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The Impact of Metal Pipe Materials, Corrosion Products, and Corrosion Inhibitors on Antibiotic Resistance in Drinking Water Distribution Systems

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Abstract

Drinking water distribution systems (DWDS) are unique engineering environments that are important routes for the acquisition and dissemination of antibiotic resistance. Antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) in drinking water pose risks to human and environmental health. Metals are known stressors that can select for antibiotic resistance. The objective of this review was to assess the state of knowledge regarding the impact of metal pipe materials, corrosion products, and corrosion inhibitors on the prevalence of antibiotic resistance in DWDS. ARGs and mobile genetic elements (MGEs) have been detected in full-scale DWDS in concentrations ranging from ~ 10^1 to 10^{10} copies/L. Metal pipe materials can select for bacteria harboring ARGs and metal resistance genes (MRGs) through co-selection processes. Corrosion products that develop in metal drinking water pipes (Cu, Fe, and Pb oxides) may also stimulate antibiotic resistance selection during distribution. Different corrosion inhibitor regimes (phosphates, sodium silicates) may also have impacts on microbial communities and the abundance of resistance genes in DWDS. Research is needed to quantify how engineering decisions related to drinking water infrastructure and corrosion inhibitor practices impact the abundance and distribution of ARG, MRGs, and MGEs in potable water systems.

Key points

- Lack of quantitative measurements of antibiotic and metal resistance genes in drinking water distribution systems.
- Pipe materials and corrosion products that develop in pipe scales may impact antibiotic resistance.
- Corrosion inhibitors with zinc or phosphate could alter antibiotic resistance.
- Management decisions should consider antibiotic resistance ramifications.

Keywords

Antimicrobial resistance, ARG, Microbiome, Public health, Biofilm

Introduction

Antibiotic resistance is considered a major global threat in the 21st century, and a return to a pre-antibiotic era is predicted without serious or immediate attention (WHO [167]). Antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) occur naturally but are selected for and enriched by exposure to antibiotics (Song et al. [152]), antimicrobials (Carey and McNamara [22]; Carey et al. [23]; Hartmann et al. [60]; Harrison et al. [59]), disinfectants (Chapman [25]; Zhang et al. [183]), and metals (Seiler and Berendonk [148]; Zhang et al. [182]) in natural and engineered environments. ARB and ARGs have been detected in a variety of environments including soils (Knapp et al. [73]), lakes (Di Cesare et al. [33]), groundwater (Mackie et al. [100]; Koike et al. [75]), aquaculture (Seiler and Berendonk [148]), rivers (Pruden et al. [133]; Pruden et al. [132]; Kappell et al. [68]), treated wastewater effluent (Auerbach et al. [8]; LaPara et al. [78]; Mao et al. [102]; Di Cesare et al. [32]; Guo et al. [51]; Kappell et al. [70]; Cacace et al. [20]), biosolids (Ma et al. [99]; Munir and Xagoraraki [108]; Kimbell et al. [71]), drinking water treatment plants (Xi et al. [170]; Lin et al. [87]; Oh et al. [113]), drinking water distribution systems (DWDS) (Xi et al. [170]; Xu et al. [174]; Garner et al. [45]), and tap drinking water (Xi et al. [170]; Bergeron et al. [14]). Natural and engineered environments are composed of complex dynamics driven by microbial ecological processes that ultimately determine the level of prevailing antibiotic resistance (Pruden et al. [131]). ARB and ARGs can be transferred between environments via exposure routes through air, water, soil, wastewater and industrial effluent discharges, bacteria carrying ARGs on meat or produce, and application of biosolid-derived soil amendments (Vikesland et al. [161]; Pruden et al. [131]). Environmental hotspots that could directly convey ARB and ARGs to people, such as DWDS, are of primary interest because management decisions could potentially reduce public health risks.

Over 100 different ARGs were detected in drinking water from two drinking water treatment plants in China with total ARG concentrations ranging from 10^5 to 10^{10} copies/L (Xu et al. [174]). Multiple studies correlated the presence of ARGs with mobile genetic elements (MGEs), suggesting that horizontal gene transfer could occur inside the DWDS (Ciric et al. [27]; Xu et al. [174]). In general, ARGs can be transferred vertically through microbial growth or acquired by horizontal gene transfer, which occurs through the uptake of free DNA (transformation), plasmid-mediated transfer (conjugation), and phage-mediated transfer (transduction) (Van Hoek et al. [160]). Horizontal gene transfer is a major mechanism for sharing ARGs between microorganisms and has been documented between pathogens, non-pathogens, and distantly related microbes, such as gram-positive and gram-negative bacteria (Levy et al. [85]; Courvalin [28]; Pruden et al. [133]). Horizontal gene transfer of ARGs is of particular concern for human health if pathogens acquire resistance (Wingender and Flemming [168]; Wang et al. [164]). Additionally, metal resistance is a common phenotype in many microorganisms, and metal resistance genes (MRGs) are present in genomes isolated from numerous different environments including humans, animals, hydrothermal vents, and ocean microplastics (Pal et al. [115]; Yang et al. [176]). Metal resistance often occurs with antibiotic resistance (Baker-Austin et al. [9]). Stagnant conditions caused by intermittent water demand, which are common in urban areas, may also promote the growth of pathogens and other microorganisms potentially harboring ARGs and MRGs in DWDS (Lautenschlager et al. [79]; Proctor and Hammes [130]; Zlatanović et al. [188]; Bédard et al. [13]; Ling et al. [88]). Additionally, locations within DWDS that support higher densities of microorganisms (e.g., biofilms, tubercles, and loose deposits) may aid in the persistence of antibiotic resistance in DWDS (Hallam et al. [54]). The overall growth of microorganisms and microbial ecology in DWDS is influenced by several distribution system characteristics and may have implications on the types and abundance of resistance genes in DWDS. Even though metals are known to select for antibiotic resistance, and they are present in DWDS due to corrosion of metal pipes and addition of corrosion inhibitors, research gaps persist around the impact of metals on antibiotic resistance in DWDS.

Previous analysis of microbial ecology in DWDS has been accomplished primarily through next-generation sequencing (NGS) technologies including 16S rRNA gene amplicon sequencing and DNA-based metagenomic analysis (Berry et al. [15]; Pinto et al. [125]; Douterelo et al. [35]; Ma et al. [97]). Many of these studies have investigated the drinking water microbiome during various stages of drinking water treatment and distribution, which can be influenced by many factors including spatial and temporal variations (Pinto et al. [124]; Prest et al. [128]; Potgieter et al. [127]), geography (Proctor and Hammes [130]), treatment processes (Ma et al. [98]; Oh et al. [113]), and distribution system characteristics (Sanganyado and Gwenzi [142]). Laboratory-scale studies have observed relationships between several distribution system parameters and the occurrence of opportunistic pathogens and microbial ecology in simulated DWDS including disinfectants (Shen et al. [150]; Zhang et al. [177]), water age (Wang et al. [165]; Wang et al. [164]), water temperature (Proctor et al. [129]), and pipe materials (Wang et al. [165]; Wang et al. [164]; Proctor et al. [129]). ARG profiles are impacted by the microbial communities in a given environment, and many of these previously studied parameters likely have impacts on antibiotic resistance in drinking water systems but have yet to be investigated. Additionally, few studies have utilized quantitative molecular tools to quantify the abundance of clinically relevant ARGs or MGEs in different phases (planktonic, biofilm, particle-associated, loose deposits) of full-scale DWDS (Garner et al. [45]).

In this review, existing information on the impacts of metal pipe materials, corrosion inhibitors, and corrosion products on the prevalence of antibiotic resistance in DWDS is critically reviewed with the goal of consolidating information to help develop more effective monitoring and mitigation strategies along with recommended future research directions. As older DWDS get upgraded, there is an urgent need for improving our understanding of engineering management decisions such as pipe material selection on the dissemination of antibiotic resistance in DWDS. Here, we provide information regarding the antimicrobial activity of metals and potential mechanisms of antibiotic resistance selection in DWDS with specific emphasis on corrosion products and corrosion inhibitors. This review also summarizes existing information available regarding the abundance of

ARGs, MRGs, and MGEs in DWDS. Additionally, recommendations are provided for future research directions with a focus on improving mitigation strategies for antibiotic resistance in DWDS.

Quantification of Resistance Genes in Full-Scale Drinking Water Systems

Understanding the sources and mechanisms of antibiotic resistance dissemination in drinking water networks is critical for mitigating risks to public health. Previous studies have highlighted that several factors related to drinking water treatment (Sharma et al. [149]; Sanganyado and Gwenzi [142]) and distribution system construction and operation can influence the abundance of bacteria in drinking water and biofilms (Douterelo et al. [35]; Sun et al. [155]; Douterelo et al. [37]). After finished drinking water enters the distribution system, it can spend hours to days inside pipes prior to reaching consumer taps, which can alter the chemical and microbiological quality of the water (Ji et al. [65]). Corrosion inhibitors, pH, dissolved inorganic carbon, disinfectant type/concentration, and other chemicals used during drinking water treatment (e.g., coagulants) may impact the presence and distribution of ARB and ARGs in DWDS (Liu et al. [91]; Zhang et al. [183]). A previous laboratory-scale study documented increased transfer of ARGs following exposure to disinfectants (free chlorine, chloramine, and hydrogen peroxide) and suggested that mechanisms including intracellular reactive oxygen species formation, SOS response, increased cell permeability, and altered expression of conjugation-relevant genes were responsible for horizontal gene transfer (Zhang et al. [183]). Additionally, Kappell et al. [69] observed increased selection for ARB and ARGs including *sul*1, *qac*H, and *intI*1 in drinking water microcosms treated with zinc-containing corrosion inhibitors compared to controls. This study reported that low concentrations of metals such as zinc in drinking water can lead to positive selection of bacteria able to assimilate metals, rather than negatively selecting against bacteria without metal resistance (Kappell et al. [69]). Although these studies have provided some insight into the potential mechanisms of antibiotic resistance selection under controlled laboratory conditions, there is a lack of data available regarding the presence of clinically relevant ARGs, MRGs, and MGEs commonly linked to horizontal gene transfer processes in full-scale DWDS. ARGs including beta-lactam resistance genes, *sul*1, and MGEs such as *intI*1 have previously been identified as potential indicators for the overall abundance of resistance genes in different environments (WHO [167]; Gillings et al. [49]; Ma et al. [96]). MRGs such as *ars*B, *cop*A, *czc*D, and *znt*A confer resistance to metals, and may be co-selected for by bacterial exposure to antibiotics, disinfectants, and other contaminants (Pal et al. [115]). Furthermore, a previous study documented the co-occurrence of MRGs and ARGs on plasmids in clinically relevant genera including *Escherichia*, *Staphylococcus*, *Salmonella*, *Klebsiella*, *Pseudomonas*, and *Mycobacterium* (Pal et al. [116]). However, no studies known to the authors have documented MRGs in samples from full-scale DWDS using quantitative molecular techniques, i.e., techniques that generate copy numbers on a per L, g, or surface area basis. Few studies have employed quantitative techniques to quantify ARGs in full-scale DWDS (summarized in Table 1).

Table 1. ARGs quantified in full-scale drinking water distribution systems (DWDS)

Reference	Garner et al 2018				Hao et al. 2019	Rocha et al. 2019	Su et al. 2018	Xi et al. 2009	Zhang et al. 2020
Sample type	Tap water	Tap water	Biofilms	Biofilms	Tap water	Tap water	Tap water	Tap water	Tap water
Method of quantification	qPCR	qPCR	qPCR	qPCR	qPCR	qPCR	qPCR	qPCR	qPCR
Units	Copies/mL	Copies/mL	Copies/swab	Copies/swab	Copies/L	Copies/mL	Copies/L	Copies/100 mL	Copies/100 mL
Replicates	44	56	40	21	36	3	9	8	71
Source water	SW, GW	SW, GW	SW, GW	SW, GW	NA	NA	NA	NA	SW
Treatment type(s)	5-stage BF, AS, DN	4-stage BF, UV, bio-filter	Dual media filter, MB	Dual media filter	NA	NA	Sed., SF, PAC, GAC, O_3	NA	NA
Pipe material(s)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Disinfectant	NH_2Cl	Cl_2	NH_2Cl	Cl_2	Cl_2	NH_2Cl	NA	NH_2Cl	NA
Observed mean absolute abundance of target genes (Log_{10} scale)									
16S rRNA	4.2	2.3–3.3	4.2	3.5	-	6.0	7.0–7.6	5.4–7.0	5.2–7.4
bla_{TEM}	1.8	1.7	1.5	1.6	3.5–5.5	-	-	2.2–3.4	2.0–5.0
bla_{SHV}	-	-	-	-	-	-	-	0–1.5	-
*erm*B	-	-	-	-	2.5–3.8	-	5.0–5.5	-	ND–5.0
*intI*1	4.7	4.9	4.2	ND	-	-	-	-	2.0–4.5
tet(M)	-	-	-	-	2.0–5.4	-	5.5	-	-
tet(W)	-	-	-	-	-	-	5.6–5.8	-	ND–4.5
tet(X)	-	-	-	-	2.2–3.8	-	ND	-	-
*qnr*A	1.2	ND	ND	2.1	2.0–3.6	-	ND	-	-
*qnr*S	-	-	-	-	-	-	5.0	-	-
*sul*1	2.7	1.2–1.7	3.2	2.1	4.6–6.8	2.1	7.5	0.9–3.2	3.0–6.0
*sul*2	-	-	-	-	3.5–5.8	-	6.0	0.1–4.2	ND–5.7
*van*A	1.4	1.9	1.5	1.3	0–2.5	-	-	-	-

AS, activated sludge; *BF*, Bardenpho; *GAC*, granular activated carbon; *PAC*, powdered activated carbon; *MB*, membrane bioreactor; *O3*, ozone; *Sed.,* sedimentation; *SF*, sand filter; *UV*, ultraviolet disinfection; *NA*, not available; *ND*, no detection; *"-"*, no measurement or value; *qPCR*, quantitative PCR. Mean abundance values for target genes were adapted from source article(s) text or approximated from figures

Studies documenting the occurrence and abundance of ARGs are important for developing effective monitoring strategies for controlling microbial drinking water quality. Total bacterial biomass (e.g., 16S rRNA) can range several orders of magnitude (~ 10^3–10^{10} copies/L) in drinking water (Table 1, Xi et al. [170]; Garner et al. [47]; Garner et al. [46]). ARGs including beta-lactamase resistance genes (*bla*$_{\mathrm{TEM}}$), sulfonamide genes (*sul*1 and *sul*2), tetracycline resistance genes (*tet*(W), *tet*(M), *tet*(X)), and the integrase gene of class 1 integrons (*intI*1) have been quantified in DWDS at concentrations ranging from approximately 10^1 to 10^7 copies/L (Table 1, Xi et al. [170]; Garner et al. [45]; Su et al. [154]; Hao et al. [57]; Rocha et al. [138]; Zhang et al. [178]). The majority of previous studies focused on measuring ARG abundance in the planktonic phase and did not measure gene concentrations in biofilms or corrosion deposits, which have been cited as important reservoirs for opportunistic pathogens and ARGs (Balcázar et al. [10]). Other studies have utilized high-throughput qPCR (HT-qPCR) for detecting ARGs in DWDS, with detections of over 100 different ARGs, transposases, and integrons in drinking water samples (Xu et al. [174]; Huang et al. [63]; Waseem et al. [166]). These studies and others have observed increases in transposase genes, β-lactam resistance genes, and MGEs in DWDS water compared to treated drinking water entering the DWDS.

Many environmental factors exist in DWDS that may influence the abundance of ARGs. It is well documented that disinfection practices (e.g., chlorination or chloramination), antibiotics, antimicrobials, and metals may exacerbate the prevalence of antibiotic resistance in engineered systems such as DWDS. However, the fate of ARGs, MRGs, and mechanisms of horizontal gene transfer in full-scale DWDS are not well understood. Additionally, previous studies have suggested that extracellular DNA may persist in aquatic systems for long periods of time and may represent an important reservoir of ARGs in DWDS (Hao et al. [57]; Sakcham et al. [141]). Due to potential public health implications associated with the presence of opportunistic pathogens, ARGs, and MRGs in drinking water, this area of research warrants further investigation.

Plausible Mechanisms for Antibiotic Resistance Selection by Metals in DWDS

Previous studies on lab-scale and full-scale DWDS have focused on the impact of a variety of factors on microbial ecology in DWDS including pipe materials (Niquette et al. [111]; Lehtola et al. [82]; Proctor et al. [129]; Douterelo et al. [36]), flow regime (Manuel et al. [101]; Lautenschlager et al. [79]), nutrients (Batte et al. [11]), and disinfectant type (chlorine/chloramines) (Wang et al. [165]; Aggarwal et al. [2]; Dai et al. [31]; Waak et al. [163]), but they have seldomly focused specifically on the impact of metals on antibiotic resistance. Drinking water networks are comprised of various metal pipe materials including cast iron, ductile iron (Fe), copper (Cu), brass, and lead (Pb). Metal species such as Cu, Fe, and Pb are primarily introduced to drinking water through corrosion processes and leaching of metal ions from plumbing materials (Kang et al. [67]; Kim and Herrera [38]). Zinc (Zn) is present when added as a corrosion inhibitor attached to phosphate (Payne et al. [119]). Additional heavy metals such as aluminum (Al), arsenic (As), chromium (Cr), and uranium (U) present at concentrations below their maximum contaminant levels (MCLs) or at non-detectable levels in treated drinking water can accumulate in deposits and corrosion scales in DWDS (Lytle et al. [95]; Schock et al. [145]; Peng and Korshin [122]; Peng et al. [121]). The primary concern with the presence of trace metals in DWDS is the potential for their release back into finished drinking water, which may result in elevated dissolved metal levels in domestic tap water (Sun et al. [157]). Heavy metals present in drinking water environments at sub-inhibitory concentrations can promote antibiotic resistance and horizontal transfer of ARGs (Baker-Austin et al. [9]; Zhang et al. [179]; Zhang et al. [182]). In addition, positive correlations have previously been observed between multiple antibiotic resistance and metal exposure (Cu, Pb, Zn) in drinking water point of use samples compared to point of entry to the DWDS, suggesting that bacteria acquired antibiotic resistance inside the DWDS (Calomiris et al. [21]).

Microorganisms have developed a variety of methods for coping with environmental stress, such as exposure to heavy metals. General mechanisms responsible for metal resistance in microbial cells include (i) exclusion by permeability barrier, (ii) active efflux, (iii) intra- and extracellular sequestration, (iv) enzymatic detoxification, and (v) decreased sensitivity of cellular targets to metal ions (Bruins et al. [18]; Harrison et al. [58]). Some microorganisms such as *Pseudomonas aeruginosa* can upregulate the expression of extracellular polymers or siderophores (metal-chelating agents) in response to metal exposure, which contain functional groups capable of binding to metal ions (Lemire et al. [84]). The role of siderophores is mainly to scavenge Fe, but can also form complexes with other essential metals (Mo, Mn, Co, and Ni) and make them available for microbial cells (Ahmed and Holmström [3]). Extracellular polymers and siderophores can precipitate metal ions in the extracellular environment, and soluble siderophores bound to metals may be subject to reduced uptake into microbial cells or increased efflux out of the cell by membrane transporters (Braud et al. [16]; Hannauer et al. [55]). Additionally, biofilms provide an advantageous way for microorganisms to survive on metallic pipes in DWDS, and a previous study reported growth of over 10^7 cells per cm^2 after only 30 days on metal pipe materials including stainless steel and copper (Morvay et al. [107]). Molecular mechanisms responsible for stimulating horizontal gene transfer after exposure to metals (Cu, Ag, Cr, and Zn) include intracellular reactive oxygen species (ROS) formation, SOS response, increased cell membrane permeability, and altered expression of conjugation-relevant genes (Zhang et al. [179]). This study and other studies regarding the potential for horizontal gene transfer following metal ion exposure have suggested that selection mechanisms such as co-resistance and cross-resistance likely play a significant role in the development of antibiotic resistance in metal-contaminated environments (Baker-Austin et al. [9]; Seiler and Berendonk [148]; Knapp et al. [72]). In addition to co-resistance and cross-resistance, co-regulatory mechanisms may also promote the co-selection process, which occurs when a single regulatory gene controls multiple resistance genes that confer resistance to different compounds (Pal et al. [115]).

Co-resistance is defined as two or more genetically linked resistance genes, indicating that the genes responsible for two or more resistances are located next to each other on one MGE (Chapman [25]; Ju et al. [66]). Hasman and Aarestrup et al. ([1]) observed a correlation between copper resistance and resistance to macrolides and glycopeptides in *Enterococcus faecium* obtained from copper-exposed pigs and documented the co-transfer of copper- and macrolide-resistant phenotypes in transconjugants (Aarestrup et al. [1]; Hasman and Aarestrup [62]; Hasman and Aarestrup [61]). The physical linkage results in the co-selection of other genes located on the same genetic element when an organism is exposed to a particular stressor, such as an antimicrobial compound or metal (Baker-Austin et al. [9]; Poole [126]). Even at environmentally relevant and sub-inhibitory concentrations, the presence of metals such as Cu have been positively correlated with ARGs, which is an indication that sublethal levels of Cu can increase ARG prevalence (Knapp et al. [72]; Zhang et al. [182]). The high redox potential of Cu has also allowed it to serve as an ideal biological co-factor, particularly in aerobic microorganisms (Outten et al. [114]; Rensing and Grass [135]). Previous studies have suggested that sub-inhibitory levels of copper ions present in DWDS can stimulate growth of microorganisms (Zhang et al. [185]), catalyze decay of disinfectant residuals (chloramines) (Nguyen et al. [110]), and cause microbial community shifts (Proctor et al. [129]; Rhoads et al. [136]). Alternatively, copper and silver ion exposure can inhibit growth of microorganisms such as *Legionella pneumophila* at concentrations ranging from 0.20 to 4.0 mg/L (Liu et al. [92]; Kusnetsov et al. [76]; Van Der Kooij et al. [159]) and a strong inhibitory effect on nitrifying bacteria has been reported following copper exposure exceeding 0.90 mg/L (Zhang et al. [181]). The enrichment of antibiotic-resistant microorganisms in metal-contaminated environments has been attributed to the selection of organisms harboring resistance genes for both agents (antibiotics and metals) on chromosomes or plasmids

(Poole [126]). Furthermore, a survey of soils in Scotland demonstrated a significant correlation between Cu levels and the occurrence of ARGs including *erm*(B), *erm*(F), *tet*(M), and *tet*(W) (Knapp et al. [73]). This study also revealed positive correlations between Fe and Pb in soils and the occurrence of ARGs including *tet(M)*, *tet(W)*, *bla*$_{\text{TEM}}$, and *bla*$_{\text{OXA}}$.

Cross-resistance is primarily observed through multidrug efflux pumps which can rapidly extrude structurally dissimilar compounds out of the cell, such as heavy metals and antibiotics (Baker-Austin et al. [9]; Martinez et al. [103]). Previous research has suggested that the abundance of class 1 integrons observed in metal-contaminated environments were associated with an increase in antibiotic resistance, as class 1 integrons are closely located to genes encoding for the multidrug efflux pump *czc*A (which can expel Zn, Cd, and Co) (Seiler and Berendonk [148]). Class 1 integrons are genetic elements capable of acquiring and exchanging DNA fragments called gene cassettes (Hall et al. [53]). The presence of integrons and other MGEs can mediate a selective advantage to microorganisms exposed to stressful environmental conditions (e.g., exposure to metals). Previous studies have observed significant positive correlations between MGEs and ARGs in aquatic environments including *bla*$_{\text{TEM}}$, *erm*A, *sul*1, *tet*(O), *tet*(W), and *tet*(X) (Pruden et al. [133]; Szekeres et al. [158]; Dong et al. [34]).

Exposure to heavy metals may trigger co-selection responses, but can also increase the level of tolerance to antibiotics due to co-regulation of resistance genes (Seiler and Berendonk [148]). Guo et. al observed an increase in the tetracycline resistance gene (*tet*(Q)) in gut microbiota of mice exposed to Fe and suggested that iron exposure alone could potentially alter the diversity and functions of gut microbiota and the abundance of ARGs and MGEs (Guo et al. [52]). Some heavy metals (e.g., Pb) have no known function in bacterial cells but can cause oxidative stress, which could promote generation of ROS and facilitate horizontal gene transfer in the distribution system (Knapp et al. [73]). The dominant mechanisms of co-selection for metal- and antibiotic resistance remain relatively unknown, especially in drinking water environments. Previous studies have suggested that there may be more limited opportunities for metals to drive horizontal gene transfer of antibiotic resistance; however, numerous possibilities exist for metals to select for ARB through chromosomal MRGs (Pal et al. [117]; Pal et al. [115]). Additionally, transposable elements originating in chromosomal DNA can jump to plasmids carrying ARGs and MRGs that can easily be transferred to other microorganisms through transformation or conjugation.

Metal pipe materials, including Cu, Fe, and Pb commonly used in DWDS including water mains, service connections, and premise plumbing, can influence microbial community composition and the presence of opportunistic pathogens (Rożej et al. [140]; Proctor et al. [129]; Neu et al. [109]). In fact, sub-inhibitory exposure to Cu and Zn can stimulate antibiotic resistance in water environments at concentrations below their respective maximum contaminant levels (MCLs) (Fig. 1). While MCLs are based on direct impacts to human health, these data imply that indirect consequences including selection for antibiotic resistance can occur at levels below the MCLs. Co-selection of ARGs and MRGs is likely ubiquitous in full-scale DWDS due to the presence of metals and disinfectants. Several bacteria genera commonly detected in DWDS contain plasmids with both ARGs and MRGs including *E. coli*, *Staphylococcus*, *Pseudomonas*, and *Mycobacterium* (Pal et al. [116]). Studies regarding the occurrence or distribution of ARGs, MRGs, or MGEs using molecular techniques such as qPCR or droplet digital PCR (ddPCR) are limited. Quantitative measurements of ARB, ARGs, and MRGs in drinking water and biofilms are essential for improving risk assessments for potable water systems. Additionally, fundamental research from laboratory-scale studies and full-scale DWDS surveys providing information on pipe materials and antibiotic resistance are both necessary to better understand how engineering management decisions impact human health.

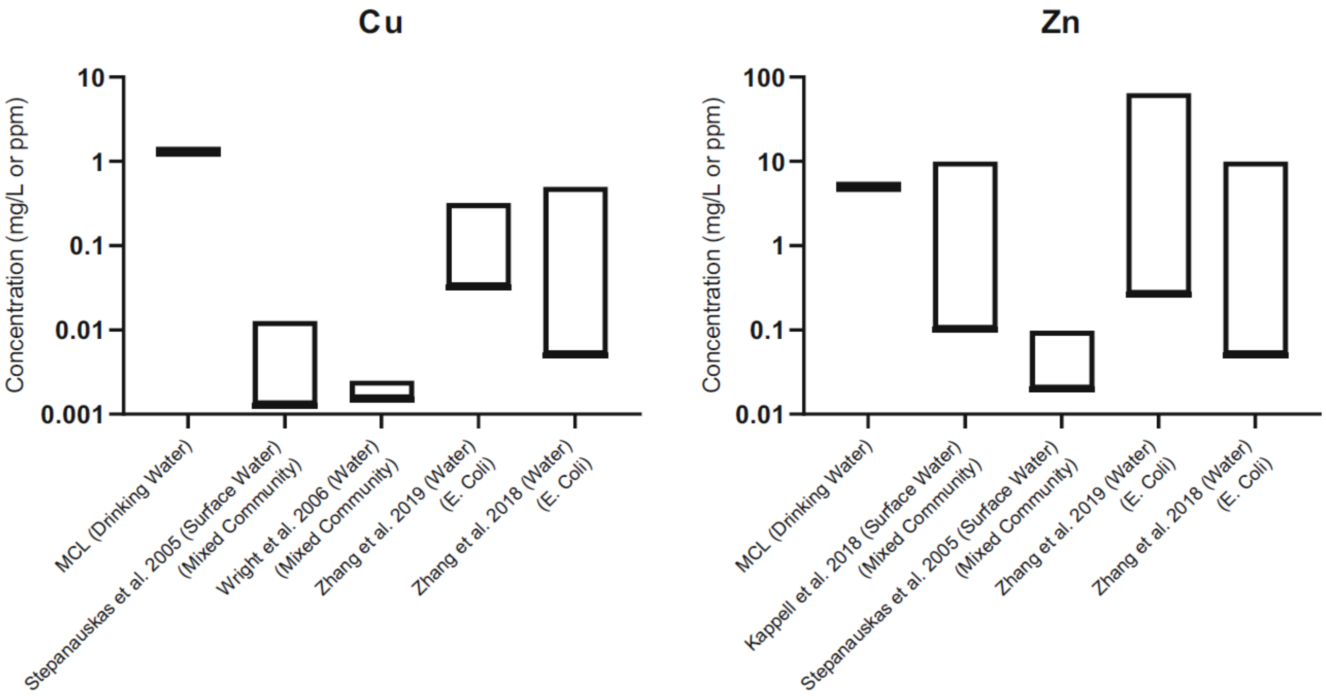

Fig. 1 Studies documenting antibiotic resistance in response to metal exposure in water environments (Cu and Zn). The US Environmental Protection Agency maximum contaminant level (MCL) for drinking water quality is plotted for reference. References for data in figure (Stepanauskas et al. [153]; Wright et al. [169]; Zhang et al. [182]; Zhang et al. [184]; Kappell et al. [69]; Zhang et al. [180])

Impact of Corrosion Products on Antibiotic Resistance

Corrosion of drinking water infrastructure occurs due to oxidation processes of metal materials and results in subsequent formation and accumulation of corrosion products on metal surfaces (McNeill and Edwards [105]). Various chemical oxidation processes that occur in drinking water environments can degrade pipe surfaces, valves, and connections, and gradually rust metal surfaces. Corrosion of drinking water pipes is responsible for destruction of the pipe material and also the deterioration of the drinking water quality in the distribution system (Sun et al. [156]). Corrosion scales are formed by the accumulation of corrosion products and other suspended particles on pipe surfaces, which reduces the capacity of the system and provides habitats for potentially pathogenic microorganisms (Wang et al. [165]; Sun et al. [156]).

Corrosion of drinking water pipes can occur due to a variety of circumstances including increased pipe service age, water chemistry, and operational parameters such as stagnation time and flow velocity (Flemming et al. [43]; Lehtola et al. [81]; Xie and Giammar [172]). Passivation of drinking water pipes occurs over time by the formation of corrosion products on pipe surfaces, and the formation of passivating scales in DWDS pipes lowers the potential for metal ions to leach into finished drinking water, but also provides increased surface area for bacterial attachment and biofilm formation (Zhu et al. [187]; Li et al. [86]). Corrosion products are comprised of scale minerals and possibly additional contaminants deposited from drinking water which may impact antibiotic resistance and horizontal gene transfer of ARGs in drinking water systems. Corrosion products that form in iron pipes typically consist of iron (III) oxyhydroxides (e.g., goethite (α-FeOOH), lepidocrocite (γ-FeOOH)), iron(II, III) oxides (e.g., magnetite (Fe_3O_4)), and/or iron(II) carbonates (e.g., siderite ($FeCO_3$)) (McNeill and Edwards [105]; Peng et al. [123]; Yang et al. [175]). Common lead corrosion products include lead(II) oxides (e.g., litharge (α-PbO)), lead(II) carbonates (e.g., cerussite ($PbCO_3$), hydrocerussite ($Pb_3(CO_3)_2(OH)_2$)), lead (II) phosphates (e.g., hydroxylpyromorphite ($Pb_5(PO_4)_3OH$)), and lead (IV) oxides (e.g., scrutinyite (α-PbO_2), plattnerite (β-PbO_2)) (Lytle and Schock [94]; Schock et al. [147]; Schock et al. [146]; Kim and Herrera [38]; Xie and Giammar [172]). Compared to iron and lead focused work, very few studies have investigated copper corrosion under conditions relevant to drinking water distribution, and cuprous oxide (Cu_2O) and/or cupric oxide (CuO) are considered the dominant copper corrosion products (Feng et al. [42]; McNeill and Edwards [106]; Xiao et al. [171]; Kang et al. [67]; Lytle and Nadagouda [93]). Furthermore, there is a paucity of research regarding the impacts of these metal corrosion products on microbial growth, ecology, and potential selection for antibiotic resistance in DWDS.

Formation of drinking water corrosion products is extremely heterogeneous and is strongly affected by water chemistry parameters, such as pH, dissolved inorganic carbon, dissolved oxygen, disinfectant type, natural organic matter, and use of corrosion inhibitors (Volk et al. [162]; Sarin et al. [143]; Xie et al. [173]; Noel et al. [112]). For instance, PbO_2 has been observed as a common lead corrosion product in various distribution systems that use free chlorine as the disinfectant, while lead(II) phosphates have been identified as the predominant corrosion products in systems using phosphate corrosion inhibitors (Lytle and Schock [94]; Kim and Herrera [38]). Furthermore, corrosion products in DWDS can exhibit significantly different morphological and structural composition and be sinks for various inorganic contaminants such as As, Cd, Cr, manganese (Mn), nickel (Ni), and vanadium (V) (Schock et al. [145]; Peng and Korshin [122]; Gerke et al. [48]). For example, some common iron corrosion products, such as goethite, lepidocrocite, and magnetite have strong affinities to adsorb and concentrate trace heavy metals present in drinking water (Sarin et al. [144]; Peng et al. [123]). Consequently, the corrosion products and additional contaminants that accumulate from drinking water on biofilms and pipe surfaces may subsequently impact the distribution and abundance of ARB and ARGs present in drinking water systems.

Similar to dissolved and particulate metals in aquatic environments, exposure of bacteria to corrosion products in DWDS may alter microbial communities and increase the potential for horizontal gene transfer of ARGs and MRGs. Previous studies have suggested that exposure of microbial populations to metal pipe materials and corrosion scales that accumulate in DWDS may eliminate some microorganisms while allowing metal-tolerant organisms to survive, which can potentially disseminate bacteria resistant to both metals and antibiotics in finished drinking water (Calomiris et al. [21]; Baker-Austin et al. [9]). Furthermore, a previous study demonstrated that exposure to cuprous oxide resulted in bacteriostatic effects against gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus faecalis*) and gram-negative bacteria including *Pseudomonas aeruginosa* and *Enterobacter cloacae* (Pang et al. [118]). Exposure of bacterial populations to copper corrosion products such as cuprous oxide and cupric oxide could increase selection for copper-related resistance genes and ARGs in organisms harboring resistance genes for both agents (Aruoja et al. [6]; Pang et al. [118]; Hans et al. [56]; Poole [126]). For example, the presence of Cu^{2+} ions and CuO nanoparticles (1–100 μmol/L) increased the conjugative transfer of ARGs across bacterial genera, increased cell membrane permeability, and caused the overproduction of ROS (Zhang et al. [180]). Bacterial exposure to CuO nanoparticles at sub-inhibitory levels resulted in expression of stress response genes including *dps*, *sodA*, *sodB*, *trxC*, *katE*, and *katG* (Zhang et al. [180]). Additionally, corrosion scales provide bacteria with organic matter and nutrients, consume residual disinfectant concentrations, provide increased surface area for bacterial adsorption, and provide iron oxides as potential electron acceptors that may increase bacterial activity (Appenzeller et al. [5]; Jang et al. [64]). Consequently, bacterial exposure to corrosion scales in DWDS containing copper and iron oxides may increase bacterial growth and selection for bacteria harboring ARGs and MRGs in finished drinking water.

There has been limited research conducted regarding different corrosion products and their effects on the abundance of ARB, ARGs, or MRGs in biofilms and drinking water in DWDS. Laboratory-scale studies are needed to understand the fundamental impacts of different corrosion products such as copper oxides and iron oxides on microbial communities and the antibiotic resistome. Full-scale studies are necessary to characterize the distribution of different corrosion products, resistance genes, and microbial communities in full-scale DWDS. Understanding the relationship of corrosion products and antibiotic resistance could provide critical information necessary to improve decisions regarding the selection of pipe materials for potable water systems.

Impact of Corrosion Inhibitors on Antibiotic Resistance

Optimized corrosion control treatment (OCCT) is a specific requirement of the Lead and Copper Rule (LCR) introduced in 1991 by the US Environmental Protection Agency (US EPA) (Brown et al. [17]). Drinking water utilities have three options for corrosion control treatment including adjusting the pH and alkalinity of drinking water, developing Pb(IV) scale by maintaining free chlorine residuals throughout the distribution system, and using corrosion inhibitors such as orthophosphate or sodium silicates (Brown et al. [17]). Corrosion inhibitors commonly applied in drinking water systems include polyphosphates, orthophosphate, zinc orthophosphate, and sodium silicates (Edwards and McNeill [39]; Schock et al. [146]; Cartier et al. [24]). Recent studies have cited the potential for phosphate-containing corrosion inhibitors to serve as a nutrient source for bacterial growth, which has raised concerns in some US drinking water utilities (Edwards and McNeill [39]; Fang et al. [41]). Therefore, it is important to gain a better understanding of the impacts of different corrosion inhibitors on microbial ecology and the abundance of ARGs and MRGs in full-scale DWDS.

A national survey of water utilities revealed that over 50% of utilities used phosphate inhibitors, and zinc orthophosphates were the most common phosphates applied (McNeill and Edwards [104]) with over half of utilities reporting doses between 0.7 and 2 mg/L as phosphate (McNeill and Edwards [104]). Bacteria typically require a ratio for C:N:P of approximately 100:10:1, and many DWDS are P deficient (LeChevallier et al. [80]; Brown et al. [17]). Research regarding the effects of phosphate addition on drinking water microbial communities has yielded mixed results. Several studies have reported increased bacterial growth in drinking water systems with phosphate exposure levels ranging from 0.001 to 0.03 mg/L P (Lehtola et al. [83]; Chu et al. [26]; Fang et al. [41]; Payne et al. [119]). Phosphorus addition to drinking water can promote biofilm cell growth, decrease EPS production, and induce biofilms with increased thickness and biomass (Fang et al. [41]). By stimulating microbial growth in drinking water biofilms, phosphorus addition may also lead to increased abundance of ARB and ARGs. Polyphosphate addition to drinking water may impact biofilm growth resulting in softer, thicker biofilms that are more prone to detachment (Shen et al. [151]). Furthermore, the addition of polyphosphate can supply nutrients to bacteria for biofilm development, play an important role in bacteria metabolic regulation, and increase bacterial resistance to environmental stress (Rao and Kornberg [134]; Gangaiah et al. [44]). Zinc orthophosphate addition has been shown to increase microbial community diversity in drinking water biofilms (Payne et al. [119]). Another study reported that phosphate addition did not increase total biomass in biofilm communities, but did cause shifts in microbial community composition (Batté et al. [12]). Similarly, Jang et al. observed increased community richness and diversity in biofilms that developed on stainless steel and ductile cast iron coupons with phosphate addition compared to controls without phosphate addition (Jang et al. [64]). The use of zinc orthophosphate for corrosion control may also result in the selection of resistant microorganisms in DWDS due to the potential for zinc to select for ARGs and MRGs (Peltier et al. [120]; Kappell et al. [69]). As a result, the use of orthophosphate and zinc orthophosphate as corrosion inhibitors influences microbial ecology and may also impact the abundance and distribution of resistance genes in DWDS. However, limited research has been conducted regarding the effects of different corrosion inhibitor treatments on the presence of ARB, ARGs, and MRGs in full-scale DWDS.

Sodium silicates are an alternative to phosphate-based corrosion inhibitors and have been reported to be an effective strategy for lead control in some systems since the 1920s (Butler and Ison [19]; Schock et al. [146]; Lintereur et al. [89]). Similar to polyphosphates, the molecular composition of sodium silicates are indeterminate, with the chemical formula (Na_2O: n (SiO_2), where *n* is a variable ratio (Crittenden et al. [29]). Typical dosages of silicates range from 4 to 30 mg/L as SiO_2, and higher doses are required for drinking water with higher hardness, higher chlorides, and/or higher dissolved solids (Lane et al. [77]). Silicates and phosphates act as anodic inhibitors when used at low doses for corrosion control treatment of drinking water, which reduces corrosion by forming a protective layer of oxide film on pipe surfaces. The Illinois State Water Survey conducted extensive testing with corrosion inhibitors and recommended that silicates were the best option for corrosion inhibition in galvanized steel and copper-based piping commonly used in domestic hot water systems (Lane et al. [77]). The use of sodium silicates may have advantages over phosphate-based treatments due to the lack of phosphorus and zinc, which could potentially limit microbial growth and levels of ARGs in finished drinking water. A previous study observed decreased average bacterial growth (e.g., lower ATP concentrations) in biofilms subjected to sodium silicate treatment compared to phosphate-containing corrosion inhibitors, but the differences were not statistically significant (Kogo et al. [74]). Additionally, Rompré et al. ([139]) compared heterotrophic plate counts (HPC) between sodium silicate and phosphate treatments in a study conducted with laboratory-scale annular reactors and in a confined section of a full-scale DWDS, but reported no significant differences between corrosion control treatments (Rompré et al. [139]). This study also concluded that surface material (unlined gray iron vs. polycarbonate) was a larger factor influencing biofilm development in DWDS pipes compared to corrosion inhibitor type. Despite previous analysis of corrosion inhibitors in DWDS, the impact of corrosion inhibitor type on the abundance of ARB, ARGs, and MRGs has yet to be elucidated in full-scale systems. Laboratory-scale and full-scale studies investigating the impacts of corrosion inhibitors and their impacts on the development of corrosion products and microbial communities are needed to better understand mechanisms of antibiotic resistance selection in DWDS.

Little information exists regarding the impacts of sodium silicates on microbial ecology and the proliferation of antibiotic resistance in full-scale drinking water systems. A previous study investigated the effects of sodium silicate addition on cucumber seedling growth and resistance to the soil-borne pathogen *Fusarium oxysporum* f. sp. *cucumerinum* Owen (Zhou et al. [186]). The study reported changes in bacterial and fungal community structure in response to two mM sodium silicate addition in addition to decreased abundance of microbial taxa containing pathogens (Zhou et al. [186]). Consequently, the addition of sodium silicates to drinking water for corrosion control may also impact bacterial community composition but has yet to be investigated. In order to mitigate public health impacts related to corrosion of drinking water infrastructure, future studies should consider the impacts of different corrosion inhibitor regimes on microbial ecology and the abundance of ARGs and MRGs in drinking water systems.

Conclusions and Future Research Recommendations

Several studies have documented the presence, though not necessarily the quantity, of ARB and ARGs in drinking water environments. Factors such as metal pipe materials, corrosion inhibitors, and corrosion products that develop in full-scale DWDS may select for bacteria harboring resistance to both metals and antibiotics. There is a lack of information regarding the abundance and fate of ARB, ARGs, MRGs, and MGEs in different phases of DWDS including planktonic, biofilm, suspended solids, and loose corrosion deposits. Previous research has demonstrated that water quality deterioration in DWDS can result in increased levels of ARB and ARGs in consumer tap water, which poses a risk to human health.

Future research on antibiotic resistance in DWDS should focus on monitoring the occurrence, fate, and distribution of ARB, ARGs, MRGs, and MGEs in multiple phases in full-scale systems. This information is critical for gaining a better understanding of the prevalence of antibiotic resistance in engineered systems capable of directly impacting human health. Previous characterization of DWDS has primarily focused on microorganisms in the planktonic phase and studies documenting and quantifying ARB, ARGs, or MRGs in drinking water biofilms are lacking. Drinking water biofilms have been cited as important reservoirs for opportunistic pathogens and horizontal gene transfer of ARGs (Wingender and Flemming [168]; Balcázar et al. [10]); however, the dominant pathways of antibiotic resistance selection in drinking water are not well documented. In addition to full-scale studies, laboratory-scale studies are needed to distinguish the impacts of different pipe materials, corrosion inhibitors, and corrosion products on the abundance of resistance genes in drinking water and biofilms. These studies will provide critical information regarding the relationship of different system parameters and mechanisms of antibiotic resistance selection in engineered systems. Locations with high densities of bacteria, such as drinking water biofilms, provide conditions which are suitable for proliferation and exchange of resistance genes, and selective pressures (e.g., metals) may increase the abundance of resistance genes in these communities. Additional research is needed to address the research gaps related to the fate and transport of clinically relevant resistance genes in DWDS.

Fundamental information regarding the impacts of pipe materials, metals, and corrosion inhibitors on pathogens and abundance of resistance genes in DWDS is necessary to reduce the prevalence of antibiotic resistance in drinking water. Different pipe materials used in full-scale DWDS may influence the composition of microbial communities and associated resistance genes that can subsequently be transferred to humans through dermal contact, consumption of contaminated drinking water, or inhalation of aerosols during bathing (Falkinham [40]; Garner et al. [47]). Further research including QMRA is needed to determine the concentration of ARB or ARGs that may translate to human health risks (Ashbolt et al. [7]). Research that links ARGs to hosts and distinguishes extracellular DNA from intracellular DNA is also needed (Rice et al. [137]). Furthermore, limited availability of exposure assessments and dose-response data regarding ARB and ARGs for different scenarios hinder the implementation of QMRA approach for evaluating human health risks in aquatic environments (Amarasiri et al. [4]).

The selection of target genes is also important for improving routine monitoring of ARGs, MRGs, and MGEs in full-scale distribution systems. Future research and microbial surveillance efforts should consider monitoring clinically relevant ARGs and other genes commonly linked to horizontal gene transfer processes including beta-lactam resistance genes, *intI*1 and *sul*1 (WHO [167]; Gillings et al. [49]; Ma et al. [96]). The prevalence of dissolved, particulate, and solid phase metals in DWDS warrants further investigation regarding their potential for selection of resistance genes in drinking water biofilms. Additionally, the collection of samples from multiple locations (biofilm/pipe surfaces, corrosion tubercles, under tubercles) within the same distribution system or even the same pipe would increase knowledge regarding impacts of biogeographical heterogeneity in drinking water biofilms on antibiotic resistance (Liu et al. [90]; Gomez-Smith et al. [50]; Neu et al. [109]; Cruz et al. [30]). Laboratory and full-scale studies regarding pipe materials, corrosion inhibitors, and corrosion products are important for gaining insights into microbial functions and could be used to provide guidance to water utilities for making engineering decisions in DWDS that could reduce human health risks.

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Authors' contributions

L.K. and P.M. contributed to the study conception and design. Literature review, data collection, and analysis were performed by LK. The first draft of the manuscript was written by LK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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