

Antibiotic resistant bacteria in terrestrial and aquatic environments: A review

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Abstract

Antibiotic resistant bacteria have become increasingly widespread in the environment and their prevalence is a serious potential problem for human health. The rise and spread of this resistance is primarily due to the overuse of antibiotics in clinical therapeutics and as growth promoters for livestock. Overuse undermines the usefulness of antibiotics by giving a selective advantage to microbes that are resistant. The problem has been exacerbated by the emergence of bacteria that are resistant to multiple antibiotics and by the ability of these resistance determinants to spread between different bacteria via horizontal gene transfer. Such transfer can, for example, take place extensively in the digestive tract of domestic animals and aquatic environments, which can become reservoirs of multiple antibiotic resistant bacteria (MARB) and these sources contribute eventually to spread of antibiotic resistance to humans

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Introduction

Antibiotics were originally defined as biochemical compounds, secreted by microorganisms, which inhibit the growth of other microorganisms, such as bacteria, fungi and protozoa [1]. However, the meaning of the term has expanded to include not only chemicals of natural origin but also synthetic and semi-synthetic drugs. On the other hand, "antibiotic" now tends to be used more narrowly to

indicate antibacterial substances, while "antimicrobials" or "antimicrobial drugs" are more appropriate general terms that include all chemotherapeutic agents used against microorganisms, whether they are bacteria, fungi or protozoa.

In this article, "antibiotic" will include synthetic and semi-synthetic antibacterial drugs or naturally occurring antibacterial compounds. The first such compounds to be produced on a large-scale and widely

used were the sulfonamides (developed by Bayer AG) and sulfanilamide in the 1930s. However, the era of antibiotics could really be said to have begun with the mass production of penicillin during World War II. Penicillin and its derivatives were the first drugs to be effective against *Streptococcus*, *Staphylococcus* and other bacteria that previously caused very serious infections. Further research in the 1940s and 1950s turned up new antibiotics produced by soil microorganisms, as well as semi-synthetic derivatives of penicillin with broader activity.

There are many uses for antibiotics, the most familiar being their use in medicine. In the last 60 years, they have become a mainstay of the physician's arsenal for fighting bacterial infections in humans, and deaths from such infections have become much less common, at least in countries where antibiotics and good health care are available. Recently it has also been found that antibiotic compounds can be of great utility in treating severe malnutrition [2-3]. Less well-known among the general public are the uses of antibiotic compounds in plant agriculture, in aquaculture, for therapy and prophylaxis in veterinary medicine, and for growth promotion of animals, mainly cattle and poultry [4-5].

In the 1940s, it was observed that chickens fed with food containing tetracycline grew faster than those with no antibiotic [6]. As a result, many antimicrobial drugs improve the average daily weight of livestock, especially cattle. Antibiotics such as bambermycins, carbadox and bacitracin, are mostly used for growth promotion and prophylaxis. Other prophylactic antimicrobial drugs include β -lactam drugs (penicillins and cephalosporins), tetracyclines and quinolones. Tetracycline residues in Oman were found in chicken [7-8]. These antibiotics are also used widely in human medicine [6]. Antibiotics also have been used for treatment of plant diseases since the 1950s [9]. The excessive use of antibiotics has also been reported in aquaculture [10]. Nhiem *et al.* [11] reported antibiotic

residues in marketed pork in Vietnam. In Indo-China, antibiotic residues have been found in shrimp ponds, rivers, canals and other habitats [12].

The use of antibiotics as growth promoters is particularly significant. It has been suggested that 40% of the antibiotic production in the United States is used in stock feeds [13]. However, others report that the figure may be closer to 80% [14]. Although the use of antibiotics under the control of veterinary prescription, farmers still tend to use them intensively, which led to successful poultry industry, but have caused the emergence of antibiotic resistant strains.

Nevertheless, awareness of public health associated with the usage of antibiotics is increasingly on the rise specifically the emergence of multi-drug resistant strains [7, 15]. Health officials worldwide recognize that the increase in the number of multi-drug resistant bacteria is a significant problem, particularly with the decline in the number of new antibiotics available for treatment, and the low number of new antibiotics approved per year.

Antibiotic resistance and its origins

Whenever antibiotics are used, and especially when they are misused or overused, bacteria can arise that are no longer vulnerable to the drugs. This is termed as antibiotic resistance. Resistance describes the relative bacterial insusceptibility to a specific treatment under a particular set of conditions. The development of bacterial resistance is a natural evolutionary response in the presence of the selective pressure of antimicrobial drug usage. Under optimal conditions, bacteria multiply very rapidly, with generation times of minutes to hours. This allows ample opportunity for spontaneous mutations to

occur, so in any population of bacteria significant genetic variation will naturally occur. It is estimated that a genetic mutation that confers some measure of resistance, usually to a single antibiotic substance, arises in a frequency of once in every 1 million to 1 billion cells [16]. When bacteria are exposed to the drug at a concentration less than what would be necessary to inhibit the growth of or kill the entire population, those cells that carry resistance determinants have a selective advantage in survival and growth over those that do not. Thus, resistant bacteria become more predominant by a process of Darwinian natural selection.

Resistance is a natural phenomenon that is as ancient as the antibiotic compounds themselves, having developed in antibiotic-producing organisms to protect them from their own products and evolving in other originally susceptible organisms that live in close proximity to the antibiotic-producers, for example in the soil [6]. In short, resistance determinants exist in nature where, as will be discussed below, they have the potential to be transferred horizontally to human pathogens [17]. However, clearly not all bacteria are resistant to naturally occurring antibiotics. If they were, compounds such as penicillin and streptomycin could not have been discovered and put to use against human pathogens. Those bacteria which are susceptible presumably never evolved resistance because they were never exposed to the antibiotics in nature. The same is obviously true of antimicrobial compounds.

Although some bacteria were exposed to naturally occurring antibiotics and evolved resistance at early stages of evolution, since the discovery and exploitation of antibiotics by man began in the 1940s many more bacteria have been exposed to these agents. As a result, resistance to both naturally occurring and synthetic antibiotics has become widespread among many species and strains of bacteria that were previously susceptible. It has become

much more common to isolate antibiotic resistant bacteria from patients, from farm animals and from the environment.

The prevalence of resistance resulted from complex interactions among antibiotics, microorganisms, hosts and the environment. However, the main factor that determines the rate of emergence and the degree of antibiotic resistance is the presence of the antibiotics themselves resulting in selection pressure [18]. Under this selection, the dominant resistant strains spread widely to animal hosts [6]. Therefore, the main cause of the emerging antibiotic resistant bacteria is exposure to antibiotics and how frequently and much the drugs are being used [19]. As a result of treatment with antibiotics in health care, antimicrobial resistance can arise in bacteria of the human body in both pathogenic and normal flora, for example, their presence in the colon. Physicians can minimize the emergence of resistance by prescribing antibiotics carefully and prudently, but this is not always done. In many countries antibacterial drugs are readily available over the counter (OTC), so they can be easily obtained by the community and used improperly. This contributes to the selection of resistant strains, especially when broad-spectrum antibiotics are used [20-21]. Antibiotic resistance can also evolve in animals, where usage of antibiotics for growth promotion is the most dominant factor contributing to the selection and emergence of antibiotic-resistant bacteria [22]. The more frequent antibiotic used, the more resistance will develop in both pathogens and normal flora bacteria in the exposed population of animals [6, 23].

Finally, antibiotic resistance can emerge in the environment. In nature, resistant bacteria may be selected as a result of exposure to antibiotics produced by organisms in the soil. However, a much more significant factor is the selection imposed by exposure to antimicrobial residues in waste products from human activity. These residues may come

from treated animals or humans, disposal of unused drugs, or runoff from agricultural land [24].

Emergence of Multiple Antibiotic Resistant Bacteria (MARB)

The use or overuse of antibiotics can lead to the emergence of antibiotic-resistant bacteria, especially when broad-spectrum antibiotics are used. Bacterial resistance to a single antibiotic might appear to be a minor problem, because so many different antibiotics are available. However, as the use of antibiotics has become widespread, bacterial strains that are resistant to multiple antibiotics have become increasingly common. In some cases, pathogenic bacteria have emerged that are resistant to all, or almost all, of the currently available antibiotics. Clearly MARB have serious implications for human and animal health, and for the environment [23]. If resistance can make antibiotics useless, it raises the specter of a return to the pre-antibiotic age when medicine was nearly powerless to fight infection. Bacterial antibiotic resistant infections double the risk of disease, hospitalization and death compared to drug-susceptible bacteria [25]. For the first time a comprehensive global study collected from 114 countries shows a threatening situation of multiple antibiotic resistant microbes and that the antibiotics are declining in their efficiency in controlling microbes [26]. If this situation continues then within few years, infections which were once easily treatable will become uncontrollable. MARB could in principle arise as a result of mutations when a population of susceptible bacteria is exposed to sub-lethal concentrations of two or more antibiotics at the same time, or when a population that is already resistant to one antibiotic is exposed to another. However, a more important route to multiple antibiotic resistance, and the spread of antibiotic resistance in

general, involves genetic rearrangements and the horizontal transfer of resistance determinants from one bacterium to another. Horizontal transfer refers to the transmission (via the bacterial processes of conjugation, transformation or transduction), from donors to recipients, of resistance genes already present in the bacterial world [27]. This sort of transfer apparently occurs quite commonly within environmental reservoirs where resistance genes are generated by mutation, where bacteria and antimicrobial agents coexist, and where the bacterial population is high. There is strong evidence for horizontal transfer of resistance genes between bacteria that cause infections in animals and those that cause infection in humans [28]. It was reported that environmental isolates of MARB could transfer resistance to previously susceptible normal flora *Escherichia coli* [29].

Widespread occurrence of plasmids carrying antibiotic resistance genes

Antibiotic resistance in pathogens makes it difficult to treat human infections efficiently, but nonpathogenic antibiotic resistance bacteria are also important in transmitting resistance genes to other bacteria by means of transmissible resistance factors (R-factors) [30]. Research indicates that plasmids, and especially R-plasmids, are very common in bacteria. In one of our studies, plasmid DNA analysis of 47 different strains of *E. coli* showed a plasmid occurrence rate of 100 %. The size of the extracted plasmids ranged from 1.2 to 54.3 kilobases (kb), while the number of different sized plasmids per cell ranged from one to nine. However, some strains resistant to one antibiotic had more than one plasmid, others containing just one or two plasmids were resistant to many antibiotics [31]. Bacteria isolated from humans with single plasmids carrying resistance to

a large number of antibiotics were also reported [32]. These plasmids ranged in size from 4.7 to 10.8 kb. Analysis of 28 *Salmonella* spp strains showed that the plasmid DNA in various strains ranged in size from 3.1 kb to 32 kb. It has been shown that a similar range of bacterial R-plasmids can be isolated from fish [33]. Plasmid occurrence at a rate of 81.7% was observed in *E. coli* isolates from chicken in Malaysia [34]. The maximum number of different plasmids per cell in this study was eight with sizes ranging from 1.8 to 180.3 Kb. It was also reported that 2.8% of the *E. coli* isolates harbored 8 plasmids and were resistant to 12 antibiotics [34]. They concluded that *E. coli* with a higher number of plasmids possessed wider resistance to antibiotics. However, it has been observed that *E. coli* isolates with only three plasmids were also resistant to 12 antibiotics [31]. Others found that *E. coli* drug-resistant isolates carried plasmids ranged from 1.5 kb to 54 kb in size, with one to six different sizes in each isolate [35]. In addition, multiple antibiotic resistant *E. coli* isolates harboring 4.3 kb and 23.1 kb plasmids were observed [36]. In another study, a common 54 kb plasmid was harbored by 55 % of local isolates of *Enterobacteriaceae* from humans and chickens in Turkey [37], while in Jordan, it was reported that the 54 kb plasmid was common in isolates from leafy vegetables [38]. Others observed *E. coli* plasmids isolated from chicken fecal samples with 21.5 kb to 27.4 kb [39]. According to Doetkott *et al.* [40], 56.7% of *E. coli* isolates from chickens had one to four plasmids greater than 50 kb in size. These examples show that plasmids, and particularly R-plasmids, are commonly observed in environmental bacterial isolates. They are regularly found not only in bacteria isolated from humans, but also in isolates from farm animals, such as chickens. This suggests that fowl may be important reservoirs of antimicrobial-resistant organisms. The prevalence of resistance determinants on mobile genetic elements means that it is possible, indeed likely, that acquired characteristics will be shared with other bacteria

[41], which can then spread to other animals, to humans, and to the environment [42].

Food-Producing animals as breeding grounds for antibiotic resistance

Bacterial strains showing resistance to multiple antimicrobial drugs are clearly a public health concern and so it is important to understand how and where they emerge. Bacterial antibiotic resistance can arise in humans, animals, or the environment, and is usually associated with excessive, inappropriate and indiscriminate usage of antimicrobials [43]. It was reported that bacterial strains of human origin were resistant to a larger number of antibiotics than those from animal, sewage and water sources [44]. This suggests that excessive or inappropriate use of antibiotics in human medicine plays a crucial role in the genesis and persistence of resistant human pathogens. However, antimicrobials usage in animals contributes to the emergence of resistant variants. For example, some investigators reported the emergence of verocytotoxin-producing *E. coli*, including *E. coli* O157:H7 [39]. The use of antibiotics for treatment of *E. coli* O157:H7 in human infections is not recommended. It is reported that sub-therapeutic administration levels of antibiotic to animals is a contributing factor. *E. coli* O157:H7 resistant isolates present in animal drinking-water is evidence that the strains spread from one animal to another [45]. Both humans and animals are obvious breeding grounds for resistant bacteria, but animals and food-producing animals in particular, may actually be more important sources. The digestive tracts of animals are the largest reservoirs of resistance genes. They form an ideal climate for horizontal gene transfer among both pathogenic and commensal species, as has been well documented [18]. Resistance genes in *Salmonella* spp.

were transferred to *E. coli* as well as between other normal intestinal flora [46].

Large amounts of different drugs are used in animals as growth promoters, as well as for disease prevention and treatment purposes [14, 43]. These practices are thought to have caused an increased frequency of multiple resistance genes in the animal gut [23]. Enteric bacteria in livestock are exposed to great selective pressure because in some countries more than half and by some reports as much as 80%, of the production of antimicrobial agents is used as feed additives for food-producing animals [14]. As a result of extensive antibiotic use and abuse, *Enterobacteriaceae* and other normal intestinal flora are the microorganisms most often exposed to antibiotics and consequently they are the ones that most commonly develop multiple antibiotic resistance. Antibiotic resistant Gram-negative bacilli from fecal specimens, especially *Enterobacteriaceae*, have been of particular interest because of the increasing risk of gastroenteritis caused by strains carrying R-plasmids. *E. coli* is the most common facultative bacterium in the intestinal microbiota of humans and many animals [47] has been reported to be a significant reservoir for genes encoding antimicrobial drug resistance [48]. The widespread use of various antibiotics as growth promoters and as treatments for chicken infections has selected antibiotic-resistant strains and has made chickens an important potential source of multiple antibiotic-resistant bacteria [7]. Since the selection pressure for antibiotic resistance in bacteria is high in poultry, their fecal flora contains a relatively high proportion of resistant bacteria [22]. Numerous studies have found high levels of antibiotic-resistance among the intestinal flora of chickens. A normal flora, *E. coli*, in chicken intestines is always exposed to antibiotics. It is considered the major carrier of resistance combinations and it is transferable in fecal flora [49]. In Saudi Arabia, *E. coli* isolated from chickens were highly resistant to many antibiotics [50]. In a later

study [21], they reported that 37.4% of strains isolated from chicken were resistant to gentamycin. They confirmed that gentamycin is heavily used on chicken farms where it is administered to almost all three-day-old chicks to treat or prevent infections. In their study, most Gram-negative organisms were highly resistant to this drug. Other studies reported resistance of *E. coli* to gentamycin [39, 42]. It was reported that low-dose of tetracycline in poultry feed affected the chicken intestinal flora. Resistance developed rapidly under antibiotic pressure and that resistance to single-drugs eventually becomes multidrug-resistance. It was also found that the intestinal bacteria of individuals who were exposed to antimicrobial agents acquired resistance and were able to spread to other chickens and humans living and working on the farm [51]. Chicken isolates from slaughterhouse in Spain were highly resistant to many antibiotics [13]. Others reported that *E. coli* isolates were multiple resistance to most antibiotics [42-43, 52-54].

Crowding and sanitation are major factors in the selection of antimicrobial resistance in bacteria [22]. These conditions are used extensively in poultry farming, which explains the high degree of resistance observed in *E. coli* of poultry feces cited above. In Oman, 100% of the isolates from chickens were resistant to antibiotics [42], whereas in an earlier study samples collected in Oman in 1986, only 30% of the isolates were multiple resistant to antibiotics [43]. These results indicate that antibiotic resistance is increasing rapidly in the poultry industry. Although regulations forbid the use of antibiotics in several countries, antibiotics are still used in poultry industry.

In summary, the extensive antibiotic usage for prophylactic and growth promotion purposes has caused the selection of resistance in both pathogenic and non-pathogenic bacteria in the animal gut. Consequently, food-producing animals have

become important breeding grounds for antibiotic resistant bacteria. This is a serious concern for two reasons. First, the presence of resistance makes the antibiotics less useful for their intended purposes of prophylaxis and treatment and reduces their economic value as growth promoters. Second, these animals and their wastes have become potential sources for the spread of these bacteria to the environment and humans.

Spread of antibiotic resistance from animals to humans

The mechanisms of MARB spreading from animals to humans remain somewhat controversial; colonization of the human intestinal tract with resistant bacteria from chickens was clearly demonstrated [47]. At slaughterhouses and poultry farms, both pathogenic and nonpathogenic strains from domestic animals can spread to humans by eating contaminated egg, meat and dairy products of the infected animals [16, 22, 36, 47, 55, 56, 57].

Infiltration of antibiotics and antibiotic resistance into the environment

Resistant bacteria spread to the environment by several different routes including treated and untreated sewage effluents, sludge and agricultural runoff [42, 58-63]. Pharmaceuticals can be dispersed by the same routes and also important for the emergence and spread of antibiotic resistance in the environment [64]. The widespread release of disinfectants and pharmaceutical products related to agricultural, medical and veterinary practices is believed to be the main contributors in the emergence of MARB [5, 63, 65-67]. Many antibiotics are poorly absorbed in the animal digestive tract, and it is estimated that

25% to 75% are excreted in feces [23]. However, antibiotics such as tetracycline are found in chicken liver, intestines and kidney, and these antibiotics find their way into the environment through urine mixed with chicken manure [8, 68]. Antimicrobial drugs used for animals enter the environment when manure is used as organic fertilizer. Since the annual waste production of waste from livestock is nearly 180 million tons in the United States, this waste is potentially a significant source of pharmaceuticals released into the environment. These antibiotics may end up either in soil, sediment, ground water or surface water where they may exert significant selective pressure favoring resistant bacteria [6].

Antibiotic-resistant bacteria can also enter the environment in runoff from feedlots and fields fertilized with manure. In a study of a pristine river in the Rocky Mountains, it was reported that certain resistance genes accumulated downstream and that they were primarily contributed by animal feeding operations located upstream and only to a lesser extent by wastewater treatment facilities [69]. In Ontario, private wells where manure is commonly applied on farms are frequently contaminated with bacteria. Feces contaminated effluents from animal farms infiltrate wells [70]. In addition, waste from septic tanks and manure storage sites can seep or spill into surrounding watersheds and ground water sources [71]. In West Virginia, it was reported that all coliforms and nearly all non-coliforms were multiple resistant to antibiotics [29]. In Oman, treated and untreated sewage effluents played an important role in the underground water pollution. In some contaminated wells *E. coli* was found to be multiple resistant to antibiotics, which is a clear indication that contamination was from sewage effluents [72].

Human waste streams can also be an important source of antibiotics in the environment. Consequently, hospital and municipal wastewater systems may play an important role in the selection of

antibiotic-resistant bacteria [5, 66-67]. Depending on their use, pharmaceuticals enter the environment through different pathways [64]. Compounds used in medicine and their metabolites are excreted with feces and urine into sewage. Disposal of surplus drugs into the sewer system via toilets may also be a significant source, although it is unknown to what extent this occurs. Antibiotics have been clearly detected in wastewater treatment facilities [73], but they are only partially eliminated during the sewage-treatment process [60, 65]. Some are subsequently released via the contaminated effluent into the aquatic environment [60, 64, 74-77] where, they are probably slowly transformed by biological and physical processes [78]. Resistant bacteria bred in the human gut can also enter the environment via sewage. Untreated sewage is the most hazardous contaminant in the environment due to its large volume, its human waste component, and its ability to transmit waterborne diseases including

viruses, bacterial pathogens and other organisms that are endemic in the community. In arid hot climate regions, or where there is a high dependence on underground potable water, the transmission of MARB is greatly increase as a result of crack septic tanks, cesspit and inadequate recycled sewage water [61, 72]. Although untreated sewage can obviously be a source of antibiotic resistant bacteria in the environment, treated domestic wastewater can also be a source [59, 72].

The diagram in **Figure 1** summarizes the various factors involved in the genesis and spread of MARB that have been discussed in this review. It also portrays the relationships between antibiotic usage, human and animal infections, and environmental contamination. As Figure 1 indicates, dispersal of antibiotics, MARB and other pollutants in the environment, which eventually manifested as contamination of ecosystems and the living organisms that inhabit them.

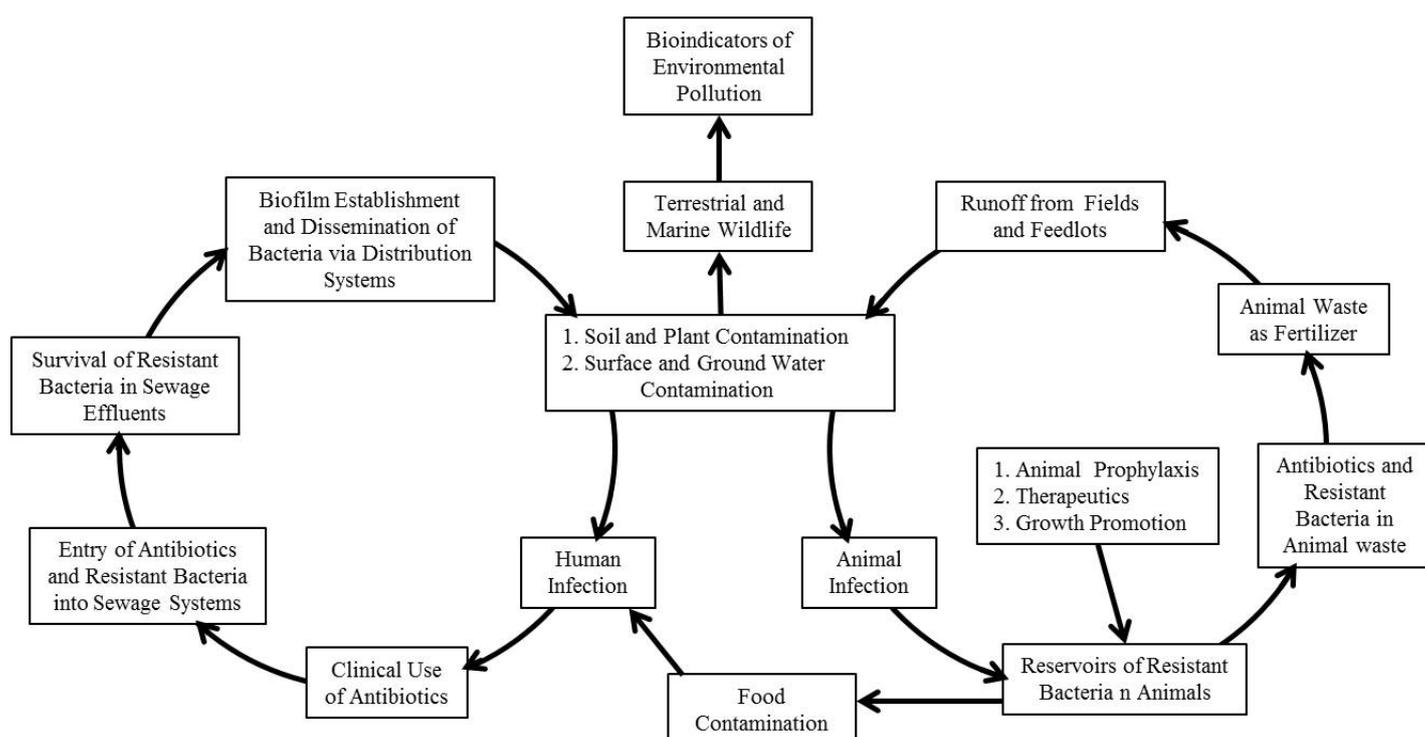


Figure 1. Relationships between antibiotic uses and environmental contamination.

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