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REVIEW ARTICLE

AMR Mitigation: From Regulations to Alternatives

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ABSTRACT
Pharmaceutical effluents are waste produced by pharmaceutical industry during the process of drug manufacturing and is the major sources of water contamination that may lead to antimicrobial resistance (AMR). WHO has declared that AMR is one of the top 10 global public health threats facing humanity. Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens. AMR still remains a serious threat to human health leading to death and monetary loss. The prevalence of antibiotic-resistant pathogens causing diseases is raising also because of antibiotic contamination in effluents which in turn develops antimicrobial resistance bacteria (ARB) in the environment. Numerous rivers throughout the globe have reportedly been found to contain significant antibiotic contamination via pharmaceutical discharges. Nevertheless, in developed nations, these wastewaters are often processed in municipal wastewater treatment run by the pharmaceutical sector. This contaminated ARB ended up with severe antibiotic resistance in the multi-cellular organisms. According to statistical survey, the mortality of antimicrobial resistant pathogen's infections was 4.5 million and this mortality figure may lead to 10 million globally by 2050. Many intervention strategies have been developed by regulatory authorities for the control of AMR. The environmental risk approach and need to have indicators to measure environmental risk is a way forward for all countries engage in antibiotic manufacturing. Overall, efforts to address the problem are isolated and fragmented. The current review focuses on how pharmaceutical effluents contribute in the development of AMR and briefly described the regulatory framework established to control AMR spreading.
Keywords: *Antimicrobial Resistance, Pharmaceutical effluents, Pharmaceutical wastewater treatment plants, Antibiotic resistant genes, Antibiotic resistant bacteria*

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INTRODUCTION

According to a survey, almost half of the world's pharmaceutical wastewater is discharged without any necessary pre-processing and was found to be a major polluter of the environment. The disposal of untreated or improperly treated pharmaceutical effluents into aquatic sources has resulted in immediate and long-term consequences affecting animals and human health. The use of conventional treatment methods is recommended since there is a lacuna in the method for effectively removing pharmaceutical wastes [1]. The morphology of the bacteria is altered by excessive antimicrobial residues in the water environment. Antimicrobials that formerly could inhibit these microorganisms no longer have much of an impact on their transformed state. AMR is already regarded as

an impending public health problem. The mechanisms used by microorganisms to develop resistance are progressing and developing continually and unabatedly. According to WHO, AMR is one of the 10 leading worldwide public health impacts which interweave the wildlife, ecological, and human environment [2]. In India 1, 30,000 instances of multidrug resistance to tuberculosis were found in 2018. An average of 58,000 infants/year in India has been reported to die from multidrug resistance illnesses. Indiscriminate use of antibiotics in human and animal populations is the major reason for AMR development. The COVID-19 pandemic has masked the AMR problem globally and is considered a silent pandemic on earth. Based on the literature, about 4.5 million people were dying every year due to antimicrobial-resistant pathogens' infections which would increase up to 10 million fatalities annually of which 2 million were expected to occur in India which lead to the cause of death globally by 2050 [3]. Around the globe, efficient programs are being implemented for finding new antimicrobial agents. These programs primarily involve monitoring soil conditions and investigating the microbial behaviour against tested isolates of infective fungi and bacteria that became resistant to various antimicrobial drugs [4]. Antibiotic residues, Antibiotic Resistance Genes (ARGs) and ARBs binge across several domains (different industries and regional contexts) had different types of waste and are identified to be the source of AMR factors [5]. In addition to human misuse and abuse in the veterinary sector, untreated sludge from pharmaceuticals is a major contributor to the spread of AMR. Pharmaceutical hotspots serve as leading contributors to environmental degradation and endanger public health by discharging wastewater which is contaminated with antimicrobial residues. Furthermore, many industries covertly discharge their wastewater via hidden ports to reduce the expenses associated with building effluent treatment facilities. The liquid wastes enter the nearby river through open streams, where it accumulates in a concentration of ng/L to mg/L concentrations. These substances have the propensity to biomagnify even at low concentrations and have detrimental impacts on living organisms Fig. 1 [6]. According to the latest research, drug manufacturers in China and India frequently discharge untreated wastewater containing pharmaceutical ingredients into the nearby land and rivers [7]. In India, Hyderabad is home to a significant pharmaceutical sector. Antibiotics were manufactured in every village and were discovered more than ten years ago that the wastewater from pharmaceutical companies discharged into the water contains incredibly high quantities of antibiotic [8]. Antibiotic levels have been exceeded up to mg/L level from industrial areas when compared to the human plasma of samples collected from various locations [9]. The research work carried out from Krishna, Godavari basin, Bay of Bengal has exposed the high incidence of bacteria resistant to antibiotics resulting in public health risks [10]. Industrial effluents from antibiotic manufacturing sites have raised concerns in recent years, and have been identified as a risk factor for encouraging AMR development and spreading. According to research antibiotic manufacturing sites stick out as hotspots retaining ARGs through ARB. Investigation reveals that the industrial effluent caused the Sava River (Europe) sediments to become contaminated with macrolides, particularly azithromycin (AZI) along with heavy metals and micronutrients. AZI was found at the highest concentrations (23 mg/kg) at the disposal site, dropping dramatically to 1 mg/kg at the site 700 m downstream. Erythromycin had sediment levels that were substantially lower than those of AZI, with the disposal site having the greatest levels (1 mg/kg) resulting in a variation of erythromycin biological degradation than that of AZI [11]. The wastewater exiting from pharmaceutical wastewater treatment plant (PWWTP) are a significant source of ARBs and related ARGs in conjunction with antibiotics. The latest evidence from PWWTP revealed that there were approximately 10^8 colony-forming units (CFU) (100 mL)-1 of AZI-resistant bacteria in the AZI manufacturing site and approximately 10^4 CFU (100 mL)-1 from the ß-lactam and quinolone manufacturing unit [12]. Furthermore, according to research on the measurement of ARGs in PWWTPs, 1012–1014, ARG copies might be released daily [13]. An increase in ARG may potentially spread the pathogenesis of bacteria by horizontal gene transfer (HGT) [14]. Various infectious agents exhibit a level of resistance that allows them to withstand to applied the ionizing. For instance, a wide variety of viruses unaffected by γ-radiation, even when it has been administered at high monotherapy (3900=5300 Gy) [15].

The current review focuses on the role of the pharmaceutical industry in spreading AMR and the legal framework for mitigating AMR.

ARB in Effluents

In the production of antibiotics, wastewater often results from the preparation or formulation of medications. Drug production is often a very chemically intensive technique that gives large amounts of effluent with harmful chemicals. Pharmaceutical effluents are frequently emitted in several underdeveloped nations without being treated via numerous pathways Fig.2 [16] Due to their massive daily emission, effluents are introducing ARGs and ARB into the atmosphere. Considering the environmental harm these effluents pose to recipient waterways. Various antibiotics concentration detected in different water samples is presented in (Table 1) [17, 18, 19, 20, 21]. According to reports,

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disinfection had no effect on reducing ARGs and ARB and in certain instances might have even caused the emergence of AMR [22]. Notably, ARGs are much more resistant to disinfection than ARBs [23].

Transmission of ARGs

In a microbial community, the probability of mobility and accumulation of new ARG has correlated with the intensity of the evolutionary pressure that those bacteria are under [24]. In Northern China, for each bacterium which reached a Waste Water Treatment Plant (WWTP), around 4-5 ARB were discharged into the water system. Additionally, areas with large densities of faecal bacteria increase the possibility of ARGs being transferred to pathogens [25]. When all of these factors are taken into account, it could be contended that WWTPs, pharma effluent disposal sites, and surface water sources near strenuous crop and livestock production represent good places to start when seeking to determine the potential dangers for the development of resistance. The possibilities for ARB transfer to animals or people, such as in recreational pool areas, through drinkable water, and in crop fields for environmental evolution to affect both humans and animals [26]. The contamination of areas around industries has not decreased despite years of advocacy work by regional NGOs and legal action before the highest courts [27].

Role of PWWTP in AMR

Pharmaceutical wastewater has a complicated composition, including a high concentration of organic matter, microbial toxicity, high salt content, and difficulty biodegrading. Advanced oxidation, aerobic/anaerobic treatment methods, and physicochemical techniques are among the common methods used to treat such effluents [28]. Nevertheless, in developed nations, this wastewater is often processed in municipal wastewater treatment run by the pharmaceutical sector (PWWTP) [29]. Therefore, the tertiary treatment processes are required to be given more consideration because they have the potential to eradicate ARGs. Tertiary treatment methods such as ozonation, activated carbon adsorption, coagulation, and nanofiltration/reverse osmosis (NF/RO) are highly successful at removing antibiotics and ARGs [30]. Removing these harmful substances makes the treated water safe to reuse, recycle, or release into the environment.

Removal Methods

According to research, the concentration of pharmaceutical levels in untreated effluents is normally >0.1 g/l, whereas >0.05 g/l in treated wastewater [31]. Techniques including oxidation, ultraviolet degradation, reverse osmosis, and nanofiltration Fig.3 [32] are used to eliminate these pharmaceuticals from waterways [33]. Cutting-edge techniques for wastewater treatment are required when drugs are detected, which is limited due to high prices, poor reusability, and disposal problems. When compared to standard medicine, WWTPs that incorporate natural and built wetlands with regular treatment systems offer a significantly more effective way of eliminating evolving organic pollutants and limiting ARB and ARGs [34]. The removal effectiveness of ARGs varies between units, and there is a tendency for secondary or tertiary processing methods to perform better than primary processes. Following primary treatment, a slight decrease between 0.09 and 0.55 orders of magnitude can be found. On the other hand, secondary treatment methods show a significant decrease of 1-2 logs (i.e. one to two orders of magnitude) in ARGs. It is known that the activated sludge process could not increase or decrease the ARG's proportions. Therefore, appropriate tertiary procedures are required for higher clearance of ARGs because of the insufficient decrease of ARGs (usually 1-2 logs) through secondary processes and possible danger by re-introducing ARGs and gene transfer [32]. It is required to integrate several treatment processes since it has been demonstrated that individualized treatment procedures are inadequate for eliminating ARB of pharmaceutical effluents, including antimicrobials.

Importance of Zero liquid discharge

Zero liquid discharge (ZLD) system, in which no effluent is discharged into the waterbodies from Pharma Company, eliminates environmental degradation [35]. Unfortunately, the primary obstacles to the widespread adoption of this method at the moment are large capital requirements and excessive energy usage. Future developments in membrane technologies could render the ZLD more reasonably priced and environmentally friendly.

Remediation Measures

Bacteriophage

The current resurgence of interest in using phages, depending on their intriguing properties, was influenced by the unregulated expanding spread of AMR. Phage treatment differs from wide-range antibiotics in that it has a more focused mode of action as only a few varieties of bacteria may be affected by phages, without any detrimental consequences on the microflora that maintains the host's health. As viruses proliferate by themselves in prokaryotic organisms, another benefit of phage therapy is that it only needs to be administered once or twice over a relatively long period. As a result, the density of phages at the infection site can be increased [36].

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Prebiotics

Prebiotics are specific food substances that the microbes in the human gut preferentially ferment to form metabolic by-products including acetate, butyrate, short-chain fatty acids (SCFAs), and propionate. By providing energy for enterocytes, enhancing epithelial junctions, promoting the formation of mucus, and enhancing regulatory T-cell activities to reduce inflammation, these by-products, especially SCFAs, promote mucosal barrier capabilities in the gut. Prebiotics, therefore, encourage the development of gut commensal bacteria and the decrease of pathogenic species [37].

Probiotics

In terms of exploring how to alter the microbiome, probiotics have received more research to date than prebiotics. Probiotics create specific antimicrobial compounds, like bacteriocins, which can eliminate infections and stop the growth of biofilms. Furthermore, by inhibiting colonization or growth through competition, these microbes play a significant part in enhancing host defence against infections. They may also treat infectious disorders in animals, which relieves the demand for antibiotic usage [38].

Vaccines

With fewer illnesses, there will be less need for antibiotics, which will lessen the pressure on organisms to develop resistance. Vaccines accomplish this precise goal; they are often given as a preventative measure to combat microbial diseases in both people and animals. While vaccinations also provide selection pressure to microbes, the likelihood of vaccine resistance developing is lower than that of antibiotic resistance [39].

Antimicrobial peptides

The term "anti-microbial peptides" (AMPs), also known as "cationic host defence peptides," refers to a group of smaller proteins that are incredibly varied and contain a variety of amino acids. Apart from their capacity to function as immune modulators, these AMPs were discovered to exhibit several biological properties, including anticancer, anti-inflammatory, antimicrobial, and antimitogenic functions. Since AMPs are efficient against MDR microorganisms, they might be used to treat AMR [40].

Regulatory Framework

The global action plan (GAP) against AMR was established by the WHO in 2015. (WHO, 2015). The GAP raised awareness about AMR, enhancing information and skills via monitoring, lowering infection rates, and the use of antibiotics in human health, animal welfare, and agriculture, and encouraging initiatives in AMR. The Antibiotic Manufacturing Framework, developed by the AMR Industry Alliance, is among the primary pledges taken by pharma enterprises. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), which hosts the AMR Industry Alliance, draws up pharma firms with generics, diagnostics, and biotech firms to cooperate on AMR with the Industry Declaration on AMR from the World Economic Forum in 2016 and a planning process approved by many pharmaceutical firms at the UN High-Level Meeting on AMR. [41, 42].

India demonstrated its ability to battle against AMR by creating the National Action Plan on Antimicrobial Resistance (NAP-AMR) in 2017 [43]. The WHO pushed member nations to build their own context-specific national action plans (NAPs), and as of July 2021, 145 countries have developed NAPs on Antimicrobial Resistance (AMR), with another 41 in the process of developing. However, over five years after these NAP were initiated, the conducted Systematic review revealed the greatest development was made in focusing on One Health arrangements and planning NAP, but the least progress was made in infection prevention and control in human health and optimising antibiotic usage in the animal. Given the fact that different countries were at various phases of implementation when COVID-19 hit, it is understandable why these initiatives lost importance.

The process of ZLD has recently been incorporated in India by a small number of pharma industries with members of the AMR Industry Alliance, including NGB Laboratories, Centrient Pharmaceuticals, GlaxoSmithKline, and Aurobindo Pharma.

To preserve environmental receptors and minimize the development of AMR, a practice procedure was created for publishing predicted no-effect concentrations (PNECs), which represent targets for risk analysis of the effluent from antimicrobials production [44]. The levels at which harmful environmental impacts are not anticipated to happen were first released in 2018 and it contains 121 antibiotics (see Table 2) but it does not include all antibiotics.

India has created a preliminary set of regulatory requirements for healthcare companies. The Central Pollution Control Board (CPCB), the scientific department of the Ministry of Environment, Forestry and Climate Change, has developed criteria for Publish Predicted non-effect concentrations ($PNEC_s$) readings for antimicrobial residues in pharma effluents (Ministry of Environment, Forest & Climate Change (2020). The limitations of effluents emitted by pharma industries are specified in the proposed guidelines published in January 2020, although the suggestion has not yet been declared as a law [45].

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Responsible Antibiotic Manufacturer's Platform (RAMP), is a worldwide forum that brings together ethical buyers, authorities, and businesses to jointly develop the business rationale for antibiotics made sustainably. The effort has started pilot initiatives and intends to standardize sustainable production throughout the whole antimicrobial sector [46].

In China, despite the absence of guidelines for the number of antimicrobial compounds in wastewater discharges, the government supports the country's healthcare companies and advocates for zero pharmaceutical release into the water bodies.

Current status of AMR regulation

Even though there have been key legislative attempts to reduce antibiotic overuse since 2017, such as a restriction on some combination drugs, on the use of colistin as a poultry growth promoter, and the establishment of antibiotic residue guidelines for pharma wastewaters, monitoring and enforcement of initiatives have been difficult. Antibiotic contamination calls for a coordinated strategy supported by a strong regulatory system. To that purpose, the environmental agency published a draft notice that set limitations for the levels of antibiotics in pharma effluent, but it is still in the process of being formalized. According to this proposal, legal proceedings would be initiated against the delinquent pharmaceutical unit if the quantities of antibiotics in the wastewater were discovered to be higher than permitted.

The decision to remove the limitations was taken over seven months after the draft guidelines were published in an official document even though the threat of AMR was publicly emphasized by researchers in India. It was mentioned that all wastewater will be labelled as "hazardous waste". Additionally, the CPCB has been instructed to recommend a surveillance system for antimicrobial residues for all domestic pharmaceutical companies that release pharmaceutical effluents directly or indirectly into the surroundings, until the regulations are finalized.

In the fight against AMR, the world has achieved considerable progress following almost 40 years of management. Of the 40 nations that submitted statistics, 12 reported reduced levels of use of antibiotics for human usage in 2020, as against 2010, with the majority of them being HICs [47]. Presently, authorities in the USA, as well as the European Union (E.U.), do not require industries to use environmental precautions while making their pharmaceuticals; instead, they mark a primary emphasis on pharmacovigilance through the GMP. There are reportedly no enforceable national or global environmental laws or regulations that would require pharmaceutical businesses to handle and get rid of their effluents in an ecologically acceptable manner. Furthermore, neither the EU nor the USA has any mandatory GMP guidelines for pharmaceutically active components. Nevertheless, several nations are actively participating and developing standards for the handling of pharmaceutical wastewater concerning antimicrobial compounds. Sweden had adopted enhanced implementation of infection prevention and control in human and animal healthcare which aims to reduce the spread of resistance and the need for antibiotic treatment. All animal health clinics in Sweden are required to implement an infection prevention and control (IPC) programme, according to legislation that went into effect in 2014 [48]. To improve the technical handling of medicines in the discharge of municipality WWTPs, the Swedish Environmental Protection Agency (SWEPA) distributes state-funded investment incentives. From 2000 to 2019, one-third of Asian research found that over 50% of antibacterial chemicals were resistant to use in aquaculture [49]. Over the past ten years, China has also gained some ground in limiting AMR. In the surveillance health facilities, the frequency of antibiotic prescription dropped significantly from 19.4% in 2010 to 7.7% in 2017, and from 67.3% to 36.8% for hospitalized patients. Similarly, the identification of the problematic resistant bacteria, including the prevalence of MRSA, cephalosporin-resistant E. coli and carbapenem-resistant *K*. pneumoniae, has decreased.

Table 1 – Concentrations of antibiotics detected in different water samples

Antibiotic	Concentration	Sample	References
Amoxicillin	1500ng/L	Raw water	[17]
Azithromycin	1577.3 ng/L	WWTPs effluent	[18]
Ciprofloxacin	28 X 10^6 –31 X 10^6 ng/l	Pharma Effluent	[19]
Erythromycin-H2O	1700 ng/L	Surface water	[20]
Norfloxacin	39 X 10^4 –42 X 10^4 ng/L	Pharma Effluent	[19]
Ofloxacin	15 X 10^4 –16 X 10^4 ng/L	Pharma Effluent	[19]
Tetracyclin	32.0±6.0 mg L−1	PWWTPS effluent	[21]
	5,481.1± 123.0 mg kg−1	Dewatered sludge	

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Table 2- List of antibiotics with respective allowable limits	
Antibiotic	**Limiting value for concentration (µg/l)**
"Amikacin	6.40
Amoxicillin	0.10
Amphotericin B	0.01
Ampicillin	0.10
Anidulafungin	0.01
Avilamycin	3.20
Azithromycin	0.01
Aztreonam	0.20
Bacitracin	3.20
Bedaquiline	0.03
Benzylpenicillin	0.10
Capreomycin	0.80
Cefaclor	0.20
Cefadroxil	0.80
Cefalonium	8.40
Cefaloridine	1.60
Cefalothin	0.80
Cefazolin	0.40
Cefdinir	0.10
Cefepime	0.20
Cefixime	0.02
Cefoperazone	0.20
Cefotaxime	0.04
Cefoxitin	3.20
Cefpirome	0.02
Cefpodoxime	0.10
Cefquinome	0.64
Ceftaroline	0.02
Ceflazidime	0.20
Ceftibuten	0.10
Ceftiofur	0.02
Ceftobiprole	0.09
Ceftolozane	0.76
Ceftriaxone	0.01
Cefuroxime	0.20
Cephalexin	0.03
Chloramphenicol	3.20
Ciprofloxacin	0.02
Clarithromycin	0.03
Clavulanic Acid	22.40
Clinafloxacin	0.20
Clindamycin	0.04
Cloxacillin	0.05
Colistin	0.80
Daptomycin	0.40
Delamanid	0.02
Doripenem	0.04
Doxycycline	0.80
Enramycin	1.92
Enrofloxacin	0.02
Ertapenem	0.05
Erythromycin	0.20
Ethambutol	0.80
Faropenem	0.01
Fidaxomicin	0.01
Florfenicol	0.80
Fluconazole	0.10
Flumequine	0.10
Fosfomycin	0.80
Fusidic acid	0.20
Gatifloxacin	0.05
Gemifloxacin	0.02
Gentamicin	0.08
Imipenem	0.05
Isoniazid	0.05
Itraconazole	0.004
Kanamycin	0.44
Levofloxacin	0.10
Lincomycin	0.72
Linezolid	2.68

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Loracarbef	0.80
Mecillinam	0.40
Meropenem	0.02
Metronidazole	0.05
Minocycline	0.40
Moxifloxacin	0.05
Mupirocin	0.10
Nalidixic acid	6.40
Narasin	0.20
Neomycin	0.01
Netilmicin	0.20
Nitrofurantoin	25.60
Norflaxacin	0.20
Ofloxacin	0.20
Oxacillin	0.40
Oxytetracycline	0.20
Pefloxacin	3.20
Phenoxymethylpenicillin	0.02
Piperacillin	0.20
Polymixin	0.80
Retapamulin	0.02
Rifampicin	0.02
Roxithromycin	0.40
Secnidazole	0.40
Sparfloxacin	0.02
Spectinomycin	12.80
Spiramycin	0.20
Streptomycin	6.40
Sulbactam	6.40
Sulfadiazine	288.00
Sulfadimethoxine	20.00
Sulfadoxine	0.24
Sulfamethoxazole	0.24
Tazobactam	17.60
Tedizolid	3.92
Teicoplanin	0.20
Telithromycin	0.02
Tetracycline	0.40
Thiamphenicol	0.40
Tiamulin	0.40
Ticarcillin	3.20
Tigecycline	0.40
Tildipirosin	0.17
Tilmicosin	0.40
Tobramycin	0.40
Trimethoprim	0.20
Trovafloxacin	0.01
Tylosin	0.33
Vancomycin	3.20
Viomycin	0.80
Virginiamycin	0.80”

Recommendations and Future Prospects

Antibiotic overuse must be prevented in the healthcare environment, and the pharmaceutical industry and hospital effluent must be cleaned to remove antibiotic residue. AMR presents complicated and numerous issues, yet they are not insurmountable. Established recommendations can assist to save millions of lives, conserve antimicrobials for future generations, and protect the world from drug-resistant infections. To limit the environmental propagation of AMR, better infection prevention measures and integrated investigations are required. A strategy for tackling this problem must be built progressively. The installation of constant monitoring of emissions from production sites globally and the setting of the discharge limits for certain antibiotics to demonstrate that effluents are maintained within acceptable limits. The pharmaceutical sector should create innovative approaches to reduce drug levels in effluent content whilst providing enough biologically active doses to the patient to adhere to the notion of prophylactic protection. According to the composition of the influent, PWWTPs should also be modernized with the appropriate technology to effectively decrease antibiotics, ARB, ARG_s and other dangerous chemicals from the effluent. Because the use of drugs cannot be controlled, additional strategies to lessen their effect on the water habitat must be developed. Regulations promise good for the sustainability of the pharmaceutical industry of mankind as a whole. It is advised that monitoring for widely used drugs be

carried out before considering any regulatory changes. Governmental intervention requires a holistic strategy including all facets of society, including hospitals, businesses, non-governmental organizations, pharmaceutical corporations, and the general public in the control of AMR. We may be astonished by how quickly our world would change for the better when the manufacturers and users of antibiotics work together to combat AMR.

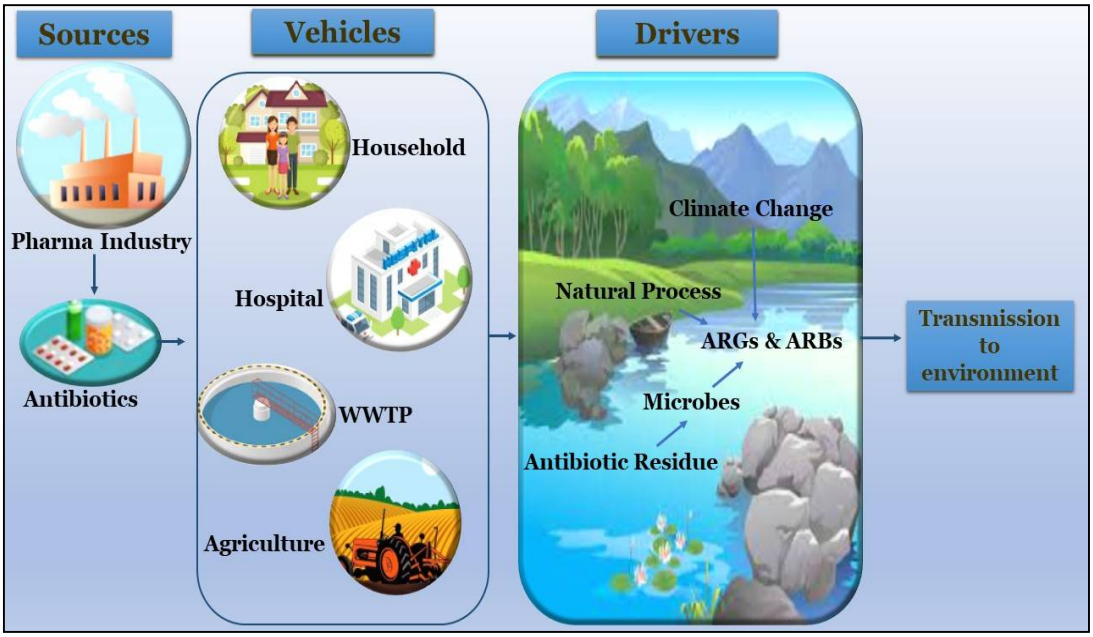

Fig. 1 - Role of Pharmaceutical companies in increasing AMR
(Page.no-3) [6]

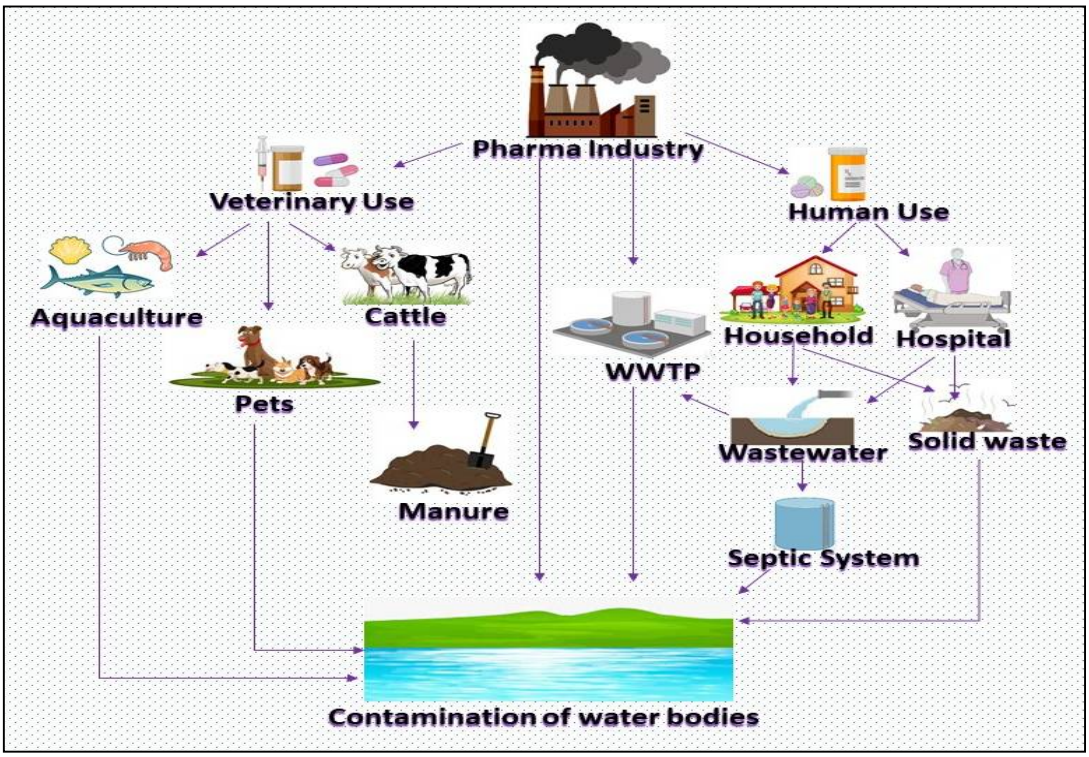

Fig. 2 – Direct/Indirect contamination of water bodies by Pharma industries
(Page.no-3) [16]

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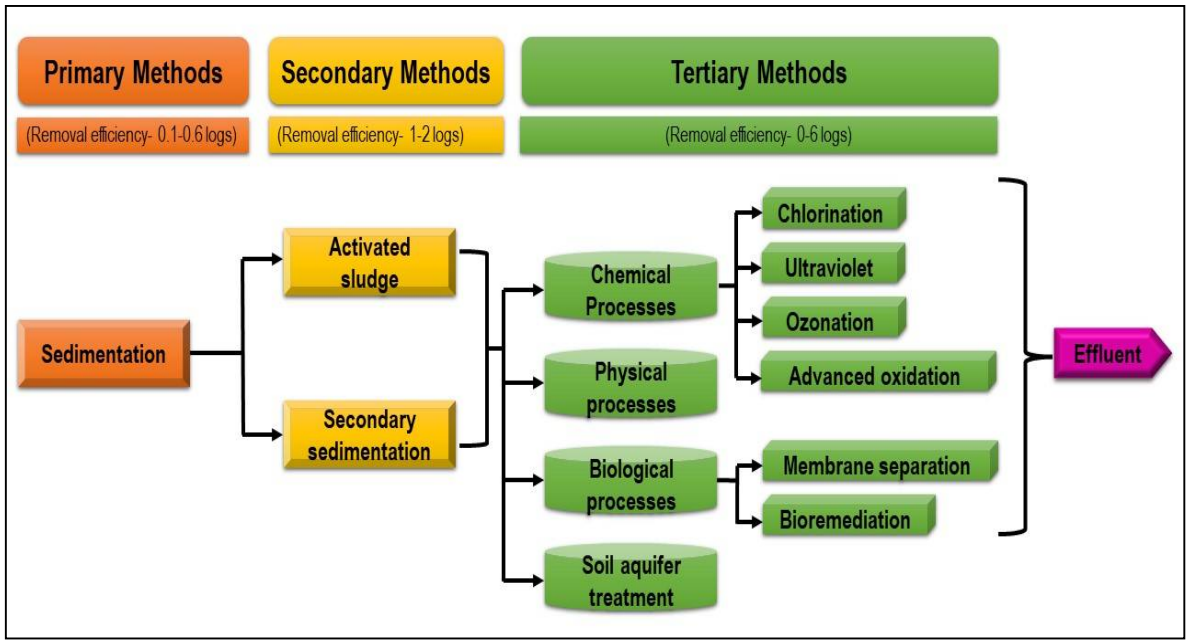

Fig. 3 –Techniques for Removal of ARGs (Pag.no-3) [32]

Table 3 – Different Sources of Antimicrobial Resistance (AMR)

Sources of AMR	Mode of Contamination	References
Wastewater and effluent from the pharma industries	• Significant antimicrobial levels in untreated wastewater • Remnant antimicrobials in solid wastes released from drug formulation processes and • Resistant microorganisms in effluent if bioremediation is used	Zhang et al., 2020
Wastewater and effluent from medical centers	• Solid hospital effluents contain antimicrobial substances and by products. • Antibiotics, ARGs and ARBs in hospital effluents	Taneja et al., 2019
Excrement and antibiotic use in agriculture	• Antimicrobial used in the manufacture of food, feed, and ingredients; weedkillers; insecticides; toxic metals; • Purposefully applying raw dung and sewage to crops that may include pharmaceutical compounds, ARGs, and ARBs • Improper disposal of leftover antibiotics (e.g. fungicides)	Checcucci et al., 2020
Inadequate sewage, waste discharge, and hygiene	• Open defecation, inadequately confined pit latrines, sewage treatment, and drains that pollute waterways and propagate AMR • Seeping from exposed trash piles • Runoff from cities • Discharges from outdated drugs dumped in toilets, trash cans, or landfills • Biosolids from effluent and faeces	Bürgmann et al., 2018

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Table 4 – Antibiotics detected in different rivers Around the world

Country (River)	Most abundant antibiotics	Concentration detected	Water sample	References
India (Yamuna River)	Ampicillin	104.2 ± 98.11 μg l^{-1}	WWTP influent	Mutiyar et al., 2014
		12.68 ± 8.38 μg l^{-1}	WTP effluent	
India (Sirsa and Sutlej rivers)	Ciprofloxacin	296 μg/l		Singh et al., 2022).
China (Yangtze River)	Fluoroquinolones	-	WWTP	Shi et al., 2020
China (Wangyang River)	Oxytetracycline	1.6 × 10^5 ng g^{-1}	Sediment Sample	Jiang et al., 2014
	Tetracycline,	1.7 × 10^4 ng g^{-1}		
	Roxithromycin	2.5 × 10^3 ng g^{-1}		
	Ciprofloxacin	2.1 × 10^3 ng g^{-1}		
South Africa (Msunduzi River)	Nalidixic acid	25.2–29.9 μg/L	WWTP influent	Agunbiade et al., 2016
	Ciprofloxacin	27.1 ± 1.21 μg /L_		
	Ampicillin	6.57 ± 0.62 μg /L_		
South Africa (Umgeni River)	Nalidixic acid	31±3 μg/L.	WWTP sample	Agunbiade et al., 2014
Vietnam	Sulfamethoxazole	252 μg/L	PWWTP sample	Thai et al., 2018
Tunisia	Gentamicin	19 ng mL^{-1}	PWWTP effluents	Tahrani et al., 2016
Iran (Firozabad Ditch)	Ciprofloxacin	656.8 ng/L	WWTP Effluent	Mirzaei et al., 2018
Iran (Kan River)	Cephalexin	184.4 ng/L	Drinking water sample	
Kenya (Nairobi River Basin)	Sulfamethoxazole	13,800 ng/L	WWTP Effluent	Ngumba et al., 2016
Bangladesh (Brahmaputra River)	Metronidazole	0.05 to 13.51 ng L^{-1}	Surface water	Hossain et al., 2018
Malaysia (Gombak River)	Ciprofloxacin	299.88 ng/L	Surface water	Praveena et al., 2018
France (Arc River)	Carbamazepine and clarithromycin	-	Surface water	Feitosa-Felizzola
Peru	Clarithromycin, trimethoprim, ciprofloxacin, sulfamethoxazole and azithromycin	1.86 to 4.47 μg/L	municipal wastewater treatment plants	Nieto-Juárez et al., 2021
Germany	Clarithromycin	up to 0.60 μg/L	Sewage treatment plants	Voigt et al., 2020
Italy	Chlortetracycline and amoxicillin.	up to 897 ng/L	WWTP	Spataro et al., 2019

CONCLUSION

AMR microbes, ARGs and transposable genetic components are now ubiquitous in the environment and get transferred through recreational pool areas, water and crop fields to living beings. Due to their massive daily emission, pharmaceutical effluents are a possible entry point for introducing ARGs and ARB into the atmosphere (waterways). Unfortunately, there is a lack of a specific method for effectively removing pharmaceuticals transmitted through waterways. Numerous initiatives were aimed by environmental authorities at controlling the threats that AMR poses to the ecosystem as well as human health. Harmonized initiatives instigated through the collaboration of regulatory experts and researchers from many industries or areas of study, including conservation biology, veterinary science, pharmaceutics, biomedical engineering, and many others, must be carried out. To combat AMR, politicians, regulators, manufacturers, researchers, civil society, and the community must work together on a worldwide scale and execute a multi-sectoral and multi-dimensional "One Health" plan.

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Conflict of Interest
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Ethical approval
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