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REVIEW ARTICLE

Presence, dissemination and removal of antibiotic resistant bacteria and antibiotic resistance genes in urban drinking water system: A review

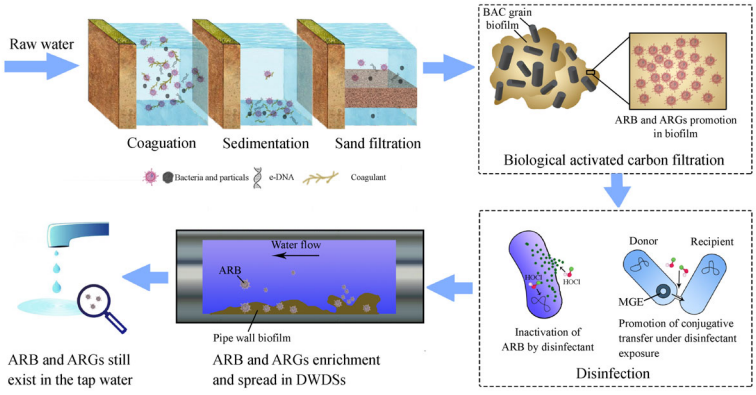
Qiaowen Tan[1,2], Weiying Li (✉)[1,2], Junpeng Zhang[1,2], Wei Zhou[1,2], Jiping Chen[1,2], Yue Li[1,2], Jie Ma (✉)[1,2]

1 State Key Laboratory of Pollution Control and Resource Reuse, Tongji University, Shanghai 200092, China
2 College of Environmental Science and Engineering, Tongji University, Shanghai 200092, China

HIGHLIGHTS

- Reviewed the change of ARGs and ARB in full-scale urban drinking water systems.
- Conventional processes are more promising than BAC process in ARGs removal.
- Mechanisms of ARGs enrichment and spread in BAC filter and DWDSs are discussed.
- Raise the need of future research on ARGs and ARB change in building plumbing systems.

GRAPHIC ABSTRACT



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ABSTRACT

Antibiotic resistance in aquatic environment has become an important pollution problem worldwide. In recent years, much attention was paid to antibiotic resistance in urban drinking water systems due to its close relationship with the biosafety of drinking water. This review was focused on the mechanisms of antibiotic resistance, as well as the presence, dissemination and removal of antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARGs) in the urban drinking water system. First, the presence of ARB and ARGs in the drinking water source was discussed. The variation of concentration of ARGs and ARB during coagulation, sedimentation and filtration process were provided subsequently, in which filtration was proved to be a promising technology to remove ARGs. However, biological activated carbon (BAC) process and drinking water distribution systems (DWDSs) could be incubators which promote the antibiotic resistance, due to the enrichment of ARGs and ARB in the biofilms attached to the active carbon and pipe wall. Besides, as for disinfection process, mechanisms of the inactivation of ARB and the promotion of conjugative transfer of ARGs under chlorine, ozone and UV disinfection were described in detail. Here we provide some theoretical support for future researches which aim at antibiotic resistance controlling in drinking water.

1 Introduction

Since the discovery of penicillin by Alexander Fleming in 1928, antibiotics have been broadly used in health care, animal husbandry, etc. (Fleming, 1929; Davies and Davies, 2010; Fauci and Marston, 2014). Over almost a century,

✉ Corresponding authors
E-mail: 123lwyktz@tongji.edu.cn (Li W Y); jma@tongji.edu.cn (Ma J)

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antibiotics have been saving millions of human lives by inhibiting bacterial infections, and promoting the development of social economy significantly. However, the abuse of antibiotics is now attracting more and more attention. In the decade from 2000 to 2010, global antibiotic consumption increased by 35%, with Brazil, India, Russia, China and South Africa contributing 76% of the growth rate (Van Boeckel et al., 2014). However, a considerable proportion of the use of these antibiotics is unnecessary. For example, 75% of American adults who suffer from acute bronchitis are treated with antibiotics, which is basically caused by viruses rather than bacteria (Fauci and Marston, 2014).

The abuse of antibiotics in the medical and animal husbandry has resulted in the release of large amounts of antibiotics into the environment through the feces of humans and livestock (Silbergeld et al., 2008). These antibiotic molecules persist in the environment (Gothwal and Shashidhar, 2015), leading to the promotion of ARB and ARGs (Berendonk et al., 2015).

Currently, antibiotic resistance has turned out to be the most critical public health threats facing humanity in this century (Sharma et al., 2016). A final review of antibiotic resistance in 2016 showed that if there was no actions to be taken, the number of deaths caused by the infections of resistant microbe was expected to increase from the current 700000 per year to 10 million in 2050, and the global economic losses will also reach 100 trillion US dollars (Robinson et al., 2016). Besides, "superbugs" (e.g., bacteria carrying the NDM-1 gene (Kumarasamy et al., 2010) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Asoh et al., 2005)) which resistant to multiple antibiotics, might cause panic worldwide. If no effective measures were taken, humans would be in a state where no medicine was available, the "post-antibiotic era" had arrived (Neville and Jia, 2019).

Since Amy Pruden proposed ARGs as emerging environmental contaminants in 2006 (Pruden et al., 2006), the presence of ARGs has been found in numerous environmental medium around the world (such as urban sewage plants (LaPara et al., 2011), livestock wastewater (Thames et al., 2012), and soil (Chen et al., 2017)). In particular, the effluent of urban wastewater treatment plant which received manure of human and animals was discharged into water, and a large amount of antibiotics was discharged into the aquatic environment simultaneously (Ye et al., 2018). Therefore, ARGs were enriched under the selective pressure of antibiotics, and the aquatic ecosystem (including drinking hwater sources) became the first and serious environmental medium contaminated by ARGs consequently (Tao et al., 2010). However, it has been proved that existing urban drinking water treatment processes cannot completely remove ARGs and ARB from water, conversely, some treatment processes (such as BAC and chlorine disinfection process) and water distribution system may enrich and promote them (Guo et al., 2014; Xu et al., 2016; Zheng et al., 2018). The present situation of drinking water system made it possible for pathogenic bacteria to obtain resistance from drinking water (Durão et al., 2018), seriously threaten the drinking water safety of residents.

Urban drinking water system undertakes two main functions which are raw water purification and water distribution. The corresponding system components include: drinking water sources, drinking water treatment plants (DWTPs), drinking water distribution systems (DWDSs), building water plumbing systems and other supporting public facilities. In this paper, we review the mechanisms of antibiotic resistance, and the presence, dissemination and removal of ARGs and ARB in urban drinking water system combined the latest literature in this field. The route discussed in this paper starts from the presence of ARGs and ARB in urban drinking water sources, involves the spread and removal of them in various processes in DWTPs and DWDSs. In addition, we also highlight the importance of the future needs of research on risk assessment of antibiotic resistance transmission to human through drinking water. This review summarizes the influence of urban drinking water system on antibiotic resistance and provides theoretical support and references for future research on risk assessment and controlling of ARB and ARGs in drinking water.

2 Mechanisms of bacterial resistance to antibiotics and transfer of ARGs

2.1 Origin and mechanisms of antibiotic resistance

Antibiotics are a class of substances that microorganisms naturally produce in order to compete within and between populations. Correspondingly, microorganisms acquire resistance genes by random mutation as a means of fighting against antibiotics to survive the competition among microorganisms (Miller, 1947; Smith et al., 2015).

The main mechanisms of bacterial resistance are as follows: 1) Some species of bacteria are "intrinsically" resistant to many antibiotics simply because they have low-permeability membrane/wall barriers or lack the genes of target protein translation (Nikaido, 1994). 2) The antibiotic molecules are actively pumped out of the cells through an efflux pump on the cell membrane (Nikaido, 1994). 3) Modification of the target protein by mutation, such as the variation of the penicillin binding protein(PBP) gene, changes the affinity of the β-lactam antibiotic to PBP, leading to bacterial resistance (Charpentier and Tuomanen, 2000). 4) Producing enzymes to inactivate antibiotics, for example, bacteria producing β-lactamase to inactivate β-lactam antibiotics by ring-opening, which is the main reason for the resistance to β-lactam antibiotics. It inactivates the β-lactam antibiotic by covalent binding onto the carbonyl group on the β-lactam ring, hydrolyzes

the amide bond and inactivate the β-lactam antibiotics (Allen et al., 2010) (Fig. 1(a)).

2.2 Transfer of antibiotic resistance

The resistance gene is the molecular biological basis for the bacterial resistance to antibiotics. There are two ways through which bacteria can acquire resistance genes: one is to inherit the resistance gene from parents to offspring, which is called vertical gene transfer (Dodd, 2012). The other is the horizontal gene transfer (HGT) of resistance genes in and between species. Due to HGT, various microbial species with resistance genes can become ecological reservoirs for pathogenic bacteria to acquire resistance genes (Salyers and Shoemaker, 2006). The mechanisms of HGT in the environment include the following three types: 1) Conjugation, which is the process of transferring a resistance gene between a donor and a recipient cell by a mobile gene element (MGE) such as a plasmid, an integron or a transposon, which is the main way of horizontal transfer of resistance genes (Ehlers and Bouwer, 1999). 2) Transduction, a method of transmitting a resistance gene by phage. When a phage infects a bacteria, the resistance gene is integrated into its own genome, and then its offspring infect other bacteria to inject the resistance gene into the recipient cell (Miller, 2001). 3) Transformation, which is, the process that the competent cells take up extracellular free DNA (including resistance genes), integrate and express them in vivo (Zhang et al., 2009) (Fig. 1(b)).

3 Presence, dissemination and removal of ARB and ARGs in urban drinking water system

3.1 ARB and ARGs in drinking water source

Numerous studies have revealed that the ARGs were detected in various types of aquatic environments, including surface water (Pruden et al., 2006) and groundwater (Koike et al., 2007). Water constitutes the route by which resistance genes are introduced in natural bacterial ecosystems. In such systems, bacteria could serve as a reservoir of ARGs for pathogens (Baquero et al., 2008). Naturally, the ARG pollution will spread to the drinking water source of human, after the DWTPs and the DWDSs, finally enter the daily drinking water, food and contact with residents, thus posing a serious threat to human health.

Machado et al. investigated the presence of ARB seasonally in wells of Guinea-Bissau (West Africa) as the source of drinking water and water of other domestic proposes. The results revealed that potentially pathogenic bacteria, which showed resistance to the most prescribed antibiotics in Guinea-Bissau, were separated from well water, posing a severe health risk to residents (Machado and Bordalo, 2014). In another study which conducted in south-east Louisiana, the USA, both gram-negative and gram-positive bacteria resistant to various antibiotics were found in the source water (Fig. 2(a)) (Bergeron et al., 2015). A subsequent study conducted by the same group showed that part of the isolates of *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeru-*

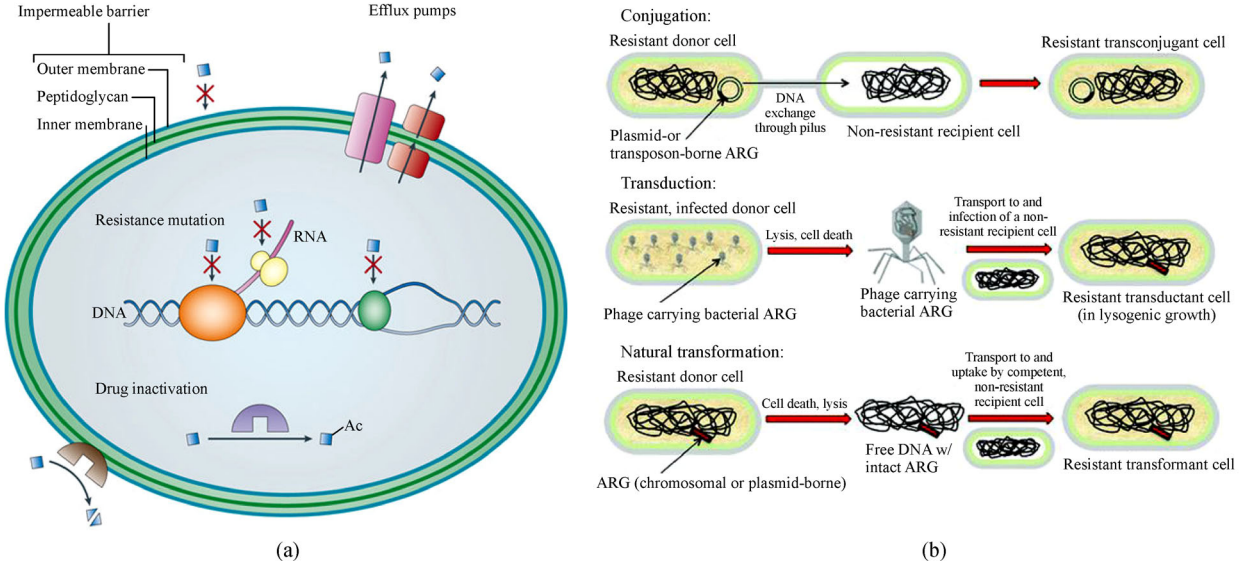


Fig. 1 (a) Mechanisms of antibiotic resistance in a Gram-negative bacterium (Adapted from Allen et al. (2010) with permission from Springer Nature). (b) Major aspects of horizontal gene transfer by means of conjugation, transduction, and natural transformation (Adapted from Dodd (2012) with permission from The Royal Society of Chemistry).

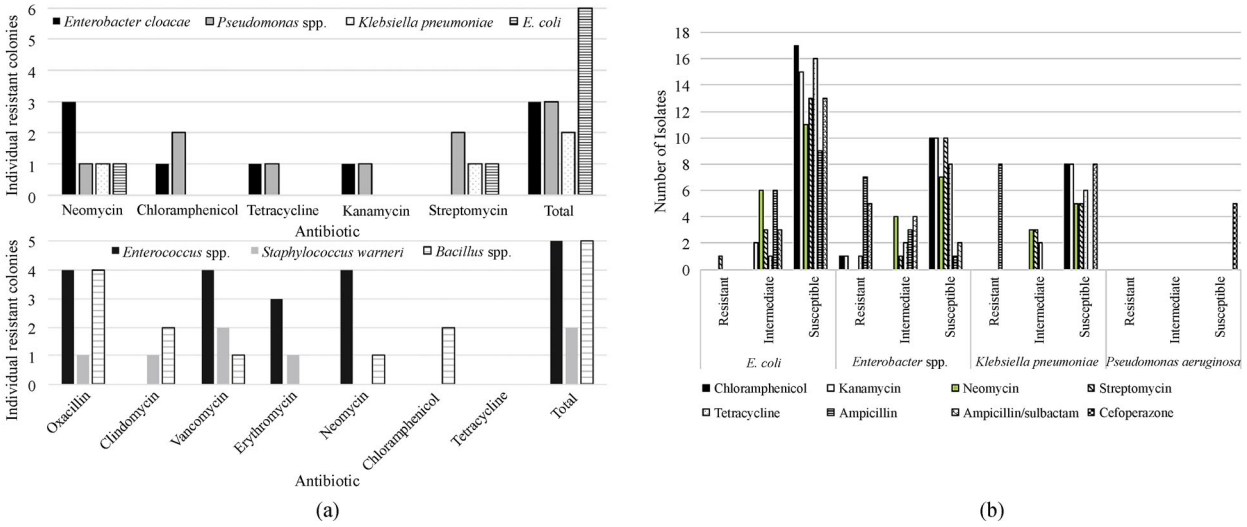


Fig. 2 (a) Antibiotic resistance of various gram-negative and gram-positive bacteria present in a raw source water in south-east Louisiana, USA (Adapted from Bergeron et al. (2015) with permission from Elsevier Inc.). (b) The number of susceptible, intermediate, and totally resistant gram negative bacteria found in a raw source water site of rural communities in the USA (Adapted from Bergeron et al. (2017) with permission from Elsevier Inc.).

ginosa in the raw source water manifested totally or intermediately resistant to 8 kinds of antimicrobial (Fig. 2(b)). s*ulI* and *tetA* resistance genes were also detected in raw water samples collected in some months (Bergeron et al., 2017).

In China, antibiotic resistance contamination of drinking water sources is also extremely severe. Xu et al. investigated ARGs in two representative DWTPs and DWDSs in Hangzhou City by using high-throughput quantitative PCR (HT-qPCR), 74 and 168 types of total 285 types of target ARGs had been detected in these two water sources (Xu et al., 2016). Jiang et al. investigated at seven surface water sites in the Huangpu River Basin of Shanghai. Similar or even higher ARGs levels compared with the other sites were observed at three sites which served as the raw drinking water of Shanghai. Sites S7 was one of those and suffered the most serious pollution, with 11 types of ARGs detected and mostly the highest concentrations (except for *sul II* and TEM) (Jiang et al., 2013).

3.2 Coagulation sedimentation/clarification and filtration process

In coagulation process, the colloids and suspended substances in the raw water were aggregated and destabilized by the effect of coagulants. Subsequently, these particulate flocs are subjected to solid-liquid separation under the action of gravity and removed in the sedimentation process. Then, the water to be treated passes through the filter medium, wherein fine solid impurities are trapped by the filter medium to complete further purification. The clarification process refers to a unit treatment process that integrates both coagulation and precipitation. The coagulation sedimentation/clarification + filtration process is an important part of the conventional water treatment processes, the purpose of which is to remove the colloid and suspended matter in the water, reduce the turbidity and chroma of the water, and remove the pollutants such as microorganisms, heavy metal and organic matter in the water (Zainal-Abideen et al., 2012).

In conventional water treatment, coagulation constitutes one of the most critical factors affecting the efficiency of water treatment. Research on the use of coagulation processes to remove ARGs in wastewater has progressed in a recent study. Li et al. studied the removal of ARGs by adding $FeCl_3$ or polyferric chloride (PFC) in the effluent of a wastewater treatment plant (WWTP) which resulted in a remarkable removal efficiency for various ARGs, ranging from 1.15 to 2.46-log, better than constructed wetlands, biological aerated filter, and UV disinfection (Li et al., 2017).

Since the pH, temperature especially the turbidity of the raw water, and the coagulants which been used in drinking water treatment have obvious difference from the wastewater treatment, the removal effect of the coagulation and the subsequent sedimentation process on the ARGs in the actual drinking water treatment plant may be different from the wastewater treatment. However, in recent years, the studies on the effect and mechanism of removing the ARGs and ARB by coagulation and sedimentation of drinking water treatment were still relatively rare which may be one of the directions of development in the field.

The filtration process has always been an indispensable and core unit in water treatment. Suspended solids and waterborne pathogens are removed by sand filtration by

both physical and biological processes (Li and Zhang, 2013), so the filtration may also influence the fate of ARGs and ARB. Xu et al. found that, the types of ARGs in DWTP-1 decreased from 70 to 67 after sedimentation, and another two were removed after filtration. The absolute abundance of ARGs in both DWTPs decreased after coagulation and sedimentation, but a slight increase of β-lactams, FCA (abbreviation for fluoroquinolone, quinolone, florfenicol, chloramphenicol, and amphenicol), Macrolide-Lincosamide-Streptogramin B resistance (MLSB), sulfonamides and tetracycline resistance genes has been observed after filtration in DWTP-1 (Table 1). However, the relative abundance of most ARGs has no significant decrease or even a slight increase was observed after the sand filter (Table 2) (Xu et al., 2016). Similar results had been obtained from Guo et al. Their studies about ARGs in seven DWTPs located at Yangtze River Delta showed that the conventional treatment processes had a limited impact on the relative abundance of resistance genes, but the absolute abundance of most target genes (*sulI*, *sulII*, *tetA*, *tetB*, *tetM*, *tetO*, *tetW*, and *tetX*) was reduced after sand filtration (Table 1 and Table 2 demonstrated one of the DWTPs: SX) (Guo et al., 2014). The research results of Su et al. also supported this assertion, and they believed that the effect of sand filtration was superior to other processes in the removal of absolute abundance of ARGs (Table 1) (Su et al., 2018). However, the research results of Zhang et al. were distinct from the above studies. In a full-scale advanced water treatment plant, a significant reduction of both the absolute abundance and the relative abundance of 11 target ARGs had been observed during sand filtration process (Zhang et al., 2016). It can be speculated that resistant plasmids carried by ARB may be partially or completely degraded after several generations, especially in an oligotrophic environment, leading to the reduction of HGT during the ARB proliferation on filtration medium (Griffiths et al., 1990).

3.3 BAC process

BAC is an advanced treatment process commonly used in drinking water treatment. Due to the huge surface area and the rough surface of activated carbon, microorganisms could grow on the carbon granule and form biofilms when passing through the BAC. The bio-degradation of microorganisms and the physical adsorption of activated carbon serve to remove contaminants in water (Korotta-Gamage and Sathasivan, 2017). However, due to the high density of biomass on the biofilm and the ideal environment for microbial growth, biofilms may become an important medium for the proliferation of ARB and the spread of ARG (Guo et al., 2018), resulting in the increase of resistance gene abundance after activated carbon filter treatment. Several articles have confirmed this conjecture in recent years, for example, the study of Zheng et al. revealed that among all the 285 targeted ARGs, there were 159 and 141 types of ARGs in the effluent of BAC and biofilm of activated carbon respectively, both of which are much higher than the influent water (average value). Regarding gene abundance, the standardized copy number of β-lactam, FCA and MLSB resistance genes in the effluent were also significantly increased (Zheng et al., 2018). In the research of Su et al., granular activated carbon filter (GAC) caused a significant rise of concentration of ARGs while a slight decrease of which had been detected after powder activated carbon filter (PAC) (Table 1). This variance may be owing to the differences of bacterial community and biomass caused by the different size of carbon particle (Su et al., 2018).

3.4 Disinfection process

Disinfection process is a vital technology in DWTPs, which is in order to kill pathogenic microorganisms and guarantee the biosafety of drinking water. The commonly used disinfectants or disinfection techniques in drinking water treatment are: Free chlorine (Cl_2), mono-chloramine (NH_2Cl), ozone (O_3) and ultraviolet technology (UV).

Many previous studies have shown that chlorine disinfection was considered not effective in controlling ARGs. In waste water treatment, Yuan et al. demonstrated that chlorination decreased limited erythromycin or tetracycline resistance genes, in which about 40% of erythromycin ARGs and 80% of tetracycline ARGs could not be removed by chlorination (Yuan et al., 2015). Furthermore, Oh et al. showed that more than 30 mg/L (the contact time was fixed at 15 min) of chlorine was needed to remove over 90% of ARB and ARGs, which is impractical in wastewater treatment (Oh et al., 2014). According to the research of Zhang et al., removal of ARGs rose slowly when adding chlorine from the dosage of 5 to 20 mg/L, but increased dramatically from 20 to 25 mg/L, with the maximum ARGs removal (1.30−1.49 logs) reached at 30 mg/L (30 min contact time) (Zhang et al., 2015), consists with study of Oh et al. (2014). In drinking water treatment, the phenomenon that chlorine/chloramine disinfection could reduce the concentration of ARG while increasing its relative abundance has also been confirmed by many studies (Tables 1 and 2) (Shi et al., 2013; Xu et al., 2016; Zhang et al., 2018a; Zheng et al., 2018).

In addition to chlorine disinfection, ozone and UV technology are also commonly used technologies in drinking water treatment. However, since it is necessary to ensure a certain amount of residual chlorine in the DWDSs, ozone or UV disinfection can hardly be adapted alone. Besides, these two methods are often utilized in disinfection of bottled water treatment, food processing or building water supply. Ozone is a highly oxidizing disinfectant with moderate or strong reactivity to lipids, polysaccharides, amino acids, nucleic acids, etc. (Dodd, 2012), thus having a potent bactericidal ability. However,

Table 1 Log removal or an increase of the absolute abundance of the ARGs in each process of the DWTP (obtain directly or calculated by the average values in the references, positive values represent removal, negative value represent increase)

Ref.	DWTP	Type	Coagulation	Sedimentation	Filtration	Ozone	BAC	Chlorine disinfection	Total of all processes
Xu et al. (2016)	DWTP-1	Aminoglycoside		0.45[a]	0.06	0.22	0.05	1.13	1.86
		β-lactam		0.69[a]	–0.12	0.54	–0.05	0.94	1.88
		FCA		1.03[a]	–0.17	0.36	0.38	0.87	2.14
		MLSB		0.76[a]	–0.06	0.33	–0.30	1.55	2.07
		Other/efflux		0.43[a]	0.11	–0.12	0.26	1.61	2.29
		Sulfonamide		0.85[a]	–0.30	0.26	0.10	1.38	2.04
		Tetracycline		0.40[a]	–0.05	0.34	0.07	1.43	2.23
Zheng et al. (2018)		Aminoglycoside		0.94[b]		0.10	0.88	2.36	4.28
		β-lactam		1.79[b]		–0.75	0.32	2.14	3.50
		FCA		0.68[b]		0.07	0.56	2.48	3.79
		MLSB		1.30[b]		0.26	0.10	2.27	3.92
		Other/efflux		0.81[b]		0.27	0.74	2.76	4.57
		Sulfonamide		0.76[b]		0.29	0.78	2.51	4.34
		Tetracycline		0.67[b]		0.27	0.45	2.54	3.93
		Vancomycin		1.20[b]		–0.74	0.25	1.58	2.29
Guo et al. (2014)	SX	*sulI*		0.10[a]	–0.31	1.06	–0.06	1.11	1.80
		sulII		0.45[a]	–0.31	0.80	–0.20	0.57	1.25
		tetC		2.62[a]	–2.29	–0.10	1.66	1.64	3.30
		tetG		0.06[a]	–1.08	2.33	–0.25	1.15	2.44
		tetX		0.88[a]	0.53	0.23	0.63	1.00	1.45
		tetA		0.39[a]	0.08	0.45	–0.10	0.78	1.39
		tetB		0.22[a]	–0.06	0.22	–0.23	1.02	1.02
		tetO		0.20[a]	–0.25	0.31	0.12	/	/
		tetM		–0.18[a]	–0.04	–0.12	–0.14	0.06	–0.59
		tetW		–0.27[a]	0.23	–0.27	–0.08	0.22	–0.55
Su et al. (2018)	Plant A	*sul1*		–0.07[a]	0.45		–0.19[c] 0[d]		
		ermB		–0.18[a]	1.05		–0.27[c] –0.13[d]		
		tetA		–0.26[a]	0.51		–0.15[c] 0.08[d]		
		tetO		0.1[a]	1.62		–0.27[c] –0.08[d]		
		tetX		–0.22[a]	0.23		–0.34[c] 0.45[d]		
		cfr		0.58[a]	0.66		–0.24[c] –0.04[d]		
		cmlA		–0.2[a]	0.35		–0.21[c] –0.09[d]		
		fexA		–0.07[a]	0.8		–0.28[c] –0.13[d]		
		floR		–0.27[a]	0.16		–0.06[c] 0.04[d]		
		oqxB		–0.28[a]	0.93		–0.22[c] –0.16[d]		
		qepA		0.4[a]	3.08		–3.25[c] –3.43[d]		
		qnrA		–0.05[a]	4.08		–3.67[c] 0[d]		
		∑ ARGs		–0.14[a]	0.35		–0.15[c] 0.01[d]		

Note: a) Total log removal or increase by both coagulation and sedimentation process; b) Total log removal or increase by coagulation, sedimentation and filtration process; c) Log removal or increase by GAC process; d) Log removal or increase by PAC process.

Table 2 Log removal or an increase of the relative abundance of the ARGs by each process of the DWTP (obtain directly or calculated by the average values in the references, positive values represent removal, negative values represent increase)

Ref.	DWTP	Type	Coagulation	Sedimentation	Filtration	Ozone	BAC	Chlorine disinfection	Total of all processes
Xu et al. (2016)	DWTP-1	Aminoglycoside	0.58[a]		–0.11	0.44	–0.34	–0.76	–0.90
		β-lactam	–0.03[a]		0.03	0.97	–0.82	–0.23	0.11
		FCA	0.16[a]		0.07	0.20	–1.02	–0.05	–0.61
		MLSB	0.03[a]		0.00	0.20	–0.69	–0.35	–0.71
		Other/efflux	–0.44[a]		0.12	–0.12	–0.15	–0.25	–0.49
		Sulfonamide	–0.01[a]		0.03	0.01	–0.36	–0.41	–0.65
		Tetracycline	–0.44[a]		–0.30	0.68	–0.39	–0.43	–0.48
		Vancomycin	0.00[a]		0.49	–0.18	–1.44	–0.40	–1.40
Zheng et al. (2018)		∑ARGs	0.08[b]			–0.07	–0.06	–0.36	–0.40
Guo et al. (2014)	SX	*sulI*	–0.50[a]		0.53	0.31	–0.55	–1.32	–1.99
		sulII	–0.17[a]		0.53	0.05	–0.67	–1.87	–2.52
		tetC	1.97[a]		–1.42	–0.86	1.20	–0.79	–0.48
		tetG	–0.58[a]		–0.22	1.58	–0.72	–1.30	–1.34
		tetX	0.26[a]		1.37	–0.50	0.14	–1.44	–2.33
		tetA	–0.24[a]		0.94	–0.31	–0.55	–1.68	–2.40
		tetB	–0.41[a]		0.79	–0.53	–0.72	–1.44	–2.76
		tetO	–0.43[a]		0.60	–0.43	–0.36	–1.01	–2.21
		tetM	–0.82[a]		0.82	–0.86	–0.60	–2.40	–4.37
		tetW	–0.89[a]		1.08	–1.01	–0.55	–2.26	–4.34
Su et al. (2018)	Plant A	*sulI*	0.27[a]		0.00		–0.10[c] 0.18[d]		
		ermB	0.17[a]		0.58		–0.04[c] 0.06[d]		
		tetA	0.07[a]		0.06		–0.14[c] 0.27[d]		
		tetO	0.44[a]		1.16		–0.08[c] 0.11[d]		
		tetX	0.11[a]		–0.23		–0.71[c] 0.65[d]		
		cfr	0.92[a]		0.20		–0.11[c] 0.16[d]		
		cmlA	0.14[a]		–0.11		–0.03[c] 0.10[d]		
		fexA	0.25[a]		0.35		–0.06[c] 0.06[d]		
		floR	0.07[a]		–0.31		–0.01[c] 0.24[d]		
		oqxB	0.07[a]		0.47		0.04[c] 0.03[d]		
		qepA	0.73[a]				0.25[c]		
		qnrA	0.28[a]						
		∑ ARGs	0.20[a]		–0.11		–0.08[c] 0.21[d]		

Note: a) Total log removal or increase by both coagulation and sedimentation process; b) Total log removal or increase by coagulation, sedimentation and filtration process; c) Log removal or increase by GAC process; d) Log removal or increase by PAC process.

UV is only reactive to the purine and pyrimidine, but does no damage to the cell wall (Chen et al., 2009; Dodd, 2012). Zheng et al. compared the removal of ARGs from the secondary effluents of wastewater by chlorine disinfection, UV and ozone. It was noted that the abundance of ARGs decreased with the increase of chlorine and UV dose. However, the ozone dose has little effect on the removal efficiency. Further experiments found that UV and ozone disinfection processes caused apoptosis and may cause ARGs to leak into extracellular as free DNA, bringing about environmental risks (Zheng et al., 2017). Also, another report suggested that the donor bacteria of the RP4

plasmid may decrease with increasing UV dose, contributing to a decrease in the frequency of conjugative transfer (Lin et al., 2016). As far as the authors are aware, there are few reports so far on the effects of UV and ozone on the ARGs in drinking water and the recovery of ARB after treatment, which need to be further explored in the future.

The removal or increase of the absolute and relative abundance of ARGs in each treatment process of DWTPs obtained from several studies were summarized in Table 1 and Table 2, respectively.

3.5 ARB and ARGs in drinking water distribution system

Water quality especially issues about biosafety in the pipeline network will directly impact the human health. It attracts more and more attention of the presence and dissemination of ARGs and ARB in the urban DWDSs recent years. For instance, the investigation of Xu et al. indicated that the absolute abundance of ARGs increased significantly after water distribution, especially the β-lactam ARGs, which increased from 1.08×10^7 copies/L in finished water to 5.12×10^8 copies/L (average value) in tap water. The relative abundance of most resistance genes also increased besides (Xu et al., 2016) (Fig. 3). Concerning this phenomenon, similar results were obtained by several other studies (Xi et al., 2009; Su et al., 2018). Furthermore, Faria et al. tested coagulase-negative *Staphylococci* (CNS) isolated from a DWDS in Portugal and found that it was less sensitive to β-lactam, tetracycline, clindamycin and erythromycin (resistance or intermediate phenotype). Further studies revealed that these CNS strains carried the *msrA*, *ermA*, *ermC* and *mecA* ARGs (Faria et al., 2009). These studies suggested that the urban DWDS may serve as an incubator for the enrichment of ARGs and ARB, and an important reservoir for opportunity pathogen to obtain ARGs (Xi et al., 2009), posing a serious threat to the health of residents.

Moreover, as far as we know, the presence and spread of antibiotic resistance in the building plumping systems has not been studied by scholars so far. The building plumping system contains a wealth of micro-ecological systems (Szewzyk et al., 2000), posing a potential threat to the safety of tap water. Due to the non-annular arrangement of pipes in the buildings, the long residence time of the water in the system, and the low concentration of disinfectant at the end of the pipeline (the faucet), it is favorable for the formation and growth of the biofilm (Ling et al., 2018). Besides, the diameter of the pipes in buildings is much smaller than the urban pipeline, increasing the contact area per unit volume of water and pipe wall biofilms, elevating the apparent reaction rate and may affect the detachment of the biofilms (Ji et al., 2015). Secondly, the roof tank of the building has always been considered as an important contamination source of building water supply (Rossman et al., 1995; Alizadeh Fard and Barkdoll, 2018). It is unclear whether it will affect the antibiotic resistance while deteriorating the water quality. In summary, these problems have a potential impact on the enrichment and spread of antibiotic resistance in the building plumbing system, which deserves in-depth study and exploration.

4 Factors impacting antibiotic resistance in urban drinking water system

4.1 Coagulants

The addition of coagulant and subsequent physical separation in the sedimentation tank are considered to be important factors in the reduction of ARGs in traditional

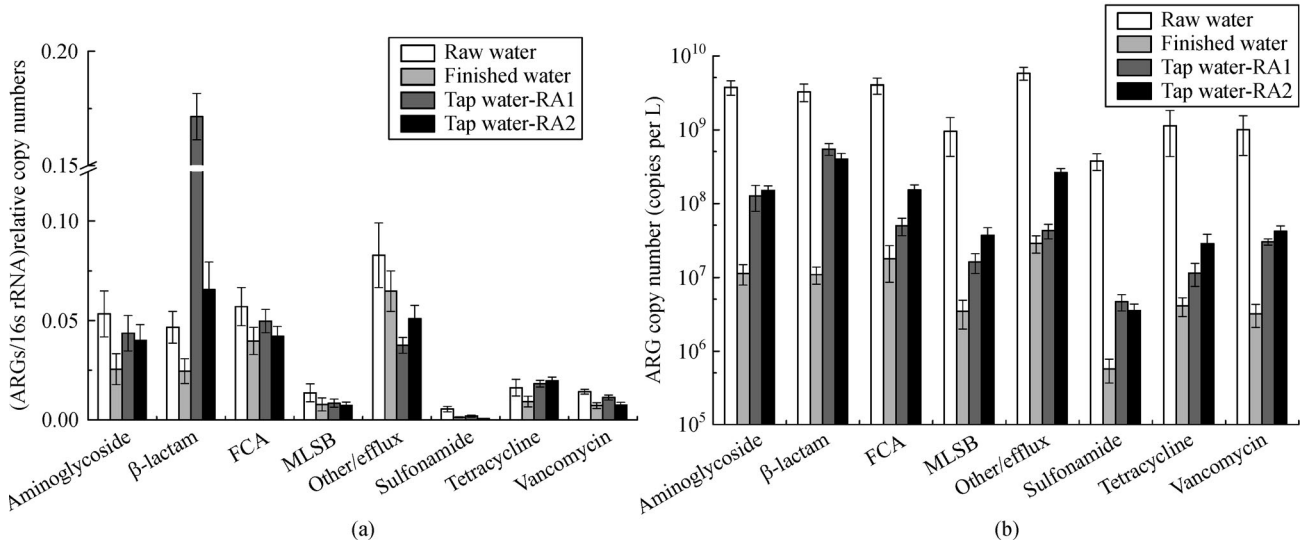


Fig. 3 The relative abundance (a) and absolute abundance (b) of the ARGs in raw water, finished water and tap water of a DWTP. RA1 and RA2 refer to the different residential areas. (Adapted from Xu et al. (2016) with permission from Elsevier Inc.).

water treatment process. Li et al. revealed a possible mechanism of the removal of ARGs from wastewater by coagulant $FeCl_3$ or polyferric chloride (PFC). Generally, after $FeCl_3$ dosing, the unstable ferric monomeric species Fe_a can be converted to positively charged colloidal or amorphous hydroxide precipitate species Fe_c through a series of hydrolysis processes. Thus, electric-double-layer compression and charge neutralization via Fe_a are the main removal mechanisms. As for PFC, however, polymeric species Fe_b are dominant in the PFC solution at basicity of 0.8. Therefore, the stable Fe_b could not be transformed into Fe hydroxide precipitate. Thus, adsorption, charge neutralization and entrapment by Fe_b may account for the removal of ARGs using PFC (Li et al., 2017). Furthermore, previous studies have reported that DNA can interact with clay minerals and various soil colloidal particles (Cai et al., 2006). Therefore, ARGs can be removed from water together with the colloid particles through enmesh and co-precipitation with Fe species (Aguilar et al., 2002).

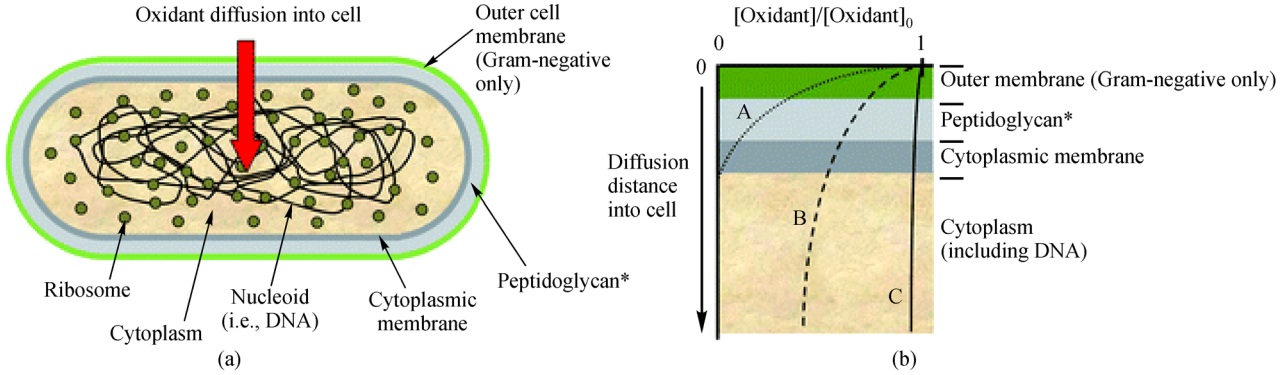
4.2 Toxic substances to bacteria and HGT

Disinfectants are the main toxic substances added artificially in drinking water in order to control microorganisms. Theoretically, it can be expected that the disinfection process can reduce the abundance of ARB and ARGs, due to the lethal effect of disinfectants on the microorganism. However, as illustrated before, studies have revealed that the practical disinfection process cannot completely remove ARGs in the water (Huang et al., 2011; Wen et al., 2016), even presented a potential risk of increasing the relative abundance of ARGs through various mechanisms (Xi et al., 2009).

Chlorine is one of the most widely utilized disinfectants in water treatment. According to Dodd (2012), HOCl, which acts as the main disinfection substance in the chlorinated water, is an oxidant with moderate to high reactivity toward amino acids, purines, pyrimidines, nucleic acids, etc., but low reactivity to lipids and sugars (oxidant B in Fig. 4), which means it possesses the ability to react with cell wall constituents but also pass into the cytoplasm and degrade the intracellular DNA (Dodd, 2012). To reduce chlorine odor and increase the duration of residual chlorine in the DWDSs, it is often added ammonia into water before chlorination to form chloramine for drinking water disinfection (Haas et al., 1992). In analogy to oxidant C in Fig. 4, NH_2Cl is an oxidant with much weaker reactivity compared to the free chlorine. Thus it can be expected to diffuse into and accumulate within cells much more effectively and build up to levels in the cytoplasm at which the kinetics of NH_2Cl can react with DNA significantly thereby deactivate the cells (Dodd, 2012).

Based on the research results of academia, the mechanisms of how chlorine promoted ARGs in drinking water can be summarized as follows:

1) Co- and cross-resistance of antibiotics and disinfectants. Huang et al. found that the average resistance to tetracycline of tetracycline resistance bacteria was improved in the case of a high dose of chlorine ($>$ 1.0mg/L) and contact time of 10 min, indicating that high dose of chlorine can present a screening effect on ARB (Huang et al., 2013). Besides, Jia et al. found that the relative abundance of chlorine-tolerant *Pseudomonas* and *Acidovorax* was greatly elevated after chlorination, which were the most important hosts of *bacA* and multidrug resistant genes (Jia et al., 2015). Accordingly, greater frequency of chlorine tolerance among antibiotic-resistant *Escherichia coli* has been found as compared to antibiotic-sensitive *E. coli* grown in the chlorine system (Templeton et al., 2009). This phenomenon may be caused by the presence of integrons which transfer both antibiotic and disinfectant resistance genes (Chen et al., 2015). As for cross-resistance mechanism, a physiologic process such as



*Gram-positive cells have a thick peptidoglycan layer, while Gram-negative cells have a thin peptidoglycan layer surrounded by protein-rich periplasm.

Fig. 4 Overview of (a) a generic vegetative bacterial cell, and (b) variations in concentrations of several hypothetical oxidants with increasing diffusion distance into the cell (where "A" represents an oxidant with high reactivity toward cell envelope constituents, "B" represents an oxidant with moderate reactivity toward cell envelope constituents and DNA, and "C" represents an oxidant with low reactivity toward all cell constituents) (Reproduced from Dodd (2012) with permission from The Royal Society of Chemistry).

efflux pumps, impermeable barrier and the inhibition of molecular transport can be resistant to disinfectants as well, may be responsible for the cross-selection of both antibiotics and disinfectants (Krige, 2009).

2) Under the pressure of the disinfectants, some bacteria show higher rate of HGT and mutation, promoting the acquisition of ARGs. Guo et al. demonstrated that low-dose chlorination (less than 40 mg active Cl min/L) significantly increased the conjugation frequency of *E. coli* Gram-negative strains in wastewater by 2−5 times compared to the control group. The related mechanism was that chlorine reacted with ammonia in water to form chloramine, increasing the permeability of cell membrane, and enhancing the outflow of ARGs from the donor bacteria and the reception of the recipient consequently (Guo et al., 2015). Zhang et al. had confirmed that disinfectants at sub-inhibitory concentration could promote the conjugation transfer of ARGs intra-genera. 0.1−1 mg/L of free chlorine and chloramine were adapted, turned out that the intra-genera conjugation transfer was increased by 3.4−6.4 and 1.9−7.5 times, respectively. (Zhang et al., 2017). ROS formation, SOS response, increase of cell membrane permeability, and the expression of outer membrane protein-encoding genes and conjugative transfer related genes may be responsible (Zhang et al., 2017). Abundance of MGEs including integrons, insertion sequences and plasmids was also found to be elevated after chlorination, leading to the acceleration of mobility of the ARGs (Shi et al., 2013). Furthermore, it has been reported that chloramine had a mutagenic effect on the cells of *Bacillus subtilis*, which may also promote the acquisition of ARGs (Shih and Lederberg, 1976).

Other toxic substances such as disinfection by-products (DBPs) and heavy metal could also promote antibiotic resistance. Lv et al. studied four typical DBPs: dibromoacetic acid, dichloroacetonitrile, potassium bromate and MX, which found that, bacterial resistance to 10 types of antibiotics and multi-resistance were elevated after the exposure of DBPs, in which norfloxacin and polymyxin B resistance were more than 10 times higher than the control group. These results demonstrated that the mutagenicity of DBPs could induce the antibiotic resistance (Lv et al., 2014). Studies had shown that the increase of the abundance of ARGs was related to the selective pressure of heavy metal ions, which was because the heavy metal resistance genes and the antibiotic resistance genes were distributed on the same plasmid, posing a co-selection effect on antibiotic resistance (Baker-Austin et al., 2006; Xu et al., 2017). Zhang et al. established a copper shock loading test, which revealed that the heavy metal co-selection occurred rapidly within 6 h, 10 and 100 mg/L of copper increased bacterial resistance to the rifampin, erythromycin, kanamycin, etc. The relative abundance of most genes, especially intergon I and transposons, was dramatically increased (Zhang et al., 2018b). In DWDSs, since the biofilm with stable structure is more likely to cause accumulation of heavy metal salts, the co-selection of heavy metals may occur more easily in the pipe networks, leading to the enrichment of ARGs.

4.3 The occurrence of biofilm and HGT

In various environments, microorganisms often attach themselves to biotic or abiotic surfaces to form intricate matrices based on biopolymer, known as biofilm. BAC process, known as removing organic substances and pollutants partly by biodegrading, could carry a high concentration of biomass and consequently generate biofilm on the surface of activated carbon. Besides, as various chemical and biochemical reactions occur through the water distribution, including corrosion (biological and abiotic) and disinfectant depletion, the growth of biofilm also commonly occurred in DWDSs (Ling et al., 2016)

The mechanisms of biofilm promoting the proliferation of ARB and the spread of ARGs in drinking water system are mainly as follows:

1) Microorganisms are more resistant to adverse conditions such as chemical stressors in the biofilm matrix (Balcázar et al., 2015). Generally speaking, in response to the adverse environment, microorganisms attach to biofilms to survive from disinfectants and other toxic substances. Since the microorganisms in biofilms live in a self-produced matrix of hydrated extracellular polymeric substances (EPS) that form a relatively nutrient-rich environment, which immobilizes biofilm cells, keeping them in long-term close proximity and, thus, allowing intense interactions to occur (Flemming and Wingender, 2010). Besides, it can also protect bacteria by inhibiting the penetration of residual chlorine into the interior, and when the concentration of disinfectant is reduced to a certain extent, it can no longer continue to inactivate bacteria (Stewart, 2003; Liu et al., 2017).

2) The high cell density in the biofilm structure, as well as the accumulation of MGEs and ARGs in the biofilm matrix, leading to a more frequent and effective communication between cells, and a promotion of the acquisition and dissemination of ARGs conducted by HGT (Sørensen et al., 2005; Guo et al., 2018). Study showed that the multidrug resistance of *S. aureus* cells in biofilm was 10000 times higher than that of free cells (Savage et al., 2013), supporting this view. Previous study illustrated that, more than 95% of the biomass in the DWDSs was present in the biofilm on the wall while only 5% of the bacteria in the water presented as suspended form (Flemming et al., 2002). Relatively high frequency genetic communication caused by high biomass in biofilms and the suitable environment for bacterial survival created an ideal condition consequently for dissemination of ARGs and proliferation of ARB. Furthermore, Molin et al. also pointed out that the efficiency of gene transfer seemed to

be related to the biofilm surface area: A higher surface area to volume ratio was more beneficial for gene transfer (Molin and Tolker-Nielsen, 2003).

3) The regulation by quorum sensing (QS) on bacterial community is also a vital factor of ARG transfer. QS refers to the community behavioral responses of cells that rely on the signal molecules to regulate gene expression program and thus affecting physiologic activities (Papenfort and Bassler, 2016). Up to now, it has been confirmed that QS played an important role in regulating the stable biofilm structure and conjunctive gene transfer of plasmid (Davies et al., 1998; Zheng et al., 2018). An experiment of conjugative transfer of resistant plasmids recently proposed a hypothesis on the promotion of antibiotic resistome by QS in BAC biofilm. Results revealed that the 6 selected Acyl-Homoserine Lactones (AHLs) had more or less influence on plasmid-based HGT in the intra-genus mating systems by up to 30-fold higher than that of the control group (Zheng et al., 2018), inferred that the QS related signaling molecules could accelerate the conjugative transfer of ARG (Zheng et al., 2018). This hypothesis may shed a new light on alleviating ARG tranfer in biofilm by controlling QS.

4) The interaction of biofilm and water flow triggered an increase of ARGs in drinking water. Xu et al. found a high concentration of MGEs (1.13×10^8 copies·L^{-1}) and an increase of the concentration of ARGs in the effluent water of BAC process. Besides there was a significant positive correlation between ARGs and MGEs, indicating that HGT could occur not only between bacteria in biofilms, but also between bacteria in the aqueous phase flowing near the biofilm (Xu et al., 2016). In addition, the detachment of biofilm causing by the scouring action of water flow may cause bio-contamination in DWDSs. Studies found that when the biofilm grown to maturity, the differentiation of part of the cells with high fluidity occurred, which left the biofilm into the water accompany with some extracellular substances (e.g. EPS) (Yan et al., 2017). Besides, changes of environmental factors such as wall shear stress (Luo et al., 2017), nutrient deficiency (Proctor et al., 2017), low dissolved oxygen (Mao et al., 2008), and the presence of residual chlorine (Shen et al., 2016) could also influence attachment and detachment of biofilm. For example, Shen et al. found that biofilm could grow stiffer under disinfectants exposure, and thus the detached *Legionella pneumophila* could be inactivated more easily (Shen et al., 2017). Zhang et al. used bacterial annular reactors to simulate the biofilm detachment in actual DWDS, and investigated several bacteria with resistance of tetracycline, sulfamethoxazole, etc. The results showed that the ratio of ARB in biofilm and effluent was higher than that in the influent. The high-throughput sequencing revealed that the relative abundance of *Acinetobacter*, *Sphingomonas* and Slow-growing *Rhizobium* in effluent and biofilm was higher than influent. Several antibiotic resistant species were also detected in these bacteria, suggesting that chlorine and chloramine can promote bacterial detachment from biofilms, which may be responsible for increased antibiotic resistance in effluent water (Zhang et al., 2018a) (Fig. 5).

5 Antibiotic resistance in drinking water and human health

Undoubtedly, the ultimate purpose of most research about the fate of ARB and ARGs in drinking water system was reducing the risk of threatening human health by antibiotic resistance. Although quiet a lot studies proved the presence of ARB and ARGs in tap water, as illustrated before, the studies associated with assessing risk of antibiotic resistance transmission to human from drinking water were still in their infancy, without which the value of subsequent studies about controlling antibiotic resistance in drinking water could be limited. It is worth noting that transmission of ARB in drinking water to human by oral contact may not cause infection in a short period. In contrast, it can be a long-term and eventually cumulative silent colonization, and develop to an infection only if the host reaches an immunocompromised state (Manaia, 2017). Hence, according to Manaia, combining current research on antibiotic resistance in drinking water, there

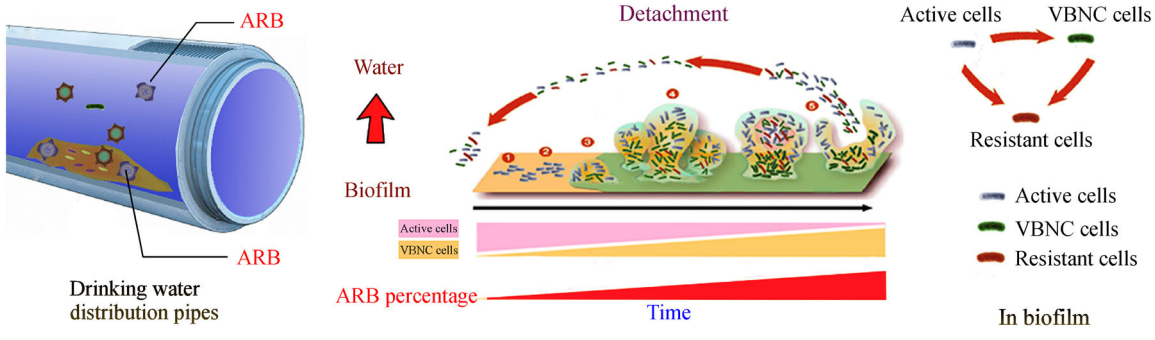


Fig. 5 The biofilm formation and detachment and the transmission of bacterial antibiotic resistance in drinking water distribution systems. (Reproduced from Zhang et al. (2018a) with permission from Elsevier Inc.).

were four main steps of risk assessment: 1) Identification of ARB/ARGs and their ability of HGT in drinking water, which has been demonstrated comprehensively by previous studies (compared to subsequent steps). 2) Evaluation of the occurrence of ARB that are able to colonize the human body in drinking water. 3) Evaluation of the doses of ARB identified in (2) that are sufficient to colonize human, that is, whether the ARB have a high capacity of colonize human or a low infectious dose. 4) Assessing the risk by combining the results of the previous three steps (Manaia, 2017). Up to now, Ma et al. have provided a novel method to identified ARG-carrying bacteria in tap water by host-tracking analysis, which was associated with step (2). They used metagenomics sequencing method, assembled and taxonomic annotated ARG-carrying contigs (ACCs), and revealed that 34.5% ACCs were classified as fragments of *Pseudomonas*, among which one contig was assigned to β-lactamase resistance gene carrying *P. aeruginosa* (Ma et al., 2017). Based on these analyses and research results, future studies are supposed to focus on the taxonomy of ARB in drinking water and the ability of them to express virulence factors, and how to determine the doses of ARB which are sufficient to colonize human body or cause an infection by combining environmental monitoring and clinical techniques.

6 Summary and outlook

In conclusion, it is commonly accepted that the conventional process is more promising on ARGs removal compared to the advanced treatment process in DWTPs, but the removal mechanisms of coagulation, sedimentation and filtration process are still not clear. BAC filters, especially GACs, often cause enrichment of ARGs due to the biofilm attached, which could subsequently contaminate the treated water. However, PAC may slightly remove ARGs in contrast. The disinfection process in DWTPs can reduce the absolute abundance of ARGs and increases their relative abundance by inducing the HGT, which is supported by most relative studies. Besides, previous studies also indicated that the DWDSs could serve as incubators of antibiotic resistance, causing the enrichment of ARGs and ARB in tap water.

To ensure the biosafety of tap water, the assessment of risk of antibiotic resistance is considered as an urgently needed work. We believe it would be a challenging but valuable work to track host bacteria of ARGs which can cause infectious disease or colonize human, and assess their expression of virulence factors based on both culture-dependent and culture-independent techniques.

Subsequently, it may be another important direction of research to study how to adjust process parameters or adapt new processes to reduce antibiotic resistance in drinking water. Based on previous analyses in this paper, here we would like to propose several interesting points of view about controlling antibiotic resistance:

1) Due to the promising effect of removing ARGs through chemical-physical process of coagulation process, which coagulant and dosage shows the superior removal performance needs to be explored.

2) It may be a novel way to control bacteria QS by blocking signaling molecules and reduce conjugative transfer of ARGs in biofilm consequently.

3) It should be explored whether disinfection technology including UV, O_3 and copper-silver ionization equipped in the building plumbing system could serve as an effective way to control ARB at the point of use.

Overall, there are fewer studies on the fate of ARGs and ARB in urban drinking water systems recently than in wastewater treatment, due to the oligotrophic environment, the lack of biomass and the difficulties of sample collection, but we believe a better understanding of their removal and spread would assist in controlling the risk to public health.

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