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Advances in Environmental and Engineering Research

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Review

Environmental and Human Health Impact of Antibiotics Waste Mismanagement: A Review

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Academic Editors: Stefania Perna and Gabriella Marfe

Special Issue: Waste Management and Human Health Impact

Adv Environ Eng Res
2024, volume 5, issue 1
doi:10.21926/aeer.2401005

Received: September 22, 2023
Accepted: January 08, 2024
Published: January 22, 2024

Abstract

The discovery of antibiotics and their use in the last century substantially shifted the management of an array of infections. However, its unprecedented irrational usage and inept disposal of their waste exposed the ecosystems to unquantifiable antibiotic deposits, triggering the emergence of antimicrobial resistance (AMR) with its immeasurable critical risk to public health. By adopting a narrative review method and accessing the available literature, the authors described what constitutes antibiotic waste, their classification, and the possible paths to access the ecological system. Further steps were taken to define the appropriate methods of disposing of antibiotic waste alongside the documented common wrong approaches in disposing of these currently undertaken in different parts of the globe, thus creating allowance for antibiotic waste mismanagement. The far-reaching consequences of inappropriate disposal of antibiotic waste into the environment were explored, emphasizing its hazardous impacts on human health and the ecosystem. Emphasis was laid on the pressing need for combined efforts involving policymakers, healthcare professionals, pharmaceutical industries, and the public to implement sustainable antibiotic waste management practices and promote their accountable utilization, and further suggested that proactive measures, such as severe regulatory frameworks, community awareness drives, and the promotion of eco-friendly options will be vital to easing the ecological and human health risks correlated with antibiotic waste mismanagement. By realizing the significance of this issue and approving integrated approaches, significant efforts could be accomplished regarding protecting the ecosystem and securing the effectiveness of antibiotics for the upcoming generation.

Keywords

Antibiotic waste; mismanagement; environmental and human health impact

1. Introduction

Drug is any element (other than food) employed to prevent, diagnose, treat, or relieve symptoms of a disease or abnormal disorder [1]. When administered to a living organism, it influences or stimulates biological functions or pharmacological actions [2]. The term drug has often been used interchangeably with such terms as medicine, pharmaceutical products, and pharmaceuticals [3]. It also refers to a notable ingredient in any pharmaceutical dosage form denoted as the active pharmaceutical ingredient (API) [3]. Traditionally, drugs were obtained naturally from minerals, plants, or animals, but more recently, as by-products of microbial growth through chemical/organic synthesis, molecular modification, or biotechnology [4]. According to the German Medicinal Products Act (Arzneimittelgesetz, AMG), drug substances are regarded as active constituents that are projected for use as therapeutically active ingredients in the manufacture of medicinal products or which, through their use in the making of medicinal products, are anticipated to become medically active constituents or API [5]. The United States Food and Drug Administration (FDA) classified drugs as analgesics, antacids, tranquilizers/anxiolytics, antiarrhythmics, antibacterials, antibiotics, anticoagulants/thrombolytics, anticonvulsants, antidepressants, antidiarrhoeals, antiemetics, antifungals, antihistamines, antihypertensives, anti-inflammatories, antineoplastics, antipsychotics, antipyretics, antivirals, barbiturates, beta-blockers, bronchodilators, corticosteroids, antitussives/expectorants, cytotoxics, diuretics, hormones/sex hormones (male/female), hypoglycaemics, immunosuppressives, laxatives, muscle relaxants, etc. [6]. Antibiotics are chemicals that possess relevant medicinal benefits that can destroy or prevent the growth of bacteria and are employed to treat bacterial infections [7]. The reputable emergence of antibiotics into the globe followed the introduction of penicillin in 1941. Subsequently, they have revolutionized the treatment of bacterial infections in humans and animals, not minding their ineffectiveness against viruses [8]. Their actions could have long been known and may explain why the ancient Egyptians practiced applying a poultice of moldy bread to infected wounds [9]. In 1928, Scottish bacteriologist Alexander Fleming observed that clusters of bacteria developing on a culture plate had been adversely affected by a mold, *Penicillium notatum,* which had contaminated the culture. A decade later, British biochemist Ernst Chain, Australian pathologist Howard Florey, and others isolated the constituent responsible, penicillin, and revealed that it was exceptionally operative against many severe bacterial contaminations. Near the end of the 1950s, scientists investigated the addition of several chemical groups to the core of the penicillin molecule to generate semi-synthetic varieties. A range of penicillin thus became obtainable to handle diseases caused by diverse forms of bacteria, comprising *Staphylococci*, *Streptococci*, *Pneumococci*, *Gonococci*, and the Spirochaetes of syphilis [10]. Antibiotics could be narrow, broad, or extended-spectrum in activity [11]. The terms Gram-positive and Gram-negative are used to distinguish between bacteria that have cell walls consisting of a thick network of peptidoglycan and bacteria that have cell walls with only a thin peptidoglycan layer in addition to lipopolysaccharide (LPS) membrane, respectively [12]. Classes of antibiotics include aminoglycosides (inhibit protein synthesis, e.g. gentamycin, tobramycin, etc.) [13], cephalosporins (inhibit cell wall synthesis, e.g. cefaclor, ceftriaxone, etc.) [14], chloramphenicols (inhibit protein synthesis) [15], fluoroquinolones (interfere with DNA synthesis, e.g. ciprofloxacin, norfloxacin, etc.) [16], lincosamides (inhibit protein synthesis, e.g. clindamycin) [17], macrolides (inhibit protein synthesis, e.g. azithromycin, clarithromycin, erythromycin, etc.) [18], nitrofurans (inactivate essential cell components, e.g. nitrofurantoin) [19], penicillins (inhibit cell wall synthesis, amoxicillin, ampicillin, etc.) [20], tetracyclines (inhibit protein synthesis) [21], miscellaneous antibiotics, e.g. aztreonam [22], isoniazid [23], metronidazole [24], rifampicin [25], vancomycin [26], etc.

Antibiotics signify one of the notable discoveries of the last century that transformed the control of an extensive range of infections in a significant way. Nevertheless, their amplified consumption has exposed bacterial communities and ecologies to a large amount of antibiotic residue. The emergence of antibiotic deposits in the natural environment results from several patterns of antibiotic usage done to fight against bacterial infections and livestock production [27]. Statistics show that consumption of antibiotics in animal husbandry is much higher than in human medicine. The first global (228 countries) map of antibiotic consumption in livestock published by Van Boeckel *et al*. provided a gross estimation of the total antibiotic consumption in 2010 (63,151 tons). It is projected that antibiotic consumption will rise by 67% by 2030 and in some BRICS countries (Brazil, Russia, India, China, and South Africa), it will nearly double [28].

While antibiotics play a significant part in bringing about recovery from a disease and the management of lingering health disorders both in recognized healthcare settings and in patients' homes [29], a vital factor in the safe utilization of antibiotic products is the appropriate disposal of unwanted antibiotic products [30] and their containers. When carried out appropriately, antibiotic waste handling can protect the atmospheric setting and prevent hazardous antibiotics from getting into the wrong hands [30, 31]. It is necessary to understand what constitutes pharmaceutical products and antibiotic waste at large and their classification.

2. Basics of Pharmaceutical Waste

Any activity resulting from the production of pharmaceuticals or the use of produced samples that amount to the release of leftover spent containers and packages or expired products contributes to the generation of pharmaceutical waste. Antibiotic waste is any remainder or expired part of it, especially those that are discarded [32]. Patients and healthcare providers gather this waste in formal settings as patients recover from sickness and in patients' residences as they struggle to control lingering disease, etc. [33]. These wastes may be solid or liquid and could be categorized based on the source. Solid pharmaceutical wastes include unused over-the-counter (OTC) medicinal products and prescription-only-medicines (POM), surgical devices such as materials used during the manufacture of pharmaceuticals comprising used and contaminated gloves, masks, syringes, dusters, rags, mops, needles, etc. Liquid wastes include wastewater and chemicals generated from manufacturing plants, etc. Others are blister packs, ointment tubes, and drug dispensing devices like inhalers and nebulizers [34]. The U.S. Environmental Protection Agency (EPA) considers about 5-10% of all medicinal product waste as "hazardous waste" [35]. However, the groupings hinge on the chemical properties of medicinal products [36]. The risks associated with improper disposal of pharmaceutical wastes, especially antibiotics, cannot be over-emphasized. If antibiotic waste is discarded incorrectly, the API could have access to the environment. Disposal of manufacturing-plant-generated pharmaceutical waste into landfills will enter such chemicals into soils and underground water, thus contaminating water sources and aquatic life. Meanwhile, inappropriate antibiotic disposal approaches can include washing them down sinks, flushing them down toilets, or flinging them away in regular garbage [37].

3. Classification of Pharmaceutical Waste

Pharmaceutical waste has been classified as either regulated medical waste as red bag waste, biohazard or infectious waste [38-40], solid waste [41] (municipal, black bag, transparent bag, or non-regulated medical waste [42], or hazardous waste (emanating from pathology, histology laboratories, pharmacies, morgue, etc.) [43].

However, the National Institute for Occupational Safety and Health (NIOSH) considers "hazardous drugs" as those that have revealed one or more of the resulting features in studies with animals, humans, or *in vitro* systems: carcinogenicity, teratogenicity or other toxicity for development, reproductive toxicity, organ toxicity at low doses, or genotoxicity [44].

4. Sources of Antibiotic Waste to The Environment

So long as antibiotics are in use, their waste will always accumulate. Their use continues globally in clinical and veterinary medicine to prevent and treat diseases and infections in agriculture as growth promoters and control of plant diseases [45]. Sources of antibiotic drug wastes in the environment include:

4.1 Human/Domestic Sources

Human or domestic sources of antibiotic waste include those arising from using these drugs by family members individually or as caregivers. Antibiotics can be accessible to humans in handling infections or used in veterinary medicine as growth promoters [46]. Essentially, contact with antibiotics from healthcare is checked as POM in advanced nations; in developing economies, there is easy access to these products alongside OTC medications [47]. Nevertheless, non-disposal or retention of unwanted antibiotics in the residential environment can be a disaster, given the presence of pediatric and geriatric age groups within the family. It could lead to unintentional ingestion, spillage, and accidental poisoning from such substances [48]. Household retention of unwanted medications is an indicator of a country's unregulated medicines access, patient's non-adherence to prescription, the experience of medication side effects, health economic output, and a gateway to the rearing of antibiotic-resistant micro-organisms that may give rise to other human and aquatic genetic effects [49]. Among US households, it was estimated that 63% throw unused medications into trash whereas their web-based study revealed that antibiotic (18%) was commonly unused medication[50].

4.2 Hospitals

Healthcare drug waste constitutes a significant environmental, financial, and public health concern [51]. Patients discharge un-metabolized or moderately low doses of non-metabolized antibiotics through urine and stool, which might enter the environment through sewage disposal and encourage the occurrence of antibiotic-resistant bacteria [51]. In a study involving the liquid hospital waste collection from the sewage of Chittagong Medical College Hospital (CMCH), Bangladesh, and from its supply position in Chittagong city, Bangladesh, an overall of 5 samples were taken from diverse spots in Chittagong city, comprising CMCH liquid waste. Subsequently, total bacteria and cefixime-resistant bacteria were counted using the total viable count (TVC) technique. The consequence of bacteriological enumeration revealed that many cefixime-resistant bacteria were accessible in all the hospital-linked waste samples. The maximum percentage of cefixime-resistant bacteria (23.35%) was found in sample 2, though 17.4, 7.6, 5.0, and 1.32% were found in samples 1, 3, 4, and 5, correspondingly. The total number of cefixime-resistant bacteria reduced with the increased distance between the sample collection site and the hospital drain. This implies that resistant bacteria developed in the hospital effluent are transferred to the environmental distribution sites [52].

4.3 Pharmaceutical Manufacturing Facilities

The control of discharge arising from the pharmaceutical industries during antibiotic manufacture goes a long way in contributing to the harmful effect of these substances on humans, animals, and the environment [53]. The amount, concentration, and type of antibiotic effluence discharged depends on the industries' manufacturing power and the personnel knowledge base [54]. Often, antibiotic pollution from industries is significantly higher than that arising from other wastes [55] and poses untoward ecological and public health issues [56].

4.4 Generally Considered Sources of Antibiotic Drug Wastes

Most antibiotics pass into the natural environment after use for human and animal health purposes, and often, there are leftovers of these products [57]. Most antibiotics taken by humans or animals are often incompletely metabolized. Some could be in their original form or slightly changed. They could be released into the environment as they pass through the urine and/or stool following their use through the toilets, wastewater, and runoff water [58]. Leftover antibiotics may often be flushed down drains or toilets and enter the environment [37]. Antibiotics in manure and other waste-based fertilizers enter waterways along with runoff from crop and grazing fields [59]. Antibiotics applied to fruit trees to treat bacterial infections can result in field runoff destined for waterways [60]. Antibiotic-containing waste from pets and unused products end up in landfills and neighborhood sewer runoff [61]. Some industrial processes generate antibiotic-containing waste that might enter the environment [62].

5. Antibiotic Waste Disposal: Global Perspective and Methods

Antibiotic waste disposal dates alongside the inception of antibiotic use [10] and is employed universally in clinical and veterinary medicine to prevent and treat diseases and infections, in agriculture as growth promoters, and to treat plant diseases [63]. Among categories of medication wastes such as analgesics, cardiovascular, anti-inflammatory, respiratory, and antibiotics, the studies undertaken in developing countries revealed that antibiotics were topmost in the ranking [64]. Antibiotic resistance and the emergence of “superbugs” negatively, directly, or indirectly on human health worldwide emanate from the irrational use of antibiotics and improper disposal of their used and unused components [65]. Wastages could result from over-prescribing by physicians, patient’s poor antibiotic compliance, resolution of illness/disease, poor storage, ineffectiveness of drug during use, stoppage of drug use following the emergence of adverse drug reactions, and use of alternative drug or treatment after initiation of therapy [66-68]. Antibiotic waste disposal contains used, unused, stored, or expired antibiotics of any dosage form [67] and could arise from sewage, hospital, and agricultural waste practices, runoffs, floods, industrial wastes, pit latrines, and underground waters [27, 69]. It has been reported that more than 80 active pharmaceutical ingredients and metabolites have been found in underground and surface water in Europe and the US [64]. In 2015 and 2018, the European Union (EU) established a watch list that included antibiotics such as amoxicillin, erythromycin, ciprofloxacin, and clarithromycin perceived to negatively affect aquatic lives and the environment in general [70]. A call to world experts and world leaders by the World Health Organization (WHO) has been made to reduce the antimicrobial pollution of our environment [71]. This calls for advancement in the procedures that improve the disposal of antimicrobial-containing waste and effluents from manufacturing facilities, homes, and other healthcare facilities. In Kenya, antibiotic waste disposal involves pit latrines, compost pits, and incineration [69].

6. Some Acceptable Approaches to Antibiotic Waste Disposal

Since antibiotic waste emanates from the domestic end/homes, hospitals/clinics/diagnostic laboratories, pharmaceutical industries, and non-human use (agricultural/veterinary arenas, aquaculture, etc.) [72], it would be ideal that policies or approaches guiding the appropriate disposal of these wastes be specified to these sources. However, some general approaches could apply to sundry sources of antibiotic waste since it is vital to discard unused, unwanted, or expired antibiotic prescriptions to circumvent needless side effects and antimicrobial resistance [46]. Nevertheless, properly discarding medications is critical in keeping the environment safe and clean [73]. Managing remaining medicines is an intricate challenge that demands attention and should be attended to from numerous perspectives [74]. Some acceptable approaches to antibiotic waste disposal will be considered in line with their respective sources.

6.1 The Homes

The essential explanations why an antibiotic could be unnecessary to a patient or ultimately becomes unused include modifying the dosage of the drug, dosage adjustment or altering the drug therapy entirely, the death of the patient, treatment non-completion, or improper use of drugs by the patient or discontinuation of the antibiotic due to undesirable effects [75]. Procedures for residents to dispose of unused/expired medications, especially antibiotics, rest on socio-economic culture and authorized guidelines and monitoring strategies [76]. Demographic parameters such as family size, level of education, marital status, occupation predicted knowledge, attitude, and perception of individuals on antibiotic waste disposal are other factors. Medication take-back programs are procedures commonly encouraged for the home disposal of medications, including antibiotics [77].

6.2 Laboratories and Pharmaceutical Industries

In each study laboratory, antibiotics are regularly utilized in cell culture or molecular biology procedures [78]. It has been reported that the unacceptable discarding of medical/research waste from hospitals, laboratories, and pharmaceutical industries allows room for antibiotics and other drugs in drinking water, producing an undesirable effect on human health and the environment [79]. To avoid these harmful influences, each establishment adopts a regulated approach for cautiously throwing away laboratory waste. It may be fundamental to consider used media as biohazard and antibiotics as chemical waste, implying that everything that accommodates antibiotics should be measured as chemical waste [80]. Autoclaving of exhausted cell culture media terminates pathogens. Nevertheless, not some types of antibiotics. Some are heat stable, whereas others are not. Antibiotics such as ampicillin, amphotericin, carbenicillin, penicillin, geneticin, kanamycin, neomycin, puromycin, streptomycin, tetracycline, etc. are destroyed through an autoclave cycle and, as an exemption, could be harmless to pour down the sink after autoclaving, then only if other destructive chemicals are removed [81]. However, autoclave does not destroy antibiotics like hygromycin B, chloramphenicol, ciprofloxacin, vancomycin, nalidixic acid, etc..

Hence, autoclaved media containing these antibiotics is considered a chemical waste and should be discarded based on the institutional scheduled approach. Though autoclaves and chemical decontaminants can neutralize antibiotics in culture media, these techniques must not be utilized to dispose of stock antibiotic solutions since they are commonly at significantly higher concentrations than those used in media and are considered hazardous chemical waste [82].

6.3 Community Pharmacies/Households

Community pharmacies have several roles in ensuring proper disposal of antibiotic waste. The Society of Infectious Diseases Pharmacists (SIDP) has mapped several options to enable community pharmacies registered with their Pharmacy board or regulatory agency to contribute to safe antibiotic use and disposal of unused, expired, or unwanted antibiotic drugs through antibiotics take-back programs. Considering this effort, individuals or homes are encouraged to put together their used, expired, or unwanted antibiotics, cross out or remove their details, and send them to any community pharmacy recognized for antibiotics take-back programs [83]. In an investigation towards the support for proper disposal of leftover medication, particularly antibiotics, a telephone study led by researchers at UC San Francisco established that less than half of California pharmacies offered disposal instructions meeting US. Food and Drug Administration guidelines [84], and just 10% followed the FDA's preferred recommendation to take back unused medications from their customers [85]. However, in a location where there is no take-back program, the FDA directed that antibiotics ought to be blended with a disgusting material and discarded in a closed vessel in the trash to preserve them from getting into the water supply or accidentally consumed [84, 86]. Various state and local law implementation agencies, communities, and organizations have recognized take-back events, mail-back, and other collection programs to collect old, expired, or unwanted prescribed and OTC medications from households. A medication take-back program for throwing away is a good way to eliminate expired, unwanted, or unused drugs from the household and lessen the coincidence of others unintentionally taking the medication [37, 86].

7. Environmental Impacts of Antibiotic Waste Mismanagement

Antibiotic contamination is a significant new global health issue that has increased the possibility of the emergence of antibiotic resistance [86]. The toll that antibiotic resistance has taken on society is evident from the number of lives lost, illness, medical costs, and lost productivity [87].

7.1 Impact of Antibiotic Waste Mismanagement on The Atmosphere

Antibiotics and their by-products are continuously released into the environment. Antibiotic pollution is initiated when partially degraded and undegraded antibiotics are released into the ecosystem. Bioremediation of this pollution is complex; hence, antibiotics with both narrow and broad spectrums have been found worldwide in various environmental samples [88]. The potentially harmful levels of antibiotic-resistant bacteria (ARB), antibiotic resistance genes (ARGs), and metal resistance genes (MGEs) present in municipal solid waste (MSW), which includes household, medical, agricultural, and other waste and their direct disposal in landfills or open dump locations without segregation or treatment is a significant problem [89]. Landfills offer a favorable habitat for the growth of antimicrobial resistance (AMR) microorganisms, which in turn spread antibiotic resistance genes (ARGs) horizontally into bacterial strains in the surrounding environment [90]. The general ecosystem, including air, soil, surface water, groundwater, animals, and public health, are all negatively impacted by this [91]. Greenhouse gases (carbon dioxide and methane) that trap heat in the atmosphere are produced in landfills by the decomposition of food leftovers and a sizable proportion of MSW. These gases have the most ability to cause global warming. In the worst circumstances, breathing landfill gas emissions repeatedly can result in tachycardia, exhaustion, nausea, vomiting, collapsing, and even death [92].

7.2 Impact of Antibiotic Waste Mismanagement on Land and Animals (Terrestrial Environment)

There is proof that antibiotics exist in the terrestrial environment. Antibiotics are widely used for therapeutic, preventative/prophylactic, and growth-promoting purposes in the cattle and poultry sectors and human medicine. Although the practice of using antibiotics to stimulate the growth of livestock, hog-dogs, and poultry, as well as to increase the effectiveness of the feeding process, was outlawed in the EU in 2006, antibiotics are still used in India and China, particularly in the agricultural and livestock industries [93]. The use of antibiotics in agriculture improves the growth of animals, beekeeping, and fish farming, but it also contaminates the environment since leftover antibiotics and their metabolites are excreted in the waste of poultry animals. Antimicrobials are routinely and repeatedly released into the environment and natural ecosystem because of their use in agriculture, human health care, livestock, and animal welfare. Antibiotics have a substantial toxicity impact on both the non-target population and the target population [94]. Recent investigations have found as many as 20 distinct antibiotic compounds in stool samples from swine, poultry, and animal production facilities, and up to 90% are expelled without being digested [95]. While antibiotics used in crops and fish aquaculture can build up in the environment and increase the pollutant concentration, antibiotics given to livestock can also be spread in fields via manure and leach into the soil and groundwater. When manure is applied to agricultural fields, antibiotics provided to the feed may contaminate the soil because they are excreted as the parent components or metabolites. These residual antibiotic compounds and their breakdown by-products are introduced to the terrestrial environment when contaminated manure, sewage sludge, or polluted water is applied to agricultural soils, where they frequently persist and remain bioavailable [96]. Proper nutrient cycling is essential for sustaining soil quality and sustainable agricultural land use. Nitrogen is one of the crucial elements of farming systems, and two Gram-negative bacterial species, Nitrosomonas and Nitrobacter, are responsible for its cycle. Sulphonamides and tetracyclines, which are broad-spectrum antibiotics, can significantly impede nutrient cycling if concentrations rise to sufficiently high levels. This outcome has been seen in laboratory experiments, but no field investigations have discovered antibiotic doses high enough to severely impair the nitrification process [97]. MSW has significantly increased due to industrialization and urbanization. Most MSW often disposed off in the same landfill includes household, medical, agricultural, and other types of trash that are not segregated [98]. Despite years of globalization, landfilling remains one of the most widely used techniques not precisely suited to stop contamination in soil and groundwater through toxic leachate percolation. Organic pollutants, antibiotics, heavy metals, pharmaceutical and personal care products [PPCPs] are a few examples of the undesirable toxic substances found in landfill leachate, which can permeate through disposable waste during rainfall and primarily contaminate the soil layers and groundwater [99].

7.3 Impact of Antibiotic Waste Mismanagement on The Aquatic Ecosystem

Antibiotics can be found naturally in the environment, as is well known. Nonetheless, it is believed that man-made activities are the leading cause of these contaminants [64]. Utilization for treating and preventing bacterial infections in humans and animals stands out among these activities. Following administration, these medications are not entirely metabolized and absorbed by the human or animal body [60]. The non-metabolized substances are discarded through the home and hospital effluents. They can also be partially removed in water treatment facilities until they reach natural aquatic ecosystems such as rivers, lakes, seas, and groundwater [100]. The negative consequences of antibiotics entering the water supplies are poorly understood because the scientific community has only recently begun to worry about them [101]. Another factor is that there are now no accurate analytical techniques available to assess the low concentrations of antibiotics typically found in waterways, typically in the few parts per billion (ppb) range [60]. Despite the modest amounts of individual antibiotics, there are so many distinct antibiotics that their combination could harm human health and the environment [102]. Antibiotic residues in surface water can potentially disrupt fundamental bacterial cycles, mechanisms, and processes essential to maintaining the balance of the aquatic ecosystem or that of the agricultural system and ensuring the production of healthy animals [103]. Also, the risk of antibiotic pollution increases by the discharge of wastes from hospitals, veterinarians, pharmaceutical factories, dairy farms, animal husbandry operations, domestic animals, poultry, and residential garbage [104]. In addition to home and industrial effluents, the pharmaceutical industries considerably contribute to the total antibiotic concentration added to the influent of the sewage treatment plant [105]. Antibiotics like beta-lactams, aminoglycosides, lincosamides, macrolides, nitrofurans, chloramphenicol, phosphonates, quinolones and fluoroquinolones, rifamycins, sulphonamides, tetracyclines, and their isomers are persistent and resistant due to their low molecular weight and quick dissolution in water bodies. Wastewater treatment plants (WWTPs) partially eliminate these substances [106]. Antibiotics are one type of micropollutant that WWTPs worldwide cannot remove. Therefore, they are continuously released into sediments and water bodies. They might also enter the food chain if they enter ditches, streams, and rivers through runoff and drain flow, groundwater leaching, etc. [107]. The improper disposal of unwanted or expired antibiotics, dumped in landfills or the sewage system, manufacturing waste effluents, or unintentional spills during production or distribution can also be considered significant contamination points [108]. Antibiotics are released into adjacent sewers, followed by rivers and seas, based on the consumption by living things. For instance, fluoroquinolones were found in samples from Hailing Island, ofloxacin in Laizhou Bay, and tetracycline and sulphonamides in the effluents of wastewater treatment plants. Sulfamethoxazole and trimethoprim are also more frequently found in the seawater in Belgian harbors. Developing nations have found antibiotics in hospital effluents commonly containing beta-lactams, macrolides, sulfamethoxazole, sulphonamides, trimethoprim, and fluoroquinolones [109]. Municipal wastewater has been shown to contain sulfamethoxazole, trimethoprim, ciprofloxacin, and ofloxacin. Aqua samples often contain oxytetracycline, florfenicol, sarafloxacin, erythromycin, and sulphonamides because these drugs are commonly employed in aquaculture. In veterinary medicine, tetracyclines, oxytetracyclines, sulfamethazine, tylosin, penicillin G, and lincomycin are frequently used to treat bacterial infections [110]. A significant concern is the presence of microbial contaminants in landfill leachate, such as ARB, ARGs, MRGs, and pathogenic bacteria, as these can spread human pathogens' ARGs through horizontal gene transfer (HGT) [89]. These factors make removing antibiotics and PPCPs from landfill leachate essential to protect the aquatic environment and prevent the spread of ARGs to humans [111].

A graphic representation of the sources of mismanaged antibiotic waste, disposal sites, routes into the environment, and possible modifications through the ecosystem is shown in Figure 1.

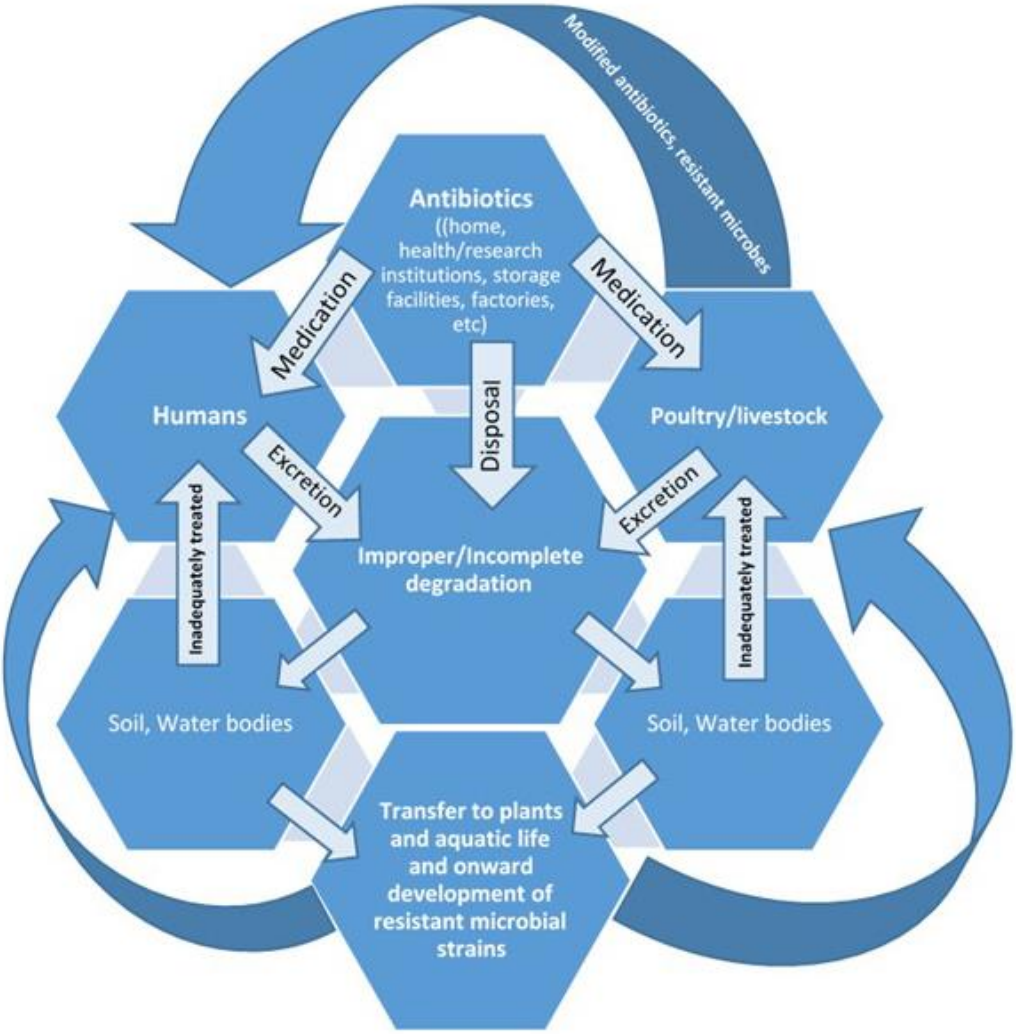

Figure 1 Graphical representation of the sources of mismanaged antibiotic waste, disposal sites, routes into the environment, and possible modifications through the ecosystem.

8. Impact of Antibiotic Waste Mismanagement on Human Health

Antibiotic waste mismanagement can have severe outcomes on human health and influence the emergent global health hazard of AMR, which occurs when bacteria, viruses, fungi, and parasites develop and become resistant to the effects of antibiotics, rendering these life-saving drugs less effective or ineffective in handling illnesses [78]. Improper disposal and mishandling of antibiotic waste contribute considerably to quickening AMR, bringing about a range of harmful influences on human health [112]. Some effects of antibiotic waste mismanagement on human health are presented below.

8.1 Increased Infections and Medication Failures

Inadequate disposal of antibiotics leads to environmental contamination involving water sources and soil [113]. Resistant bacteria can evolve and spread over the surroundings, leading to increased diseases initiated by drug-resistant pathogens [114]. Failures in the drug management of diseases may arise as available recommendable antibiotics of choice become ineffective against these resistant strains, making it difficult to manage diseases and endangering the lives of patients [115].

8.2 Prolonged Illness and Hospitalization

Antibiotic-resistant diseases can be more challenging, frequently involving more potent and costly antibiotics and extended hospitalization [116]. This can put extra liability on healthcare systems and raise the risk of complications, disability, or death for patients [117]. A study published in the Lancet estimates that AMR could lead to 10 million deaths per year by 2050 if not adequately addressed [118].

8.3 Increased Healthcare Expenses

It is not cost-effective to manage antibiotic-resistant diseases compared to controlling sensitive infections since more potent or specific antibiotics will be indicated coupled with prolonged hospitalization of patients [101]. The Centre for Disease Dynamics, Economics & Policy (CDDEP) 2015 report estimated that AMR could cost the global economy up to 100 trillion USD by 2050 if not handled efficiently [119].

8.4 Diminished Efficiency of Medical Techniques

Recent health techniques like surgeries, organ transplants, and cancer controls require the use of antibiotics pre - and post-procedures. However, the accessibility of effective antibiotics is necessary to inhibit the implicating microorganisms and generally handle diseases. Continually increasing antibiotic resistance may jeopardize these life-saving procedures, exposing patients to higher risk [120].

8.5 Influence on Susceptible Populaces

Some factions of individuals are more vulnerable to antibiotic-resistant diseases, including the elderly, infants, pregnant women, and persons with diminished immune systems [116]. Mishandling of antibiotic waste aggravates the consequences on these endangered individuals, possibly causing extreme morbidity and mortality scales [121].

8.6 Universal Health Risk

AMR does not have borders [122], and antibiotic waste mishandling can influence the existence of resistant bacteria globally [123, 124]. As pathogens transverse the aquatic systems, food, and intercontinental tourism, they can become a macro health concern [125]. The World Bank has cautioned that AMR could push over 28.3 million people into extreme poverty by 2050 [126].

8.7 Restricted Medication Alternatives

The advancement of new antibiotics has reduced extensively in contemporary times, relatively due to monetary and controlling encounters [127]. Hence, the advent of antibiotic-resistant contaminations leaves physicians with restricted therapeutic alternatives, and in these scenarios, there are no efficacious antibiotics [127]. To alleviate these influences and contend antibiotic waste mismanagement, collaborative attempts are necessary from governments, healthcare providers, pharmaceutical industries, environmental agencies, and the public [128]. Appropriate waste managing approaches, incorporating safe disposal and management of antibiotic waste, and encouraging responsible antibiotic use are central measures to lower the advent and extent of AMR [129].

9. Issues of Antimicrobial Resistance in Nigeria and Other African Countries

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines, making infections more challenging to treat [116]. The antimicrobial agents employed in the management or prevention of transmittable ailments in humans, plants, and animals are correspondingly found in the ecosystem. They are simultaneously increasing the promotion of resistant genes [130] as the inappropriate use of antimicrobials in these intensify the hazard of contamination with microbes that are resistant to existing therapies and can cause severe illness and death, thereby stressing the significance of One health perspectives to address AMR [131]. AMR has been noted as one of the top 10 global health threats [118] in a wide range of transmittable agents and remains the foremost risk to human, animal, and ecological health, with its economic impact on the universal economy projected at one hundred trillion dollars per annum in addition to triggering the loss of millions of lives if adequate measures are not put in place to tackle it [132]. Ten million individuals, including 4.1 million in the African Region, are expected to die from AMR organisms by 2050, while nations across Africa could lose up to 5% of their gross domestic product (GDP) [126]. Nigeria considers AMR to be of significant interest to the national public health agenda. Her response to AMR led by the Nigeria Centre for Disease Control (NCDC) commenced in 2016 after a situational investigation considering common AMR-resistant pathogens recovered from hospitals, livestock, agricultural, and ecological sources. The NCDC also supervised systematic reviews to evaluate the prescription patterns of antimicrobials in hospitals across the country. These attempts informed the development of the National Action Plan (NAP), designed with a 5-year focus (2017–2022). Overall, the Nigeria NAP focused on five key pillars under the WHO Global Action Plan on AMR. The pillars include increasing consciousness and knowledge of health-care workers and the general public on AMR; building a One Health surveillance system; increasing infection inhibition and control and biosecurity; encouraging rational use of antimicrobials and access to genuine medicines, and research into alternatives to antimicrobials, new diagnostics, and therapeutics [133, 134]. Addressing AMR is a requisite for achieving global priorities such as the Sustainable Development Goals (SDGs) and ensuring global health security as stipulated by the International Health Regulations (IHR) (2005) [135]. Modern treatments depend on effective antimicrobial medications, yet high rates of resistant infections across various microorganisms have been admitted in all World Health Organization (WHO) regions [133, 136]. Considering its undesirable impact on the well-being of the global economy and advancement, the Member States of the World Health Organization (WHO) accepted the Global Action Plan on Antimicrobial Resistance at the World Health Assembly in May 2015, which was then recognized by governments universally at the United Nations General Assembly in 2016. The WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) was launched in 2015 to adopt AMR surveillance and inform strategies to contain AMR [136]. Globally, AMR brought about more deaths than HIV/AIDS or malaria, with 4.95 million deaths linked to drug-resistant bacterial infections in 2019 [137, 138]. The most extensive burden occurred in the sub-Saharan Africa Region, where 1.07 million people died due to bacterial antimicrobial resistance [139]. The most recent 5th GLASS report (December 2022) confirmed a global increase of AMR rates by more than 15% in 2020 correlated with 2017 in pathogens causing bloodstream infections (*Klebsiella pneumoniae* and *Acinetobacter* spp.). This, thus, demands for inputs to reinforce infection prevention and control measures in hospital settings [24, 136]. In the WHO African Region (AFRO), 45 [96%] nations instituted a national action plan (NAP) on AMR [134]. As of June 2023, 37 (79%) AFRO states are registered in the Global AMR and Use Surveillance System (GLASS). Among Gram-negative bacteria, *Escherichia coli* isolates reported a high resistance percentage for recommended first-and second-line antibiotics. In contrast, among Gram-positive bacteria, *Streptococcus pneumoniae* displayed high resistance percentages against the key tested antibiotics [136].

10. Conclusion

This review has emphasized the fundamental need to address antibiotic waste mismanagement to alleviate its adverse effects on the environment and human health. The inappropriate disposal and release of antibiotic residues into the atmosphere have triggered the emergence of antibiotic-resistant bacteria, posing a severe risk to public health. Furthermore, water bodies and soil pollution with antibiotics have wide-ranging ecological consequences, influencing various organisms and ecosystems. Critical and organized efforts are relevant from policymakers, pharmaceutical industries, healthcare professionals, and the public to realize the need for strict waste management practices, enhance understanding of the issue, and encourage justifiable options. Only through mutual measures and accountable practices can the environment and human well-being be protected from the menace and harmful impacts of antibiotic waste mismanagement.

Author Contributions

Kenneth Ugoeze received the invitation as a guest author. He co-opted other authors and conceptualized the title and outline of the paper which was distributed to the authors who were paired to develop them. Chidozie Ibezim compiled the submissions from each pair of authors and executed the first level of editing. Bruno Chinko and Christian Alalor refined the references. Peter Owonaro and Deghinmotei Alfred-Ugbenbo managed plagiarism checks. Each author edited the manuscript individually at the second level and gave feedback. Kenneth Ugoeze and Chidozie Ibezim coordinated the feedback of all the authors. Clement Anie, Ngozi Okoronkwo, Amaka Mgbahurike, Chijioke Ofomata and Geraldine Ndukwu conducted the final proofreading.

Funding

This review was not funded by any agency.

Competing Interests

The authors have declared that no competing interests exist.

References

1. National Cancer Institute. Definition of drug [Internet]. Bethesda, MD: National Cancer Institute; 2011 [cited date 2023 April 21]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/drug.
2. Marino M, Jamal Z, Zito PM. Pharmacodynamics. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2023 [cited date 2023 December 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507791/.
3. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New concepts in nutraceuticals as alternative for pharmaceuticals. Int J Prev Med. 2014; 5: 1487-1499.
4. Dias DA, Urban S, Roessner U. A historical overview of natural products in drug discovery. Metabolites. 2012; 2: 303-336.
5. Federal Ministry Federal Office. Medicinal Products Act (Arzneimittelgesetz – AMG) [Internet]. Berlin: Bundesministerium der Justiz; [cited date 2023 April 22]. Available from: https://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html.
6. Food and Drug Administration. General Drug Categories [Internet]. Silver Spring, MD: FDA; 2018 [cited date 2023 December 25]. Available from: https://www.fda.gov/drugs/investigational-new-drug-ind-application/general-drug-categories.
7. Society M. Antibiotics [Internet]. London: Microbiology Society; [cited date 2023 December 25]. Available from: https://microbiologysociety.org/why-microbiology-matters/what-is-microbiology/microbes-and-the-human-body/antibiotics.html.
8. Waksman SA. What Is an antibiotic or an antibiotic substance? Mycologia. 1947; 39: 565-569.
9. American Chemical Society. Alexander Fleming Discovery and Development of Penicillin [Internet]. Washington, DC: American Chemical Society; [cited date 2023 April 22]. Available from: https://www.acs.org/education/whatischemistry/landmarks/flemingpenicillin.html.
10. Tan SY, Tatsumura Y. Alexander Fleming (1881–1955): Discoverer of penicillin. Singapore Med J. 2015; 56: 366-367.
11. Melander RJ, Zurawski DV, Melander C. Narrow-spectrum antibacterial agents. MedChemComm. 2017; 9: 12-21.
12. Silhavy TJ, Kahne D, Walker S. The bacterial cell envelope. Cold Spring Harb Perspect Biol. 2010; 2: a000414.
13. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An overview. Cold Spring Harb Perspect Med. 2016; 6: a027029.
14. Gad SC. Cephalosporins. In: Encyclopedia of Toxicology. 4th ed. Oxford: Academic Press; 2024. pp. 705-710.
15. Abdollahi M, Mostafalou S. Chloramphenicol. In: Encyclopedia of Toxicology. 3rd ed. Oxford: Academic Press; 2014. pp. 837-840.

16. Walker RC. The Fluoroquinolones. Mayo Clin Proc. 1999; 74: 1030-1037.
17. Aronson JK. Lincosamides. In: Meyler's Side Effects of Drugs. 6th ed. Oxford: Elsevier; 2016. pp. 581-588.
18. Katz L, Mankin AS. Macrolides. In: Encyclopedia of Microbiology. 3rd ed. Oxford: Academic Press; 2009. pp. 529-558.
19. Le VV, Rakonjac J. Nitrofurans: Revival of an "old" drug class in the fight against antibiotic resistance. PLoS Pathog. 2021; 17: e1009663.
20. Dumancas GG, Hikkaduwa Koralege RS, Mojica ER, Murdianti BS, Pham PJ. Penicillins. In: Encyclopedia of Toxicology. 3rd ed. Oxford: Academic Press; 2014. pp. 768-772.
21. Chopra I, Roberts M. Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev. 2001; 65: 232-260.
22. Scholar E. Aztreonam. In: xPharm: The Comprehensive Pharmacology Reference. New York: Elsevier; 2007. pp. 1-5.
23. Scholar E. Isoniazid. In: xPharm: The Comprehensive Pharmacology Reference. New York: Elsevier; 2007. pp. 1-7.
24. Weir CB, Le JK. Metronidazole. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2023 [cited date 2023 April 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539728/.
25. Scholar E. Rifampin. In: xPharm: The Comprehensive Pharmacology Reference. New York: Elsevier; 2007. pp. 1-8.
26. Patel S, Preuss CV, Bernice F. Vancomycin. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2023 [cited date 2023 April 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459263/.
27. Polianciuc SI, Gurzău AE, Kiss B, Ştefan MG, Loghin F. Antibiotics in the environment: Causes and consequences. Med Pharm Rep. 2020; 93: 231-240.
28. Tiseo K, Huber L, Gilbert M, Robinson TP, Van Boeckel TP. Global trends in antimicrobial use in food animals from 2017 to 2030. Antibiotics. 2020; 9: 918.
29. Piat M, Sabetti J, Bloom D. The importance of medication in consumer definitions of recovery from serious mental illness: A qualitative study. Issues Ment Health Nurs. 2009; 30: 482-490.
30. Chisholm JM, Zamani R, Negm AM, Said N, Abdel daiem MM, Dibaj M, et al. Sustainable waste management of medical waste in African developing countries: A narrative review. Waste Manag Res. 2021; 39: 1149-1163.
31. Breve F, LeQuang JA, Batastini L. Controlled substance waste: Concerns, controversies, solutions. Cureus. 2022; 14: e22564.
32. Danner MC, Robertson A, Behrends V, Reiss J. Antibiotic pollution in surface fresh waters: Occurrence and effects. Sci Total Environ. 2019; 664: 793–804.
33. van Seventer JM, Hochberg NS. Principles of infectious diseases: Transmission, diagnosis, prevention, and control. In: International Encyclopedia of Public Health. 2nd ed. New York: Elsevier; 2017. pp. 22-39.
34. United States Environmental Protection Agency. Criteria for the definition of solid waste and solid and hazardous waste exclusions [Internet]. Washington, DC: EPA; 2016 [cited date 2023 December 25]. Available from: https://www.epa.gov/hw/criteria-definition-solid-waste-and-solid-and-hazardous-waste-exclusions.

35. United States Environmental Protection Agency. Management of hazardous waste pharmaceuticals [Internet]. Washington, DC: EPA; 2015 [cited date 2023 April 22]. Available from: https://www.epa.gov/hwgenerators/management-hazardous-waste-pharmaceuticals.
36. United States Environmental Protection Agency. Defining hazardous waste: Listed, characteristic and mixed radiological wastes [Internet]. Washington, DC: EPA; 2015 [cited date 2023 April 22]. Available from: https://www.epa.gov/hw/defining-hazardous-waste-listed-characteristic-and-mixed-radiological-wastes.
37. Bashaar M, Thawani V, Hassali MA, Saleem F. Disposal practices of unused and expired pharmaceuticals among general public in Kabul. BMC Public Health. 2017; 17: 45.
38. Noel K. What waste goes in red bag waste? [Internet]. Fortuna, CA: Eco Medical; [cited date 2023 December 25]. Available from: https://www.ecomedicalwaste.com/blog-posts/what-goes-in-red-bag-waste.
39. The University of Tennessee, Knoxville. Biosafety Program. Biohazardous Waste Categories [Internet]. Knoxville, TN: The University of Tennessee, Knoxville; [cited date 2023 December 25]. Available from: https://biosafety.utk.edu/biosafety-program/waste/.
40. WHO. Health-care waste [Internet]. Geneva: WHO; 2018 [cited date 2023 December 25]. Available from: https://www.who.int/news-room/fact-sheets/detail/health-care-waste.
41. WHO. Guidance on solid waste and health [Internet]. Geneva: WHO; [cited date 2023 December 25]. Available from: https://www.who.int/tools/compendium-on-health-and-environment/solid-waste.
42. Ugoeze K, EO A, Oluigbo K, Nwachukwu N. Environmental and public health impacts of plastic wastes due to healthcare and food products packages: A review. J Environ Sci Public Health. 2021; 5: 1-31.
43. United States Environmental Protection Agency. Universal Waste [Internet]. Washington, DC: EPA; 2015 [cited date 2023 December 25]. Available from: https://www.epa.gov/hw/universal-waste.
44. Domingo-Echaburu S, Lopez de Torre-Querejazu A, Valcárcel Y, Orive G, Lertxundi U. Hazardous drugs (NIOSH's list-group 1) in healthcare settings: Also a hazard for the environment? Sci Total Environ. 2022; 817: 152954.
45. Van TT, Yidana Z, Smooker PM, Coloe PJ. Antibiotic use in food animals worldwide, with a focus on Africa: Pluses and minuses. J Glob Antimicrob Resist. 2020; 20: 170-177.
46. Dantuluri KL, Bonnet KR, Schlundt DG, Schulte RJ, Griffith HG, Luu A, et al. Antibiotic perceptions, adherence, and disposal practices among parents of pediatric patients. PloS One. 2023; 18: e0281660.
47. Nepal G, Bhatta S. Self-medication with antibiotics in WHO southeast Asian region: A systematic review. Cureus. 2018; 10: e2428.
48. Santos DF, Silveira MP, Camargo AL, Matijasevich A, Santos IS, Barros AJ, et al. Unsafe storage of household medicines: Results from a cross-sectional study of four-year-olds from the 2004 Pelotas birth cohort (Brazil). BMC Pediatr. 2019; 19: 235.
49. Institute of Medicine (US) Forum on Emerging Infections, Knobler SL, Lemon SM, Najafi M, Burroughs T. Factors Contributing to the Emergence of Resistance. In: The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment: Workshop Summary [Internet]. Washington, DC: National

Academies Press; 2003 [cited date 2023 April 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK97126/.
50. Law AV, Sakharkar P, Zargarzadeh A, Tai BW, Hess K, Hata M, et al. Taking stock of medication wastage: Unused medications in US households. Res Soc Adm Pharm. 2015; 11: 571-578.
51. Mankes RF, Silver CD, Mankes RF, Silver CD. Hospital antibiotic wasting and evaluation of potential ecologic effects. Ann Environ Sci Toxicol. 2016; 1: 012-022.
52. Mozola M, Gray RL, Feldpausch J, Alles S, McDougal S, Montei C, et al. Validation of the Soleris NF-TVC method for determination of total viable count in a variety of foods. J AOAC Int. 2013; 96: 399-403.
53. Chowdhury AM, Uddin KN. Analysis of the occurrence of antibiotic resistant bacteria in the hospital's effluent and its receiving environment. Microbiol Insights. 2022; 15: 11786361221078211.
54. Larsson DJ. Pollution from drug manufacturing: Review and perspectives [Internet]. London, UK: The Royal Society; 2014 [cited date 2023 April 22]. Available from: https://royalsocietypublishing.org/doi/10.1098/rstb.2013.0571.
55. Sathya K, Nagarajan K, Carlin Geor Malar G, Rajalakshmi S, Raja Lakshmi P. A comprehensive review on comparison among effluent treatment methods and modern methods of treatment of industrial wastewater effluent from different sources. Appl Water Sci. 2022; 12: 70.
56. Buelow E, Ploy MC, Dagot C. Role of pollution on the selection of antibiotic resistance and bacterial pathogens in the environment. Curr Opin Microbiol. 2021; 64: 117-124.
57. Iskandar K, Molinier L, Hallit S, Sartelli M, Catena F, Coccolini F, et al. Drivers of antibiotic resistance transmission in low-and middle-income countries from a "one health" perspective—A review. Antibiotics. 2020; 9: 372.
58. Sosa-Hernández JE, Rodas-Zuluaga LI, López-Pacheco IY, Melchor-Martínez EM, Aghalari Z, Limón DS, et al. Sources of antibiotics pollutants in the aquatic environment under SARS-CoV-2 pandemic situation. Case Stud Chem Environ Eng. 2021; 4: 100127.
59. Yang Q, Gao Y, Ke J, Show PL, Ge Y, Liu Y, et al. Antibiotics: An overview on the environmental occurrence, toxicity, degradation, and removal methods. Bioengineered. 2021; 12: 7376-7416.
60. Quaik S, Embrandiri A, Balasubramani R, Hossain K, Ismail N, Al-Dhabi N, et al. Veterinary antibiotics in animal manure and manure laden soil: Scenario and challenges in Asian countries. J King Saud Univ Sci. 2019; 32: 1300-1305.
61. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications. Molecules. 2018; 23: 795.
62. Uluseker C, Kaster KM, Thorsen K, Basiry D, Shobana S, Jain M, et al. A review on occurrence and spread of antibiotic resistance in wastewaters and in wastewater treatment plants: Mechanisms and perspectives. Front Microbiol. 2021; 12: 717809.
63. Koch N, Islam NF, Sonowal S, Prasad R, Sarma H. Environmental antibiotics and resistance genes as emerging contaminants: Methods of detection and bioremediation. Curr Res Microb Sci. 2021; 2: 100027.
64. Aminov RI. A brief history of the antibiotic era: Lessons learned and challenges for the future. Front Microbiol. 2010; 1: 134.

65. Bataduwaarachchi VR, Weeraratne C. Global medication waste management practices: Challenges and opportunities in developing countries. Int J Basic Clin Pharmacol. 2016; 5: 2290-2294.
66. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010; 74: 417-433.
67. Insani WN, Qonita NA, Jannah SS, Nuraliyah NM, Supadmi W, Gatera VA, et al. Improper disposal practice of unused and expired pharmaceutical products in Indonesian households. Heliyon. 2020; 6: e04551.
68. Anwar M, Iqbal Q, Saleem F. Improper disposal of unused antibiotics: An often overlooked driver of antimicrobial resistance. Expert Rev Anti Infect Ther. 2020; 18: 697-699.
69. Bettington E, Spinks J, Kelly F, Wheeler AJ. Returning unwanted medicines to pharmacies: Prescribing to reduce waste. Aust Prescr. 2018; 41: 78-81.
70. Karimi KJ, Ahmad A, Duse A, Mwanthi M, Ayah R. Prevalence of antibiotic use and disposal at household level in informal settlements of Kisumu, Kenya. Int J Environ Res Public Health. 2022; 20: 287.
71. Harrower J, McNaughtan M, Hunter C, Hough R, Zhang Z, Helwig K. Chemical fate and partitioning behavior of antibiotics in the aquatic environment—A review. Environ Toxicol Chem. 2021; 40: 3275-3298.
72. WHO. World leaders and experts call for action to protect the environment from antimicrobial pollution [Internet]. Geneva: WHO; 2022 [cited date 2023 December 25]. Available from: https://www.who.int/news/item/02-03-2022-world-leaders-and-experts-call-for-action-to-protect-the-environment-from-antimicrobial-pollution.
73. Iwu CD, Korsten L, Okoh AI. The incidence of antibiotic resistance within and beyond the agricultural ecosystem: A concern for public health. MicrobiologyOpen. 2020; 9: e1035.
74. Kinrys G, Gold AK, Worthington JJ, Nierenberg AA. Medication disposal practices: Increasing patient and clinician education on safe methods. J Int Med Res. 2018; 46: 927-939.
75. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011; 86: 304-314.
76. Singleton J, Nissen L, Barter N, McIntosh M. The global public health issue of pharmaceutical waste: What role for pharmacists? J Glob Responsib. 2014; 5: 126-137.
77. Rogowska J, Zimmermann A. Household pharmaceutical waste disposal as a global problem—A review. Int J Environ Res Public Health. 2022; 19: 15798.
78. Sitotaw B, Philipos W. Knowledge, attitude, and practices (KAP) on antibiotic use and disposal ways in Sidama Region, Ethiopia: A community-based cross-sectional survey. Sci World J. 2023; 2023: 8774634.
79. Uddin TM, Chakraborty AJ, Khusro A, Zidan BR, Mitra S, Emran TB, et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. J Infect Public Health. 2021; 14: 1750-1766.
80. Samal K, Mahapatra S, Hibzur Ali M. Pharmaceutical wastewater as Emerging Contaminants (EC): Treatment technologies, impact on environment and human health. Energy Nexus. 2022; 6: 100076.
81. Nwachukwu NC, Orji FA, Ugbogu OC. Health care waste management–Public health benefits, and the need for effective environmental regulatory surveillance in federal Republic of Nigeria. In: Current Topics in Public Health. London, UK: IntechOpen Limited; 2013. pp. 149-178.

82. Clinisciences. Antibiotics for cell culture [Internet]. Nanterre: Clinisciences; [cited date 2023 December 25]. Available from: https://www.clinisciences.com/es/comprar/cat-antibiotics-for-cell-culture-1809.html.
83. Biological Safety [Internet]. Blacksburg, VA: Virginia Tech; [cited date 2023 December 25]. Available from: https://ehs.vt.edu/content/ehs_vt_edu/en/programs/biological-safety.html.
84. Hashmi A, Ul Haq MI, Malik M, Hussain A, Gajdács M, Jamshed S. Perceptions of community pharmacists regarding their role in antimicrobial stewardship in Pakistan: A way forward. Heliyon. 2023; 9: e14843.
85. Food and Drug Administration. Where and How to Dispose of Unused Medicines [Internet]. Silver Spring, MD: FDA; 2021 [cited date 2023 May 10]. Available from: https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines.
86. Ives J. Proper disposal of leftover medication can help reduce antibiotic resistance [Internet]. Manchester, UK: News Medical; 2019 [cited date 2023 May 10]. Available from: https://www.news-medical.net/news/20191231/Proper-disposal-of-leftover-medication-can-help-reduce-antibiotic-resistance.aspx.
87. SCDHEC. Household Medicine/Pharmaceutical Disposal [Internet]. Columbia, SC: SCDHEC; [cited date 2023 May 10]. Available from: https://scdhec.gov/household-medicinepharmaceutical-disposal.
88. Thermo Fisher Scientific. Antibiotic Overuse & Resistance [Internet]. Norristown, PA: Thermo Fisher Scientific; [cited date 2023 July 28]. Available from: https://www.thermofisher.com/procalcitonin/wo/en/antibiotic-stewardship/antibiotic-overuse-resistance.html?cid=0se_gaw_25052021_AR3IFK.
89. Sarpong EM, Miller GE. Narrow- and broad-spectrum antibiotic use among U.S. children. Health Serv Res. 2015; 50: 830-846.
90. Anand U, Reddy B, Singh VK, Singh AK, Kesari KK, Tripathi P, et al. Potential environmental and human health risks caused by antibiotic-resistant bacteria (ARB), antibiotic resistance genes (ARGs) and emerging contaminants (ECs) from municipal solid waste (MSW) landfill. Antibiotics. 2021; 10: 374.
91. Wang JY, An XL, Huang FY, Su JQ. Antibiotic resistome in a landfill leachate treatment plant and effluent-receiving river. Chemosphere. 2020; 242: 125207.
92. Aluko OO, Obafemi TH, Obiajunwa PO, Obiajunwa CJ, Obisanya OA, Odanye OH, et al. Solid waste management and health hazards associated with residence around open dumpsites in heterogeneous urban settlements in Southwest Nigeria. Int J Environ Health Res. 2022; 32: 1313-1328.
93. Sharma A, Gupta AK, Ganguly R. Impact of open dumping of municipal solid waste on soil properties in mountainous region. J Rock Mech Geotech Eng. 2018; 10: 725-739.
94. Gonzalez Ronquillo M, Angeles Hernandez JC. Antibiotic and synthetic growth promoters in animal diets: Review of impact and analytical methods. Food Control. 2017; 72: 255-267.
95. Grenni P, Ancona V, Barra Caracciolo A. Ecological effects of antibiotics on natural ecosystems: A review. Microchem J. 2018; 136: 25-39.
96. Hou J, Wan W, Mao D, Wang C, Mu Q, Qin S, et al. Occurrence and distribution of sulfonamides, tetracyclines, quinolones, macrolides, and nitrofurans in livestock manure and amended soils of Northern China. Environ Sci Pollut Res Int. 2015; 22: 4545-4554.

97. Hong B, Lin Q, Yu S, Chen Y, Chen Y, Chiang P. Urbanization gradient of selected pharmaceuticals in surface water at a watershed scale. Sci Total Environ. 2018; 634: 448-458.
98. Jensen J. Veterinary medicines and soil quality: The Danish situation as an example. ACS Symp Ser. 2001; 791: 282-302.
99. Meena MD, Dotaniya ML, Meena BL, Rai PK, Antil RS, Meena HS, et al. Municipal solid waste: Opportunities, challenges and management policies in India: A review. Waste Manag Bull. 2023; 1: 4-18.
100. Patel M, Kumar R, Kishor K, Mlsna T, Pittman Jr CU, Mohan D. Pharmaceuticals of emerging concern in aquatic systems: Chemistry, occurrence, effects, and removal methods. Chem Rev. 2019; 119: 3510-3673.
101. Lapworth DJ, Baran N, Stuart ME, Ward RS. Emerging organic contaminants in groundwater: A review of sources, fate and occurrence. Environ Pollut. 2012; 163: 287-303.
102. Serwecińska L. Antimicrobials and antibiotic-resistant bacteria: A risk to the environment and to public health. Water. 2020; 12: 3313.
103. Llor C, Bjerrum L. Antimicrobial resistance: Risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014; 5: 229-241.
104. Kulik K, Lenart-Boroń A, Wyrzykowska K. Impact of antibiotic pollution on the bacterial population within surface water with special focus on mountain rivers. Water. 2023; 15: 975.
105. Zeng H, Li J, Zhao W, Xu J, Xu H, Li D, et al. The current status and prevention of antibiotic pollution in groundwater in China. Int J Environ Res Public Health. 2022; 19: 11256.
106. Kumar M, Jaiswal S, Sodhi KK, Shree P, Singh DK, Agrawal PK, et al. Antibiotics bioremediation: Perspectives on its ecotoxicity and resistance. Environ Int. 2019; 124: 448-461.
107. Al-Hasan MN, Wilson JW, Lahr BD, Thomsen KM, Eckel-Passow JE, Vetter EA, et al. β-Lactam and fluoroquinolone combination antibiotic therapy for bacteremia caused by Gram-Negative Bacilli. Antimicrob Agents Chemother. 2009; 53: 1386-1394.
108. He Y, Nurul S, Schmitt H, Sutton NB, Murk TA, Blokland MH, et al. Evaluation of attenuation of pharmaceuticals, toxic potency, and antibiotic resistance genes in constructed wetlands treating wastewater effluents. Sci Total Environ. 2018; 631: 1572-1581.
109. Akici A, Aydin V, Kiroglu A. Assessment of the association between drug disposal practices and drug use and storage behaviors. Saudi Pharm J. 2018; 26: 7-13.
110. Meena VD, Dotaniya ML, Saha JK, Patra AK. Antibiotics and antibiotic resistant bacteria in wastewater: Impact on environment, soil microbial activity and human health. Afr J Microbiol Res. 2015; 9: 965-978.
111. García-Fernández A, Dionisi AM, Arena S, Iglesias-Torrens Y, Carattoli A, Luzzi I. Human campylobacteriosis in Italy: Emergence of multi-drug resistance to ciprofloxacin, tetracycline, and erythromycin. Front Microbiol. 2018; 9: 1906.
112. Zhang XH, Xu YB, He XL, Huang L, Ling JY, Zheng L, et al. Occurrence of antibiotic resistance genes in landfill leachate treatment plant and its effluent-receiving soil and surface water. Environ Pollut. 2016; 218: 1255-1261.
113. Hospital Healthcare Europe. Waste disposal in healthcare and effects on AMR [Internet]. London: Hospital Healthcare Europe; 2016 [cited date 2023 December 25]. Available from: https://hospitalhealthcare.com/latest-issue-2016/waste-disposal-in-healthcare-and-effects-on-amr/.

114. Kraemer SA, Ramachandran A, Perron GG. Antibiotic pollution in the environment: From microbial ecology to public policy. Microorganisms. 2019; 7: 180.
115. Read AF, Woods RJ. Antibiotic resistance management. Evolution, medicine, and public health. Evol Med Public Health. 2014; 2014: 147.
116. Ventola CL. The antibiotic resistance crisis. Pharm Ther. 2015; 40: 277-283.
117. Poudel AN, Zhu S, Cooper N, Little P, Tarrant C, Hickman M, et al. The economic burden of antibiotic resistance: A systematic review and meta-analysis. PLoS One. 2023; 18: e0285170.
118. World Organisation for Animal Health. Antimicrobial resistance [Internet]. Paris: World Organisation for Animal Health; [cited date 2023 April 23]. Available from: https://www.woah.org/en/what-we-do/global-initiatives/antimicrobial-resistance/.
119. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet. 2022; 399: 629-655.
120. Alpuche Aranda CM, Arias CA, Espinal Tejada C, Forde C, Park B, Rossi F, et al. Scientific evidence for the control of antimicrobial resistance. Rev Panam Salud Pública. 2020; 44: e128.
121. Chinemerem Nwobodo D, Ugwu MC, Oliseloke Anie C, Al-Ouqaili MT, Chinedu Ikem J, Victor Chigozie U, et al. Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. J Clin Lab Anal. 2022; 36: e24655.
122. Global Research on Antimicrobial Resistance. Antibiotic resistance caused more than 1.2M deaths in 2019, according to landmark GRAM study [Internet]. Global Research on Antimicrobial Resistance; 2022 [cited date 2023 July 28]. Available from: https://www.tropicalmedicine.ox.ac.uk/gram/news/global-burden-of-bacterial-antimicrobial-resistance.
123. Tadesse BT, Ashley EA, Ongarello S, Havumaki J, Wijegoonewardena M, González IJ, et al. Antimicrobial resistance in Africa: A systematic review. BMC Infect Dis. 2017; 17: 616.
124. Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. Perspect Medicinal Chem. 2014; 6: 25-64.
125. Stewart JR, Gast RJ, Fujioka RS, Solo-Gabriele HM, Meschke JS, Amaral-Zettler LA, et al. The coastal environment and human health: Microbial indicators, pathogens, sentinels and reservoirs. Environ Health. 2008; 7: S3.
126. World Bank. Drug-Resistant Infections: A Threat to Our Economic Future [Internet]. Washington, DC: World Bank; [cited date 2023 July 28]. Available from: https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future.
127. Miethke M, Pieroni M, Weber T, Brönstrup M, Hammann P, Halby L, et al. Towards the sustainable discovery and development of new antibiotics. Nat Rev Chem. 2021; 5: 726-749.
128. Murugaiyan J, Kumar PA, Rao GS, Iskandar K, Hawser S, Hays JP, et al. Progress in alternative strategies to combat antimicrobial resistance: Focus on antibiotics. Antibiotics. 2022; 11: 200.
129. Nijsingh N, Munthe C, Larsson DG. Managing pollution from antibiotics manufacturing: Charting actors, incentives and disincentives. Environ Health. 2019; 18: 95.
130. Maillard JY, Bloomfield SF, Courvalin P, Essack SY, Gandra S, Gerba CP, et al. Reducing antibiotic prescribing and addressing the global problem of antibiotic resistance by targeted hygiene in the home and everyday life settings: A position paper. Am J Infect Control. 2020; 48: 1090-1099.
131. Wegener HC. Antibiotic resistance—Linking human and animal health. In: Improving Food Safety Through a One Health Approach: Workshop Summary [Internet]. Washington, DC:

National Academies Press; 2012 [cited date 2023 December 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114485/.
132. Velazquez-Meza ME, Galarde-López M, Carrillo-Quiróz B, Alpuche-Aranda CM. Antimicrobial resistance: One Health approach. Vet World. 2022; 15: 743-749.
133. WHO. Global antimicrobial resistance and use surveillance system (GLASS) report: 2022 [Internet]. Geneva: WHO; 2022 [cited date 2023 December 22]. Available from: https://www.who.int/publications-detail-redirect/9789240062702.
134. Achi CR, Ayobami O, Mark G, Egwuenu A, Ogbolu D, Kabir J. Operationalising one health in Nigeria: Reflections from a high-level expert panel discussion commemorating the 2020 world antibiotics awareness week. Front Public Health. 2021; 9: 673504.
135. Fuller WL, Hamzat OT, Aboderin AO, Gahimbare L, Kapona O, Yahaya AA, et al. National action plan on antimicrobial resistance: An evaluation of implementation in the World Health Organization Africa region. J Public Health Afr. 2022; 13: 2000.
136. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: A global multifaceted phenomenon. Pathog Glob Health. 2015; 109: 309-318.
137. de Kraker ME, Harbarth S. Global burden of antimicrobial resistance: Essential pieces of a global puzzle. Lancet. 2022; 399: 2347.
138. UNESCO. 'Sub-Saharan Africa has the highest mortality rate due to antimicrobial resistance' [Internet]. Paris: UNESCO; 2023 [cited date 2023 December 22]. Available from: https://www.unesco.org/en/articles/sub-saharan-africa-has-highest-mortality-rate-due-antimicrobial-resistance.
139. WHO. AFRO builds capacity of 12 member states to improve antimicrobial resistance surveillance [Internet]. Geneva: WHO; 2023 [cited date 2023 December 22]. Available from: https://www.afro.who.int/countries/namibia/news/afro-builds-capacity-12-member-states-improve-antimicrobial-resistance-surveillance.