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Review Article

Pharmaceutical effluent evokes superbugs in the environment: A call to action

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ABSTRACT

Antimicrobial resistance (AMR) is a growing global threat, especially in low- and middle-income countries (LMICs), causing prolonged illnesses, heightened antimicrobial use, increased healthcare expenses, and avoidable deaths. If not tackled, AMR could force 24 million people into severe poverty by 2030 and hinder progress on Sustainable Development Goals (SDGs). AMR spreads through interconnected ecosystems, with humans, animals, and the environment serving as reservoirs. Pharmaceutical wastewater, loaded with antibiotics and resistance genes, poses a significant environmental risk, mainly due to inadequate treatment and irresponsible disposal. The pharmaceutical industry is a notable contributor to environmental antibiotic pollution, with varying effluent management practices. Contaminated pharmaceutical wastewater discharge harms water sources and ecosystems. Urgent collaborative efforts are needed across policymakers, regulators, manufacturers, researchers, civil society, and communities, adopting a One Health approach to curb AMR's spread. Developing global standards for pharmaceutical effluent antibiotic residues, effective treatment methods, and improved diagnostics are vital in addressing AMR's environmental impact while safeguarding public health and the environment. National action plans should encompass comprehensive strategies to combat AMR. Preserving antibiotic efficacy and ensuring sustainable production require a united front from all stakeholders.

1. Introduction

Antimicrobial resistance (AMR) is a growing global health issue that poses social, environmental, and financial risks to businesses and society. AMR occurs when microorganisms such as bacteria, viruses, protozoa, and fungi develop resistance to antimicrobial substances, rendering them ineffective. The misuse and overuse of antibiotics in human health, food-animal production, and agriculture, as well as poor waste management in households, farms, factories, and human and veterinary healthcare settings, are major contributors to AMR [1,2].

The rise of 'hospital superbugs' such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococcus (VRE) in developed countries and the use of antibiotics to prevent tropical diseases in the developing world are alarming. Growing AMR is linked to the discharge of drugs and specific chemicals into the environment, and it is one of the most concerning health threats today [1]. The European Commission (EC) has grossly underestimated the scope of the problem, and AMR could have killed 400,000 citizens of the European Union (EU) since 2001, based on the EC's own very conservative estimates [3].

The long-term consequences of antibiotic contamination in surface water can be significant and far-reaching. It can have harmful effects on human health. Antibiotics in the environment can be enriched in humans through the food chain, and they can be very harmful to young children and pregnant women. Exposure to antibiotics can also increase the risk of developing antibiotic-resistant infections. Antibiotic contamination in surface water can increase the development of superbugs [4]. Superbugs are bacteria that have become resistant to multiple antibiotics, making them difficult to treat. Antibiotic contamination in surface water can have damaging effects on the environment. Antibiotics can accumulate in aquatic environments and affect aquatic life, including fish and other aquatic organisms[5]. Antibiotic contamination can also disrupt the balance of the ecosystem and affect the quality of the water [4,5].

The consequences of continued AMR development and spread could be catastrophic[2]. The environment plays a key role in AMR, and the World Health Organization (WHO) believes we may be entering a post-antibiotic era in which treating previously simple bacterial infections will be impossible. Bacterial AMR was responsible for 1.27 million deaths in 2019, and the total global death toll from antibiotic-resistant infections is expected to reach 10 million per year by 2050, overtaking heart disease as the leading cause of death, with economic losses exceeding US$100 trillion [5–8]. The economic ramifications of AMR on a global scale are substantial, with projections indicating that

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it could lead to approximately 24 million individuals falling into severe poverty by the year 2030. This situation poses a threat to the achievement of several Sustainable Development Goals (SDGs), namely 2, 3, 6, 9, 12, and 17, if swift and decisive action is not taken [6].

This narrative review intends to investigate how pharmaceutical waste contributes to AMR in the environment. Unlike the previous research that discussed mainly the environmental consequences of AMR from risk and technology perspectives, the primary focus here is on preventing the negative environmental effects caused by these pharmaceuticals from both technical and policy perspectives with in-depth scope on policy. The review examines the presence of antibiotics and genes responsible for antibiotic resistance within pharmaceutical waste, which are significant sources of environmental pollution and AMR proliferation. Additionally, it underscores the pharmaceutical industry's role in harboring antibiotics and antibiotic resistance genes in the environment and underscores the diverse practices for treating and disposing of pharmaceutical waste. The review concludes by advocating for innovative collaborative endeavors to embrace a One Health approach, aiming to restrict the dissemination of AMR. It also opens the door for further research into novel areas of understanding the factors driving and impeding the environmental development and transmission of antibiotic resistance.

2. Methods

This narrative review is based on a comprehensive search of relevant literature on the environmental impact of pharmaceutical effluent associated with AMR in the environment. The search was conducted using various databases, including PubMed, Google Scholar, Scopus, and Web of Science. The search terms used were “pharmaceutical effluent”, “antimicrobial resistance”, “environmental impact” and “one health”. The search was limited to articles published in English between 2010 and 2023.

3. Findings

The search results revealed that pharmaceutical effluent is one of the sources contributing to AMR in the environment [6,7]. The improper disposal of unused pharmaceuticals and excretion are the two main ways by which pharmaceuticals enter the environment. The concentrations of drugs found in the environment are under therapeutic levels [8]. Nevertheless, the existence of antibiotic remnants within pharmaceutical waste could potentially act as a pathway for these medications to enter the ecosystem [6,7]. Disparities in approaches to managing and discarding effluent were observed, with larger multinational corporations employing advanced methods, while smaller and medium-sized pharmaceutical firms maintained effluent treatment facilities in compliance with regulations, yet frequently not fully exploited [7].

Releasing untreated and polluted pharmaceutical wastewater directly into water sources and rivers has a cumulative effect on the environment over various timeframes [9]. The dispersion and elimination of antibiotic resistance genes within wastewater treatment facilities (WWTPs) constitute a multifaceted process, contingent upon both the WWTP's nature and the specific antibiotic resistance genes found in the wastewater [10–13]. The contribution of pharmaceutical firms to antimicrobial resistance (AMR) is notable, as they function as a repository for antibiotics and antibiotic resistance genes in the environment, aligned with the principles of the one health approach [6,14].

Antibiotic contamination in surface water can affect the development of antibiotic resistance in bacteria compared to other sources of antibiotic exposure. Surface water serves as a common source of exposure to antibiotics for both aquatic organisms and terrestrial organisms that rely on surface water for drinking or irrigation. This increased exposure can contribute to the selection and proliferation of antibiotic-resistant bacteria [15]. Antibiotics in surface water can be transported over long distances, leading to the widespread dissemination of antibiotic-resistant bacteria and resistance genes. This dissemination can occur through water flow, runoff, and the movement of aquatic organisms [16]. Antibiotics in surface water can persist in the environment for extended periods, providing continuous selective pressure for the development and maintenance of antibiotic resistance in bacteria [17]. Biofilms, which are commonly found in water distribution systems, can promote the development and persistence of antibiotic-resistant bacteria. Biofilms provide a protective environment for bacteria, allowing them to exchange resistance genes and develop resistance mechanisms [16].

Rivers play an important role in the spread and evolution of resistance, acting as a major reservoir of AMR [18]. The presence of AMR germs and genes in rivers is a significant concern, as it can lead to the transmission of antibiotic-resistance genes from environmental bacteria to clinically important pathogens [19]. The co-occurrence of antibiotic resistance genes (ARGs) and mobile genetic elements (MGEs) in rivers contributes to the spread of AMR [20]. ARGs encode resistance mechanisms that allow bacteria to survive exposure to antibiotics. ARGs have been found in various bacteria present in river ecosystems [19]. Some commonly detected ARGs in rivers include blaTEM-Confers resistance to beta-lactam antibiotics such as penicillin; ermB-Confers resistance to macrolide antibiotics; tetA-Confers resistance to tetracycline antibiotics; and sul1-Confers resistance to sulfonamide antibiotics. MGEs facilitate the transfer of ARGs between different bacteria, including clinically important pathogens. MGEs, such as plasmids, transposons, and integrons, have been identified in river environments [20,21]. They play a crucial role in the spread of AMR by facilitating the horizontal transfer of resistance genes.

The prevalence of AMR genes in different types of rivers varies depending on factors such as land use, sources of contamination, and types of antibiotics used in the surrounding areas. A research investigation identified a robust connection between indicators of fecal matter and genes associated with AMR within river ecosystems. This suggests that fecal contamination could potentially play a role in contributing to the presence of AMR within the environment [22]. Another study highlighted the emergence of AMR as one of the most pressing global health issues, with rivers playing a significant role in the spread and evolution of resistance. The study emphasized the need for comprehensive research programs to investigate the occurrence, extent, and major drivers of AMR in urban rivers globally [20]. The European Centre for Environment and Human Health identified rivers as a major reservoir of AMR and emphasized the need to understand the role of rivers in the spread and evolution of resistance [18]. A review article discussed the presence of antibiotics and ARGs in water bodies, including rivers, and highlighted the severity of the AMR problem in these environments. The review also emphasized the need for active monitoring of antimicrobial residues in the environment and control of disposal into the environment to reduce the rate of AMR emergence/development [21]. An additional review paper examined the antibiotics and linked ARGs that have been most frequently identified and quantified in river systems. The research underscored the existence of multiple antibiotics and their corresponding ARGs within river ecosystems, underscoring the potential for significant concern. An analysis of databases revealed the identification of more than 20,000 potential resistance genes encompassing around 400 distinct variations, predicted within established bacterial genomes present in rivers [19].

According to studies, the most common antibiotics found in water sources include Sulfamethoxazole-a one of the most studied antibiotics and has been detected in 96% of the analyzed samples; Trimethoprim-a frequently detected in water sources and is often found alongside sulfamethoxazole; Ciprofloxacin-a another commonly detected antibiotic in water sources [23]. Various other antibiotics have been detected in water sources, including but not limited to tetracyclines, macrolides, fluoroquinolones, and beta-lactams [4,5,24,25]. Regarding the effectiveness of different remediation systems in removing antibiotics from water sources, the research suggests that current technology is not enough to completely remove the amount of antibiotics in wastewater. Nonetheless, various methods have been created to tackle the issue of antibiotic pollution, encompassing approaches like physical adsorption, chemical oxidation, photodegradation, and biodegradation [24]. The efficiency of these techniques may vary depending on the specific antibiotic and the treatment conditions. WWTPs are unable to completely remove AMR genes and ARBs from water, allowing for their buildup in large water bodies [21].

Several studies have investigated the effectiveness of different types of water treatment in removing AMR genes from river water. A review article discussed the inefficient performance of conventional and advanced water treatment processes in removing antibiotics and bacteria, mainly in removing ARGs. The study emphasized the need for more efficient and affordable remediation systems that remove emergent pollutants, including antibiotics, ARB, and ARG, from the environment and water sources [17]. A study proposed a framework for standardized methods and quality control for monitoring antimicrobials, resistant microorganisms, MGEs, and ARGs in water environments. The study highlighted the need for effective monitoring schemes for AMR in water treatment systems [26]. Another study reviewed the efficiency of water treatment processes in disseminating antibiotic resistance throughout the water distribution system. The study found that the biological activated carbon water treatment leads to an increase in ARGs [17]. An opinion article underlined the key role of controlling the release/discharge of antimicrobial contaminants in water bodies and their buildup in checking the development and spread of AMR. The article suggested that active monitoring of antimicrobial residues in the environment and control of disposal into the environment could help reduce the rate of AMR emergence/development [21]. Another study investigated the impact of process configuration, geographical location, and season on the antimicrobial resistome in WWTPs. The research discovered WWTPs have the potential to function as reservoirs for AMR, holding it within the activated sludge and potentially releasing it into the treated effluent [27].

The improper utilization and excessive application of antimicrobial agents, inadequate availability of clean water, sanitation, and hygiene, along with subpar waste management, are primary catalysts for the development of AMR [28]. The direct contact of both humans and animals with extensively polluted river water, combined with the significant movement of organisms like aquatic animals, pathogenic and non-pathogenic bacteria, as well as genetic components like ARGs and MGEs, plays a role in the dissemination and progression of AMR within river ecosystems [20]. Treated sewage sludge represents a further reservoir of AMR, which can increase the abundance of antimicrobial resistance genes in soil when applied as fertilizer [29]. Antibiotics present in rivers could also have adverse impacts on essential cycles, mechanisms, and processes carried out by vital natural microbial communities [19].

4. Discussion

4.1. Antimicrobial resistance in the environment

AMR poses a serious threat to people, animals, plants, and the environment on a global scale. AMR has garnered greater focus in relation to human or animal well-being compared to its manifestation in the environment. The natural environment, on the other hand, is a significant reservoir of AMR. Drug-resistant microbes can be found in humans, animals, food, and the environment (in water, soil, and air). Water and soil may be perfect settings for AMR growth and transmission, especially in areas with insufficient water supply, sanitation, and hygiene. Superbugs can spread from person to person and through animal-sourced food between humans and animals [30]. The environment can be exposed to antibiotics and their metabolites from production sites, untreated sewage from households and hospitals, wastewater treatment facilities, municipal waste streams, animal husbandry, sewage sludge, and aquaculture, to name a few [31]. Improved monitoring and surveillance systems help policymakers identify where AMR is found in the environment [1].

The release of antimicrobial drugs into the environment, along with direct contact between local bacterial populations and discharged resistant microbes, appears to be promoting bacterial evolution and the formation of progressively resistant strains. The environmental effects of antibiotic usage are complicated. Resistant microbes and antimicrobial medication residues have been discovered in drinking and recreational water. Wildlife that meets wastewater treatment plant discharge or livestock farms where antimicrobials are used can become colonized with drug-resistant organisms, even if they have never received drug treatment. The United Nations Environment Assembly (UNEA) also acknowledged that AMR is a growing threat to global health, food security, and sustainable development, emphasizing the importance of learning more about the role of environmental pollution in the development of AMR [31].

In a recent investigation concerning pharmaceutical contamination of global rivers, elevated quantities of antibiotic-resistant microorganisms were identified within low- to middle-income countries (LMICs). These occurrences were linked to regions characterized by inadequate wastewater and waste management systems, as well as pharmaceutical production facilities. Five major pollutant sources, according to the UNEP report, contribute to the development and spread of AMR (Fig. 1): poor sanitation, sewage, and waste effluent, exacerbated, for example, by open defecation and the overuse of antibiotics to treat diarrhea; effluent from pharmaceutical manufacturing; waste from healthcare facilities; use of antimicrobials and manure in crop production; and animal production releases are among them [2].

Waste and run-off from a variety of sources, such as food systems, manufacturing facilities, and human health systems, can contain biologically active antimicrobials, antimicrobial-resistant bacteria (ARB), unmetabolized antimicrobials, and AMR determinants (e.g., resistance-conferring genes-ARGs) that are released into the environment. These emissions have the potential to harm the environment and aid in the spread of AMR. Understanding and addressing global antimicrobial contamination should be a top priority for all countries. People all over the world are drinking antibiotic-laced water unintentionally, which could lead to an increase in drug-resistant bacteria and potentially fuel another global pandemic. These emissions possess the capacity to contaminate the surroundings and contribute to the dissemination of AMR. It is imperative for all nations to give precedence to comprehending and effectively controlling worldwide contamination caused by antimicrobials[32]. Although the exact scope of worldwide antimicrobial contamination remains uncertain, indications indicate that it could exert a substantial influence on AMR. For instance, multi-drug-resistant bacteria are already prevalent in marine environments and sediments adjacent to locations where aquaculture, industrial, and municipal discharges occur [1].

Released before World Health Day, the research unveiled a concerning oversight regarding the menace of AMR. Most antibiotics are introduced into the environment via toilets or open defecation, as highlighted in the study. In 2015, a staggering 34.8 billion daily doses of antibiotics were consumed, and up to 90% of these doses were expelled into the environment as active substances. These drugs then interact with bacteria in the water, which can evolve resistance within these environments, which can then transfer to human-associated bacteria, making antibiotics less likely to be effective. Approximately 80% of global wastewater remains untreated, and even in developed nations, treatment plants often struggle to remove harmful microorganisms. This situation has the potential to give rise to superbugs

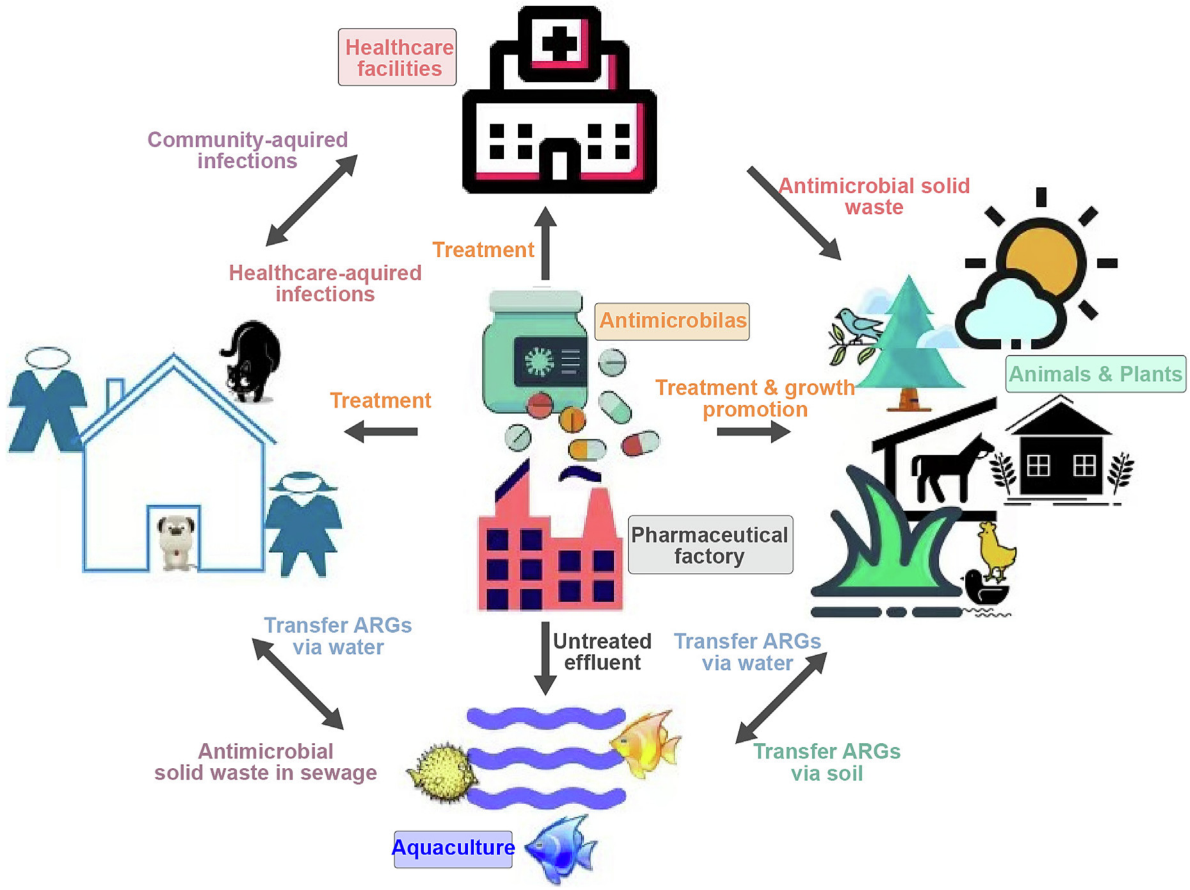

Fig. 1. The pathways of antimicrobials in the ecosystem. Abbreviation: ARGs, antibiotic resistance genes.

capable of resisting modern medical treatments and triggering a widespread epidemic [1]. As recent research demonstrates that present measures are unsafe, scientists are urging for new antibiotic safety limits in sewage to be strengthened to curb the rise of resistant bacteria [33].

Elevated temperatures are additionally linked to a rise in infections caused by microbes resistant to antimicrobials. Numerous illnesses are sensitive to climatic conditions, and alterations in environmental factors and temperature can expedite the dissemination of bacterial, viral, parasitic, fungal, and vector-borne diseases. Extreme weather occurrences and escalating water levels can result in the overflow of wastewater and sewage treatment facilities, facilitating the transmission of untreated sewage, replete with microbes resistant to antimicrobials, into neighboring populations. Policy-makers should remain vigilant, even as the impact of the coronavirus disease 2019 (COVID-19) pandemic subsides." The COVID-19 pandemic is a wake-up call to better understand and improve all areas of infectious disease preparedness and prevention, including their environmental dimensions" [2].

4.2. Pharmaceutical industry and AMR in the environment

AMR is a major global health concern, and pharmaceutical contamination threatens ecosystems and human health worldwide. The devastation is already visible in India and China, where most active pharmaceutical ingredients (APIs) are manufactured [3]. If antibiotic production waste containing a high concentration of APIs is dumped into the environment, it poses a significant danger of contributing to AMR. While solid waste is typically incinerated or disposed of in landfills, liquid waste is dumped into bodies of water such as rivers, where APIs can cause bacteria to develop new and dangerous forms of resistance. The release of APIs into the environment poses the greatest risk to the health of people living near manufacturing sites in the short term. However, in the long run, resistance will inevitably spread and contribute to the global problem [34].

According to a recent report from the Center for Infectious Disease Research and Policy's Antimicrobial Stewardship Project (CIDRAP-ASP), India has at least 40 APIs-manufacturing plants. These facilities manufacture APIs on a large scale and release the resulting wastewater into nearby rivers and streams. The CIDRAP-ASP report draws attention to studies conducted by environmental groups in India, which revealed the presence of multi-drug resistant bacterial strains and significant antibiotic levels in water sources close to sites where antibiotics are produced. These manufacturing hubs are concentrated across various regions in India [35]. Research conducted in Hyderabad, India, has unveiled exceedingly elevated levels of pharmaceutical substances surpassing established regulatory thresholds or safe exposure limits. Because APIs and finished dose antibiotic production is concentrated in certain places, the ensuing point-source contamination is extremely high and promotes the development of drug resistance. This approach has a significant impact on vulnerable communities that reside near manufacturing companies and wastewater treatment plants in these countries. Every year, an estimated 58,000 Indian neonates die because of multidrug-resistant infections. A Swiss study found that 75% of thirty-eight tourists who traveled to India returned home with antibiotic-resistant bacteria in their guts. Furthermore, 11% of tourists had bacteria that were resistant to the last-resort antibiotic colistin. Additionally, a highly resistant strain of typhoid fever has emerged in Pakistan with over two thousand cases confirmed in the first six months of 2018. Because untreated typhoid fever is fatal in 15% of cases, a large outbreak of the disease could be disastrous. This underscores the immediate threat to the entire planet if the problem of pharmaceutical pollution is not handled promptly and properly [3].

The issue of pharmaceutical pollution extends beyond the countries with the highest production rates, as campaign groups are urging the EU to enact legislation to protect citizens globally. Currently, there are no legally binding guidelines for businesses on proper waste disposal, and companies' internal policies are not transparent. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has made promises to act, but their efforts seem focused on shifting responsibility onto patients rather than addressing the problem directly. Industry lobbying has hindered EU policymakers from incorporating environmental criteria into the Good Manufacturing Practices (GMP) framework. The development of new antibiotics to combat AMR presents significant challenges for the industry. However, the European Parliament recognizes the urgency and has voted for effective legislation to combat AMR. To reduce pharmaceutical pollution, corporations must clean up their production and supply networks and invest in biodegradable drugs. The Safer Pharma campaign by Health Care Without Harm aims to push for pharmaceutical pollution legislation in the EU and involve health professionals in addressing the issue. New legislative measures and incentives are crucial to address both pharmaceutical pollution and AMR over the next decade [3].

The AMR Benchmark assessed seventeen major research-based pharmaceutical companies and generic medication producers in 2021 regarding their environmental practices related to antibiotic production. Fifteen companies provided information on their manufacturing sites and suppliers. Compliance with antibacterial discharge limits was reported by large research-based companies at more than two-thirds of their sites, while generic medicine manufacturers reported compliance at slightly over one-third of their sites. Out of 1,057 sites across companies and suppliers, only 142 followed antibacterial discharge limits. However, there has been progress, with an increase in companies requiring suppliers to set limits on antibiotic wastewater discharge since 2018. Some companies are collaborating with suppliers to improve standards, leading to increased compliance. Still, a significant number of supplier sites fail to measure discharge levels for compliance. There is currently no internationally agreed-upon regulation for safe antibacterial concentrations in the environment, and companies rely on voluntary targets from the AMR Industry Alliance. Despite progress, pharma companies must ensure limits are set and enforced at all supplier sites to reduce antibiotic waste discharge, especially given the extensive involvement of third-party manufacturing sites in the supply chain. Continued efforts to enforce wastewater discharge limits will lead to significant progress in combatting AMR [34].

4.3. Combining efforts

Combating AMR is gaining traction around the world as public awareness of the problem grows. The achievement of the SDGs is jeopardized by AMR. Decision-makers in politics, business, and civil society are increasingly aware of the magnitude of the problem that the world faces and must work together to combat it urgently [1].

4.3.1. Treatment strategies

Recent studies have investigated novel approaches for eliminating antibiotics, bacteria with resistance, and resistance genes from potable water. These strategies aim to enhance the efficiency of water treatment processes and minimize the dissemination of antibiotic resistance. Some of the strategies identified are Advanced Oxidation Processes (AOPs), Membrane Filtration [17], Activated Carbon Adsorption [36], Chlorination and UV Disinfection [37,38], Biological Treatment [36], and Combination Approaches [17]. It is important to note that the effectiveness of these strategies may vary depending on the specific antibiotics, resistant bacteria, and resistance genes present in the water, as well as the overall water quality and treatment conditions. Several affordable remediation systems that can remove antibiotics, ARB, and ARG from water sources such as Constructed Wetlands (CWs) [39,40] and Non-Thermal Plasma Assisted Inactivation[41]. Overall, these affordable remediation systems offer promising solutions for removing antibiotics, ARB, and ARG from water sources.

4.3.2. Industry guidelines

Antibiotics overuse and overexposure help to breed resistant bacterial strains that can grow in the presence of drugs. A lack of international regulations and a reliance on self-reporting by companies undermine efforts to ensure unused antimicrobials are safely discharged into the environment. While many people want new controls, the industry alliance's measures are the “only solution” that has been proposed [42]. A coalition comprising pharmaceutical, biotechnology, and diagnostic companies has introduced fresh directives designed to aid producers of antibiotics in curtailing the discharge of waste generated during antibiotic manufacturing into the ecosystem. Developed in collaboration with the British Standards Institute (BSI) by the AMR Industry Alliance, the Antibiotic Manufacturing Standard furnishes antibiotic manufacturers with guidelines to ensure their production processes are responsible and do not contribute to the proliferation of AMR in the environment. This document formalizes a framework originally formulated by the Alliance in 2018 to set industry benchmarks for the release of APIs from antibiotic production sites. The implementation of the Alliance's Standard marks the commencement of a new era of conscientious manufacturing practices throughout the global antibiotic value chain [35].

The creation of these guidelines was prompted by growing apprehensions that the release of wastewater containing antibiotics from manufacturing sites might be contributing to the proliferation of AMR among environmental bacteria. Although direct correlations between environmental AMR and drug-resistant human infections have not been definitively established, healthcare facilities are recognized as substantial contributors to antibiotic pollution in the environment. The AMR Industry Alliance and other organizations have been advocating for stricter regulations on the emission of APIs to address the role of antibiotic manufacturing. In response to these concerns, numerous pharmaceutical companies operating manufacturing facilities in India and affiliated with the AMR Industry Alliance have committed to adopting the “zero liquid discharge” approach, which aims to minimize the release of pollutants into water bodies [35].

To support these endeavors and establish a shared framework addressing this concern, the Antibiotic Manufacturing Standard mandates that antibiotic manufacturers establish an effective environmental management and wastewater treatment system aimed at curbing the discharge of APIs in wastewater. Furthermore, the standard necessitates that the concentration of antibiotics in manufacturing wastewater remains below the projected no-effect concentration, a level defined as not expected to cause adverse environmental effects. The AMR Industry Alliance and BSI also intend to institute a certification program wherein an unbiased third party assesses whether manufacturing facilities meet the stipulations of the standard. These novel guidelines and subsequent certification initiatives will significantly heighten global awareness, prompt resolute actions, provide an external, impartial validation mechanism, and exert influence throughout the broader supply chain, ultimately ushering in a new model of transparency for the industry [35,42].

Furthermore, additional measures and directives exist to control the release of antibiotics into water bodies and mitigate the development of antimicrobial resistance. The National Primary Drinking Water Regulations (NPDWR) consist of legally binding primary standards and treatment methodologies applicable to public water systems. These primary standards and treatment methods play a crucial role in safeguarding public health by restricting the concentrations of pollutants within drinking water. The NPDWR encompasses guidelines for microorganisms, disinfectants, disinfection byproducts, inorganic chemicals, organic chemicals, and radionuclides [43]. Industry Directives - A collaborative alliance of pharmaceutical, biotechnology, and diagnostic firms has introduced fresh guidelines designed to assist antibiotic manufacturers in curtailing the discharge of waste generated during antibiotic production into the environment. These guidelines have the objective of reducing the amount of pollutants released into water bodies, thereby working to mitigate the emergence of AMR in environmental bacteria [35]. Water management initiatives within healthcare institutions play a crucial role in safeguarding at-risk patient groups, as well as the well-being of staff and visitors. These programs are designed to mitigate the potential for infections originating from water sources and to curtail the proliferation and dissemination of pathogens resistant to antibiotics [44]. The Environmental Protection Agency (EPA) has implemented guidelines governing the release of contaminants, including antibiotics, into surface water bodies. Under the Clean Water Act, enforced by the EPA, the discharge of pollutants from specific sources into navigable waterways is regulated [24].

4.3.3. International treaties

There are some international agreements and treaties in place to regulate the discharge of antibiotics into water sources and reduce the emergence of antimicrobial resistance. The United Nations (UN) 2030 Agenda for Sustainable Development includes a goal to ensure the availability and sustainable management of water and sanitation for all. This objective encompasses aims to enhance the quality of water by diminishing pollution and mitigating the discharge of unsafe chemicals and substances into water reservoirs [45]. The Stockholm Convention concerning Persistent Organic Pollutants (POPs) is an international agreement to safeguard human health and the environment against persistent organic pollutants. It encompasses regulations intended to curtail and eradicate the manufacturing, utilization, and emission of POPs, which encompass specific antibiotics as well. On a similar note, the European Union (EU) Water Framework Directive is a policy framework aimed at the preservation and enhancement of water resource quality within the EU. This directive involves measures to decrease the release of perilous substances, including antibiotics, into water reservoirs [25].

Starting in 1978, the United Nations Environment Program (UNEP) has overseen the management of the Global Environment Monitoring System for Freshwater (GEMS/Water) Program. This initiative is responsible for aiding Member States in the surveillance and evaluation of their water quality, with the subsequent reporting of their observations to UNEP's worldwide water quality database [2]. On September 21, 2016, the UN convened a meeting with policymakers to address AMR comprehensively and multiculturally [46]. The UN Secretary-General convened the Interagency Coordination Group (IACG) on AMR in 2016, realizing that more must be done sooner to maintain health achievements made over the last century and assure a secure future. The objective was to improve international organization cooperation and enable an effective worldwide response to this complex challenge. The IACG finished its mandate in 2019 by presenting its report, 'No Time to Wait'. While evidence is limited, the report emphasizes that concerns about the impact of AMR on the environment and natural ecosystems are growing. AMR development and spread must be addressed as soon as possible through a multisectoral, coordinated approach. The joint efforts of the Food and Agriculture Organization (FAO), the World Organization for Animal Health (WOAH), and the WHO constitute the Tripartite Collaboration on AMR [1]. Furthermore, the World Water Quality Alliance, initiated by UNEP in 2019, advocates for the significance of freshwater quality in attaining both prosperity and sustainability. Its main responsibility involves crafting a comprehensive assessment of global water quality [2].

The WHO, in conjunction with the FAO and the WOAH, formulated a Global Action Plan (GAP) on AMR. This comprehensive strategy entails advocating for the establishment and execution of national action plans aimed at countering AMR. The plan encompasses measures to diminish antibiotic application in agriculture and enhance wastewater management to curtail the discharge of antibiotics into water reservoirs [45]. AMR has been categorized as a One Health concern within the GAP on AMR, owing to its substantial connections to the health of humans, animals, and the environment. The concept of "One Health" pertains to the interconnectedness of human, animal, plant, and environmental health. The participating member states of these three organizations concurred to adopt the GAP, with an additional invitation for members to establish their own Antimicrobial Resistance National Action Plans (NAPs) by the year 2017. The Tripartite has been assisting countries in developing and implementing multi-sector 'One Health' NAPs that are aligned with the GAP objectives and address AMR in all relevant sectors including human, animal, and plant health, food, and the environment [1,2]. In 2018, the Tripartite signed a Memorandum of Understanding on One Health and AMR. An effective response to AMR necessitates a cross-sectoral and interdisciplinary strategy, which ensures effective communication, cooperation, and alignment among pertinent ministries, agencies, stakeholders, sectors, and fields of expertise. Adopting a 'One Health' approach, which brings together medical, veterinary, and environmental expertise, assists governments, businesses, and civil society in achieving long-term health for people, animals, and the environment [47].

Today, global leaders and experts are emphasizing the need for worldwide initiatives to tackle the escalating levels of drug resistance while simultaneously safeguarding the environment by mitigating the presence of antimicrobial pollutants. The AMR Global Leaders Group (GLC) has advised every government to curtail the introduction of antimicrobial waste into the ecosystem. This goal can be achieved by assessing and implementing effective strategies for eliminating antimicrobial waste from various sources, including food systems, human and animal health sectors, and production facilities. This call to action precedes the United Nations Environment Assembly, held both in Nairobi and online from February 28 to March 2, 2022, aiming to address the planet's most critical environmental issues. Reducing the pollution of antimicrobials in the environment is imperative to uphold the efficacy of antimicrobial treatments. The GLC is urging all nations to establish and enforce regulations and standards that enhance the oversight and control of the distribution and release of antimicrobials into the environment. A significant step in this direction involves devising national standards for antimicrobial manufacturing pollution within the production sector to more effectively manage and monitor antimicrobial pollution [32].

However, as indicated by the search findings, there are presently no nations that have enforced obligatory guidelines pertaining to the permissible levels of antibiotics released into surface water. The absence of compulsory standards regarding antibiotic release levels into surface water is emphasized in several references [4,48]. While some countries have regulations in place to prevent environmental contamination, including regulations that limit the discharge of antimicrobial residues into the environment, these regulations are not comprehensive and are insufficient to protect the environment from the hazards of antimicrobial production [49]. G. Le Page et al. proposed a limit of 100 ng/L antibiotic discharge for the protection of the ecosystem function and to limit the risk of antibiotic resistance development [48]. However, this proposal has not yet been adopted as a mandatory standard. The absence of mandatory standards for the limits of antibiotic fugitive levels in surface water highlights the need for better regulation and monitoring of antibiotic use in agriculture, human and veterinary medicine, and other sectors to reduce and control antibiotic usage and antibiotic discharge into the environment [21,24].

4.4. The way forward

This global menace can be effectively tackled by diminishing the discharge of antibiotic-contaminated pollutants, achieved through enhanced wastewater treatment and more judicious antibiotic usage – these medications are frequently excessively utilized. Enhancements in data collection and monitoring regarding antimicrobials and their disposal are necessary. Moreover, an improved framework of environmental management and the formulation of NAPs aimed at constraining antimicrobial release are imperative. Nations should adopt the One Health paradigm, which underscores the interconnection between human and animal health with the well-being of the ecosystems they coexist in. Mitigating deforestation is crucial, as it often leads to human interaction with wildlife carrying pathogens, facilitating cross-species transmission. The COVID-19 pandemic imparts valuable insights, including the necessity to proactively address and prevent multiple health hazards concurrently, particularly their environmental aspects [47].

Over the next decade, we hope to see industry accept responsibility for pharmaceutical pollution and, more importantly, hospitals take the lead in addressing the issue. Hospitals can take simple steps such as incorporating environmental criteria into hospital procurement decisions and requiring manufacturers to disclose the source of their APIs as well as their post-manufacturing pollution control practices/policies. Healthcare professionals can also play a leadership role in educating patients about the environmental impact of the drugs they use [3].

Countries should take several measures to address the environmental impact of antimicrobial use and AMR. This includes developing or expanding regulatory frameworks, guidelines, standard operating procedures (SOPs), and standards to establish safe levels of antimicrobials, ARB, and AMR determinants released into the environment from food systems, manufacturing facilities, and human health systems. They should also include prevention and management measures in national policies. To effectively address AMR environmental risks, countries should develop and implement legal and policy frameworks for antimicrobial manufacturing, taking a lifecycle approach to consider the entire impact duration of pharmaceuticals on surrounding systems. Promoting well-balanced and incremental environmental policies for manufacturing facilities, along with providing support for environmental inspections, holds utmost importance. Focusing on industry adherence and its role in advancing the SDGs can cultivate excellence within the industry. Nations ought to strengthen the One Health surveillance encompassing the utilization of antimicrobials and the discharges that contribute to AMR across diverse origins, including food systems, human health networks, manufacturing establishments, and sewage systems. This surveillance must consider factors such as building upon existing systems, cost-effectiveness, comparability of data, and addressing critical knowledge gaps concerning the impact and consequences of discharges on the environment and organisms. The collection of data is essential for comprehending risks to human and animal health, identifying discharge routes, and guiding the management of waste and the establishment of limits for antimicrobial discharges. To augment transparency and engender public confidence, nations should encourage the disclosure of industry data pertaining to waste and wastewater management, as well as measures for mitigation. The initiation of data disclosure could commence with regulatory bodies and impartial third parties, subsequently extending to public access. This inclusive approach contributes to ongoing research endeavors and integrates environmental standards into procurement practices. Overall, these strategies aim to mitigate the environmental repercussions associated with antimicrobial use and AMR, thus safeguarding both public health and the environment [32].

Manufacturing corporations ought to commit to strategies for both preventing and managing issues in order to diminish the impact of discharges from their manufacturing processes on the environment. This objective can be achieved through the adoption of effective technologies and practices for waste management, adherence to established guidelines for antibiotic manufacturing, and the implementation of independent certification systems suggested by the AMR Industry Alliance. All parties involved should contemplate potential approaches and lend support to initiatives aimed at cultivating an environment conducive to investment, which includes incentives and measures for pharmaceutical waste management, all the while ensuring continued access to antibiotics. These assessments could encompass an evaluation of sustainable procurement protocols, integrating environmental considerations into sound manufacturing practices, appraising environmental risks prior to authorizing antimicrobial agents, and instating an autonomous product-certification program [32]. Transparency can be improved by making information about the origin of APIs and evidence of good manufacturing practice compliance of manufactured APIs imported by the European Union and the United States available to the public. WHO good manufacturing practice guidelines for workplace safety, environmental protection, pollution prevention, and the adoption of cleaner manufacturing technology should be adopted and consistently enforced for all countries responsible for AMR [50].

Additional endeavors involve enhancing and orchestrating research efforts to attain a comprehensive comprehension of the hazards posed to human and animal well-being by the presence of antimicrobials, resistant microorganisms, and mobile genetic elements within discharges. This also encompasses investigating potential focal points, environmental implications, pathways of AMR, and measures to mitigate these concerns. Encouraging research and development within both the public and private sectors for cost-effective and environmentally friendly waste management technologies is another crucial step. These may encompass techniques for eliminating antimicrobial residues, resistance genes, and resilient organisms, as well as the utilization of tools like climate-sensitive incinerators and measurement technologies. Employing standardized monitoring techniques and promoting the widespread adoption of optimal practices in process and waste management across various sectors are also essential. Additionally, crafting policy briefs related to AMR and coordinating policy discussions among decision-makers are vital for bolstering evidence-based policy formulation [32].

5. Conclusion, recommendations, and future perspectives

Environmental health plays a critical role in preventing infectious diseases and combating AMR, particularly in LMICs. Improper antibiotic use, including the discharge of pharmaceutical effluent and the excretion of unused drugs, significantly contributes to the spread of AMR. While antibiotic concentrations in the environment are usually below therapeutic levels, antibiotic residues in pharmaceutical effluent serve as an entry point for AMR development in bacteria, leading to the proliferation of resistant organisms, superbugs, biofilm formation, and horizontal gene transfer. AMR poses a grave threat to global public health and the economy, jeopardizing effective treatments for human and animal infections. If left unchecked, it could render antibiotics ineffective, disrupting healthcare systems worldwide. Addressing this one-health issue requires a unified approach, acknowledging the interconnectedness of humans, animals, and the environment in the context of AMR.

While efforts like the WHO's GAP-AMR and NAP-AMR have been initiated to combat AMR, environmental involvement and interventions demand further emphasis. Urgent and robust initiatives are needed to treat pharmaceutical effluent and reduce AMR drivers in river ecosystems. Active monitoring of antimicrobial residues and strict disposal practices are essential to mitigate the emergence and spread of AMR. Additionally, eradicating AMR germs and genes, along with removing antibiotics from urban river ecosystems, necessitates further research and the development of effective strategies. To effectively combat AMR, it is imperative to devise efficient and reliable methods for removing antibiotics and establish mandatory standards for antibiotic levels in surface water. Sustainable antibiotic manufacturing can be utilized to reduce antibiotic release into the environment to levels that do not trigger AMR, according to current knowledge. Policymakers, regulators, manufacturers, researchers, civil society, and communities must all work together through surveillance, legislation enforcement, and research to ensure that antibiotics are produced in a sustainable manner and remain effective in treating bacterial infections.

To truly combat AMR, the world's leading organizations and countries must adopt a multi-sectoral and multidimensional "One Health" approach. By embracing these challenges collectively, we can make significant strides in the fight against AMR and promote global health and well-being while safeguarding the efficacy of antibiotics and ensuring a sustainable future for healthcare and the ecosystem.

Conflict of interest statement

The author declares that there are no conflicts of interest.

Author contributions

Rehab A. Rayan: Investigation, Conceptualization, Writing – original draft, Resources.

Supplementary data

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