What is the effect on antibiotic resistant genes of chlorine disinfection in drinking water supply systems? A systematic review protocol

Esfandiar Ghordouei Milan1, Amir Hossein Mahvi1,2, Ramin Nabizadeh1,3 and Mahmood Alimohammadi1,3,4,5*

Abstract
Background: Antibiotic-resistant bacteria (ARB) usually enter water sources in different ways, such as via municipal and hospital wastewaters. Because conventional technologies used to treat water inefficient in removing these contaminants (especially antibiotic-resistant genes; ARGs), these contaminants easily enter drinking water distribution networks and pose serious threats to consumers’ health. This study’s main purpose is to systematically investigate the effect of chlorine disinfection on ARGs in drinking water supply systems. This study could play an important role in elucidating the effect of chlorine disinfection on ARGs.

Methods: The systematic review outlining this protocol will be performed according to the Collaboration for Environmental Evidence (CEE) guidelines. The main question is, “what is the effect of chlorine disinfection on ARGs in drinking water supply systems?” For this purpose, the articles will be considered, in which chlorine’s effect on ARGs is investigated. The search includes electronic resources, grey literature, and related websites. Electronic resources include Scopus, PubMed, Embase, Web of Science Core Collection, and Science Direct. After the final search, the obtained articles will be collected in the reference management software (Endnote X8). Upon removing the duplicate articles, the first stage of article screening will be performed based on the title and abstract the articles. In the second stage, the articles obtained from the first screening stage will be screened based on the full text of the articles based on the eligibility criteria. Then, two members of the expert team extract the data. To assess the validity of the articles, bias sources will be determined by an expert team. Biases will be defined according to the criteria designed by Bilotta et al. Finally, a narrative synthesis will be performed for the extracted data; if appropriate data are available, quantitative analysis will also be performed.

Keywords: Antibiotic-resistant bacteria (ARB), Antibiotic-resistant genes (ARGs), Drinking water, Water supply, Drinking water treatment plant, Chlorination, Disinfection
antibiotic resistance to the world economy could reach 100 billion US dollars by 2050 [7–9]. According to World Health Organization (WHO), if immediate action is not taken to combat antibiotic resistance, humans will face deadly infections in the “post-antibiotic era” that can take decades to cure [10]. ARBs enters water sources through municipal wastewater, hospital wastewater, municipal waste, agricultural waste, manure used as fertilizer on agricultural lands, runoff and even the effluent of some industrial treatment plants [11, 12]. After discharge, these contaminants enter surface water and, sometimes, groundwater. Because conventional technologies used for water treatment cannot efficiently remove these contaminants (especially ARGs) [13, 14], and thus, they may easily enter the drinking water distribution networks and turn into a serious threat to consumer health. Some studies have shown that ARBs and ARGs are present in bottled water, wells, rivers, lakes and various sources of drinking water [8]. ARBs and ARGs have also been recorded in drinking water treatment plants and drinking water distribution networks [10, 15]. Genes are transmitted between the bacteria in natural environments and engineering systems such as water and wastewater treatment plants [16]. Water supply systems can act as a suitable reservoir for transferring ARBs and ARGs from the aquatic environment to humans [17]. The main concern is that ARGs (which by themselves pose a little risk) can be easily passed through the water treatment system and transmit resistance to bacteria in the distribution network, including pathogenic bacteria. In this way, they pose serious threats (such as death, deadly and, sometimes, long-term infections) to human health. This expansion of potential bacterial resistance can be accomplished through horizontal transfer of genes (HGT), plasmids, transposons and integrons among different bacterial species [8, 18–21]. In large cities, drinking water is often supplied from surface water resources close to the city after proper and strict treatment processes [22]. The water treatment plant uses various processes such as flocculation, sedimentation, filtration and disinfection to improve water quality. Among these processes, disinfection is the most important process for controlling microorganisms that reach the point of consumption from the treatment plant [23]. Chlorine is used as a disinfectant in drinking water supply systems in many countries due to its cost-effectiveness and simplicity of use [24]. It plays an important role not only in killing bacteria, but also in stabilizing the microbial conditions of water in the distribution network [25, 26]. Recent findings show that chlorine may increase the number of ARGs in drinking water [25, 27, 28]. Depending on the concentration of chlorine in the water, bacteria use different strategies to resist and transmit ARGs [17, 29]. In some studies, the frequency of mobile genetic elements (MGEs), including integrons and plasmids, increases after chlorination, which accelerates ARG transfer [20, 25, 30]. The results of some studies show that chlorination increases ARGs [22, 25, 28], while the results of some other studies indicate a decrease in ARGs after chlorination [31–34]. Therefore, there is debate among researchers and scientists about the effect of disinfectants, especially chlorine, on ARBs and ARGs. Since we did not find any systematic reviews in literature in this field. According to the overview we have done in this area, several review studies have investigated the effect of the chlorination process on ARGs in municipal and hospital wastewater [35–40]. Some reviews have investigated the impact of disinfectants on ARGs in biofilms [41]; others have studied the effect of chlorine on intracellular ARGs [42]; furthermore, others have examined the effectiveness of various treatment technologies and processes in removing ARGs from different aquatic environments [43–46]. Nevertheless, no systematic review article has explicitly investigated the effect of chlorine on ARGs in drinking water supply systems; however, there are several reviews in a similar field that have examined the presence, dissemination and removal of ARG in raw and drinking water. In addition to chlorine, these articles have investigated other processes such as ozone, UV, ultraviolet light and, sometimes, biological activated carbon (BAC) [8, 17, 44, 47, 48]. Because these reviews are not “systematic” and have considered various treatment processes, the effect of chlorine on ARGs has not been studied in details. Thus, the present review can play an important role in elucidating the role of chlorine disinfection on the removal of ARGs. No organization, institution, or individual will be engaged in designing and conducting this study except the authors. Therefore, this study does not have stakeholder engagement.

Objective of the review

The main purpose of the present work is to investigate systematically the effect of chlorine disinfection (the most widely used disinfection in water supply systems) on ARGs of drinking water supply systems. It is not clear exactly what type of effect chlorine can have on ARGs. Herein, this review explains the effect of chlorine and its compounds on ARGs in drinking water supply systems. It can indicate which ARGs are most present in disinfected (chlorinated) drinking water. It also shows at what dosages chlorine is the most effective in terms of limiting and inactivating ARGs.

Primary question

“What is the effect of chlorine disinfection in drinking water supply systems on ARGs?” The question includes the following components: Population: Drinking water
supply systems such as springs, wells, treatment plants and drinking water distribution networks; Intervention/exposure: Chlorine and chlorine compounds are added to drinking water as a disinfectant; Comparator: The presence of ARGs pre/post chlorination comparison; Outcome: The abundance and presence of ARGs after drinking water chlorination.

Secondary questions

1. What ARGs are the most commonly present after chlorination?
2. What are the maximum and minimum effects of chlorine dosages on ARGs?
3. What is the optimal chlorine contact time for inactivating or limiting ARGs?

Methods

This protocol, along with the systematic review outlined, will be performed according to the Collaboration for Environmental Evidence (CEE) guidelines for systematic review and evidence synthesis in environmental management [49], and will be reported according to ROSES reporting standards for systematic review evidence syntheses (see Additional file 1) [50]. This systematic review protocol has been registered in the PROSPERO database (Registration Number: CRD4202124307).

Searching for articles

In this study, for the scoping exercise, the articles investigating the effects of chlorine on ARGs were considered. At first, a pre-search was performed to determine the approximate number of articles in this field. The articles obtained in this stage were reviewed quantitatively and qualitatively. Also, search terms were identified. After consultation and discussion with the team members, the search strings were revised. High-sensitivity search strategies were designed to identify most of the evidence in this field. The expert team developed a search strategy for each database based on PICO/PECO framework. In the next stage, the search will be based on the published reviews on the topic and suggestions from expert team members in at least four areas, including electronic databases, grey literature, related websites and contact with the authors. The electronic databases included are Scopus, PubMed, Embase, Web of Science Core Collection and Science Direct. We will use Boolean operators to combine search terms and substrings. The 'OR' operator will be used to combine synonym terms that increase search sensitivity. The 'AND' operator will be used to combine the components of a research question (PICO/PECO framework); this will limit the search and increase the search accuracy for retrieving the related articles. It is usually not recommended to use the 'NOT' operator because it may cause the loss of some of the related articles, but to limit a large number of irrelevant articles and specificity of the topic, the 'NOT' operator will be used in this case. Asterisk (*) will be used to include the different search term characters. Finally, if not accessible by the usual retrieval of articles, authors will be directly contacted to request the full texts of their publications [51, 52].

Language

The primary search was conducted in Persian and English. However, due to the lack of related studies in Persian, the final search will be limited to English and we will not have a time limit.

Estimating the comprehensiveness of the search

To evaluate the performance of the search strategy, a test list (see Additional file 2) of 15 articles was collected from primary search, experts and previous reviews according to the method used by Livoreil et al. [51]. At first, our search strategy could not retrieve the test listing articles; we changed the search strategy again until it retrieved all the test listing articles. Our search strategy was able to find all the test list articles. In addition, we reviewed references to the relevant articles obtained in the search based on the existing search strategy. Most of the relevant articles were found in the references in our search strategy, which confirmed the proper functioning of our search strategy.

Publication databases

Search terms will be searched in Scopus based on “TITLE-ABS-KEY”, PubMed based on “MeSH”, Embase based on “EMTREE”, Web of Science Core Collection based on “Topic” and Science Direct based on “Title, abstract or author-specified keywords”. Search strings will be used to search the following five databases (see Additional file 3).

- Scopus (http://www.scopus.com);
- MEDLINE using PubMed (https://pubmed.ncbi.nlm.nih.gov);
- EMBASE (http://www.embase.com);
- Web of Science Core Collection (https://webofknowledge.com); and
- Science Direct (http://www.sciencedirect.com).

Example of a search string in PubMed:

("Drinking Water"[Mesh] OR "Fresh Water"[Mesh] OR "Water"[Mesh]) OR "Water Resources" [Mesh] OR "Water Supply"[Mesh] OR "supply and distribution"
Internet searches
Internet search will be done in Google Scholar. We will search Google Scholar using the Publish or Perish software. The search will be done based on a simplified search string (see Additional file 4) then the results of the first 1000 hits will be downloaded.

Specialist searches
Searching for the systematic study will not be limited to electronic databases. Also, it will be done to minimize the bias caused by publishing separate searches in grey literature and websites. In this context, our search will be limited to the keywords “drinking water”, “drinking water treatment plant”, “water supply”, “tap water”, “distribution system”, chlorine*, disinfect*, “antimicrobial resistance”, “antibiotic resistance”, “antibiotic resistant”. These keywords will be used in most searches for grey literature, but are not the same for all the sources and vary according to the source. Searching in grey literature will be done in the following databases and websites [51] (see Additional file 5).

- ProQuest Dissertations and Theses Global;
- Open grey literature in Europe;
- World Alliance against Antibiotic Resistance;
- Center for Antibiotic Resistance Research;
- Centers for Disease Control and Prevention;
- European Committee on Antimicrobial Susceptibility Testing;
- Open Access Theses and Dissertations (OATD);
- Food and Agriculture Organization of the United Nations (FAO);
- British Library for Development Studies (BDLS);
- British Library e-theses online service;
- Directory of Open Access Journals; and
- Bielefeld Academic Search Engine.

Supplementary searches
For supplementary searches, citation chasing will be used to identify the potentially relevant studies. If not accessible by the usual retrieval of articles, authors will be directly contacted to request the full texts of their publications.

Search updating
Evidence is constantly evolving. New studies are always likely to be undertaken and published. Therefore, if necessary, a search strategy update for all the resources will be performed before the final analysis. The searches will be updated before publication if this systematic review takes more than a year.

Article screening and study eligibility criteria
Screening process
After the final search, the articles will be collected in the reference management software (Endnote X8). After removing the duplicate articles, screening will be done in two stages (according to Fig. 1). The first screening stage
will be based on the title and abstract of the articles. In the second stage and upon full text retrieval, the relevant items will be screened based on the full text criteria. The full text of articles that are not found will be obtained by contacting the authors. For three levels, two team members will perform the screening. In the case of disagreement between the two reviewers, the third reviewer will give the final opinion. All the team members will review articles that have been excluded at the full-text screening level. The project manager will double-check all the excluded articles to verify that no relevant articles are inappropriately excluded [53, 54]. For the procedural independence, we followed the method proposed by Ebrahimi et al. [55]. Systematic reviewers (who have also authored articles to be considered within the review) will not participate in decisions regarding inclusion or study validity assessment of their own work. The reasons for excluding the articles in the screening process (full text) should be reviewed by all the team members and will provide a list of full text articles excluded with reasons for their exclusion.

Eligibility criteria

Eligibility criteria are described in Table 1. Before screening all the articles (pre-screening), 10% of the articles (minimum 50) randomly will be screened by two reviewers, and Kappa tests will be calculated as a part of consistency checking and to assure consistency among reviewers. The reasons for excluding the articles in the screening process (full text) should be reviewed by all the team members and will provide a list of full text articles excluded with reasons for their exclusion.

| Table 1 Eligibility criteria |
|-------------------------------|
| **Type of study** | Original articles, studies presented in theses and conferences | Books, letters to editor, review studies (literature reviews, systematic reviews, and meta-analysis), risk assessment and modeling studies |
| **Language** | English | Non-English papers |
| **Population** | Water treatment plants, water sources (springs and wells) used as drinking water after disinfection with chlorine and chlorine compounds (such as Cl₂, Ca(OCl)₂, NaOCl) | Municipal wastewater, hospital wastewater, sewage, surplus water, runoff |
| **Intervention/exposure** | Contact with chlorine and its compounds disinfectant | Contact with other disinfectants (UV, O₃, etc.) |
| **Outcome** | Report of ARGs in chlorinated disinfected water prevalence or concentration of ARGs | No report of ARGs in water before and after chlorine disinfection or only report ARB |
| **Study design** | Observational studies (cross-sectional studies) and experimental studies (such as pilot): 1. Study designs with appropriate comparators, including before/after, control/treatment, different interventions (chlorine dosage) as well as studies including both these types of comparisons will be included 2. Studies examining the presence or prevalence of ARGs in chlorinated drinking water | – |
| **Geography** | This review is not limited to geographical area (it is global) | – |
| **Period** | No time limit | – |

Study validity assessment

The team manager will check again all the articles excluded from the screening process before evaluating the validity of the articles. To evaluate the validity of studies and the internal validity of each included study, sources of bias will be determined by an expert team according to the criteria designed by Bilotta et al. [57, 58] and the criteria defined by Schindler et al. [59]. Table 2 includes the bias assessment framework of the articles. The bias areas include: (1) selection and performance, (2) measurement of outcome, (3) publication and (4) other biases. The score range for each article will be in the range of 0–100. Articles will be classified into three categories with low, medium and high bias. Articles with a score of higher than 67 will be placed in the low bias article class, articles with a score of 33–67 will be placed in the class with moderate bias, and articles with a score below 33 will be placed in the high bias class (see Additional file 6). Articles in category with high bias will be excluded from the quantitative synthesis.

External validity to determine the generalizability will be assessed using the eligibility criteria in the section above. We will consider for external validity: population (drinking water treatment plant/distribution network/
tank/transmission line/tap water), disinfection (chlorine and its compounds), study scale (pilot/field) and presentation of results (absolute versus relative abundance) as well as global susceptibility to bias (low external validity if definitively low internal validity). The critical appraisal could be used to qualify conclusions (i.e., weight studies in the synthesis) if we find a large variance in biases among studies. To assess accuracy in validity assessment, the validity assessment will be conducted on a random sample (at least 20% of the articles) by two reviewers. Disagreements will be resolved after discussion, with the opinion of the third reviewer. Finally, all the included articles will be controlled and confirmed by the team.

**Data coding and extraction strategy**

We will extract raw data from appraised full texts. The extracted data will be recorded on a pre-configured Excel spreadsheet (see Additional file 7). In accordance with

| Bias area                               | Characteristic                      | Bias assessment                                                                 | Bias score |
|-----------------------------------------|-------------------------------------|---------------------------------------------------------------------------------|------------|
| Selection and performance bias: study design | Sampling                            | Description of sampling method and transfer of samples to the laboratory        | 10         |
|                                         |                                     | Description of the sampling method or transfer of samples to the laboratory     | 5          |
|                                         |                                     | Method of sampling and transfer of samples to the laboratory is not described    | 0          |
| Sample size                             | Number of samples > 5 or sample size > 10 L |                                                                                 | 10         |
|                                         | Number of samples < 5 or sample size < 10 L |                                                                                 | 5          |
|                                         | Lack of sample size and number of samples |                                                                                 | 0          |
| Replicates                              | Replication of samples               |                                                                                  | Yes [10]   |
|                                         |                                     |                                                                                 | No [0]     |
| Study timeframe                         | Sampling time of more than two seasons (cold and hot seasons, winter and spring or summer) |                                                                                  | 10         |
|                                         | Sampling time of less than two seasons (hot or cold seasons) |                                                                                | 5          |
|                                         | Sampling time is not described       |                                                                                 | 0          |
| Assessment bias: measurement of outcome | Detection of ARGs                    | The laboratory method and DNA extraction are clear (such as PCR, qPCR, HT-qPCR, high-throughput sequencing (HTS)) | 10         |
|                                         |                                     | Metagenomics                                                                    |            |
|                                         |                                     | Laboratory methods and DNA extraction are unclear or not described               | 0          |
|                                         | Chlorine measurement                | Using standard methods to measure chlorine (exposure)                           | 10         |
|                                         |                                     | Using non-standard or unknown methods to measure chlorine (exposure)             | 0          |
|                                         | Confounders                         | Measuring confounding factors and their effects are applied (such as pH, temperature, DO, TOC, phosphate, and nitrate) | 10         |
|                                         |                                     | Measuring confounding factors, but their effects are not applied                 | 5          |
|                                         |                                     | Unmeasured confounders                                                          | 0          |
| Bias linked to clarity and publication bias | Statistical analyses               | Using and describing the statistical data analysis method                      | Yes [10]   |
|                                         |                                     |                                                                                 | No [0]     |
|                                         | Reporting bias                      | All the statistical tests, measurements, and variables mentioned in methods are reported in the results or additional files | Yes [10]   |
| Other biases                            | Detection bias                      | Having significant differences in the results before and after chlorination     | Yes [10]   |
|                                         |                                     |                                                                                 | No [0]     |
|                                         | Attrition bias                      | Measuring the concentration or frequency of ARGs before and after chlorination  | Yes [10]   |
|                                         |                                     |                                                                                 | No [0]     |
|                                         | Research aim consistency            | Objectives of the study are clearly stated and the answer is consistent with the objectives | Yes [10]   |
|                                         |                                     |                                                                                 | No [0]     |
the pre-designed form, author, year of publication, location of study, sample size, type of study (bench, pilot or full scale), laboratory method, type of ARGs, concentration of ARGs, removal rate of ARGs, type of ARBs, type of antibiotic, type and dosage of used disinfectant, type of water such as springs, wells, surface water, groundwater, properties of water such as temperature, pH, DO, total organic carbon (TOC), nitrate and phosphorus as well as existence or absence of biofilm (in the form of existence) will be extracted from the full text of the articles. In the case of incomplete data, the authors of the article will be contacted and the complete data will be obtained. To reduce bias in data reporting and ensure all data are extracted correctly, data extraction will be performed by two team members (at least for 10% of the articles). Moreover, in case of disagreement, the article will be reviewed by the rest of the team [54–56].

Potential effect modifiers/reasons for heterogeneity
Potential effect modifiers will be identified and recorded from the included articles. In this study, several factors may cause heterogeneity:

- Type of drinking water source (such as springs, wells, surface water, groundwater, water treatment systems, and drinking water distribution network);
- Properties and characteristics of the drinking water sources (physical, chemical, and biological quality);
- Study design (pilot or field);
- Type of chlorine compounds and dosage of chlorine;
- Monitoring duration;
- Sample size or number of samples;
- Laboratory methods for detection and measuring ARGs [such as PCR, qPCR, HT-qPCR or high-throughput sequencing (HTS)];
- Type of ARGs; and
- Study location.

The list (potential effect modifiers) will be reviewed and completed by the expert team after consultation (if necessary).

Data synthesis and presentation
Narrative synthesis will be done for all the included articles. The results will be summarized in the tables and figures, and will be accompanied by an interpretation and discussion. Quantitative data analysis will be done for those articles that meet the requirements for quantitative synthesis. ARGs and chlorine doses will be presented based on the mean and standard deviation. Studies with different methods of measuring ARGs concentrations will be analyzed separately. If the studies have sufficient and similar data, meta-analysis (using random-effects models) can be used to analyze the data. Studies with incomplete or missing data will not be included in the meta-analysis. If heterogeneity exists, meta-regression analyses or Cochrane’s Q test will be done depending on the study process to assess between-study heterogeneity. The I² test statistic can be used to measure the extent of this heterogeneity. A funnel plot comparing the study effect size with the standard error may be used to check the publication bias.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1186/s13750-022-00266-y.

Acknowledgements
This work is part of the MSPH thesis of the first author. The authors wish to thank the financial support from the Department of Environmental Engineering of the School of Public Health Tehran University of Medical Sciences (TUMS). (Project No. 98-01-27-39639)

Authors’ contributions
The authors of the present protocol declare that they have cooperated in the formulation of the question, ideas and writing of the protocol. EGM: describing literature research method, study screening, data extraction, evidence evaluation, content drafting and approval and statistical analysis (if applicable); AHM: systematic review methods consultation, content review and approval; RN: microbiology consultation, statistical consultation, systematic review methods consultation, content review and approval; MA: study screening, data extraction, evidence evaluation, content review and approval. All authors read and approved the final manuscript.

Funding
Tehran University of Medical Sciences, through its Research Vice-Chancellor, funded the systematic review protocol described here. This study is related to theses number IR.TUMS.SPH.REC.1399.297, Tehran University of Medical Sciences, Tehran, Iran. Tehran University of Medical Sciences supports this protocol (as a part of a Master’s thesis) and the forthcoming review.

Availability of data and materials
Not applicable.

Declarations
Ethics approval and consent to participate
This study is related to the thesis with ethics number IR.TUMS.SPH.REC.1399.297, Tehran University of Medical Sciences, Tehran, Iran.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
Author details
1Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. 2Center for Solid Waste Research (CSWR), Institute for Environmental Research, Tehran University of Medical Sciences, Tehran, Iran. 3Center for Air Pollution Research (CAPR), Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran. 4Center for Water Quality Research, Institute for Environmental Research, Tehran University of Medical Sciences, Tehran, Iran. 5Health Equity Research Center (HERC), Tehran University of Medical Sciences, Tehran, Iran.

Received: 13 June 2021 Accepted: 15 March 2022
Published online: 22 March 2022

References
1. Bitton G. Wastewater microbiology. Hoboken: Wiley; 2005.
2. Dimavičienė B. Lithuanian and translated young adult literature in the contemporary Lithuanian literary system as conditioned by historical factors: an analysis using polysystem theory. 2016.
3. Bai X, Ma X, Xu F, Li J, Zhang H, Xiao X. The drinking water treatment process and its potential influence on antibiotic resistance. Sci Total Environ. 2019;694:133381.
4. He H, Zhou P, Shimabuku K, Fang X, Li S, Lee Y, et al. Degradation and deactivation of bacterial antibiotic resistance genes during exposure to free chlorine, monochloramine, chlorine dioxide, ozone, ultraviolet light, and hydroxyl radical. Environ Sci Technol. 2019;53(4):2013–26.
5. Li R, Jay JA, Stenstrom MK. Fate of antibiotic resistance genes and antibiotic-resistant bacteria in water resource recovery facilities. Water Res. 2019;155:5–20.
6. Liu S-S, Qu H-M, Yang D, Hu H, Liu W-L, Qiu Z-G, et al. Chlorination and low-pressure ultraviolet removal of antibiotic-resistant bacteria in a full-scale wastewater treatment plant. Water Res. 2018;136:131–6.
7. Wang R-N, Zhang Y, Cao Z-H, Wang X-Y, Ma B, Wu W-B, et al. Occurrence of super antibiotic resistance genes in the downstream of the Yangtze River in China: prevalence and antibiotic resistance profiles. Sci Total Environ. 2019;695:11946–97.
8. Sanganyado E, Gwenz W. Antibiotic resistance in drinking water systems: occurrence, removal, and human health risks. Sci Total Environ. 2019;669:785–97.
9. Giannakis S, Leff T-TM, Entenza JM, Pulgarin C. Solar photo-Fenton disinfection of 11 antibiotic-resistant bacteria (ARB) and elimination of representative AR genes. Evidence that antibiotic resistance does not imply resistance to oxidative treatment. Water Res. 2018;143:334–45.
10. Sullivan BA, Vance CC, Gentry TJ, Karthikeyan R. Effects of chlorination and ultraviolet light on environmental tetracycline-resistant bacteria and tet (W) in water. J Environ Chem Eng. 2017;5(1):777–84.
11. Laroche E, Fawlik B, Berthe T, Skurnik D, Petit F. Occurrence of antibiotic resistance and class 1, 2, and 3 integrons in Escherichia coli isolated from a densely populated estuary (Seine, France). FEMS Microbiol Ecol. 2009;68(1):118–30.
12. Mantilla-Calderon D, Pleva MJ, Michoud G, Fodelianakis S, Daffonchio D, Hong P-Y. Water disinfection byproducts increase natural transformation rates of environmental DNA in Acinetobacter baylyi ADP1. Environ Sci Technol. 2019;53(1):6520–8.
13. Destiani R, Templeton M. Chlorination and ultraviolet disinfection of antibiotic-resistant bacteria and antibiotic resistance genes in drinking water. AIMS Environ Sci. 2019;6(3):222–41.
14. Zhang M, Wang L, Xu M, Zhou H, Wang S, Wang Y, et al. Selective antibiotic resistance genes in multiple samples during biofilm growth in a simulated drinking water distribution system: occurrence, correlation and low-pressure ultraviolet removal. Sci Total Environ. 2019;649:146–55.
15. Miranda AC, Leppretti M, Rizzo L, Caputo I, Vaiano V, Sacco Q, et al. Surface water disinfection by chlorination and advanced oxidation processes: inactivation of an antibiotic resistant E. coli strain and cytotoxicity evaluation. Sci Total Environ. 2016;554:1–6.
16. Luo Y, Mao D, Ryzs M, Zhou Q, Zhang H, Xu L, et al. Trends in antibiotic resistance genes occurrence in the Haihe River, China. Environ Sci Technol. 2010;44(19):7220–5.
17. Tan Q, Li W, Zhang J, Zhou W, Chen J, Li Y, et al. Presence, dissemination and removal of antibiotic resistant bacteria and antibiotic resistance genes in urban drinking water system: a review. Front Environ Sci Eng. 2019;13(3):1–13.
18. Guo X, Li L, Yang F, Yang J, Yin D. Prevalence of sulfonamide and tetracycline resistance genes in drinking water treatment plants in the Yangtze River Delta, China. Sci Total Environ. 2014;493:626–31.
19. Zhang M, Chen S, Yu X, Vikesland P, Pruden A. Degradation of extracellular genomic, plasmid DNA and specific antibiotic resistance genes by chlorination. Front Environ Sci Eng. 2019;13(3):1–12.
20. Zhang J, Li W, Chen J, Wang F, Qi W, Li Y, et al. Effect of hydraulic conditions on the prevalence of antibiotic resistance in water supply systems. Chemosphere. 2019;235:354–64.
21. Yoon Y, Dodd MC, Lee Y. Elimination of transforming activity and gene degradation during UV and UV/ H 2 O 2 treatment of plasmid-encoded antibiotic resistance genes. Environ Sci Water Res Technol. 2018;4(9):1239–51.
22. Xu L, Dasyang W, Qian Y, Su C, Su J, Chen H. High-throughput profiling of antibiotic resistance genes in drinking water treatment plants and distribution systems: Environ Pollut. 2016;213:119–26.
23. Khan S, Beattie TK, Knapp CW. Relationship between antibiotic-and disinfectant-resistance profiles in bacteria harvested from tap water. Chemosphere. 2016;152:132–41.
24. Zhang H, Zhang F, Shi P, Yang Y, Liu Z, Zhou Q, Pan Y, et al. Antibiotic resistance alteration by different disinfection strategies in a full-scale drinking water treatment plant deciphered by metagenomic assembly. Environ Sci Technol. 2019;53(4):2141–50.
25. Shi P, Jia S, Zhang X-X, Zhang T, Cheng S, Li A. Metagenomic insights into chlorination effects on microbial antibiotic resistance in drinking water. Water Res. 2013;47(1):111–20.
26. Ding W, Jin W, Cao S, Zhou X, Wang C, Jiang Q, et al. Ozone disinfection of chlorine-resistant bacteria in drinking water. Water Res. 2019;160:339–49.
27. Huang J-J, Hu H-Y, Wu Y-H, Wei B, Lu Y. Effect of chlorination and ultraviolet disinfection on tetracycline resistance of Escherichia coli. Chemosphere. 2013;90(8):2247–53.
28. Ja S, Shi P, Hu Q, Li B, Zhang T, Zhang X-X. Bacterial community shift drives antibiotic resistance promotion during drinking water chlorination. Environ Sci Technol. 2015;49(20):12271–9.
29. Guo M-T, Yuan Q-B, Yang J. Distinguishing effects of ultraviolet exposure and chlorination on the horizontal transfer of antibiotic resistance genes in municipal wastewater. Environ Sci Technol. 2015;48(9):5711–8.
30. Munir M, Wong K, Xagoraraki I. Release of antibiotic resistant bacteria and genes in the effluent and biosolids of five wastewater utilities in Michigan. Water Res. 2015;45(2):681–93.
31. Bertelli C, Courtos N, Rosikiewicz M, Pipioro P, Aebly S, Robert S, et al. Reduced chlorine in drinking water distribution systems impacts bacterial biodiversity in biofilms. Front Microbiol. 2018;9:2520.
32. Hao H, Shi D-Y, Yang D, Yang Z-W, Qiu Z-G, Liu W-L, et al. Profiling of intra- and extracellular antibiotic resistant genes in tap water. J Hazard Mater. 2019;365:340–5.
33. Zhang T, Hu Y, Jiang L, Yao S, Lin K, Zhou Y, et al. Removal of antibiotic resistance genes and control of horizontal transfer risk by UV chlorination and UV/chlorination treatments of drinking water. Chem Eng J. 2019;358:589–97.
34. Stange C, Sidhu J, Toze S, Tiehm A. Comparative removal of antibiotic resistance genes during chlorination, ozonation, and UV treatment. Int J Hyg Environ Health. 2019;222(3):541–8.
35. Triggiano F, Calia C, Diella G, Montagna MT, De Giglio O, Caggiano G. The role of urban wastewater in the environmental transmission of antimicrobial resistance: the current situation in Italy (2010–2019). Microorganisms. 2020;8(10):1–12.
36. Wang J, Chu L, Wojnárovits L, Takács E. Occurrence and fate of antibiotics, antibiotic resistant genes (ARGs) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: an overview. Sci Total Environ. 2020. https://doi.org/10.1016/j.scitotenv.2020.140997.
37. Rizzo L, Manaia C, Merlin C, Schwartz T, Dagot C, Ploy M, et al. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. Sci Total Environ. 2019;673:347–60.
38. Hassoun-Kheir N, Stabholtz Y, Kreft J-LU, De La Cruz R, Romanal JE, Nesme J, et al. Comparison of antibiotic-resistant bacteria and antibiotic resistance genes in wastewater treatment plants and distribution systems: occurrence, removal, and human health risks. Sci Total Environ. 2018;649:1355–65.
39. Marchetti R, De Muro S, Ghezzi P. Antibiotic resistance in drinking water distribution systems: occurrence, correlation, and risk assessment. Front Environ Sci Eng. 2019;13(3):1–12.
resistance genes abundance in hospital and community wastewater: a systematic review. Sci Total Environ. 2020. https://doi.org/10.1016/j.scitotenv.2020.140804.

39. Mania CM, Macedo G, Fatta-Kassinos D, Nunes OC. Antibiotic resistance in urban aquatic environments: can it be controlled? Appl Microbiol Biotechnol. 2016;100(4):1543–57.

40. Dodd MC. Potential impacts of disinfection processes on elimination and deactivation of antibiotic resistance genes during water and wastewater treatment. J Environ Monit. 2012;14(7):1754–71.

41. Zhang J, Li W, Chen J, Qi W, Wang F, Zhou Y. Impact of biofilm formation and detachment on the transmission of bacterial antibiotic resistance in drinking water distribution systems. Chemosphere. 2018;203:368–80.

42. Zarei-Baygi A, Smith AL. Intracellular versus extracellular antibiotic resistance genes in the environment: prevalence, horizontal transfer, and mitigation strategies. Bioresour Technol. 2021. https://doi.org/10.1016/j.biortech.2020.124181.

43. Li S, Zhang C, Li F, Hua T, Zhou Q, Ho S-H. Technologies towards antibiotic resistance genes (ARGs) removal from aquatic environment: a critical review. J Hazard Mater. 2021. https://doi.org/10.1016/j.jhazmat.2021.125148.

44. Sharma VK, Johnson N, Cizmas L, McDonald TJ, Kim H. A review of the influence of treatment strategies on antibiotic resistant bacteria and antibiotic resistance genes. Chemosphere. 2016;150:702–14.

45. Herraiz-Carboné M, Cotillas S, Lacasa E, de Baranda CS, Riquelme E, Cañizares P, et al. A review on disinfection technologies for controlling the antibiotic resistance spread. Sci Total Environ. 2021. https://doi.org/10.1016/j.scitotenv.2021.149150.

46. Zhang G, Li W, Chen J, Zhou W, Chen J. Problems of conventional disinfection and new sterilization methods for antibiotic resistance control. Chemosphere. 2020. https://doi.org/10.1016/j.chemosphere.2020.126851.

47. Zhang T, Lv K, Lu Q, Wang L, Liu X. Removal of antibiotic-resistant genes during drinking water treatment: a review. J Environ Sci. 2021;104:415–29.

48. Wan K, Lin W, Zhu S, Zhang S, Yu X. Biofiltration and disinfection code-termine the bacterial antibiotic resistome in drinking water: a review and meta-analysis. Front Environ Sci Eng. 2020. https://doi.org/10.1007/s11783-019-1189-1.

49. Petrokofsky G. Guidelines and standards for evidence synthesis in environmental management: version 5.0. 2018.

50. Haddaway N, Macura B, Whaley P, Pullin A. ROSES for systematic review protocols. Version 1.0. 2017.

51. Livoreil B, Glanville J, Haddaway NR, Bayliss H, Bethel A, de Lachapelle FF, et al. Systematic searching for environmental evidence using multiple tools and sources. Environ Evid. 2017;6(1):1–14.

52. Stanton IC, Bethel A, Leonard AF, Gaze WH, Garside R. What are the effective solutions to control the dissemination of antibiotic resistance in the environment? A systematic map protocol. Environ Evid. 2020;9(1):1–8.

53. Goulas A, Belhadi D, Descamps A, Andremont A, Benoît P, Courtois S, et al. How effective are strategies to control the dissemination of antibiotic resistance in the environment? A systematic review. Environ Evid. 2020;9(1):1–32.

54. Rodríguez-Molina D, Mang P, Schmitt H, Chiffiriuc MC, Radon K, Wengenroth L. Do wastewater treatment plants increase antibiotic resistant bacteria or genes in the environment? Protocol for a systematic review. Syst Rev. 2019;8(1):1–8.

55. Ebrahim SM, Reyhani RD, Asghari-JafarAbadi M, Fathifar Z. Diversity of antibiotics in hospital and municipal wastewaters and receiving water bodies and removal efficiency by treatment processes: a systematic review protocol. Environ Evid. 2020;9(1):1–9.

56. Goulas A, Livoreil B, Grant N, Benoît P, Oudrerc-Obert C, Dagit C, et al. What are the effective solutions to control the dissemination of antibiotic resistance in the environment? A systematic review protocol. Environ Evid. 2018;7(1):1–9.

57. Bilotta GS, Milner AM, Boyd IL. Quality assessment tools for evidence from environmental science. Environ Evid. 2014;3(1):1–14.

58. Higgins JP, Altman DG, Gatsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011. https://doi.org/10.1136/bmj.d9328.

59. Schindler S, Bayliss HR, Essl F, Rabitsch W, Follak S, Pullin AS. Effectiveness of management interventions for control of invasive common ragweed Ambrosia artemisiifolia: a systematic review protocol. Environ Evid. 2016;5(1):1–10.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.