



Zoonosis: An Emerging Link to Antibiotic Resistance Under “One Health Approach”

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Received: 20 October 2019 / Accepted: 27 February 2020 / Published online: 4 March 2020
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Abstract Current scenario in communicable diseases has generated new era that identifies the “One health” approach to understand the sharing and management of etiological agents with its impact on ecosystem. Under this context the relevance of zoonotic diseases generates major concern. The indiscriminate and higher use of antibiotics in animal husbandry creates substantial pressure on the gut microbiome for development of resistance due to shorter generation time and high density. Thus, gut works as a bioreactor for the breeding of ARBs in this scenario and are continuously released in different niches. These ARBs transfer resistance genes among native flora through horizontal gene transfer events, vectors and quorum sensing. About 60% of infectious diseases in human are caused by zoonotic pathogens have potential to carry ARGs which could be transmitted to humans. The well documented zoonotic diseases are anthrax cause by *Bacillus anthracis*, bovine tuberculosis by *Mycobacterium tuberculosis*, brucellosis by *Brucella abortus*, and hemorrhagic colitis by *Escherichia coli*. Similarly, most of the antibiotics are not completely metabolized and released in unmetabolized forms which enters the food chain and affect various ecological niches through bioaccumulation. The persistence period of antibiotics ranges from < 1 to 3466 days in environment. The consequences of misusing the antibiotic in livestock and their fate in various ecological niches have been discussed in this review. Further the light sheds on antibiotics persistence and its biodegradation through different abiotic and biotic approaches in environment. The

knowledge on personnel hygiene and strong surveillance system for zoonotic disease including ARBs transmission, prevention and control measures should be established to regulate the spread of AMR in the environment and subsequently to the human being through a food web.

Keywords Antibiotic resistance · Livestock · Zoonosis · Half-lives of antibiotic · Gut microbiome

Introduction

Managing human health is finding new challenges in the recent years. The emergence of new opportunistic pathogens and drug resistance in prevailing pathogen is major concern globally. Most of the emerging diseases have crossed the trans-boundaries and entered almost every environment. The emerging hypothesis suggests that the evolved disease pattern considers the breeding of pathogenic determinants in ecosystem using any possible available biological host. The most common biological host for breeding of resistant pathogen is animal. Animal gut is composed of various microbial communities that act synergistically to benefit their host [1]. The introduction of drug resistant pathogen in gut microbiome alters the community structure by transferring the resistant gene to other pathogen in gut. Opportunistic pathogens find a route from animal to human either by direct interaction (zoonoses) or by vectors thus affecting the human health. The interconnection of human with animal via ecosystem creates a scenario which is now being considered under “one health” approach.

Transmission of diseases from animal to human via zoonoses route is major concern growing worldwide. The zoonotic diseases might emerge as the reason for

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intermittent disease outbreaks, new epidemic diseases or a geographically restricted curiosity. The management of all the factors contributing in emergence of new zoonotic infections comes under “one health” approach. One health approach links human health, animal health and the environment. Rise of antimicrobial resistance among human population spread by zoonotic pathogens needs to be addressed through one health approach. The one health approach for zoonoses management involves the multi-disciplinary teams of mammalogists, ecologists, entomologists, epidemiologists, ornithologists as well as physicians for successful investigations.

Discovery of antibiotics in early 1900s have transformed the human health by saving millions of lives. Antibiotics are complex compounds inhibiting the growth of microorganism by a various mechanism of action which includes, cell membranes alteration, inhibiting cell wall synthesis, antimetabolite activity, inhibition of nucleic acids synthesis, inhibition of protein synthesis, and competitive antagonism. Antibiotics are employed in animal husbandry and livestock to increase the production of dairy products and meat by preventing the infectious diseases. It is also used for promoting the growth and weight of animals on a large scale. Although antibiotics are beneficial, an uncontrolled usage of antibiotics and their dissemination into the environment is of great concern [2] (Fig. 1).

Most of the antibiotics entering the human and animal bodies are not completely metabolized, resulting in the discharge of unmetabolized forms in the environment. They are excreted out of the body and run through municipal wastewater, animal manure and sewage sludge in a different environment. The elevated concentration of antibiotics in various environments puts selective pressure for the growth of ARBs resulting in changed sensitivity of bacterial population and antimicrobial resistance among the native microbiome [3, 4]. Antibiotics existing in the environment leads to the alterations in genetic makeup of bacteria resulting in the rise of antibiotic resistance genes (ARGs). The transfer of ARGs through associated mobile genetic elements (MGEs) such as transposons, plasmids, and genomic islands to other microbial population increases the prevalence of ARBs in the environment. These ARBs become potent zoonotic pathogen causing severe infections in the human population worldwide.

The antibiotic use in veterinary medicine and food-producing animal is promoting the emergence of ARBs among zoonotic pathogen as well as normal bacterial flora. The relationship of AMR with animal and human morbidity is a major concern for modern medicine. Although extensive research on zoonotic pathogens is being conducted, it is still lacking the proper management and regulation of antimicrobial agent along with judicious use by a human being. Moreover, the use of antibiotic in manure for

agriculture practices transfers the antibiotic various ecological niches such as soil and water. Antibiotic from soil leach down to water bodies and thus spreads in various ecological niches. Dispersion of antibiotic resistance in environment is viewed as global threats and AMR has been listed as pre eminence in World Bank’s recent One Health approach framework (World Bank Group 2018). One health approach to AMR addresses wildlife, aquaculture and environment [5]. This approach acknowledges various sectors that plays important role in the progress and spread of AMR and focus efforts on actionable, impact driven research.

One Health Approach for Combating the Widespread Resistance

The AMR can be lethal; while, the effective adoptable solutions to AMR remain subtle. Understanding AMR pattern is complex due to its multilayered, interconnected, and multifaceted ecological features. The management of widespread resistance can be done on the basis of decision taken by individual and society which must concern the appropriate uses of antimicrobial products in various sectors. To grasp the complex AMR situation, a holistic supervision is required that includes multiple-sectoral teams such as healthcare personnel, environmentalists, veterinarian and stakeholders. The “One Health” is an approach that involves the interdisciplinary collaboration of researchers, policy makers, and leaders working at regional, local, national and international levels [6]. This approach goal to achieve for improved health outcome of human, animals and environment. The outbreak of epidemic infections involving AMR is on priority of “one health” approach. This approach connects multiple sectors working in the area for understanding the AMR problem and finding proficient solutions to develop suitable usage guidelines, and provide effective risk communications. The dissemination of AMR is another problem that needs a broader explanation of bacterial movement between human hosts, animals (wild and domestic) as well as respective environment in which resistant bacteria and its resistance genes or elements can propagate.

AMR management under one health approach can be implemented by considering several factors like (1) guidelines and regulations for the critical usage of diverse classes of antimicrobials employed for animal and human health (2) understanding the dissemination through environment (i.e., air, water, and soil) because they serve as a pool of resistant bacteria and ARGs, and become a pathway for the propagation of AMR between host animal and human populations (3) established and innovative solutions with novel technology for quantifying AMR that ranges

from animal husbandry and herd management (4) effectual communication strategies for awareness in consumers about the risks associated with spreading AMR from food production and other nonhuman sources.

The understanding of zoonoses mediated AMR is the universal problem extending from scientific community to food animal producers, health professionals, patients, and consumers. To continue the effective usage antibiotics in animal and human medicine, ‘One Health’ comes with a range of approaches to restrict the trans-boundary and zoonotic spread of AMR.

Zoonotic Pathogens as a Carrier of AMR

In past years animal and human health has been threatened by environmental pollution, antimicrobial resistance, and chronic diseases resulting in high mortality and high morbidity rate [7]. Emergence and the spread of zoonoses, epizootics, and epidemics have highlighted the increased health risk at the global level and the importance of understanding human-animal interface in infectious agents transfer. Most of the infectious diseases are considered to be serious health issues having a zoonotic origin. The World Health Organization (WHO) describes zoonotic disease or zoonosis as “*any disease or infection that are naturally transmitted between vertebrate animals and humans.*” The disease-causing agent may be virus, fungi, bacteria, parasites or prions. In today’s scenario around 200 zoonoses are recognized; some of them are localized to a particular geographical area while others are reported to have a worldwide distribution. The mode of zoonotic pathogen transmission could be through ingestion, inhalation or other routes that contaminate mucous membranes. Zoonotic pathogens are also transmitted through eating habits which include animal tissue of undercooked meat, unpasteurized milk, dairy products, seafood, and contaminated vegetables. Other well documented zoonotic diseases are anthrax, animal influenza, bovine tuberculosis (BTB), brucellosis, hemorrhagic colitis, zoonotic diphtheria, rabies, and Q fever (Table 1).

The widespread of zoonotic diseases is the result of interplay between many factors such as biological, genetic, social, ecological, political, physical and environmental. More than 60% of infectious diseases in human are caused by zoonotic pathogens. Among them, ARBs are most widespread zoonotic pathogens found commonly in the environment. The bacteria have shorter generation time and are liable to strong selection pressure from host immunity as well as antimicrobial drugs. Thus these communities have significant evolutionary changes which affect human health through its interaction with pathogen-host species acting as a reservoir of the infection.

Pseudomonas aeruginosa, *Pseudomonas fluorescens*, *Proteus mirabilis*, *Klebsiella pneumonia* and *Staphylococcus* sp. were found to be resistant against few antibiotics [8]. One health approach identifies that emergence of ARBs is directly related to the increased use of antibiotics in farm animals and aquaculture industry.

The ARBs reach the human gut through zoonotic disease transmission where they disturb the native gut diversity. Zoonotic pathogen carrying ARGs reaches to the human body where they transfer the resistant genes to human gut microbiome and thus disrupting the gut ecosystem. Furthermore, the ARGs or ARBs are excreted out of the human body and reach to the environment through municipal wastewater or soil. From the wastewater or soil ARG genes are transmitted ARBs entering the food web, affect the animal health and thus the cycle of transmission of ARBs continues.

Antibiotic Resistance in Zoonotic Pathogens

One health approach identifies the most animals that serve as a reservoir for zoonotic diseases are domesticated with which man is commonly associated. Animal husbandry is an intrinsic part of the agricultural economy and plays a vital role to support the livelihood of the rural population. Animal husbandry provides milk, meat, eggs, and wool which directly interact with the human population. The chances of zoonotic diseases from host to human in animal husbandry are very high. Despite the much risk of zoonotic diseases, livestock plays a crucial role in the income of many farmers, nutrition for households, and animal products consumption.

Recently many zoonotic diseases have been reported to carry ARGs which reaches human population upon infection. ARGs in zoonotic pathogens have arisen due to irrational use of antibiotic [9, 10]. In animal husbandry in spite of the presence of clinical symptoms in some animals, whole herd is treated with antibiotics for any infectious diseases to prevent the transmission of illness in the herd. This process of administering high dosage of antibiotics for a short course is known as metaphylaxis while prophylaxis denotes mixing of antibiotics with the feed in small doses for extended time course, usually for several weeks. Although in this period, the animals do not exhibit any clinical symptoms, but the threat for infection still persists. The unwise use of antibiotics poses the selective pressure in pathogens resulting in antibiotic resistance to the sub-therapeutic level of antimicrobial concentration. Bacterial species gain resistance via various mechanism including mutation, cell permeability changes, horizontal gene transfer, drug efflux and quorum sensing [11, 12]. The transmission of ARGs and high usage of antibiotics have

Table 1 Zoonotic pathogens transmitting disease and AMR/MDR to human

Animal	Diseases	AMR/MDR	Antibiotic	References
Cats, Dogs and Horses	Pyoderma	<i>Staphylococcus pseudintermedius</i>	Methicillin, Ofloxacin	[40]
	Allergis and blood infection	<i>Staphylococcus</i> sp.	Methicillin, Clindamycin, Fluoroquinolones	[41]
Sea fish	Gastritis, diarrhea,	<i>Salmonella</i> and <i>Vibrio</i> spp.	Cephalothin Ampicillin Chloramphenicol	[42]
Birds	Meningitis	<i>Streptococcus suis</i>	Cephalosporin, Cefotaxime	[43]
	Cellulites and septicaemia	<i>E. coli</i> , <i>Salmonella</i> sp. <i>Campylobacter</i> sp.	Methicillin	[44]
Pigs	Elementary tract infection	<i>Klebsiellapneumoniae</i> , <i>Salmonella</i> spp.	Various Beta lactamases	[45]
	Urinary tract infection	<i>Enterococcus faecium</i> , <i>Campylobacter</i> sp.	Nalidixic acid. Quinolones, Fluoroquinolones	[46]
	Septicemia	<i>Staphylococcus aureus</i> , <i>Campylobacter</i> , <i>Salmonella</i>	Levofloxacin, Penicillin, Tetracyclin	[47]
Livestock Dairy Cattle	Urinary tract infection	<i>E. coli</i>	Ampicillin, Fluoroquinolones, Cefotaxime	[48]
	Mastitis	<i>Staphylococcus aureus</i> , <i>Klebsiellapneumoniae</i> , <i>Salmonella</i>	Methicillin, Amoxicillin, Clavulanic acid	[49]
	Bovine Tuberculosis	<i>Brucellaabortus</i> , <i>Mycobacterium bovis</i>	Norfloxacin, Amoxicillin	[50]
	Typhoid	<i>Salmonella typhimurium</i> , <i>Salmonella enterica</i>	Penicillin, Oxytetracycline, Streptomycin, Sulfonamide	[51]
Avian (Poultry) (Duck and Chicken)	Avian Tuberculosis	<i>Mycobacteria</i> , <i>Neisseria gonorrhoeae</i>	Azithromycin, Gentamycin, Chloramphenicol	[52]
	Enterocolitis	<i>Campylobacter</i> , <i>Salmonella</i>	Ciprofloxacin, Tetracycline, Enrofloxin, Nalidixic acid	[53]
	Enteritis	<i>Campylobacter</i> sp.	Nalidixic acid, Ciprofloxacin, Tetracycline	[54]
	Mortality	<i>Salmonella</i> spp, <i>Klebsiellapneumoniae</i>	Methicillin	[55]
	Diarrhea	<i>E. coli</i> , <i>Salmonella</i> , <i>Campylobacter</i>	Sulfamerazine, Dihydrostreptomycin	[56]

been associated with higher frequency of resistant bacteria in the gut flora of swine, chickens and other farm animals.

Direct or indirect contact of farmers and animal health workers with animals causes the high probability of transmitting ARBs. The transmission routes for zoonotic pathogens between humans and animals are numerous. But the most probable route for transmission is through the food chain. Humans are at high risk of exposure to animal originated ARBs through ingestion of animal-derived foods such as milk, egg, meat, and protein. ARBs are more probable in fermented, less processed or raw food stuffs comprising higher load of microbial cells. The existence of pathogenic bacteria in animal derived food creates worrisome situation in human gut, which results in the appearance of resistant strains in humans.

Livestock as Potential Reservoirs for Antibiotic Resistance

Zoonotic pathogens are causing more threats as they are adapting for antimicrobial resistance. The emergence of various strains of methicillin-resistant *Staphylococcus* (MRSA) from farm animals like CC93 in Denmark, ST 130 in Europe and ST398 in the Netherlands was found to be transmitted within human's populations [13]. The possibility of zoonotic transmission raises growing concerns about livestock as a capable reservoir for zoonotic infection which adapt to circulation within the human population. There are findings that correlate the antibiotic usage in food animals to upsurge ARBs in humans. Fluoroquinolone are largely used group of antibiotics for treating infectious diseases [12]. Barza and Travers [14] reported the outbreak of fluoroquinolone-resistant *Campylobacter* infections,

caused by overuse of fluoroquinolone use in animals. Later on, an assessment conducted by the United States, Food and Drug Administration (FDA) on the human health stated the existence of fluoroquinolone-resistant *Campylobacter* in humans was directly related to the consumption of chicken. The finding later on supported the withdrawal of fluoroquinolone from the poultry in USA [15].

The epidemiology of vancomycin resistance element differs in the Europe and USA. In Europe, *Enterococcus faecium* carrying vanA resistance gene (VRGs) has been detected in the gastrointestinal microbiome of livestock animals as well as healthy human, but these were absent in livestock animals and healthy human in United States until 2008. This variation was expected because of extensive use of avoparcin within agricultural practices in Europe since 1970s, while in the United States this glycopeptide has never been approved for agricultural use. It has been proven that Avoparcin, conferring cross-resistance to vancomycin, puts the selective pressure for VRGs in animals [16]. The presence of VRGs in animals provides many opportunities for human infection as well as colonization of ARBs in the human niche. Molecular approach and epidemiological studies have found that VRGs possessing organism isolated from humans and animals are similar proving the potential for VRGs transmission. Knowledge on zoonotic pathogen, disease transmission, control measures and its prevention is essential for livestock workers. It will help in prevention and control of zoonotic diseases as an occupational hazard. Furthermore, it can reduce the prevalence of zoonotic diseases in human as well as farm animals.

Perspective of AMR Through Aquaculture

Aquaculture is a well-established industry with much larger farms. Aquaculture is highly diverse production system used for culturing different species, and is profoundly interconnected with food web through numerous pathways. Use of antimicrobial agents in aquaculture for reducing the mortality of fishes and growth acceleration intends to sustain aquaculture stocks and is practiced by farmers from the last several years. Because of the wide variety of chemicals in aquaculture, public health hazards have been increased. Since aquaculture system is dynamic, highly complex and interconnects various biological, environmental, socio-economic, cultural, and human behavioral factors, it is mandatory to monitor the flow of antibiotic resistance in other niches through zoonotic pathogens. In aquaculture practices, feed is mixed with antibiotics either prior to feeding of animals or directly into the aquatic environment. These water bodies leads to the dissemination of antibiotics into the natural environment and change the microbial population dynamics. Currently, several zoonotic

pathogens have been isolated from various aquaculture systems across the globe, by different researchers.

Various studies have shown the resistance transferring between aquatic bacteria and fish and human pathogens. Wang et al. reported the occurrence of 20 common antibiotics in finfish and shrimp collected from the various water resources in Shanghai City [17]. Moreover, common pathogens infecting fishes in aquaculture are *Streptococcus iniae*, *Aeromonas hydrophilia*, *Vibrio vulnificus*, *Photobacterium damsela*, and *Mycobacterium marinum* [18]. These zoonotic pathogens carry extended-spectrum beta-lactamases (ESBL) and other ARGs that spread through food web [19].

The inefficient regulations and surveillance system are solely responsible for improper usage of antibiotic in livestock and aquaculture. Moreover, there is a still the lack of knowledge about the changes of AMR pattern in the system as a whole and/or in operating mode which indicates failure in existing research in field of AMR to competently address the challenge from an ecosystems perspective. An ecosystems approach can be used to ascertain the possible human exposure points to zoonotic pathogens in livestock industry which is a key step for reducing human health risks.

Transmission of ARGs from Livestock

Zoonotic AMR pathogens can transfer in farm animals to humans through consumption of contaminated water or food, and direct contact with animals. There are different stages and reactions in the food production chain in which ARB can transfers. The physical environment, such as soil, air, and water are the important factors for transfer of ARBs from animals. On the farm, there could be more direct transport of resistant bacteria between animals in the herd and those nearby, as well as between farmers and their animals. Similarly, the consumption of ARBs contaminated water, feed, and waste by animals increase the chance transfer [20]. There are various examples of the presence of ARBs in livestock, which are documented by several authors. These include ESBL producing bacteria, MRSA, vancomycin-resistant *Enterococcus*, MDR *Salmonella* and *E. coli*, [20]. Other ARGs such as plasmid-mediated colistin resistance, New Delhi Metallo- β -lactamase-1 and *Klebsiella pneumoniae* carbapenemase-2 in livestock animals becomes threats to animal and human health [21, 22].

Irrational use of antibiotics in livestock industry increases the emergence of specific resistant bacteria. High level of antibiotic usage is directly related with the level of specific resistance in commensal *E. coli* isolates from poultry, swine, and cattle. Metagenomic data have also

proven the unwise use of antibiotics in animal results in development of resistance in human commensal microbial population [13]. Vounba et al. 2019 had reported the use of third-generation cephalosporins in poultry results in human deaths caused by resistant *E. coli* [23]. Gastrointestinal tract of animals is an important reservoir for ARBs. It is well established that bacteria transfers gene between strains of the same species, and another species, using various mechanisms which includes phagocytic transduction, plasmid transfer, and natural transformation. Resistance genes of sulfonamides, tetracycline, quinolones, aminoglycosides, vancomycin, and β -lactams have been detected in animals. ARBs and ARGs continuously circulate in soil, animals, plants and spreading resistant microorganism in a different living being.

Vector Borne Zoonotic Diseases

Most of the antibiotic resistant zoonotic disease is often conceptualized as a point of direct contact between host and receiver. The non-linear association of resistant pathogen, host and human are often affected by vector-borne disease leading to unexpected complexity. Vector-borne zoonotic diseases (VBZDs), are an important subset of zoonotic diseases that are emerging at an increasing rate relative to directly transmitted antibiotic resistant infectious diseases. VBZDs comprise 22% of all emerging infectious diseases of humans and are thus disproportionately represented among emerging infectious diseases [24] transmitted primarily by blood-feeding, or hematophagous, and arthropods. More than 90% of all vectors involved in emerging VBZDs comprises of mites, ticks, flies and mosquitoes. Many wide spread bacterial infections like Lyme disease, Rocky Mountain spotted fever and ehrlichiosis are transmitted by Ixode and Amblyomma.

Dynamics and Drivers of Vector Borne Diseases

Vector-borne diseases are often affected by many factors that bridge the transmission of infection from native host to recipient. Decrease in the abundance of host is a major driving factor for vector-borne diseases. This factor has been highly associated with decrease in abundance of rates as target host, *Yersinia pestis* moves to human population through vector as an alternative host [24]. An important factor driving the dynamics of vector-borne diseases is environmental changes and anthropogenic activities. VBZDs have extensively emerged in new regions in last three decades. The emergence of VBZDs is primarily caused by pathogen shifting from host to human due to anthropogenic activities. In new regions occurrence is primarily caused by trade and travel whereas in local region it

is caused by the environmental changes such as urbanization and deforestation. Control of vector-borne zoonotic diseases needs combined efforts by clinicians and public health officials to treat patients and promote behaviour likely to minimise risk of infection and by disease ecologists, urban planners, and medical entomologists to advise on development, restoration of ecological communities, and vector control to reverse the ecological drivers of transmission.

Quorum Sensing

Bacterial population is turning into superbugs by acquiring various phenotypic and genotypic mechanisms to develop resistance against frequently used antibiotics. Quorum sensing (QS) is one such mechanism through which microbes interact using small signal molecules [25]. QS primarily depends upon cell density phenomenon which mediates the formation of biofilms in which bacteria can withstand up to 1000 times higher antibiotic concentration. Resistant bacteria exchange the information to transmit resistant infectious diseases in animals and humans by expressing their pathogenic molecule through QS regulation and evading their defense mechanism [26]. Halting the QS process by its inhibition i.e. Quorum sensing inhibition (QSI) proves to be a promising strategy.

QSIs act by different mechanisms that include: (1) inhibition of signal molecules synthesis; (2) enzymatic degradation of the signal molecules; (3) competition of signal molecules for receptor sites; (4) interfering with the binding of signal molecules to gene promoters and inhibiting gene expression; and (5) scavenging of autoinducers by antibodies and macromolecules such as cyclodextrins [27]. QSIs are from diverse origins and have been shown to act as potential antipathogens [3, 10]. An enzyme mediated degradation of QS signal molecules have been reported which include lactonases, oxidoreductases, acylases, and phosphotriesterase-like lactonases [27]. A wide variety of plants are also known to synthesize QSIs that either degrade QS signals or compete for signal receptors. Extracts from different parts of *Emblica officinalis* (medicinal plant), *Medicago truncatula*, *Curcuma longa*, cinnamon, grape fruit, and other edible plants and fruits have been reported to be effective against infections caused by plant pathogens. A QSI attenuates virulence of the resistant pathogenic bacteria by targeting the QS signaling pathway. QSI necessarily does not affect the growth of bacteria, [28, 29] rather stops the resistant pathogenic bacterium to establish a community. Hence combinatorial treatment of QSI with antibiotics will be a promising approach.

Fate of Antibiotics in Environment

Unmetabolized antibiotics are continually disposed into the environment such as soil and water from veterinaries, hospital waste, pharmaceutical industries, poultry, dairies, domestics and municipal waste [30] conferring the threats of pollution. The antibiotics are frequently detected in various water bodies such as rivers, groundwater, and lakes that originated from waste water treatment plant (WWTPs) surface runoff or aquacultural activities. WWTP are well known hotspots for evolution of ARBs as they receive unmetabolized antibiotics from diverse sources through wastewater, thereby playing a crucial role in spread of ARB and ARGs [31]. Apart from water bodies antibiotics are also detected in soil ranging from few nanograms to milligrams per kg of soil [60]. Antibiotics in soil mainly come from the manure, sewage sludge, and areas of livestock. Aquatic and soil organisms are chronically exposed to the continuous and steady introduction of antibiotics into the environment. The microbes in the environment may develop the resistance to those particular antibiotics through gene mutation or from other resistance microbes through horizontal gene transfer. Even at low concentrations, antibiotics into various water bodies and soil pose a significant human health risk and also contaminate different ecological environment. The dispersion of antibiotics contributes to the development and dissemination of ARGs globally. The continuous rise in ARGs and ARB strains leads to severe infections.

The dispersion of antibiotic from sources to the environment goes through the cycle of bioaccumulation and partial biotransformation and gradual deposition in soil or waters [6]. The high intrinsic persistence of antibiotics in the environment results in accumulation of antibiotics in higher concentrations and spreading wider. Although few antibiotics such as penicillins are easily degraded, while others antibiotic like fluoroquinolones, tetracyclines, and macrolides are more persistent due to a longer half-life (Table 2) and therefore remains for a longer time in an environment [32]. The half-life of antibiotics in environment ranges in between < 1 to 3466 days. Walter et al. [33] reported the half-life of ofloxacin for 866–1733 days in a sand clay loam of USA and persistence of azithromycin for with half-lives of 408–3466 days. It is notable that the half-life of antibiotics differs even if they belong to same groups which could be due to the differences observed in condition, composition and variation in soil. Antibiotic degradation in soil is often affected by different functional groups which remain in soil with huge range of half-lives. The persistence of antibiotic for longer time in environment provides more time to bring changes in genetic makeup of bacteria residing in respective niche.

Effect of Antibiotics Contamination on Water Bodies

The aquatic environment is a major reservoir for antibiotics and ARGs. The unmetabolized antibiotics excreted from animals in animal husbandry along with effluents from hospitals and STPs reaches to different water bodies. The majority of antibiotics are carried through wastewaters in metropolises and urban regions, and released in the environment. STPs, livestock, poultry farms, aquaculture and hospitals are an important sources in addition to the intrinsic resistance of microbes in the environment [34]. Conventional STPs are designed for the removal of antibiotic, but their inefficiency of removing antibiotic releases the antibiotics directly into the receiving environment.

The presence of antibiotics in water bodies are relatively low but still more enough to induce the resistance in the microorganism. Selected antibiotic-resistant bacteria get enough nutrients from wastewater and they flourish more as compared to non-resistant bacteria. Trimethoprim, ciprofloxacin, and ofloxacin are commonly found in disproportionate concentrations for inlet and final effluents from WWTPs. A drinking water from four towns of Michigan and Ohio was analyzed for the ARBs by Xi et al. and they confirmed the presences of ARBs for resistant to 7 antibiotics including ciprofloxacin, tetracycline, and amoxicillin [34]. Munir et al. [35] reported the concentration of ARBs and ARGs in the effluents of STPs from Michigan. The ARGs concentration in final effluent was reported to be ranging from non-detectable to 10^6 genomic copies in per 100 ml of water. The ARBs concentration ranged from 10^2 to 10^5 CFU per 100 ml of effluent. The impact of effluent carrying ARBS and ARGs in the downstream process was evaluated by Marti et al. [36]. They reported an increase in the relative concentration of ARGs in Ter river of Catalonia which receives effluent from the wastewater plant.

The effluent from STPs are further treated and recirculated as reclaimed water. Reclaimed water is used widely for irrigating agricultural lands and landscape. The occurrence of antibiotics in irrigation water reaches to agricultural land where it kills the advantageous microbiota involved in the nitrogen fixation and other plant benefitting process. Furthermore, antibiotics in water bodies and puts selective pressure on the microbial community of the soil resulting in the emergence and selection of ARBs. Apart from reclaimed water, the effluents of STPs released in rivers are also of great concern. River facilitates the rapid transportation of antibiotics in and ARGs to various landscapes. Lakes are an important source of freshwater and drinking water holding about 90% of liquid surface freshwater. The discharged antibiotics slowly circulate around

Table 2 Half life and concentration of commonly used antibiotics in different environmental niches

Groups of antibiotics	Antibiotic	Lowest MIC*(mg/L)	Half life (days)	Conc (mg/kg/L)	References
Cephalosporin	Cefradine	8	6.3	10 (surface water)	[57]
	Cefuroxime	32	3.1		
	Ceftriaxone	4	18.7		
Beta Lactam	Amoxicillin	16	0.43	0.2 (soil)	[58]
	Ampicillin	16	3.89 h	10 (aquatic environment)	[59]
Tetracycline	Doxycycline	64	49	10 (water)	[60]
	Tetracycline		578	0.1 (soil)	[61]
Fluoroquinolones	Ofloxacin	64	990–1386	0.045 (soil)	[62]
	Levofloxacin	8	4.2	0.225 (waste water)	[63]
	Norfloxacin	32	62	30 (soil)	[64]
	Ciprofloxacin	2	1153–3466	0.542 (soil)	[62]
Aminoglycoside	Gentamicin	32	4–5	–	[65]
	Vancomycin	4	16	10 (sandy loam)	[28]
Sulfonamides	Sulfamethoxazole	15	49	10 (waste water)	[60]
	Trimethoprim	64	11.5	0.17 (surface water)	[66]
Macrolides	Azithromycin	64	12.82	1 (soil)	[67]
	Clarithromycin	32	36.48	1 (soil)	

*As per EUCAST database

the lakes and reach to lake surface water. The residence time of antibiotics increases in lakes because of the longer retention time and thus has the potential to store and accumulate ARGs.

Effect of Antibiotics on Soil Microbiome

The continuous release of antibiotics into the environment through animal urine, feces, animal manure, and sewage sludge puts adverse impact on soil microbial community. Antibiotics are given to animal for treating diseases but often antibiotics do not metabolize in the bodies and large portion of unmetabolized antibiotics ends up either in municipal wastewater or soil. Many reports suggest that 60, 50–90 and 75–80% of the given doses of lincomycin, erythromycin and tetracycline respectively, goes unmetabolized and is excreted out from the body. Tetracyclines most frequently detected in manure followed by fluoroquinolones, sulphonamides, and macrolides. The high concentration of antibiotics in soil selects the growth of ARBs which ultimately changes the microbial population sensitivity towards antibiotics. The antibiotics in soil environments facilitate the genetic alteration in bacteria along with transfer of ARGs among the bacterial population. The spread of ARGs also affects the autochthonous bacteria of soil making them resistant and reservoir of ARGs in the environment. Antibiotics in the soil also affect the microbial activity, enzyme activity, nitrogen cycle and

carbon mineralization along with changes in genetic, structural and functional diversity. From the soil and water environment ARBs are transferred to the human body where they colonize in gut and change the antibiotic susceptibility in humans. Moreover, studies have also indicated that presence antibiotics in soil have resulted in emergence of new enzymes and genes conferring resistance to bacteria [31].

Different Approaches for Antibiotic Degradation

Increased usage and disposal of antibiotics into the environment disturbs the water quality and other biological process. The degradation of antibiotics thus becomes necessary to control the emergence of novel resistant strains and ARGs. Antibiotics are degraded by abiotic and biotic process. It is facilitated by bioelectrochemical methods, hydrolysis, metal-assisted photolysis, adsorption mechanisms, oxidation and reduction.

Physico-Chemical Degradation of Antibiotic

Abiotic degradation largely depends on the physicochemical properties and molecular structure of antibiotics. β -lactam antibiotics are reported to be more susceptible for hydrolytic degradation in comparison with macrolides and sulfonamides. The degradation of fluoroquinolone

antibiotics is mainly achieved by photo-degradation. Wajahat et al. [37] investigated two methods for the degradation of commonly used antibiotic ciprofloxacin. They employed ozonation and anatase facilitated photocatalysis. They concluded that the degradation rate was higher in photocatalysis process as compared to ozonation. Treatment of waste water by chlorination and UV radiation helps in decontamination of waste water reducing the level of antibiotics. Besides degrading the antibiotic the natural polysaccharide chemical conjugates can be employed into inhibit the growth of resistant bacteria to prevent the spread of ARBs and ARGs. The antibiotic in soil binds to its particles forming the complex which causes the loss in antibacterial properties of antibiotics. This process is known as adsorption and desorption of antibiotics. The pH of soil and water retention capacity of soil plays an important role in sorption methodology. As the antibiotics such as sulfonamides gets adsorbed in soil the changes in its cationic form to the neutral and anionic form are observed. The abiotic degradation of antibiotic is depends upon the various physical and chemical parameters. The change in pH, salt concentration and presence of other compound in system may interfere with the abiotic treatment. In such cases biotic processes that include application of microorganism may play a crucial role in removal of residual antibiotics from the environment.

Degradation of Antibiotic Through Bioaugmentation

Biotic degradation involves the antibiotic degradation through the potential metabolic pathway of microorganisms. Microorganisms aiding the bioremediation [38] of antibiotics mainly involve ARGs that efficiently break down the parent antibiotic or functional group and release the byproducts. Bioaugmentation have been proven in successfully removing the antibiotic from industrial effluent. Bacterial strains have been extensively applied for the removal of antibiotics from wastewater and soil. Maia et al. employed *Labrys portucalensis* F11 and *Rhodococcus* sp. FPI for degrading the frequently used antibiotics Ofloxacin & levofloxacin [33]. Similarly, bioaugmentation of membrane bioreactor with *Achromobacter dentrificans* have also been reported to enhance sulfamethoxazole removal [66].

The bacteria capable of degrading antibiotics are mainly isolated from soil with anthropogenic activity, feces, sludge and sea water. Hirth et al. inoculated *Microbacterium* sp. C448 in soil containing Sulfamethazine and reported 59.23% degradation of antibiotic [39]. Another report states the 97% degradation of erythromycin by bacteria *Ochrobactrum* sp. [40]. Bioaugmentation has appeared as an advantageous cleanup technique for

antibiotics in environment (Table 3). This approach enhances the degradation of unwanted compounds and also complements the activity of native microorganisms playing crucial role in lowering the half-life of antibiotic.

Transboundary Spread of AMRs

The spread of ARGs globally and their ability to be transmitted between human, animals and environmental reservoirs is a major challenge in reducing the AMR threat. The well-known contributors for spread of resistance are animal husbandries, aquaculture industries, WTPs, and hospital generated wastes. ARGs can be transferred through, zoonoses, HGT or from the environment to human opportunistic bacteria with the aid from genetic elements. Apart from these, airborne microorganisms are often found to be multidrug-resistant, which poses a significant health risk to human and animal population via airborne transmission. Air borne AMR has been reported in literatures. Pal et al. 2016 analyzed the smog in Beijing Harboring a richness of 64.4 types of ARGs as compared to any other environments [41]. Li et al. 2013 reported the occurrence of tetracycline resistant genes in indoor air occupied by humans in Colorado [42]. Echeverria-Palencia et al. also detected the beta-lactam resistant genes in urban park of California [43]. The antibiotic usage, meteorological parameters, physico-chemical parameters and microbial community affect the distribution of air-borne AMR.

The easy transportation system and frequent traveling of humans globally contributes towards the spread of air-borne ARGs and ARBs in different cities. The air-borne AMRs are being considered as biological pollutant, when inhaled could disturb the human gut flora and affect the immune system. The aerial transmission of AMRs is affecting the remote areas where antibiotics are not even used; thus exposing the areas with second hand ARGs which are developed in different regions and carried away to other areas. The research in the area of air-borne developed resistance is still lacking and needs attention to trace the pattern and spread of AMRs through air.

Conclusion

Growing environmental pollution is a major global threat and has gain more attention in present days. Unwise usage of antibiotics in livestock industry develops the resistance in gut microbiome which works as a bioreactor for breeding pathogens and increases the chance of emergence and spread of new ARGs in environment. Similarly, the unmetabolized antibiotic is excreted out in environment and disturbs the biogeochemical cycle through food chain.

Table 3 Degradation of commonly used antibiotics through bioaugmentation

Class	Antibiotic	Degradation by microorganism	Degradation (%)	Experimental condition	References
Fluoroquinolones	Ofloxacin and levofloxacin	<i>Labrys portucalensis</i> F11 and <i>Rhodococcus</i> sp. FP1	96	Degradation evaluated under dark aerobic conditions at 25 °C with and without acetate as an additional carbon source at an initial concentration of 5.9 mM	[63]
	Ciprofloxacin	<i>Thermus</i> sp.	59.23	The biodegradation experiments were performed at different temperature and pH and maximum degradation was observed at 70 °C and pH 6.5	[61]
Sulfonamides	Sulfamethazine	<i>Microbacterium</i> sp. C448	57	Bacterial strain was inoculated in soil containing antibiotic and incubated in the dark at 20 ± 1 °C, water tension of –15 kPa, and soil density of 1.3 g cm ⁻³ , for 49 days	[68]
	Sulfamethoxazole	Consortium of <i>Achromobacter denitrificans</i> PR1 and <i>Leucobacter</i> sp. GP	100 transformation	Lab conditions: Culture medium with 4 mM ammonium sulfate, 7 mM succinate, 0.2 g/l yeast extract, 0.6 mM SMX and inoculated with consortium and incubated in the dark at 30 °C, continuously stirred at 120 rpm	[69]
	Trimethoprim	<i>Bacillus subtilis</i>	90	<i>Bacillus subtilis</i> inoculated in inorganic salt media containing 5 mg/L antibiotic and 5% yeast powder and incubated at 30 °C at 140 RPM	[70]
Penicillin	Penicillin G	<i>Serratia</i> sp. R1	84	The bacterial isolate was plated on the salt medium containing 10 mg L ⁻¹ Penicillin G antibiotic agar plates and incubated at 32 °C for 3–4 days	[19]
	Amoxicillin	<i>Bacillus cereus</i> , <i>Enterobacterludwigii</i> and <i>Enterobacter</i> sp.	75–99	Freshwater with antibiotic concentration 120 ppm incubated with strains at 28 °C with shaking at 100 rpm	[71]
Cephalosporin	Ceftriaxone sodium	<i>Achromobacter xylooxidans</i>	100 transformation	50 ml bottle volume ratio 0.39 and 7.973 g Ceftx/L modified tryptic soy broth for 39 h under aerobic static conditions at 30 °C	[72]
	Cefuroxime	<i>Bacillus clausii</i> T and <i>Bacillus clausii</i> O/C	100	Sterile medium contained basal salts, glucose with added antibiotic and inoculum at 220 rpm and 37 °C in the dark under aerobic conditions	[73]
Tetracycline	Tetracycline	<i>Stenotrophomonas maltophilia</i> DT1	100	Strain DT1 inoculated in LB medium containing 20 mg/L tetracycline and incubated at 30 °C with pH 9 on a shaker set at 150 rpm	[62]
Macrolides	Erythromycin	<i>Ochrobactrum</i> sp.	97	Marine mineral culture medium containing antibiotic 100 mg/L as carbon source, pH 6.5 and temperature 32 °C	[74]
	Azithromycin	Macrolide acclimated sludge micro-organism	99	Azithromycin as carbon source and NH ₄ Cl as nitrogen source inoculated acclimatized consortia incubated at 28 °C on a rotary shaker at 180 rpm for 12 days	[75]

The microbial community, enzyme activity, nitrogen cycle and carbon assimilation is altered due to outgrowth of resistant bacteria and suppressed autochthonous microorganisms. Future workplan should be focused on persistence, accumulation, bioaugmentation, biostimulation and

biotransformation of antibiotics in environment since it elevates the breeding risk of ARBs through HGT events. While focusing on these plans, the combination of biotic and abiotic degradation process must be taken into consideration.

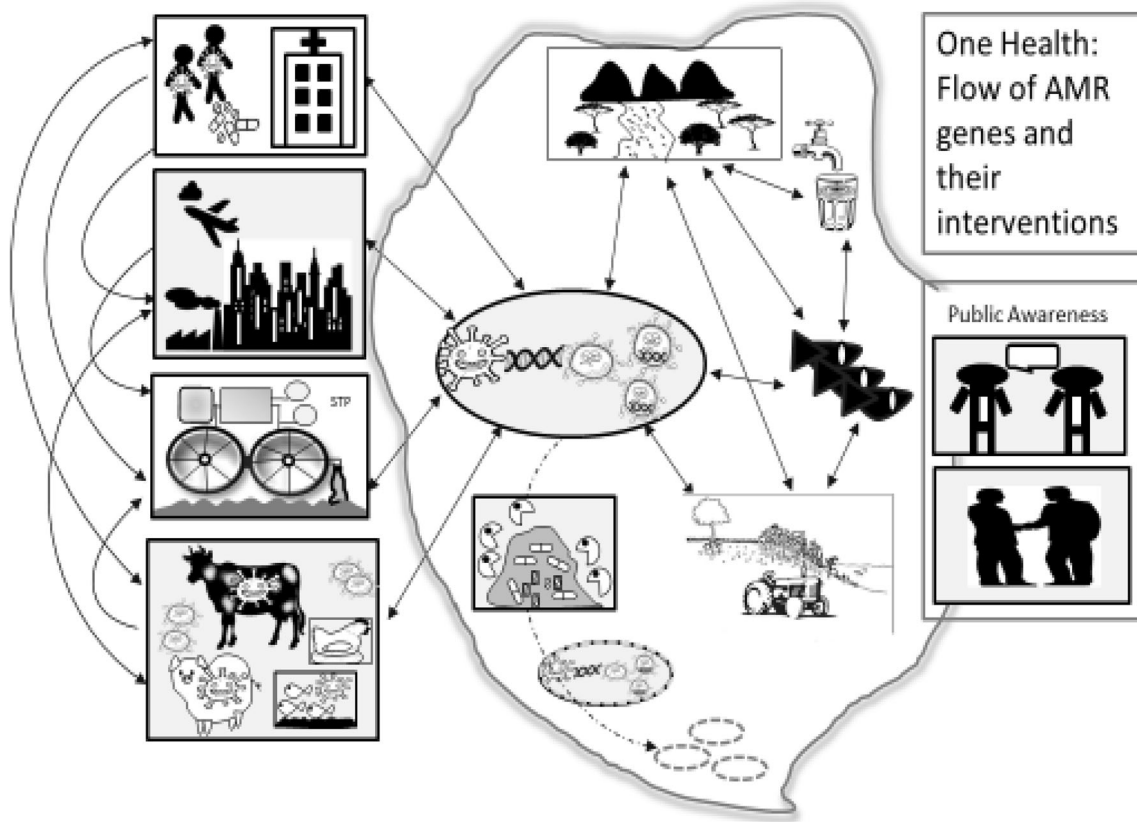


Fig. 1 Schematic representation of resistance gene flow in environment and its intervention through “One Health” approach. Black solid line interconnects the breeding hotspots for ARBs and dotted line indicates the bioremediation approach in environment

As the animal gut is breeding hotspot for antibiotic resistance the emerging resistance pattern should be regulated and investigated under “one health approach” through ARBs monitoring system for facilitating timely public health response. Furthermore, there is a need for the development of multiple agency coordinated response that will enhance communication on time, informs and spreads the awareness for appropriate use for antibiotics in agriculture, animal husbandry and aquaculture industries. The outcome of these measures will not only control human and animal disease but also increases the efficacy of both existing and new antibiotics in environment. Moreover, there will also be reduction in spread of antimicrobial resistance among zoonotic pathogens causing serious untreatable infection in humans.

Acknowledgements This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The manuscript has been checked for plagiarism by Knowledge Resource Centre, CSIR-NEERI, Nagpur, India and assigned KRC No.: CSIR-NEERI/KRC/2019/OCT/EBGD/1.

Compliance with Ethical Standards

Conflict of interest The authors declare no financial or commercial conflict of interest.

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