror images of sustainability. The Green Deal [1] is a key element of the EU strategy to implement the United Nation’s Sustainable Development Goals (SDGs) [2] pertinent to reducing air, water and soil pollution, reducing the loss of biodiversity and climate change [3, 4] ensuring sustainable use of energy and natural resources and well-being of citizens [5, 6]. To ensure a toxic-free environment, the Commission will present a chemicals strategy for sustainability. The Commission will review how to use better the EU’s agencies and scientific bodies to move towards a process of ‘one substance - one assessment’ and to provide greater transparency when prioritising action to deal with chemicals. In parallel, the regulatory framework will need to rapidly reflect scientific evidence on the risk posed by CEC endocrine disruptors, hazardous chemicals in products including imports, combination effects of different chemicals and very persistent chemicals. Green sustainable growth is also very important in China [7].

Around the world, environmental contamination is a severe problem. Uncontrolled use of synthetic chemicals, pesticides, plastic, phenolic compounds, industrial waste, and/or nondegradable materials are the main contributors to it. These pollutants impoverish soil, have negative effects on the quality of the air and water, and cause a wide range of illnesses, such as cancer, genetic diseases, blindness, and infertility. These contaminants can have detrimental effects on plants and animals and are also passed along the food chain. Development of technologies, methodologies, or the identification of plants or microbes that can be utilised to remove or reduce pollutants in an economical and environmentally acceptable way has become urgently necessary. By changing the environment and encouraging the microorganisms or plants, several of these are being utilised to remediate contaminants from soil, water, and surface materials. Phytoremediation, mycoremediation, bioleaching, landform, bioreactor, composting, and bioaugmentation are a few of the bioremediation technologies that enable the removal or reduction of pollutants. This review emphasises the explosion of knowledge for removing or reducing CEC using a variety of methods, including metagenomics, bioreactor, molecular biology tools, microbial indicators, biosurfactants, biofilm, genetically modified organisms, engineered fungi and bacteria, synthetic biology tools, and genome editing CRISPR-Cas9 technology.

Due to the biochemical pathways found in their genomes or plasmids, a number of plants and microbes have the innate potential to breakdown or detoxify contaminants. Heavy metal contaminants such as cadmium, chromium, lead, and uranium that cannot be degraded are also remediated (toxicity is reduced). Thus, bioremediation lessen the toxicity of these hazardous substances and their subsurface mobility, hence lowering the risk of exposure to humans and the environment.

Pollution abatement is a core of European Union Green Deal Strategy. Thus, there is pressing need for pollution abatement. Green Deal advocates for *A zero pollution ambition for a toxic-free environment.* Creating a toxic-free environment requires more action to prevent pollution from being generated as well as measures to clean and remedy it. To protect Europe's citizens and ecosystems, the European Union (EU) need to monitor, report, prevent and mitigate pollution from air, water, soil, and consumer products. To achieve this, the EU and Member States will need to look more systematically at all policies and regulations. To address these interlinked challenges, the Commission adopt "a zero-pollution action plan for air, water and soil" in 2021.

Wastewater effluents are a major source for many of these emerging contaminants, due to their use in products we use in our households, from pharmaceuticals, detergents, fabric coatings, foam cushions, lotions, sunscreens, cosmetics, hair products, foods and beverages, and food packaging. After use, these chemicals are released in wastewater, and because many are incompletely removed in wastewater treatment, they enter our rivers and drinking water supplies. Surface run-off and agricultural run-off can also be important sources of their entry into the environment. Moreover, many of these contaminants can transform in the environment, from such processes as microbial degradation, photolysis, and hydrolysis, and they can also react with disinfectants in drinking water or wastewater treatment to form disinfection by-products. Issues surrounding these emerging contaminants, include widespread occurrence, bioaccumulation, persistence, and toxicity.

Table 1

Category of PPCP and major sources [8]

Category of PPCP	Sub-category	Major contaminants	Sources
Pharmaceutically active complexes	Nonsteroidal anti-inflammatory medicines, antidepressant, antibiotics, anticonvulsants, lipid regulators, β-blocker, and hormones	Diazepam, ciprofloxacin, metoprolol, diclofenac, carbamazepine, clorfibric acid, testosterone	Effluent of medicine manufacturing facility, hospitals and health centers, livestock farms, and domestic wastewater
Endocrine disruptors (EDCs)	Bisphenol, xenohormone, and phthalates	Bisphenol A, xenoestrogen, and dioctyl phthalate	Drinking water, surface water, sediments, soil and secondary sludge

Pharmaceuticals and Personal Care Products (PPCP)

Human health is impaired by CECs and their bioavailability via the biogeochemical cycle. Pharmaceutically active chemical (PhACs) contamination of surface water, round water and untreated wastewater are of serious concern. PhACs can enter the environment through a number of different direct and indirect mechanisms and routes (Fig. 1). Numerous scholars have claimed that products used by people for personal health/well-being or cosmetic reasons are referred to as pharmaceutical and personal care products (PPCPs). They include, but are not limited to, prescription and over-the-counter medicines for humans, veterinary medicines, diagnostic tools, dietary supplements, and other consumer goods like fragrances, cosmetics, lotions etc. They are made up of a wide range and diverse group of organic compounds, along with their respective metabolites and transformation products. There are thousands of such chemicals (Fig. 1). Number of papers in each year are labelled on the top of the respective year bar. This indicates the magnitude of environmental and health issue.

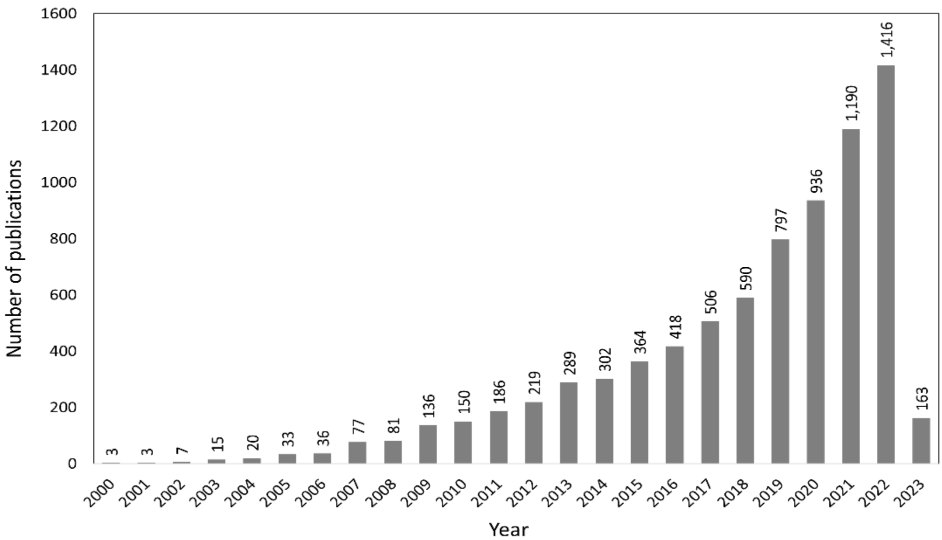

Fig. 1. Articles published in the past two and half decades beginning 2000 to 2023 on pharmaceuticals and personal care products (PPCP) [7]

Table 2

Historical resume of bacterial resistance to antibiotics [9]
[Source: Centres for Disease Control and Prevention, USA]

Year of invention	**Uses of antibiotics in curing specific diseases**	**Year in which bacterial resistantance reported**
1943	**Penicillin** Pneumonia, meningitis, skin, bone, joint, stomach and blood infections	1965, Penicillin-*R Pneumococcus* (this bacteria became resistant to the drug)
1950	**Tetracycline** Pneumonia, acne infections of respiratory tract, genitals, urinary systems and stomach ulcers	1959, Tetracycline-R *Shigella*
1953	**Erythromycin** Bronchitis, diphtheria, whopping cough, pneumonia, rheumatic fever	1968, Eiythromycin-*R Streptococcus*
1960	**Methicillin** Staph infections	1962, Methicillin-R *Staphylococcus*
1967	**Gentamicin** Lung, skin, bone, joint, stomach, blood and urinary tract infections	1979, Gentamicin-R *Enterococcus*
1972	**Vancomycin** colitis	1988, Vancomycin-R *Enterococcus* 2002, Vancomycin-R *Staphylococcus*
1985	**lmipenem and celtazidime** Lung, skin, bone, joint, stomach, blood and gyneacoiogical and urinary tract infections	1987, Ceftazidime-R Enterobacteriaceae
1996	**Levofloxacin** Pneumonia, chronic bronchitis, and sinus, urinary tract, kidney, prostate and skin infections	1996, Levofloxacin-R *Pneumococcus*
2000	**Linezolid** Pneumonia and skin and blood infections	2001, Linezolid-R *Staphylococcus*
2010	**Ceftaroline** Injection is used for skin infections and pneumonia	2011, Ceftaroline-R *Staphylococcus*

A globalised pharmaceutical industry has emerged, and its growth has accelerated since the World Trade Organization's accord on trade-related IP rights (TRIPs). The big pharmaceutical companies, many of which are based in the United States and Europe, are now accustomed to outsourcing production to emerging nations where labour is inexpensive, workforces are skilled, and environmental laws not stringent. As a matter of fact, China and India today produce the great majority of the world's active pharmaceutical ingredients (APIs) and bulk medications antimicrobial resistance (AMR), a significant concern (detailed in later sections), can be sparked by pharmaceutical pollution. For environmental sustainability, a comprehensive evaluation of the pharmaceutical industry's environmental impact is required. Pharma industry waste that is solid, liquid, or airborne poses major health dangers. Aquaculture concerns and water contamination have increasingly caught the attention of global scientists. A vast amount of knowledge has now been accumulated regarding the harmful consequences brought on by the buildup of pharmaceuticals in the environment, which vary from the almost complete eradication of entire species to the feminisation of fish and the spread of AMR. Health threats posed by pollution from antibiotic production is believed to be contributing to soaring drug resistance rates (Table 2). This has serious implications for global health as antibiotic resistance genes spread around the world through.

Horizontal transfer of antibiotic resistance genes in the environment

The genetic material in the Bacteria consists of DNA, which comprises of 4 base pairs Adenine, Guanine, Cytosine and Thymine. Genes are sequences of DNA that code for proteins and several Non-coding RNAs. These two molecules control various cellular processes and metabolism in a living cell. The genes usually are inherited by offsprings from parents. This type of inheritance is called Vertical transfer of genes. This is usually observed in microbes. However, a second type of transfer of genes is observed that is called Horizontal Gene Transfer (HGT). In this process genes are transferred rapidly in a bacterial population between the members of the colony. Antibiotics are widely used to combat bacterial infections. However, many bacteria are becoming resistant to antibiotics. The genes that confer resistance are called Antibiotic Resistant Genes (ARG). These genes are rapidly transferred between the members of bacterial population in a given environment through the process of HGT. The bacteria can infect humans cause diseases and could be resistant to antibiotics due to the ARGs. This gives advantage for the bacterium to live in altered environments in the presence of drugs that kills them. The bacteria containing ARG genes are usually resistant to antibiotics and the disease becomes untreatable by doctors, in many cases the victim dies. The ARG genes containing bacteria are responsible for the death of about 700,000 people every year. The alarming fact is that several models predict about 10 million deaths in the next 30 years. Researchers say that the death rate from the antibiotic resistant illnesses could be higher than the Cancer related deaths globally. The medical professionals are concerned about these illnesses as this could affect wellbeing of humans [10]. Recently, a global alliance on disease burden from the ARG associated infections were studied. They estimated that 4.9 million deaths were associated with ARGs in microbes, globally, and the highest death rate was observed in Sub-Saharan Africa. Predominantly, six species of bacteria, *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa* were responsible for highest morbidity [11]. The patients acquire the bacteria that are resistant to antibiotics sometimes in the hospital environments. In a study done in China, many infections in the patients who are hospitalised acquired infections from several bacteria that are resistant to antibiotics. The bacteria that were found were *Klebsiella pneumoniae* that could produce extended-spectrum *β*-lactamases and Carbapenem-resistance. *Escherichia coli* was observed that was resistant to Carbapenem. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were resistant to multiple drugs (MDR strains). *Staphylococcus aureus* was resistant to methicillin. The ARGs can be transferred quickly between different strains of bacteria and also among various species making this method of transfer of genes more conducive to the growth of bacteria [12].

The gene transfer is due to the process of transformation, transduction, conjugation, mobile elements, and membrane vesicles. Two cells come together, and the gene transfer takes place from the Donor to the recipient directly. This process is termed transformation and is highly involved in HGT and can transfer ARG genes across the bacterial species [13].

Sometimes bacteria will be lysed, and the donor DNA can be taken up by recipient cell. This process is transformation and plays a prominent role in HGT. There are several viruses that live along with bacteria. When they infect bacterial cells, they carry genes from one cell to another. This process is termed as Transduction which facilitate HGT and carry ARGs from one species to another [14]. Recently, another method of HGT is elucidated that involved membrane vesicles containing DNA. These are taken from the donor to the recipient bacteria resulting in the transfer of ARGs in the recipient species. Additionally, DNA/genes can be transferred by mobile elements [15]. However, the precise mechanisms are unknown and is an area of huge research interest in the scientific community. The recipient bacteria usually have defence system and chop off the new DNA that is entering the cell. However, these bacteria have developed mechanisms to overcome the cells inherent defence systems. Bacteria have several nucleases termed as Restriction endonucleases that can act on specific DNA sequences of a gene and degrade the DNA. However, there are several proteins that can regulate the endonucleases and make them non-functional enabling the ARG genes to be expressed in the recipient bacteria. Similarly, another protection mechanism against foreign DNA in the bacterial cell is the clustered regularly interspaced short palindromic repeats associated system (CRISPER-Cas system that can function to degrade transferred DNA using small RNA called guide RNA (gRNA)). However, several anti-CRISPER proteins (ACP) are known that can facilitate HGT [16]. Therefore, finding inhibitors to the ACPs and improving the CRISPER/Cas system for promoting antibiotic sensitivity is another area of research to reduce HGT and make bacteria more susceptible to the antibiotics [17, 18]. The other ongoing effort to combat the ARG phenomenon is to develop vaccines against ARG containing bacteria. The types of vaccines developed consists of peptides, conjugates, outer membrane vesicles, mRNA therapeutics, nanodrugs etc. Peptides are explored extensively explored for adult Tuberculosis disease where ARG is very common [19]. A vaccine is tested against typhoid fever in several countries for efficacy and it confers protection against this disease [20]. Another interesting technology is mRNA vaccines against the ARG bacteria. An immunopeptidomic map of the bacterium can be first obtained. These molecules would be the potential antigens and vaccines can be designed against the epitopes. Then, mRNA vaccines against the epitopes can be designed and put in Lipid nanoparticles for protection and can be delivered. This technology has been used against COVID 19 virus with great success. Now this technology is being applied for Bacteria with ARG genes that don’t respond to conventional therapies [21]. Another option that is pursued is using monoclonal antibodies as therapy for the ARGs containing bacteria (super bugs). There are 3 FDA approved Monoclonal antibody drugs and several are in the development [22]. The novel therapy drugs are needed to cure people from bacterial illnesses and several efforts are underway. However, it is wise for the people to be aware and work towards lessening the superbugs in the environment as these can be present in soil, water and they can be transferred back to humans through food chain.

Environmental factors and human activities resulting in HGT leading to Antibiotic Resistance

The one health concept involves health of animals, humans, and natural environment. Water is connecting link between all the three. Antibiotics are released into the wastewater sludges, ponds rivers and soils from pharmaceutical industrial waste, hospital waste, domestic house old waste, farm animal waste etc. Therefore, antibiotics are considered as emerging contaminants and several antibiotics are present in the water and soil. They are known to take long time to degrade in the environment and they become emerging pollutants that are harmful, as they result in the ARG in the microbes present in these environments due to HGT. These could come back to humans and cause severe health issues. The COVID 19 pandemic has claimed several lives and the use of masks has become mandatory for the spread of the disease. However discarded masks were regions where ARG containing bacteria were observed [23]. Therefore, proper disposal techniques should be used by people.

Recently the surveillance of hotspots of ARG bacteria in the region and research activities to study them are summarised. Interestingly the research output was proportion to the economic conditions in a country. High publications (50 %) on ARGs were observed from the high-income countries. Upper middleincome countries had 40 % publications, Lower Middle-income countries had 9 % publications and Low-income countries had 1 % research publications indicating that Low-income countries lack resources to address the problem of ARGs in the human healthcare and in natural ecosystems [24]. Therefore, an integrated consortium containing all countries should be formed to monitor ARGs in bacteria for better understanding this global problem. The integrated research on Cholera is one such example. Cholera is the disease caused by *Vibrio cholerae* and is usually a water borne disease. The disease prevalence is higher in low- and middle-income countries due to lack of safe drinking water. An analysis of published literature suggested that these species were resistant to tetracycline, sulfphonamide, quinolone, lactamase, chloramphenicol, macrolides, and aminoglycosides. The resistance for these antibiotics were found in 622 *Vibrio* spp. out of 1920 isolates. The resistance was observed in Haiti, Malaysia, Iran, India, China, Brazil, and Southern Vietnam. Interestingly, resistance was also observed in developed country Austria. The occurrence of the ARGs in this species needed global attention and studies [25].

The problem of ARGs in microbes is higher in middle- and low-income countries. The reasons could be lack of surveillance for antibiotics and more need due to higher bacterial infections in these countries. Additionally, hospitals could be crowded enabling more spread of ARGs in humans. They may not have accesses to newer expensive antibiotics enabling overuse of cheaper antibiotics in these countries. Further cheaper manufacturing costs of antibiotics in India and China resulted in pollution of environments from industrial wastes [26]. However, the prevalence of ARG due to HGT is a problem irrespective of economic status of countries**,** whether they belong to high-middle- or low-income countries. There were reports in Sweden where ARG bacteria were identified in the municipal waste and hospital waste [27]. Recently, France reported this problem in its territories and observed that the effluents from wastewater plants were considered as main source of pollutants that cause ARG. The National level data was modelled; however, heterogeneity was observed, and attention was bought into need for country wide policies and studies [28]. Similarly, researchers in Japan have used the technique of sequencing the whole genome of contaminated samples and identified the ARGs [29]. Further, this technique was used to identify ARGs in public restrooms in Taiwan, between the hospitals and water ecosystems nearby in China [28, 29]. The meta genome sequencing and ribosomal RNA coding genes were used as techniques to find out information about ARGs in irrigational waters, surface waters and recycled waters. A longitudinal study containing multiple data sampling points was performed in several regions in USA to understand sessional variations and help policy makers for public health surveillance and water quality management. The study was performed by CONSERVE initiative to save water and food. There was high level of ARGs that coded for resistance against Macrolide, lincosamides and streptogranins. Amino glycosides, fluoroquinolones, anti-microbial peptides, rifampin, tetracyclins and elfamycins [30]. Further, bacteria from wastewater and sediments from river bodies also showed ARGs in African countries such as Congo and in India [31, 32]. The cheaper and most reliable methods that can be employed is by using QPCR to look for ARGs in low-cost settings. Therefore, standard conditions for the assays should be employed globally [33-36]. A list of ARGs is found in the Comprehensive Antibiotic Resistance Database where researchers can access information about ARGs (Fig. 2, (https://card.mcmaster.ca/).

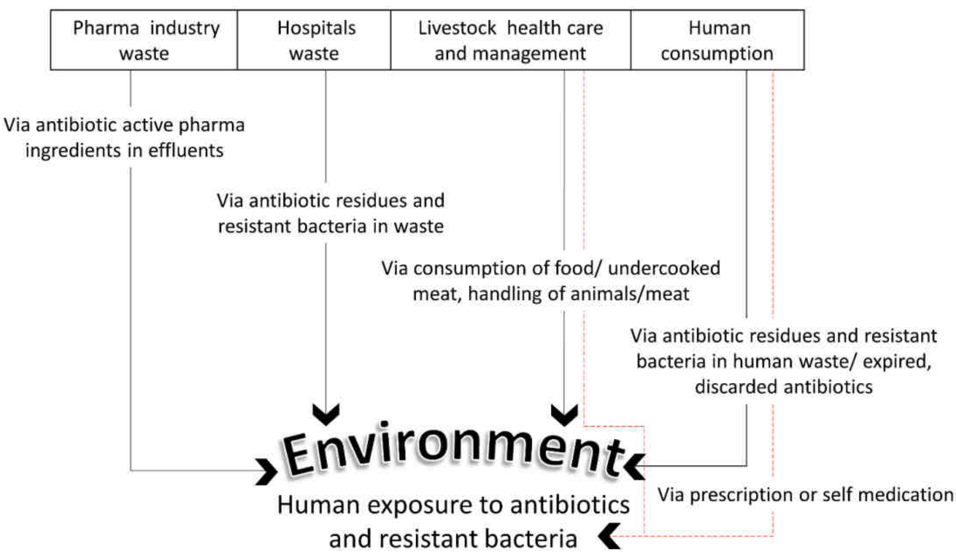

Fig. 2. Flow of to antibiotics and exposure of humans to antibiotic resistant bacteria. Pollution from antibiotics is fueling the global rise of drug-resistant infections

Flow of antibiotics and exposure of humans to antibiotic resistant bacteria

Aquaculture is livelihood for humans and is recognised as main source of food for people by FAO. Like agriculture, intensive farming techniques are employed for high yield including food. Application of antibiotics is higher and there is a great concern now as the ARG containing bacteria find a way into food chain in the Ecosystems and in humans. The ARG containing bacteria can move from aquatic to terrestrial ecosystems and cause a problem in humans and animals [37]. The factors effecting HGT in the aquatic environments are reviewed recently. The presence of Nanomaterials, oxidants and light influence the transfer of ARG genes. Biofilms are considered as the hotspots for the ARG transfer. However, more studies are needed to understand the phenomenon in these hotspots [38]. Heavy metals and microplastics make way into aquaculture environments due to contaminated water from human activities. These play a role and interact with each other and increase HGT. The selective pressure for heavy metals can enable co-selection of metal resistant genes and ARGs by HGT giving more advantage to the bacterial survival [39].

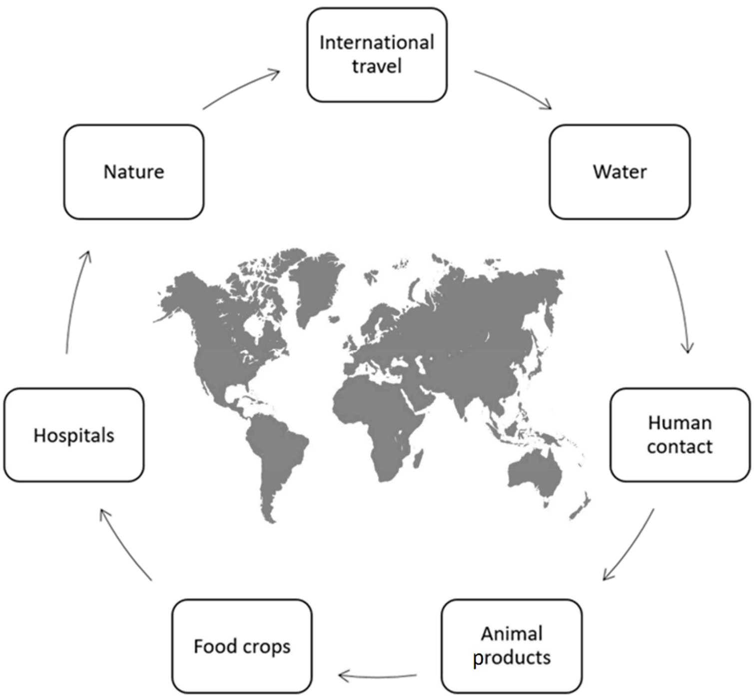

Fig. 3. AMR is spreading around the world rapidly. Drug resistant bacteria are able to travel around the world. Thus, everyone is at risk. For e.g. the resistant bacteria carrying the genetic code New Delhi metallo-β-lactamase-1 (NDM-1) was first identified in India has already been found in more than 70 countries due to globalisation and modern style of living. Any local health problem can become a global level disaster due to AMR (like Covid 19 pandemic)

Mariculture is culture of marine organisms in aquatic systems for commercial purposes. The produce is valuable as food (http://www.searoundus.org) maintained by University of British Columbia, Canada. In addition to this, lot of industries use marine animal-based products. The Mariculture fishes such as Salmon, groper, seabasses, and prawn are favoured by Western Nations thereby creating a global market for these and one third of aquaculture farming is by Mariculture. This is energy intensive, lot of feeding material and antibiotics are added during the culturing conditions. Modifications in habitat, development of microbial diseases and ARG are common detrimental side effects of Mariculture. A study in Hainan province of China observed that antibiotics concentration was higher in this system compared to sea water. Additionally, ARGs were observed in the microbes of cultured waters, fish gills and gut [40].

The ARG containing microbes were identified in pristine environments where man's influence on the environment is much lower. The genetic makeup can help us understand the mechanism of resistance and genetic diversity in Natural ecosystems. Several studies conducted in Antarctic Sea water and soils found ARG harbouring Bacteria. Recently, ARBs in the crustacean *Euphausia superba* (Antarctic krill) were documented by researchers. This crab forms a prominent part of Antarctic ecosystem as birds and animals feed on these organisms. A total of 99ARGs were identified in the bacterial population inhabiting the crab. Man started exploiting arctic resources. Therefore, there is a danger of ARGs to spill into other ecosystems [41] (Table 1, Fig. 3).

Processes/treatments that can reduce ARGs

The waste waters contain antibiotics and the selection pressure of bacteria gain ARGs and several treatment options are available [42, 43]. The anerobic digestion is process usually done by anaerobic bacteria in the anaerobic membrane bioreactors for biogas production. This process is widely utilised in waste sludge treatments that harbours ARG containing bacteria. Several beneficial bacteria belonging to Proteobacteria, Firmicutes, Chloroflexi, Bacteroidetes, Thermotogae, Euryarchaeota, Elusmicrobia, Chlorobi, Spirochaetes, Synergistetes, and Actinobacteria can be utilised for biogas production [44]. Recent research is focused on improving the process and optimising the conditions to increase methane production. Researchers have used extracellular polymeric complexes and thermal treatment of wastewater sludges to remove antibiotics associated ARG in the bacteria before Anaerobic digestion [45]. However, several pre-treatment processes such as microwave, alkaline and several additives are done before the anaerobic oxidation to enhance the reactions [46]. The anaerobic treatment of sludges and organic waste are greatly enhanced by the Extracellular electron transfer (EET) in microbes. This process is known to help in higher degradation of micropollutants. There is cyclic oxidation and reduction happening in the molecules forming an electron shuttle that can degrade pollutants including antibiotics. The natural electron shuttles such as cytochrome C, riboflavin and humus substances can aid in degradations. However, several artificial shuttles including chemicals, metals and carbon-based materials aid in degrading antibiotics and several ARG containing plasmids, mobile elements after lysing the bacterial cells. Carbon nanotubes, graphene oxide, are carbon based nanomaterials that can act as electron shuttles and reduce ARGs and HGT in anaerobic degradations [47]. Another graphene compound graphitic carbon nitride can be used for reducing micropollutants and ARG containing bacteria [48]. Biochar is produced from biological materials such as rice straw and peanut shells by the process of pyrolysis. The biochar could effectively reduce the prevalence of ARGs and HTG [49]. The possible mechanism of biochar reducing the ARG through the process of conjugation has been elucidated recently. The biochar can reduce the energy needed for the gene transfer from a donor to recipient, effect the permeability of cell membranes, expression of transfer genes and promote oxidative stress in the bacterial species, thereby reducing the HGT [50]. However, both nanoparticles and oxidative stress are double edged swords. At low concentrations they are known to promote ARG and HGT in microbes of waste waters and at different concentration of nanoparticles can also cause reduction in ARG and HGT. Nowadays, nanoparticles are widely used in the industry, and they are leached into the wastewater and could reach water bodies raising the concern to the contamination issues [51]. In addition to nanoparticles heavy metal pollutants in wastewaters such as mercury, cadmium, arsenic play a role in increasing the ARG by HGT [50-53]. The metals make the bacterial membrane leaky, increase the expression of genes that can increase conjugation and DNA replication process that helps in the formation of conjugation tube between the donor and recipient bacteria. Additionally, the metals can interfere with free radicles regulation in a bacterial cell thereby facilitating the transfer of ARG between the bacterial strains and species. Ag nanoparticles are predominantly used to reduce ARG in bacteria [54]. The toxicity of nanoparticles enabled the search for alternate technologies. Green Nanotechnology using plant, fungi and algal sources for the synthesis of nanoparticles consisting of Ag, Au, Zn, Ti are widely explored to reduce the ARGs in bacteria [55]. However, the toxicity of Nanoparticles synthesised by green synthesis are unknown presently. Therefore, additional studies and regulations are needed to utilise these particles in large scale for addressing the issue of ARGs in bacteria. These bacteria are found in landfills and the above methods can be used to reduce their occurrence [56].

The presence of heavy metals and ARGs in the microbes of 4 rivers in India and UK were investigated recently. Researchers observed a positive corelation between the heavy metal concentrations and resistance for both heavy metals and antibiotics. These were transmitted by class I integrons (mobile DNA elements harbouring resistant genes) in the bacterial systems [57]. Human activities and water treatment methods were reviewed for the presence of ARGs in the bacteria and HGT of these genes in the aquatic environments. Chlorination is usually performed in water systems used for human consumption and recreational purposes. This process seemed to remove ARGs containing bacteria. However, researchers found some bacteria with ARGs to be resistant to this treatment processes [58]. The chorine in the water acted like a environmental clue for the bacterium to evolve more efficiently to survive by modulating ARGs. There were 224 ARGs there were found in several microbes by employing the technique of metagenomics. Further 195 ARGs from *E. coli* were observed that could evade chlorination. The common methods of chlorination, UV treatment and photocatalysis of water might not eliminate ARGs from the bacteria inhabiting water ecosystems. A combination of these processes might be useful in getting rid of bacteria with ARGs [59]. The property of free chlorine/ photolysis by sunlight is suggested as viable method to reduce ARGs in bacteria from water bodies. This is usually accomplished by the generation of free radicles such as reactive chlorine species, reactive OH. species that can effectively eliminate ARGs [60]. This process can eliminate contaminants of emerging concern and pathogens too [61]. Further, the process of electrochemical treatment gained importance where electricity can be passed using chemicals that conduct electricity. This method could interfere with bacterial membrane permeability, ARGs and transfer methods of ARGs [62]. Recently, combination of low energy requiring anaerobic treatments with treatments such as Advanced oxidation processes using biochemicals and electrochemicals is proposed. Further, the treatment methods of ultra-filtration using membranes, sonication and photocatalysis are proposed for effective removal of ARGs [63]. However, research is evolving and ongoing that is focussing on best and economically viable method of removing ARGs from bacteria in aquatic environments. A major setback is presence of microplastics in the wastewater treatment plants and adequate approaches are needed to address this issue in addition to ARGs in these waters [64]. Additionally, constructed wetlands and membrane bioreactors are biological process that can aid in reducing ARGs in bacteria. However, no process is perfect in removing ARGs and further research is needed [65].

ARGS can be carried by aerosols and soils

Farm animals are important as food source and for commercial and industry purposes. They harbour bacteria containing ARGs. It is observed that aerosols from the animals could travel 10 km in the direction of wind flow. This could have implications for people working in the farms and residing close by [65-67]. A study conducted in China observed that farm workers had higher ARG containing bacteria in their sputum compared to people close by who do not work in the farms. Interestingly, ARGs presence in the bacteria were different in various samples of atmosphere indicating heterogeneity in the atmosphere around us. Higher incidence was present in atmosphere samples from animal farms and Hospitals identifying these places as hotspots for ARGs containing bacteria [68]. Adequate care can be taken by farm and healthcare workers to prevent ARGs containing bacteria from aerosols. A panel on biohazards has identified that transport of farm animals from place to place involved spread of clinically important multidrug resistant pathogens. There are lot of unmet needs and research needed to regulate the transport process to reduce ARGs in microbes. The aerosols are alarming as they not only effect humans they can affect wild animals. Recently researchers in Canada have initiated a multi country and multi cite project to understand the aerosols' role in ARGs transmission. The aerosols released from farms, agricultural practises, water bodies, soils into the air are studied at multiple cites. Additionally, particulate matter and urban smog can also contain high levels of ARGs containing microbes. Therefore, monitoring aerosols in big cities is also part of the study. The need for surveillance and as a consortium to work on various topics about air transport of ARGs is identified as topic of outmost importance. The work is in progress and results are expected soon [69].

Another matter of concern is presence of ARGs containing bacteria in soils. The soil is known to be a reservoir of these bacteria and can contain about 10^9 ARGs per gram of dry soil [70]. When the bacteria die, the cells are lysed and the DNA of a bacteria with resistant genes can be released into the surroundings and is termed as eDNA. This DNA could be taken up by neighbouring cells by the process of transformation which is one of the methods of HGT. This process is dependent on soil moisture content, concentration of eDNA, antibiotics and structure of the soil. The moist soils can aid in more HGT in the susceptible bacteria [71]. The bacterial concentration can increase due to the process of untreated sludge, aerosol dust settlements and contaminated water from industrial affluents, domestic use and hospitals into the soils. Additionally, heavy metal and organic pollutants in the soil can promote ARGs in the soil microbes [72]. Recently, the effect of climate conditions is studied on HGT. Two sites were chosen in China containing planted site and neighbouring forest site. Researchers observed that increasing temperature could greatly increase the microbial species that are harbouring ARGs. Surprisingly, climate effect was more observed in the natural forest ecosystem. They observed increase in 15 ARG genes for common antibiotics such as aminoglycoside, beta-lactam, macrolide-lincosamide-streptogramin B, multidrug, sulphonamide, and tetracycline, enrichment due to the warming treatment [73]. These findings have implications that Global warming due to anthropogenic activities in future can enable evolution of super bugs in the terrestrial ecosystems.

The ARGs containing bacteria migrated vertically into the deeper layers of the soil in addition to soil surface [74]. The organic manure aided in HTG during the cultivation of vegetables. Additionally, the diversity of bacteria and the antibiotic resistance was different in different kinds of manures used in the agricultural land. Therefore, the manure received into the agricultural soils is an additional concern now [75]. Several methods such as a erobic composting and aerobic/anaerobic treatment of manure is suggested to reduce the ARGs in the soil microbes [76]. Further, microplastics thrown into the soils are enhancing this phenomenon [77]. The microplastics have become major initiating factor in Mangroves to transmit ARGs by HGT. Therefore, use of these in delicate ecosystems should be minimised [78]. The presence of bacteria with ARGs could alter the microbial ecosystem and have deleterious effects on the soil microbial communities that can affect production of crops. The ARGs are observed in vegetables produced in the soil such as lettuces and can be transferred to humans as food. Additionally, the process of microbial degradation to ensure cycling of nutrients in the ecosystems could be affected as the superbugs can interfere with the growth of beneficial microbes that can decompose and release nutrients back into the soil and atmosphere. The effective survival of all species depends on the balancing of various nutrients and gases in the atmosphere and soil. Therefore, policies should be implemented, and awareness must be created in people about the ARGs induced health hazards and pollution of various Earth resources by anthropogenic activities. A multidisciplinary effort by researchers could find more efficient policies that regulate antibiotic resistance in future.

Conclusion

As stated by Charles Drawin: *it is not the strongest of species that will survive, or the most intelligent; it is the one most adaptable to change*. The climate change phenomena further aggravate the situation by circulating these via biogeochemical cycles in all phases of the environment causing resuspension and retransportation during floods/storm water. The lack of clear rules and quality standards that address the acceptable levels of CECs is one of the main obstacles to controlling the mobility of CECs. As a result, CECs were not typically studied in the environment, which increases their potential to harm the ecosystem. In numerous nations, the prevalence of CECs containing pesticides, pharmaceuticals, and personal care products (PPCPs), as well as endocrine-disrupting chemicals (EDCs), is of grave concern. According to research, the bioaccumulation of PPCPs in the aquatic ecosystem disturbs human hormone balance, which has a number of negative impacts, including lower fertility, breast and testosterone cancer risk, and reproductive problems. Therefore, a global cooperation among nations is needed to address the issue of CECs, uniform standards, detection methods and remediation methods to keep animal, human and environment, triad healthy.

Credit authorship contribution statement

MNVP delivered keynote on "Emerging contaminants and micropollutants in the environment - selected remediation technologies" on 21st October 2022 at the 31st annual Central European Conference ECOpole'22, organised in Krakow by the Ecological Chemistry and Engineering Society, Poland. MNVP mentored SE and contributed equally to this manuscript.

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