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REVIEW ARTICLE

Impact of wastewater treatment plant effluent discharge on the antibiotic resistome in downstream aquatic environments: a mini review

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HIGHLIGHTS

- Impact of WWTP effluent discharge on ARGs in downstream waterbodies is hotspot.
- Various mechanisms influence the diffusion of ARGs in effluent-receiving waterbodies.
- Controlling AMR risk of WWTPs needs further investigation and management strategies.

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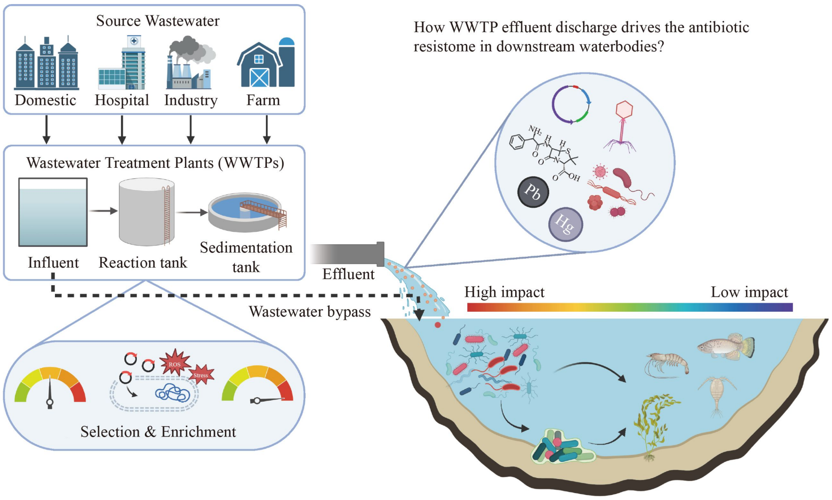
GRAPHIC ABSTRACT



ABSTRACT

Antimicrobial resistance (AMR) has emerged as a significant challenge in human health. Wastewater treatment plants (WWTPs), acting as a link between human activities and the environment, create ideal conditions for the selection and spread of antibiotic resistance genes (ARGs) and antibiotic-resistant bacteria (ARB). Unfortunately, current treatment processes are ineffective in removing ARGs, resulting in the release of large quantities of ARB and ARGs into the aquatic environment through WWTP effluents. This, in turn, leads to their dispersion and potential transmission to human through water and the food chain. To safeguard human and environmental health, it is crucial to comprehend the mechanisms by which WWTP effluent discharge influences the distribution and diffusion of ARGs in downstream waterbodies. In this study, we examine the latest researches on the antibiotic resistome in various waterbodies that have been exposed to WWTP effluent, highlighting the key influencing mechanisms. Furthermore, recommendations for future research and management strategies to control the dissemination of ARGs from WWTPs to the environment are provided, with the aim to achieve the "One Health" objective.

1 Introduction

Antimicrobial resistance (AMR) is a pressing issue in

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modern times, presenting a significant challenge within the realm of human health. If not effectively addressed, it is projected that over 10 million individuals will die by 2050 due to infections caused by antibiotic-resistant bacteria (ARB) (Kwon and Powderly, 2021; Hou et al., 2023). Recently, antibiotic resistance genes (ARGs) have been frequently detected in various environments, such as surface water, groundwater, sediment, soil, and air (Zhuang et al., 2021; Larsson and Flach, 2022). This poses a potential threat to both ecological balance and human well-being. Numerous studies have confirmed that human activities, including livestock breeding, disease treatment, and industrial production, significantly contribute to the widespread occurrence and dissemination of ARGs in the environment (Holmes et al., 2016; Vikesland et al., 2019). Wastewater treatment plants (WWTPs), as a connection between human activities and the natural environment, collect sewage and wastewater from various aspects of human society. With high microbial density, abundant nutrients, and sub-inhibitory concentrations of antimicrobial substances, WWTPs create favorable conditions for the selection and spread of ARGs (Karkman et al., 2018; Manaia et al., 2018; Berglund et al., 2023).

However, current treatment processes do not specifically target the complete removal of ARGs or ARB in wastewater environments, lacking treatment and discharge standards. In fact, these processes may even contribute to their increased abundance and diversity. Studies have indicated that WWTP effluent releases significant amounts of ARB and ARGs into the environment. For instance, it has been reported that WWTPs release approximately 10^{12}– 10^{15} CFU of ARB or 10^{12}–10^{18} copies of ARGs daily (Ben et al., 2017). The effluent discharge of WWTP into rivers, lakes, oceans, and other aquatic environments therefore leads to the dispersion of ARGs. This poses a concern, as ARB and ARGs present in the environment can potentially be transmitted to humans through drinking water, the food chain, or direct contact, thereby enabling certain human pathogens to acquire antibiotic resistance traits and endanger public health (Forsberg et al., 2012; Hernando-Amado et al., 2019). Consequently, within the framework of “One Health”, the relationship between long-term WWTP effluent discharge and the development of AMR in the waterbodies receiving such effluents has emerged as a highly active area of research. However, existing studies merely provided evidences for the increase of ARGs in the aquatic environment associated with WWTP impacts (Bueno et al., 2017; Rodríguez-Molina et al., 2019). The influencing mechanisms underlying WWTP effluent discharge have not been discussed systematically. This paper examines recent literature, summarizes eight potential influencing mechanisms, highlights the limitations of existing research, and presents recommendations for future research priorities and management strategies.

2 Potential influencing mechanisms of WWTP effluent discharge on antibiotic resistome

Most of the existing studies have shown that the discharge of WWTP effluent has a significant impact on the distribution and diffusion of ARGs in the effluent-receiving waterbodies. This impact is primarily observed as a significant enrichment of ARGs or ARB within a certain distance from the discharge point. A summary of the potential mechanisms influencing this phenomenon is presented in Fig. 1, based on a review of the literature.

2.1 Influent composition and capacity of WWTP affect the discharge of ARGs

WWTPs receive wastewater from various sources, and the composition of the influent from different sources affects the final discharge of ARGs. Certain wastewater treatment systems in hospitals, livestock farms, as well as industrial wastewater treatment systems in pharmaceuticals, dyeing, and pesticides, have a higher concentration of ARGs compared to domestic wastewater treatment systems (Jia et al., 2017; Jiao et al., 2017; Lorenzo et al., 2018; Bengtsson-Palme et al., 2019; Buelow et al., 2020; Su et al., 2020; Semedo and Song, 2023). Particularly hospital wastewater acts as the link between clinical settings and environment, which contains more high-risk ARGs conferring resistance to major clinic antibiotics like last-resort antibiotics (Buelow et al., 2020; Zhu et al., 2023). Due to the feature of livestock industry, large amounts of veterinary antibiotics and metals are frequently used for animal growth promotion and disease control, consequently making farm wastewater become a significant AMR hotspot constituting risk to public health (Jia et al., 2017; Zhao et al., 2021). Industrial wastewater contains organic pollutants like benzene series, polycyclic aromatic hydrocarbons, and quaternary ammonium compounds, which can significantly increase the frequency of conjugation transfer of antibiotic resistance plasmids, thereby enhancing the risk associated with effluent discharge (Jiao et al., 2017; Su et al., 2023). Therefore, the physicochemical properties or antibiotic resistome profiles in these types of wastewater are certainly different, and their relative contributions to downstream AMR development should be further explored to support the formation of targeted regulatory measures.

The size of a WWTP may also have a close relationship with the discharge of ARGs. On the one hand, WWTP size represents the density of their served urban populations to some extent (Su et al., 2017; Zhou et al., 2022). Some researchers found a strong positive correlation between WWTP capacity and the relative abundance of ARGs discharged into the aquatic environment, which suggested downstream antibiotic resistome was clearly linked to the intensity of upstream anthropogenic activities (Pruden et al., 2012; Elder et al., 2021). On the other hand, other studies discovered that small-scale WWTPs showed the higher contributions for the dissemination of ARGs in the aquatic environment (Pärnänen et al., 2019; Harnisz et al., 2020; Osińska et al., 2020). These results might be attributed to high variations in quantity of wastewater inflows and less removal efficiency of ARGs in small WWTPs (Harnisz et al., 2020).

2.2 Particulate matter from WWTP serves as a significant carrier of ARGs

WWTPs release a large amount of suspended particulate matter into the water environment every year, which is a crucial pathway for direct emission of particle-attached ARB and ARGs (Proia et al., 2018). Even the relative abundances of some ARGs in particle-attached fraction were significantly higher in the effluent compared to the influent (Lorenzo et al., 2018). Despite erosion and degradation are likely to reduce the amounts of wastewater-born particles in aquatic environment, a considerable proportion of particle-attached ARGs can be transported to sediments via sedimentation (Brown et al., 2020). For instance, Brown et al. (2019) found a strong correlation between the abundance of particle-attached ARGs in effluent and the abundance of ARGs in downstream river sediments. Microcosm experiments also demonstrated that while the introduction of particulate matter in wastewater could rapidly increase the abundance of ARGs in water and sediments by several orders of magnitude (Brown et al., 2020). In general, ARGs associated with small particles might exhibit greater persistence and had the potential for long-distance transport in aquatic environments compared to ARGs associated with large particles (Brown et al., 2020; Ginn et al., 2023). This was due to the lower deposition rate and more "sticky" surface area observed in smaller particles. Meanwhile, researchers also found that elevated ARGs in river sediments induced by sedimentation of wastewater particles could underwent a particular or complete decay (Brown et al., 2020). Therefore, it implies that the application of membrane filtration or coagulation techniques is meaningful to effectively control the release of ARGs from WWTP effluent by removing the particulate load (Cui et al., 2020; Ni et al., 2020). However, microplastic particles (MPs) as emerging pollutants are also largely released into the aquatic environment through wastewater discharge (Sathicq et al., 2021). Compared to other general particulate matters, MPs show different characteristics including peculiar density, surface charge, bioavailability, and toxicity (Galafassi et al., 2021). Therefore, MPs can significantly stimulate biofilm formation (plastisphere) to enhance the proliferation and dissemination of ARGs and ARB, further leading to the persistent impact of wastewater plastisphere on aquatic environment (Arias-Andres et al., 2018; Eckert et al., 2018). The environmental behavior of MPs and their contributions on AMR development should be highlighted in the future.

2.3 Persistent ARGs and ARB are selected and enriched during wastewater treatment

In the WWTP environment, many bio-physic-chemical factors and conditions can influence the survival and transmission of ARGs and ARB, such as biotic factors (e.g., bacterial densities, biomass, mobility elements), abiotic factors (e.g., temperature, pH, electric conductivity), stress caused by pollutants (e.g., antibiotics, biocides, heavy metals), and process parameters (e.g., hydraulic retention time, sludge retention time) (Karkman et al., 2018; Manaia et al., 2018; Ju et al., 2019; Manaia, 2023). Particularly in the biological processing compartments, various stressors, high biomass and nutrient load, and the close proximity of cells in the flocs can promote the proliferation and dissemination of ARGs (Manaia et al., 2018). Even some of the advanced treatment technologies, such as photocatalysis and advanced oxidation processes, may induce the SOS response in bacteria, further stimulating bacterial mutation and horizontal gene transfer (HGT) of ARGs (Karkman et al., 2018). In this sense, although WWTP can partially reduce the occurrence of total ARGs and ARB, many persistent ARGs with high mobility and ARB with multiple resistance are selected and enriched after treatment. Hence, when finally released, these genes or bacteria in the effluent may persistently spread in the receiving waterbodies. For instance, An et al. (2018) found that the relative abundance of 71 ARGs in WWTPs effluent was enriched by an average of 1361 times. Zhang et al. (2009) performed antibiotic susceptibility tests on 366 *Acinetobacter* strains isolated from WWTPs, and these strains in the effluent showed a significant increase in resistance to multiple antibiotics. Other studies demonstrated that wastewater treatment processes might enhance genetic mobilization of persistent ARGs that were then released from effluent to aquatic environment (Petrovich et al., 2018; Berglund et al., 2023). Additionally, several studies had regarded the presence of specific ARGs (e.g., *aadA*, *sul1*, class A beta-lactamase genes, bla_{SHV}, bla_{NDM}, *tetQ*, *tetW*, and *qacEdelta1*) (LaPara et al., 2011; Devarajan et al., 2016; Pärnänen et al., 2019; Lee et al., 2021; Lee et al., 2023) and MGEs (e.g., *intI1*) (Bueno et al., 2017; Wu et al., 2023), as well as conditional antibiotic-resistant pathogens (e.g., vancomycin-resistant *Enterococcus faecium*, *Klebsiella pneumoniae*, *Acinetobacter* sp., and *Pseudomonas* sp.) (Czekalski et al., 2014; Luczkiewicz et al., 2015; Lorenzo et al., 2018; Kvesić et al., 2022) in the effluent-receiving waterbodies as indicators of wastewater-related pollution.

2.4 Residual antimicrobial substances and MGEs in effluent continue to play key driving roles

Conventional WWTPs usually have limited efficiency in removal of most so-called antimicrobial substances such as antibiotics, biocides, and heavy metals. Therefore, residual antimicrobial substances in the WWTP effluent should be considered as a key stress factor to downstream waterbodies (Corno et al., 2019; Tamminen et al., 2022). Studies have shown that discharge of WWTP effluents, particularly the direct discharge of pharmaceutical wastewater, can result in a 2–10-fold increase in antibiotic concentration in effluent-receiving waterbodies (Rodriguez-Mozaz et al., 2015; Barancheshme and Munir, 2018; González-Plaza et al., 2019; Milaković et al., 2020). On the one hand, such environmental concentrations of antibiotics could lead to a continuous selection pressure for bacterial resistance, instead of bacterial growth arrest or cell death (Balcázar et al., 2015). On the other hand, wastewater-born heavy metals and biocides contamination could exert a widespread co-selection effect for antibiotic resistance through genetic coupling mechanisms including co-resistance, cross-resistance, and co-regulation (Pal et al., 2015; Li et al., 2017). There were some evidences that the enrichment of ARGs near WWTP effluent discharge points was associated with antibiotics, quaternary ammonium compound (QAC) detergents or heavy metals (Devarajan et al., 2015; Amos et al., 2018; Beltrán de Heredia et al., 2023).

Additionally, various mobile genetic elements (MGEs) like plasmids, bacteriophages, integrons, and insertion sequences were frequently detected in the effluent, which played an important role in the acquisition and spread of ARGs (Karkman et al., 2018; Che et al., 2019). For example, plasmids are prone to conjugation, transposition and recombination, which can cross the interspecies barrier to promote the HGT frequency of ARGs (Che et al., 2021). Bacteriophages not only act as a key environmental reservoir of ARGs but also can transfer ARGs among bacteria via transduction (Debroas and Siguret, 2019). Many studies have suggested that MGEs significantly contribute to the mobilization of ARGs in the aquatic environments receiving treated wastewater discharge (Kristiansson et al., 2011; Lekunberri et al., 2017; Amos et al., 2018; Lekunberri et al., 2018; Osińska et al., 2020; Raza et al., 2021; Berglund et al., 2023).

2.5 Microbial community structure of effluent-receiving waterbodies is altered

The phylogenetic relationship of microbial communities is a key driving force for the proliferation and spread of ARGs (Forsberg et al., 2014; Hu et al., 2016; Qin et al., 2022; Wang et al., 2023). Several studies have demonstrated that the discharge of WWTP effluent can result in substantial changes to the diversity and composition of microbial communities in effluent-receiving waterbodies (Marti et al., 2013; Tang et al., 2016; Milaković et al., 2020; Pascual-Benito et al., 2020; Wang et al., 2022; Dai et al., 2023). These alterations of microbial community largely account for the antibiotic resistome changes. Firstly, high microbial diversity can build a biological barrier to prevent the invasion and spread of ARGs (Chen et al., 2019). However, WWTP effluent discharge may cause the diversity loss in downstream waterbodies (Wang et al., 2022; Dai et al., 2023), thus leading to the higher abundance of ARGs. Secondly, WWTP effluent discharge can induce the shift of downstream microbial community composition and increase the relative abundance of various potential bacterial pathogens, which belong to advantaged hosts of ARGs such as Gammaproteobacteria, Firmicutes, and Chloroflexi (Marti et al., 2013; Tang et al., 2016; Guan et al., 2022). Thirdly, WWTP effluent discharge may cause a great shift in species-species interactions, and create favorable conditions for the HGT of ARGs and invasion of ARB in downstream microbial communities (Bagra et al., 2023; Dai et al., 2023; Su et al., 2023).

2.6 Wastewater bypass is a major temporary source of ARG pollution

Untreated wastewater has higher concentrations of ARGs and other pollutants (Fresia et al., 2019). Due to technical/operational failure and storm overflows, uncontrolled direct discharge of untreated wastewater from WWTP may increase the abundance of ARGs in rivers by tens of times (Devarajan et al., 2016; Marathe et al., 2017; Manaia, 2023). Lee et al. (2022) found that during heavy rainfall events, combined sewer network overflow effluent (untreated rain-sewage mix) that exceeds the maximum design discharge of the WWTP is a major contributor to ARGs and multiple resistance risk factors in rivers where the effluent is discharged. Therefore, we must admit that wastewater treatment facilities still play the first line of defense to protect the ecological environment. If proper management measures and advanced treatment technology are taken, the impact of WWTP effluent discharge on ARGs in receiving waterbodies will be significantly reduced (Bondarczuk and Piotrowska-Seget, 2019; Chen et al., 2020).

2.7 Effects of WWTP effluent discharge are limited by the spatial factors

By analyzing the distribution of sampling points in previous studies on effluent-receiving waterbodies, it was determined that the impact of WWTP effluent discharge appears to be localized within a range of 0–5 km. Additionally, the abundance of ARGs exhibited a trend of decreasing with distance (sp;C, Ploy M C, Michael I, Fatta-Kassinos D (2013). Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. Science of the Total Environment, 447: 345–360 to 5 km.

Additionally, the abundance of ARGs exhibited a trend of decreasing with distance (Czekalski et al., 2014; Chu et al., 2018; Thornton et al., 2020). LaPara et al. (2015) demonstrated that multiple discharges of treated municipal wastewater had little effect on ARG concentration in the surface water of the Mississippi River. This suggested that the occurrence and diffusion of ARGs from effluent in effluent-receiving waterbodies might be affected by natural processes like dilution, adsorption, photolysis and hydrology (Pruden et al., 2012; LaPara et al., 2015). In addition, the impacts of WWTP effluent discharge on antibiotic resistome might be much greater in downstream water habitats rather than sediments (Lee et al., 2023; Wu et al., 2023). One reason may be that sediments form the complex and stable microbial communities over long periods of time, thus limiting the invasion of wastewater-born bacteria. Another reason is that high water flow velocity may hamper the exchange processes of ARGs or ARB from water to sediment in a short time.

2.8 Environmental biofilms amplify the effects of WWTP effluent discharge

In aquatic habitats, microbial biofilms perform key ecosystem functions such as biogeochemical cycling, primary production, as well as maintenance of good water quality (Balcázar et al., 2015; Tamminen et al., 2022). However, by being exposed to various environmental and chemical stress, aquatic biofilms can be strongly influenced by human activities such as continuous wastewater discharge from WWTP (Carles et al., 2021). Under such conditions, these biofilms effectively accumulate substances that are present in waterbodies, including nutrients, heavy metals and antibiotics, which can support the propagation of ARGs (Balcázar et al., 2015). Meanwhile, high microbial densities as well as high ecological connectivity in biofilms also increase the frequency of HGT among different microorganisms converting biofilms into hotspots of antibiotic resistance (Abe et al., 2020). Some studies had indicated that ARGs could be found in the biofilms on stones of the riverbed or riverbank, and wastewater discharge caused a significant increase of ARG diversity and abundance in downstream biofilms (Marti et al., 2013; Proia et al., 2016; Aubertheau et al., 2017). In Yangtze Estuary, most ARGs in biofilms showed higher detection frequency and abundances than those in sediment and water samples (Guo et al., 2018). Unfortunately, aquatic biofilms developing on benthic substrata or microaggregates can also participate in food web interactions, thereby leading to the biological amplification of ARGs at the trophic level (Aubertheau et al., 2017; Lee et al., 2023). Therefore, environmental biofilms are considered as good indicator for ecological health risk of aquatic habitats under anthropogenic pollution, and valuable to be enhanced monitored in the future.

Overall, WWTPs with varying influent compositions and capacities worldwide can not only select and enrich persistent ARGs and ARB, which are released directly into the receiving waterbodies by attaching to particulate matters, but also influence the microbial community structure of the receiving waterbodies by releasing residual antimicrobial substances and MGEs, thereby indirectly driving the diffusion of ARGs. Meanwhile, unexpected discharges or storm overflows of WWTP, spatial factors and environmental biofilms of receiving waterbodies may also have considerable impacts on antibiotic resistome. However, some studies found that the discharge of WWTP effluent might not be the major driver on the distribution and spread of ARGs in receiving waterbodies (Moura et al., 2014; LaPara et al., 2015; Bondarczuk and Piotrowska-Seget, 2019; Chen et al., 2020; Yu et al., 2020; Wang et al., 2021). The impacts of other pollution problems or natural processes should also be given enough attention. For instance, Moura et al. (2014) emphasized that integrons and the associated ARGs in beach environments were primarily formed by the introduction of pollution from wild animal feces rather than from effluent discharge. High pollution and eutrophication levels in waterbodies may create favorable conditions for the overgrowth of anthropogenic bacteria (Chu et al., 2018). Natural processes like flood and drought events also play a vital role in determining the severity and scope of impacts caused by WWTP (Manaia, 2023). Therefore, these knowledges inspire that more systematic understanding and effective control measures on the spread of antibiotic resistome in effluent-receiving waterbodies are needed in the future.

3 Concluding remarks and future perspectives

3.1 Insufficient points for existing researches

In summary, the relationship between the WWTP effluent discharge and the emergence and development of AMR in the aquatic environment is still unclear and requires further investigation.

1) Current studies primarily focus on freshwater ecosystems, such as rivers and lakes, but pay little attention to the coastal environment, which experiences complex hydrological conditions and receives a large volume of effluents. Furthermore, compared to aqueous environment, there is an inadequate amount of research on the sediment environment, which has a more abundant microbial composition and accumulates pollutants over the long-term.

2) There is a lack of studies to explore the differences in the impacts of different types of WWTPs on the distribution of ARGs in effluent-receiving waterbodies.

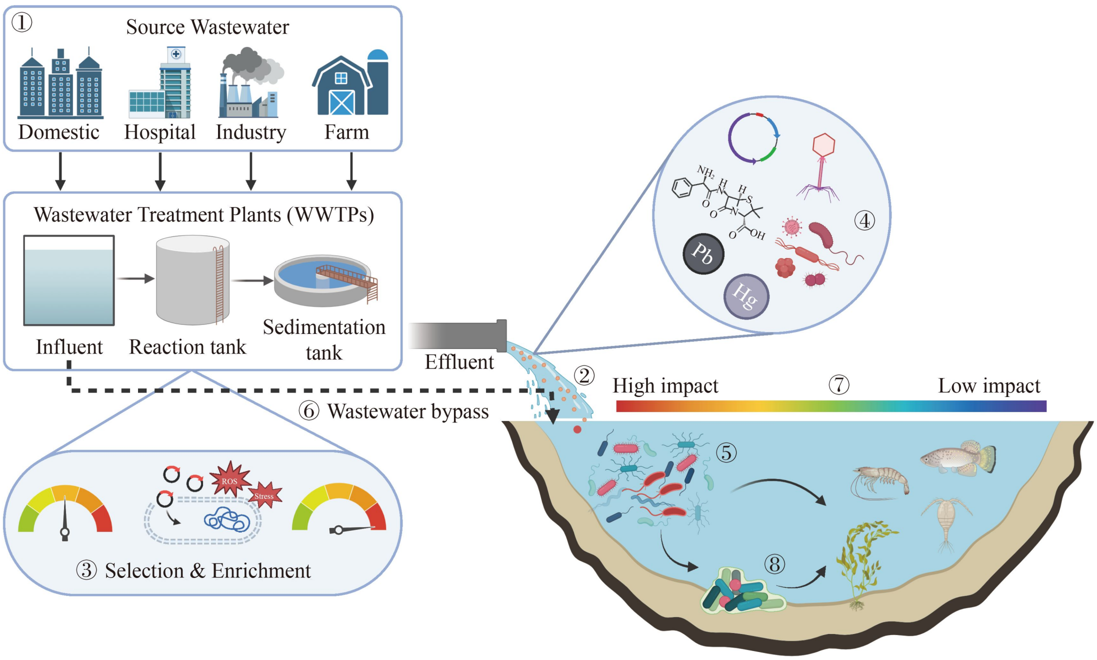

Fig. 1 Influencing mechanisms of WWTP effluent discharge on the distribution and diffusion of ARGs in effluent-receiving waterbodies. ① Influent composition and capacity of WWTP affect the discharge of ARGs; ② Particulate matter from WWTP serves as a significant carrier of ARGs; ③ Persistent ARGs and ARB are selected and enriched during wastewater treatment; ④ Residual antimicrobial substances and MGEs in effluent continue to play key driving roles; ⑤ Microbial community structure of effluent-receiving waterbodies is altered; ⑥ Wastewater bypass is a major temporary source of ARG pollution; ⑦ Effects of WWTP effluent discharge are limited by the spatial factors; ⑧ Environmental biofilms amplify the effects of WWTP effluent discharge. Created with BioRender.

Compared with domestic wastewater, potential risk of hospital, farm and industrial wastewater should be highlighted and further studied. These studies could provide insight into the relative contributions of different human activities upstream.

3) Most studies still rely on traditional methods such as PCR, qPCR, and bacterial cultivation to conduct environmental investigations and analyze common ARGs or ARB. There is a need for more in-depth studies based on metagenomics and direct evidence from laboratory experiments.

4) The majority of studies use the increase in ARG diversity and abundance as the sole indicator to characterize the impact of WWTP effluent discharge. However, the biological significance of this increasing trend and the change in environmental risk are not well understood. How to accurately identifying ARGs from WWTP sources and quantitatively assessing the severity of impacts caused by WWTP remain significant challenges.

3.2 Promote comprehensive and in-depth scientific and technological research

Firstly, it is important to thoroughly investigate the fate of ARGs in different types of WWTPs and various waterbodies where the treated effluent is released. Additionally, a research model should be developed between WWTPs and effluent-receiving waterbodies to understand the “source-sink” relationship of ARGs in the continuous flow system, also help clarify the environmental health risks associated with the transmission of ARGs along the food chain.

Secondly, it is necessary to establish a microcosm experiment system to comprehensively examine the effects of different factors (both biotic and abiotic) on the spread of ARGs in effluent-receiving waterbodies. This research should be conducted at the molecular and cellular levels to identify the key influencing factors and the HGT mechanism of ARGs.

Thirdly, significant emphasis should be placed on developing multi-omics techniques (e.g., metagenomic, metatranscriptomic, and metaviromic) to provide strong support for the comprehensive screening of environmental antibiotic resistome and facilitate accurate analysis of the molecular genetic characteristics of ARGs.

3.3 Explore reasonable and effective management strategies

On the one hand, an efficient risk monitoring and traceability platform should be established by utilizing advanced technologies such as high-throughput sequencing and cloud computing for big data to integrate various analyses. These include screening the environmental antibiotic resistome, conducting risk assessments, analyzing pollution sources, and identifying indicator genes. This integrated platform will enable real-time monitoring of antibiotic resistome characteristics in WWTP outfalls and effluent-receiving waterbodies. It will also track the transmission process of ARGs and ARB in the food chain. Ultimately, the platform will provide rapid risk early warning and targeted policy recommendations for land-based pollution management.

On the other hand, upgrading the treatment processes in WWTPs is a common approach to further reduce pollutant discharge and improve water quality. Previous studies had demonstrated that the addition of advanced treatment processes in WWTPs along rivers could significantly reduce antibiotic concentrations and the abundance of high-risk ARB in the receiving rivers (Su et al., 2021; Mao et al., 2023). This suggests the potential for controlling the discharge of antibiotic resistance determinants (such as antimicrobial substances, ARGs, MGEs, ARB, etc.) at the source (Jia et al., 2023). Future research should continue to investigate the reduction effects of different process modifications or upgrading strategies on antibiotic resistance determinants, and explore the target-oriented technological optimization strategies based on water ecological health.

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