

Antimicrobial Resistance Information for Water Professionals

Key take-home messages

- Antimicrobial resistance (AMR) makes diseases more difficult to treat; it has been spreading and is considered a major public health concern.
- Antibiotic-resistant bacteria (ARB) and antibiotic-resistant genes (ARGs) are widely detected, including in natural environments and food, but their associated human health risks remain poorly understood and inadequately characterized.
- The risk of getting infected by ARB is not greater than the risk of getting infected by the same antibiotic-susceptible bacterium. Humans are exposed to millions of microbes with antibiotic-resistant traits every day via natural and necessary activities, such as the ingestion of water and food ([Pepper et al., 2018](#)). Most of these exposures do not cause infections.
- Antibiotic-resistant bacteria and ARGs are detected at water resource recovery facilities (WRRFs), but treatment processes, including coagulation, clarification, filtration, disinfection, and anaerobic digestion, generally reduce their levels.
- The Global Water Pathogen Project ([2019](#)) estimates that conventional WRRFs reduce the types of ARGs observed and their numbers in raw wastewater by approximately 33% to 98%, but some ARGs and mobile genetic elements (such as [integrons](#)) are not reduced.
- Current practices for wastewater and municipal drinking water treatment are adequate to prevent enteric bacterial infections from ARB via drinking water.
- Workers at WRRFs could be exposed to ARB and ARGs through contact with wastewater, solids, and bioaerosols. The associated risks are uncertain, but can be mitigated by following the worker safety recommendations of the Centers for Disease Control and Prevention ([n.d.-a](#)) and WEF ([2020](#)).
- Wastewater-based surveillance is an emerging approach to complement public health data but is not intended to inform risk assessment from wastewater exposure.
- Water resource recovery facilities are important critical control points and are one of the most effective means of removing or reducing the occurrence of ARB and ARGs in wastewater and the environment.

Why we prepared this document

Over the last two decades, numerous projects investigated the occurrence of antimicrobial resistance (AMR), especially antibiotic resistance, in wastewater. In 2023, several papers (e.g., [Berglund et al., 2023](#); [Wang & Smith, 2023](#); [Zhao et al., 2023](#)) reported the detection of antibiotic-resistant genes (ARGs) and mobile genetic elements (MGEs) in wastewater, resulting in negative news stories and media inquiries at water resource recovery facilities (WRRFs) about AMR and potential risks from wastewater or biosolids ([Wigglesworth, 2023](#)). In addition, the Centers for Disease Control and Prevention (CDC) has expressed interest in including wastewater-based surveillance (WBS) of AMR targets in its National Wastewater Surveillance System, which will lead to continued focus on AMR. This document is intended to help inform the water sector as attention to this complex topic grows. It provides a summary of concepts related to antimicrobial and antibiotic resistance and the current state of the science related to antibiotic resistance at WRRFs.

Background on antimicrobial compounds, antimicrobial resistance, antibiotic-resistant genes, and antibiotic-resistant bacteria

- Antimicrobial compounds may be natural or synthetic. Antimicrobials are naturally produced by certain soil bacteria, such as Actinomycetes, fungi, and other microbes (Pepper et al., 2009). Synthetic [antimicrobials](#) are derived from natural antimicrobials and are commonly used to treat or prevent infections affecting people, animals, and crops.
- Antimicrobial compounds can have antibiotic, antiviral, antifungal, or antiparasitic properties.
- Antibiotics are antimicrobials that are specifically administered in living organisms with the aim of killing bacteria (bactericidal) or preventing their multiplication (bacteriostatic) (Nankervis et al., 2016).
- Disinfectants are antimicrobials that kill microorganisms on inanimate objects (also called *fomites*) or in other non-living matrices (e.g., water, wastewater, biosolids).
- To survive and be competitive against other microbes, many bacteria have become resistant to these compounds over time. Resistance is encoded in their genetic material or ARGs.
- Some ARG variants are of greater concern because they encode resistance to important antibiotics used in people. For example, some Enterobacteriaceae have the *bla* gene (or its variants such as *bla*_{TEM/SHV} or *bla*_{CTX-M}), which encodes for extended-spectrum β -lactamase (ESBL) enzymes that provide resistance against penicillin and other commonly used antibiotics. Organisms can also be resistant to multiple antimicrobials at once, which is called *multi-drug resistance* (MDR).
- Bacteria containing ARGs are called *antibiotic-resistant bacteria* (ARB). Antibiotic-resistant bacteria can occur naturally in the environment and are also common in animals and humans, such as on the skin and in the gut. For example, both harmless (commensal) and disease-causing (pathogenic) bacteria containing ESBL genes are commonly found in the gastrointestinal tract of animals and humans and, therefore, are present in wastewater (Lamberte & Schaik, 2022).
- Antibiotic-resistant bacteria by themselves do not pose a human health risk. There are thousands of known variants of ARGs and some have even been found in pristine environments (such as water, soil, arctic permafrost, sediment, and air) (D'Costa et al., 2011; Diaz et al., 2017; Rahman et al., 2008). Antibiotic-resistant genes only pose a direct risk to humans when present in or transferred to pathogens.
- While AMR is a natural process, human activities (e.g., antibiotic use and farming) accelerate AMR development.

Acronyms

AMR: antimicrobial resistance

ARB: antibiotic-resistant bacteria

ARGs: antibiotic-resistant genes

ESBL: extended-spectrum β -lactamase enzymes that provide resistance to penicillin and other β -lactam antibiotics

HGT: horizontal gene transfer

MDR: multi-drug resistance

MGE: mobile genetic element

MRSA: methicillin-resistant

Staphylococcus aureus

WASH: water, sanitation, and hygiene

WBS: wastewater-based surveillance

WRRF: water resource recovery facility

VRE: vancomycin-resistant enterococci

Why people worry about antimicrobial resistance

- Anti-microbial resistance is frequently discussed in both medical and public health contexts.
- The World Health Organization (WHO) ([2021](#)) describes AMR as a change that occurs in microorganisms—bacteria, viruses, fungi, or parasites—over time when they stop responding to the medicines used to treat or prevent their infections.
- The spread of AMR is a serious public health concern because antibiotic-resistant pathogens defy treatment, leading to infections that cause more complications, last longer, and increase the risk of death.
 - The World Health Organization ([2021](#)) has declared that AMR is one of the top 10 global public health threats facing humanity.
 - According to CDC’s [2019](#) report, Antibiotic Resistance Threats in the United States, [AMR causes](#) more than 2.8 million antimicrobial-resistant infections in the United States annually, resulting in more than 35,000 deaths. For comparison, the [National Center for Health Statistics](#) reported more than 87,000, 51,000, and 49,000 deaths related to diabetes, kidney disease, and influenza and associated pneumonia, respectively, in the United States in 2019.
 - Global estimates attribute 1.27 million deaths in 2019 to exposure and infection with ARB (Murray et al., [2022](#)).
 - Most public health organizations consider AMR to be a “One Health” issue that affects the interconnected health of people, animals, and the environment because it can potentially spread through communities, the food supply, healthcare facilities, and the environment (including soil and water), making it harder to treat certain infections in animals and people (CDC, [n.d.-b](#)).

How bacteria acquire antibiotic-resistant genes and become resistant

- Bacteria may acquire ARGs through genetic mutations or through horizontal gene transfer (HGT) of foreign DNA (genetic material) from another microbe. This foreign, transferred DNA is contained in an MGE (Vale et al., [2022](#)). Once acquired, the resistance genes are then passed on by vertical gene transfer as the bacteria reproduce.
- *Mobile genetic element* is a generic term used for segments or units of foreign DNA than can move or be physically transferred from one bacterium to another using one of several different mechanisms depicted in [Figure 1](#), and when the bacterium reproduces. Mobile genetic elements include plasmids, transposons, and integrons (Pray, [2008](#)).
- Mobile genetic elements can be found in the cell’s chromosome or in a plasmid (DNA outside the chromosome), as free DNA in the cell, or in a bacteria virus (a phage).

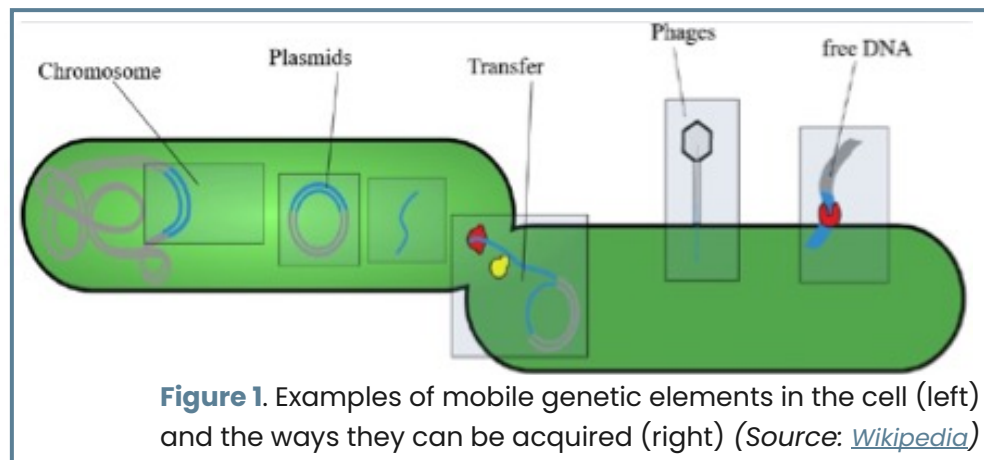


Figure 1. Examples of mobile genetic elements in the cell (left) and the ways they can be acquired (right) (Source: [Wikipedia](#))

What factors increase antimicrobial resistance

- Antimicrobial resistance can occur from a combination of genetic changes and selective pressures:
 - Extended exposure to antimicrobials can prompt organisms to develop AMR.
 - Exposure to an antibiotic can also eliminate susceptible organisms that have not acquired ARGs while allowing resistant organisms to persist, dominate the microbial community, and potentially transfer their genes to other organisms.
 - Environments with high densities of bacteria, particularly ARB, and high concentrations of antimicrobials may be at higher risk of HGT. Consequently, facilities such as hospitals are considered to have a relatively higher probability for HGT occurrence (Evans et al., [2020](#)).
 - Some studies have referred to WRRFs as potential “hotspots” for ARB and ARGs, although evidence is mixed as to whether wastewater treatment selects for or against ARGs ([Quach-Cu et al., 2018](#); [Rizzo et al., 2013](#)).
- According to WHO ([2021](#)), the main drivers of AMR include the misuse and overuse of antimicrobials; lack of access to clean water, sanitation, and hygiene (WASH) for both humans and animals; poor infection and disease prevention and control in health care facilities and farms; poor access to quality, affordable medicines, vaccines, and diagnostics; lack of awareness and knowledge; self-medication; and lack of enforcement of legislation.
- Removing AMR drivers can help to limit AMR. The CDC ([2019](#)) attributed a decrease in AMR-related deaths in the United States between 2013 and 2019 to improved antibiotic management and infection prevention and control practices in humans, animals, and the environment.

Common antibiotics

β-lactam antibiotics: Include penicillin, cephalosporins, monobactams, and carbapenems

Carbapenems: Often used to treat MDR bacteria

Colistin: The only last-resort antibiotic treatment for life-threatening infections caused by carbapenem-resistant Enterobacteriaceae

Linezolid: The last-resort antimicrobials for the treatment of infections caused by MRSA or vancomycin-resistant enterococci

How are antibiotic-resistant bacteria and antibiotic-resistant genes detected and quantified?

- There is currently no standardized method to quantify AMR in environmental samples. There is also no consensus on which ARGs are the most helpful or important to monitor (Water Research Foundation [WRF], [2023](#)).
- Historically, ARB have been detected by culturing them in a growth medium containing the antibiotic. Bacteria that can multiply in the medium are considered resistant. Bacteria whose growth is inhibited are considered susceptible. Some are categorized as moderately susceptible. Such culture-based methods are still considered the gold standard and are widely used in medical and environmental microbiology. However, culture is tedious and only allows for the assessment of one microbial target (e.g., *Escherichia coli*) at a time.
- Molecular methods, such as quantitative polymerase chain reaction and metagenomic DNA sequencing, can be used to detect and quantify ARGs. Using these data for risk assessment can be challenging because:
 - Interpretation of molecular data from a complex mixture of bacteria (like those in feces or wastewater) can be difficult to interpret because this method analyzes gene fragments, which may

be associated with multiple organisms in the mixture.

- Molecular tests also lack the ability to directly distinguish living and inactivated organisms.
- Molecular methods are often most useful when a reduction in ARB or ARG concentrations is being explored across a process and the same methods and targets are used.
- An increasing number of WBS studies, such as Wang and Smith ([2023](#)), are detecting ARGs in wastewater using molecular methods. The intention of WBS is to track such disease markers in the human population contributing to the raw wastewater. Given the challenges associated with molecular data interpretation, WBS results should not be over-extrapolated to assess risk from exposure to wastewater.

Effects of wastewater treatment processes on antibiotic-resistant bacteria and antibiotic-resistant gene levels

- Water resource recovery facilities are critical control points and are one of the most effective means of removing or reducing the occurrence of ARB and ARGs in wastewater.
- Antibiotic-resistant bacteria and ARGs have frequently been recovered from raw influent, treated effluent, biosolids, reclaimed water, and receiving surface waters ([Beltrán de Heredia et al., 2023](#)).
- The most commonly detected ARGs in influent, effluent, and activated sludge of WRRFs in different countries are β -lactam, macrolide, quinolone, tetracycline, sulphonamide, trimethoprim-resistance genes, and the genes that code for bacterial cell membrane pumps that expel multiple antibiotics at once (known as *multidrug efflux genes*) ([Pazda et al., 2019](#)).
- The Global Water Pathogen Project ([2018](#)) estimates that conventional WRRFs reduce the numbers and kinds of ARGs found in raw wastewater by approximately 33% to 98%. However, some ARGs and MGEs are sometimes not reduced by WRRFs (e.g., [integrons](#)).
- Antibiotic-resistant bacteria and ARG removal and amplification in wastewater are complicated and dependent on process configuration, operational conditions, sewershed contributors (e.g., hospitals or landfill leachate), the target ARG and ARB being tested, testing methodology, and influent properties.
- When optimized, coagulation and sedimentation can be effective at removing ARB and ARGs (approximately 1 to 4 log removals) ([Ni et al., 2020](#)).
- Concentrations of many ARGs and ARB may increase in secondary treatment (e.g., conventional activated sludge, bioreactors, aeration basins) under aerobic conditions because microbial growth is encouraged and residual pollutant concentrations (e.g., heavy metals, antibiotics) exert selective pressures during long retention times ([Kang et al., 2022](#)). However, studies suggest that systems designed for biological phosphorus removal that sequence anaerobic and aerobic treatment in secondary reactors remove ARB and ARGs more effectively compared to aerobic reactors (reviewed by [Li et al. \[2022\]](#)).
- Concentrations of many ARGs and ARB are reduced through filtration processes, such as membrane bioreactors (approximately 2 to 7 log removals) ([Munir et al., 2011](#); [Wang et al., 2020a](#)).
- Concentrations of many ARGs and ARB are reduced through disinfection by UV, chlorine, ozone, and other oxidants.
 - Free chlorine doses of approximately 30 mg/L achieve approximately 1.3 to 1.5 ARG log removals in treated secondary effluent ([Zhang et al., 2015](#)). Note that this is removal of the genes, not the microbial inactivation typically associated with disinfection.

- The highest levels of removals are the result of combining multiple disinfection options. For example, while low doses of chlorine stimulated HGT, pairing UV (8 mJ/cm²) and chlorine (2 mg/L) increased UV inactivation by 1.4 log compared to UV alone (Wang et al., [2020b](#)).
- In laboratory experiments in phosphate-buffered saline and filtered wastewater, damage of ARGs required greater UV doses (200 to 400 mJ/cm² for 3- to 4-log reduction) than ARB inactivation (10 to 20 mJ/cm² for 4- to 5-log reduction) (McKinney & Pruden, [2012](#)).
- Gram-positive ARB, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci, are more resistant to UV disinfection than Gram-negative ARB (such as *E. coli* and *P. aeruginosa*) (McKinney & Pruden, [2012](#)).
- Reclaimed water is typically subject to varying levels of tertiary treatment (e.g., filtration, disinfection, polishing), which are expected to further reduce the prevalence of ARB and ARGs in the final product.
- Solids management practices can be effective at reducing ARB and ARGs in sludge and biosolids.
 - Sludge and biosolids contain up to 1,000 times the concentrations of ARGs and antimicrobials present in wastewater effluent (Munir et al., [2011](#)).
 - Levels of ARGs and ARB in mesophilic and thermophilic anaerobic digestion are frequently reduced as a result of heat exposure, but performance is highly dependent on feedstock characteristics and temperatures used in the digestion process (e.g., thermophilic versus mesophilic) (Goulas et al., [2020](#); Wang et al., [2021](#)).
 - Biodrying (10 to 15 days) can achieve 0.4- to 3.1-log reductions in ARGs and performs better than traditional composting (30 to 50 days) (Global Water Pathogen Project, [2019](#)).
 - Although ARB and ARGs are present in biosolids, research suggests that the majority of antibiotic resistance in soil after land application is due to natural phenomena and not anthropogenic activities (Pepper et al., [2018](#)).
- Current practices for wastewater treatment and drinking water treatment are adequate to prevent enteric bacterial infections from ARB via drinking water.
- Current conventional wastewater process water quality parameters do not adequately support monitoring ARB and ARG persistence at WRRFs (Turolla et al., [2018](#)).

What is known about antibiotic-resistant bacteria and antibiotic-resistant gene transmission routes that could result in illness

- Proven transmission to date:
 - Person-to-person or community-acquired ([Knox et al., 2015](#)).
 - Animal-to-animal transmission, especially in concentrated animal feeding operations ([Gilchrist et al., 2007](#)).
 - Health care settings and associated potable water systems (e.g., hospital sinks and premise plumbing), in addition to contaminated in-dwelling catheters and other medical equipment and instruments ([Hidron et al, 2008; Mulvey & Simor, 2009](#)).¹

¹ Ongoing research (WRF, n.d.) included a comprehensive review of scientific articles linking presence of resistant organisms in the environment with resulting AMR infections. The vast majority of epidemiological evidence (69%) was connected to water contamination in health care settings (e.g., health care sink fixtures, premise plumbing). Studies showing a link to potable water (9%) evaluated decentralized drinking water systems or inadequately treated water.

- Fomites (or contaminated inanimate objects) are also an important source of ARB exposure and transmission in hospitals and communities (Stephens et al., [2019](#)).
- Zoonotic transmission from animal to human (e.g., farm workers and veterinary workers) (Armand-Lefevre et al., [2005](#); Meijs et al., [2021](#); Price et al., [2012](#)).
- Less frequently documented transmission to date:
 - Foodborne transmission, such as meat, poultry, cattle products, ground beef, and milk (Ryan et al., [1987](#)), especially when cross-contamination occurs during food handling and preparation ([Brown et al., 2017](#); [Folster et al., 2017](#); [Xiang et al., 2020](#)).
 - Recreational waters (e.g., pools, spas, and surface waters) (Nappier et al., [2020](#)).
 - Inadequately treated drinking water in decentralized and low-resource settings.
- Unproven and undocumented but plausible transmission routes to date (e.g., ARB and ARGs are frequently detected, but no epidemiological evidence is available):
 - Asymptomatic transmission (Kariuki et al., [2006](#)).
 - Reclaimed irrigation water (i.e., water reuse) (Garner et al., [2021](#)):
 - Several studies explore the risk of increased gastrointestinal illness in workers exposed to reclaimed water compared to control populations, but none look at risk associated with ARB transmission specifically (Dickin et al., [2016](#)).
 - Schoen et al. ([2021](#)) conducted a quantitative microbial risk assessment and concluded that minimally treated wastewater and graywater (< 4.5 log removals for MRSA) can result in a public health risk that exceeds the 10⁻⁶ disability-adjusted life years per person per year health benchmark. This has not been confirmed by epidemiological data (Durand & Schwebach, [1989](#); Rosenberg Goldstein et al., [2014](#)).
 - Adequately treated municipal drinking water—the only ARB outbreaks associated with drinking water are related to untreated or improperly treated drinking water.
 - Wastewater and biosolids.
 - Stormwater ([Hamilton et al., 2020](#)).

Antimicrobial resistance exposure and risks

- The widespread presence of ARB and ARGs is documented, but the associated human health risks remain poorly understood and inadequately characterized. Exposure to ARB or other resistant pathogens of human health concern does not always result in infection and disease transmission.
 - Humans are exposed to millions of microbes with antibiotic-resistant traits every day via natural and necessary activities such as the ingestion of water and food ([Pepper et al., 2018](#)). Most of these exposures do not cause infections.
 - Other factors must be considered in assessing human health risk, such as an individual's health status and susceptibility, the magnitude and frequency or duration of exposure, route of exposure and pathogen susceptibility to stressors.
- The European Agency for Safety and Health at Work ([2013](#)) suggests that the highest levels of occupational exposure are likely to occur in health care and in the agriculture, livestock, and food

Other studies identified linkages to recreational surface or pool/spa water (3% to 4% each), reclaimed irrigation water (2%) and wastewater/WASH-related accidental exposure (4%).

industries (Aarestrup, [2015](#)). However, workers in laboratories, at WRRFs, and in areas with badly designed HVAC systems and high humidity are also assumed to be at risk.

- Risks to workers at WRRFs are being evaluated (Wengenroth et al., [2021](#)) because workers may be exposed to wastewater, solids, and bioaerosols carrying ARB and ARGs through different transmission routes: inhalation, dermal contact, and ingestion.
 - The same practices recommended by the CDC ([n.d.-a](#)) that protect workers from any pathogen will be effective at mitigating risks from ARB and ARG.
 - The level of risk, while uncertain, can be mitigated by following the WEF's ([2020](#)) worker safety recommendations.
 - The CDC ([n.d.-c](#)) also provides recommendations for the general public on actions to protect individual health and prevent the spread of AMR ([e.g., wash your hands, get vaccinated, practice healthy habits around animals, use antimicrobials properly](#)).

Other wastewater considerations

- Water resource recovery facility operators should be aware that accepting untreated wastewater from hospitals, landfill leachate, stormwater ponds, concentrated animal feeding operations, and agricultural operations is likely to contribute high levels of ARB and ARGs relative to received domestic wastewater. If AMR surveillance studies are being planned, consider adding these matrices to the samples being analyzed to inform decisions around accepting wastewater from these customers.
- Wastewater-based surveillance practitioners and researchers are reminded that sample providers, such as WRRFs and utilities, should be informed of any WBS analytical target expansion. Sample providers and WRRF operators also appreciate being alerted and consulted before manuscript submissions and media interviews.
- Researchers conducting AMR studies at WRRFs should be aware that most utilities do not sterilize bottles in their 24-hour composite samplers and collect their bacteria compliance samples separately using grab samples. To obtain an accurate picture of AMR in wastewater, the use of composite samples is advised, but this may result in ARG contamination carryover and confounding of results when composite samples are split with the WRRF (Lou et al., [2023](#)).

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