Review Article

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Antimicrobial resistance: A significant public health issue of both human and veterinary concern

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Abstract

Introduction – The discovery of antibiotics and the subsequent realization that these medications are the most effective treatments for a wide range of illnesses affecting the health of humans and animals constituted a revolution in medical history.

Methods – A review of the literature was done, looking for pertinent studies, using an explorative review method to discuss how the widespread use of antibiotics often led to bacterial resistance and antibiotic residue in food animals, which negatively impacted humans and animals.

Results – The study showed that treating bacterial resistance is a therapeutic challenge for physicians and veterinary professionals. Increased treatment failure rates, the severity of disease-causing infections, the frequency of blood infections, the length of time patients were sick, and the death rate in both humans and animals are all signs that the overuse of antibiotics is becoming a catastrophe.

Discussion – To prevent the negative effects of antibiotics in people, animals, and the environment, especially in developing nations, this article ends by recommending that strict guidelines, laws, and regulations regarding the use of antibiotics in clinical human and veterinary medicine be implemented. Concern must be expressed about the effects of inactivity on public health, both now and in the future. We may attempt to reverse the global resistance issue by increasing the use of antibiotics and reducing the frequency of resistance genes at all levels. Ultimately, the safety of animal products depends on the proper use of antibiotics in animal husbandry under the supervision of a veterinarian.

Keywords: bacteria, antibiotic resistance, man, animal husbandry, public health

1 Background

Antibiotic resistance has far-reaching public health ramifications that must not be overlooked. Antibiotic resistance requires collaboration, which begs the question, “How do human, environmental, and animal health work together to address antibiotic use and resistance?” Bacteria have been acknowledged as causal agents of several diseases in medical terminology, and they need to be controlled. The discovery of these chemicals and antibiotics resulted in enormous medical progress.

Antibiotics are drugs that stop bacteria from growing or killing them. Antibiotics are described by Giguère [1], as any agent of natural, semi-synthetic, or synthetic origin that destroys or slows down the development of bacteria at *in vivo* concentrations by interacting with a specified target. Alexander Fleming inadvertently discovered antibiotics in 1928 when he noticed a fungus killing Staphylococci (*Penicillium notatum*). Selman Waksman discovered antibiotics such as streptomycin in 1943 when he isolated streptomycin from Streptomyces. Streptomycin was discovered to be active against all Gram-negative bacteria, and it was the first antibiotic to kill *Mycobacterium tuberculosis*. Gram-negative bacteria and *Mycobacterium tuberculosis* were the most common causes of death [2]. Penicillin’s discovery and subsequent adoption by the world as the most effective life-saving medicine in the world for treating

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some of mankind's oldest plagues, such as syphilis and gangrene, marked a watershed moment in medical history. Because of the discovery of antibiotics, human society has enjoyed reduced morbidity from combat, improved food production, and higher life expectancy. The discovery of antibiotics has enabled additional reductions in infectious disease deaths and disability, despite major advances in community health and medicine and a fall in communicable disease deaths before the discovery of penicillin [3].

Antibiotic and antibacterial are two terms that are interchangeable and are classified as natural (e.g., penicillins produced by fungi in the genus Penicillium) or semisynthetic or synthetic (e.g., sulfonamide, the quinolones, and oxazolidinones). Antibiotics were divided into two groups centered on their biological activity: bactericidal agents (those that kill germs) and bacteriostatic agents (those that prevent bacteria from multiplying) (i.e., slow down or stall bacterial growth). According to Pankey and Sabath [4], the success of antibiotic treatment using antibacterial chemicals is dependent on several causes, including the site of infection, the host defense mechanism, and the bacteria's pharmacodynamic qualities. Antibacterial drugs can be taken orally (ingested), injected intravenously, intramuscularly, or through the subcutis, and applied topically to the intended user's body. Antibiotics are necessary pharmaceuticals for human and animal health and welfare; nevertheless, any chemical that qualifies as antibiotics must be safe for the host (non-toxic), and its usage as chemotherapeutic agents for the management of bacterial infectious illnesses on the host must be tolerated [5]. The properties of antibiotics in veterinary and plant agriculture, as well as aquaculture, were quickly employed when they were developed to treat human infectious diseases. The medicinal, growth-promoting, and preventative use of antibiotics was introduced into agricultural practice in the 1940s, according to Marshall and Levy [6], and became ubiquitous in Europe and the United States. Antibiotics are now widely accepted in both terrestrial and aquatic species. Worldwide, a projected 50% of all antibiotics serve veterinary purposes. Antibiotics are used in veterinary medicine on pets, farm animals, and aquaculture animals, and their use can be classified as therapeutic, prophylactic, or metaphylactic [7]. The term "therapeutic use" refers to the treatment of infections that have already been developed. Antibiotic prophylaxis refers to the use of antibiotics to prevent the spread of infection in individuals or groups. Metaphylaxis is a word for a group-medication process in which sick animals are treated while others in the group are medicated to prevent disease. This review article describes antibiotic mechanisms, presents selected research and findings on antibiotic usage, highlights specific antibiotic resistance findings, links their origins, and provides advice on avoiding their hazards. It contributes to knowledge by recommending that tight measures, legislation, and regulations on antibiotics in clinical human and veterinary medicine be enforced to avoid the detrimental effects of antibiotics on humans, fauna, and the environment, particularly in developing countries.

2 Types and mechanisms of antibiotics

Antibiotics used in both veterinary and human medicine include penicillins, cephalosporins, tetracyclines, chloramphenicol, aminoglycosides, spectinomycin, lincosamide, macrolides, nitrofurans, nitroimidazoles, sulfonamides, trimethoprim, polymyxins, and quinolones [8]. Antibiotics' modes of action can be classified into a variety of groups depending on how they affect bacteria [9]. Antibiotic medicines come in a variety of chemical forms. Different aspects of the bacterial process are targeted by the actions. Antibiotics work by using one of the mechanisms shown in Figure 1:

i. Interference with cell wall synthesis: antibiotics in this group kill bacteria by damaging any of the bacterium's cell contents or walls. Cephalosporins, metronidazole, and penicillin are examples of antibiotics in this group.
ii. Protein synthesis inhibition: when antibiotics interfere with the host, bacterial protein production and other cellular metabolisms are halted. Examples include chloramphenicol, tetracyclines, and macrolides.
iii. Interference with nucleic acid: DNA replication disruption, for example, fluoroquinolones.
iv. Sulfonamides, for example, inhibit metabolic pathways.
v. Bacterial membrane disruption, e.g., polymyxins.

3 The use of antibiotics in humans and animals

Antibiotics have long been used in the battle against bacteria, and they have long been found in the environment. Antibiotics kill germs and minimize infection, allowing billions of people to live longer and healthier lives. The development of antibiotics for the treatment of communicable illnesses has considerably reduced morbidity and mortality [10]. Antibiotics play a big role in improving the general public's health. Antibiotics are potent drugs that combat infections and, when taken correctly, can save lives. They either prevent bacteria from multiplying or kill them. The host's immune system, which acts as the host's natural defense force, can typically destroy bacteria before they

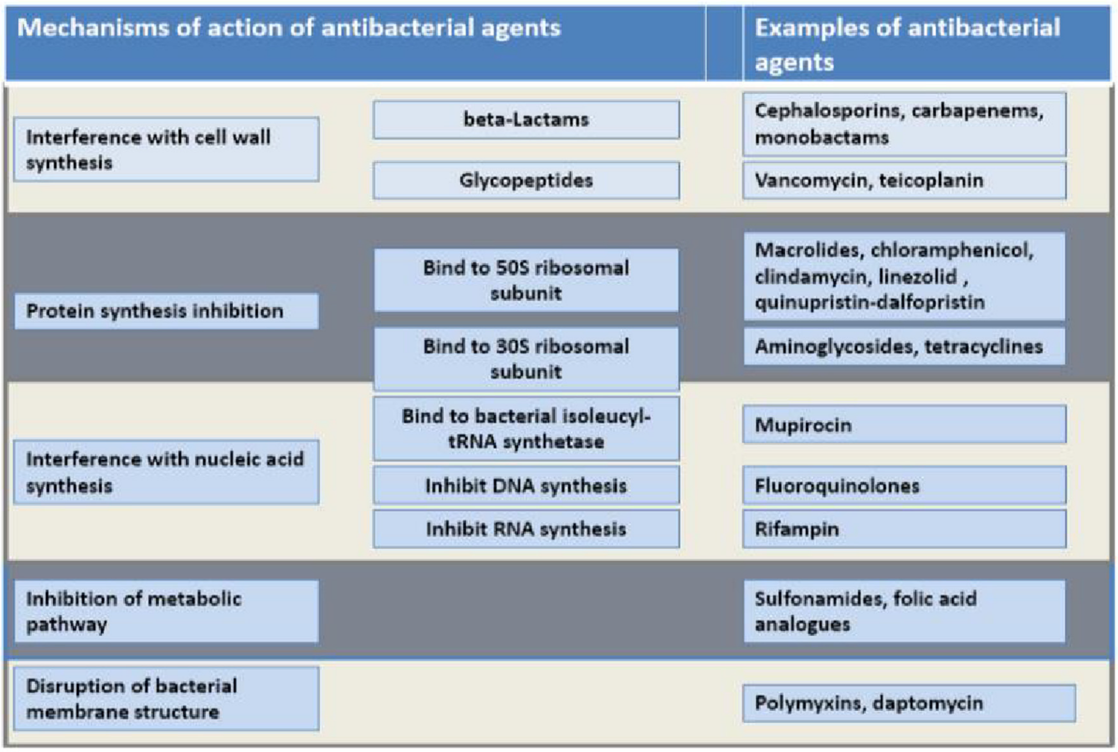

Figure 1: Different mechanisms of action of antibiotics.

proliferate and cause symptoms. White blood cells destroy harmful germs, and even if symptoms appear, the immune system is typically able to manage and combat the infection. However, there are occasions when the number of hazardous germs is excessive, and the immune system is unable to combat them all. Antibiotics come in handy in this situation. Antibiotics do not work against viruses, although they can aid in the treatment of secondary bacterial infections that arise as a result of viral infections. However, Jing et al. [11] reported that extended use of certain antibiotics could result in adverse effects, such as diarrhea, nausea, vomiting, rash, and upset stomach, as well as fungal infections of the mouth, digestive system, and vaginal area.

Antibiotics are used directly by man and indirectly through antibiotics in livestock (food, companion, work, recreation, and aquaculture). According to Van-Boeckel et al. [12], global antibiotic use in food animals, including aquaculture, is rapidly increasing, with estimates of 63,151 tons in 2010 and a projected increase of 67% by 2030. More than 50% of the antibiotics that are used for human therapy are now being commercialized and utilized in animal farming in many countries of the world [13]. The largest estimated global antibiotic usage is in Brazil, Russia, India, and South Africa [12,14] pointed out that antibiotic consumption in Russia, Brazil, South Africa, and China is likely to double by 2030 as the population is projected to increase by 13%. The overall quantity of antibiotics used worldwide in agriculture is estimated to range between 63,000 and 240,000 tons [14], although this figure is not precise because of inadequate collection of data and surveillance of antibiotic resistance in certain countries, especially African countries. Half of all antibiotics manufactured globally are used in animal production, and they account for the biggest share of pharmaceutical sales in terms of both volume and dollar value of any medications used in animal production [15]. According to Odwar [16], around 12.5 million kg of the annual 17.5 million kg of antibiotics produced in the United States are used for non-therapeutic uses in cattle production, whereas just 1.5 million kg are used for human medical therapy. However, there is a lack of dependable data on antibiotic intake by humans and animals in Africa [17]. Farm animals are given antibiotics for therapy and prevention, as well as to boost growth and feed efficiency. Enteric and lung infections, skin and organ abscesses, and mastitis are the most common infectious disorders treated. They are commonly utilized in the early stages of an animal's life, such as in broiler chickens, weaning pigs, and calves. Individual antibiotics are also used to treat illnesses caused by a number of bacterial diseases in individual animals.

Antibiotics are utilized by the majority of poultry and livestock farmers in most African countries to prevent and treat disease. Antibiotic use is regulated in certain advanced countries, particularly in the animal industry. In industrialized countries, strict controls on the use of veterinary medications are in place to protect consumers. Nevertheless, in poor countries, the situation is the opposite [18]. Antibiotics at therapeutic levels, for example, are commonly given to groups of fish that share tanks or cages via the oral route for brief periods in aquaculture. Antibiotics have played an essential role in the aquaculture sector in terms of treatment and growth promotion [19]. While antibiotics are administered via parenteral and oral routes in terrestrial animals, the most common method for delivering antibiotics to fish is to mix the antibiotic with the prepared feed. Antibiotics, on the other hand, are not properly metabolized by fish, and they are passed largely unused back into the environment in feces. According to Burridge et al. [20], around 75% of the antibiotics supplied to fish are excreted into the water, and this fact has prompted most countries with a significant aquaculture business to take some control measures through government organizations. The government agency in charge of veterinary medicine must authorize all medications used legally in aquaculture and terrestrial animals. The food and drug administration in the United States has approved the following antibiotics: oxytetracycline, florfenicol, and sulfadimethoxine/trimethoprim for use in aquaculture. Antibiotic use standards may be established by regulatory bodies, which may include authorized administration routes, dose forms, withdrawal durations, tolerances, and use by species, as well as dose rates and limitations. In Norway, for example, antibiotics require a veterinarian's prescription, before making their use in therapy. Antibiotics are only available in pharmacies and feed plants that have been approved by the Norwegian Medicines Agency. It is mandatory in Norway to report the number of antibiotics used and to keep track of prescriptions. Antibiotics were frequently added to poultry feed by the majority of poultry producers to prevent disease and boost productivity. Farmers' most regularly utilized antibiotics were tetracyclines (oxytetracycline and chlortetracycline) [21].

The majority of poultry producers did not use a veterinarian for prescriptions and instead self-administered medications to their animals, with only a minority reporting treating their flocks based on professional advice and prescriptions. The cattle producers also treated their animals with antibiotics and antiprotozoal medications on their own, claiming to have prior experience. When treating their animals, once they feel they are ill or stressed, the majority of the farmers mix at least three antibiotics for each treatment. Oral medicine in drinking water and intramuscular injections have been mentioned as common means of administration. Farmers reportedly obtained the drugs via veterinary retail outlets located throughout the country, particularly in cattle markets, while some farmers obtained drugs directly from company sales representatives and hawkers. The withdrawal period specified on antibiotic packages was the amount of time that had to pass before the animal treated was safe to be consumed. Farmers are unaware of the antibiotic withdrawal period or do not follow it. They were unable to stop selling or eating their eggs, milk, or meat to observe the antibiotic withdrawal period on the animals. They frequently sell their eggs and meat after administering veterinary medications to the flock for curative or sub-therapeutic purposes. International standards defined by the combined Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) Codex Alimentarius Commission make food safety initiatives and monitoring mandatory. Maximum residual limits (MRLs) of approved veterinary pharmaceuticals in food are established based on legally permissible amounts of parent medications and/or metabolites in food products from treated animals that are safe for consumers [22]. As recognized by the WHO based on their importance to human health, antibiotics that are allowed to be used in both animals and humans are listed in Table 1. In addition, in advanced countries, maximum antibiotic residue limits are prescribed and legalized, as illustrated in Table 2.

4 Development of resistance, resistance mechanisms, and cross-resistance

As a result of indiscriminate antibiotic usage, the development of antibiotic resistance among microorganisms has become a global concern. Antibiotic resistance is defined as a microorganism's ability to resist an antibiotic's growth inhibitory or killing activity beyond the typical susceptibility of the specific bacterial species [25]. A bacterium can develop resistance to an antibiotic it was previously sensitive to, meaning the antibiotic will no longer be able to kill or hinder the microorganism's development at the same level. Antibiotic resistance is explained in terms of its various kinds and mechanisms. Antibiotic resistance can either be a natural characteristic of the infected organism or be acquired. The intrinsic resistance is a natural property of the bacteria resulting from mutation or acquisition of new genetic material [26]. Intrinsic resistance refers to bacteria in their natural state that are insensitive to an antibiotic without acquiring resistance factors. The mutations that result in antibiotic resistance are spontaneous

Table 1: Antibiotics prescribed in both animals and humans, as classified by the WHO according to their significance to human health

Sl. no.	Antibiotic classes	Human	Animal			
			Species	Therapeutics	Prophylactics	Growth promoter
1	Aminoglycosides: gentamicin, neomycin, streptomycin	Yes	Beef cattle, goats, poultry, sheep, swine, certain plants	Yes	Yes	NA
2	Penicillins: amoxicillin, ampicillin	Yes	Beef cattle, dairy cows, fowl, poultry, sheep, swine	Yes	Yes	Yes
3	Cephalosporins, third-generation: ceftiofur	Yes	Beef cattle, dairy cows, poultry, sheep, swine	Yes	Yes	NA
4	Glycopeptides: Avoparcin, vancomycin	Yes	Poultry, swine	NA	NA	Yes
5	Macrolides: erythromycin, tilmicosin, tylosin	Yes	Beef cattle, poultry, swine	Yes	Yes	Yes
6	Streptogramins: Virginiamycin, quinupristin-dalfopristin	Yes	Beef cattle, poultry, swine	Yes	Yes	Yes
7	Quinolones: (fluoroquinolones) sarafloxacin, enrofloxacin	Yes	Beef cattle, poultry	Yes	Yes	NA
8	Carbapenems, lipopeptides, oxazolidinones, cycloserine, ethambutol, ethionamide, isoniazid, para-aminosalicylic acid, pyrazinamide	Yes	NA	NA	NA	NA
9	Tetracyclines*: chlortetracycline, oxytetracycline, tetracycline	Yes	Beef cattle, dairy cows, honey bees, poultry, sheep, swine, catfish, trout, salmon, lobster	Yes	Yes	Yes
10	Sulfonamides*: sulfadimethoxine, sulfamethazine, sulfisoxazole	Yes	Beef cattle, dairy cows, fowl, poultry, swine, catfish, trout, salmon	Yes	NA	Yes
11	Polypeptides**: bacitracin	Yes	Fowl, poultry, swine	Yes	Yes	Yes
12	Lincosamides**: lincomycin	Yes	Poultry, swine	Yes	Yes	NA
13	Babermycin***: flavomycin	NA	Beef cattle, poultry, swine	NA	Yes	Yes
14	Ionophores***: monensin, salinomycin, semduramicin, lasalocid	NA	Beef cattle, fowl, goats, poultry, rabbits, sheep	NA	Yes	Yes

*Antibiotics classified by the World Health Organization as highly important for humans; **antibiotics classified by the WHO as important for humans; ***antibiotics classified by the WHO as not known to be used in humans; and NA = not applicable.
Source: Ref. [23].

Table 2: MRL (μg/kg) for veterinary residues

S/N	MRL (μg/kg)	Antibiotics
1	0	Nitrofurans, nitroimidazoles, chloramphenicol, novobiocin
2	4	Benzyl penicillin, ampicillin, amoxycillin
3	20	Cefquinome
4	30	Oxacillin, cloxacillin, dicloxacillin
5	40	Erythromycin
6	50	Polymyxine, tylosine, trimethoprime
7	75	Quinalones
8	100	Tetracycline, oxytetracycline, chlortetracycline, ceftiofur, neomycin, sulfonamides
9	200	Dihydrostreptomycin, gentamycin, spiramycin

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Source: Ref. [24].

events involving changes in chromosomal nucleotide sequences [26]. Intrinsic resistance is a characteristic of bacteria that develops as a result of mutation or the acquisition of new genetic material [27]. Low and sporadic medication dosage favors the establishment of mutational resistance [28]. Resistance can be acquired through mutation or the transfer of extrachromosomal genetic material, which is then followed by the selection of resistant organisms during therapy [29]. If an acquired resistance gene is expressed, it triggers a resistance mechanism. Depending on whether the resistance gene can be produced in the presence of the antibiotic treatment, resistance mechanisms can be either constitutive or inducible [30]. Different resistance mechanisms are linked to the methods of action of various antibiotic medications on the bacterial cell, yet a single organism might have many resistance mechanisms. Antibiotic drug modification, reduced intracellular accumulation, and target site alteration are the most common resistance mechanisms [31]. Antibiotic drug modification is the enzymatic alteration or inactivation of an antibiotic medication to prevent it from reaching its target site. In Gram-positive and Gram-negative bacteria, enzymatic inactivation includes the inactivation of penicillins and cephalosporins by lactamases and aminoglycosides by acetyl-, adenyl-, and phospho-transferases [32]. Another process is a change in bacterial cell-wall porins, which results in either a lower absorption or a higher clearance of the antibiotic medication from the cell. The antibiotic drug's normal intracellular action is hampered by the lower intracellular accumulation. The presence of tetracycline efflux genes, which can be present in a wide variety of bacteria, can cause an increase in tetracycline clearance [33]. A chemical change at the target location can result in a resistance mechanism [34]. For example, mutations in the DNA gyrase and topoisomerase genes can result in structural alterations that prohibit antibiotics like fluoroquinolones from binding to their target locations. Finally, a bypass effect hinders the antibiotic drug's inhibitory action, which is a fourth but less common method. This is a well-known situation. Conjugation is the most prevalent and crucial method of resistance transfer, in which two organisms exchange R-plasmids via sex-pilus contact. R-factors can also be secreted by one bacteria and absorbed by another through the cell wall (transformation). R-factors can thus circulate in humans, animals, and the environment, as well as between humans and animals [35].

Antibiotic resistance in pathogenic bacteria can spread to other bacteria, resulting in zoonotic infections, whereas resistant non-infectious bacteria can serve as a reservoir for R-plasmids in other virulent organisms. At least four biochemical pathways are encoded by R-factors: enzymatic degradation, antibiotic change by the cell, antibiotic target site alteration, and production of a resistant variant of a key metabolic enzyme that is typically sensitive to various antibiotics [36]. Cross-resistance is caused by a resistance mechanism in bacteria that makes them resistant to many antibiotics. Because they are structural analogues, this is typically true for different molecules of a given class of antibiotic medications, such as tetracyclines. Tet (M) genes, for example, cause oxytetracycline, doxycycline, chlortetracycline, and minocycline resistance [36]. Multidrug efflux pumps (mex) genes, on the other hand, can generate cross-resistance to a wide range of structurally diverse harmful chemicals, including antibiotics [37]. Analogue antibiotic medicines that act on the same target location of bacteria can cause cross-resistance. Resistance to macrolides, lincosamides, and B-compounds of the streptogramins is caused by the presence of one erm (X) gene. This gene has been discovered in bovine udder streptococci, swine pneumonic lungs, and fecal enterococci from various animal species in livestock [38]. Co-selection may be caused by solitary genes that produce cross-resistance or by diverse resistance genes aggregated on a single mobile genetic unit (transposons or plasmids) [39]. Co-selection occurs when bacteria develop resistance to multiple antibiotics when only one antibiotic is employed. As a result, co-selection is quite important. Co-selection in poultry caecal coliforms was proven by Levy et al. [40]. Tetracyclines taken orally reduced the susceptibility of the bacterial caecal flora to tetracyclines, ampicillin, streptomycin, and sulfonamides. After the use of avoparcin (glycopeptide) as a growth stimulant was banned, Sorum et al. [41] discovered a substantial difference in the persistence of glycopeptide-resistant enterococci (GRE) in Danish swine and poultry. Within the same period, GRE levels in poultry dropped from 80 to 10%, whereas levels in swine dropped from 25 to 20% within the same period. The glycopeptide resistance level was maintained by the vanA gene, which was selected using tylosin due to its relationship to the ermB gene [42].

5 Information about antibiotic resistance worldwide: Evidence of antibiotic resistance has been documented

Antibiotic resistance is common in low-income countries among bacteria that are likely to spread in the community, such as those that cause pneumonia, diarrheal diseases, tuberculosis (TB), sexually transmitted diseases, and malaria [43]. According to Nugent et al. [44], drug resistance has drastically increased the cost of battling TB and malaria, as well as hindered progress against infantile diarrhea and pneumonia. Table 3 shows documented antibiotic resistance findings in certain low-income and developing countries around the world.

6 Consequences of antibiotic resistance for public health

Two trends are driving a global scale-up in antibiotic consumption, according to the State of the World's Antibiotics report [55]. First, as earnings increased, so did access to antibiotics. It saves lives, but it also encourages the development of resistance through increased use, both acceptable and unsuitable. Second, the growing demand for animal protein, which resulted in the intensification of food animal production, has led to increased antibiotic use in agriculture, which is fueling resistance once again. Without efficient antibiotic treatments, the fall in infectious diseases and many gains in public health and modern medical achievements, such as major surgery, organ transplants, treatment, and cancer chemotherapy, would not be conceivable [56]. Antibiotic resistance mechanisms are evolving, re-emerging, and spreading globally, posing a threat to our ability to cure infectious diseases, resulting in extended sickness, debility, and death, as well as an increase in health care costs. Resistant infections lengthen hospital stays and increase patient mortality. According to Hernando-Amado et al. [57], antibiotic-resistant organisms can be found in people, food, animals, plants, and the environment, and they can travel between habitats. Due to improvements in global transportation systems, the world has become a global village with quick mobility of people and goods. When microorganisms (such as bacteria, fungi, viruses, and parasites) are exposed to antibiotic compounds, they become antibiotic-resistant naturally and over time [57]. As a result, therapies fail, and infections remain in the body, increasing the chance of the infection spreading to others [57]. According to O'Neill [58], and other experts, antibiotic resistance is a natural phenomenon, but it is caused by the misuse and overuse of antibiotics.

There is no doubt that human overuse and/or misuse of antibiotics contributes to the development of antibiotic resistance [59], and this is linked to healthcare providers' prescribing patterns and patients' medication-taking practices [60]. Since the early 1960s, problems linked to the development and spread of antibiotic resistance in hospitals have been on the rise and are now seen as a major threat to clinical practice, resulting in high mortality and healthcare costs. Many specialists believe that if we want to reduce the occurrence of bacterial resistance, we need to reduce the inappropriate and overuse of antibiotics. Human antibiotic consumption, on the other hand, is steadily increasing throughout the world. Empirical antibiotic therapies are used by doctors when they need to treat a patient right away and cannot wait for laboratory results, but they can fail if the organism has developed resistance. Experimental therapies are therapeutic regimens based on prior experience that are usually given before a confirmed diagnosis is made and this practice has led to catastrophic. Quinolone failure in the treatment of invasive salmonellosis has been described, as has vancomycin failure in the treatment of nosocomial vancomycin-resistant enterococci (VRE) infection [61]. VRE and other antibiotic-resistant respiratory pathogens, including *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*, are becoming epidemic [10]. Globally, the pandemic of drug-resistant *Staphylococcus aureus* and *Enterococcus* spp. poses the largest risk among Gram-positive pathogens [62,63].

Antibiotics are now widely used in modern livestock production for illness prevention and treatment, as well as growth stimulation. Due to a lack of legislation, poor management methods, and illness endemicity, antibiotics have been freely administered to food animals in numerous nations [64]. Antibiotic-resistant bacteria have caused an increase in the number of foodborne diseases [65]. A few recent studies [66,67] have found a link between antibiotic usage in food animals and the emergence of antibiotic resistance in human and animal diseases. A complex antibiotic resistance transmission route exists between livestock and humans, thus posing health risks to both animals and humans [68]. The cohesion of the antibiotic's related

Table 3: Documented evidence of antibiotic resistance exhibited by isolated bacteria from different media worldwide

S/N	References	Location	Objectives	Findings
1	[45]	Ibadan and Ikorodu, Nigeria	To isolate and identify bacteria from diseased *Clarias gariepinus*, as well as to analyze the presence of antibiotic resistance in these isolated bacteria	Antibiotic resistance has been established, possibly as a result of the widespread use of unlicensed or authorized antibiotics in aquaculture, posing serious public health risks
2	[46]	Lebanon	To determine certain bacteria isolated from raw milk samples' possible microbial resistance	All of the *S. aureus*, *E. coli*, and *L. monocytogenes* isolates showed high resistance to gentamicin and streptomycin, indicating that antimicrobial-resistant strains of the pathogens have become exceptionally common in raw milk
3	[47]	Porto, Portugal	To consider the likelihood that the existence of antimicrobial residues and antibiotic-resistant bacteria (ARB) in sewage is related to the structure and makeup of the bacterial community as well as the effluent's ARB	Antibiotic residues, bacterial community structure and composition, and antibiotic resistance have all been linked
4	[48]	Madrid, Spain	Determination of antibiotic-resistant patterns of Gram-negative bacteria isolated from manure produced by dairy and beef cattle farms	Gram-negative bacteria obtained were resistant to a variety of antibiotics, with multi-resistant bacteria being more prevalent in beef farms than in dairy farms
5	[49]	Calbuco Archipelago, Chile	Determined the number of culturable bacteria and ARB in marine sediments	Antibiotic-resistant bacteria were discovered in marine sediments, possibly as a result of the use of huge doses of antibiotics in aquaculture
6	[50]	Ibadan, Nigeria	To determine the pattern of antibiotic resistance in isolated bacteria from different aquatic environments and fish obtained randomly at different locations in Ibadan	The study determined the prevalence of contributive resistant bacteria in bacteria isolated from various aquatic settings, including captured and cultured fish, all of which have a significant impact on public safety
7	[51]	Kolkata, India	To determine the association of opportunistic human bacterial pathogens in cultured freshwater fishes and their sensitivity to broad-spectrum antibiotics	The study established that there is an increased likelihood of antibacterial resistance developing in new human bacterial infections originating from freshwater aquaculture, with such ARBl pathogens infiltrating the food chain
8	[52]	Nankoku, Kochi Japan	To determine the occurrence and resistant efficiency of bacteria collected from four shrimp farming zones	Antibiotic residues were found in abundance in shrimp pond mud, as well as a significant level of antibiotic resistance
9	[53]	Ogbomoso, Nigeria	To determine the resistance pattern of bacterial isolates obtained from clinical origins, soil, industrial effluent, orange juice products, and drinking water to the commonly used antibiotics	Seven distinct resistance patterns were detected among the bacterial isolates acquired from water, effluent, and orange juice products among the eight antibiotics tested for resistance on five strains of each bacterium
10	[54]	Kainji Lake Basin, Nigeria	To determine the pattern of antibiotic resistance in enteric bacteria isolated from fish and their aqueous environment	Resistance markers found in separated bacteria and water were found to be in the 55.8–64.8% range

structural components induces cross-recognition and cross-resistance for all or most antibiotics in the same antibiotic class. The introduction and spread of VRE in hospitals as a result of the widespread use of avoparcin in animals, a glycopeptide antibiotic with structural similarities to vancomycin. Another example is resistance to virginiamycin cross-reacting with quinupristin-dalfopristin, a human streptogramin [69]. In extreme cases, therapeutic failure of the antibiotic of last resort can result in mortality. When alternative, less toxic, less expensive, or broad-ranging medications have failed, these treatments are usually reserved as a last resort. Antibiotics are commonly provided without a confirmatory diagnosis in most impoverished and underdeveloped nations in small animal veterinary facilities, and experimental therapies based on experience are also prevalent. Antibiotic resistance caused by a specific antibiotic used in food animals may diminish the efficacy of most or all members of the same antibiotic family, some of which are critical in human medicine [70].

Antibiotic residues in the environment are another source of human health risk. Although human antibiotic use is the most common cause of antibiotic contamination in aquatic and terrestrial environments, antibiotic use in livestock, poultry, and aquaculture also contributes considerably to this developing problem. A variable number of antibiotics may stay active in the expelled biological matter (usually feces or urine) after passing through the animal [71]. In addition to human-use antibiotics, the cattle, poultry, and aquaculture industries are major contributors to antibiotic contamination in aquatic and terrestrial environments. Surface run-off, drift, and leaching into the Earth's deeper layers can all occur as a result of antibiotic-laden manure or slurry being sprayed on agricultural lands or when grazing animals deposit dung directly into the environment [72]. Antibiotics that make their way into the environment will stay biologically active in some form. Antibiotics in low sub-therapeutic quantities that accumulate over time may have serious consequences for particular ecosystems. Antibiotic concentrations in the environment may impose selective pressure on bacteria and encourage the transmission of resistance genes, resulting in the "resistive" mixing pot [73]. Antibiotics will be used indefinitely, resulting in the emergence of resistance in the target bacteria. The amount and types of ARB in the colon vary from day to day, approximately 40% of people have some ARB in their colon at any given time [74]. Antibiotic-resistant bacteria tend to do little harm in the great majority of cases, and they normally make up a small percentage of total bacteria in the intestines, perhaps one antibiotic-resistant bacterium. Ingestion of contaminated animal products and environmental exposures resulting from contaminated animal waste expose humans to antibiotic residues. The greatest evidence suggests that ARB are consumed with meals on a daily basis, that they normally do not establish themselves in competition with bacteria already present in the intestine, and that their numbers fluctuate due to the opposing effects of ingestion and excretion. Antibiotics, of course, can change that pleasant state. According to Allen [75], if a person receiving an antibiotic ingests a bacterium that is resistant to that antibiotic, the bacterium consumed will have an edge in terms of development over the other bacteria. They may then multiply to become the gut flora's dominating component, resulting in disease. Antibiotic-resistant microorganisms, which were originally obtained from food-producing animals, have a complicated and diversified role in the emergence and spread of antibiotic resistance in humans. Food or other animal product contamination, occupational exposure for farm workers and fish keepers, fish sellers, milk sellers, abattoir employees, veterinary surgeons, and health workers are the main routes germs can travel from animals to people. Bacteria can also spread through leisure activities such as swimming and fishing, as well as environmental contamination such as manure harboring resistant bacteria, resistance genes, and antibiotic residues [76].

Furthermore, many enterprises, particularly pharmaceutical companies, lack effluent treatment systems, resulting in untreated wastes being dumped on the ground or discharged into neighboring natural water bodies [77]. Fecal matter from diverse sources is washed from polluted land and eventually conveyed into different water bodies due to the deposition of human and animal excreta, and other environmental contaminants into natural water during the rainy season. The aquaculture sector is concerned about the growth of resistant bacteria in rivers as a result of fish farming practices, terrestrial agriculture run-off, or sewage outflow surrounding fish farms. Antibiotic residues pose a public health concern based on the amount of antibiotics encountered or taken, i.e., the exposure. In an FAO/OIE/WHO consultation on scientific issues related to non-human usage of antibiotics held in Geneva in December 2003, it was concluded that antibiotic residues in foods represent a significantly less important human health risk than the risk related to ARB in food. The presence of ARB in foods of animal origin is a potential health threat because resistance can be transferred among bacteria, and antibiotic-resistant pathogens may not respond to antibiotic treatments. Several human diseases, including *E. coli, Salmonella, Shigella,* and *Vibrio* spp., were found among the resistant isolates. Antibiotic-resistant bacteria in cattle and aquaculture pose a health danger to the general public [78]. The emergence of acquired resistance in fish infections and other aquatic bacteria means that these bacteria can serve as a reservoir for resistance genes, which can then be transmitted and eventually end up in human pathogens. In 2013, the Centers for Disease Control (CDC) stated that "the human race is in the post-antibiotic era," cautioned that antibiotic resistance is becoming dreadful. The plasmid-borne resistance genes have been transferred from the fish pathogen *Aeromonas salmonicida* to *Escherichia coli*, a human-derived bacterium with pathogenic strains for humans [79]. In other cases, plasmid-borne drug-resistance genes have been transferred from *Vibrio anguillarum*, a fish pathogen, to *Vibrio cholera*, the bacterium that causes human cholera [80].

In a study conducted by Tiamiyu [81] on the bacterial flora of wild and cultured *Clarias gariepinus* (African Catfish) and their public health implications in some aquatic environments in Ibadan, Oyo state, some bacteria strains isolated and suspected to have originated from humans as a result of consumer and worker interaction with the fish and environment were subjected to antibiotic sensitivity testing. The Gram-positive disc (Abtek Biological Ltd) containing the following: cotrimoxazole (Cot), 25 µg; gentamycin (Gen) 10 µg; nalidixic acid (Nal) 30 µg; ofloxacin (Ofl) 30 µg; chloramphenicol (Chl), 10 µg; augmentin (Aug), 30 µg; amoxycillin (Amx) 25 µg; and tetracycline (tet), 10 µg; and poly disc Gram-negative, Mutti susceptibility disc (Poly-tesMed Laboratories) containing the following: nitrofuratin (Nit), 100 µg; ciprofloxacin (Cip), 5 µg; tetracycline (Tet) 50 µg; norfloxacin (Nfl), 10 µg; amoxicillin (Amx), 30 µg; ofloxacin (Ofl), 5 µg; chloramphenicol (Chl), 10 µg; cefuroxime (Cfx), 30 µg; ampicillin (Amp), 10 µg; and gentamycin (Gen), 10 µg were used. The antibiotic sensitivity tests on the bacterial isolates demonstrated multiple drug resistance of 4–8 antibiotics among the 16 bacterium strains from the genera *Escherichia* and *Salmonella* (Table 4), and *Staphylococcus* and *Streptococcus* (Table 5). The relatively high proportion of antibiotic resistance found in this experiment resulted from antibiotic misuse or abuse in the environment. The study determined the prevalence of contributing resistant bacteria in bacteria isolated from various aquatic environments, captured and cultured fish, and concluded that the drug-resistant food-borne infections discovered could have unfavorable public health consequences.

Table 5: Antibiogram of some strains of *S. aureus* and *Streptococcus* spp. obtained from the fish samples

Isolates	Nal	Gen	Ofl	Tet	Aug	Nit	Cot	Amx	**** (%)
*St	−	+	−	−	−	−	−	−	87.5
*St	−	+	−	+	+	−	−	−	75.0
**St	−	+	+	−	−	−	−	−	62.5
**St	−	+	+	+	−	−	−	+	50.0
*Sp	−	−	−	−	−	+	−	−	87.5
*Sp	−	−	+	−	−	−	−	−	87.5
**Sp	−	−	−	−	−	+	−	−	87.5
**Sp	−	−	+	−	−	−	−	−	87.5
%***	100	50	50	75	87.5	62.5	100	87.5	

Antibiotics abbreviations as defined in the narrative; *Streptococcus* sp.; St, *S. aureus*; +, susceptible; −, resistance; *, wild catfish; ** cultured catfish; ***, % resistance of the isolates to each antibiotic; ****, cumulative % resistance of each bacterium to all the antibiotics.
Source: Ref. [81].

Since the majority of medicines used to treat diseases are produced by environmental bacteria, antibiotic-resistant genes must have emerged in non-clinical or artificial settings as well [82]. A better understanding of the ecological role of antibiotics and antibiotic resistance in natural environments may eventually help to predict and counteract the emergence and evolution of resistance in order to reduce this scourge, which has been estimated to kill around 700,000 people each year, with that number expected to rise to an estimated 10 million deaths annually by 2050 [83].

Table 4: Antibiogram of some strains of *Salmonella* sp. and *E. coli* obtained from the fish samples

Isolates	Nit	Gen	Amp	Cfx	Chl	Ofl	Amx	Nfx	Tet	Cip	**** (%)
*Ec	−	+	−	−	−	+	−	−	+	−	70
*Ec	+	+	−	−	−	−	−	+	−	−	70
**Ec	+	+	−	−	−	−	−	+	−	−	70
**Ec	+	+	−	−	−	−	−	−	−	−	80
*Sa	+	+	+	−	+	−	+	−	−	−	50
*Sa	−	+	+	+	+	−	+	−	−	−	50
**Sa	−	+	+	−	+	−	+	−	−	−	60
**Sa	−	+	+	−	+	+	+	−	−	−	50
%***	50	0	50	87.5	50	75	50	62.5	100	100	

Antibiotics abbreviations as defined in the narrative; Ec, *E. coli*; Sa, *Salmonella* sp.; +, susceptible; −, resistance; *, wild catfish; ** cultured catfish; ***, % resistance of the isolates to each antibiotic; ****, cumulative % resistance of each bacterium to all the antibiotics.
Source: Ref. [81].

7 Does animal or human resistance to antibiotics exist?

Antibiotic resistance is an issue that must be addressed in light of the increasing use of antibiotics in humans and animals. Antibiotics were created to treat human infectious diseases, but their widespread use in agriculture has transformed agriculture worldwide. Arguments about the appropriateness of using antibiotics to treat sick animals frequently occur. Antibiotics are used to treat individual animals with bacterial diseases and to prevent infections in herds or flocks, as well as to boost growth, which is a contentious and common application. Concerns about hazards have dominated discussions regarding subtherapeutic usage, but the fact that they continue while being sanctioned by multiple government authorities is compelling evidence that they provide advantages to consumers. Whatever the hazards, any decision about sub-therapeutic usage will take into account both risks and benefits, and continuous efforts to better nail down risk estimates at the expense of benefits may have minimal impact on judgments. In any event, determining the true danger of subtherapeutic use is a difficult task. More debate erupts regarding sub-therapeutic applications in prophylaxis and growth promotion, as well as the possibility of antibiotics licensed solely for therapeutic purposes being diverted to other uses. According to Katakweba et al. [84], treating animals with antibiotics could result in the contamination of meat with ARB, which could result in three issues. First, pathogenic microorganisms that are resistant to antibiotics may be transmitted to people. Second, antibiotic-resistant genes can be transmitted from non-pathogenic bacteria in animals to pathogenic bacteria in humans. Third, people on antibiotic therapy will swallow ARB that does not typically infect humans, the medication will have affected the human flora, and the alteration will promote the growth of germs that are harmful to human health. Any of these side effects can be harmful to a person's health. Antibiotics are necessary for animal health and production, but they are also important for human health. Thus, their use in animal populations may have a negative influence on human health. Antibiotic use on farms is unquestionably harmful to human health. Antibiotic use can stimulate the growth of germs that can contaminate meat and poultry and create difficult-to-treat disease issues in humans. Nonetheless, the cattle sector maintains that, while antibiotic use may contribute to antibiotic resistance in farm microorganisms, it is not a major human health concern and that little change in present procedures is required. In extreme cases, therapeutic failure of the antibiotic of last resort can result in mortality [85].

Animals transmit resistant organisms to people through contaminated meat-eating, animal-to-human transfer, animal-to-animal transfer, and the environment [86]. Clinical isolates resistant to a specific antibiotic were discovered in ecological investigations after the antibiotic was introduced into feeding operations [87], and less resistant isolates were found in humans after the antibiotic's usage was stopped [88]. Resistant organisms have been connected to humans, farm animals, and grocery store meats in cross-sectional studies [89], and resistant bacteria in food products have been linked to animal antibiotic use [90]. Multiple connections exist between the human, animal, and environmental compartments, allowing for the migration of germs as well as mobile genetic elements and medications [91]. Antibiotic resistance, which arises when bacteria develop the ability to withstand the effects of an antibiotic, is responsible for at least 2 million illnesses per year. According to the Centers for Disease Control and Prevention, it also causes at least 23,000 deaths per year. Overuse, poor infection control among health personnel, and dwindling research into new drug development are all contributing to this. Workers in antibiotic manufacturing companies and farms where antibiotics are incorporated into animal feedstuffs are all exposed to antibiotics and individuals who are not exposed to antibiotics, on the other hand, carry R-plasmids at small levels [92], and R-plasmids form and disseminate in the environment, as well as in humans and animals, even when antibiotics are not present [93]. Animals that have been given antibiotics frequently have more R-plasmids carrying colibacilli flora [94]. On the other hand, R-plasmids have been found on farms where antibiotics are not utilized for treatment or growth promotion. As a result, R-factors are detected in both animals and people in the absence of any selective pressure from antibacterial medicines [94]. Many of the antibiotics used in animal feed are also used to treat human infections. Antibiotics in feed have aroused concerns among public health officials and consumers since such high levels of drug use may result in bacterial resistance in these animals' gastrointestinal tracts [95], and resistance to antibiotics can be passed on to bacteria in the gastrointestinal tract.

8 What options do we have? What can we do?

One of the reasons for the emergence of ARB in the environment has been attributed to the usage of antibiotics as feed additives in food animals. Governments should "terminate or rapidly phase out the use of antibiotics for growth promotion in animals if they are also used for the treatment of humans," according to the WHO Global Strategy for Antibiotic Resistance Containment [95]. Appropriate antibiotic usage will heal some sick animals and hasten the recovery of others, as well as increase the well-being of those who have been treated and minimize the transmission of infection to others. The problem is figuring out how to use antibiotics wisely while reducing the possibility of resistance. According to Baquero et al. [96], understanding the molecular and genetic basis of resistance is crucial for creating ways to prevent resistance from emerging and spreading, as well as novel therapeutic techniques for multidrug-resistant organisms. Antibiotics are no longer effective against certain bacterial illnesses. The resistance problem may be reversible, but only if society starts to think about how pharmaceuticals influence both "good" and "bad" microorganisms. To better understand ARB dynamics and inform containment and mitigation solutions to safeguard human and animal health as well as the ecosystem, rigorous policy interventions are critical.

Another important point to consider is whether or not "antibiotic usage in livestock and aquaculture" should be prohibited. Despite the pressing need to develop alternatives to antibiotics in animal husbandry, there is still a case to be made for some amount of antibiotic therapeutic administration. A comprehensive restriction on the use of antibiotics in animal production will come at a cost, so it is critical to ensure that veterinary antibiotic medications are used effectively in veterinary treatment while retaining their efficacy. The National Regulatory Authority, which is in charge of approving the safe use of veterinary antibiotics in food-producing animals, should develop current data requirements for evaluating veterinary antibiotic medication applications. Consumers of animal food (milk, eggs, meat, and fish) must be protected in terms of their health. However, the use of antibiotics in animal production at subtherapeutic levels should be closely scrutinized. Antibiotic use in fish farming and antibiotic medication of terrestrial food animals should be avoided.

Investigating the impact of low-quality veterinary pharmaceuticals as a cause of antibiotic resistance would help stakeholders gain a better understanding of how antibiotic resistance develops and how interconnected factors contribute to the development of resistance. To have an impact, governments, international organizations, pharmaceutical companies, farmers, and meat consumers will need to act on their newfound knowledge. To combat antibiotic resistance and promote good health and wellness for all, each of these stakeholders will have to make modifications to their duties to ensure the appropriate use of quality veterinary medicine. Antibiotics are extensively used in intensive livestock farming and aquaculture. Increased public concern about antibiotic resistance, as well as the need to preserve the ever-dwindling arsenal of antibiotics that work in humans for as long as possible, has led to increased scrutiny of antibiotic use in animal agriculture, particularly for prophylactic and growth-enhancing purposes. What does it cost to use antibiotics responsibly without jeopardizing food safety, the environment, or human health, as well as animal health, welfare, and productivity?

Vaccine and immunostimulant advancements in feed, as well as general preventative health initiatives, must be promptly explored. Appropriate antibiotic treatment will heal some sick animals and hasten the recovery of others, as well as increase the welfare of those who have been treated and minimize the spread of infection to other animals or, in the case of zoonotic diseases, to humans.

9 Conclusion and suggestions

Antibiotics' indiscriminate and extended use in human and animal medicine has the potential to accelerate the emergence and evolution of resistant and multiresistant microorganisms. These resistances can be passed from one species to another and vice versa. Given this, antibiotics must, therefore, be used with caution in both humans and animals. Antibiotic use can be sustained, but only with extreme caution, given the enormous surge in production as a result of antibiotic medication and the increasing demand for farmed food animals and aquatic food. The focus should be on raising production without the use of antimicrobial growth promoters, as it is becoming more common in high-income countries.

Resistance detection and monitoring necessitate appropriate laboratory-based surveillance. Improvements in access to diagnostic laboratories, improved surveillance of the emergence of resistance, better regulation, and better education of the public, clinicians/prescribers, and veterinarians in the appropriate use of antibiotics are all needed to extend the useful life of antibiotics in developing countries. Significantly, resistance levels for at least some antibiotics drop when use decreases, preserving and even recovering some antibiotic effectiveness. Antibiotic resistance levels have stabilized or fallen in several high-income nations where antibiotic stewardship has taken hold, and public health is good. When antibiotic use drops, the prevalence of ARB tends to diminish. Antibiotic demand in higher-income nations has been controlled by vaccines against a variety of infections, as well as improved water and sanitation, and per capita use has begun to level off in many of these countries.

Lack of awareness, lack of extension operations, inadequate literature offered by manufacturers, lack of safer medications, and exploitation of additional production and profit from animals are some of the causes of indiscriminate use. There is a need to raise awareness about the various forms of modern antibiotics that are accessible, including over-the-counter and prescription medications, as well as the dangers of not paying attention to how these two major categories of antibiotics are used. Pharmaceutical chemist stores should be discouraged from making indiscriminate sales. Antibiotics are prescribed by a doctor for the treatment of bacterial illnesses, not for viral infections.

Medicinal plants are the principal source of curative therapy for at least two-thirds of the world's population. Given the importance of medicinal plants that abound in our environment, active research into nutraceutical plants that may be employed in our food animals instead of antibiotics for growth promotion should be encouraged. Producers should be responsible for controlling disease outbreaks and conducting health and welfare programs on their farms, according to Good Aquaculture Practices. Extension small workshops and written materials in relevant languages should be used to spread information on proper husbandry and pond management for disease prevention. Measures should be taken to prevent dangerous compounds from being released into the environment, and this should be incorporated into the design, operation, maintenance, and management of agricultural projects.

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