Chapter 13
Antibiotics: Multipronged Threat to Our Environment

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Abstract The use of antibiotics in different fields of human societies is increasing since the discovery of penicillin, the first antibiotic discovered in 1928. Initially, they were used to treat human ailments; later, they found their way in industry, horticulture, animal husbandry, honey production, fish farming and aquaculture, ethanol production, antifouling paints, disinfectants, and food industry. This unprecedented use of naturally occurring and synthetic antibiotics led to the development of broad-spectrum resistance in the bacterial communities against the commonly used antibiotics. As the exposure of antibiotics to our environment is increasing, so is the development of antibiotic-resistant bacterial communities not only in the medical settings and industry but also in our environment. There is a concern that increased presence of antibiotics in the environment can contribute to the recruitment of resistance factors from the environmental resistome to human pathogens which may further complicate the issue of resistant pathogens. In this chapter, we will discuss about different routes and sources responsible for the antibiotic pollutants and their environmental consequences and evaluate different management strategies for their control to reduce the risk associated with the presence of antibiotics in our environment.

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13.1 Introduction

Antibiotics are undoubtedly one of the most effective drugs being utilized for human and animal therapy. They are not only used for preventing and treating different infectious diseases in humans and animals but also for agricultural and farming purposes. There is an increasing concern over the past years about the effects of irrational use of antibiotics and their disposal on both human and environment health. Environmental media which include air, soil, and water act both as a transmission medium and reservoir for antibiotic-resistant bacteria. The worrisome aspects regarding the ever-increasing use of antibiotics in the environment are that the drug-resistant bacteria may proliferate and make their way to the food chain and that they may wipe out trophic levels entirely in some of the ecosystems. These fears are being realized globally now, and since the awareness of the impacts of antibiotic pollution in the environment, the scientific community has recognized the importance of devising strategies to regulate this phenomenon. The coming sections explain about our current knowledge of the presence of antibiotics in the environment and its widespread consequences and also highlight the measures to protect human and environmental health.

13.2 Routes of Antibiotics Contamination to the Environment

Antibiotics enter the environment through different routes (Fig. 13.1). Antibiotics are usually partially metabolized in humans and animals after their administration (Kümmerer et al. 2009b) and are excreted through urine, stool, and sweat and enter into the sewerage system. Sewage treatment plants, hospital waste, inappropriate disposal of unused and expired drugs, animal husbandry, and aquaculture are the major sources that contribute to the environmental load of antibiotics (Harris et al. 2012). The active substances in these antibiotics end up in various environmental compartments such as water and soil since most of them are water soluble and are therefore not likely to be degraded (Jianan Li et al. 2015). Antibiotics used in human medicines enter sewers from households and healthcare facilities. From there, they enter wastewater treatment plant without any pre-treatment, and via treated wastewater they finally enter drinking water. When sewage sludge gets applied to soil from the wastewater treatment plants, active substances from antibiotics make their way to fields. Antibiotics may enter groundwater through soil or from streams, lakes, and rivers. Antibiotics may enter the environment directly via wastewater that is discharged from the facility where antibiotics are formulated or indirectly through the wastewater treatment plant (Küster and Adler 2018). The routes of antibiotics' entry into the environment are linked with the excretion of manure from livestock where a major portion of antibiotics is discharged into the environment in an active form. The overuse of antibiotics as feed additives in aquaculture has aggravated the

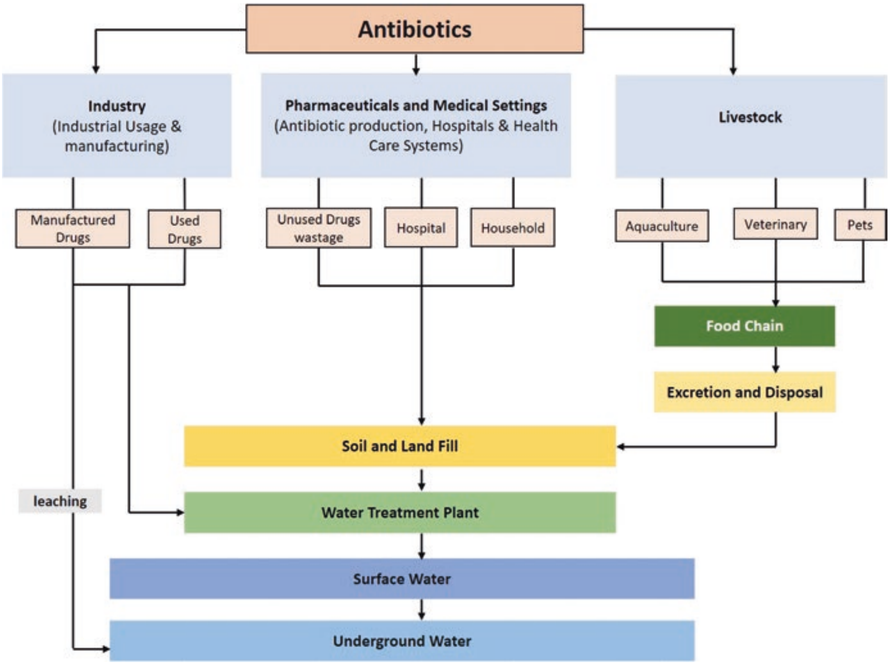

Fig. 13.1 Routes of antibiotic entry into the environment

problem of antibiotics contamination in the environment. Antibiotics get orally administered to the patients where they get partially metabolized along with their misuse in the hospitals due to which huge amounts of antibiotics are released in the hospital waste. Moreover, the detection of high concentrations of antibiotics in effluents from antibiotics manufacturing facilities has contributed to environmental contamination. The wastewater treatment plants represent a major source where sludge as well as treated wastewater are prominent pathways. Mutual interactions take place between all the entry routes that generate novel threats of spread of ARGs and ARB to humans as well as animals.

13.2.1 Antibiotics from Poultry, Veterinary, and Aquaculture

It has been speculated that in Europe, nearly two-thirds of all the antibiotics present are used in human medicine whereas one-third is employed for veterinary purposes. Recent reports estimate that in the United States, livestock producers use antibiotics nearly 11,200 tons for objectives other than therapy to promote growth of livestock and poultry (Whitacre 2015). The administration of antimicrobials in livestock depends on the reason of usage. Antibiotics are orally administered via drinking water or feed, whereas they are administered through injections for therapy (Pareek et al. 2015). Antibiotics are used in the livestock to treat diseases, prophylactically at subtherapeutic doses to alleviate infection by bacteria and to promote growth (Chee-sanford et al. 2009). Antimicrobials are routinely added to drinking water as well as animal feed as growth promoters and are an important part of swine production since the 1950s (Cromwell LG 2001). Some antibiotics get sprayed on crops; all the spray does not remain on the plant, but rather major portion is washed into soil and thereby reaches groundwater (Pareek et al. 2015).

Coccidiostat are found in broiler rations that are broad-spectrum antimicrobials like ionophores as well as sulfonamides. Antimicrobials such as chlortetracycline, bambermycin, bacitracin, penicillin, and virginiamycin get incorporated in the food of turkeys as well as broilers for increase in growth. Bacitracin is an antimicrobial drug which is not only used for promoting growth but also to control necrotic enteritis, which is an intestinal infection caused by *Clostridium perfringens*. Virginiamycin is another such drug used for the same purpose. The old drugs like tetracyclines are now unsuccessful due to the rapid increase in antibiotic resistance. Because of this, modern antibiotics such as fluoroquinolones are used for curing *Escherichia coli* diseases that are frequently prevalent in poultry (Wiedner and Hunter 2013). For controlling the mortality rate of the poultry, fluoroquinolones are the only effective drugs for the cure of some infections, specifically the *E. coli*.

The application of antibiotics in animals causes their release into the environment since majority of these antibiotics are designed in a way that they get quickly excreted from the treated animals (Burkholder et al. 2007). In 2006, the production of agricultural waste in the United States exceeded 200 million tons (Graves et al. 2011). Antimicrobials can be excreted as urine or feces in both unchanged form of the drug and parent form like drug metabolites, prodrug, and active compound (Bártíková et al. 2016). Furthermore, antibiotic metabolites may be modified back to the biologically active form even when they were excreted in an altered and inactive form. For instance, *N*-4-acetylated sulfamethazine, which is in fact a sulfamethazine metabolite, gets easily converted to its active form in liquid manure (Sarmah et al. 2006). Many different antibiotics have the ability to persist in the environment, and their presence may be easily detected not only downstream of the wastewater treatment plants but also in the adjacent fields receiving animal wastes. Moreover, in spite of the antibiotic remains, even a huge number of antibiotic resistant bacteria colonizing the gut of animals treated with antibiotics may be discharged into the environment. Commensals being the important carriers of antibiotic-resistant genes can act as a reservoir of such genes that flows across the entire microbial ecosystem. These microbes particularly bacteria harbor ARG and mobile genetic elements in agricultural effluents that promote it while exchanging among bacteria (Finley et al. 2013).

The role of veterinary antibiotics for the risk in the environment needs to be addressed. The burial of dead animals on the farm highly contaminates groundwater by nitrogen species as well as dissolved organic matter. The extent of the risk it poses to human and environmental health depends upon the quantity of dead animals buried as well as the site's hydrogeological conditions (Feeds et al. 1980).

Effluents from veterinary clinics also contribute to antibiotic pollution. Hotspots for occurrence of ARB include livestock keeping and farms. From here, ARB gets introduced to the environment through wastewater or via spread of sewage sludge or fermentation residues. Aquaculture is another pathway where antibiotics are overused. When medicated foods are used by fisheries, antibiotics are released directly into the surface water (Whitacre 2015). Antibiotics may enter the environment by animal farming when manure is used as a fertilizer.

It is known that antibiotics get poorly metabolized in animals' guts. Consequently, large amounts of active substances are excreted. Mainly excrements get stored as slurry (mixture of urine and feces), and small amounts mixed with straw get stored as manure. Antibiotics are indirectly incorporated when manure or slurry is used as a fertilizer. Through runoff and leaching, the antibiotics get introduced to the soil from slurry/manure storage. Antibiotic degradation takes place in the soil due to which groundwater and surface water might contain antibiotic residues. This entry of antibiotic residues in the soil affects soil microbiota (Van De Vijver et al. 2016). Plants take up some of these compounds; thus humans and animals that consume these plants get affected.

Development of the antibiotic-resistant bacteria is associated with indiscriminate use of antibiotics. Livestock can carry antibiotic-resistant bacteria as a result of antibiotics being directly administered and development of antibiotic resistance after administration as well. Other ways of developing antibiotic resistance include intake of the contaminated feed and breathing of the air containing resistant bacteria. The natural reservoirs present in the environment can be a source of further spread of antibiotic resistance.

13.2.2 Administration of Antibiotics in Humans for Cure

Antibiotics get administered in humans for treatment of several bacterial infections. About 40–90% of the administered antibiotics get actively excreted as parent compound in the urine and feces, ultimately reaching the environment, contaminating soils and water (Polianciuc et al. 2020). The major classes of antibiotics used for the treatment of bacterial infections worldwide are quinolones. These antimicrobials are significant for treatment against both gram-positive and gram-negative bacteria. These antibiotics work much effectively against the anaerobic bacteria especially the ones resistant to sulfonamides and β-lactams, making them important for therapy. The therapeutic action of quinolones is critical in the infections by organisms resistant to other antimicrobials. The most commonly used antimicrobials in human medicine are **ofloxacin** and **ciprofloxacin**. They are widely used in treating tuberculosis, joint infection, typhoid fever, and sexually transmitted diseases. Recently introduced antibiotics such as gemifloxacin, gatifloxacin, and moxifloxacin are used in treating chronic bronchitis, urinary infections, cystitis, acute sinusitis, pyelonephritis, and gonorrhea. Increased antibiotic consumption is considered to cause treatment failures in human medicine thus leading to an increase in illness duration, morbidity, as well as mortality (Merlin 2020). Unregulated antibiotic consumption causes increased levels of antibiotic residues as well as transformation products in the environment.

13.2.3 Antibiotics from Hospitals and Other Medical Settings

Hospitals are important sources for the discharge of antibiotics in municipal wastewater. Hospitals are focal points for spread of many antibiotic-resistant bacteria. The transmission occurs from patient to patient through contact with patients, healthcare workers, and contaminated objects. Pathogens carrying antibiotic resistance genes can epidemically spread between patients, or the genes can be transmitted via horizontal gene transfer (Whitacre 2015). The transmission of antibiotic-resistant bacteria in hospitals is further driven by antibiotic pressure (Almagor et al. 2018). Selection density has an important influence regarding antibiotic pressure in hospitals. Selection density refers to the amount of antibiotics used per person in an area. The selection density is high in a hospital where the number of antibiotics in the formulary is small and gathering of few patients in a small space like ICU also contributes to high selection density. Colonization pressure influences the transmission of microorganisms in hospitals. Higher colonization pressure increases the spread of multidrug-resistant organisms in the hospitals (Cantón et al. 2013). Increasing use of antibiotics in the medical settings since the last decade has been observed which has reached about 200,000 tons per year, making them potential environmental contaminants because of their synergetic and prolonged effects when they enter into the environment (Wise 2002).

13.2.4 Medical Waste, Hospital Wastewater, and Spread of Antibiotic Resistance

Intensive care units and hospitals are significant breeding grounds for the development and dissemination of antibiotic-resistant bacteria. Around 10% of generated hospital waste is pathogenic and infectious, which can cause great hazards to the public (Chartier et al. 2014). Hospital wastewater acts as a rich reservoir for antibiotic resistance as well as other genetic influences that foster the extension of antimicrobial resistance to the environment (Berendonk et al. 2015). This takes place since the hospitals receive vast amounts of antimicrobial substances and human pathogens. A study got conducted in Singapore to assess antimicrobial resistance in hospital wastewater by analyzing the presence of antibiotic resistance factors in hospital effluents such as resistant bacteria, antibiotic residues, and genetic determinants. Levels of trimethoprim, azithromycin, clarithromycin, sulfamethoxazole, and ciprofloxacin were quite reduced (around tenfold) as compared to those reported in another research study (Rodríguez-Blanco et al. 2012). Bulk of antibiotics deployed in hospitals gets discharged into wastes, and thereby a selection pressure on bacteria is generated. As a result, bacteria depicting resistance become prevalent in hospital wastewater at such concentrations which are capable enough to terminate susceptible bacterial growth (Beyene and Redaie 2011). Therefore, hospital wastewater may enhance level of microbes depicting resistance in recipient sewers through selection pressure as well as introductory channels (Stalder et al. 2014). The environmental exposure with the resistant pathogens may cause crucial health concerns because of the existence of transmittable genes. Resistant pathogens may also function as a reservoir of resistance genes that lead to serious health concerns (Keen and Patrick 2013). *Campylobacter, Clostridium, Salmonella, Pseudomonas aeruginosa, Shigella, Vibrio, Staphylococcus aureus,Leptospira, Enterobacter, Klebsiella*, and *E. coli* are the most prevalent bacteria in hospital wastewater (Arshad Sid 2017).

Studies have shown that limiting the use of antibiotics could increase or decrease the phenomenon of antibiotic resistance depending upon the antibiotic class. Treatment of antibiotics may accelerate the dissemination of drug-resistant bacteria in multiple ways. Firstly, commensal flora that protects against invading bacterial colonization gets disrupted by antibiotics, making patients more vulnerable to acquire new bacterial strains. Thus, patients exposed to antibiotic resistant bacteria after or during antibiotic treatment are more likely to become colonized. Secondly, antibiotics have the potential to remove competing commensal bacteria in patients whom antibiotic resistant bacteria have already colonized which allows overgrowth of the bacteria that are resistant. This enhanced load of antibiotic-resistant bacteria may lead to greater shedding and hence greater contagiousness (Kraemer et al. 2019). Consequently, superbugs are becoming common and claiming lives. The most prevalent among them are **CRE**, **MRSA**, **ESBL-producing** *Enterobacteriaceae*, **VRE**, multidrug-resistant *Acinetobacter*, *Pseudomonas aeruginosa*, and *Klebsiella*. Interventions to limit the use of antibiotics can potentially reduce the spread of antibiotic resistance. CDC's Antimicrobial Resistance Threat Reports 2019 include the recent death as well as infection estimates that highlight the urgent threat of antibiotic resistance in the United States. It has been stated that around 2 million people in the United States acquire an antibiotic infection and around 23,000 people die each year (Table 13.1).

13.2.5 Disposal of Unused and Expired Antibiotics

Antibiotic consumption has been reported to be increased in 76 countries (Klein et al. 2018). The increased antibiotic consumption is greater among the low- as well as middle-income nations as compared with the higher-income countries. The inappropriate disposal of unused and expired antibiotics is much often ignored driver of AMR. The vast majority of the drug users do not know how to properly dispose unused and expired antibiotics and simply throw away their unwanted medications. This improper disposal of antibiotics leads to their piling up in the landfills, drains,

Table 13.1 Bacteria listed in antibacterial resistance threat report in 2019 (Biggest Threats and Data | Antibiotic/Antimicrobial Resistance | CDC, n.d.)

Serial no.	Name of bacteria	Estimated cases in 2017	Deaths in 2017
1.	Carbapenem-resistant *Acinetobacter*	8500	700
2.	*Clostridioides difficile*	223,900	12,800
3.	Carbapenem-resistant *Enterobacteriaceae*	13,100	1100
4.	Drug-resistant *Neisseria gonorrhoeae*	550,000	–
5.	Drug-resistant *Campylobacter*	448,400	70
6.	ESBL-producing *Enterobacteriaceae*	197,400	9100
7.	Vancomycin-resistant *Enterococcus*	54,500	5400
8.	Multidrug-resistant *Pseudomonas aeruginosa*	32,600	2700
9.	Nontyphoidal *Salmonella*	212,500	70
10.	Drug-resistant *Shigella*	77,000	Less than 5

and water supplies that leads to both environmental contamination and toxicity to human, animal, and aquatic life. The disposed of drugs when not properly removed during wastewater treatment process thereby reach surface water and are ultimately released into the aquatic environment (Anwar and Saleem, 2020). The concentration of these antibiotics has sufficient capability to promote resistance by target modification or by HGT. Host genomes get repositioned and thereby function as vehicles for acquiring resistance and dissemination. Therefore, the indiscriminate discharge into the environment compromises the antibiotics' effectiveness as well as augments resistance as less harmful microbes mutate to deadly pathogens (Anwar et al. 2020). As a result, the same bacteria when spread to humans are already resistant to those antibiotics causing increased mortality and morbidity.

13.2.6 Industrial Discharge of Antibiotics from Drug Manufacturing Facilities

Industrial discharge of antibiotics from drug formulation facilities is considered a crucial risk factor leading to antibiotic resistance dissemination. Detection of high levels of antibiotics (mg/L) specifically fluoroquinolones, tetracycline, and penicillin in effluents from antibiotics manufacturing bodies in India and China highlights the significance of analyzing and monitoring the results of the high selection pressure on the microbial communities (González-Plaza et al. 2019). Enhanced level of antibiotics in the environment can foster the development of ARGs because of natural selection and may help establish environment as a reservoir for further proliferation of antibiotic resistance genes to microbes through water and food webs. These industrial discharges which pollute receiving aquatic bodies are recognized to lead to an enrichment of ARGs, accelerating their dissemination. The practice of discharging hazardous industrial waste from drug manufacturing facilities is not limited to only Asian countries but can be observed around world. Industrial discharge of antibiotics from drug formulation facilities is considered a substantial point source with levels higher than other routes (Khan et al. 2013).

13.2.7 Municipal Sewage, Wastewater, and Sewage Treatment Plants

The traditional wastewater treatment plants have been designed to effectively remove certain pollutants and pathogens but are not effective in eliminating antibiotics or antibiotic resistance genes. Wastewater treatment plants serve as hotspots for the spread of antibiotic resistance genes. Antibiotics get discharged into WWTPs from hospitals, pharmaceutical industries, and households. Antibiotic residues from households enter together with sewage to wastewater treatment plants. Sewage microbiota consists of human commensal microbiota which gets mixed with bacteria that colonize the sewage system. The fraction of antibiotic-resistant bacteria in sewage can reach more than 50% in a given group like *Enterobacteria*. Leachate from municipal solid waste pollutes environment by antibiotics thrown into household rubbish bins.

Wastewater from wastewater treatment plants contains a significant load of antibiotics. Tetracyclines, β-lactams, quinolones, sulfonamides, and macrolides have frequently been detected from emissions of WWTPs. The biological treatment processes create favorable conditions for the development of antibiotic resistance genes and horizontal gene transfer under sub-inhibitory concentrations of antibiotics. Variations in the concentrations of antibiotics in wastewater are due to several reasons: the size of wastewater treatment plant, seasonal fluctuations, and antibiotics usage patterns. Activated sludge is an important wastewater treatment process for controlling pollutants and it serves as an important route for the spread of antibiotic resistant genes in the environment. Antibiotic resistant bacteria present in the activated sludge go down into the water of aeration tank and sedimentation tank and get released with the effluent. These bacteria can potentially contaminate soil when the activated sludge is used as a fertilizer. Moreover, the antibiotic resistance genes in the treated water are released through effluent into the surrounding water (Gupta and Singhal 2018).

13.2.8 Antibiotics from Surface Treatment Compounds in the Environment

Contaminating bacteria can sustain for long time periods on any surface exhibiting resistance to the applied disinfectants. Nosocomial pathogens may survive on dry surfaces for weeks, but some pathogens, including *Acinetobacter baumannii* and

P. aeruginosa, require humidity for their survival. These pathogens can easily transmit if disinfection is not done properly. The multidrug-resistant bacteria *Klebsiella pneumoniae* and *E. coli* survive for several weeks on steel surfaces according to a study. Research has shown that horizontal gene transfer of β-lactamase genes occurs when recipient and donor cells are mixed upon steel. The study shows the potential of bacteria to retain on touch surfaces plays a vital role in horizontal gene transfer of resistance genes. Recent reports demonstrate that biofilm producing strains of *A. baumannii* can persist on the inanimate surfaces longer than the non-biofilm producing ones (Cantón et al. 2013). Excessive and inappropriate use of antibiotics in this situation may contribute to the persistence of antibiotic resistant bacteria. Inappropriate control of infection can propagate the antibiotic resistant bacteria and can further lead to endemics. The used antibiotics in hospitals get discharged into aquatic environment through wastewater leading to an increase in the rate of antibiotic resistance in the environment (Kraemer et al. 2019).

13.2.9 Antibiotics from the Aquatic Environment

Antibiotics are discharged into the aquatic environment through wastewater effluents and improper disposal from livestock and humans. Antibiotic resistance genes have been frequently detected in surface river water, municipal wastewater, water supply reservoirs, and drinking water (Huerta et al. 2013). Runoff from agriculture and damaged sewage pipes are responsible for the entry of antibiotic resistance bacteria into groundwater. Antibiotic concentrations in untreated wastewater were measured in the United States according to a report. The estimated concentrations ranged from 4 ng/L to 27,000 ng/L. The basis of this estimation was the number of administered antibiotic prescriptions. It was found that the major classes of antibiotics present in the aquatic environment were quinolones, sulfonamides, and macrolides. Among quinolones and sulfonamides, ciprofloxacin and sulfamethoxazole were the most prevalent in municipal water effluents, and sulfamethazine was the most prevalent in farm runoff (Huang et al. n.d.). Antibiotic concentrations were much lower in the effluents of highly advanced treatment processes because of significant eradication of antibiotics by these processes. Levels of antibiotics in drinking water are mostly reported to be minute when compared to the high levels in surface waters, agricultural runoff, and wastewaters.

13.2.10 Antibiotics from Sediments

Sediments often contain antibiotic-resistant bacteria because of the unmonitored application of antibiotics in aquaculture. Substances used in aquaculture may directly enter the sediments from water without any pre-treatment process. This leads to high concentration of antibiotics in sediments. Sulfonamides, tetracyclines, and quinolones get readily adsorbed in sediments. Antibiotics have both quantitative and qualitative effects on the microbial communities residing in sediments. The excess use of antimicrobials for treatment of bacterial diseases in aquaculture has led to antibiotic resistance development in *Aeromonas salmonicida*, *Vibrio anguillarum*, *Pasteurella piscicida*, and *Aeromonas hydrophila*. Therefore, the high antibiotic load in sediments is strong enough to inhibit bacterial growth for aquaculture (Kümmerer et al. 2009a).

13.3 Airborne Antibiotic Resistance Genes in the Environment

The airborne bacteria in healthcare environment are mostly multidrug resistant and hence pose a threat to humans even outside medical settings through airborne transmission. Antibiotic resistance genes have been reported from air samples collected wastewater treatment plants (WWTPs), livestock, and hospitals. Airborne particles in highly contaminated places provide greater number of adhesion sites which facilitates microorganisms to suspend with increased stability in air. Airborne transmission plays an important role in the environmental dissemination of antimicrobial resistance. Distribution pattern of airborne drug-resistant bacteria depends on physiochemical factors, bacterial communities, meteorological parameters, antibiotic usage, and air quality (Jing Li et al. 2018). Detailed information on airborne pathogens and their impacts on human and environmental health is unfortunately not enough, and further research is required in this domain.

13.4 Hazardous Consequences of Antibiotics in the Environment

There is a great concern about the deleterious effects of antibiotics on our environment over the last few years; therefore much is not known about the hazards of antibiotics entering the water sources. Moreover, the concentration of the antibiotics present in waters is generally very low due to which it cannot be reliably measured by common analytical methods. Although individual concentrations of antibiotics in waters are low, but a large number of antibiotics when combined can cause serious environmental and health problems (Kümmerer et al. 2009a). Horizontal gene transfer between bacterial species in wastewater may be fostered by rich nutrient content and high density of bacteria in the biofilms. Co-selection through substances like heavy metals and biocides that are present in sewage sludge, wastewater, and fermentation residues is another mechanism via which antibiotic-resistant bacteria occur in the environment (Gupta and Singhal 2018). Effluents from veterinary clinics and hospitals also contribute to antibiotic pollution. Hotspots for the occurrence of antibiotic-resistant bacteria include livestock keeping and hospitals. From here, antibiotic-resistant bacteria get introduced to the environment through wastewater or via spread of sewage sludge or fermentation residues. Aquaculture is another pathway where antibiotics are overused. When medicated foods are used by fisheries, antibiotics are released directly into surface water (Whitacre 2015). Antibiotics may enter the environment by animal farming when manure is used as a fertilizer. Some antibiotics get sprayed on crops; all the spray does not remain on the plant rather major portion is washed into the soil and thereby reaches groundwater (Pareek et al. 2015). Leachate from municipal solid waste pollutes the environment by antibiotics thrown into household rubbish bins. Antibiotic resistance genes (ARGs) have been observed in the air samples from places that are around WWTPs. Mutual interactions take place between all the entry routes that generate new threats of spread of ARGs and ARB to humans and animals through airborne aerosols and dust. Some of the major hazards regarding the antibiotic presence in the environment include elimination of the entire trophic levels in ecosystems and entry of multidrug-resistant bacteria into the food chain. Microbial communities are complex and have the major task of nutrient cycling. Cycling of the nutrients is important for maintaining quality of soil and for sustainable agricultural land use. Nitrogen is one such essential nutrient, and two main genera of gram-negative bacteria drive its cycling that are **Nitrosomonas** and **Nitrobacter**. Broad-spectrum antibiotics like tetracyclines and sulphonamides at high concentrations disrupt the nitrification process and inhibit nutrient cycling significantly (Frade et al. 2014). Antibiotics primarily affect microorganisms like bacteria, fungi, and microalgae. Sensitivity of microalgae varies to antibiotics. For example, cyanobacteria (blue-green algae) show sensitivity to sarafloxacin. Antibiotics exposure to the environment influences the early life stages of various organisms and exhibits adverse effects on reproduction (Pareek et al. 2015). Behavior of the aquatic organisms is also impacted by antibiotics exposure to the environment (Fig. 13.2). One such example is that the antibiotics impact locomotion (phototaxis) of the aquatic organism *Daphnia magna*. Primary antibiotic resistance is present naturally in microorganisms. Secondary resistance on the other hand develops when microorganisms encounter antimicrobial drugs during therapy. Through horizontal gene transfer or conjugation, the plasmid mediated resistance is easily transferred between microorganisms. Resistance then reaches the environment with the ability to adversely affect terrestrial and aquatic organisms. Important examples are methicillin-resistant *Staphylococcus Aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE). The drug-resistant bacteria can get transferred to humans when manure is used as a fertilizer or when plants get watered with surface water (Küster and Adler 2018). The problem of antibiotic resistant bacteria is accelerating, and tools to combat this problem are decreasing in power.

13.5 Effect of Irrational Use of Antibiotics on Human Health

Misuse of antibiotics in humans in therapeutic regimens ultimately develops antibiotic resistance (Animals et al. 1999). Two main human health consequences of increased AMR due to misuse of antibiotics are rise in foodborne diseases and

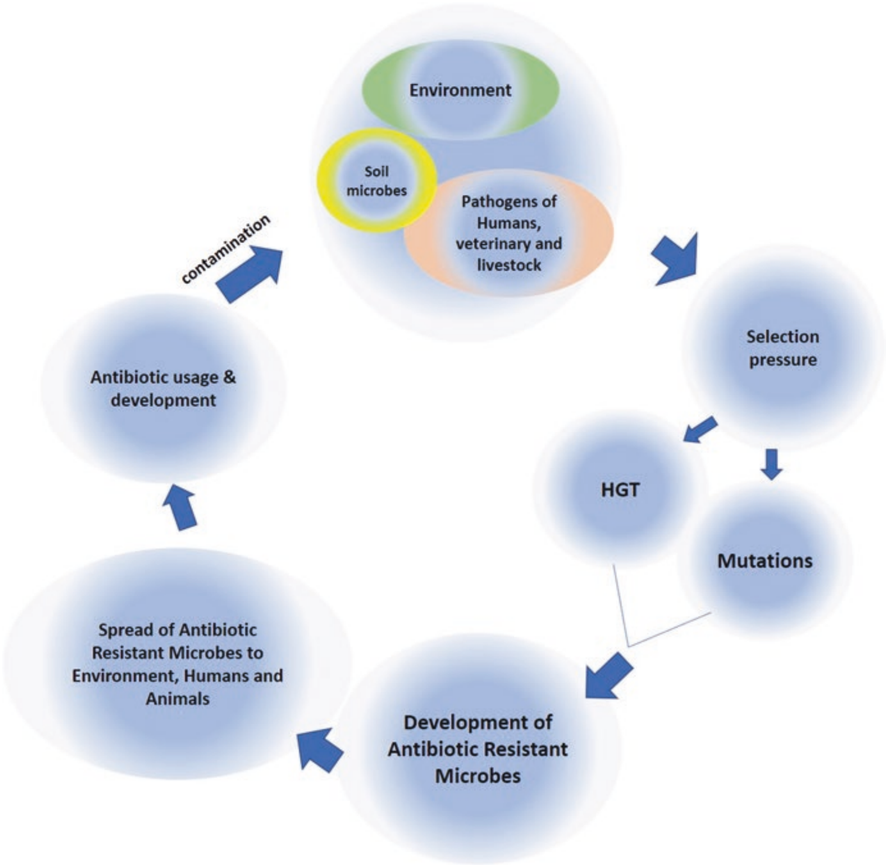

Fig. 13.2 Environmental hazards of antibiotics

increased cases of treatment failures (de Kraker et al. 2016). Increased human infections by resistant bacteria from food take place as there is rise in the prevalence of antibiotic resistance because of increased human exposure to antibiotics (Smith et al. 2005). Consuming an antibiotic can reduce the infectious dose for *Salmonella*, if the bacteria is resistant to that antibiotic, and the same goes for other foodborne bacteria. Several analyses of outbreaks of antibiotic-resistant *Salmonella* have shown that prior exposure to antibiotics may result in a huge number of cases as compared to the cases that would have taken place if a sensitive strain had caused the outbreak (Mølbak 2005). It has been observed in the case of *Salmonella* outbreaks that unrelated previous treatment with an antibiotic can predispose humans to infection with susceptible or resistant *Salmonella*. As bacteria become more and more resistant, treatment of patients with antibiotics for whatever reason enhances risk for patients to develop subsequent infections caused due to resistant bacteria. Thereby the public health impacts are increased cases of infections and larger outbreaks (Anderson et al. 2003). In addition, increasing AMR in bacteria can lead to treatment failures if the bacteria are resistant to an antibiotic used for treatment.

An example of treatment failure is a case in Denmark where an AMR *S. typhimurium* **DT104** outbreak due to contaminated pork got traced back to a swine herd (Mølbak et al. 1999).

13.6 Management Strategies for Control of Antibiotics Release in the Environment

The deaths estimated per year because of antibiotic resistance are approximately 70,000 globally (Kraemer et al. 2019), which makes its management crucial. Dissemination of antibiotic resistance can be effectively controlled by the application of appropriate measures for improving wastewater treatment processes as well as by restricting the antibiotic use in livestock as well as agriculture. "One Health Model" which connects animal, human, and environmental health domains should be applied to resolve this issue worldwide. Understanding antibiotic resistance and antibiotic pollution as one health approach may help in creating more effective policies. Little has been known about the fate, occurrence, risks, and effects linked with the discharge of antibiotics and antimicrobials into the environment. There must be fundamental data on the fate, sources, and effects of antibiotics in the environment for appropriate risk management. The discharge of antibiotics into the environment should be greatly reduced, and for this purpose, the unused drugs should never be flushed down the drains (Kraemer et al. 2019). The misuse of antibiotics by the general public should be stopped by making people aware that the antibiotics only help against the bacterial diseases and not against the viral diseases. There should be procedures to regulate suppliers in the pharmaceutical industry to make sure that antibiotics do not get released into surrounding waters during their production (Fig. 13.3). Future antibiotic interventions should be "targeted antimicrobials" with a narrow spectrum of activity to facilitate early responses instead of broad-spectrum agents. Furthermore, the usage of these antibiotics should be implemented with antimicrobial susceptibility testing. Moreover, the usage of biomarkers should be encouraged to pinpoint when any antibiotic is essentially required and also when antibiotic treatment should be terminated. Resultantly, the selection impact would be lower on the microbiota (Cantón et al. 2013). Societies should publish proper guidelines for appropriate antibiotic use and to reduce the antibiotic resistance in the environment. These guidelines must include coordination between clinicians, infection control teams, pharmacists, microbiologists, and drug-use prescribers. A collaboration between the disciplines of epidemiology, microbiology, nursing, pharmacy, and infectious diseases could result in an efficient program to mitigate antibiotic pollution in the environment.

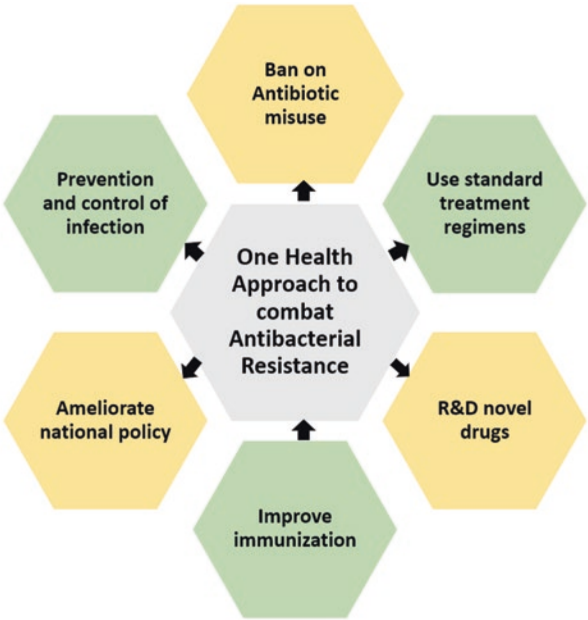

Fig. 13.3 One health approach to combat antibacterial resistance

13.7 Conclusion

Antibiotic pollution has not only contributed to antibiotic resistance but also directly affected human and environmental health. However, little information is present on the sources, occurrence, fate, effects, and risks associated with antibiotic consumption globally.

There is a significant gap in understanding the interactions between antibiotics and their metabolites and development of antibiotic resistance after their discharge in the environment. Multiple approaches should be considered to reduce release of antibiotics in the ecosystem for appropriate risk management. Currently, no proper regulations are present for antibiotics monitoring in surface water, drinking water, or groundwater. The scientific community has started to realize the significance of designing plans to regulate antibiotic pollution in the environment in the past few decades. New policies should be implemented locally to restrict the dissemination of antibiotic resistant bacteria and antibiotic resistance genes through environmental routes.

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