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Environmental propagation of antibiotic resistance: The roles of rivers and dams—an underexplored dimension of a global crisis

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ABSTRACT

Antibiotic resistance is inevitable; thus, better understanding the origins and the sources that support the spread of resistance genes among microorganisms is crucial. The rapid spread of resistance elements among the most prevalent bacterial pathogens poses an active threat to public health.

Indeed, such threat will continue looming if experts fail to control the skyrocketing dissemination of antibiotics into the natural environment, through mass human migrations, or within clinical, husbandry, or veterinary settings. Any policy governing antibiotic administration in human or veterinary medicine must consider the transmission of antibiotic-resistant microorganisms between environmental sources and humans or animals. In this context, dams and rivers represent two major environmental sources of antibiotic-resistant bacteria, acting as reservoirs and conduits for resistance genes via horizontal gene transfer. In such a scenario, routine surgeries (e.g., cesarean sections, joint replacements) would become high-risk procedures due to the absence of prophylactic antibiotics; bacterial pneumonia, once easily cured, would revert to its historical status as a leading cause of death; and the management of immunocompromised patients (transplant recipients, cancer patients undergoing chemotherapy) would be severely compromised. The emerging high incidence of antibiotic-resistant or multidrug-resistant bacterial infections, coupled with the extant arsenal of antibacterial drugs that have waning values and applicabilities, forewarns of an imminent and unknown post-antibiotic era—a time when even common infections may become untreatable, underscoring the urgent need for global surveillance and stewardship.

Keywords: antibiotic resistance, dams, multidrug-resistance, rivers

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Emergence of antibiotic resistance—a formidable challenge

As progressive development of primitive versions of microscopes revolutionized our understanding of the bacterial pathogens, so did the discovery of antibiotics revolutionize the fight against infectious diseases caused by microscopic pathogens. Paul Ehrlich, Alexander Fleming, Howard Florey, and Ernst Chain are historically credited with the initial development and introduction of antibiotics to the clinical practice (1-3). They shared the Nobel Prize in Physiology or Medicine in 1945 “for the discovery of penicillin and its curative effects in various infectious diseases” (4).

Before the 1930s, the main bedside strategy was to diagnose infectious diseases according to their clinical manifestations and subsequently administer the relevant traditional medications to treat the diseases mainly symptomatically (5, 6). However, during the antibiotics’ golden ages (the 1950s–1960s (7)), the clinical aim shifted to eliminating the pathogens. This paradigm shift was facilitated by better understanding of medical and microbiological nature of infectious diseases supported by advanced diagnostic and molecular-detection techniques, the discovery and clinical applications of antibiotics, and by application of personalized medicine (8). Gradually, the uncontrolled and widespread administration of the antibiotics with the aim of eliminating the causative agents of infectious diseases—mainly misuse or overuse of antibiotics in agricultural, medical, and veterinary settings worldwide (9)—increased the antibiotic pressure by removing the susceptible microorganisms (10-12). This led to emergence of the antibiotic-resistant and

multidrug-resistant (MDR) infections (7, 13, 14) as a result of inefficiency of antibiotics in the battle against bacterial infections (15-18).

The MDR strains cause disease outbreaks through persistent infections acquired from hospitals and communities (19-22). For example, statistics purport that around 4% of patients die each year as a result of infections with MDR bacteria in Germany (23). Moreover, prolonged hospitalizations reportedly increase the probability of contracting the MDR microorganisms (24, 25). Only a small number of northern European countries presently have maintained their relatively acceptable level of antibiotic efficacy against infectious agents (26). Recent resurgence of vaccine-preventable infectious diseases also threatens the public health globally (27-29). Many bacteria have become highly resistant to second-line or third-line antibiotics, thus excluding them as therapeutic options (30-33).

Although antibiotic resistance was first recognized in the 1940s (6), subsequent worldwide efforts to prevent, or stop the progression of antibiotic resistance have failed (34-36). Decades after the discovery of antibiotics and their consequential miraculous therapeutic outcomes against infectious diseases, particularly over the World War II period, extraordinary rates of resistance to prescribed antibiotics were documented (37, 38). For example, studies from India report that certain superbugs carrying antibiotic resistance are alarmingly deadlier than cancer (39). Accordingly, many microbiologists, clinicians, epidemiologists, and public-health decision-makers acknowledge that antibiotic resistance is now a global threat that needs to be seriously considered by experts and politicians alike (6, 40, 41). Disappointingly, the prospective clinical use of antibiotics is complicated because the pharmaceutical companies have continually subdued their intellectual efforts and investment in designing or developing novel or effective antibiotics (42-44). Redressing the resistance threat to global health, however, is an imperative mission of the World Health Organization (WHO) (45). WHO reports that antibiotic resistance ranks fifth among the ten high-priority threats to the human health globally (42, 46, 47), thus, ranked after "air pollution and climate change," "non communicable diseases," "global influenza pandemic," and "fragile and vulnerable settings."

In 2019, the US's Centers for Disease Control and Prevention reported that fungi and antibiotic-resistant bacteria are responsible for more than 35,000 deaths per year in the United States (48). Reportedly, more than 223,900 cases needed to be hospitalized due to infection with *Clostridioides difficile*, leading to 12,800 deaths (48). More than 10 million people have been estimated to die per year by 2050 because of infection with antibiotic-resistant bacteria, a record grimmer than worldwide cancer statistics (49). This represents not merely a healthcare crisis but a fundamental threat to modern medicine, as antibiotics underpin much of contemporary medical practice—from surgery and transplantation to intensive care and neonatal medicine. The economic burden of such a scenario has been estimated at US$100 trillion globally by 2050.

In this review, we summarize the characteristics of the multidrug-resistant bacteria; briefly explore the origins of, and the mechanisms underlying, resistance; discuss the reasons behind failing therapies; and highlight the importance of the rivers and dams in environmental propagation of antibiotic resistance.

Antibiotic-resistant and multidrug-resistant bacteria

An antibiotic-resistant bacterium is characterized by i) the expression of genes conferring resistance and ii) resisting the killing by the antibiotics—while the same antibiotics can effectively kill the susceptible bacteria. Besides carrying the resistance genes, the resistant bacteria propagate the resistance phenotype among different bacterial populations globally, indicating that resistance cannot be restricted to bacterial populations in hospitals or certain communities (50, 51).

Genetics of transmission of antibiotic resistance among pathogenic bacteria

Through millions of years of evolution, bacteria have evolved mechanisms to enable them to resist the compounds with antibiotic properties. The genetic mechanisms underlying acquisition of the resistant phenotypes differs among the various bacteria; however, some general mechanisms have been recognized and

extensively discussed elsewhere (11, 52, 53). We briefly mention these mechanisms below.

Bacterial mutations

A large proportion of the bacterial genomes consist of plasticity regions that enables propagation of a new subset of mutations that can be transferred to the new generation of bacteria and enable them to resist harsh environmental conditions, including acidic microniches, exposure to heavy metals, or exposure to antibiotics. The new population will be equipped with the machinery to propagate the resistance and thrive under harsh conditions.

Acquisition of foreign DNA by horizontal gene transfer

Horizontal gene transfer comprises the acquisition of foreign DNA, including resistance genes, from the same or different bacterial species. Horizontal gene transfer is reportedly the most predominant factor underlying distribution of resistance genes among the clinically important bacteria. Horizontal gene transfer includes transduction (mediated by phages), transformation (incorporation of external naked DNA), and conjugation (plasmid-mediated or transposon-mediated gene transfer). Conjugation is important whereby cell–cell contact between two bacteria is necessary, for example, among members of the *Enterobacteriaceae* family.

Efflux pumps

Development of bacterial machineries that generally expel toxic compounds can also achieve antibiotic resistance. Many different bacterial families are known to exploit such a machinery—that is, the efflux pumps. Efflux pumps are classified into five main groups based on their requirement for cellular energy, structural conformation, range of substrates, and the classes of bacteria that exploit them. The five families of efflux pumps include the multidrug-and-toxin-extrusion family, the resistance-nodulation–cell-division family, the small multidrug-resistance family, the ATP-binding-cassette family, and the major-facilitator superfamily (52, 54-57). The resistance-nodulation–cell-division family is specifically expressed in the Gram-negative bacteria, whereas the other four families are present in both Gram-positive and Gram-negative bacteria. Efflux pumps intrinsically have relatively high capacity to extrude toxins from the cell and show some degree of substrate specificity (reviewed in (58)).

Antibiotic modification

Antibiotic modification is one of the most beneficial mechanisms that achieves antibiotic resistance and is known to be used by many clinically relevant pathogenic bacteria. Radical additions or modifications of some sites on an antibiotic may affect its function drastically; for example, causing reduction of affinity to antibiotics targets (59, 60). The archetypal example of this mechanism, which was reported some four decades ago, concerns the aminoglycoside-modifying enzymes of the *Streptomyces* species (61, 62) that inactivate the aminoglycoside antibiotics (reviewed in (63, 64)). Another example is the β-lactamase of *Staphylococcus aureus* encoded by the *blaZ* gene (65) which inactivates the antibiotics by hydrolysis (reviewed in (66)).

Modifications of drug targets

Most of clinically important bacteria use this strategy to avoid the lethal effects of the antibiotics. They achieve this mainly by decreasing an antibiotic's affinity to its target site. One of the classical examples of this strategy is illustrated by *S. aureus*. The *mecA* gene—which is part of an extensive genomic cassette called Staphylococcal chromosomal cassette (SCC*mec*)— encodes an alternative penicillin-binding protein—PBP2a—which has low affinity for semisynthetic penicillin. Thus, the transpeptidase domain of PBP2a is not sensitive to the prescribed β-lactams, making the bacterial strain resistant (reviewed in (67)).

Propagation of antibiotic-resistant bacteria

Antibiotic resistance is mainly driven by continual natural selection among bacterial populations. Because antibiotic resistance is a clonal property, certain groups of bacteria tend to obtain the resistance elements by gene-transfer mechanisms. Epidemiological studies show that clonal strains carrying the same resistance elements cause the corresponding disease outbreaks under some clinical settings (68-73), challenging the global public health. Thus, the sources of resistant bacteria and their propagation routes are equally important. Presently, screening of antibiotic-resistant bacterial strains happens at hospitals, which are also checkpoints for

controlling the spread of infections. Although hospital screening can capture the symptomatic patients, it potentially fails to detect the asymptomatic population infected with the resistant strains. To control cross-border dissemination of the resistant bacterial strains, screening tests should be performed at entry points across national borders before permission of entry or residency is granted. A recent meta-analysis following the 2015 unrest in the Middle East suggests that the prevalence of carriage of antibiotic-resistant bacteria was more than 25% in the migrants into Europe; the carriage was higher in the asylum seekers than the other migrant groups (74). Presently, screening does not happen in target countries; thus, a new wave of infections with antibiotic-resistant bacteria could emerge as expected due to mass migrations. The alarming statistics and lack of proper screening call for new policies for timely screening and early detection of resistant bacterial strains. The transmission of antibiotic-resistant bacteria across borders, particularly through migration and travel, represents a critical gap in current surveillance systems. Without implementing screening protocols at entry points, we risk introducing resistant strains into new geographical regions where they may establish endemicity. This underscores the need for coordinated international policies to monitor and control the global dissemination of resistance.

Reasons underlying the failing antibiotic therapies Uncontrolled prescriptions

Today, more than 13 different classes of antibiotics constitute the arsenal against the bacterial infections (75). Meanwhile, thousands of tons of these antibiotics are used yearly in the human and veterinary clinics and in farming, compromising the susceptibility to antibiotics of the human bacterial infections. One of the critical causes of antibiotic resistance is unacceptable prescription of antibiotics which causes rapid emergence of antibiotic-resistant microorganisms in both hospitals and communities. This problem is ripe among the developing countries where policies on infection control are not upheld or implemented, and no screening is done to check for dosage and susceptibility profiling before antibiotic administration. Indeed, uncontrolled prescription of antibiotics is a cultural problem whereby some patients insist on taking them under almost every, or irrelevant, clinical situation. Some patients take a prescribed list of antibiotics instead of one or two; this problem mostly occurs in developing countries with weak socioeconomical levels and weak healthcare policies or practices. This problem is crucial particularly for controlling the Gram-negative bacteria because they can be resistant to almost all available antibiotics. Spread of MDR isolates is another complex problem because excluding a single antibiotic and prescribing an alternative one does not work as the bacteria are resistant or become resistant upon exposure to different antibiotics; eradication of MDR isolates thus becomes unlikely or difficult. This dilemma compromises the management of infectious diseases.

Agricultural and pastoral applications of antibiotics

Application of antibiotics as supplements to increase the growth rate of livestock underlies promotion of resistance phenotypes among certain bacteria (6, 12, 76, 77). This practice in pastoral settings has been fiercely debated and is presently prohibited in only the European countries. Transferability of the antibiotic-resistant bacteria from the livestock to humans has been confirmed in the last two decades. Antibiotics fed to animals in farms finally reach the human gut following consumption of animal products (78). Antibiotics used in farming can also easily spread through the environment and cause resistance in many bacteria, including *Enterococci*, *Salmonella*, and *Escherichia coli*, that cause gastrointestinal infections. Environmental release of antibiotics used in animal farming (through livestock urine or stool) can increase the risk of transfer of resistance to environmental organisms through acquisition of genetic elements responsible for resistance. The antibiotic-resistant bacteria in the environment can then easily reach humans. Therefore, malpractice in animal farming constitutes a potential threat for increasing the risk of emergence and spread of MDR bacteria in the environment and to human hosts. Discharged antibiotics from farm animals are mainly blamed for increasing the antibiotic-resistance pressure in nature.

Lack of hope for new antibiotics

Presently, research and development for novel

antibiotics is not the highest priority of pharmaceutical companies worldwide (79, 80). Most recent global economic crises have been the rationale for downgrading efforts to develop new antibiotics in developing and developed countries. Thus, the unpredictable timeline for developing new antibiotics reduces the likelihood of having better therapeutic options for treating infectious diseases in the future. Reportedly, some academic efforts in developing new antibiotic therapeutics may not be clinically relevant or useful (81). Indeed, in most cases, the potential outcomes *in vivo* may not be equivalent to findings *in vitro*. Presently, different combinations of available antibiotics are prescribed against infectious diseases. Despite the grim picture painted on the development of new antibiotics, hope is still alive as novel methods, such as deep learning and neural networks, are being developed and used, at least in some academic realms, to develop new and potentially effective antibiotics (82).

Roles of rivers and dams in propagating resistance to antibiotics

In 2006, a significant link was reported between increased levels of resistance genes isolated from bacteria in rivers and agricultural activity around those rivers (83). Thus, assessing and documenting elevated concentrations of antibiotics in rivers has become a high priority. Table 1 lists some of the global studies on some antibiotics of which concentrations were measured in the last decade.

Some antibiotics have reportedly exceeded the ‘‘safe’’ levels by 300-fold (84). Trimethoprim was the most prevalent antibiotic found in 307 of the 711 tested sites. Seemingly, the roles of rivers in facilitating the transfer of the genetic elements necessary for antibiotic resistance have been underestimated (Figure 1). Related to rivers, the roles of dams in maintaining and transferring the resistant bacteria or resistance elements are still unknown. Although some studies have investigated antibiotic concentrations in dam reservoirs and impounded water bodies (e.g., Hu et al., 2018; Jiang et al., 2014), systematic global data on the distribution of antibiotics and resistance genes specifically in dam ecosystems remain sparse. The roles of dams in maintaining and transferring resistant bacteria or resistance elements are still insufficiently characterized. Thus, rivers and dams may add another dimension to the resistance problem and to the management of antibiotic resistance.

Rivers and dams have implications for the present design of water-recycling systems; the redesign must be able to reduce the chance of propagating and transferring the responsible resistance elements among the bacteria. The roles of rivers in increasing the probability of antibiotic resistance is still underappreciated (Figure 2) but gradually recognized; thus, urgent action is necessary (85, 86).

Table 1: Concentrations of various antibiotics measured in some rivers worldwide

Country	Year	[Antibiotics] ng/L												Reference
		TMP	SD	TC	CIP	OTC	ERM	ROX	ERM	SMX	OFL	SMZ	NOR	
China	2014	242	24	4278	205	97433	98	622	n.d.	n.d.	1582	n.d.	n.d.	(92)
China	2011	100	140	26	110	41	n.d.	27	n.d.	n.d.	170	n.d.	n.d.	(93)
Italy (Milan)	2010	n.d.	n.d.	n.d.	32	n.d.	n.d.	n.d.	0.39	n.d.	7.7	n.d.	n.d.	(94)
Italy (Como)	2010	n.d.	n.d.	n.d.	108	n.d.	25	n.d.	n.d.	n.d.	20	n.d.	n.d.	(94)
China	2012	n.d.	n.d.	n.d.	101	n.d.	n.d.	n.d.	62	62	9.9	12	118	(95)
United Kingdom	2006	4	n.d.	n.d.	n.d.	n.d.	4	n.d.	n.d.	<20	n.d.	n.d.	n.d.	(96)
Japan	2007	5	<150	n.d.	n.d.	n.d.	448	n.d.	n.d.	23	n.d.	n.d.	n.d.	(97)
Germany	2004	<30	n.d.	n.d.	n.d.	n.d.	30	n.d.	n.d.	30	n.d.	<30	n.d.	(98)
China	2012	3.7	3.4	n.d.	n.d.	n.d.	50	n.d.	n.d.	10	n.d.	3.3	n.d.	(99)
France	2008	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	544	55	n.d.	n.d.	(100)
Australia	2009	n.d.	n.d.	100	n.d.	350	n.d.	n.d.	n.d.	2000	n.d.	n.d.	n.d.	(101)

Abbreviation:
TMP: trimethoprim, SD: sulfadiazine, TC: tetracycline, CIP: ciprofloxacin, OTC: oxyetracycline, ROX: roxithromycin, OFL: ofloxacin, ERM: erythromycin, SMX: sulfamethoxazole, SMZ: sulfamethazine, NOR: norfloxacin; n.d: not detected

Figure 1: Shahid Rajaei dam in south of Sari, Mazandaran province, Iran. Photo credit: ATBA. Rivers and dams have implications for the present design of water-recycling systems; the redesign must be able to reduce the chance of propagating and transferring the responsible resistance elements among the bacteria.

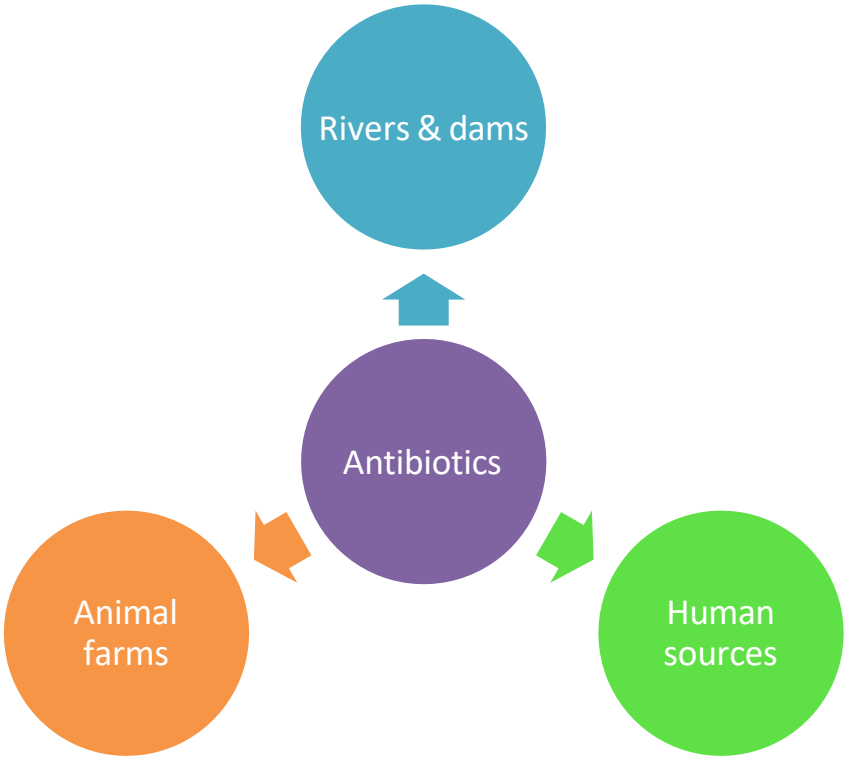

Figure 2: Interacting links between environmental and industrial sources that contribute to the crisis of resistance to antibiotics. The figure illustrates the complex network of anthropogenic activities—including animal farming, wastewater discharge, and agricultural runoff—that introduce antibiotics into water bodies. These environmental reservoirs serve as hotspots for horizontal gene transfer, ultimately facilitating the dissemination of resistance genes back to clinical and community settings

Discharge of antibiotics into the river streams or any other natural environment inevitably has public-health consequences which may not be reversible. Accordingly, animal farms close to the rivers inevitably contribute to increasing the content of antibiotics discharged into the rivers (86-88). Policy advisors should encourage the governments to revise their current policies on managing rivers, dams, and water-recycling plants. Any new policy on administration and use of antibiotics in human or animal clinics—or in pastoral settings—must consider the high chance

of transmission of resistant microorganisms between environmental sources and humans or animals.

What measures should be implemented to tackle the resistance problem?

In the presence of antibiotic-resistant bacteria, a new approach and a stepwise program is necessary to tackle this global threat. Unfortunately, almost all global counterprograms have failed (41, 89, 90). This universal problem worsens because the initiatives for researching and developing novel antibiotics have been dwindling. Moreover, the disappointing number of R&D projects for new antibiotics, even in the developed countries, and heightened uncontrolled antibiotic resistance must be prioritized higher than other topics discussed in medical sciences. The prevalence of antibiotic-resistant bacteria and also emergence of MDR isolates can be even more concerning if we accept that the present situation will be followed by worse—and the worst—scenarios as time passes (91). A decade after the golden ages of antibiotics, clinicians have only a few effective antibiotics available. In the past, antibiotics were thought to be degraded in the environment with time, but studies on levels of antibiotics in rivers paint a different picture. The moisture content of the soil and soil temperature are the two critical factors that determine the duration of time required for degradation of antibiotics. Therefore, antibiotics must be treated as hazardous chemicals before they could be found in the natural resources, like rivers and dams, because they can persist in the environment. Through a boarder perspective, antibiotic resistance is a critical issue for decision-makers and others involved in managing or delivering public-health services. Hence, engagement of government politicians and global media to initiate and promote new environment-protection programs is necessary in the immediate future. General population must be educated about the importance of the present preventive programs for ensuring that the available antibiotics remain effective. Understanding the exact mechanisms resulting in transformation of resistance genotypes from environmental bacteria to the clinical isolates is clearly another enormous challenge. Furthermore, genotyping studies to characterize the relationships between these strains can be promising in the fight against the spread of antibiotic resistance, particularly concerning the natural water resources. Determining how farming-originated antibiotic-resistant bacteria are released in the rivers and dams around the world and preventing this immense release are important in the fight against dissemination of resistance. Although our understanding of horizontal gene transfer among the bacteria in natural ecosystems is limited, generating such an understanding will help us manage and control the emergence and propagation of resistance. Undoubtedly, urgent efforts are needed to control, decrease, and prevent the release of high concentrations of antibiotics in the river streams around the world. Otherwise, the complexity of antibiotic resistance will be insurmountable.

Final remarks

Current global estimations suggest a skyrocketing growth of antibiotic-resistant bacterial populations capable of establishing life-threatening infectious diseases. The policies related to the administration and the uncontrolled release of antibiotics or other chemical products containing antibiotics must be urgently revised. National and international entities must initiate coordinated measures to prevent the release of high concentrations of antibiotics and monitor their concentrations in rivers and dams around the globe. The challenge demands a multi-pronged strategy: (i) implementation of strict regulatory frameworks limiting antibiotic discharge from agricultural, industrial, and municipal sources; (ii) investment in advanced water treatment technologies capable of removing antibiotic residues and resistance genes; (iii) establishment of a global surveillance network for monitoring antibiotic concentrations and resistance gene prevalence in freshwater ecosystems; and (iv) enhanced international collaboration, particularly between developed and developing nations, to share resources, data, and best practices. Without immediate and sustained global action, the complexity of antibiotic resistance will become insurmountable, and we will face a future where even minor infections carry fatal consequences

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Conflict of interest

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Glossary of Terms

Antibiotic resistance, Conjugation, Efflux pumps, Horizontal gene transfer, Multidrug-resistant (MDR), Plasmid, Transduction, Transformation, Transposons, and β-Lactamases.

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